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Leonard L. Gunderson
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Louis B. Harrison

Intraoperative Irradiation

Techniques and Results

Second Edition

Humana Press

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Current Clinical Oncology

Maurie Markman, MD, Series Editor

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ISBN 978-1-61779-014-0 e-ISBN 978-1-61779-015-7
DOI 10.1007/978-1-61779-015-7
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2011924474

Printed on acid-free paper

Humana Press is part of Springer Science+Business Media (www.springer.com)

To Katheryn, my wife and best friend, to our children and their spouses (Chad and Chrissy, Whitney and Jeff, Stacie and Nick, Ryan and Danna, Scott and Cindy) and to our grandchildren (Olivia and Adam; Rebecca, Andrew, Katie and Matthew; Sam, Anna, Michael and Ellie; Grant; Landon and Parker) for their love and support

To colleagues in Surgery, Medical Oncology, and Radiation Oncology for the opportunity to work together as a team in the delivery of multimodality treatment, including IORT, for our patients with cancer

Leonard L. Gunderson

To Mary Sunday for 25 years of love and support

Christopher G. Willett

To my family: wife Marta and children Almudena, Marta, Maria, Covadonga, Felipe-Angel, Sonsoles, Francisco and Paloma; beloved parents Lucia and Felipe, brother Elpidio and sister Tuti; my first love, the school of values in which I learned to understand and serve society

To my teachers, especially Dr Jose Otero and Professor Luther W Brady, with deep gratitude for the privilege of their superb and caring education

To colleagues and institutions involved in IORT procedures during the last three decades for their outstanding and generous commitment to excellence in cancer medicine.

Felipe A. Calvo

To my 6 favorite kids, my 2 daughters, 3 nephews and 1 niece: Barbara Harrison, Michella Harrison, Alan Levy, Ryan Farago, Lance Levy and Sophia Levy. I love all of them and have been lucky to have them in my life.

Louis B. Harrison

Preface

Intraoperative Irradiation: Techniques and Results, *Second Edition* is a comprehensive textbook on intraoperative irradiation therapy (IORT) that covers topics of interest to those who have intraoperative electron radiation therapy (IOERT), high-dose-rate brachytherapy (HDR-IORT) or electronic brachytherapy/low KV IORT capabilities. Issues of basic science and physics are covered in addition to techniques, indications, and results by disease-site. Most disease-site chapters have multinational and multidisciplinary authorship that includes both radiation oncologists and surgeons, which provides a more balanced presentation of techniques and results by disease-site.

The rationale for using IORT as a component of treatment is based on the realization that tolerable doses of external beam radiation therapy (EBRT) are often insufficient to achieve local control of locally advanced abdominal or pelvic malignancies, even with 3-D conformal or intensity-modulated radiation techniques (3-D CRT; IMRT). A preferred treatment approach is to deliver preoperative EBRT of 45–54 Gy in 1.8–2 Gy fractions, often in conjunction with concurrent chemotherapy, followed by maximal surgical resection and IORT. The IORT component of treatment becomes the optimal conformal technique of irradiation, since dose-limiting organs or structures can either be surgically displaced (stomach, small intestine, liver, etc.) or protected by surgical placement of lead shielding or by proper selection of electron energy.

The textbook is again divided into five major sections. The book begins with chapters on the general rationale for and historical perspectives of IORT and the radiobiology of IORT. It then proceeds to a discussion of methods and techniques of treatment and a presentation of normal tissue and organ tolerance to IORT. In the methods and techniques section, a new chapter is included on "Electronic Brachytherapy/Low KV IORT: Physics and Techniques" which is a possible alternative IORT treatment approach. The tolerance chapter is essential reading for any individual or institution contemplating a program in IORT; the implications of tolerance are far-reaching both for the patients who receive IORT as a component of treatment and the physicians who deliver the IORT. The largest section of the text is the presentation of techniques and results by disease-site which includes outcomes data on disease control, survival, and treatment tolerance. Outcomes with non-IORT treatment approaches are compared with those using IORT-containing regimens in many of the chapters. The closing section is a chapter on conclusions and future possibilities that was written by the four coeditors of the textbook.

One of the conclusions of the closing chapter is that long-term experience has shown that the use of IORT as a component of treatment in conjunction with other modalities (EBRT, concurrent and maintenance chemotherapy, maximal surgical resection) is feasible and practical if close multidisciplinary cooperation exists. In addition, the IORT-containing, multimodality regimens appear to improve local disease control, if not survival, in many disease-sites when compared with non-IORT treatment approaches. For patients in whom gross total resection of their cancer is not safely feasible, the ability to achieve central or local control is lessened, thus creating the need for prospective clinical trials that address the addition of radiation dose modifiers during both EBRT and IORT.

Patients with locally advanced or locally recurrent cancers who are candidates for IORT containing regimens often have high systemic risks as well. Prospective trials that address the addition of aggressive systemic therapy to the locally aggressive combined treatment are also necessary. The closing chapter also addresses improvements in technology that make IORT more feasible in a larger number of institutions and thus facilitate the conduct of prospective trials in a multi-institution national or international setting. This technology includes mobile IOERT equipment (Mobetron, Novac-7, LIAC), HDR brachytherapy, and electronic brachytherapy/low-KV equipment that can be used in either an outpatient or operating room setting.

The four coeditors have personally been involved in utilizing IORT as a component of treatment in the care of thousands of patients in a multispecialty, multimodality setting. We are therefore delighted that IORT is becoming available to more physicians and patients worldwide as a result of the changes in technology that are discussed in *Intraoperative Irradiation: Techniques and Results, Second Edition.*

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Part I
General Rationale and Historical Perspective

Chapter 1
Rationale and Historical Perspective of Intraoperative Irradiation

Leonard L. Gunderson, Felipe A. Calvo, Christopher G. Willett, and Louis B. Harrison

Keywords IORT rationale • History of IORT • Dedicated IORT facilities • Patient selection for IORT

Introduction

Most of the major advances in clinical applications of radiation therapy in the treatment of cancer have been due to differences in dose distribution between tumor and dose-limiting normal tissue. For most tumor types, the likelihood of obtaining local tumor control improves if irradiation doses delivered to the tumor mass can be safely increased. However, in many clinical situations, the dose which can be delivered safely to the tumor volume is limited by the normal tissues which are in close proximity to the tumor volume.

Intraoperative irradiation (IORT) in its broadest sense refers to the delivery of irradiation at the time of an operation. IORT evolved as an attempt to achieve higher effective doses of irradiation while dose-limiting structures are surgically displaced.

In this second edition of the IORT textbook, the rationale for and results of IORT will be discussed including the use of intraoperative electrons (IOERT), high dose rate brachytherapy (HDR-IORT) and electronic brachytherapy/low kilovoltage (KV) IORT in conjunction with surgical exploration and resection ± external beam irradiation (EBRT) and chemotherapy. The radiobiology and physics of IORT will be discussed in addition to its techniques, indications, and updated results/outcomes by disease site (survival, relapse, tolerance).

This chapter provides the rationale for and history of IORT, patient selection, and evaluation, sequencing of EBRT + IORT components of treatment and guidelines for reporting data from IORT trials. If conventional treatment methods with EBRT, chemotherapy, and surgical resection were providing high local control rates with minimal complications, the addition of IORT as a component of treatment would be unnecessary. Since that is not the situation, there is a need to develop guidelines for determining when the additional treatment is indicated (extent of disease, location, etc.)

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_1,

and what might be the best method. General guidelines will be presented in this chapter, and specific guidelines by disease site will be expanded upon in the disease-site chapters.

Rationale for IORT

EBRT + IORT

In view of dose limitations of EBRT, IORT has been employed in an attempt to improve the therapeutic ratio of local control vs. complications. In Japanese IOERT trials instituted in the 1960s [1], as well as early US trials [2], IOERT was usually the sole irradiation modality. Investigators delivered single doses of 20–40 Gy to the site of interest with electron beams and rarely used supplemental EBRT.

Massachusetts General Hospital (MGH) and Mayo Clinic investigators preferred to use IOERT as a "boost" dose in combination with conventional fractionated EBRT + concurrent chemotherapy and maximal surgical resection as indicated by site [3]. This preference was based on several advantages that potentially exist when a combined EBRT-IORT approach is used instead of IORT alone: (1) improvement in local-regional control because of a decreased risk of marginal relapse (areas at risk are included in the EBRT fields) and the radiobiological advantages of fractionated irradiation and (2) less risk of normal tissue damage or necrosis. The excellent long-term results achieved with EBRT plus boost techniques for breast, gynecologic and head and neck cancers support the concept of this combined approach since good local control is achieved with relatively low morbidity to dose-limiting normal tissues. The only difference is the method of delivering the boost dose. Patients with head and neck and breast lesions require interstitial techniques or fractionated outpatient electrons; gynecologic lesions are treated with an intracavitary technique; IORT boosts (electrons, HDR brachytherapy, electronic brachytherapy/low-KV IORT) can be used for intra-abdominal, pelvic or thoracic lesions plus breast, trunk, extremity, or head and neck sites.

The combination of IORT with EBRT has the potential to improve the therapeutic ratio of local control vs. complications by a multitude of factors. These include the following: (1) decrease the volume of the irradiation "boost" field by direct tumor visualization and appositional treatment with IORT; (2) exclude all or part of dose-limiting sensitive structures by operative mobilization or shielding and/or the use of appropriate electron beam energies; and (3) increase the "effective" dose by virtue of number 1 and 2.

EBRT Local Tumor Control or Survival: Selected Disease Sites

The incidence of local relapse with conventional treatment of selected abdominal or pelvic malignancies will be discussed in an attempt to delineate examples where increased dose may be of benefit or where there is a need to minimize dose to certain structures [4–20]. Select data from colorectal and gynecological cancer and retroperitoneal sarcoma non-IORT series will be presented. A more detailed discussion of local control results with standard treatment ± an IORT supplement will be found in each disease site chapter.

Colorectal Cancer

EBRT has been combined with resection and chemotherapy for locally advanced colorectal cancers. In separate series from Princess Margaret Hospital (PMH) [7] and Mayo Clinic [8], using EBRT alone (PMH, Mayo) or combined with systemic therapy (Mayo), the local relapse rate was >90% in evaluable patients (PMH – primary cancers, Mayo – primary plus locally recurrent). Although a

combination of pre- or postoperative EBRT (±5-FU) with maximal resection for initially unresectable for cure cancers produces a local control rate better than no resection, the risk of local relapse remains too high at 30–70% [9]. For locally recurrent nonmetastatic rectal cancers, standard treatment with EBRT ± chemotherapy results in excellent short-term palliation for 6–12 months, but both local control and long-term survival are infrequent (0–5% at 5 years) [9]. Accordingly, use of IORT as a supplement to preop EBRT and maximal resection for locally advanced primary or locally recurrent colorectal cancers is an attractive option.

Gynecologic Cancer

A number of centers have treated primary cervical carcinoma patients with metastatic para-aortic nodal disease with EBRT in the hope of producing cures. Although there appears to be definite evidence of the ability to cure a subset of 15–20% of patients if an EBRT dose of 55–60 Gy is employed, the high complication rates in two series [10, 11] indicate that different radiotherapeutic techniques need to be employed if aggressive treatment to this location is to be done on a large scale.

For patients with relapse in the pelvic sidewalls or para-aortic nodes, salvage therapy results in overall 5-year SR of 0–5% for endometrial and 2–30% for cervical cancer, according to the size of the relapse. In previously irradiated patients, retreatment with meaningful doses of EBRT is compromised, and utilization of IORT as a supplement to low-dose EBRT ± multidrug chemotherapy becomes one of the available options to treat patients with tumor bed or nodal relapses [12–16].

Retroperitoneal Sarcoma

When surgery is the sole treatment modality for retroperitoneal sarcomas, subsequent local relapse rates have been as high as 70–90%. If EBRT is combined with resection, the dose of EBRT that can be delivered safely is much lower than with extremity sarcomas in view of dose-limiting structures (small intestine, stomach, liver, kidney, spinal cord). In a randomized NCI trial, patients with primary sarcomas randomized to EBRT alone after marginal resection had a local relapse rate of 80% and excessive acute and chronic small bowel morbidity [17]. The use of IORT supplements with IOERT [17–20] or HDR-IORT are therefore reasonable and practical.

Influence of Dose on Local Control

As irradiation dose is increased to a tumor, there is an increased amount of cell killing with an increased likelihood of tumor control. This concept has been validated in many animal experiments in that local tumor control increases sharply with increasing irradiation dose, and the shape of this curve follows closely the theoretical model [21]. The animal data also clearly show that the irradiation dose needed to control a certain percentage of tumors will increase as the tumor volume increases and conversely that the percentage of tumors which will be controlled at a certain dose level will decrease as the volume of the tumor increases. Thus, although a given irradiation dose may be able to control a small tumor mass with high probability (and with acceptable patient morbidity), that same dose may be quite ineffective against larger volume tumors which contain a larger number of clonogenic cells.

A significant body of information has gradually developed to show that this same concept holds true for human tumors irradiated in vivo. This includes a large spectrum of tumors of various sizes and histologic types as summarized in Fig. 1.1. One of the earliest series related to tumor control vs. dose was reported by Hale and Holmes [22] in the treatment of basal and squamous cell carcinomas of the skin. They found that the local relapse rate decreased from 33 to 4% as the radiation dose was increased from 24 to 45 Gy, delivered over 1 week. This analysis is especially valuable since skin

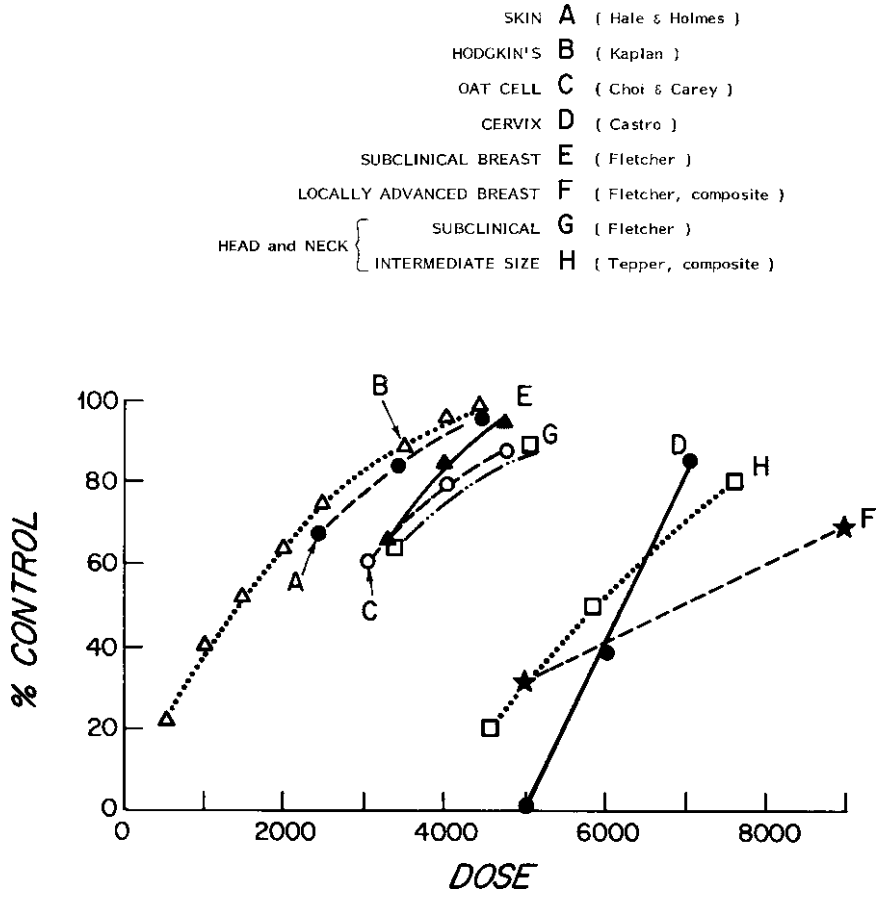

Fig. 1.1 Local control vs. dose of irradiation. (**a**) skin [22]; (**b**) Hodgkins [23]; (**c**) lung – oat cell; [24]; (**d**) cervix; (**e**) breast subclinical [25, 26]; (**f**) breast locally advanced [25, 26]. (**g**) head and neck subclinical [25, 26]; (**h**) head and neck intermediate [28]. From Gunderson et al. [3].

cancers are usually well demarcated prior to treatment, are of a fairly uniform size, and can be accurately evaluated for local persistence or relapse, both because of the ease of examination and the small likelihood of metastatic disease and patient death prior to adequate follow-up. Kaplan [23] analyzed local control after treatment of Hodgkin's disease with fractionated irradiation alone and demonstrated that the local relapse rate decreased from approximately 60% at 10 Gy to 26% at 25 Gy, 11.5% at 35 Gy, and 1.3% at 44 Gy (~10 Gy per week, 2 Gy per fraction). The very shallow slope of tumor control vs. dose in this clinical situation may be related to the relatively small number of clonogenic cells in even large masses of Hodgkin's disease. Choi and Carey [24] analyzed the local control of disease in the chest in patients with small cell carcinoma of the lung. Control was obtained in 60% of patients who received 30 Gy, 79% at a dose of 40 Gy, and 88% at 48 Gy.

Fletcher and colleagues [25, 26] performed an extensive evaluation of dose–response curves of human tumors emphasizing adenocarcinoma of the breast and squamous cell carcinomas of the head and neck (Table 1.1). In breast cancer, the probability of controlling subclinical nodal or chest wall disease was 60–70% with a dose of 30–35 Gy, 85% with 40 Gy, and 95% with 45–50 Gy (usual fractionation of 10 Gy per week in 2 Gy fractions). For locally advanced breast cancers, local control can still be obtained, but only when much higher doses are employed. For these large tumors, doses of 50–60 Gy produced local control in 35% of patients in the series of Griscom and Wang [27], compared to 70% local control at doses of 90 Gy (with protracted fraction) obtained by Fletcher [26].

Table 1.1 Tumor control probability correlated with irradiation dose and volume of cancer

SCC – upper aerodigestive tract	
Dose (Gy)	*Tumor control probability*
50[a]	> 90% Subclinical
	60% T1 lesions of nasopharynx
	~ 50% 1–3 cm neck nodes
60[a]	~ 90% T1 lesions of pharynx and larynx
	~ 50% T3 and T4 lesions of tonsillar fossa
	~ 90% 1–3 cm neck nodes
	~ 70% 3–5 cm neck nodes
70[a]	~ 90% T2 lesions of tonsillar fossa and supraglottic larynx
	~ 80% T3 and T4 lesions of tonsillar fossa
ACA of the breast	
Dose (Gy)	*Tumor control probability*
50[a]	>90% subclinical
60[a]	90% clinically positive axillary nodes 2.5–3 cm
70[a]	65% 2–3 cm primary
70–80 (8–9 weeks)	30% >5 cm primary
80–90 (8–10 weeks)	56% >5 cm primary
80–100 (10–12 wk)	75% 5–15 cm primary

[a]10 Gy in five fractions each week
SCC squamous cell carcinoma, *ACA* adenocarcinoma
Modified from Fletcher and Shukovsky [26]

The most extensive information on local control vs. dose is available for squamous cell carcinomas of the head and neck. These data have been summarized by Fletcher and Shukovsky [25, 26] and Tepper [28]. For microscopic disease in lymph nodes, a dose of 30–40 Gy produces local control in 60–70% of patients, compared to greater than 90% control at doses of 50 Gy in 25 fractions over 5 weeks. A strong dose–response curve has not been demonstrated for early-stage primary tumors of the head and neck, with good control at virtually all doses commonly used. The lack of a strong correlation is because no centers have had any need to decrease the dose (as morbidity is so low) below that which is commonly used and where high local control rates are obtained. The data compiled by Tepper indicate that 20% local control results after a dose of 46 Gy, 50% control with 58.5 Gy, and 80% control only with a very high dose of 75.5 Gy. Thus, a marked improvement in local control results from the ability to increase the tumor dose significantly.

An estimation of curative irradiation dose required for various tumor types on the basis of site, histology, and size was made by Dr. Philip Rubin in the text Clinical Oncology [29] (Table 1.2). As shown, for unresected tumors at most sites, irradiation doses would be ≤65 Gy only for early lesions (T_1-larynx, breast) with most lesions requiring 70–80 Gy or higher.

That a strong correlation exists between local control and total tumor dose in human tumors seems quite clear, even though a good dose–local control curve cannot be shown for all clinical situations. The fact that this relation exists gives us much optimism that if we can safely increase the total dose given to a tumor mass by using IORT as a supplement to EBRT (±concomitant chemo) and maximal resection, increases in local control and total cure rate should result.

Impact of Local Control on Distant Metastases

In the ASTRO Gold Medal paper of Dr. Herman Suit [30], the theme of distant metastases developing from a locally recurrent tumor was discussed as a component of the overall premise that local control benefits survival. Data was presented from several spontaneous tumor systems to suggest that the rate of distant metastases was related to both tumor size and disease presentation as primary vs. locally

Table 1.2 Curative doses of radiation for different solid cancers

50–60 Gy	
Embryonal	Ewing's
Medulloblastoma	Retinoblastoma
60–65 Gy	
Larynx (<1 cm)	
Breast (T_1)	
70–75 Gy	
Oral cavity (<2 cm, 2–4 cm)	Oro-naso-laryngo-pharyngeal
Breast (T_2)	Bladder
Cervix	Uterine fundal
Ovarian	Lung (<3 cm)
80 Gy or above	
Head and neck (>4 cm)	Breast (>5 cm)
Glioblastomas (gliomas)	Osteogenic sarcomas (bone sarcomas)
Melanomas	Soft tissue sarcomas (>5 cm)
Thyroid	

Modified from Rubin and Siemann [29]

Table 1.3 Distant metastasis rates for spontaneous primary or locally recurrent tumors of the C_3H/Sed mouse

			Distant metastasis	
Tumor size (mm)	Tumor category	Treatment	F Sa II (%)	SCC VII (%)
6	Primary	Surgery	2.6	8
		Radiation	3.1	6.9
	Recurrent	Surgery	12.5	43.0
12	Primary	Surgery	14.3	41.3
	Recurrent	Surgery	46.6	70.3

FSA fibrosarcoma; *SCC* squamous cell cancer
Modified from Suit [30]

recurrent disease. In both the spontaneous fibrosarcoma FSaII and squamous cell carcinoma SCC VII lines in the C3H/Sed mouse. Ramsey et al. reported increased rates of distant metastases with 6 mm vs. 12 mm tumor size and primary vs. recurrent tumors (Table 1.3) [31]. Ramsey's work confirmed an earlier evaluation by Suit et al. [32]. In Suit's analysis, 12 mm isotransplants of C3H mouse mammary tumors were treated with single-dose irradiation and evaluated for disease control both locally and distantly. The rate of distant metastases increased with lack of local control with rates of 31% (16 of 52) in mice with local control, 50% (9 of 18) in those with local relapse who were salvaged with further resection and 80% (12 of 15) of mice with local relapse in whom salvage was not attempted.

Human data were also quoted supporting the thesis of metastases arising from the local relapse. In patients with squamous cell cervix cancers, the metastatic frequency was higher in patients with local relapse vs. those with local control [33]. In a Sloan-Kettering analysis of prostate cancer patients treated with I125 implants, the rate of distant metastases increased by stage and grade in patients with local relapse vs. local control [34]. Liebel et al. [35] found similar results in disease outcome analyses of RTOG patients with head and neck cancers for all sites except nasopharynx.

Local Tumor Control vs. Complications

For patients with locally advanced abdominal or pelvic malignancies in whom all disease cannot be surgically removed with negative margins (R0 resection), EBRT (±concurrent chemotherapy) is

Table 1.4 GI radiation tolerance doses in Gy[a]

Organ	Injury at 5 years	1–5% $TD_{5/5}$	25–50% $TD_{50/5}$	Volume or length
Esophagus	Ulcer, stricture	60	75	75 cm^3
Stomach	Ulcer, perforation	45	50	100 cm^3
Intestine	Ulcer, stricture	45	65	100 cm^3
Colon	Ulcer, stricture	45	65	100 cm^3
Rectum	Ulcer, stricture	55	80	100 cm^3
Pancreas	Secretory functions	–	–	–
Liver	Liver failure, ascites	35	45	Whole
Biliary ducts	Stricture, obstruction	–	–	–

[a]Data based on supervoltage (1–6 mV), 10 Gy/week (5×200)
Modified from Gunderson and Martenson [36]

often only palliative since doses greater than 45–50 Gy in 25–28 fractions often cannot be delivered safely even with 3-D conformal or intensity-modulated irradiation (3-D CRT, IMRT). Gastrointestinal normal tissue (organ) tolerance to fractionated EBRT is demonstrated in Table 1.4 [36]. If treated with tolerable doses, patients will usually have local persistence or relapse of disease with secondary complications that may require hospitalization and/or reoperation for small bowel obstruction, ureteral obstruction, bowel perforation, etc.

If microscopic residual exists after gross total resection (R1 resection), EBRT doses necessary to accomplish local control are ≥60 Gy in 1.8–2 Gy fractions. Dose requirements would be even higher if gross residual remains after maximal resection (R2 resection). With doses ≥60 Gy, the radiation tolerance of numerous organs and structures in the abdomen and pelvis would be exceeded in both adults and children. Therefore, while an aggressive EBRT philosophy may allow better local tumor control, it may also cause severe treatment-related complications which could require hospitalization and surgical intervention (see solid lines, Fig. 1.2). If small or large bowel problems result from excessive irradiation, complications such as fistulae, perforation, etc., can occur which usually require a reoperation.

A preferred treatment alternative for patients with locally advanced primary or local-regionally recurrent malignancies is to give tolerable EBRT doses of 45–50 Gy preoperatively (1.8 Gy fractions) and deliver IORT as a supplement at the time of surgical exploration and maximal resection. The IORT component of treatment becomes the optimal conformal technique of irradiation, since dose-limiting organs or structures can either be surgically displaced (stomach, small intestine, liver, surgical anastamoses, etc.) or protected by surgical placement of lead shielding or by proper selection of electron energy. This approach allows an increase in local control (local control curve shift to the left – dotted line Fig. 1.2) with a lower risk of complications than with an EBRT-only approach (complication curve shift to the right – dotted line Fig. 1.2).

Shrinking Field Techniques

Rationale for the use of shrinking field irradiation techniques has been in existence for decades using either EBRT alone or EBRT plus brachytherapy. The initial EBRT field is usually designed to include a 3–5 cm margin beyond the primary or recurrent tumor plus regional nodal areas that are at risk for metastatic spread. Initial fields are treated to an accepted subclinical dose level of 45–50.4 Gy in 1.8–2.0 Gy fractions. Subsequent boost techniques are used to bring gross disease to the level of 65–80 Gy with EBRT or brachytherapy techniques. The excellent long-term results achieved with EBRT plus boost techniques for breast, gynecologic and head and neck cancers support the concept of this combined approach since good local control is achieved with relatively low morbidity to dose-limiting normal tissues. Combining IORT with EBRT and surgical resection for abdominal and pelvic cancers is a natural extension of this philosophy.

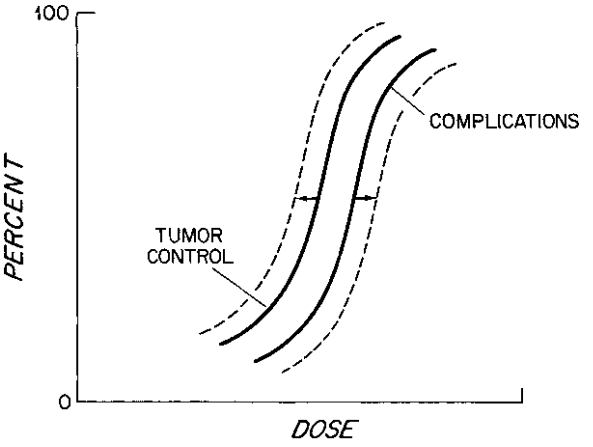

Fig. 1.2 Radiation dose vs. incidence of tumor control or complications. From Gunderson et al. [3].

History of IORT

Orthovoltage IORT Era: Europe and USA

Pioneering European countries in the field of IORT are Spain [37, 38], Austria [39] and Germany [40]. However, most of the scientific information generated before the 1980s was of little practical influence in the oncology community [41–43].

The initial use of IORT in the treatment of gastrointestinal cancers was described by Finsterer in 1915 for a patient with advanced gastric carcinoma who received an X-ray treatment with simultaneous jejunostomy [44]. The tumor was surgically exposed and irradiated by a technique called "eventration treatment." This approach gained limited popularity for unresectable gastric and colorectal cancer [45].

In the 1930s, surgeons and radiation oncologists re-advocated IORT because of the development of shock proof, 50–100 kV short-distance X-ray equipment ("contact therapy"). This machine approximated the treatment conditions obtained with radium treatment with regard to dose distribution but offered the advantages of safety, cost, and convenience. The poor tissue penetration of irradiation at this energy prevented extensive use.

Between late 1930s and late 1950s, a number of institutions utilized higher-energy orthovoltage units for IORT. In 1937, Eloesser of Stanford reported on the use of intraoperative X-ray therapy with 200 kV energy in six patients with advanced gastric and rectal tumors [46]. Sterile lead shields were placed over normal tissues, and doses up to 4,500 R were used without the report of acute complications. In 1947, Fairchild and Shorter [47] described a technique of "direct" treatment of unresectable gastric carcinoma with 500–1,300 R from a 250 kV unit in the operating room and were the first to propose combining this treatment with postoperative EBRT. Of 32 patients treated in this fashion, two lived beyond 2 years without any late complications.

A large series of patients with head and neck, thoracic and abdominal malignancies was reported by Barth in 1959 using intraoperative 90 and 150 kV X-rays [48]. Many patients were treated with "subcutaneous" therapy in which the skin and subcutaneous tissues were temporarily peeled back to allow the delivery of multiple short-distance treatments. By extending this concept to abdominal tumors, Barth was among the first to suggest treatment of malignancy by a combination of preoperative EBRT and a single IORT treatment. Encouraging results, especially with advanced head and neck cancer, were initially reported but long-term follow-up was not published since this was

considered mainly palliative therapy. The interest in this technique waned with the introduction of megavoltage X-rays which could deliver high doses to deep structures without the necessity of surgical exposure.

Megavoltage IORT Era: Japan/Other Asian Experience

The modern approach to IORT began with studies by Abe at the University of Kyoto in the early 1960s [1, 48]. Their approach to overcome the limitations of surgery and EBRT in advanced abdominal tumors was to combine resection of the tumor when possible, followed immediately by a single massive dose (25–30 Gy) of radiation during the operation. Higher doses (up to 40 Gy) were used if the tumor was unresectable. The first patients were treated with cobalt-60. In 1965, a betatron was installed in an operating room within the radiotherapy department, and subsequent patients were treated with intraoperative electron irradiation (IOERT). By the early 1980s, this technique had spread to 27 hospitals in Japan, and in a 1981 publication, Abe and Takahashi reported the combined Japanese results in 727 patients [48].

As of September 2009, nearly 100 IOERT facilities are functioning in Asia (Japan – 43, China – 54). Most IOERT programs still require patient transport (Japan – 41, China – 50), but mobile IOERT machines are now functioning in 6 institutions (Japan – 2, China – 4).

Modern US IORT Era (1970s–Present): IOERT or Orthovoltage

Because of Henschke's earlier interests in IORT [39], in 1970, he and Goldson planned a special IOERT facility for the new Howard University Hospital which was under construction. One of the supervoltage suites of the new radiotherapy department was equipped as an operating room. A Varian Clinac 18® MeV linear accelerator was selected as the machine for this undertaking. The first IOERT treatment was given at Howard University in November 1976, and by December 1982, 114 patients had been treated with variable electron energies [2, 49, 50]. Based on the exploratory work performed in Japan and at Howard University, a number of other US institutions subsequently began investigations into the use of IOERT.

The MGH was the second American center to use this technique with the first patient treated in May 1978 [51]. As previously discussed, the MGH investigators made one significant change; most patients were treated with IOERT plus fractionated conventional EBRT doses of 45–55 Gy in 1.8–2.0 Gy fractions. In addition, many patients had maximal surgical resection if this was thought to be technically feasible. Patient transport from the regular operating room (OR) suites to the radiation oncology department was required for IOERT delivery from 1978 to 1996 when a dedicated facility became available in the regular OR suites at MGH. A total of 780 MGH patients have received IOERT as a component of treatment from 1978 to November 2009 (478 in the dedicated facility since June 1996) with major disease site emphasis on colorectal and pancreas cancer, soft tissue sarcoma, and recurrent gynecologic cancer.

The National Cancer Institute (NCI) began using IOERT in September 1979 [52]. They also did not use IOERT alone, but rather emphasized the combination of maximal surgical resection with the IOERT and in most clinical situations did not utilize conventional doses of EBRT (i.e., in the NCI retroperitoneal sarcoma trial, the EBRT component of treatment was limited to ~40 Gy in 1.8–2 Gy fractions). As the initial emphasis at NCI was on IOERT alone or combined with lower-dose EBRT, the IOERT field size was often very large, and included abutting as many as three separate IOERT fields.

These large IOERT fields, combined with aggressive surgical resection, were found to be feasible, and no major acute complications were attributed to the IOERT.

In the early 1980s, IORT programs also became active at the Mayo Clinic in Rochester (MCR) [53] (April 1981) and the New England Deaconess Hospital (NEDH) division of the Joint Center for Radiation Therapy (January 1982). At Mayo Clinic, IOERT was incorporated as a component of treatment with the same general approach and philosophy as at MGH. A major difference was the initial physical plant in that a sterile OR was developed in the radiation oncology department since routine patient transfer from normal OR suites was challenging. This facility was used to treat 240 patients from 1981 to 1989 until a dedicated IORT facility became available in the Methodist Hospital operating suites as a part of new OR construction. An additional 1,850 patients received IORT from April 1989 to August 2009 in the dedicated IORT suite (a total of 2,090 patients had IORT as a component of treatment at MCR from April 1981 to August 2009; IOERT – 2,085 patients, HDR-IORT, 5 patients). Disease sites treated with IOERT include gastrointestinal (colorectal, pancreas, esophago-gastric, biliary), gynecologic, genitourinary (mostly recurrent renal), head and neck and pediatric cancers and soft tissue sarcomas (extremity, retroperitoneal).

At NEDH, a lower energy X-ray machine (orthovoltage irradiation) was placed in the operating room in January 1982. The philosophy was that if orthovoltage IORT was shown to be as good as IOERT, this would be advantageous as the low-energy machines were less expensive, required less shielding, and would therefore be more generally available.

From the mid-1980s–1990s, IORT programs existed in many US institutions, although the frequency of utilization varied widely. In a Patterns of Care study reported in 1992, Coia and Hanks noted that of 1,293 US radiation oncology facilities, 108 reported using IORT [54]. Most IORT programs at that time required patient transport from the OR to the radiation oncology department with dedicated or semi-dedicated facilities in less than ten institutions (Howard University, Mayo Clinic in Rochester, NCI, Thomas Jefferson University Hospital (TJUH), Medical College of Ohio – Toledo, MD Anderson Cancer Center (MDACC), MGH; see subsequent section).

From 1985 to 1993, the Radiation Therapy Oncology Group (RTOG) had active phase II protocols in a number of disease sites (colorectal, pancreas, biliary, gastric, retroperitoneal soft tissue sarcoma, other), with excellent participation by surgeons, radiation oncologists and physicists in both protocol development and patient accrual. The radiation dose modifier, etanidazole, was successfully evaluated in a Phase I–II trial for colorectal cancer, and dose levels and timing of etanidazole relative to IORT were established for a subsequent phase III trial. However, when RTOG IORT institutions were unsuccessful in accruing sufficient numbers of patients to subsequent phase III protocols in pancreas and colorectal cancer in the early 1990s, RTOG closed most IORT protocols, and the RTOG IORT committee was dissolved. As a result, the forum for generating discussions between US surgeons and radiation oncologists about IORT applications and potential protocols dissipated, and interinstitution IORT efforts and cooperation have been minimal since that time.

For the past 10–15 years, most IORT efforts in the USA have been restricted to single-institution series or phase II protocols, and participation in international meetings including ISIORT (International Society of Intraoperative Radiation Therapy). The number of institutions using IORT as a component of treatment has sharply decreased from the more than 100 reported in 1992 to 36 in a 2005 survey performed by Biggs prior to the ISIORT 2005 meeting in Miami and presented as a poster at that meeting [55]. However, the introduction of new dedicated or semi-dedicated IORT facilities in existing and new IORT institutions (see subsequent section) and mobile IOERT equipment (subsequent section), have revitalized US interest in the use of IOERT as a component of treatment. Of the 36 US IORT programs in 2005, only eight still required patient transport from the OR to the radiation oncology department, seven had a dedicated IORT facility in the radiation oncology department, and the remaining 21 had IORT available in the OR (includes 5 HDR-IORT). Hopefully, this will lead to a resurgence of interest in US interinstitution collaboration and protocol efforts.

Modern Europe IORT Era (1980s–Present): IOERT or Orthovoltage

In the early 1980s, several European institutions implemented an IORT program using either high-energy electron beams (IOERT) or orthovoltage. A literature review of abstracts from early International IORT Symposia [56–58] identifies some of the active IORT groups in the mid-1990s which became involved in IORT 7–15 years earlier.

The following list generates a chrono-geographical relationship regarding the historical origins of modern European IOERT: Caen (France) 1983, Pamplona (Spain) 1984, Innsbruck (Austria) 1984, Lyon (France) 1985, Milan (Italy) 1985, Munchen (Germany) 1986, Brussels (Belgium) 1987, Groningen (Holland) 1988, Oslo (Norway) 1990, Stockholm (Sweden) 1990. A modern orthovoltage IORT program was started in Montpelier (France) in 1984 with transition to a dedicated IOERT facility in 1996.

In the last 10–20 years, additional IORT programs have been started including some that are very active. Aachen (Germany) started their IORT program in 1989 and treated 947 patients through the end of 2008 with major emphasis on colo-rectum ($n=226$), head/neck ($n=209$), sarcoma ($n=108$), genitourinary ($n=71$) and breast ($n=65$). Heidelberg (Germany) began their IOERT program in 1991 (dedicated linear accelerator in the OR) and have treated ~1,700 patients with emphasis on rectal cancer (primary and recurrent), sarcoma (extremity and retroperitoneal), pancreatic cancer, and recurrent gynecologic cancer. Eindhoven (Netherlands) started IOERT in 1994 and have treated 1,000 patients with emphasis on locally advanced primary ($n=600$) and recurrent rectal cancer ($n=300$), with more limited experience in breast ($n=55$), sarcoma ($n=35$), and urogynecologic ($n=20$). Madrid (Spain) started IOERT in 1995 and treated 889 cases through December 2009 with emphasis on rectal (56%), gastro-esophageal (10%), pancreas (5%) and pediatric cancers (2%), sarcomas (23%), and pelvic (10%) and extrapelvic recurrences (5%). Salzburg (Austria) started IOERT in 1998 and had treated 1,840 patients through August 2009 with emphasis on primary breast cancer ($n=1,630$), with more limited experience with base of skull ($n=74$), pancreas ($n=25$), stomach ($n=30$), colorectal ($n=35$), and sarcoma ($n=20$). Rome (Universita Cattolica, Italy) began IOERT in 1990 and have treated 231 patients with emphasis on rectal ($n=158$), pancreas ($n=36$), and breast cancer ($n=16$). Novara (Italy) started IORT in 2005 and have treated 102 patients with emphasis on genitourinary ($n=56$), gastrointestinal ($n=25$), and breast cancer ($n=12$).

In a 2004 survey by ISIORT-Europe, 35 European IORT programs existed (Fig. 1.3a) [59]. The number of IORT programs has expanded to 57 in 2009, largely as a result of mobile linacs in 34 institutions.

There are several remarkable features concerning the expansion of IORT in Europe. First, the number of institutions involved in the modality has increased progressively in every country. Second, IORT has been tested in several tumor sites (Fig. 1.3b), histologic types and disease status (including recurrent and primary cancer) following the initial tendency in Japan to evaluate the technique at the time of a variety of cancer surgical procedures. Third, IORT was adopted very early in the modern clinical experiences as a method of boost dose irradiation integrated in a treatment program following maximal surgical resection and in which additional fractionated EBRT (pre- or postoperative) was a mandatory treatment component alone or combined with the best established systemic management known.

The European natural evolution of IORT has led to a promising present in which the development of National Groups of IORT Experts (France, Spain, Italy, Germany, Austria, Netherlands, and others) joined efforts including the establishment of a pooled database for outcomes analysis as data matured in terms of patient sample size, treatment homogeneity and long-term follow-up. These parameters help establish scientific reference points regarding feasibility, treatment tolerance, local control, and survival data to generate the consensus for randomized clinical trials. Generally, active European IORT institutions have been enthusiastic in reporting their results and in supporting

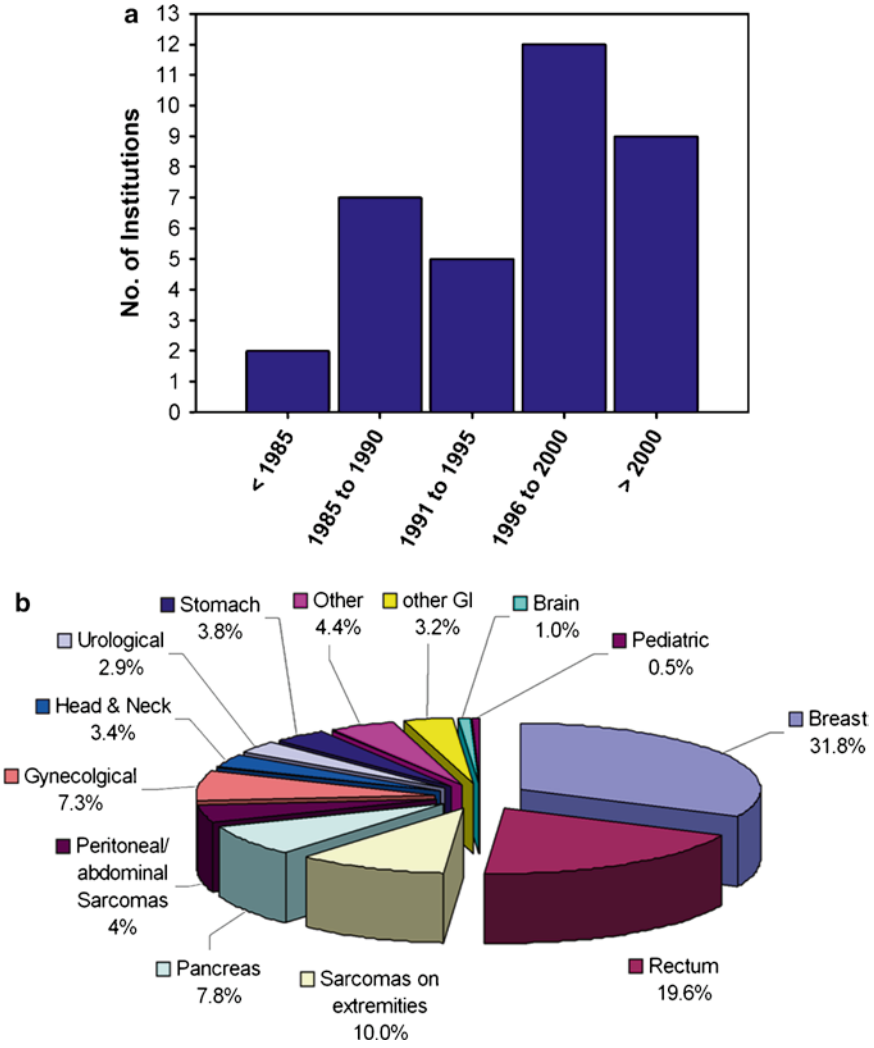

Fig. 1.3 IORT programs in European institutions (**a**) ISIORT-Europe 2004 survey [58]. (**b**) Frequency of IORT indications for cancer treatment in European patients since the onset of IORT at their respective institutions (ISIORT-Europe 2004 Survey) [59].

trans-national ventures to promote improved quality and more influential IORT science, including the International Society of IORT (ISIORT).

Although US institutions were more actively involved in interinstitution IOERT efforts and protocols in the 1980s to mid-1990s, Europe has had a more vibrant and active group of IOERT institutions from 2000 to the present with regard to interinstitution collaboration, including pooled analyses. A number of the European pooled analyses outcomes were presented at the 2008 ISIORT meeting in Madrid including pancreas cancer (270 patients, 5 institutions; Valentini et al. [60]), primary colorectal cancer (651 patients, 4 institutions; Rutten et al. [61]), retroperitoneal soft tissue sarcomas (122 patients, 3 institutions; Krempien et al. [62]) and extremity soft tissue sarcomas (320 patients, 3 institutions; Krempien et al. [62]). ISIORT-Europe IORT investigators have been meeting once or twice yearly since 2004, usually in conjunction with other European radiation oncology or oncology meetings. These meetings have been developed under the auspices of GEC-ESTRO biannual congress. The information presented and discussed was published as abstract contributions [63, 64]

and included in the Web site of ISIORT in the full presentation format for consultation (http://www.isiort.org).

An additional multi-institutional development in Europe working group has been the ISIORT-Europe Registry. The rationale for the ISIORT-Registry is to share data for future retrospective analysis, assist in designing new prospective trials, contribute to homogenize treatment modalities, motivate centers to participate with information in the scientific network and increase visibility of small/developing centers in the IORT community. The coordinator is Dr. Marco Krengli from the University of Navarra [65] and is electronically accessible at http://www.isiort.org/htm/isiort_europe.htm

HDR-IORT: US and Europe

HDR-IORT was developed in the late 1980s in an attempt to combine the technical and dosimetric advantages of brachytherapy with the conceptual and logistic advantages of IOERT [58, 66–72]. Although HDR remote afterloaders were initially utilized in 1964 and have become common in modern radiation oncology departments, they have been used primarily in the outpatient setting. HDR-IORT developed as a result of the merging and improvements of this existing technology, applied to the intraoperative setting. It was also developed as a strategy to create new technical possibilities for intraoperative treatment which other IORT approaches could not easily satisfy.

There were several perceived problems preventing the widespread application of IOERT. First, it is expensive to have a dedicated linear accelerator in an operating room. Second, even if the first issue is overcome by transporting anesthetized patients from the OR to the radiation oncology department for their IORT, other medical and logistic issues need to be overcome. Third, by virtue of the inflexibility of electron applicators, it may be challenging to treat complex anatomical surfaces such as the deep or anterior pelvis, lateral or anterior chest, etc. with IOERT (see Chap. 6). Fourth, the dosimetry of IOERT is akin to EBRT, being quite homogenous (seen as advantageous by those who use IOERT). This does not lend itself to the possibility of dose escalation within a target volume or surface, however, as can be done with the inhomogeneity of brachytherapy dosimetry. HDR-IORT was born out of the desire to deal with some of these issues.

Part of the concept of HDR-IORT is to create a shielded OR in which the entire surgical procedure as well as the radiation can be performed. The Memorial Sloan-Kettering Cancer Center (MSKCC) HDR-IORT facility was created in the radiation oncology department instead of within the general OR suites, and a complete description of the facility is found in existing publications [68, 69] as well as in this textbook (Chap. 4). The development of the Harrison–Anderson–Mick (HAM) applicator [68, 69] or other superflab applicators [66, 70] provided a vehicle through which the HDR machine could connect to the desired target surface or volume. Because the HAM applicator is both flexible and transparent, there is literally no surface that cannot be accessed or treated [68, 69]. The HDR machine is portable and can be used either in the outpatient area or the OR. This simple fact makes HDR-IORT a possibility for any medical center that is willing to introduce sufficient shielding in either new OR construction (preferred) or existing ORs (much more challenging and expensive).

In the late 1980s and early 1990s, HDR-IORT was started in the USA and Europe in an attempt to address some of the above issues and concepts. HDR-IORT using plastic needles in a superflab applicator was first reported from Munich in 1991 by Lukas et al. [66]. In 1992, a similar, independently developed protocol was implemented at MSKCC in New York, using superflab "HAM" (Harrison–Anderson–Mick) applicators in which plastic catheters had been embedded at the time of manufacture [68, 69]. All of the above studies made use of Gamma Med remote HDR afterloaders. A micro-Selectron HDR machine has been used at Ohio State University Hospital (OSUH) in Columbus for HDR-IORT with assorted applicators, both rigid and flexible [67, 72].

In the USA, early clinical experience was developed at MSKCC [68, 69, 71] and Ohio State University [67, 72]. The MSKCC experience included colorectal cancers [68, 69] (Chaps. 15 and 16), pediatric malignancies [71] (Chap. 22), retroperitoneal sarcomas (Chap. 17), as well as selected thoracic and gynecologic cancers (Chap. 20). The early Ohio State clinical experience [67, 72] was primarily with locally advanced colorectal (Chap. 15) and head and neck cancers (Chap. 9).

Simultaneously with the MSKCC program, investigators in Germany were also evaluating HDR-IORT [66, 70]. These investigators also concentrated on locally advanced colorectal cancers.

To date, the preliminary data for the clinical studies noted above, including colorectal, sarcoma, and pediatrics (multiple sites) reveal promising oncologic outcomes in challenging groups of patients. Most of this early work is presented in the appropriate disease site-specific chapters of this textbook.

In the past decade, new HDR-IORT programs have been developed in both the USA and Europe. A shielded room was developed and built in a new OR suite at the Beth Israel Medical Center in New York in January 2001 and 152 patients have received HDR-IORT as of December 2009 with emphasis on head and neck ($n=107$), colorectal ($n=11$), breast/chest wall ($n=8$), and recurrent gynecologic cancer ($n=2$) and retroperitoneal sarcomas ($n=16$). While the MSKCC program with a shielded OR in the radiation oncology department worked well, the obvious advantages of being in the main OR (resource utilization, professional staffing, accessibility of ancillary staff, sterile supplies, blood products, laboratories, drugs, etc.) enhances the efficiency of the HDR-IORT program. The Duke University facility was created in 2000 as a shielded "room within an existing OR" in the regular OR suites to facilitate HDR-IORT. One hundred and five patients have received HDR-IORT with the focus on recurrent rectal and gynecologic cancers and retroperitoneal sarcomas. The Pamplona Spain IOERT program which started in 1984 was replaced with a perioperative HDR-IORT program in 2000 (1,132 IOERT cases and 355 periop HDR). While using IOERT the disease site emphasis was the most inclusive in the world (head/neck – 19 patients, soft tissue sarcoma – 169, bone sarcoma – 148, colorectal – 157, lung – 198, gynecologic – 83, stomach – 61, pancreas – 69, bladder – 81, kidney – 24, CNS – 21, prostate – 11, misc – 91); with periop HDR the emphasis has been more limited (head/neck – 133, soft tissue sarcoma – 113, bone sarcoma – 10, colorectal – 16, lung – 10, gynecologic – 38).

Some institutions developed both HDR-IORT and IOERT (Ohio State and Mayo Clinic-Rochester). While it is unlikely that one of these techniques will ever be demonstrated to be oncologically preferable, they certainly can be complimentary. The relative advantages and disadvantages of each are discussed in Chap. 6.

Dedicated IOERT or HDR-IORT Facilities

Some of the technical problems and nuisance aspects of IORT, encountered in the 1980s and early 1990s, were overcome with dedicated or semi-dedicated IOERT or HDR-IORT facilities. These can be built as an operating room (OR) in the Radiation Oncology Department as done for IOERT at NCI, Medical College of Ohio, Thomas Jefferson University, Howard University, and others and as done at MSKCC for HDR-IORT. The most ideal situation is to place a facility within or near the OR suite which has been done at Mayo Clinic-Rochester (MCR), MGH, MDACC, and some European institutions for IOERT, at Ohio State University for both IOERT and HDR-IORT and for HDR-IORT at the Beth Israel Medical Center (NYC) and Duke University. Either approach simplifies the treatment of patients, necessitates fewer reoperations (refused by some patients and physicians), and avoids transportation and sterility problems. It also prevents the need to shut down the outpatient treatment machine in the radiation oncology department for a "potential" case. However, the dedicated IORT option in an OR setting is quite expensive if an existing OR has to be retrofitted for proper shielding (for either IOERT or HDR-IORT) and a new linear accelerator is purchased as the electron source for IOERT.

A dedicated or semi-dedicated facility usually increases the implementation of IORT as a component of treatment. For example, when MCR had to transport patients to the radiation oncology department for IOERT, often 1–7 days following surgical resection in a regular hospital OR, only 30–40 patients/year had IOERT as a component of treatment from 1981 to 1989. When a dedicated IOERT facility was developed in the new OR construction at MCR within the regular OR suites at Methodist Hospital, the IOERT patient volume increased to 70–140 patients/year from 1990 to the present.

Mobile IOERT and HDR-IORT Equipment

New technologies have improved the availability of IORT from the perspective of cost-effective alternatives. These technologies include mobile HDR-IORT units, as being used at MSKCC, Beth Israel (NYC), Mayo Clinic-Rochester and European institutions, and the mobile IOERT machines – Mobetron, Liac and NOVAC-7. For the mobile HDR-IORT machine, a shielded facility is necessary in either the OR area or in the radiation oncology department. Instead of shielding an entire OR room, however, technology now exists to create a shielded box (room within a room), as done at Duke University, into which the patient can be placed for the HDR-IORT component of treatment after surgical resection and placement of the HAM applicator have been accomplished. NOVAC IOERT equipment is currently used only in Europe, primarily in Italy (Italy – 20 units, other Europe – 3).

The initial Mobetron unit was evaluated at UCSF starting in December 1997. Subsequent units have been placed in eight other US institutions, including University of North Carolina, Mayo Clinic in Arizona and Stanford University, as well as 11 European and 6 Asian institutions (Japan-2, China-4). The Mobetron unit has built-in shielding in a C-arm design and could theoretically be moved from one operating room to another, if indicated.

The Mobetron IOERT program at Mayo Clinic in Arizona was started in January 2002 with 365 patients treated as of August 2009. Disease sites are the same as at MCR except for the addition of adjuvant breast cancer patients in which IOERT replaced the EBRT boost. Two single-institution phase II breast cancer protocols were completed from 2002 to 2006; an IOERT boost was given at the time of local excision and axillary staging in 97 node-negative patients followed by postoperative EBRT.

Low-KV IORT

The Zeiss Intrabeam is an alternative technology using low-energy X-rays delivered with spheroidal applicators, requiring minimal radiation protection, based on a fixed generator platform and a transportable radiation source. The Intrabeam low-KV source was originally used to treat brain tumors, but since 1998, it has been used primarily for IORT of breast cancer patients after breast conserving surgery. It has expanded rapidly through Europe and Australia based on breast cancer treatment and a multi-institutional trial (TARGIT) ([73, 74]; see Chap. 5).

Patient Selection and Evaluation

Patient Selection Criterion

Appropriateness for an IORT boost should be determined by the surgeon and radiation oncologist in the setting of a joint-preoperative consultation, whenever feasible. This allows input from both specialties with regard to studies that would be helpful for IORT and EBRT planning as well as

whether IORT is appropriate. An informed consent can be obtained with regard to potential benefits and risks, and optimal sequencing of surgery and EBRT can be discussed and determined.

The following general criterion have guided the selection of appropriate patients for IORT at our institutions: (1) Surgery alone will not achieve acceptable local control (i.e., ≥microscopic residual disease after maximal resection). By definition, there must be no medical contraindications for exploratory surgery and an attempt at gross total resection. (2) EBRT doses needed for adequate local control following subtotal resection or unresectable disease (60–70 Gy in 1.8–2.0 Gy for microscopic residual (R1 resection), 70–90 Gy for gross residual (R2 resection) or unresected disease) would exceed normal tissue tolerance. (3) IORT will be performed at the time of a planned surgical procedure. (4) The IORT plus EBRT technique would theoretically result in a more suitable therapeutic ratio between cure and complications by permitting direct irradiation of unresected or marginally resected tumor with single or abutting fields while surgically displacing or shielding dose-limiting structures or organs. (5) There is no evidence of distant metastases or peritoneal seeding (rare exceptions: resectable single organ metastasis, excellent systemic therapy options, slow progression of systemic disease).

Patient Evaluation

The pretreatment patient workup should include a detailed evaluation of the extent of the locally advanced primary or locally recurrent lesion combined with studies to rule out hematogenous or peritoneal spread of disease. In addition to history and physical exam, the routine evaluation includes CBC, liver and renal chemistries, chest film or computed tomography (CT), and tumor-specific serum tests (CEA, CA 19-9, CA-125, etc.). When palpable pelvic primaries or relapses are immobile or fixed on rectal or bimanual exam or symptoms suggest pelvic recurrence following primary resection, CT or magnetic resonance imaging (MRI) of the pelvis and abdomen can confirm lack of free space between the malignancy and a structure that may be surgically unresectable for cure (i.e., presacrum, pelvic sidewall). In such patients, preop EBRT + concurrent chemotherapy should be given prior to an attempt at resection. Distant metastatic spread should also be excluded with appropriate imaging (CT chest/abdomen/thorax, PET-CT (positron emission tomography), other). If hematuria is present or findings on CT or MRI suggest bladder involvement, cystoscopy can be performed prior to or at the time of surgical exploration/resection.

Sequencing and Doses of EBRT and IORT

Sequencing of EBRT, IORT, and Surgery

Optimal sequencing of surgery and EBRT for locally advanced cancers should be discussed and determined at the time of a joint multispecialty consultation involving a surgeon, radiation oncologist, and medical oncologist. This allows input from all specialists with regard to studies that would be helpful for IORT and EBRT treatment planning as well as whether IORT may be appropriate.

Whenever feasible, total or gross total resection of disease is performed before or after EBRT. Resection is an almost uniform component of IORT-containing regimens with esophago-gastric, colorectal, gynecologic and renal cancers and sarcomas (extremity, retroperitoneal/abdominal-pelvic) but is less feasible with biliary and pancreatic cancers. Single-institution pilot studies have evaluated resection plus IOERT following preoperative EBRT and chemotherapy for borderline resectable or initially unresectable pancreatic cancers [75].

For many patients with locally advanced primary or locally recurrent lesions, preoperative EBRT of 45–50 Gy in 1.8–2.0 Gy fractions (plus concurrent chemotherapy as indicated by disease site)

followed by exploration and resection in 3–5 weeks offers theoretical advantages over a sequence of resection and IORT followed by EBRT. The potential advantages include the following: (1) deletion of patients with metastases detected at the restaging workup or laparotomy thus sparing the potential risks of aggressive surgical resection + IORT; (2) possible tumor shrinkage with an increased possibility of achieving a gross total R0 or R1 resection; (3) alteration of implantability of cells that may be disseminated at the time of an R1 or R2 surgical resection; (4) reduction of treatment interval between EBRT and IORT (when resection and IORT precede EBRT, if postoperative complications ensue, the delay to EBRT ± chemotherapy may be excessive); (5) intact vascular supply to tumor with better oxygenation.

Doses and Technique: EBRT

The method of EBRT has been fairly consistent in most USA and European single-institution and group IORT studies. EBRT doses of 45–54 Gy are delivered in 1.8 Gy fractions, 5 days per week over 5–6 weeks in patients with no prior irradiation. For pelvic lesions, treatments are given with linear accelerators using >10 mV photons and 3-D CRT or IMRT external beam techniques. With extrapelvic lesions, unresected or residual disease plus 3–5 cm margins of normal tissues are included to 40–45 Gy with 3-D CRT or IMRT. Reduced fields with 2–3 cm margins are treated to 45–54 Gy. With a variety of disease sites (gastrointestinal (GI), gynecologic (Gyn), other), concurrent chemotherapy is often given during EBRT with 5FU- or cisplatin-based regimens.

For previously irradiated patients, an attempt is made to re-irradiate with low-dose preop EBRT (20–30 Gy in 1.8 Gy fractions or 1.5 Gy bid) preferably with concurrent chemotherapy. The use of routine patient immobilization devices, CT-based treatment planning, PET/CT fusion, IMRT, and image-guided irradiation (IGRT) with on-board imaging has been instituted in some institutions for patients with prior EBRT in attempts to improve patient tolerance and facilitate dose escalation of the EBRT component of treatment.

Doses and Technique: IORT

The technical aspects of both the surgical and irradiation components of IORT procedures will be discussed in detail in Chaps. 3–5 (IORT, HDR-IORT, electronic brachytherapy/low-KV IORT) and will not be reiterated in this chapter. For such procedures, a carefully constructed team needs to exist which includes a surgeon(s), radiation oncologist(s), anesthesiologist(s), operating room nursing, radiation physics and dosimetry, and radiation therapists. Following maximal resection, IORT is given with IORT, HDR-IORT, or electronic brachytherapy/low-KV IORT dependent on institutional preference and technology.

IORT energy and dose are dependent on the amount of residual disease remaining after maximal resection, and on the EBRT component that is feasible. For patients who have received preoperative doses of 45–54 Gy (1.8 Gy fractions, 5 days per week), the IORT dose usually varies from 10 to 20 Gy: ≤microscopic residual, 10–12.5 Gy; gross residual, 15–20 Gy. In previously irradiated patients, the IORT dose is usually 15–20 Gy if EBRT doses of 20–30 Gy can be safely given pre- or postoperatively. IORT doses of 25–30 Gy have been given to patients in whom no or limited EBRT is planned, but such doses have higher risks of nerve intolerance.

The biologic effectiveness of single-dose IORT is considered equivalent to 1.5–2.5 times the same total dose of fractionated EBRT (see Chap. 2 for more complete discussion of this issue). The effective dose in the IORT boost field, when added to the 45–50 Gy given with fractionated EBRT, is as follows: 60–70 Gy, IORT dose of 10 Gy; 75–87.5 Gy, 15 Gy IORT boost; 85–100 Gy, 20 Gy IORT boost.

Dose-Limiting Structures

In patients with locally advanced malignancies, the issue of morbidity following aggressive treatment is placed into clearer perspective by a comparison with tumor-related morbidity. For instance, when EBRT is used as the main treatment modality for locally advanced primary or locally recurrent rectal cancers, more than 90% of patients have local persistence or relapse of disease and most are dead in 2–3 years (end result is nearly 100% tumor-related morbidity/mortality). A complete discussion of IORT tolerance of surgically dissected and undissected organs and structures is found in Chap. 7.

Guidelines for Reporting IORT Data

IORT requires technical sophistication in the local treatment delivery, which implies complexity at the time of data analysis and report. IORT clinical experiences are established and continued only with remarkable cooperation between surgeons, radiation oncologists, and physicists in the development of a quality IORT component of cancer management. Among the limitations of this technique is the slow patient accrual for the different treatment programs or clinical trials, due to the complexity of professional and institutional coordination. Contemporary IORT is usually delivered as a component of therapy (generally integrated in multimodal programs), in an effort to enhance local treatment intensity and promote local tumor control. Since it is a local technique, publications need to include careful analyses of local effects. The impact of possible local benefits in the general outcome of cancer patients have to be evaluated in the context of initial tumor sites and stages, integral treatment intensity and quality-of-life parameters [76]. In addition, the potential impact of improved local control on distant control and survival should also be evaluated and reported.

Analysis and publication of data requires meticulous description of sequential treatments components (local and systemic) with particular emphasis on surgical maneuvers and the IORT parameters. In the last two decades, reports on IORT published in peer review journals have progressively refined the information presentation, with particular consideration to patient, tumor and treatment characteristic descriptions, IORT methodology, local effects observations (tolerance of normal tissues and local tumor control rates), patterns of disease relapse and survival outcomes (Table 1.5). Institutional experiences have updated the results of their pilot studies showing, in consecutive publications, a transition from the description of technical methodology, and clinical feasibility toward emphasis on local tissue tolerance and tumor control results (local and distant) [53, 77–80]. Survival and patterns of disease relapse are generally reported, but phase I–II oriented studies (or comparison with existing historical control data from conventional treatment programs in comparable tumor sites, histology, and stage) should be interpreted with caution.

Local Normal Tissue Tolerance Analyses

Local normal tissue tolerance has been prospectively analyzed in clinical IORT trials in western institutions. Patients entered in controlled studies and their long-term events were monitorized periodically. Unquestionable data is available identifying peripheral nerves as dose limiting and ureters as dose sensitive in IORT experiences [79–81]. Anecdotal reports have described severe toxicity in IORT patients in bone (vertebral collapse) [82], vessels (fatal bleeding) [83], and brain (demyelinization) [84]. Local toxicity in IORT trials is, by definition, a multifactorial event in which the biological conditions of the tissues at risk for complications is modulated by multiple possible causes of tissue damage. Although the predominant factor for a biological lesion might be the IORT component of treatment, the clinical observation needs to be interpreted in the context of other risk

Table 1.5 Database guidelines for reporting IORT trials or experiences

General information
Patient's name
Institution
Chart number
Surgeon
Radiation Oncologist
Medical Oncologist
Physicist
Anesthesiologist
Date of IORT
Time of IORT
Incidences (?)

Patient characteristics
Age
Sex
Karnofsky
Symptoms
Previous illnesses
Previous treatments
Tumor markers
Disease status
  Primary
  Recurrent

Tumor characteristics
Site/size/location
Stage
  T description
  N description
Histology
Cellular differentiation
Molecular findings

Treatment characteristics
General factors
  Integral program description
  Modality segments sequence
  Place of IORT component
Surgery
  Type of procedure (name)
  Distant disease
Margins
  Involved
  Close
Residual disease (area/size)
  No resection
  Resection
    Macroscopic
    Microscopic
    High risk (negative, narrow)
Adjacent organ manipulation
Reconstruction of surgical defect
Maneuvers for IORT exposure

External beam irradiation
Preoperative
Postoperative
Chemoradiation
Volume
Fractionation
Total dose
Dates

Chemotherapy
Neoadjuvant
Adjuvant
Concurrent
Drugs
Courses
Dates

Treatment for recurrent disease

IORT characteristics
Target volume definition
Normal tissues included
Normal tissues excluded
Number of IORT fields
Applicator size/shape/beveled end
Electron energy
Total dose

Toxicity, acute/chronic
IORT related
  Date of observations
  Type of damage
  Severity scale
  Evolution
IORT not related
  Responsible modality
  Date of observation
  Type of damage
  Severity scale
  Evolution

Patterns of tumor relapse
Date of observation
Central
  Infield IORT
  Marginal IORT
Local
  External beam field
Distant
  Site(s)
Mixed (local + distant)

Patient follow-up
Date of last follow-up
Status
  Disease related
    NED
    AWD
    DWD
    DOD (cause)
  Toxicity related
    Improving
    Worsening
    Stable
  Treatment related
    Responding
    Progressing
    Stable

Table 1.6 Valuable information for normal tissue toxicity evaluation in IORT trials

Pre-IORT identification of biological compromised tolerance
Symptomatic or imaging evidence of tissue deterioration
Symptoms suggesting direct tumor involvement
Surgical manipulation
Previous treatments: radiotherapy, chemoradiation, chemotherapy
IORT per se contribution to tissue damage
Type of tissues at risk in the IORT volume
Tissue structure and dimensions at IORT risk
Estimated dose received (location in the IORT dosimetric treatment volume)
Post-IORT parameters of additional damage:
Local infections, abscesses, etc.
Surgical re-interventions with further tissue manipulation
Macro- and microvascularization status
Complementary treatments: external beam irradiation, chemoradiation, chemotherapy, etc.
Tumor relapse and involvement of toxic tissues

factors (i.e., other components of treatment including the magnitude of current surgery, EBRT, and chemotherapy and prior treatment with surgery or EBRT; disease factors including extent of disease and normal tissue toxicity produced by the malignancy such as peripheral neuropathy, etc.). Table 1.6 describes a systematic and integral analysis scheme for evaluation of local toxicity.

Local Tumor Control Analyses

IORT is generally delivered after a surgical alteration of the normal anatomy, either by tumor resection or normal tissue manipulation (for instance, biliary-digestive bypass in unresected pancreatic cancer). Postsurgical changes (presacral hematoma, etc.) ought to be well documented by pre- and postoperative image techniques in an effort to establish a base-line condition for comparison in the follow-up period.

The determination of the IORT treatment volume is not homogeneous among institutions. The use of surgical clips, or other means, to identify the IORT boost region is a valuable system to be able to distinguish central recurrences (in the IORT field), from local/marginal relapse (in the EBRT field). This information is not generally available in the literature except for highly expert institutions [79, 80]. There are anatomical limitations for such a precise evaluation. For instance, in the pelvic cavity, the technical difficulty for applicator positioning implies uncertainty of the dosimetric behavior of the electron beam (lateral pelvic wall region).

In contemporary radiation oncology, the principle that tumor control probability is a function of the total dose of irradiation is still valid. Local recurrences, when suspected, need to be histologically proven when feasible. The documentation of this event requires a retrospective reconstruction of the integral dosimetric plan designed for that particular case, and its relationship with the present anatomical findings of the recurrence. Through the meticulous analysis of local recurrences, expert scientists will establish the limitations and indications of precision radiation boost techniques (with IOERT or HDR-IORT brachytherapy) and their role as a loco-regional treatment intensification modality (Fig. 1.4).

Institutional IORT Methodology Description

Active IORT institutions are recommended to publish their program description, with particular emphasis in technical methodology adopted, the dosimetric characteristics of their IORT devices (applicators, flaps, etc.), the criteria for radiation dose prescription and the intramural protocols developed for quality

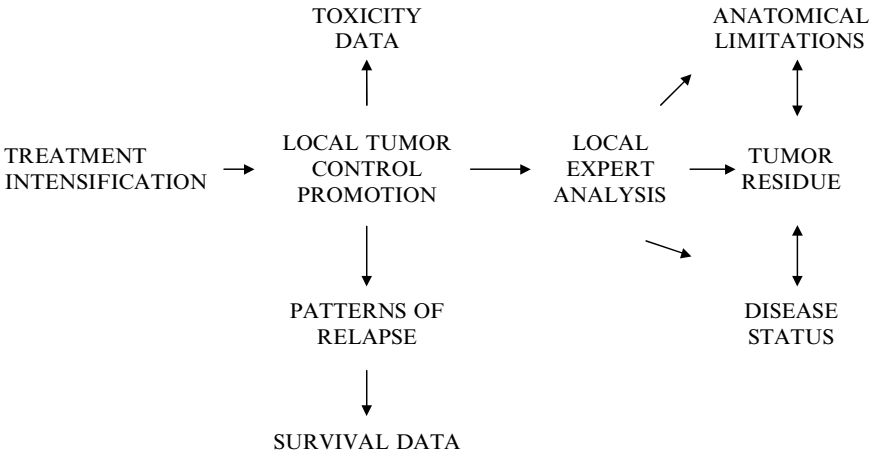

Fig. 1.4 Process of disease control and tolerance analyses in IORT clinical experiences and trials.

Table 1.7 Description of relevant parameters for an IORT institutional methodology report

Materials
Radiation source(s)
IORT applicators – size, shape
Image documentation system
Check list protocols for professionals involved
Multidisciplinary protocol for individual IORT procedure description
Methods
Dosimetric properties of applicator
Dosimetric treatment planning
Dose-specification criterion
Surgical–radiation oncology interaction: case discussion, technical cooperation for applicator positioning, consensus in target volume selection, etc.
Anesthesiology–radiation oncology interaction: transportation and/or patient monitoring during IORT
Prospective follow-up protocols: selective analysis of local effects and disease outcome
Institution
Hospital description
Clinical oncology coordination characteristics
Surgical oncology characteristics activity
IORT program implementation
Dedicated Unit (IOERT, HDR-IORT, other)
Semi-dedicated Unit
Prolonged transportation required
Mobile IOERT equipment

control parameters. This report has been generally published by expert institutions at the time of IORT program initiation [85–87], and does not need to be updated unless new technology is incorporated with time [88]. The methodology description report is frequently coded in the Methods and Materials portion of clinical results publications and offers the opportunity to interpret the data in terms of technical methodological similarity among institutions (situation in which homogeneous clinical results are expected unless patient selection varies) or the opposite situation wherein technology and clinical decisions involved in IORT treatment are markedly different (different radiation quality, applicators sizes and shapes, dosimetric properties and dose-specification criterion) [89]. In Table 1.7, relevant parameters of IORT institutional methodology are listed for the elaboration of a program descriptive report.

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Chapter 2
Biology of Large Dose per Fraction Irradiation

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Keywords Radiobiology of IORT • Tumor oxygenation • Hypoxic radiation sensitization

Introduction

Experimental radiobiology has by happenstance focused on the implications of intraoperative and high-dose-per-fraction radiotherapy in more detail than it has standard fractionated radiotherapy. This is because the majority of radiobiological literature of tumor and normal tissue features in vivo and in vitro studies in which the radiation was administered in a single fraction. Similarly, when fractionation is used experimentally, fraction sizes near the clinical 1.8–2 Gy size used for most external beam irradiation therapy (EBRT) are rarely utilized. As a result, much of our radiobiological understanding of tumor and normal tissue response should and does relate well to that observed clinically for intraoperative irradiation therapy (IORT).

The first and most important implication of single, large-fraction irradiation is the clear disadvantage it gives to tumor kill compared with sparing of normal tissue. The majority of radiosensitive organs, including the lung, kidney, small bowel, and brain, have substantial ability to recover between daily radiation treatments [1], whereas the ability of the tumor is typically much less pronounced [2]. Thus, on first principle, intraoperative radiation places normal tissues at a disadvantage if they remain in the IORT field (Fig. 2.1). Other classical advantages of fractionation, including reoxygenation and redistribution of the cell cycle, must be considered and it is difficult to justify single-fraction intraoperative radiation as the sole method of irradiation on radiobiological grounds. In particular, the dose required to control 50% of tumors is on average only minimally changed with fractionation because of reoxygenation, redistribution, and repopulation (Fig. 2.2).

The principal advantage of IORT is the ability to exclude nontarget normal tissues from the radiation field. The success of IORT, therefore, requires full knowledge of the partial organ tolerances of normal tissues. However, the radiobiological literature falls short with respect to fully characterizing the toxicity

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_2,

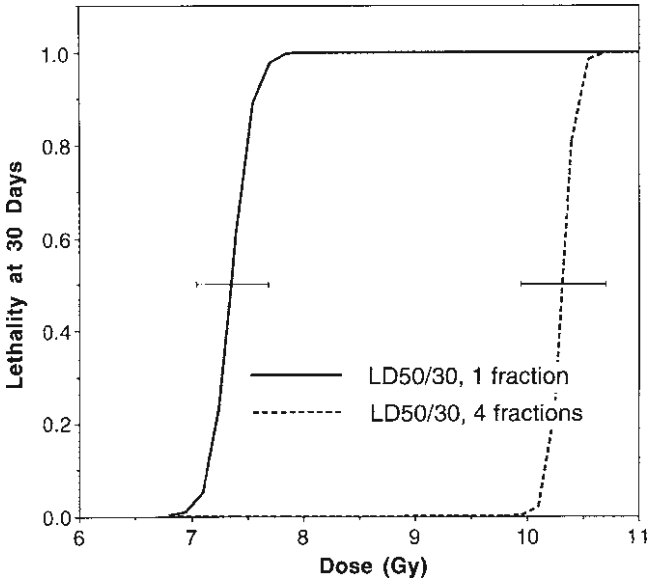

Fig. 2.1 Normal tissues benefit greatly from fractionation. The greatest benefit to fractionation is found in late reacting tissues like the lung, but even acutely reacting normal tissues benefit from fractionation. Bone marrow, for example, is an acutely reacting tissue. If whole-body irradiation is administered to C3H mice in a single fraction, the $LD_{50/30}$ is 7.4 ± 0.2 Gy versus 10.3 ± 0.3 Gy if the treatment is given in four fractions over two days. The calculated dose modifying factor of 1.4 is significant (95% CI 1.29...1.51) [105]. The error bars represent the 95% CI of $LD_{50/30}$. Late-reacting tissues have larger dose-modifying factors with fractionation compared with a single fraction, usually greater than 2.

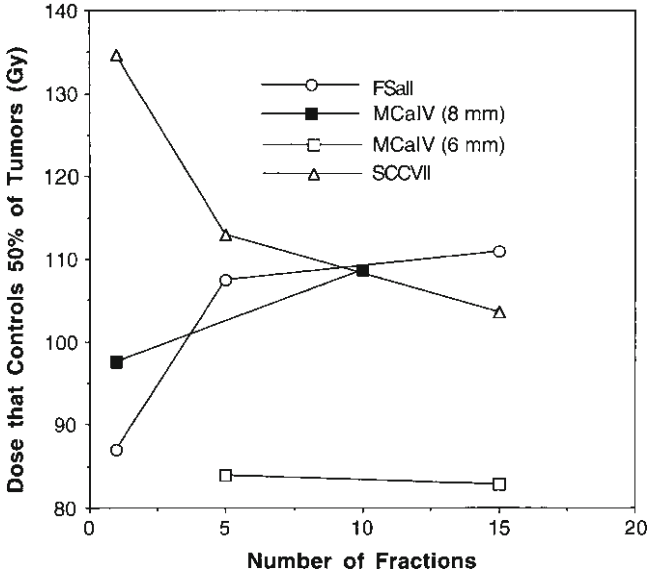

Fig. 2.2 On average, tumor benefits little from fractionation due to competing effects of reoxygenation and cell cycle redistribution between fractions. Data from three different C3H tumor models and the dose that controls 50% of tumors (TCD_{50}) are shown. Tumors are the FSaII fibrosarcoma, the MCaIV mammary carcinoma, and the SCCVII squamous cell carcinoma. The therapeutic gain factors with fractionation were not significantly different from 1, and ranged from 0.77 to 1.28, with an average of 1.05 ± 0.23 [64, 65, 106]. The absence of a clear increase in TCD_{50} is remarkable considering that there can be substantial tumor growth between fractions, if the interfraction interval is long [107].

modification due to partial organ radiation. Lastly, delivering large-fraction radiation dose is appealing in view of the recent discovery that large, single doses of radiation may produce tumor autoimmunity.

This chapter reviews the classical radiobiological principles and some of the experimental and clinical data to help better understand the tolerances of normal tissues and tumor to large radiation doses.

Model Used to Predict Radiation Effects

Several models have been used over the years to understand and quantify the radiation tolerances of tumor and normal tissues [3]. Perhaps the most successful and useful models are the clonogenic cell survival models. Based on these models, successful treatment results if all tumor clonogenic cells are killed by the treatment. By the same model, normal organ damage results if a regenerative unit is not preserved. For modeling tumor response, the clonogenic model has withstood extensive experimental scrutiny and has generally performed well. Use of the clonogenic model has been less successful in predicting normal tissue tolerance. The normal tissue model predicts tolerance best when the whole organ is treated. A limitation of the normal tissue model is the invention of a regenerative unit of tissue [1, 4]. This tissue unit is difficult to define based upon known organ physiologic and proliferative function.

Two clonogenic survival models are commonly used: the linear-quadratic model and the multitarget model. The former model predicts that survival of clonogenic units follows the shape of a parabola on log-linear coordinates while the latter model predicts that low doses of radiation kill few clonogenic units, and at higher doses the survival curve becomes linear on log-linear coordinates. The formulae for each of these survival curves are:

$$\text{Linear-quadratic surviving fraction} = S / S_{\text{o}} = \left[e^{(-\alpha d - \beta d^2)} \right]^n$$

$$\text{Multi-target surviving fraction} = S / S_{\text{o}} = \left[1 - \left(1 - e^{-d/d_{\text{o}}} \right)^N \right]^n$$

where d is the fraction dose, n is the number of fractions, and the remaining variables (N, d_{o}, α, β) are fit parameters for the two models. In general, the linear-quadratic formula fits experimental data better at low doses (e.g., under 3 Gy), whereas the multitarget model better explains results at survivals under $\approx 10^{-3}$ (e.g., above 10–15 Gy). In the dose range typically used for IORT (10–20 Gy), both models perform comparably.

Using the linear-quadratic model, the shape of the survival curve is determined by the α/β ratio. This ratio has units of radiation dose. A low α/β ratio is typical of late-reacting normal tissues. Most late-reacting tissues have α/β ratios less than 5 Gy while acute-reacting tissues and tumor often have α/β ratios of over 7 Gy. The simple, exponential mathematics make for convenient estimations of equivalent doses using the linear-quadratic model. Equivalent doses to compare IORT with standard 2-Gy fractionation can be estimated using the equation:

$$D_{\text{IORT}} = (1/2)(([\alpha/\beta]^2 + 4\text{D}_{2\text{Gy}}[\alpha/\beta + 2])^{0.5} - \alpha/\beta)$$

A graphic comparison of estimated equivalent doses, based on the above equation, is given in Fig. 2.3. For example, if one estimates the EBRT dose required to control a squamous cell carcinoma at 60 Gy delivered at 2 Gy per daily dose ($D_{2\text{Gy}} = 60$), and the α/β of a squamous cell tumor is 10 Gy, then the equivalent single fraction needed to control the tumor would be $D_{\text{IORT}} = 22.3$ Gy. This dose is in good agreement with the ≈20 Gy estimated by classical Strandqvist plots [5, 6]. Evidence that the formulations actually produce the expected response has been shown in several clinical studies wherein the local control rate was predicted in the study design and then achieved.

Calculating the tolerance of a peripheral nerve with a conservative α/β of 2 Gy and a generous tolerance dose of 70 Gy at 2 Gy per fraction, yields an equivalent IORT tolerance dose of only

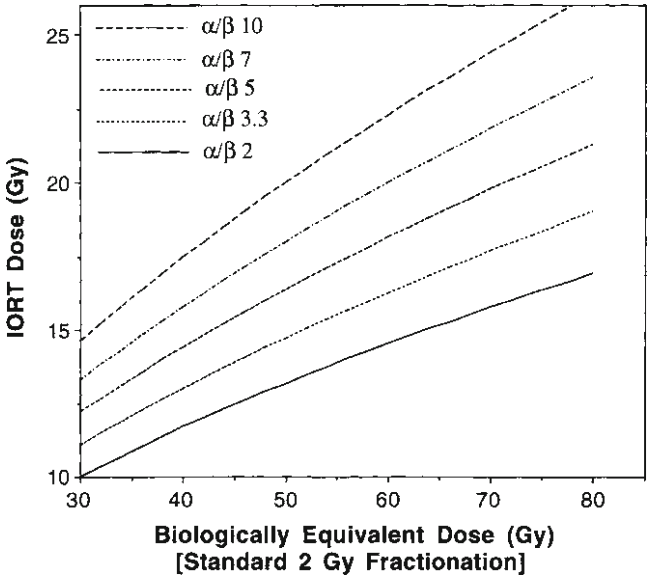

Fig. 2.3 The estimated biological effect of a given IORT dose is compared with that of radiation given in standard 2 Gy daily fractionation. α/β values are chosen for conservative late reacting normal tissue 2, brain 3.3 [108], acute-reacting normal tissue 7 [109], and tumor 10 [110, 111].

16 Gy. This number is similar to those obtained in canine and human studies. For the sacral plexus, the canine 5 year ED_{50} was 16.1–17.2 Gy, although the safe dose to nerve was 10 Gy and 25% of animals developed sacropathy at 15 Gy [7]. Sacral plexopathy in humans occurs at a slightly lower dose, with an estimated ED_{50} of 15 Gy at 2 years. The lower dose is probably related to the associated external beam, concurrent disease such as atherosclerosis and to chemotherapy [8].

With fractionation, the tolerance of peripheral nerve is higher than the tumor control dose. When radiation is administered in a single fraction, the tumor control dose becomes greater than the tolerance of the peripheral nerve. Thus, the normal tissue has a greater loss of tolerance due to the absence of fractionation. This phenomenon underscores the potential disadvantage inherent in any large hypofractionated radiation treatment approach. To be successful, therefore, IORT must take advantage of the surgical procedure to either exclude the nerve or other dose-limiting structure from the planned radiation field, or to accomplish a gross total resection of tumor so that lower IORT doses can be used. Since nerve rarely can be excluded from IORT fields, IORT should be used as a boost dose to supplement adjuvant EBRT (typically 45–50 Gy at 1.8–2.0 Gy fractions) and maximal resection as discussed in Chap. 10 of this text.

Radiobiology of Normal Tissues

Dose Response of Normal Tissues

Over the years, primarily based upon clinical studies with laboratory confirmation, the tolerance doses of normal tissues have been estimated and tabulated by several authors [9]. The dose-response curve of normal tissues is very steep. That is, small changes in dose near tolerance levels can result in large changes in the rate of complications [3]. For example, in estimating the whole body dose of radiation that causes half of C3H mice to die of gastrointestinal lethality (e.g., $LD_{50/6}$), none will die at doses under 11 Gy, and none will survive doses over 14 Gy (Fig. 2.4); at 12.5 ± 0.1 Gy, half will survive the GI endpoint. Further, these tolerance doses can decrease 30% or more in animals that are not maintained in pathogen-free conditions.

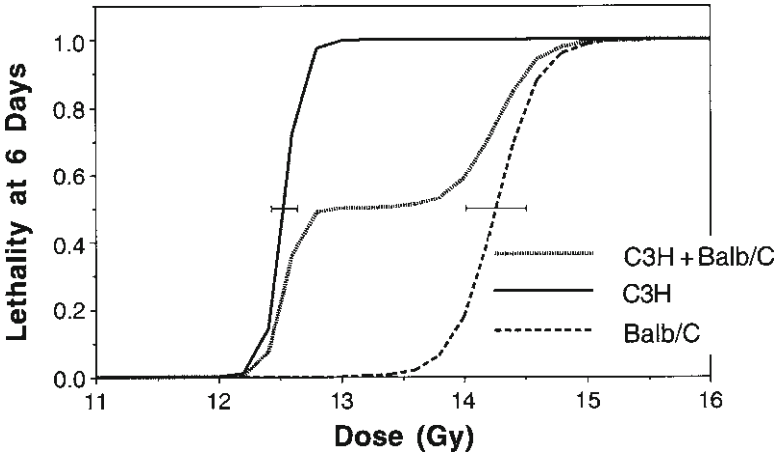

Fig. 2.4 Radiation toxicity to normal tissues typically occurs with a steep dose response. Figure 2.1 shows the steep dose response of bone marrow. In this figure, gastrointestinal toxicity is measured using the lethal dose at 6 days ($LD_{50/6}$) following irradiation. For C3H mice, gastrointestinal death is rare below 11 Gy, and survival is rare above 14 Gy. A steep increase in lethality occurs between 11 and 14 Gy, with half the animals dying at a dose of 12.5 ± 0.1 Gy. Gastrointestinal death occurs with a similarly steep dose response in BALB/c mice, but at a much higher dose. The effect of gastrointestinal irradiation of human subjects is likely to be just as steep for any individual. When populations of patients, each with individual genetic predispositions to gastrointestinal complications, are treated, the dose-response curve appears to be less steep. In the example, this is illustrated by the dose-response curve that might have been obtained had half the animals been C3H and half BALB/c. Also, note that if the C3H + BALB/c combinations model human population studies, one might conclude that mortality was 50% at 13 Gy, a dose at which no gastrointestinal deaths are expected in the BALB/c component of the population.

Clinically, the steepness of the response curve and the impact of fraction size can be seen easily. Two patients treated a few months apart with mantle irradiation fields are shown in Fig. 2.5. The first (left) was treated using single daily fields, anterior or posterior, using ^{60}Co at 80 cm. The second (right) was treated with opposed fields. Both had a fraction size at midplane near 2 Gy; however, the second patient also had MOPP chemotherapy. The prescribed dose to the first patient was 40 Gy, but the effective fractionation at maximum, due to the inhomogeneous technique, was 3.5 Gy × 10 fractions (anterior field) + 1 Gy × 10 fractions (posterior field) = 45 Gy. The second had 1.8 Gy × 25 fractions = 45 Gy. Despite the added chemotherapy, the late effects, including muscle wasting and permanent hair loss, are evident in the patient treated with a large fraction size. Hence, the dose response was steep enough that the change in fraction size had severe impact on late effects despite the similarity in total dose. Rib fragility, pulmonary fibrosis, pericardial constriction, and myocardial ischemia are other risks of altered-fractionation schemes.

The steepness of the dose-response curve aids in the selection of dose and of targets in IORT. If the radiation oncologist can maintain the IORT dose below the threshold dose for complications, then the risk of complication is expected to be minimal. Alternatively, if the radiation dose is above the tolerance range, then the oncologist can expect that the organ will be damaged and must assess the consequences of losing the function of the organ. When organ function is critical, the oncologist must either choose to omit the IORT or lower the dose delivered.

Vascular Effects of Single-Fraction Irradiation

Radiation has a number of effects on vascular healing and angiogenesis. Vascular damage due to radiation is greatest for the smallest vessels, and is more pronounced in arteries compared to veins [10, 11]. Capillaries are typically the most severely affected by radiation, in part because of their

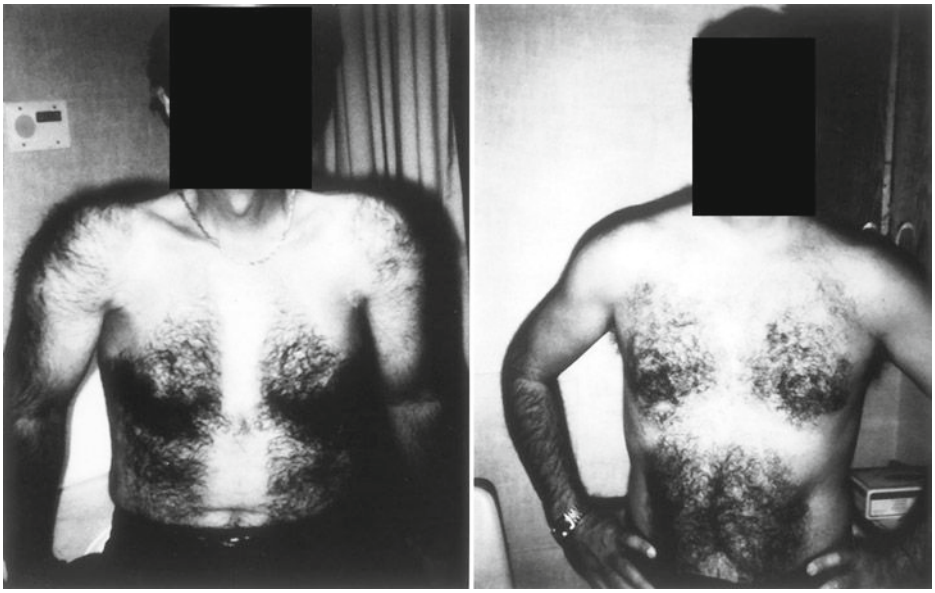

Fig. 2.5 Clinically, the steepness of the response curve and the impact of fraction size can be seen easily. Two patients treated a few months apart are shown. The first (*on left*) was treated using single daily fields, anterior or posterior, using ^{60}Co at 80 cm. The second (*on right*) was treated with opposed fields using 4 MV X-rays at 100 SAD. Both had a fraction size at midplane near 2 Gy. The prescribed dose to the first patient was 40 Gy, but the effective fractionation at maximum, due to the inhomogeneous technique, was 3.5 Gy × 10 fractions (anterior field) + 1 Gy × 10 fractions (posterior field) = 45 Gy. The second had 1.8 Gy × 25 fractions = 45 Gy. The late effects, including muscle wasting and permanent hair loss, are dramatically evident with the larger fraction size.

natural fragility, and in part because antiangiogenic effects of radiation can prevent their regeneration [11]. As with other late-responding tissues, damage to blood vessels is dependent upon both total dose and the dose of each fraction. It is already possible to detect differences in angiogenesis in skin after 6 Gy in mice, and after 11–16 Gy given in a single fraction there is a vast decrease in the capacity of mouse skin to generate microvasculature (Fig. 2.6). Likewise, in response to radiation-induced antiangiogenesis, angiogenic factors are among the early genes activated in irradiated connective tissue. These cytokines are, however, unable to correct completely the antiangiogenic deficit induced by radiation. Interestingly, large vessels have a complex response to irradiation that is incompletely understood. In the case of angioplasty damage to pig coronary arteries, low doses of radiation appear to increase intimal proliferation compared with angioplasty alone while intermediate doses of radiation reduce the natural, intimal proliferation seen 1–6 months after angioplasty [12]. In contrast to the beneficial prevention of endothelial proliferation at lower doses, fractionated irradiation taken to a total dose over 40 Gy is associated with a detectable increase in ischemic heart disease in pediatric lymphoma patients followed for over 5 years [13]. Hence, radiation can both increase (Fig. 2.7) and decrease hyperplasia of larger arteries, each with a different time course and dose response.

Studies of vascular tolerance in IORT of canine and human subjects appear to reproduce this complex dose and time response. Most vascular complications, like many of the neurological complications, are associated with fibrovascular proliferation and stenosis. In contrast, some data suggest that at the highest IORT doses (e.g., ≥25 Gy) radiation may actually decrease the natural intimal proliferation after vascular anastomosis [14]. Vascular rupture and aneurysm have also been described when large arteries must be taken to full dose. In this case, it appears that the vasa vasorum that feed the arterial wall have been damaged, with the small vessel disease then precipitating the large vessel complication [15].

The lack of a clear understanding of the dose-time effects of radiation on arteries limits our ability to fully understand the toxicity to any perfused tissue. Canine and clinical studies of radiation tolerance

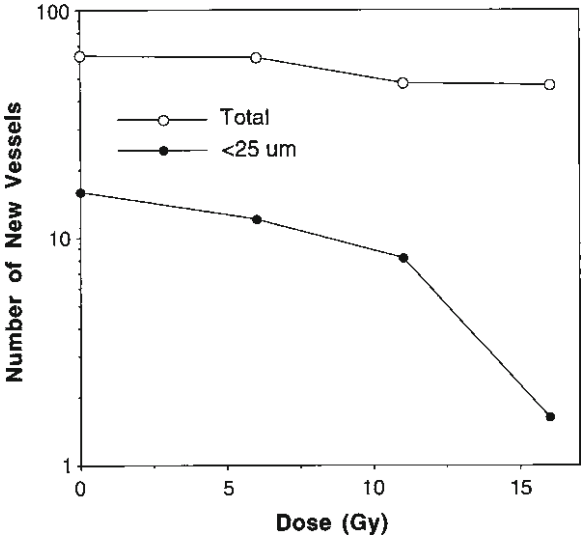

Fig. 2.6 Radiation doses of 0, 6, 11, or 16 Gy were given to the skin of C3H mice immediately prior to the injection of intradermal FSaII tumor cells. The tumor cells supply an angiogenic stimulus. Three days later, the angiogenesis was measured by a photographic technique [11]. Pre-irradiation of the skin results in a reduction of neovascular formation that is most severe as the dose exceeds 11 Gy in a single fraction. Large vessel number is well preserved at the full range of doses. Microvessels, however, were severely reduced, indicating that capillaries and nutritive vasculature are the most severely affected by irradiation of normal tissues. Conduit flow, which occurs in larger vessels, is better preserved.

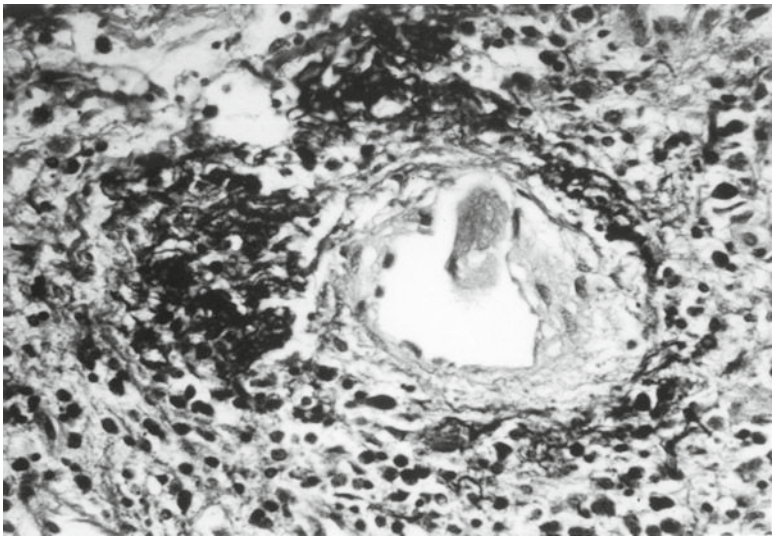

Fig. 2.7 The pulmonary arteries are normally thin-walled vessels. Four months after irradiation to a dose of 62 Gy at 2 Gy per fraction, there is substantial perivascular connective tissue proliferation, intimal proliferation, exposure of vascular basement membrane, and associated platelet thrombus. Vascular effects of large-dose-per-fraction irradiation are complex and can be difficult to predict; however, in most cases, the damage is more severe than with fractionated irradiation.

of large arteries, however, suggest that clinically significant complications are rare under 15–17 Gy and become common if circumferential irradiation over approximately 20 Gy is administered. In contrast, fractionated irradiation is usually safe even to coronary arteries at doses up to 40 Gy. Other large arteries are commonly given over 60 Gy safely when fractionation is employed. When fractionated

and single-fraction IORT irradiation are both given, the frequency of complication is similar to that expected from the IORT treatment alone. In either case, vascular ischemic complications increase with time, are dose dependent, and can take over a decade to occur.

Partial Organ Tolerance

The radiation dose safely tolerated by many critical organs is determined by the volume of tissue irradiated. For the central nervous system, the dose-volume relationship is well understood and can be easily quantified using several models [16–18]. The volume-response curve, like the dose-response curve, is steep. Namely, at a given radiation dose, the frequency of toxicity is low at small volume and, above a threshold volume frequency of complications rises quickly to near certainty. As an example, with a single dose treatment of the brain, the frequency of complication is minimal for targets under 3 ml (frequency under 3%) and rises to 40% for volumes over 10 ml [19]. Likewise, lung tolerance is generally quoted as less than 20 Gy with standard fractionation of the whole lung and under 16 Gy for total body irradiation [9]. In contrast, pulmonary dysfunction is rarely symptomatic even when doses of over 70 Gy are given to small lung volumes [20]. Similar observations have been made for partial organ treatment of the liver (Fig. 2.8) [21].

Unfortunately, more precise parameters for estimating partial organ tolerance are not available; however, certain rules apply. Circumferential treatment to a high dose is unwise for any hollow viscous organ or large vessel [14, 22]. Transmural treatment is tolerated less well than glancing treatment of hollow organs. Organs involved by tumor are at higher risk for fibrovascular complication. For example, ureteral and peripheral nerve tolerance appears to be lowered by tumor involvement [23]. Care should be made to limit irradiation of vascular grafts and bowel anastomoses, and all sutures should be placed securely and with some redundancy. Finally, portions of organs that can be sacrificed surgically can also often be safely treated to a high radiation dose (i.e., lung, liver).

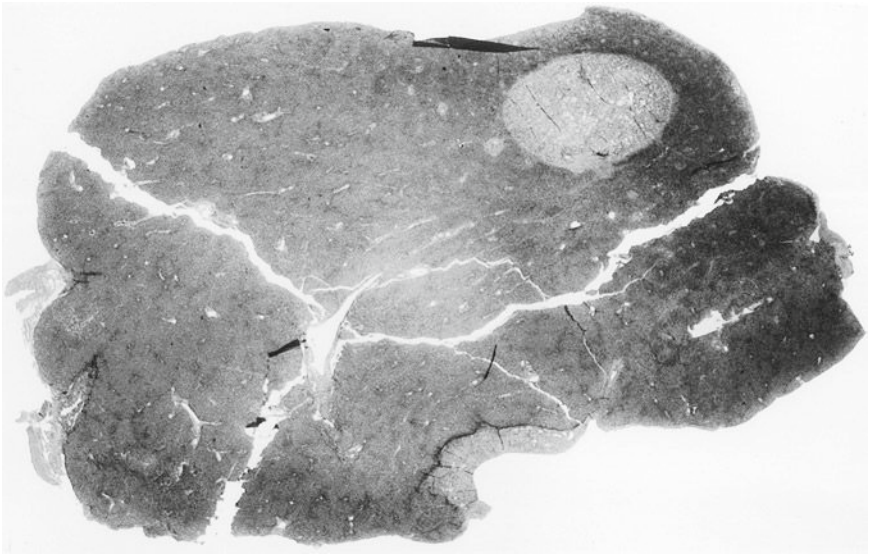

Fig. 2.8 A canine's liver was irradiated using a point source. At 1 month following irradiation, the liver shows a region of necrosis 3 cm in diameter, corresponding to the 15-Gy isodose volume. The animal had no detectable increase in liver function tests and no detectable hepatic dysfunction. Necrosis-inducing doses of radiation are well tolerated with no detectable metabolic abnormalities if only a small portion of the liver is irradiated [105].

Exceptions include the small bowel, which might perforate or obstruct if overdosed compared with benign resection of the same region of bowel [14, 22].

Dose Rate Effects

Dose rate effects rarely enter into IORT. This is because the surgical procedure must be completed in a timely manner. Dose rate effects do not become important clinically until rates under 5–10 cGy/min are achieved [24, 25]. Experimental models suggest that even lower dose rates are required to take full advantage of the dose rate effect [26]. In clinical practice, it is rarely, if ever, possible to slow dose rate to these levels when IORT is employed since the procedure duration would be lengthened by a minimum of 2–5 h.

Clinical Modifiers of Normal Tissue Radiosensitivity

Patients undergoing IORT have commonly undergone several surgical procedures, previous EBRT and multiple cycles of chemotherapy. Patients may also have other conditions, including cardiovascular disease, diabetes, collagen vascular disease, autoimmune disease, or undetected genetic instability syndromes (e.g., heterozygosity of ataxia telangiectasia, heterozygosity of Fanconi's anemia) [27–29].

The interaction between standard radiation and surgery on the IORT site is usually limited to the specific anatomy or its physiology. Delayed treatment-induced fibrosis is known to be more pronounced in patients who undergo irradiation before, after, or concurrent with a surgical manipulation. Delayed fibrosis can also worsen with time. Acute surgical toxicities may be exacerbated by irradiation. Toxicities include impaired granulation of irradiated tissue, and wound strength can be reduced. In performing IORT, it is usually possible to avoid treatment of skin, making the frequency of wound closure complications low. The interaction of radiation and surgery, however, in the tumor bed cannot be avoided.

Radiation and surgery can sometimes interact in more complex ways. For example, in animal models, if the left kidney is removed, and the entire right kidney is irradiated 1 month later, the radiation tolerance of the right kidney increases substantially [30, 31]. The hypertrophic response apparently leads to radiation protection in this animal model. In contrast, if the entire left kidney is irradiated, and the right kidney is immediately nephrectomized, the left kidney develops nephritis at a reduced dose [30, 31]. Here, the induction of a proliferative response seems to result in a stress that is poorly handled by an irradiated kidney.

Chemical Modifiers of Normal Tissue Radiosensitivity

The impact of chemotherapy on radiosensitization of tumor and normal tissues is difficult to predict. The enhancement ratio is a measure of radiosensitization induced by combinations of drug and radiation. The enhancement ratio is the differential cell kill obtained by the combination of radiation and drug after correction for the independent cytotoxicity of the individual therapies. The enhancement ratio may increase either due to a steeper slope and/or reduction in the shoulder of the radiation dose-response curve.

In general, a therapeutic gain is only obtained if the normal tissues irradiated are not similarly sensitized by the combination of radiation and drug. If the enhancement ratio seen by the tumor is

also experienced by the normal tissue, and the normal tissues must be irradiated, radiosensitizing drugs are of no theoretical advantage. IORT can be advantageous from this perspective, since it is frequently possible to exclude sensitized organs from the IORT port.

Enhancement ratios for chemical sensitizers are almost always greater when given with large radiation doses, such as IORT, because the enhancement ratio is diluted in a fractionated course of radiotherapy. An enhancement ratio of 2 indicates that cell kills normally seen at a given dose are seen at one-half of that dose. If such effects were seen clinically, responses would be dramatic. However, fractionation severely attenuates the enhancement ratios that are observed when radiation is given in a single fraction. It is common for large enhancement ratios of 2 or 3 to decrease to 1.1 or less with fractionation. This dilution is probably due to redistribution of tumor cells in the cell cycle, repopulation of tumor between fractions, reoxygenation, and other modifiers of the radiation dose-response curve. Since IORT emulates the experimental model in which radiation is given in a single fraction, the utility of combining radiation and radiosensitizing drugs are expected to be significant. Thus, radiosensitizing drugs with enhancement ratios of 1.1–1.5 might still be expected to be important biologically when radiation is given in large single fractions.

The interaction between drugs and radiation is most pronounced when both are used simultaneously [32]. Some drugs interact with radiation even if separated substantially in time, a phenomenon termed recall (Table 2.1). The most well-known drug in this category is doxorubicin, and related intercalating drugs include bleomycin [33, 34]. For other chemotherapeutic drugs, the interaction seems to be more pronounced if the chemotherapy is given following radiation. The possibility of

Table 2.1 Radiosensitizing drugs with potential application to IORT

Drug	Proposed mechanism	Mode of radiosensitization
Adriamycin, Bleomycin, Actinomycin D, and Mitomycin C	Antibiotics: intercalation into DNA where it can remain for long periods of time	Greatest radiosensitizing effect if given concurrent with radiation Radiosensitization sometimes seen when given months or years before or after irradiation. Commonly associated with pulmonary fibrosis or cardiac toxicity
Cis-Platinum	Alkylating agent	Sensitizer of hypoxic cells even at very low concentration
Cyclophosphamide	Alkylating agent	Primarily interacts in lung and heart Toxicity greatest when given in close proximity to radiation
5-FU and Gemcitabine	Antimetabolite: primarily S-phase cytotoxin. Complex mechanism of action	Sensitizer of cells in the most radioresistant portion of the cell cycle. Particularly useful for gastrointestinal malignancies
Methotrexate	Antimetabolite	Primarily interacts in CNS. Worse if given with or after irradiation
Paclitaxel	Tubulin binder. Synchronizes cells in G2/M	Places cycling cells in the most radiation sensitive portion of the cell cycle. Sensitization requires appropriate schedule of drug before irradiation
Topotecan and Camptothecin	Topoisomerase inhibition	Greatest effect when given concurrently or in close proximity. Believed to sensitize by unraveling DNA and contributing to double-strand breaks
Misonidazole, SR2508	Nitromidazole Radiosensitizers Oxygen mimetic, hypoxic cell radiosensitization	Typically neurotoxic at radiosensitizer dose levels
IUDR and BUDR	Halogenated pyrimidines Thymidine replacement in DNA	Sensitizes only actively replicating cells

deleterious interaction is decreased if the drug administration schedule is completed well before radiation. An example of a drug in this category is high dose methotrexate. If high dose is given following whole brain radiation, the neurocognitive complications are substantially greater than if it is given before the radiation [35]. This is probably due to the chronic subclinical radiation effects interacting with a drug toxicity that would have otherwise been subclinical and temporary.

In animal models and probably humans, alkylating agents can worsen pulmonary toxicity if given in close sequence to irradiation [36, 37]. Cisplatinum, a bifunctional alkylating agent, is a powerful radiosensitizer of both tumor and normal tissues [38–45]. The effects are most pronounced at low doses [46–49]. At higher doses, cisplatinum kills tumor cells and thus cannot sensitize those cells (cells cannot die twice). At low drug doses, however, radiation appears to enhance the sublethal drug toxicity. Both oxic and hypoxic tumor cells are prone to cisplatinum-induced radiosensitization [50, 51].

Other chemotherapy drugs with independent cytotoxicity have also been studied with clinical success. Perhaps the most important of these being 5-fluorouracil (5-FU) [52, 53]. This drug has a complex mechanism of action and is particularly cytotoxic to S-phase cells. For radiation, S-phase is the least sensitive portion of the cell cycle and killing of these cells is undoubtedly a component of the 5-FU-mediated synergistic effects. Another cell cycle active drug, paclitaxel, sensitizes cells by synchronizing them in G2/M, the most radiosensitive portion of the cell cycle [54–56].

A final category of radiosensitizing drugs worth discussing are the topoisomerase inhibitors [57–60]. Topoisomerases uncoil supercoiled DNA by nicking one strand and serving as a swivel to allow uncoiling without tearing of the remaining single strand of DNA. By inhibiting the swiveling of the DNA, topoisomerase inhibitors preserve the single-strand break. The effective single-strand break may allow for easier breakage of the remaining DNA strand, leading to a lethal double-strand break. The effects of topoisomerase inhibitors are primarily observed in cycling cells, but topoisomerase activity occurs in all cells.

Radiobiology of Tumor

Tumor Oxygenation and Hypoxic Radiation Sensitization

When experimental tumors are treated with a single fraction, tumor response is usually determined by the hypoxic fraction of cells. This is because well-oxygenated cells are far more sensitive to radiation than those with poor oxygenation. The differential sensitivity is exponential with dose. Hence, even if oxygenated cells outnumber the hypoxic cells by one or two orders of magnitude, the hypoxic cells can still dominate as the cause of treatment failure. When fractionation of the radiation dose is employed, the impact of hypoxia is diminished due to a spatial redistribution of the oxygenated cells between treatments, a process termed reoxygenation [61]. While in experimental animals the hypoxic fraction of tumor consistently increases with tumor size, in humans the relation is less consistent. Thus, even small tumors can be hypoxic in human subjects. Hypoxic fractions for human tumors are often similar to that of small murine tumors, and like small murine tumors, oxygenation is quite variable even among tumors of the same size and histologic type. Thus, many human tumors have no significant hypoxia, and in others, hypoxic cells can comprise more than half the tumor. The use of vascular ligation, clamps, and anesthesia during surgery add to the potential of increased tumor hypoxia during IORT.

Several clinical approaches have been taken to reduce hypoxia. First, patients are anesthetized and blood pressure is maintained by appropriate hydration and transfusion. Anesthesia can cause vasodilation, which, in the absence of concomitant hypotension, can actually improve tumor blood flow. During irradiation, patients can be ventilated with near pure oxygen. In this case, increasing

the oxygen partial pressure can improve the oxygen carrying capacity modestly and does appear to at least temporarily increase tumor oxygenation [62]. Interestingly, tumor metabolism is often oxygen limited, and when oxygen breathing is allowed to continue for over approximately 30 min, some tumors augment their metabolic rate and consume the added oxygen. Hence, the inspired oxygen should not be unnecessarily increased until just before radiation is to be delivered.

Hypoxic radiosensitizing drugs, and in particular the nitroimidazole drugs, have been used in combination with IORT. While the data is still inconclusive, this approach has much theoretical merit. The major toxicity of the nitroimidazole radiosensitizers is neurologic. The effect is cumulative with total drug dose. The concentrations of drug that are required to significantly sensitize tumor are often prohibitive in fractionated studies, given that humans appear to tolerate these drugs poorly compared with rodents. As a result, many clinical studies of fractionated irradiation have given the drug at doses that do not even sensitize animal tumors treated in a single fraction. Successful use of these drugs with fractionated irradiation, a condition where hypoxia is less important than single fraction irradiation, has thus been difficult to achieve. Single fraction therapies, like IORT, allow for a therapeutic dose of nitroimidazole radiosensitizer to be delivered. Only hypoxic cells would be sensitized by this therapy, and dose modifying factors over 2 are typically achieved with these drugs (Fig. 2.9) [63–65]. If a doubling of dose effect were to be observed in the clinic, it should have an important benefit to patients.

While most normal tissues are well oxygenated and are thus not expected to be sensitized by increased inspired oxygen or nitroimidazole drug, it is known that brain involved by tumor can be quite hypoxic [66, 67]. Skin and liver are two other organs that commonly have high natural hypoxia and would be sensitized by procedures aimed at hypoxic cells [68]. Normal tissue radiation toxicity, therefore, can sometimes occur when tissue oxygenation is increased. For example, augmenting the inspired oxygen in the case of IORT for brain tumors might be expected to increase the oxygenation

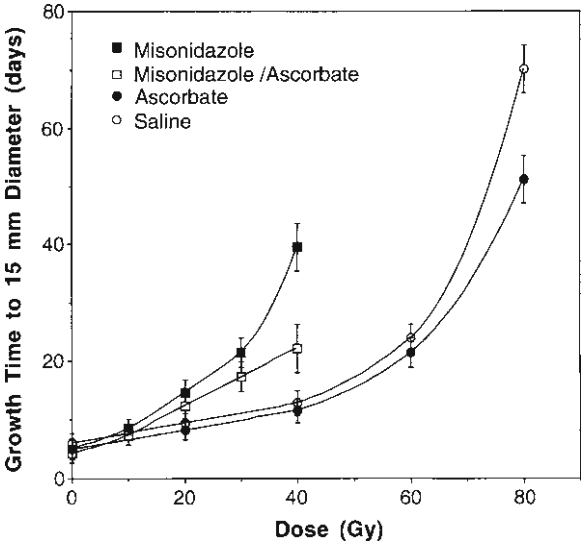

Fig. 2.9 In single fraction irradiation treatment, the response of tumor is primarily determined by the fraction of tumor cells that are radiobiologically hypoxic. For example, using the hypoxic sensitizer misonidazole at a dose of 0.3 mg/g body weight, dose modifying factors of 1.5–2.5 are typically observed [64, 65]. Likewise, drugs that only radioprotect well-oxygenated cells, like ascorbate, do not protect tumor in single fraction studies. Ascorbate can reduce some of the sensitizing effects of oxygen mimetic drugs like misonidazole. The data shown were measured using FSaII fibrosarcoma tumors growing in C3H mice. Tumors were irradiated at 8 mm diameters and time to reach 15 mm was tabulated. Values are means ± 1 SE. At 40 Gy some misonidazole-treated tumors had permanent control. Likewise, at 80 Gy, the tumors in some ascorbate or control animals were permanently controlled.

of the normal brain and thus increase the risk of necrosis. Hence, an understanding of the actual physiology of the tissues being treated should be taken into consideration when any radiosensitizer is employed.

Oxygen diffusion distances change depending upon the metabolic rate of tumor, the cell density of tumor, and the availability of carbon substrate (e.g., sugars and protein). Over the years, several drugs have been developed for improving tissue hypoxic cell sensitivity. These drugs include the oxygen mimetic sensitizers, oxygen unloading drugs, vasodilatory drugs, hyperbaric and hyperoxic breathing, blood doping, hypo- and hyperthermia, drugs that alter the oxygen consumption rate, and therapies that alter tumor angiogenesis. The diffusion of oxygen is primarily limited by metabolism, and since the latter is rarely known, the oxygen status is rarely known. Hence, the ability to evaluate the benefit of employing these toxic drug therapies, aimed only at hypoxic cells, is plagued by the problem of identifying tumors that have substantial hypoxia [69]. Progress is being made in imaging hypoxia using PET and electrode technology, and this should ultimately impact the successful routine use of hypoxic radiosensitizers [70].

Many drugs with independent tumor cytotoxicity are known to function as radiosensitizers, and some are routinely used clinically. These drugs are of obvious interest as an adjunct to IORT. Some chemotherapy, interestingly, is more effective at killing hypoxic cells and thus might synergize with radiation given during IORT [71–74].

Dose Response of Human Tumors and Implications for IORT Dose

There is little discussion of dose response for tumor control in the IORT literature despite the large range of doses used in various studies. In contrast, there is a more comprehensive discussion of the correlation between dose response and complications. Thus, it appears that the heterogeneity of tumor response to IORT may be more determined by the ability to safely encompass the tumor and less by the selected dose. Radiobiologically, this can be explained if even the lowest IORT doses are already sufficient for in-field control of most tumors.

The dose response of human tumors had been published in multiple clinical series and organized by several authors [75–78]. The median dose range that locally controls 50% of adult solid tumors (TCD_{50}) is approximately 45–65 Gy in standard fractionation (Fig. 2.10). The TCD_{50} for microscopic residual disease is closer to 25–50 Gy for typical adult solid tumors [75]. As previously discussed, the dose response curve is steep. The γ_{50} factor was defined to estimate the steepness of the dose response curve [4, 75]. It has units of percent change in local control divided by percent change in dose measured at the TCD_{50}. Thus, a γ_{50} of 1 to 2, which is typical of most tumors, suggests that a 1% increase in dose near the TCD_{50} level increases control by 1–2%. As an example, if the γ_{50} is 1–2%/% change in dose, and the TCD_{50} is 50 Gy, then 55 Gy (10% increase in dose) would increase local control 10–20% (i.e., 60–70% local control).

No detailed analyses are possible for IORT because of the complexity of cases treated, and the routine combination of EBRT and IORT. As an estimate, however, an IORT boost of 10, 15, or 20 Gy, using data in Fig. 2.3, preceded or followed by 45 Gy fractionated EBRT, would have a theoretical biological effect equivalent to 61, 76, or 95 Gy, assuming an α/β of 10. Since these doses exceed the expected TCD_{50} for most solid tumors, there is little radiobiological justification to ever exceed total IORT doses of 15–20 Gy, if EBRT is also delivered. Perhaps the only exception to this rule would be in the case of a known severely hypoxic tumor. The experience with stereotactic radiosurgery of brain metastases supports the conclusion that tumor can be controlled locally with radiation doses ≈15 Gy when combined with external beam radiation. For example, fractionated whole brain radiation doses of 30 Gy, combined with 10–15 Gy stereotactic boost, yields local control in ≈90% of patients [79].

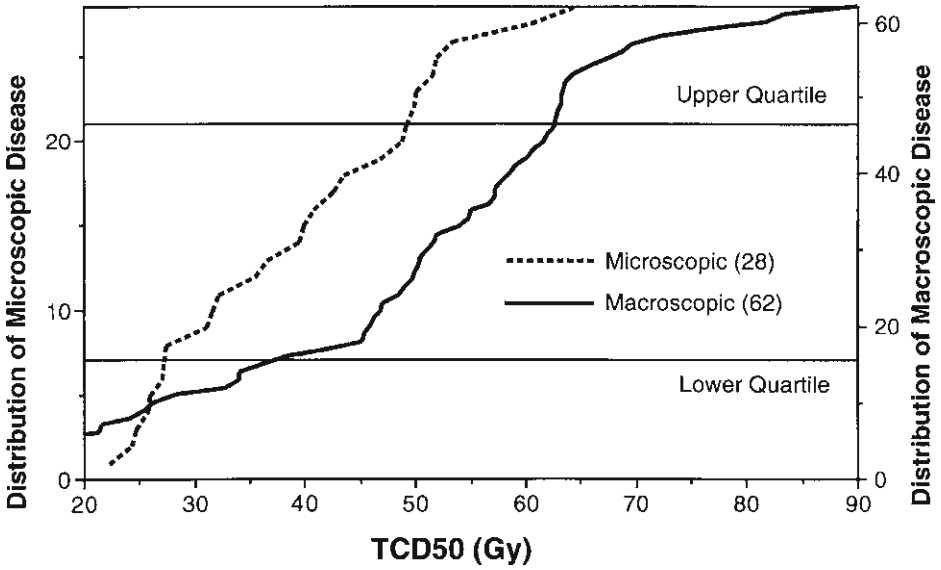

Fig. 2.10 The distribution of 100 dose response curves for human malignancies were collected based upon single and multi-institutional studies [75]. Sixty-two calculations of TCD_{50} were made for unresectable tumor, and 28 calculations for patients at high risk of recurrence or with positive margins. The calculated TCD_{50}s are displayed as a cumulative histogram. Typical tumors, based on the middle quartiles, had TCD_{50}s of 45–65 Gy for gross tumor and 25–50 Gy for resected tumor. In most studies, the radiation was administered with standard fractionation using external beam. The lowest TCD_{50}s occurred in hematopoietic and pediatric malignancies, the highest TCD_{50}s were for unresectable esophageal cancer. In the context of steep dose response curves, these data suggest that total effective doses over 70 Gy rarely are indicated for control of macroscopic disease and that doses over 60 Gy should obtain in-field control for microscopic disease.

Radiobiological Benefits of Low-Dose IORT When a Full Dose Cannot Be Delivered Safely

Rationale for Field Within a Field

Considering the steepness of the radiation dose response curve, one might predict that if doses of radiation near the tumor control dose cannot be administered safely or are not delivered for other reasons, the efficacy of IORT is in question. This concept, however, is true only when IORT is the only therapy being delivered. If the patient has received preoperative EBRT, is planning to receive postoperative EBRT, or has had a gross total resection, then IORT could yield tumor control even if the dose of IORT is not optimal. The rationale for this stems from the expectation that the largest number of potentially surviving clonogenic tumor cells are in the primary mass or surgical bed, and that potential disease outside the field can be controlled by EBRT, chemotherapy, or surgical excision. Under these circumstances, even a low boost dose of radiation given by IORT may improve control rates [77, 80]. Theoretical estimations of improved control rates have been proposed by several authors. The concept of partial tumor boost is still controversial, but the conditions of IORT make its consideration particularly important. Some estimates suggest that, for many tumors, as much as 10% of the tumor can be excluded from the IORT boost field and still yield 10–20% improvements in local control [4, 81]. Theoretically, therefore, if the entire tumor cannot be safely taken to full dose, it is still worth considering giving the safe dose to the entire tumor and an additional intraoperative dose (field within a field) to the volume which excludes the dose-limiting sensitive tissue.

Future of Radiobiology and Relevance to IORT

New Biological Parameters of Consideration

It has been established that patients with certain inherited abnormalities are substantially more radiation sensitive than "normal" patients [28, 82]. It is hypothesized that many apparently normal people are more radiosensitive than true "normals" due to undetected heterozygosity for an inheritable disorder [27]. With recent advances in molecular technique, it is becoming possible to test for disorders of DNA repair. Interestingly, deficiencies in any DNA repair pathways cause increased radiation sensitivity, although double-strand break repair mechanisms appear most important. Radiation may be unique in this ubiquitous effect; cytotoxic drugs typically affect only one or two DNA repair pathways. As the enzymes and genes are sequenced and mutant patterns identified, ultimately it might be possible to identify patients with increased risk for complications from IORT. Gene array profiling is already available and is being used for clinical investigations [83, 84].

Recent studies of cytokine expression also suggest that toxicities to normal tissues resulting from IORT may be predicted. Rubin et al. showed that transforming growth factor ß (TGFß) was elevated preceding the development of radiation pneumonitis [85]. TGFß is one of many fibrogenic and proinflammatory cytokines induced to different degrees in animal and human following radiation. Experimentally, the levels of cytokine expression appear to depend on animal species and strain, the type of tumor growing in the animal, and the type of therapy delivered. As with different mouse strains, the levels of expression in different human subjects are highly variable [86, 87]. Correlative studies in humans confirm that many tumors produce TGFß and that individuals who chronically have elevated levels of these cytokines, whether endogenous, disease-induced, or therapy-induced, are at increased risk for late radiation complications. TGFß and tumor necrosis factor (TNF), for example, have been associated with pulmonary and/or hepatic fibrosis following radiation or chemotherapy [86, 87]. These cytokines can be readily measured by ELISA, paving the way for predictive assays. It is interesting to speculate that medications designed to alter the chronic expression of these cytokines may prevent some complications of IORT.

Oncogenesis

The oncogenic potential of radiation is well known. In general, as with other complications of radiation, the frequency of late radiation-induced cancers are related to fraction size, total dose, and field size. Oncogenesis in the IORT field is common in canines [88], although not yet reported in human subjects. Malignancies attributed to IORT, however, must originate in the IORT field, must be of a different histology than the original primary, and must occur after a significant time lag (usually, over 6 months and often years or decades). Radiation-induced oncogenesis can include leukemias, carcinomas, and sarcomas [89]. IORT-induced malignancies in canines, however, are most commonly sarcomas of bone or soft tissue. The type of cancer induced by treatment is related to the form of radiation used, the target tissue irradiated, and the size of the radiation dose used for the treatment. For example, orthovoltage techniques have the disadvantage of severe dose inhomogeneity; thus, high dose regions can occur in nonmalignant tissues included in the IORT field. Murine models suggest that single doses of ≥ 35 Gy are associated with near certain sarcomatous degeneration [90]. Estimates of carcinogenesis in canine models are typically not actuarially corrected, resulting in an underestimation of long-term oncogenic risk. In two canine studies from the National Institute of Health, one found that animals that received over 20 Gy have a crude long-term malignancy rate of

1/8 (12%), and, in a shorter analysis, 10/46 (22%) developed sarcomas, all but one of which received over 20 Gy [88]. None of the sham irradiated animals in either study developed cancers.

The frequency of malignancy due to IORT is difficult to discern in patients. Unlike the animal models, most patients treated with IORT already have aggressive tumors and a high rate of death from other causes. Therefore, follow-up is often short due to high mortality. Further, the usual IORT dose of 10–20 Gy is lower than the reported doses needed for inducing a second malignancy. Perhaps for these reasons, oncogenesis is and will be rare in patients treated with IORT.

The mechanism of radiation-induced oncogenesis is unknown in most cases since few cancers occur within the first years after irradiation. However, it is unlikely that direct DNA damage from the irradiation is the primary cause of most cancers. In some cases, the mechanism of radiation-induced oncogenesis is well-defined. For example, patients with hereditary retinoblastoma are at high risk of developing multiple malignancies, including sarcomas of bone and soft tissue. Cancers in these patients develop due to radiation-induced mutation of the remaining normal Rb gene [91–93]. Recently, it was discovered that cycles of hypoxia and reoxygenation can select for cells with p53 mutations [94]. As previously discussed, radiation causes a prolonged antiangiogenic effect that includes intimal proliferation, thrombosis, and intermittent vascular occlusion [11]. An important function of p53 is the promotion of apoptosis in cells which have incurred genetic damage [95]. p53 mutant cells selected by years of impaired blood flow would fail to undergo apoptosis and could, therefore, accumulate genetic damage [96, 97]. If this proves to be an important mechanism of oncogenesis, strategies aimed at preventing the vascular effects of radiation might also reduce the incidence of radiation-induced malignancy.

Finally, as previously described, the normal tissues in the IORT bed can develop chronically elevated proliferative and fibrogenic cytokine levels. It is now known that elevated levels of many cytokines inhibit apoptosis [98]. As with mutations in the p53 pathway, this process could predispose to oncogenesis, and might be preventable using anticytokine therapies.

Radiation-Induced Tumor Autoimmunity

A holy grail of cancer therapy has been the development of tools that can help the body produce natural immunity to malignancy. Among the best documented is immune surveillance. There is substantial evidence that immune surveillance is an integral component of cancer prevention and contributes to tumor responses and possible reduction in the number of metastases. Fully satisfactory and ubiquitous antigens against a class of tumors are rare, an example being B1 for lymphoma or Her2/neu for breast cancers. Although patient-specific antigens can sometimes be employed, and there are some cytocidal immune reactions documented for melanoma and renal cell carcinoma, producing and employing these antigens is technically demanding. Radiation is known to activate tumor specific immunity in animals [99, 100]. For example, innoculation of irradiated tumor cells in animal models, or curative treatment of animals with transplanted tumors, yields specific resistance to subsequent tumor challenge. Tools to detect similar effects in humans after irradiation are beginning to provide evidence that a similar effect may be observed in humans [101]. A mechanism of the possible effect has been attributed to the depletion of regulatory T cells (T(reg)) and myeloid-derived suppressor cells that otherwise limit the function and proliferation of autoimmune cells [102]. Older hypotheses include unrepaired radiation-induced cell membrane damage leading to prolonged antigen exposure. In animals, the tumor autoimmune phenomenon is dose-dependent and appears to require a large fraction size. Fortunately, it appears to be tumor histology-independent and might be augmented by appropriate systemic or locally administered cytokines that act as immune adjuvant [103]. IORT is uniquely positioned to create tumor “vaccines” of this sort given both the ability to directly inject the tumor with immune adjuvant and to administer the large single

doses of radiation. We suggest that vaccination conferred by IORT combined with an immune adjuvant might protect against the development of future micrometastases and/or cytoreduce existing metastatic or primary disease [104]. Reducing existing and future disease burden should prove to be clinically beneficial. More work is needed in this promising field.

Conclusions

The most important advantage of IORT is the potential for high-dose irradiation of the tumor, while minimizing radiation to nontarget tissues. Another advantage of IORT is the potential for delivering concurrent radiosensitizing drugs under circumstances where a minimum of normal tissue experiences the sensitization effects. Finally, IORT offers the potential for optimizing the dose and dose distribution, thereby allowing us to test the hypothesis that radiation induces tumor autoimmunity. Since tumor response to a single fraction is predominantly determined by the hypoxic cell fraction, strategies aimed at this population of tumor cells should be pursued. Normal tissue complications are the main limitation of IORT, and they can be minimized by avoidance of full organ irradiation and by procedures designed to reduce dose to nontarget organs. Reducing dose is reasonable in many cases since there is experimental and theoretical evidence that even low-dose IORT can improve local control when employed in conjunction with other therapies. Late side effects of radiation are currently difficult to predict, and they occur with a steep dose and volume response. Ongoing research investigating the mechanisms and genetics of fibrosis, angiogenesis, and oncogenesis suggest that some of these effects eventually are alleviated or obviated by appropriate therapeutic interventions.

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Part II
Methods and Techniques of Treatment

Chapter 3
Intraoperative Electron Beam Irradiation: Physics and Techniques

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Keywords Physics of intraoperative electron irradiation (IOERT) • IOERT techniques • Mobile electron accelerators • Mobetron • Liac • Novac-7

Introduction

Since IORT using electron beams first became popular in the late 1970s and early 1980s, enthusiasm for the technique using conventional accelerators waned. The reasons for this are manyfold. The main factor was that IORT required considerable effort on the part of physicians, physicists, and therapists, as well as the loss of time on the linear accelerator for treating external beam irradiation therapy (EBRT) patients. While a dedicated facility alleviates some of these problems, the cost of building a shielded room for a low use (~3–5 cases per week) linear accelerator was hard to justify in the face of declining reimbursements. The problem with reimbursements was in part related to the fact that in the USA there is no specific CPT code for this procedure, so the utilization costs were harder to recover. Finally, in some institutions, the lack of definite improvements in survival in certain disease-sites of interest made it hard to justify the additional departmental resources to carry out the procedure.

In the late 1990s, a resurgence in IORT came about as a result of two confluent factors. Firstly, there was a rapid development of mobile linear accelerators and, secondly, major advances have come about in the treatment of breast cancer with IORT electron beam therapy, particularly in Europe. Because these machines produce only electron beams of energy less than or equal to 12 MeV and do not use bending magnets, the secondary radiation from these machines is generally sufficiently low as not to require permanent shielding to meet the regulatory guidelines for personnel

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_3,

directly outside the operating room (OR). This greatly reduces the cost of either constructing a new facility in the OR or retrofitting an existing OR. For that reason plus their mobility, they can be used in different ORs, as needed.

Accelerators

Conventional Linear Accelerators

Treatments using conventional linear accelerators, i.e., nonmobile accelerators, can be performed either with dedicated units that are used only for the intraoperative treatments or with units that are routinely used for EBRT and occasionally for IORT. In the former case, these units are generally installed in the operating room and in the latter, they are located in the Radiation Oncology department, in which case the patients are transported from the OR to the Radiation Oncology department (the so-called transport technique). A hybrid case occurs when an operating room holding a linear accelerator is built in the Radiation Oncology department so that the whole surgical case takes place outside the conventional OR. For the nondedicated units, surgical closure often takes place in the Radiation Oncology room, for logistical reasons. However, if additional major surgery is required, the patient is transported back to the OR. For the dedicated machine, all the surgery takes place in the same room as the linear accelerator. There is no instance where the linear accelerator is in one room in the OR and the patient is transported there from another OR room.

The Siemens ME[1] (Fig. 3.1) is a dedicated electron-only linear accelerator generating beams of 6, 9, 12, 15, and 18 MeV, giving 90% doses at 1.7, 2.6, 3.7, 4.5, and 5.0 cm, respectively, for a 7-cm diameter circular field. The machine is isocentric with an isocenter height of 112 cm compared with about 130 cm for a conventional linear accelerator. Since only a limited range of gantry angles is

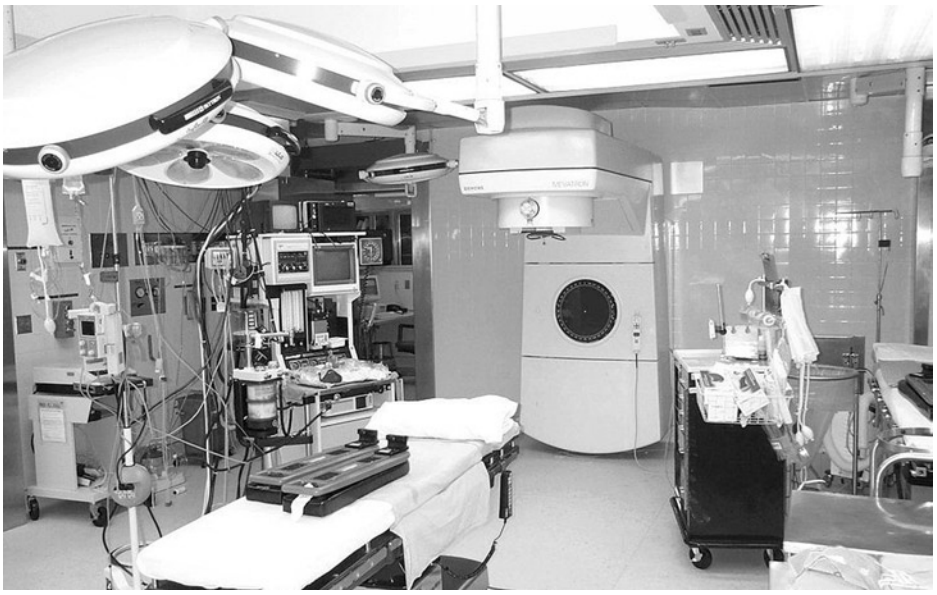

Fig. 3.1 Siemens ME dedicated IORT electron-only linear accelerator.

[1] Siemens Medical Solutions, Concord, CA 94520.

needed for IORT, the angular range can be mechanically restricted, thereby reducing the shielding requirements. The design and physical properties of this device have been discussed by Hogstrom et al. [1] and Nyerick et al. [2], respectively. Mills et al. [3] provide a review of the shielding requirements of this unit in an OR. Neutron leakage from this machine has been addressed by Jaradat and Biggs [4]. Only six units were ever made and two are still in strong clinical use. Two other sites exist in Germany, these machines are rarely used.

Mobetron

The Mobetron[2] (http://www.intraopmedical.com) is one of the three mobile linear accelerators designed for electron beam IORT treatments. A photograph of this unit is shown in Fig. 3.2. Note some important mechanical features of the unit: (a) the unit is isocentric, as with all conventional medical linear accelerators, but with an SAD of 50 cm; (b) the unit has a beam stopper that always intercepts the primary beam; (c) the head, or X-ray unit, can tilt out of the plane of gantry rotation in both directions. However, because of the typical setup for IORT treatments, the gantry rotates only over the range ±45° and the head tilts ±30° in the orthogonal plane. The gantry can also move distances of ±5 cm in the two orthogonal horizontal planes while along the axis of the guide, the head can move a total distance of 30 cm for docking with a variable speed of 0–2 mm/s. Thus, there are five degrees of motion for the gantry head. The isocenter is 99 cm above floor level. The linac uses an X-band waveguide to reduce its size, compared to an S-band waveguide in conventional linear accelerators, and accelerates electrons to energies of 4, 6, 9, and 12 MeV, giving 90% depth doses of 1.1, 1.9, 2.9, and 3.5 cm in water [6], respectively. Circular applicators are available for field sizes between

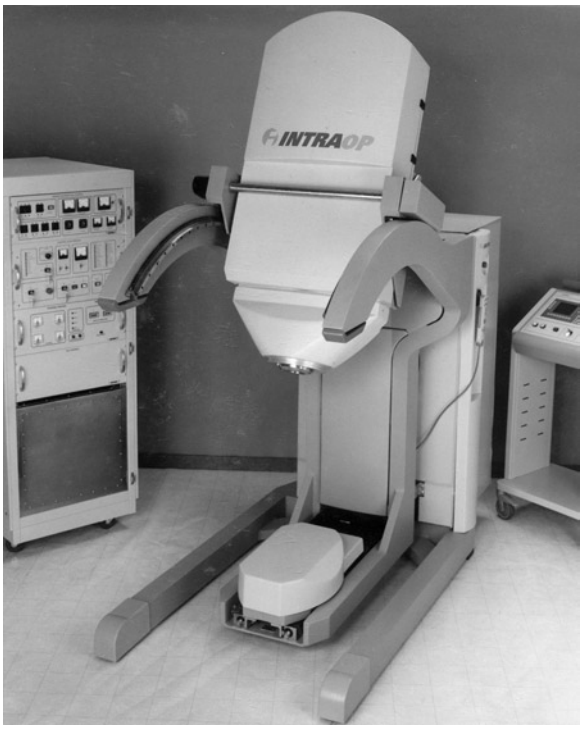

Fig. 3.2 IntraOp Mobetron mobile electron linear accelerator.

[2] IntraOp Medical, Sunnycale CA 94085.

3 and 10 cm with bevel angles of 0°, 15°, and 30°. Some elliptical and rectangular applicators have also been developed to give more flexibility with regard to the treatment of para-aortic nodes or patients with retroperitoneal or extremity sarcomas. The dose rate for this machine in the clinical mode is 10 Gy/min, thus giving a maximum treatment time of around 2 min. For warm-ups and physics tests, a lower dose rate of 25 cGy/min is available. This machine uses the soft-docking technique (see "Soft Docking" below).

The physical properties of this device have been reviewed by Meurk et al. [5] while Mills et al. [6] and Daves and Mills [7] provide a comprehensive review of the commissioning and shielding requirements of a Mobetron accelerator. The potential problem of neutrons at 12 MeV was addressed by Loi et al. [8], but was not felt to be a major issue (see "Neutrons").

Mobetrons are globally in North and South America, Europe, and Asia. As of January 2011, 31 are in operation (North America – 16, Italy – 5, Belgium – 3, Poland – 2, Japan – 2, Latin America, SE Asia, Spain – 1).

Novac7 and LIAC

The Novac7[3] (http://www.newrt.com) and the LIAC[4] (http://www.sordina.com) are two models of mobile linear accelerator which appear basically rather similar to each other, at least when compared to the Mobetron. In general, the key difference is that they are robotic devices that use the hard-docking technique, but have in common the reduced weight, compared with conventional linacs, and mobility. Both machines use a magnetron operating in the S band (3 GHz) while the accelerating structure consists of a set of self-focussing resonant cavities. Also, the beam collimation system is similar and consists of different polymethylmethacrylate (PMMA) applicators with diameters ranging from 3 to 10 cm, flat-ended or beveled up to 45°. Unlike conventional linear accelerators, no adjustable X-ray collimators are used. Both machines use an assembly of two independent, unsealed and very thin metallic ionization chambers as a dose monitoring system while no automatic compensation for air density variations is provided.

For radiation protection purposes, the Novac7 and the LIAC are equipped with a movable beam stopper, consisting of a very thick lead shield, which has to be manually positioned by the operator below the surgical couch to intercept the primary beam. An electronic device is used to check the correct alignment of the beam stopper in the actual configuration of the radiation head.

The dosimetric properties of the electron beams produced by the Novac7 and the LIAC are unusual for linear accelerators in that they run at a very high dose per pulse (up to approximately 9 cGy) to achieve a typical dose rate of 10–20 Gy/min, depending on beam energy and applicator type. As widely discussed in the Italian guidelines on QA in IORT [9], the use of ionization chambers for absorbed dose determination under such critical conditions is strongly discouraged, due to the uncertainty in the calculation of the correction for charge recombination at such high dose per pulse values. Fricke (ferrous sulfate) or alanine/EPR dosimetry is recommended because the response of those detectors is independent of the dose per pulse. More recently, experimental procedures for the determination of the ion recombination correction factor (k_s) for different types of ionization chambers exposed to high dose per pulse electron beams have been reported [10, 11]. In 2006, a general method for k_s determination using flat ionization chambers, with an uncertainty of 2% (1 SD), was proposed and experimentally validated [12].Their procedure was based on Boag's theory to account for the presence of free electrons in the air of the ion chamber cavity and did not require any previous calibration of the ion chamber itself against an absorbed dose standard independent of the dose per pulse [12].

[3] NRT SpA, Roma, Italy.

[4] Sordina SpA, Saonara (PD), Italy.

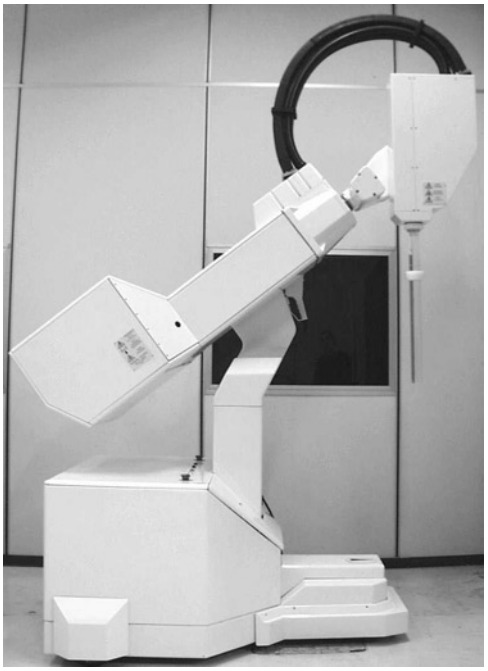

Fig. 3.3 Novac 7 mobile electron linear accelerator.

Fig. 3.4 LIAC mobile electron linear accelerator.

The Novac7 (see Fig. 3.3) was developed in Italy and became available for clinical use in the late 1990s. Its weight is about 650 kg while the dimensions are approximately 230 cm length × 100 cm width × 190 cm height. It operates at four different nominal electron energies available in two options, namely, 3, 5, 7, and 9 MeV (R_{50} equal to approximately 16, 20, 24, and 29 mm, respectively [13]) or 4, 6, 8, and 10 MeV (R_{50} equal to approximately 16, 22, 30, and 36 mm, respectively). The pulse repetition frequency (PRF) in the clinical mode is set at 5 Hz. The nominal treatment SSD is 80 cm (100 cm for 10 cm applicator only). To reduce radiation leakage, the Novac7 does not use any scattering foil for beam broadening.

Some years later, the LIAC (see Fig. 3.4) was manufactured again by an Italian company and installed in a clinical environment starting in 2003. The four following nominal energies are available: 4, 6, 8, and 10 MeV (R_{50} respectively equal to 17, 22, 30, and 38 mm). A special version of the LIAC delivering 12 MeV electron beams as maximum energy (R_{50} equal to 47 mm) can also be ordered. The dimensions of the LIAC are 210 cm × 80 cm × 180 cm (length × width × height) while the weight is 400 kg. The PRF is in the range 10–50 Hz, depending on beam energy, and the nominal SSD is 60 cm. A thin brass scattering foil (80 μm thick) is provided.

Globally, there were approximately 20 Novac7 and 10 LIAC linear accelerators installed as of 2008. All of them are in Europe and mostly in Italy.

Method of Docking

Hard Docking

In the hard-docking system, used for example by the Novac7 and LIAC, the electron applicator is divided into two parts: at the time of IORT, when the field size has been chosen, the superior part is directly connected and fixed to the radiation head of the linear accelerator, typically by a nurse under sterile conditions, while the lower is placed by the radiation oncologist or the surgeon in contact with the tumor bed to be irradiated. Then, the therapist moves the machine toward the patient, simultaneously aligning and minimizing the distance between the two components of the applicator. Once this procedure is complete, the two parts are then rigidly connected, in order to guarantee the precise alignment of the electron beam axis. In this way, no air gap is left between the head of the machine and the electron applicator. For safety reasons, to prevent collisions between the radiation head and the tumor bed, in the last phase of the procedure, it is mandatory for the therapist moving the machine to select on the hand-controller the minimum speed of all rotational and translational movements. The time needed for the whole docking procedure is usually very short (only a few minutes) while the influence of motion due to patient breathing on the quality of the alignment, visually checked, is generally negligible, provided that only light pressure is kept on the patient surface. For conventional medical linear accelerators, a system to disable the motors controlling movements (couch, gantry and collimator) is necessary to avoid potential patient injury.

Soft Docking

The soft-docking process decouples the machine from the applicator to ensure patient safety in the event that an uncontrolled motion of the machine occurs. The difficulty then arises as to how to align the central axis of the linear accelerator with that of the applicator and set the correct treatment distance. This requires some optical or mechanical alignment system. Many soft-docking systems have been described in the literature.

The system used in the Siemens ME machine consists of two lasers, one of which produces four dots in the isocenter plane and the other produces four lines in the isocenter plane, all of which are arranged at 90° intervals. The beam is then coaxial with the applicator and the applicator at the correct distance (100 cm) when the dots lie on a predetermined circle in a plane at the top of the applicator and the lines intersect these dots (see Fig. 3.5).

For the Mobetron, a set of lasers, located in the head, project beams onto a mirror mounted on the applicator clamp. The reflected laser beams activate electronics that illuminate LEDs to indicate the position of the Mobetron central axis with respect to the axis of the applicator. Three

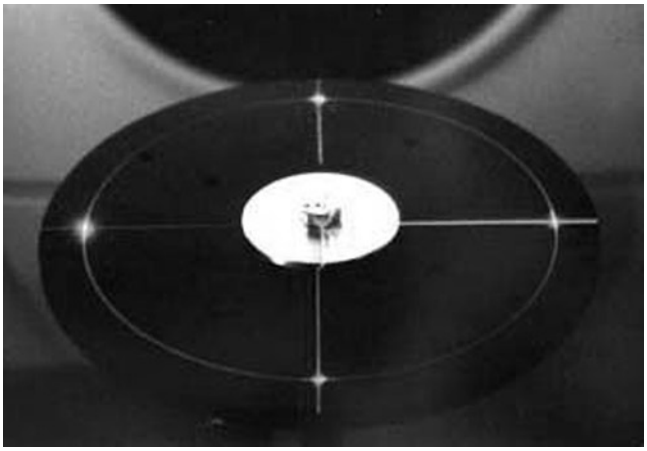

Fig. 3.5 View of final soft docking indicator for the Siemens ME (see text for explanation of alignment).

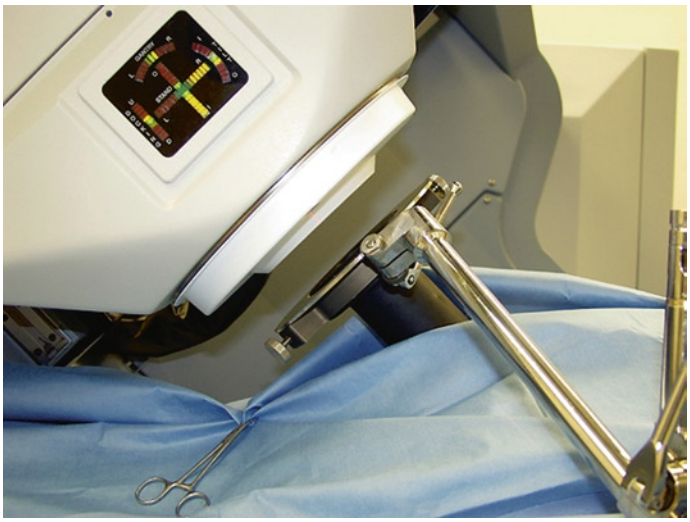

Fig. 3.6 View of the final docking indicator for the IntraOp Mobetron.

translational axes (in/out; left right; up/down) and two rotational axes (gantry and tilt) are displayed. When the Mobetron is properly positioned with respect to all of these axes, a green indicator light for each correctly positioned degree of freedom is displayed (see Fig. 3.6). Unless a green light is obtained for each axis of motion, indicating that the central axis is properly aligned with the central axis of the applicator in use, it is not possible to initiate irradiation.

Noncommercial optical systems have been developed by individual physicists [14, 15]. An example is the system published by Bjork et al. [16]. In their system, a two level sight containing circles is attached to the applicator such that the circles are concentric with the applicator. A video camera hooked up to a TV monitor can view directly along the axis of the beam by means of a mirror located in the tertiary collimator. The viewer sees four circles corresponding to the tertiary collimator aperture, the inside surface of the applicator and the two sight circles. When properly aligned, all four circles are concentric.

Facility Design and Shielding

Nondedicated Facilities

For treatments using the transport technique, shielding is not a consideration since the workload for EBRT photon treatments is far larger than the photon leakage from IORT electron beam treatments and electrons are, in any case, more readily absorbed than are photons. However, the room has to be sufficiently large to include all the necessary OR equipment that is brought down with each case as well as the greater number of personnel involved in the procedure.

Dedicated Facilities

The shielding for a dedicated facility depends greatly on the environment in which it is to be located. In the unlikely event, it is below ground level (as described above), conventional design using concrete for the wall and ceiling barriers and a combination of lead and borated polyethylene for the door and possibly HVAC ducts suffices. If the dedicated unit is located in an OR above ground level, concrete is a poor choice of shielding material due to the required thicknesses of the barriers. Instead, a combination of lead and borated polyethylene (5%) is needed; the lead is to stop the secondary photons and the borated polyethylene is to stop the neutrons. While there are always secondary photons produced by the machine, neutrons are only produced when the electron energy exceeds a threshold. In principle, electron beams with energies as low as 9 MeV can produce neutrons. However, since electro-neutron production is a second order process, the yield of neutrons at this energy is negligible. Even at 12 MeV, neutron background is low enough [4] (6×10^{-7} Sv/Gy) that assuming a workload of 10 cases per week at 20 Gy, the neutron background outside the walls of a normal-sized OR would be 0.012 mSv/week, that is, within regulatory limits However, for a machine without a beam stopper, the primary beam would require shielding. Mills et al. [3] have described the measurement of stray radiation around the Siemens ME in an OR setting and the exposure outside the room, which was located on the fourth floor. This was a retrofitted room so additional lead was used to line the walls and the floor (for the primary beam). Borated polyethylene was used to shield against neutrons in the ceiling and one of the walls. No additional shielding was possible due to weight restrictions, which limited the number of cases that could be performed in a week.

For shielding purposes, a conservative approach would be to assume that all cases are performed at the maximum energy. This ensures that a person located anywhere around the facility is never subjected to a dose greater than the regulatory limit. However, this is clearly not the case and energies less than the maximum can and will be used. The caseload mix can be taken from a comparable cohort of patients treated at another facility, but the danger lies in the fact that this may not represent the true workload experienced for that facility and may underestimate the true value.

Mobile Linear Accelerators

As already pointed out, mobile linear accelerators are quite compact and operate only in the electron mode up to 10–12 MeV, so they are safe to use, from a radiation protection standpoint, in almost any existing operating room with perhaps the addition of mobile shields and can be moved from one operating room to another. A few basic parameters must be considered to determine if the operating room is suitable for the installation of a mobile unit [9, 17]: these include electrical requirements, floor load capacity, which should be at least equal to 500 kg/m^2, the height of the ceiling and

entrance door, the dimensions of the operating room itself and the location of the existing instrumentation. Moreover, a storage area is needed for the machine, treatment console and accessories, such as applicators and shields, and the requirements for all possible transportation routes (for example, corridors and elevators) have to be fulfilled.

The physicist needs to calculate the radiation protection requirements for the workload at his/her facility. As an indication, two detailed analyses of the photon leakage and scatter from a Mobetron and an LIAC machine showed that 3–4 IORT treatments per week at a prescribed dose of 20 Gy typically represent a safe patient workload in an existing operating room with little or no added shielding [7, 18]. In the case of an unshielded operating room and for higher patient loads, it is recommended that IORT treatments be performed in more than one room or use mobile barriers [17, 18]. Once the machine is installed, a radiation survey must be performed for all the rooms where it is used, to ensure that the maximum exposure limits in the adjacent areas, as well as on the floors below and above, do not exceeded regulatory limits [17].

In calculating the workload for the room, the Monitor Units delivered for daily machine warm-up and constancy checks have to be included; as an alternative, some centers have adopted the policy of performing those irradiations outside normal working hours [18]. Acceptance testing, commissioning and annual quality assurance measurements should be performed in a dedicated vault or room (dosimetry room), using temporary barriers and signs to define controlled areas, if the chosen location is not sufficiently well shielded.

A severe limitation to the use of electron beams at energies higher than 10–12 MeV in an operating room is represented by neutron production. The threshold set at 12 MeV appears safe on the basis of the results reported by Loi et al. [8]. They showed that the neutron dose equivalent rates from a Mobetron linear accelerator operated at 12 MeV, measured using passive bubble detectors, are quite low (at least one order of magnitude lower than those produced by a conventional linear accelerator), so the machine can be used at 12 MeV in an unshielded room for a weekly workload up to 250 Gy, provided that the photon component is properly shielded.

Neutrons

The maximum electron energy of mobile electron accelerators has been kept at or below 12 MeV, not only because the X-ray leakage presents an increasing problem, but also because, above that energy, neutron production will start to become important. A serious neutron problem might imperil the ability to run these machines in any OR without the need for permanent shielding. For that reason, there has been considerable effort in recent years to quantify the neutron contamination from these accelerators.

Strigari et al. [19] measured the photon and neutron leakage around a LIAC accelerator. For the neutron measurements, they used a detector with a sensitivity of 3.15 cts/nSv compared with a photon response of $(0.69 \pm 0.05) \times 10^{-3}$ cts/nSv. The sole neutron measurement they made was made at 1 m from the isocenter in the patient plane for an electron energy of 10 MeV. For an electron absorbed dose of 10 Gy, a neutron dose equivalent of 140 nSv was measured. Assuming a workload of 200 patients per year, the authors estimate an annual neutron dose equivalent of 0.03 mSv at 1 m.

Loi et al. [8] measured the neutron production from a Mobetron at 12 MeV and a Saturne 42, a conventional linear accelerator, at the same energy. They made a more extensive set of measurements than did Strigari et al. for the LIAC. For both machines, these measurements were made in the plane of the scattering foil, close to the head, in the isocenter plane at several distances from isocenter and on the floor. For the Mobetron, the highest reading was on the beam axis in front of the beam stopper (2.91 μSv/Gy, reduced to 0.31 μSv/Gy after the beamstopper); the neutron leakage at 1 m from the head, from the isocenter in the patient plane and from the beam axis on the floor was 0.04, 0.06, and 0.02 μSv/Gy, respectively. For the Saturne, on the other hand, the neutron

leakage at 1 m from the isocenter in the patient plane was found to be 22.4 ± 6.1 μSv/Gy. Assuming a weekly workload of 250 Gy, the authors calculate a weekly dose of 14.3 μSv on the beam axis below the Mobetron beam stopper. However, in the lateral direction, the dose at 1 m would not exceed 1.7 μSv/week. Comparison of the beam axis readings for the two machines indicated that for the Saturne 42, the neutron leakage was 42× higher than for the Mobetron.

Chen et al. [20] measured the neutron leakage from the 10 MeV electron beam from a Varian 21EX in a conventional room with a maze. The only point of comparison with other data was a point at 100 cm from the isocenter, which gave a reading of 22.5 μSv/Gy, comparable to the Saturne reading [8].

Jaradat and Biggs [4] measured the neutron leakage for a conventional linear accelerator (Varian 21EX, 2000C/D) at 9, 12, 16, and 20 MeV and a Siemens ME electron-only, nonmobile linear accelerator at 9, 12, 15, and 18 Mev. The results showed that, along the beam axis, the neutron dose equivalent measured for the Varian machines at 12 MeV was 2.7× higher than for the Siemens ME (2.1×10^{-5} vs. 7.7×10^{-6} Sv/Gy at 1 m). However, at 90° from the beam axis, this ratio increased to 6.5 (1.7×10^{-6} vs. 2.6×10^{-7} Sv/Gy at 1 m). Neutron leakage for the IORT machine is characterized by a peak at 0° relative the beam and flat after 45° [$(2.6–5.9)\times10^{-7}$ at 12 MeV; $(1.4–2.2)\times10^{-6}$ at 15 MeV; $(2.7–4.7)\times10^{-6}$ at 18 MeV]. Using the upper limit of 6×10^{-7} Sv/Gy at 12 MeV for the IORT machine for azimuthal angles >0° and assuming a workload of 200 Gy/week and an inverse square factor of 10, the neutron dose equivalent is calculated to be 0.012 mSv/week at the barrier. For the primary beam at 12 MeV (0°), the 10× higher dose would be compensated by the attenuation of a primary beamstopper in a mobile linear accelerator. These neutron radiation levels are below regulatory values. Mills et al. [3] measured the neutrons from an ME using gold foil activation for 18 MeV electrons along the beam axis and at 90°. Along the beam axis, the neutron dose was about 3×10^{-5} Sv/Gy and at 90° varied between about 2×10^{-5} Sv/Gy in front of the machine to about 3×10^{-6} Sv/Gy at the side of the machine.

Direct comparison between the three data sets for the IORT machines is possible at 0° and 90°. At 0°, the neutron leakage at 12 MeV for the Siemens ME electron-only accelerator is slightly greater than for the Mobetron (7.75×10^{-6} vs. 3.33×10^{-6} Sv/Gy). The neutron leakage for the Siemens ME at 9 MeV is only slightly lower than that at 12 MeV. At 90°, the 12 MeV data for the Siemens ME and the Mobetron show a similar difference, with the Mobetron again lower (2.6×10^{-7} vs. 4.0×10^{-8} Sv/Gy). The data for the LIAC at 10 MeV is slightly lower than these two points (1.4×10^{-8} Sv/Gy), but consistent with the Siemens ME data at 9 MeV. The interested reader is referred to the original publications for more details.

Measurements for Commissioning

To commission a machine for IORT, whether it is a conventional or mobile linear accelerator, a minimum set of dosimetry measurements are required to deliver the prescribed dose. The assumption, for conventional linear accelerators, is that an applicator system, whether commercial or privately developed, is available for the machine in question. This system would include a set of applicators, of varying shapes and bevels, and a tertiary collimator system. If a hard-docking system is used, a means for viewing the treatment field after the applicator has been docked with the machine is also required. The measurements required are: (a) Percent depth doses, (b) Applicator ratios, (c) Beam profiles, in two orthogonal planes if applicator is not circular or beveled, (d) Isodose curves, in two orthogonal planes if applicator is not circular or beveled.

These measurements should be made for all applicators and energies. This amounts to a considerable amount of work, given the standard inventory of applicators in most centers. To ensure accuracy of data, measurements of the percent depth doses and applicator ratios should be repeated at least once. If the two readings for the applicator ratios differ by more than 3%, a third measurement should be made. The applicator ratios are compared to a reference applicator for which the output

of the machine is calibrated. For a conventional external beam linear accelerator, this reference applicator would be a 10×10 cm^2 field. In the case of the Siemens ME electron-only machine, the reference field is a 12-cm diameter circle. For the mobile linear accelerators, the reference applicator is typically the 10-cm diameter tube.

Note also that since the depth of d_{max} changes with field size, measurements of the applicator ratio is made at different depths for different applicators. Since the depth of maximum dose and maximum ionization are located at different depths, electron diodes are the preferred methods of measuring applicator ratios.

A special caution should be paid in the choice of the dosimetry instrumentation for the commissioning of the Novac7 and LIAC beams having very high dose per pulse values, as already mentioned. The dependence of the detector response on the dose per pulse has to be carefully evaluated with regard to dosimetry under nonreference conditions, in particular, for PDD curves and applicator ratios [9, 12].

The percent depth dose and isodose data should be stored so that it is readily available to the medical physicist and radiation oncologist for each case when deciding which energy to use and whether or not bolus is required. Note also that this is particularly important for isodose curves since, in general, they are dissimilar to electron isodose curves using conventional applicators. For example, the Siemens ME beams are designed [1] to have "horns" at the edge of the applicator to spread out the 90% isodose curve as much as possible. On the other hand, other systems may have much more rounded profiles, leading to a reduction in the 90% dose coverage.

In addition to those basic measurements, some special dosimetry aspects should be investigated: these include the measurement of the dose transmitted through the applicator walls, especially for PMMA tubes, and the performance of internal shielding (if used) in terms of beam attenuation and backscattered radiation production (range and magnitude).

Finally, the absorbed dose under reference conditions has to be determined, as well as machine monitor units calibrated, following the international dosimetry protocols [9, 13, 21]. It should be noted that the presence of the IOERT applicator produces a degradation of the radiation beam characteristics (energy spectra and angular distributions), influencing parameters such as the mass collision stopping-power ratio, as recent Monte Carlo simulations have shown [22, 23]. As a consequence, an increase in the dose to water determination uncertainty can be expected.

Quality Assurance

Quality assurance procedures have been addressed by AAPM committees for conventional linear accelerators [24] and mobile linear accelerators [17]. In addition, quality assurance issues for mobile linear accelerators have been addressed in Italy (9).

Treatment Machine

Dedicated Units

Daily Checks

Unlike linear accelerators used for EBRT, where, if the linear accelerator malfunctions in any way, the patient can be taken off the table, the malfunction diagnosed and fixed and the patient treatment resumed, in IORT, there is no chance to fix the machine once the patient is on the operating table and "under the knife." Hence, quality assurance must ensure that the uptime of the machine is as high as possible and higher than that for a conventional treatment machine. As with conventional linear

accelerators, this requires calibration at all energies on the day of each procedure. Calibrating all energies is important since different energies may use different scattering foils. A fault with one of the scattering foils was detected using the daily output check [25]. If a soft-docking approach is in use, this system also has to be checked prior to each treatment. For hard-docking systems, this is unnecessary.

For those centers with a dedicated unit, the door interlocks need to be checked to ensure that they are functioning correctly and will turn the beam off if the door or one of the doors is opened.

Monthly Checks

In addition to calibration of the electron beams at all energies and checking the soft-docking alignment system, if applicable, the energy should be checked for each electron beam. This can be done by measuring percent depth doses and comparing the results with those measured at the time of commissioning. Alternatively, since this is a time-consuming process involving a motorized water tank, if reference values are taken at the time of the commissioning of the depth of the 90% isodose using solid water, this method can be used as a constancy check. The calibration can be performed either in water or solid water. However, given the time constraints in the OR at an early hour, solid water calibration is recommended.

Annual Checks

A broader range of tests need to be performed annually. This requires using the water tank to measure the depth doses for a substantial portion of the clinical applicators. If there is a large inventory of such applicators then a fraction, say half, could be measured each year, alternating the following year with the other half. In either case, the resulting data should be compared carefully to the original commissioning data to ensure that no change has occurred. Applicator ratios for the same fraction of applicators should also be checked. Where applicable, primarily for conventional medical linear accelerators, dose rate and gantry angle dependence as well as dose linearity should be checked.

In the USA, according to TG51 [21], an annual calibration must be performed in water for each energy.

Mobile Linear Accelerators

Following acceptance testing performed according to the specifications of the manufacturer and commissioning measurements for beam characterization (see, for example, Tables I and II in [2]), a program of periodic checks must be applied to ensure that the performance of the treatment machine remains stable with time. Although, in principle, the QA program for mobile units used for IORT must follow general recommendations reported for medical linear accelerators, specific issues have to be added [9, 17, 24].

On the one hand, a QA program for mobile machines needs to take into account the relevant technical characteristics of the unit itself and differences with respect to a conventional, stationary linear accelerator, such as the lack of adjustable collimators or bending magnets. Moreover, the alignment of the soft-docking system represents a critical issue and must be checked regularly. On the other hand, from a radiation protection point of view, the use of the machine in an unshielded environment implies the need to limit the beam-on time as much as possible. Furthermore, the use of huge devices, such as a standard water phantom, in an operating room is often impractical. It is then advisable to define an efficient QA program, implying rapid procedures and dedicated instrumentation, like small size water phantoms, solid phantoms with holes for the ion chamber at two depths, dual

channel dosimeters and films. Another important issue concerns the decision when to perform daily checks: depending on the distribution of patient workload during the week, the reliability demonstrated by the machine and logistics, they can be done one day before clinical use or early in the morning of the day of treatment, to permit some degree of troubleshooting, if necessary. Detailed descriptions of the periodic tests specifically recommended for a mobile unit, including suggested methods, frequencies, and tolerance levels, can be found in various reports [9, 17, 24].

Treatment Documentation

IORT treatments are single fraction treatments with doses ranging from 10 to 20 Gy, hence the dose calculation has to be verified by a qualified medical physicist prior to initiating the treatment. The physics documentation for the dosimetry should include the following:

1. Name of patient.
2. Medical record number of patient.
3. Area of disease.
4. Names of personnel attending the procedure (radiation oncologist, surgeon, physicist, and radiation therapist).
5. Size and bevel angle of applicator.
6. Electron energy used (depth of prescribed dose).
7. Prescribed dose.
8. Percent isodose at which dose is prescribed.[5]
9. The output calibration for the prescribed energy for the day of treatment.
10. An inverse square law factor in case the applicator does not seat directly over the tissue to be irradiated.
11. Whether or not bolus was used and if so, was it removed after the irradiation.

The treatment shall also be recorded in the patient's chart or medical record and initialed by the radiation therapist or physicist operating the linear accelerator and the radiation oncologist prescribing the treatment.

There are some issues related to treatment documentation that are not covered by the descriptors noted above. Unlike EBRT, where complex technologies and accurate methods of treatment documentation, recording, and verification are quite developed, the situation in IORT still needs to be strongly improved. For example, in most cases, the answer to the problem of accurately reconstructing the irradiated volume in case of retreatment is still based on simple procedures, such as careful description of the treatment in the patient's chart, beam's-eye view photographs or fiber-optic imaging, use of surgical clips, hard copy of ultrasound images acquired just before the positioning of the electron applicator [24, 26]. More desirable, though less likely until IORT becomes much more widely practiced, is the use of in vivo imaging. An initial experience using a mobile C-arm X-ray unit for the verification of the applicator position by means of two orthogonal images, during IORT for prostate cancer, has been reported [27].

In Vivo Dosimetry Procedures

In EBRT, in vivo dosimetry nowadays represents a common practice of quality assurance performed as an overall check of the delivered dose to the patient and well-established procedures for entrance

[5] In the USA this is conventionally taken as 90%, but there are exceptions.

and exit dose measurement exist, typically using TLDs or silicon diodes. This may be less true in the USA because of reimbursement issues. In IORT, however, several technical difficulties appear to limit the feasibility and reliability of appropriate methods for an extensive implementation of in vivo dosimetry programs. The main problems are related to the choice of suitable detectors in terms of accuracy, real-time response, low field perturbation, directional independence, as well as reliability of measurements in a critical area, such as the surgical bed, where sterility has to be preserved [9, 28]. Nonetheless, in principle, there are several reasons to investigate the role of in vivo dosimetry in IORT: these include the single-shot nature of IORT itself, the lack of an individualized, image-based treatment plan and, in some circumstances, the usefulness of acquiring information on the dose to critical organs close to the tumor bed.

A number of papers published in the last years deal extensively with this issue and describe off-line procedures using radiochromic films, as well as real-time methods by means of MOSFET detectors [28–30], reporting an overall uncertainty of entrance and exit dose measurement estimated around 4%, mainly in breast cancer IORT. Promising results of in vivo dosimetry in the rectal and urethral lumen during IORT for locally advanced prostate cancer have also been reported [26, 27]. On the basis of these experiences, showing that suitable detectors for in vivo-dosimetry are available and related procedures feasible and reliable, it appears nowadays no more utopian at least to encourage centers delivering IORT to plan a strategy for the implementation of in vivo dosimetry.

Interaction with Surgeons in OR and Surgical Factors

Resection of the tumor and use of IORT to the area of risk is preferably not a single modality treatment, but is part of multimodality treatment [31]. The most important moment for the patient may be when the treating physicians recognize that an IORT containing multimodality treatment would be appropriate. It is obvious that discussion of a patient's management between the members of the treatment team must occur before any multimodality treatment starts.

Imaging and work-up of patients have changed drastically over the last decennium; multislice CT and MRI have developed as tools providing the surgeon with reliable preoperative, near anatomical information. Areas at risk during the surgical resection can be identified preoperatively.

If downsizing and downstaging occur as a result of neo-adjuvant treatment, it is often easier for the surgeon to achieve a radical resection, and responders to neo-adjuvant treatment often benefit from a better prognosis as a result of tumor downstaging. In the pursuit of more powerful downsizing and downstaging neo-adjuvant, treatment, however, toxicity has also increased. Whereas in the past, a moderate course of EBRT was used as neo-adjuvant treatment, nowadays concurrent chemotherapy is usually given during EBRT (CCRT). The increased toxicities related to neo-adjuvant CCRT may, however, increase surgical risks, i.e. when preop CCRT is combined with surgical resection and IORT, normal organ/tissue tolerance may be more limited, and the important regeneration processes a surgeon relies on may fail [32]. Resection in an area where tumor and normal tissue have been replaced by fibrotic tissue can be difficult and often has to follow extra-anatomical planes. For example, in cases of T4-tumors, structures outside these anatomical routes may be severed. Complications may range from perioperative bleeding, nerve damage, and even organ loss. The tissue resistance to infections may be diminished by the combination of EBRT, CCRT, and IORT. Otherwise innocent seroma accumulation, which can be dealt with in a healthy tissue environment, may lead to infections that can break down reconstructive surgical procedures. Presacral abscess formation can result in anastomotic leakage or disruption of vascular sutures.

Preventive measures can be taken by reducing empty spaces after surgery to avoid accumulation of seroma. In the pelvis, an omentoplasty can be used for this purpose. Alternatives to reduce empty spaces include vascularized transposition musculo-cutaneous flaps, which may be important in

patients with recurrent disease and prior EBRT, in which the new blood supply may improve postop healing. Vascularized muscle-cutaneous flaps can also be used for the reconstruction of an area with skin loss.

A completely new role for IORT exists for patients with limited metastatic disease, as identified by PET-CT or other imaging. In the past, metastatic disease was considered an absolute contra-indication for IORT-treatment. However, this paradigm has changed. The availability of more potent cancer drugs and the use of alternative administration routes, for example intraperitoneally, have led to full treatment with curative intent of patients with limited metastases. A patient with a limited number of liver metastases and a locally advanced rectal cancer may be treated with multidrug neo-adjuvant chemotherapy followed by CCRT, and, in case of a favorable response, resection with IORT may be an option. Another example is a patient with a locally advanced rectal cancer and pelvic peritoneal seeding. Such a patient may still be a candidate for resection after neo-adjuvant CCRT. This resection can be combined with hyperthermic intraperitoneal chemotherapy (HIPEC) and IORT followed by adjuvant chemotherapy. Identification and selection of patients that may be salvageable even in the presence of metastatic disease is a new challenge for the surgeon and the whole treating team. The surgeon and radiation oncologist are, by nature, interested in local–regional treatment, but together with the medical oncologist they can offer curative treatment plans to a new group of patients. These even more aggressive approaches, may, however, further increase perioperative morbidity and mortality.

In the operating theater, resection after neo-adjuvant chemo-radiation may be difficult. Consequently, identification of the area at risk for an IORT boost is also not always easy. Frozen sections have often to be taken to identify the most threatened area, in addition to the preoperative imaging information. It is mandatory that radiation oncologist and surgeon together in the operating room decide which area is to be irradiated with IORT. IORT is a very intense treatment to a very small treatment volume. Future developments could be navigation devices, which will transform preoperative imaging information into actual anatomical information during the surgery, to avoid mismatch of the IORT dose volume and the area at risk.

Another important aspect of surgery with IORT is the protection of radiosensitive structures that do not need to be irradiated. These structures may be shielded with lead sheets or may be dissected and moved out of the IORT-field which can easily be done with a structure like the ureter or noninvolved bowel. It is important that the radiation oncologist and surgeon define precisely all the normal tissues that remain within the IORT field. This may help to understand both acute postop complications as well as long-term toxicities (i.e., intestines may develop strictures, the stomach is prone to ulceration). Surgical anastomosis can have major postop complications and are preferably excluded. Ureters are relative sensitive to IORT, can often be moved out of the IORT field unless adherent to tumor, but may need to be stented if left in the field. The bile duct can also obstruct secondary to IORT, and stenting may be necessary. Large blood vessels may develop long-term stenoses, but they can usually sustain relatively large IORT doses without complications. Bone also can resist radiotherapy very well, but there is a chance of late bone necroses, which may be a problem in the follow-up period. Treatment of the spinal cord should either be avoided or limited to low dose by use of appropriate IOERT energies when used for midline tumors (pancreas, retroperitoneal sarcoma) or peri-aortic nodes [33, 34].

The use of IOERT poses different surgical problems than the use of HDR-IORT. The IOERT accelerator has limited mobility, which means that the patient has to be moved toward the accelerator and that applicator has to be brought in line with the area at risk. Sometimes, it is necessary to change the position of the patient. If the prostate capsule is the area at risk, the beam cannot be directed through the perineal wound in all patients and the patient may need to be turned from prone to spine position (i.e., with the Mobetron). The docking procedure in IOERT is a relatively straight forward procedure, and usually does not take too much time. In HDR-IORT, the irradiation time is much longer than in IOERT. Whereas an IOERT-treatment time is in the range of minutes, this can extend to an hour or more in HDR-IORT [35]. Anesthesiological surveillance systems need to be quite different for both types of treatment. In the latter, full remote control is necessary [36].

Anesthetic Factors

The administration of an IORT-dose does not have direct consequences for the anesthesiologist. However, the necessary logistics of delivering an IORT-dose interferes with the anesthesiological routine. In case of an operation in a dedicated radiation suite, all the necessary equipment has to be transported outside the operating theater. Depending on the physical distance between the radiation suite and the OR-complex, more or less items have to be replaced in order to be prepared for any incidents. From the anesthesiologist's point of view, a dedicated operating theater is a more convenient solution. The need for transportation is limited within the operating room. Change of position may disturb hemostatic stability of the patient, especially if the patient has to turn from prone to supine position. With IOERT, irradiation time is in the range of 3–5 min. Standard anesthesia equipment may be used if the anesthesiologist can closely monitor the patient with a closed circuit television system. There is no need for controlling gas insufflators or fluid pumps from a distance during the treatment time, quite contrary to HDR-IORT, where treatment time may be as long as an hour. In these cases, tele-monitoring as well as tele-controlling of the anesthesia equipment is required.

Furthermore, it is important that the anesthesiologist realizes that surgery with IORT is just one step in a sequence of multimodality treatments. Most of the patients present with locally advanced disease after neo-adjuvant treatment. This treatment may have weakened their general condition. Response of the cardiopulmonary system after chemotherapy to anesthesia may be different compared to healthy patients. Functional reserves may be less. Often cancer patients suffer from malnutrition and disturbed fluid intake. These patients sometimes are not in the optimal condition to undergo major surgery, and despite the fact that these adverse conditions may be corrected to some degree preoperatively, deficits may persist [37].

In some tumor resections, blood loss can be a real problem. For example, locally recurrent pelvic tumors infiltrating in venous plexus or major vessels are difficult to resect and resection can lead to major blood loss [38]. Blood preservation techniques, like delusion, antilogous blood transfusion or even cell saver techniques can be used to anticipate these preoperative complications. Operating time is prolonged, not only by the need of IORT, but also by the need of doing frozen sections, repositioning and of course by the magnitude of the surgical resection itself. Therefore, temperature has to be monitored very closely in these patients, receiving major amounts of intravenous fluid. Heated mattresses, warmed closed air circulation and heating infusion lines have to be used. However, if the anesthesiologist and surgeon discuss the expected procedure thoroughly, the anesthesiologist can prepare himself for the procedure and minimize the risk of the patient as in any major oncological surgery.

Applicator Selection and Intraoperative Shielding

When an institution is going to embark on the use of IOERT, a full set of treatment applicators must be made available with full physics calibration. The exact applicators to be used depend on the tumors to be treated at that institution. It is essential that a large variety is available because even one tumor type requires many different sizes for adequate treatment. For the treatment of tumors that are commonly irradiated (rectal cancer with pelvic sidewall or sacral involvement, pancreas, bile duct, gastric bed, and abdominal or pelvic lymph node diseases), we recommend a wide assortment of applicators. As a minimum, round applicators should be available at 6, 7, 8, and 9 cm both with no bevel on the edge of the applicator and with a 15° and 30° for each of the nominal applicator diameters (Fig. 3.7a). Small diameter applicators of 3 and 4 cm are sometimes used, but have a more limited application. For the treatment of some pancreatic tumors and for intra-abdominal tumors, such as gastric carcinoma, retroperitoneal sarcomas, and colonic tumors, either rectangular or

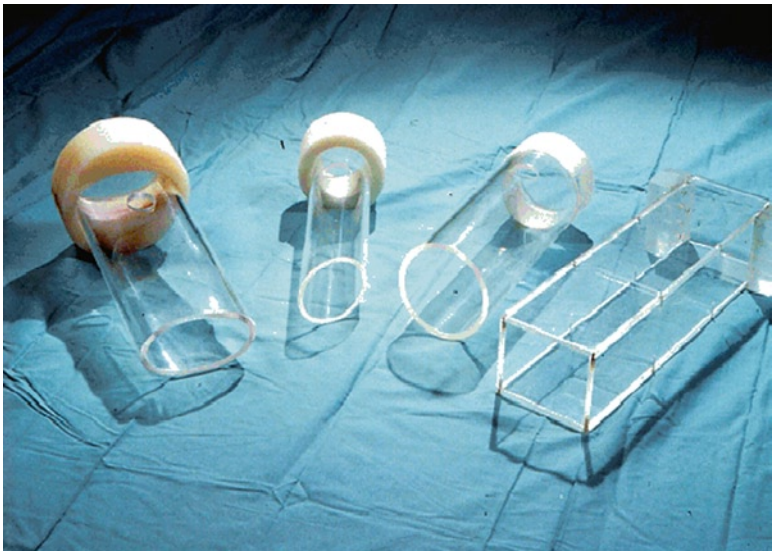

Fig. 3.7 Applicators of different shapes.

elliptical applicators should be available. Elliptical applicators of 7×9, 7×12, 9×12, 8×15, and 8×20 cm have been very helpful for both abdominal and extremity cases, and are easier to position than rectangular ones (Fig. 3.7). The NCI had an applicator called the "squircle" which has one end circular and the other end rectangular. This simplifies the problem of field abutment in patients who require more than one IOERT field.

At the time of surgery, the tumor volume (tumor bed after resection or unresectable tumor) to be irradiated is defined by the surgeon and radiation oncologist and marking sutures are placed around the perimeter of the lesion. An applicator is then selected that encompasses the tumor bed, usually with a 1-cm margin. A margin of at least 1 cm is optimal to allow for both dose and tumor variability. When visualizing the tumor or tumor bed through the applicator, the marking clips or sutures should be readily identified well within the perimeter of the applicator, thus ensuring adequate coverage of the tumor volume.

If an applicator with a bevel is used, it is easy to overestimate the beam coverage toward the heel of the bevel (depth of penetration is less at heel vs. toe end of beveled applicator) (Fig. 3.8). Because tissues directly below the heel may be underdosed, the treatment cylinder must be carefully placed. In addition, the bevel decreases the total beam penetration from what would be obtained without a bevel.

Although the IOERT applicator can often function adequately as a normal tissue retractor to hold sensitive normal structures out of the IOERT field, patient respiration or spontaneous movement of the bowel can allow normal tissues to move under the applicator and insinuate themselves inside the IOERT field. The applicator must be observed to confirm that this is not occurring. If there is evidence that bowel or other normal tissues slip into the IOERT field, surgical packing must be used to hold them out of the way. It is important that the packing itself does not enter into the field as this decreases the electron-beam penetration, resulting in underdosage of a portion of the tumor volume.

There are certain situations in which normal tissues cannot be physically moved out of the radiation field. Thus, it is essential that a technique be available for secondary shielding. Standard lead sheets, which can be cut to the appropriate shape, should be available and an appropriate number used to attenuate 90% of the radiation beam. The lead is covered with saline-soaked gauze and placed over the normal tissues. Lead shielding is often essential if abutting IOERT fields are to be used. Other methods for secondary collimation may be employed, but this method has been found to be effective.

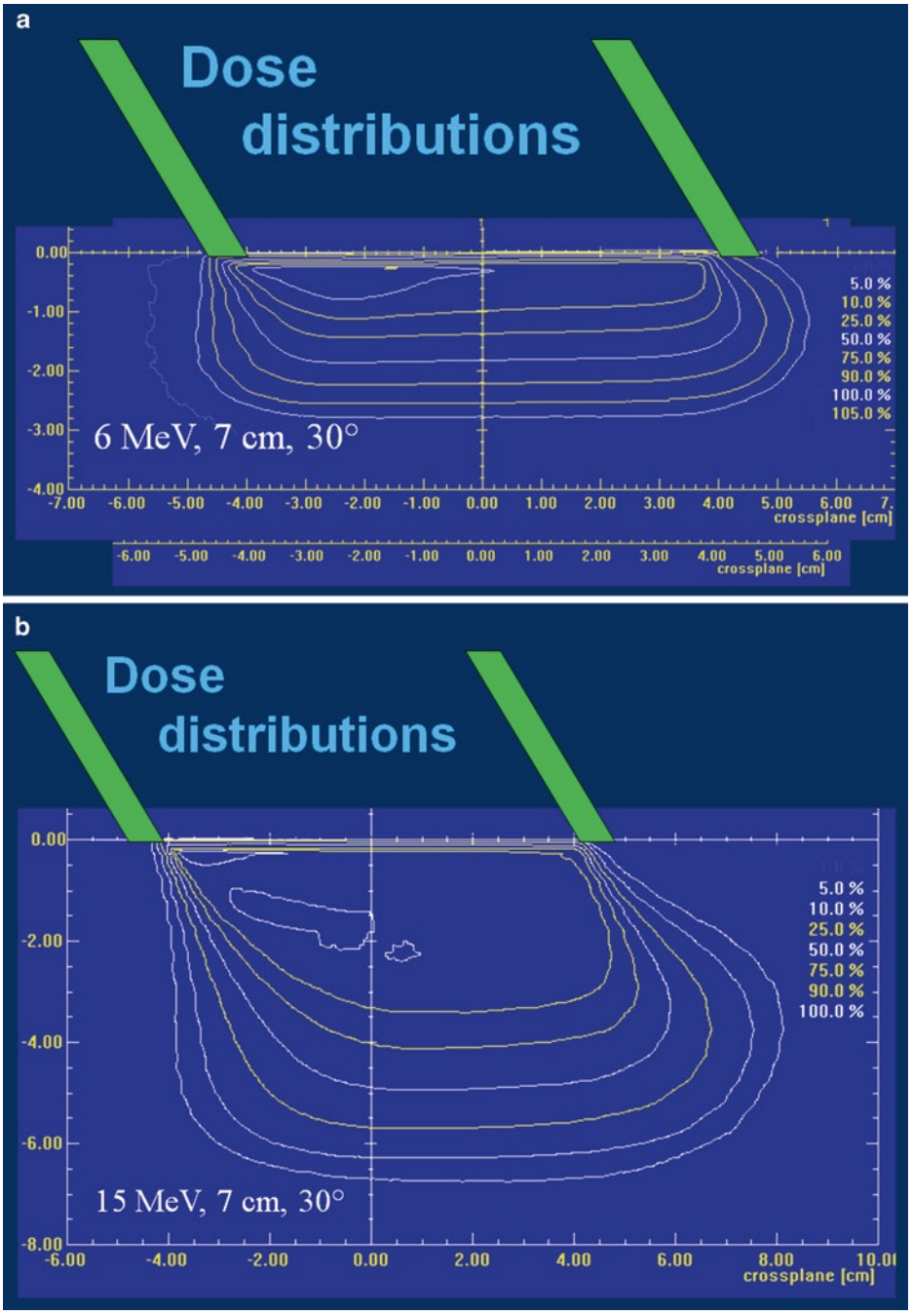

Fig. 3.8 Dosimetry of 7 cm circular applicators with 30 degree bevel angle at 6 (**a**) and 15 Mev (**b**).

Two-layer metal attenuation plates are used in IOERT for breast cancer patients (in select institutions using IOERT as the sole method of irradiation instead of a boost dose combined with EBRT) to protect normal tissue posterior to the residual mammary gland. Several combinations of materials and thicknesses have been tested and used worldwide so far: for example, in Milan, disks made of lead (2–4 mm thickness) plus aluminum (4 mm) have been used since 1999 on more than 4,000 patients,

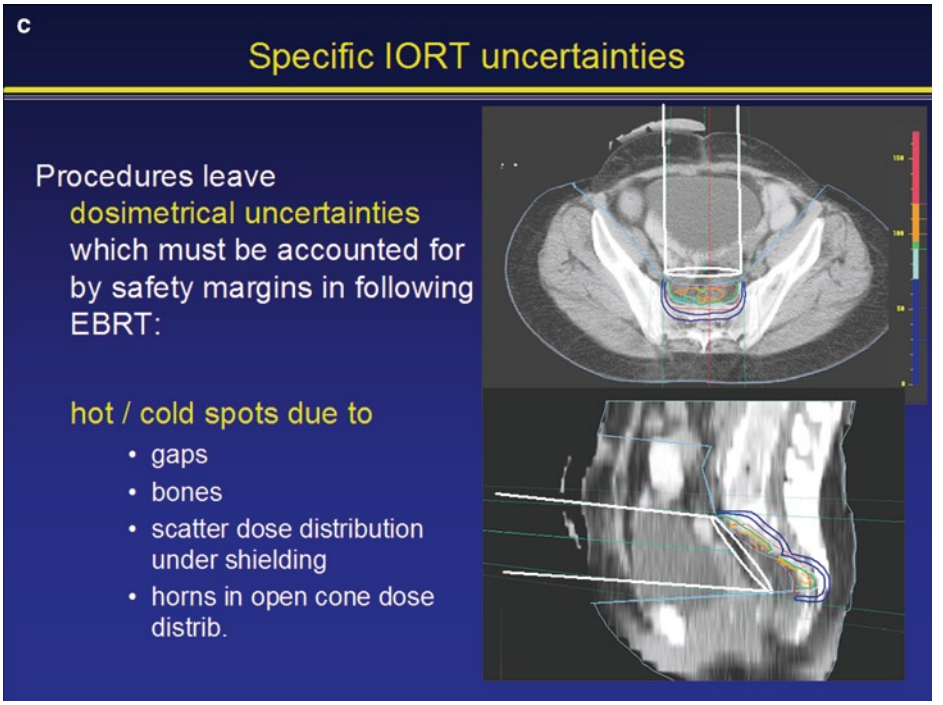

Fig. 3.8 (continued) (**c**) Dosimetric uncertainties/hot and cold spots must be accounted for in choice of applicator and electron energies.

while in Trento, copper (3 mm) plus aluminum (6 mm) plates are used [18, 39]. In principle, the first layer (i.e., the one facing the radiation beam) should be composed of a low-Z material to stop low-energy electron backscatter from the second layer, which vice-versa should be made of a high-Z substance to completely stop the electron beam. Detailed analyses of metal and PMMA plates, based on Monte Carlo simulations and experimental data, have been recently reported [39, 40].

Energy and Dose vs. Residual Disease, Fluid Accumulation, Critical Structures

IOERT is currently utilized as a component of a comprehensive treatment program of pre- or post-operative EBRT (45–54 Gy in 25–28 fractions) usually with concurrent chemotherapy and surgery (maximal resection) for a locally advanced malignancy. Because most patients have received a course of full-dose preoperative EBRT, IOERT doses are usually in the range of 7.5–20 Gy.

IORT dose and electron energy are dependent on the amount of residual tumor remaining after maximal resection and the dose of EBRT that can be given as a component of treatment. IOERT doses in most institutions are quoted at the 90% isodose line and D_{max} as recommended by the NCI IORT working group guidelines. Electron energies are chosen so that the 90% depth dose encompasses the maximum thickness of any residual or unresectable tumor. After gross total resection, energies of 6 and 9 MeV are commonly used with or without surface bolus (with bolus to improve surface dose, if necessary).

Guidelines recommended for previously unirradiated patients are as follows for doses at the 90% isodose line: resection margin negative but narrow (R0), 7.5–10 Gy; margin microscopically positive

(R1), 10–12.5 Gy; gross residual (R2) or unresected disease, 15–20 Gy. Doses of 20 Gy or higher are preferably not utilized unless there have been limitations of delivery of EBRT, as in previously irradiated patients.

One of the major problems that can occur during the actual delivery of the IORT is a build-up of fluid in the field. This is especially a problem in dependent areas, such as the posterior portion of the pelvis, when relatively low electron energies are employed. Accumulation of 1.0–1.5 cm. of fluid decreases the beam penetration by an equivalent amount and may result in underdosing of tissues at risk for tumor involvement. Therefore, suction always needs to be available at the time of the IORT procedure. It is usually adequate to place the suction on the outside of the base of the treatment applicator. However, if the most dependent area is in the center of the applicator, an alternative suction device, such as the Micromat, may have to be considered.

Conclusions

Technical developments in the field of IORT continue apace. The field has moved completely away from conventional linear accelerators, in the sense that none are purchased specifically for IORT, in the direction of mobile, electron-only, low energy linear accelerators. There are currently three manufacturers in this field. Undoubtedly, this has been spurred on by their utility in the treatment of breast cancer through the ELIOT [41] trial. Noteworthy developments from the technical standpoint are a better understanding of the dosimetry of high dose per pulse machines (Novac7 and LIAC) and a realization that electron energies up to 12 MeV can be used in an unshielded OR because the neutron background is sufficiently low.

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Chapter 4
HDR-IORT: Physics and Techniques

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Keywords Physics of HDR-IORT • HDR-IORT techniques • OR shielding for HDR-IORT

Introduction

Intraoperative irradiation using a high dose-rate remote afterloader [1–3] (HDR-IORT) employs the technical and dosimetric advantages of brachytherapy to deliver a large single fraction of irradiation of the target area, while avoiding the surrounding normal tissues.

The high activity source afforded by remote afterloading in a shielded room results in clinical treatment times of about 15–60 min, which enables treatment during a surgical procedure. Treating during a surgical procedure enables retraction and physical shielding of adjacent structures, leading to lower doses to normal tissue. The therapeutic ratio is therefore significantly enhanced because the normal tissue dose is minimized while the tumor dose is quite high. These advantages may substantially offset the radiobiological disadvantage associated with a single-fraction treatment. The entire procedure takes place in a full service, shielded operating room, requiring no intraoperative patient transport.

The HDR-IORT technique is feasible only after near gross total resection can be accomplished. The maximum depth of coverage after maximal resection is typically 0.5 cm deep from the surface of the tumor on the basis of depth-dose factors. Therefore, the use of HDR-IORT is best suited in situations for which an oncologic resection is anticipated. It must be emphasized that this entire program is a coordinated effort between the surgical oncology, radiation oncology, and reconstructive teams.

Characteristics of HDR Remote Afterloaders

The HDR afterloader consists of a small, high activity source attached to a thin cable. The position of the source and the amount of time it spends at each position ("dwell time") are computer controlled; the desired dose distribution is generated by superimposing a large number of single-source radiation distributions at different locations and dwell times.

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_4,

Since its introduction more than 30 years ago, high dose-rate remote afterloading with a single ^{192}Ir source has become a prominent brachytherapy modality. The afterloader eliminates radiation exposure to staff and facilitates treatment plan optimization by permitting a variable dwell time at each source location. At the same time, the potential for harm to both patients and staff from an uncontrolled source is such that a high level of precaution is necessary in all aspects of facility and machine maintenance on the one hand and treatment planning and delivery on the other.

Design and Dosimetry

The concept of afterloading in brachytherapy was introduced in 1960 [4]. A single radioactive source is kept in a shielded safe, and travels through catheters into a patient applicator after the staff leaves the room. The source is software-driven using a motor [5]. Dwell times could be programmed to the nearest tenth of a second at 1 mm increments along a 20-cm treatment catheter. Dwell times are generally entered for a nominal activity, and the software adjusts the time to reflect source decay. A source indexer provides for an automated delivery of multiple catheters.

The ideal source energy must be sufficiently high to avoid local necrosis, yet low enough to protect distant healthy tissue. Furthermore, sources must be able to deliver a high dose rate, pass through narrow lumen, and negotiate sharp turns. The isotope of choice must therefore be able to contain high activity within a small volume or have a high specific activity. Balancing the needs for suitable energy, high specific activity, and reasonably long half-life, one arrives at the radionuclide ^{192}Ir.

^{192}Ir decays via β^- or electron capture, and the daughter isotopes emit γ-rays of various energies. Since the excited states of the daughter isotopes are short lived, ^{192}Ir and its daughters are in secular equilibrium. The beta decay is absorbed by the source capsule. The average energy of the emitted photons is 370 keV with a 73.8 days half-life. Recently, ^{169}Yb became commercially available [6], with a lower shielding requirement due to an average energy of 93 keV. However, the logistical feasibility of a 32 days half-life and the clinical impact of this energy on tissue necrosis need to be evaluated.

Dose calculation is based on the AAPM TG-43 formalism [7, 8]. The dose rate to water is defined as

$$D'(r,\theta) = S_k \Lambda \frac{G(r,\theta)}{G(r_o,\theta_o)} g(r) F(r,\theta),$$

where S_k, the Air Kerma Strength of the source must be measured, while the remaining terms can be obtained from "consensus datasets," published in peer-reviewed publications [9]. The consensus datasets are manufacture-specific since they vary with source design. Recent treatment planning software is capable of accommodating the TG-43 formalism, but older planning software might still use exposure rate or apparent activity, in which case extreme care must be taken to use consistent values of conversion coefficients. Accurate dose calculation therefore depends on applying the proper consensus dataset, but using an air kerma rate constant of 4.03 U/mCi, a 10 Ci source of ^{192}Ir would deliver dose to air 1 cm away at a rate of 672 cGy/min (or 752 cGy/min to water using a dose-rate constant of 1.12 cGy/U).

The TG-43 formalism calculates dose in an infinite water medium, ignoring heterogeneities, which is acceptable because imaging is limited in HDR-IORT applications and complete applicator geometry is often lacking. However, some treatment planning systems incorporate simple corrections for shielded applicators [10].

Accurate dose calculation also depends on obtaining the proper strength of each new source. Although the manufacturers supply calibration certificates for new HDR sources, the American

Table 4.1 Characteristics of currently used high dose-rate remote afterloaders

Manufacturer	Varian Medical Systems	Varian Medical Systems	Nucletron	Nucletron
Afterloader	GammaMed*plus* (iX and 3/24 iX)	VariSource iX	microSelectron	Flexitron
Number of channels	3 or 24	20	18	40
Number of dwell positions per channel	60	60	48	401
Step size	1–10 mm in 1 mm increments	2–99 mm in 1 mm increments	2.5, 5.0, 10.0 mm	1.0 mm
Min. dwell time	0.1 second (s)	0.1 s	0.1 s	0.1 s
Max. dwell time	999.9 s	999.9 s	999.9 s	999.9 s
Direction of travel	Source travels to distal position then steps back	Source travels to distal position then steps back	Forward	Forward
Source travel	71 → 130 cm	70 → 150 cm	150 cm	140 cm
Source mechanical life	5,000 transfers	1,000 transfers	25,000 transfers	30,000 transfers
Safe construction	Tungsten	Tungsten	Tungsten	Tungsten
Maximum source strength	15 Ci	11 Ci	14 Ci	22 Ci
Source active length	3.5 mm	5 mm	3.6 mm	3.5 mm
Source diameter	0.6 mm	0.34 mm	0.6 mm	0.6 mm
Wire/cable diameter	0.9 mm	0.59 mm	0.9 mm	0.85 mm

Association of Physicists in Medicine (AAPM) task group 40 (TG-40) and state regulations mandate institutions to independently verify source strength [11]. S_k may be measured using either an in-air [12] or a well chamber [13] calibration. A well chamber calibration is generally simpler to measure and calculate and is therefore more routinely used. Well chambers could also be directly calibrated at the ^{192}Ir energy spectrum by the Accredited Dosimetry Calibration Laboratories (ADCLs), which offer a National Institute of Standards and Technology (NIST) traceable calibration. Independent verification of the source strength is obtained by comparing the derived source strength with the manufacturer's certificate.

The ^{192}Ir HDR remote afterloaders currently marketed in the USA are the microSelectron and Flexitron (Nucletron, Veenendaal, The Netherlands), the GammaMedplus, and the VariSource (Varian Medical Systems, Crowley, England). A detailed description of their characteristics has been published [14]. Machine specifications are summarized in Table 4.1.

A longitudinal cross section of the Nucletron source used with the microSelectron® afterloader is shown in Fig. 4.1. The dimensions of the microSelectron and Flexitron sources are similar to those of the GammaMedplus, while the VariSource source is longer and thinner, but with roughly the same active volume.

Afterloader Safety Features

Safety features have been developed to protect the general public from inappropriate use of the source, and to prevent unnecessary exposure to staff and patient. To prevent unauthorized use, extending the source out of the afterloader safe requires a mechanical key and a password. Additionally, the afterloader unit should be secured in a locked cabinet when not in use. Preventing unnecessary staff and patient exposure is addressed by automatic retraction of the source when all dwell positions have been treated, when detecting resistance in a guide tube (potentially due to obstruction), when opening the treatment room door, and when pressing either the interrupt or emergency switches. The interrupt button, mounted on the console, interrupts treatment for routine

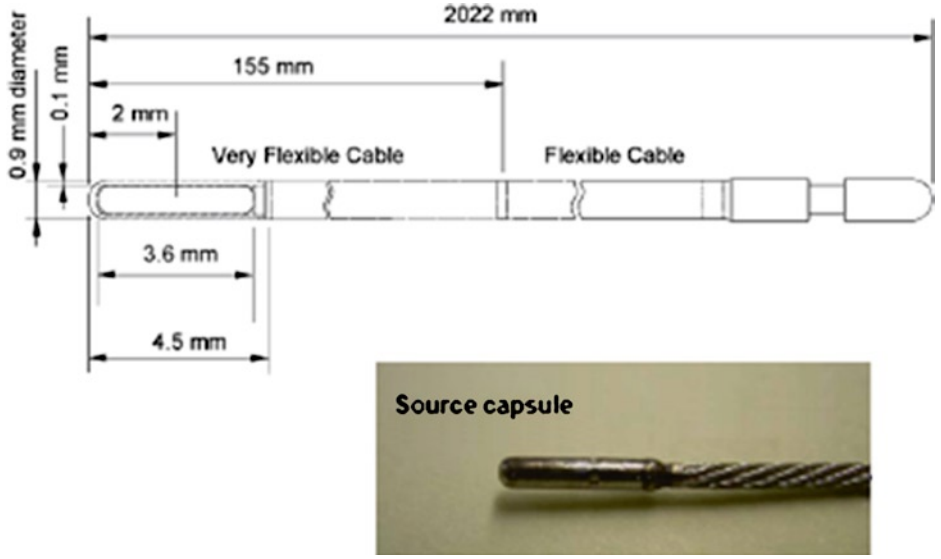

Fig. 4.1 ^{192}Ir source in stainless steel capsule, which is welded to a stainless steel cable.

use such as allowing the anesthesiologist to enter the room. The emergency switches are mounted on the console, on the wall near the door, and on the afterloader itself. The emergency switch activates an independent, more powerful, emergency motor and requires the use of the emergency reset key to continue treatment. An illuminated radiation sign is also useful and is often mandated by state regulations.

Patient and staff exposure is also avoided by preceding source extension with a check cable extension to verify that the planned travel path is unobstructed and of sufficient length. Source extension is also prevented when a source guide tube is not connected to the proper channel, an indexer is disengaged, the source key lock is disabled, or the treatment-room door is open. The afterloader has rechargeable batteries designed to assure safe operation in the event of a power failure, but electricity should also be provided via an uninterruptable power source. Should the power still fail, the source can be retracted manually. Radiation detectors in the afterloader and elsewhere in the operating room activate visual and audible signals when the source is extended, allowing staff to check that a given treatment is proceeding as expected and, in an emergency, to determine if measures to reshield the source have been successful.

Construction and Shielding Considerations

Constructing a HDR-IORT facility requires satisfying unique surgical, anesthesia, and shielding requirements, which usually means existing HDR or OR facilities cannot be easily converted into an HDR-IORT facility. Construction of a dedicated facility [15] inside the main OR complex allows for efficient utilization of staff and instruments, and reduces logistical issues in transferring the patient to the Recovery Room and the Surgical ICU.

The shielded operating room must be equipped with door interlocks, room radiation monitor, and an audio-visual monitoring system. The afterloader as well as all monitoring equipment must have a backup power supply such as the hospital emergency generator.

Accommodations must be made for the entire operating room personnel, who must wait outside the room during treatment but remain sterile in case emergency re-entry is required. In addition to

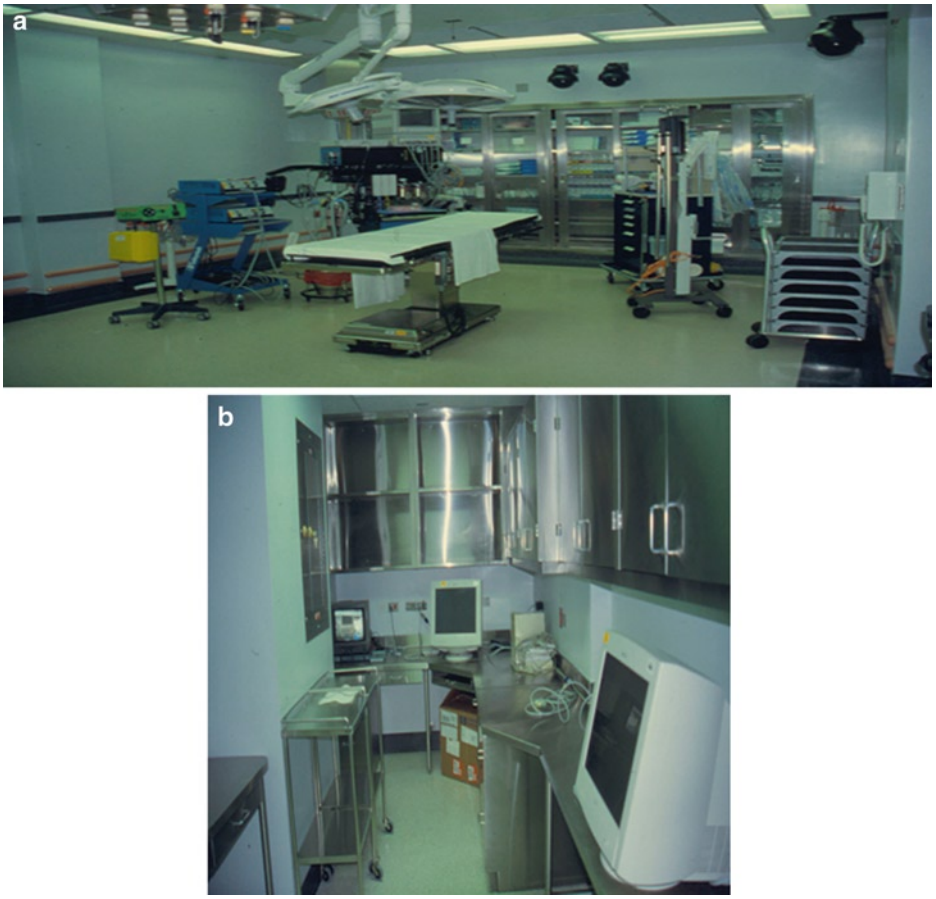

Fig. 4.2 (**a**) View of the operating room that is fully lined with lead shielding. Seven cameras are in place throughout the room including one within the handle of the OR light to monitor the immobilization of the applicator and observe entry of the source into the applicator. (**b**) The surgical team, anesthesiologist, and radiation oncology team assemble in an adjacent room outside of the OR while the IORT is delivered.

physical space, anesthesia and surgical monitors must be duplicated outside the operating room, as shown in Fig. 4.2. An additional video camera should monitor the operative field, packing, and treatment progress.

Shielding design should generally follow the formalism outlined in Report No. 49 of the National Council on Radiation Protection and Measurements (NCRP) [16], as well as the "As Low As Reasonable Achievable" (ALARA) principle [17]. The shielding barrier transmission factor B can be calculated using

$$B = \frac{P \cdot d^2}{W \cdot T},$$

where P is the desired radiation protection level, d the distance between the HDR source and the location to be protected, W the workload, and T the occupancy factor. The maximum dose rate is derived using the same expression but with $T = 1$. NCRP-49 provides tables and graphs to convert the barrier transmission factor into barrier thickness for various materials.

Dose limits should also be ascertained in the relevant state or NRC regulations. Using NCRP-116 recommendations [18], unrestricted areas, occupied by nonradiation workers, have a maximum annual permissible dose limit of 1 mSv (100 mrem), while the dose in any 1 h must be below 0.02 mSv (2 mrem). The higher annual dose limit of 50 mSv (5,000 mrem) for restricted areas,

occupied by radiation workers, is generally not applicable to the OR staff. New facilities should reduce these dose limits by a factor of 10 in anticipation of potential future reductions in regulatory dose limits [17]. These limits are typically satisfied by shielding the walls with concrete, and the doors with lead. The additional lead weight necessitates a motorized door.

Dose Delivery

The irradiation process consists of identifying the target, securing an applicator, retrieving a plan, reviewing the plan independently, and irradiating the tumor bed. The applicator is needed to place the source at a fixed geometry with respect to the tumor bed, yet conform to the tumor bed curvature. The microscopic nature of the target, the inability to transfer the patient, and the multiple metal objects routinely attached to or close to the patient render imaging both logistically difficult and ineffective. The lack of imaging and the compressed timeframe of the intraoperative environment can be addressed using a precalculated treatment plan atlas together with an applicator.

Applicator Design

Generally, the applicator must be sufficiently rigid to secure the catheters in a fixed and reproducible manner during the irradiation, yet sufficiently flexible to conform to the tumor bed. Although a thinner applicator would be more flexible, the resulting shorter source-surface distance could lead to tissue necrosis [15]. On the other hand, thicker applicators, or a longer source-target distance, result in longer irradiation time.

Applicators could be created using Delrin® (a DuPont trademark) or Silastic® (the Dow Corning trademark for a particular silicone material) [1, 2, 15, 19, 20], but their relative stiffness necessitates anatomy-specific applicators.

At Beth Israel Medical Center, we chose to work with a silicone-based applicator, which is transparent and flexible [21]. The Harrison–Anderson–Mick (HAM) applicator [1, 2] (Mick Radio-Nuclear Instruments, Inc., Bronx, NY) is shown in Fig. 4.3. The applicator is precut to specific sizes. Source guide tubes are incorporated into the applicator pad and are 5 mm from the surface of the applicator. Flexibility is enhanced by adding surface grooves and by reducing the applicator

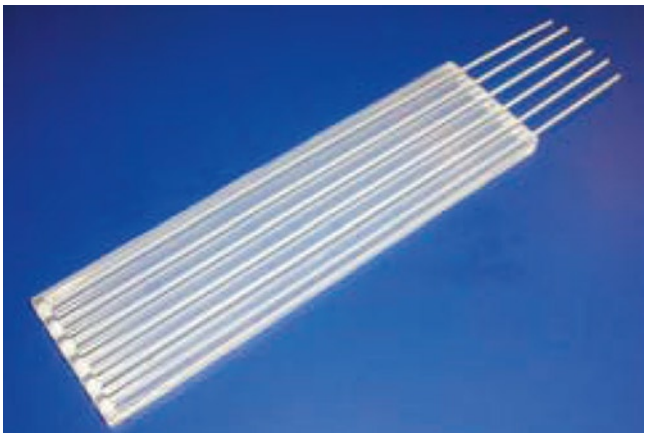

Fig. 4.3 Silicone mold "Harrison–Anderson–Mick applicator" (HAM) applicator with embedded catheters.

thickness to 0.8 cm, while retaining the 0.5 cm distance between source plane and treatment surface. Clear labeling of the "thin" side is required to ensure it is not used as the treatment surface. The applicator bends and contours to any surface within the pelvis, abdomen, or chest, thus becoming an intraoperative surface mold. Treatment is customized as any size rectangular field can be used.

Prescribing and Treatment Planning

Since a typical HDR-IORT radiation target contains only microscopic remains of tumor, the dose is generally prescribed at the center of the irradiated area to 0.5 cm depth. Dwell times for all source positions can be kept constant, calculated to deliver the desired dose at the center of the target [20], but yielding a lower dose at the peripheries. Dwell times at each position can also be optimized to achieve a uniform dose to the prescription depth plane [2].

Plans incorporating optimized dwell times are most effective in the form of a plan atlas, which expedites the treatment process and diminishes the probability of making an error. The atlas can be generated by creating and storing as many plans as might be clinically anticipated. For example, at Beth Israel Medical Center, the atlas covers active areas 2 cm × 2 cm (3 × 3 source positions) to 35 cm × 19 cm (36 × 20 source positions). Nucletron's Plato treatment planning system [10] was used with distance optimization and a dwell time gradient of 0.50. Dose points were generated 1 cm below each active dwell position (0.5 cm from the applicator surface), and the dwell weights were optimized to deliver a nominal 10 Gy uniformly at these points. Caution should be exercised when optimizing a specific plane's uniformity, as the more uniform the dose is forced to be in one plane, the bigger the differences in other planes. The dwell times can be rescaled to deliver any dose, but changing the prescription depth requires a recalculation of the plan. It is possible to incorporate applicator curvature [22], but the merit of correction should be weighted against the lack of imaging and the possibility of using an inappropriate curvature. Although planning using a plan atlas does not accommodate organ sparing, critical structures are often physically shielded using lead disks, available in a variety of shapes and sizes (see Figs. 4.4 and 4.5). These disks are approximately 3 mm thick and can be manually shaped to a desired curvature.

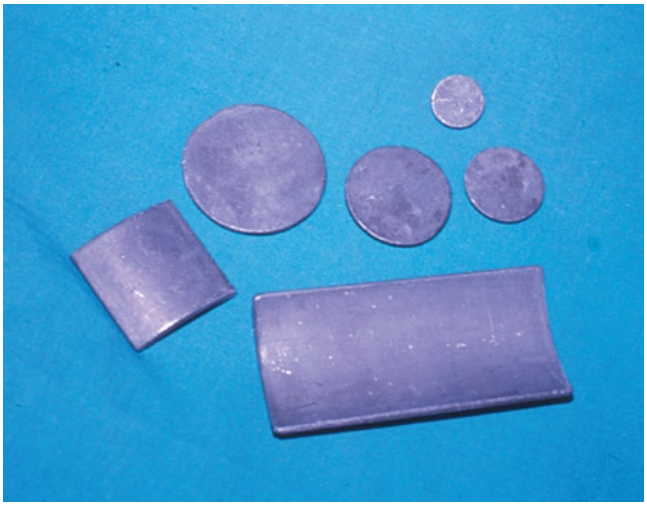

Fig. 4.4 Lead discs of various shapes, sizes, and curvatures can be used to protect normal tissue.

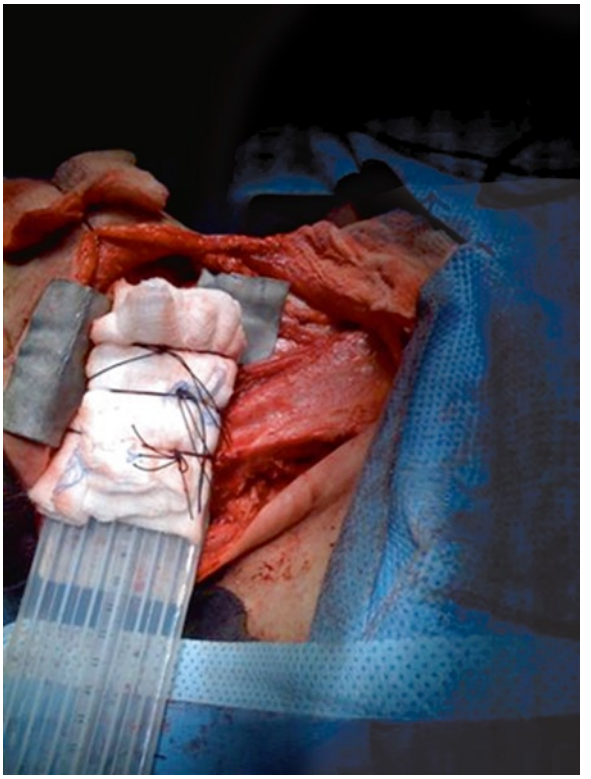

Fig. 4.5 HAM applicator sutured in treatment position. Lead shields are used to protect the skin, *on the left*, and the carotid artery, *on the right*.

Dose Delivery Quality Assurance

The HDR quality assurance program generally follows the guidelines discussed in the various AAPM task group reports [23, 24], although state or NRC regulations should be consulted to determine the afterloader Quality Assurance (QA) procedures required. The following discussion focuses on additional QA tests relevant to HDR-IORT.

Upon receipt from the vendor, each new HAM applicator is visually inspected to verify that it is firmly connected, the catheters are parallel, and there are no visible defects. The afterloader check-source cable is then used to confirm each channel has an unobstructed path and the proper length. New transfer tubes are similarly inspected for unobstructed path, having a proper length, and proper operation using the afterloader check-source.

Twenty four hours prior to each HDR-IORT procedure, a series of QA checks must be performed with the afterloader unit in the OR. The QA checks include verifying proper operation of the room radiation monitors as well as the corresponding illuminated "Radiation" door indicator, the console lights and buzzer. In addition, it is verified that the source will not project unless a guide tube is properly connected or if the treatment room door is open. If extended, the source will retract when the door is opened and when the interrupt or emergency buttons are actuated. Afterloader source positioning accuracy is checked using a radiographic film in a dedicated phantom [25], and the decayed source strength is confirmed using a manual calculation. The QA procedure also confirms the functionality of the patient audio-visual monitoring system and the availability of a calibrated and functioning survey meter. Finally, the availability of a source container, long forceps, and wire cutters is confirmed to handle emergency source retraction. This QA can either be performed the night before or the morning of a HDR-IORT procedure. Since surgical HDR-IORT preparations typically start at 7 AM, the physics staff generally prefers to perform the QA on the evening preceding the HDR-IORT procedure.

During the procedure, once a plan is retrieved, plan correlation with the physician's intent, proper data entry and source decay correction are reviewed by a second physicist. The physicist then verbally confirms target size, dose, depth, and initial position with the radiation oncologist.

Clinical Workflow

After the surgeon completes the resection, the area to be treated with HDR-IORT is delineated jointly by the surgeon and the radiation oncologist. Adequate margins are placed around the surface to allow for proper anatomic coverage and to include the periphery where microscopic disease may surround the dimensions of the tumor bed. The HAM applicator is then placed onto the appropriate surface and is fixed in place with proper packing or sutures (Figs. 4.5 and 4.6). It is important to confirm that the applicator is in contact with the tissue surface throughout the entire target area and for the entire treatment time, as a 0.5 cm separation can result in a 30% dose reduction [3]. To aid in the protection of normal tissues/organs, packing to maximally displace normal organs or tissues from the field is recommended. In situations where the adjacent normal structures cannot be moved away, intraoperative lead disks have been prepared. These disks have proven particularly useful to protect anastomotic edges during HDR-IORT such as the primary anastomosis of the distal rectum

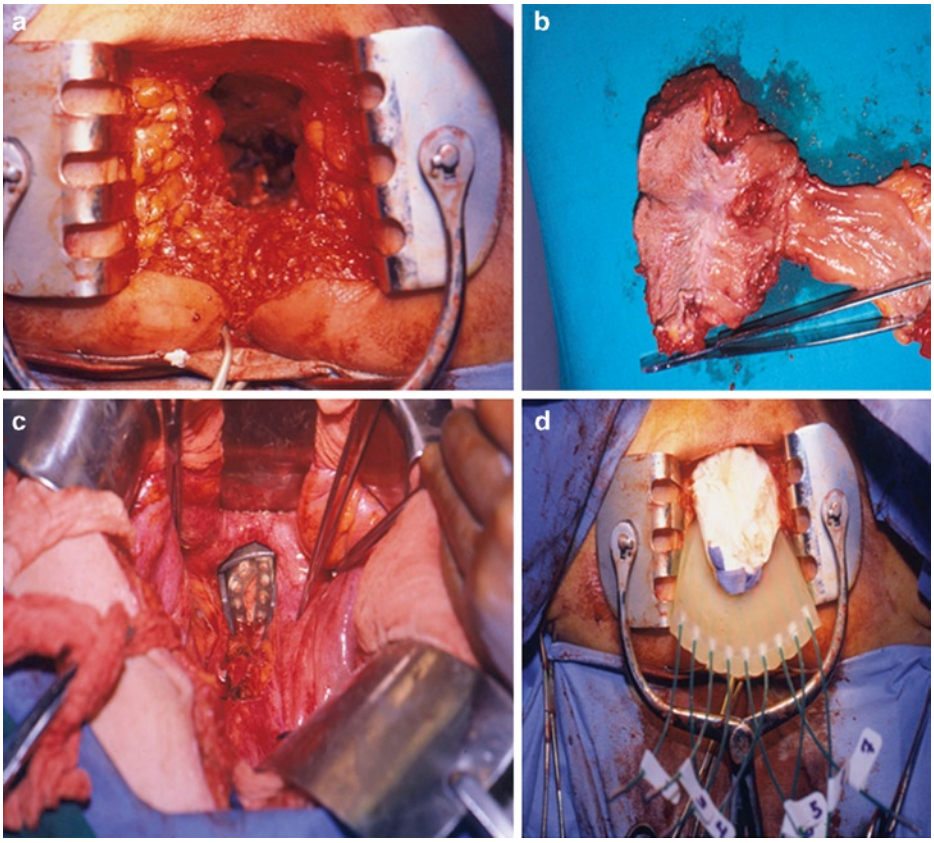

Fig. 4.6 The operative field is visualized after an abdominal perineal resection is performed (**a**) with the distal rectal tumor specimen removed (**b**). The superior view from the pelvis is seen with lead shields in place with packing. Retractors displace the bladder and bowel away from the field. (**c**) The distal view is seen with the applicator exiting the patient. (**d**) Packing is placed to move the anterior portion of the surgical bed away.

after an anterior resection. Other uses include protecting the ureter, peripheral nerves such as the vagus nerve, major vessels such as the carotid artery, or an extraneous loop of bowel that cannot be moved far enough away from the treatment field for the inverse square law to provide protection.

The single dose range of HDR-IORT delivered following gross total resection is 10–20 Gy. When choosing a specific dose, the radiation oncologist must weigh prior radiation therapy, pathology, surgical margins, intent to deliver further external beam therapy, the proximity of critical structures and whether reconstruction with previously unirradiated flap tissue will be performed to insure optimal healing. Typical doses prescribed are 10–12.5 Gy in the primary setting in which negative margins have been achieved, while 15–17.5 Gy is considered in patients with recurrent tumors who have positive margins.

Once the dimensions of the target area, prescription depth, dose, and initial position have been specified, the plan is retrieved from a plan atlas. The precalculated plan, defined at 10 Gy and 10 Ci, automatically adjusts for the current decayed source strength. The plan is then reviewed independently by another physicist as discussed above. The HAM applicator is then connected to the high dose-rate remote afterloader using source guide cables.

Since the entire staff must leave the room during the HDR-IORT delivery, remote patient monitoring is provided for the anesthesiologist and surgeon. At this point, the physicist reviews the treatment plan and dose distribution with the radiation oncologist. The Radiation Oncologist, who must be an authorized user listed in the institutional license, physically enables the "start treatment" button. Both the radiation oncologist and physicist continuously monitor treatment progression. The radiation oncologist must monitor the operative field, packing, and irradiated area, observing the applicator and its connection to the source guide tube. The physicist monitors the source traveling in and out of each tube, both visually and using the afterloader software. Any inappropriate connection, disruption of the applicator, or movement of the brachytherapy system would be observed, and can be rapidly corrected. In such an event, the source would be retracted and the door to the operating room opened. The room can be entered within seconds, any type of problem corrected, and the treatment immediately resumed. The same process would be followed if there were any bleeding or other problems in the surgical field, or for any urgent problem that requires the attention of the anesthesiologist. In practice, it has been uncommon for the room to be entered during the treatment.

Once the HDR-IORT treatment is completed, the physicist surveys the room to ensure the source has retracted. The guide tubes are disconnected from the remote afterloader and the applicator is removed. At this point, the surgical team can complete the operative procedure and close the patient.

Emergencies

Emergencies rarely occur, but treatment team members should be thoroughly familiar with their responsibilities, and rehearse their roles annually. The emergency procedures as well as contact information for both technical support and the institution's radiation safety officer (RSO) should be posted prominently. The emergency source retraction instructions should list possible retraction paths in order of increasing staff exposure. At Beth Israel Medical Center, for example, the physicist should be cognizant of the radiation level following a source retraction. If the source fails to retract, the physicist activates the emergency switch outside the room. If retraction still fails, the physicist must enter the room and activate the afterloader's own emergency switch. The next step would require manual retraction of the source using a crank. In the event that the survey meter or the room radiation detectors indicate the source is still outside the afterloader safe, the radiation oncologist

must remove the applicator into an emergency container using long forceps and, if necessary, wire cutters. The entire retraction procedure should be timed and the participants' personal dosimeters must be processed immediately afterwards.

Conclusions and Future Possibilities

The HDR remote afterloader with its small source and indexer, have rendered HDR-IORT brachytherapy feasible and versatile. The use of a semirigid applicator and plan atlas was found to be suitable for most clinical cases, as long as good contact with the tissue surface is confirmed. Early treatment results with colorectal cancer [1, 2, 26] are consistent with other data using electron beam IORT [27, 28]. This approach may have certain technical, dosimetric, and logistic advantages over a linear accelerator-based electron program.

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Chapter 5
Electronic Brachytherapy/Low KV-IORT: Physics and Techniques

Uta Kraus-Tiefenbacher, Peter Biggs, Jayant Vaidya, and Dario Francescatti

Keywords Low-KV IORT • Zeiss Intrabeam • Electronic brachytherapy • Xoft Axxent system

Introduction

In the past, intraoperative radiotherapy (IORT) was reserved for centres equipped with dedicated linear accelerators in specially shielded operating rooms (ORs) or, with great inconvenience, in a conventional radiotherapy room using transport from the operating room. By using mobile/portable IORT devices with low-kV X-rays that have a steep dose gradient, the possibility of treating patients with IORT is no longer restricted to the availability of special operating rooms, but can be done in regular, unshielded ORs. Another disadvantage of IORT devices in the past was that the anesthetised patient had to be moved for the treatment from the OR table to the accelerator.

Within the last few years, the radiotherapy equipment industry has developed mobile devices for IORT using low-kV X-rays. Over the last 12 years, considerable experience has been gained with the use of Zeiss Intrabeam™, which was originally developed along with clinical academics [1]. More recently, Xoft Axxent™ has been developed. The reduced radiation protection required for these devices due to the characteristic dose distribution of low-kV X-rays is a great advantage on the one hand, but comes with a restriction of indications for use on the other hand. In order to make extensive use of the spherical dose distribution of these devices, the targets should ideally be spherically shaped with a maximum tissue treatment radius of 1–2 cm.

Originally, the Intrabeam X-ray source was used to perform radiosurgery on brain tumours [2], but between 1996 and 1998 spherical applicators with diameters from 1.5 to 5.0 cm were developed to expand the indications for this device in collaboration with clinical scientists. The Intrabeam has subsequently been used for other indications such as peripheral soft-tissue sarcoma and primary and

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_5,

recurrent rectal cancer [3]. Since 1998, Intrabeam™ has been used primarily for IORT of breast cancer patients after breast conserving surgery, initially at University College, London in Great Britain, followed soon after by several institutions in USA, Germany, Australia and Italy.

The spherical Intrabeam applicators are inserted into the tumor cavity after lumpectomy/wide local excision, and the tissue close to the applicator surface can be treated immediately with low-energy X-rays at a single high dose. In addition to the initial spherical applicators, other applicators were developed for Intrabeam to expand the clinical indication spectrum.

The first application of the Axxent system is with the use of inflatable balloons for breast cancer treatment and has been reported recently. This applicator is quite similar to the one used in the Mammosite™ system. However, the depth dose curves are different from either Mammosite or Intrabeam.

IORT with low-kV X-rays is an innovative option of radiotherapy that can be used both for exclusive APBI (accelerated partial breast irradiation) and for intraoperative boost in breast cancer patients. Whereas a geographic miss in covering the boost target often exists in external beam boost radiotherapy, the advantage of low-kV IORT is to cover the tumor bed fully and to shorten the EBRT treatments.

Indication for Using Low-KV Devices

Below, some clinical data from IORT with low-kV X-rays are reported. These data refer mainly to the Intrabeam device, since Intrabeam has been used in clinical practice for years. Xoft, on the contrary, is much newer, and a broad clinical experience does not exist. Although both devices are run with soft X-rays, it is not acceptable to apply all clinical data to Xoft. It is very important to stress that all technical details of low-kV X-ray devices (X-ray spectrum, applicators, depth dose curves, dose rates) may play an important role. Intrabeam, for example, runs with a gold target, whereas Xoft uses a Wolfram target. This different technical detail could have an effect on both clinical effectiveness and toxicity. It is mandatory that each low-kV X-ray system generates its own clinical data.

General

The X-ray system produces low-energy photons (30–50 keV) that are attenuated rapidly within tissue, with minimal exposure to surrounding normal tissues, e.g. lung tissue in breast irradiation. If necessary, the chest wall and skin can be protected (>93% shielding) by radiopaque tungsten-filled silicone shields or even wet pieces of gauze, which can be cut to size on the operation table, to obtain the necessary separation, another advantage of using soft X-rays. With this elegant approach, the pliable breast tissue around the cavity of surgical excision wraps around the radiotherapy source, i.e. the target is “conformed” to the source. This simple, effective technique avoids the unnecessarily complex and sophisticated techniques of using interstitial implantation of radioactive wires to provide high-dose radiotherapy to the tumor bed or the even more complex techniques necessary for conformal radiotherapy by external beams from a linear accelerator. The rapid attenuation of the radiation dose allows the treatment to be carried out in a routine OR. Furthermore, the highest radiation dose is received by tissue nearest the primary tumor and a much lower dose by the skin. Thus, in theory, the biological effect and cosmetic outcome could be better than those of EBRT. The treatment times for the Intrabeam system depend on the chosen applicator size and dose (10–20 Gy) and vary between 2 and 50 min (Table 5.1). After the treatment, the applicator is removed and the wound is closed as usual. The safety of this technique has been well established and rehearsed elsewhere [4–8].

Table 5.1 Treatment time for 20 Gy at the Intrabeam applicator surface according to applicator size

Applicator (mm)	Treatment time (min)
15	7.07
20	11.53
25	17.43
30	24.98
35	18.57
40	26.8
45	36.58
50	48.82

Breast Cancer: IORT as a Boost

Whole-breast external-beam irradiation (EBRT) combined with additional radiation dose to the tumor bed (i.e. a boost) leads to the maximum reduction of local recurrence [9]. A boost for breast-cancer patients is nowadays a daily routine in many centres; nevertheless, it has been estimated that the externally delivered boost misses the target volume in 24–88% of cases [10, 11]. Although it is widely accepted that the additional boost reduces the risk of local recurrence, there are also reports of an increased risk of side effects. Bartelink et al. [12] demonstrated an increase in the rate of moderate-severe fibrosis at 3 year following treatment from ~10% vs. ~ 25% in patients without vs. with boost dose irradiation to the tumor bed. For patients without boost irradiation, the rate remained relatively constant after 3 years, whereas the rate of moderate-severe fibrosis slightly increased for the boost patients to ~30% after a 10-year follow-up.

In view of the risk of geographical miss and the increased fibrosis rates after EBRT delivered boost irradiation, a reasonable method of delivering radiation to the tumor cavity is possible by using mobile IORT devices in the OR during surgery when the tumor bed is eminently accessible. The goal of the intraoperative procedure using a low kV X-ray device is to obtain a maximal irradiation of the tumor cavity up to a 1–2 cm tissue depth. To sterilize such a segment with surgery and IORT means reducing the residual invasive tumor foci to less than 5%, according to the Holland studies [13, 14]. Recent studies could show that low-KV-X-rays may create a microenvironment that is not conducive to tumor growth or invasion [15].

Breast Cancer: IORT as Single Treatment

Owing to the increasing use of screening mammography, breast carcinomas are found more frequently in very early stages, so the question arises whether all patients have to be treated by whole-breast radiotherapy. Since local recurrences after breast-conserving surgery occur mainly in the area around the original primary tumor [16–23], radiotherapy directed to peritumoral tissue by IORT could be an appropriate method to prevent local relapse in selected patients with early-stage breast cancer.

The hypothesis that IORT of the tumor bed using low-energy X-rays is equivalent to a conventional 5.5–6-week course of EBRT of the whole breast in terms of local relapse rates is currently being tested in the ongoing TARGIT trial [24] launched in March 2000. The recruiting goal of 2,232 patients was achieved in early 2010. TARGIT is a pragmatic trial that compares two treatment policies in patients with early breast cancer who have undergone local excision of a good-prognosis tumour. The conventional policy is that each patient receives a radical course of EBRT (with or without a boost) according to local treatment guidelines. The experimental policy is to give targeted IORT in a single dose, recognising that some patients randomised to this treatment, because of unfavourable features found subsequently in the pathological examination of the excised lesion, will need to have additional EBRT (without the boost that has been provided by the targeted dose). This could

happen in 10–15% of cases and has been accounted for in the power calculations. The TARGIT core protocol allows even randomisation of patients to IORT or EBRT after the pathological examination of the removed lesion. Patients in this randomization scheme who are allocated IORT will require a second surgical procedure for administration of the radiation.

Characteristics and Design of Intrabeam and Axxent

Intrabeam

Intrabeam (Zeiss Surgical, Oberkochen Germany) has a miniature X-ray source at the end of a 10-cm long probe, 3.2 mm in diameter. At its end, the accelerated electrons strike a gold target resulting in a nearly isotropic X-ray distribution around the tip (Fig. 5.1). The energy can be set at 30, 40 or 50 kV with currents of 5, 10, 20 and 40 μA. The X-ray unit is small and lightweight (weight = 1.8 kg; dimensions: X-ray generator body 7 cm × 11 cm × 14 cm) and is combined with a floor stand with a balanced support that provides 6 degrees of freedom to gain access to target sites throughout the body (Fig. 5.2). This flexibility enables radiation therapy in any operating theatre in any direction. Because the X-rays are of low energy, no special wall, floor or ceiling shielding is required, and the treatment can be carried out in conventional ORs, which normally have adequate shielding for intraoperative diagnostic radiology.

A typical dose rate is 2 Gy/min at 1 cm from the center of the target in water with no applicator in place and for the highest current at the 50 kV setting. Since the dose falls off in tissues almost as the inverse cube of the distance, for a lesion 3 cm in diameter that needs to be treated to 18 Gy, the treatment time would be approximately 30 min. Clinical commissioning of this device has been

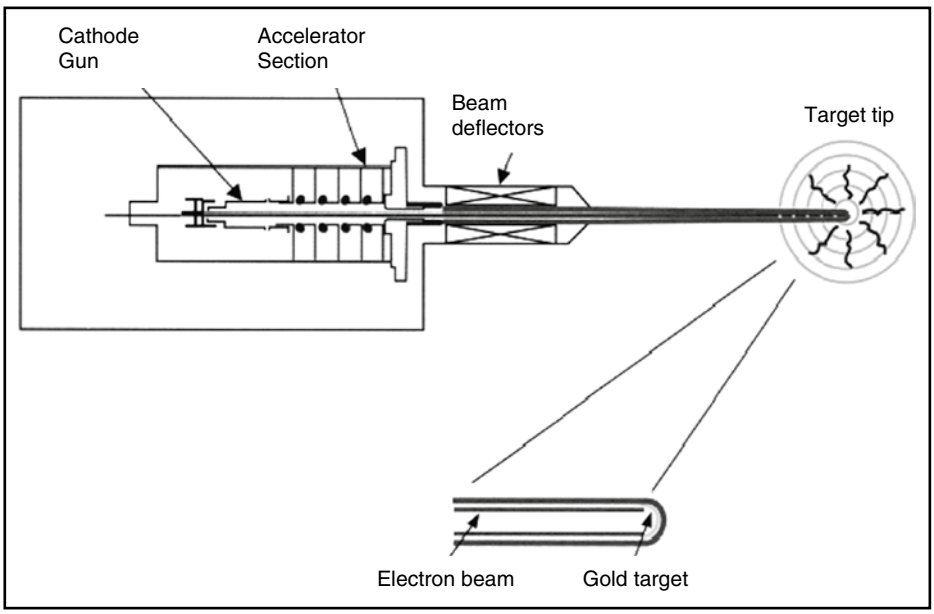

Fig. 5.1 The miniature X-ray source PRS400 features a miniature X-ray source consisting of an electron accelerator with a gold target at the end of the probe. The probe is designed to provide an intense source of X-rays at the tip. The electrons are accelerated to the desired energy level and focused down the probe to strike the gold target, resulting in an isotropic distribution of radiation around the tip of the probe.

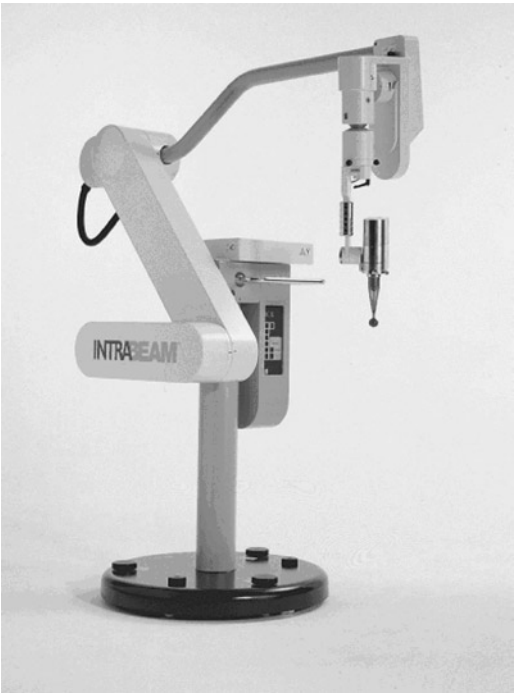

Fig. 5.2 The Intrabeam floor stand provides a mobile, flexible and reliable setting for IORT treatment in any operating room. It has been optimized from a proven design to balance the PRS400 miniature X-ray source during positioning and treatment delivery.

described by Beatty et al. [25], and a Monte Carlo simulation has been performed by Harte and Yanch [26]. The first clinical use was in July 1998 (Vaidya et al. 2002, PhD thesis, University College London).

Axxent

The Xoft S700 Axxent® system is an electronic brachytherapy device that operates at energies between 20 and 50 kV [27–32]. However, from a practical standpoint, only the highest energies are clinically useful. It differs, principally, from the Intrabeam system in that it is a flexible device. That means the device can be used in many of the applications used for ^{192}Ir high-dose-rate brachytherapy, which theoretically increases its range of applications. A microminiature X-ray tube is located inside a flexible, disposable sheath that permits water cooling of the X-ray tube (Fig. 5.3). This water-cooling allows the device to be operated at higher dose rates than by a similar air-cooled device. A dedicated control console is shown in Fig. 5.4. This unit also includes the X-ray cooling pump and a well chamber and an electrometer for constancy check of the output. Rivard et al. [27] have described physical measurements of the dosimetric parameters of this device at 40, 45 and 50 kV using a small parallel plate ionization chamber. With a maximum beam current of 300 μA, the air-kerma strength can vary up to 1400 Gy cm^2 h^{-1}.

The manufacturer quotes a nominal dose rate of 0.6 Gy/min at 3 cm in water. This dose rate is considerably higher than those for the Intrabeam system and is feasible because of the water-cooling of the X-ray target. Heavier filtration also means that the dose also falls off less slowly than the Intrabeam system. Note, however, that the typical source lifetime is about 2.5 h [27] compared with the Intrabeam system that has a very extended lifetime of over 10 years. The system has been in clinical use for a very short time (since 2008), and published evidence of short-or long-term safety or toxicity is not yet available.

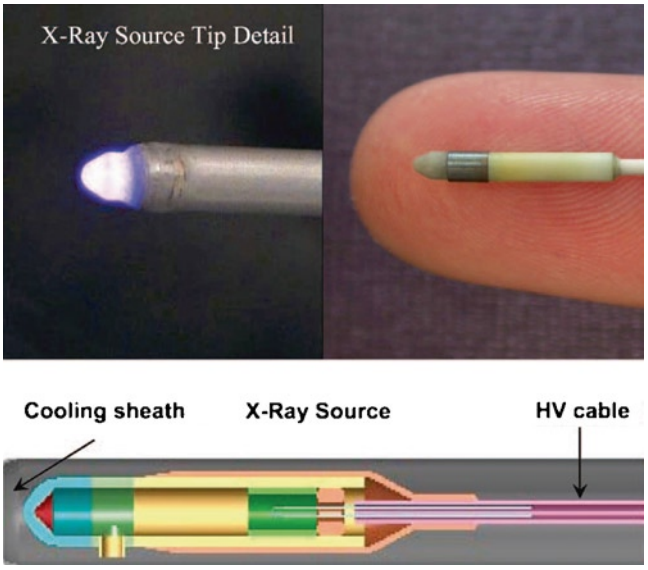

Fig. 5.3 Close-up of the Axxent 50 kVp X-ray source. Anticlockwise from *top right*: (**a**) probe superimposed on a finger to illustrate the small size of the device; (**b**) a view of the tip of the X-ray probe when it is producing X-rays; (**c**) cutaway diagram of the source showing the HV connection and the water-cooling sheath.

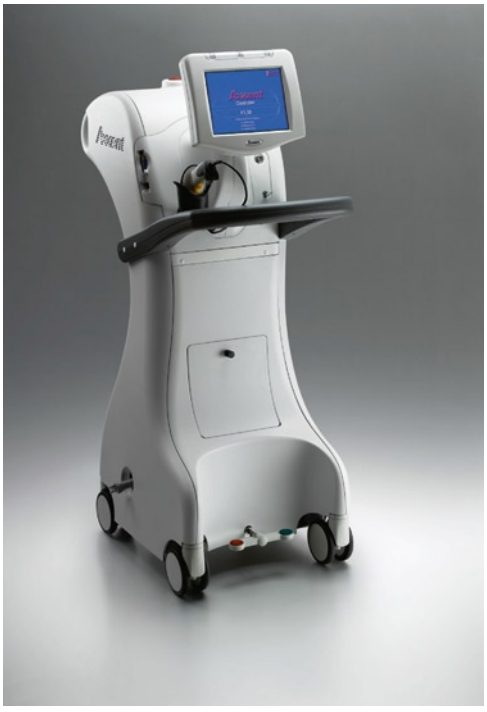

Fig. 5.4 Controller unit for the Axxent electronic brachytherapy system, which includes a touch-screen monitor, USB port, pull-back arm, bar-code scanner, X-ray source cooling pump, well chamber and electrometer. The USB port is for communicating dwell files and storing log files. The pull-back arm is an adjustable arm with a high-voltage port for the source connection.

Spectral measurements have been made using a high-purity germanium detector and a cadmium telluride detector [27, 31] together with Monte Carlo simulations using MCNP5 [27] and GEANT4 [31].

Surgical Aspects and Workflow

Intrabeam

The procedure has been used extensively in over 50 centres around the world over the last 12 years, and over 2,000 patients have been treated. A single prophylactic dose of intravenous antibiotics (Cefuroxime 1.5 g) is given during the duration of anaesthesia. Wide local excision (WLE) is carried out in the usual way, and haemostasis is achieved. One or two gauze pieces are left in the breast wound and sentinel lymph-node biopsy or axillary dissection is performed. Hemostasis of the breast wound is now rechecked. This is very important because even a tiny ooze from capillaries can collect significant amount of blood over the duration of radiotherapy. This could potentially cause a distortion of the cavity around the applicator, which might change the dose that the target tissues receive. In addition, a slight increase of the temperature of 1–2°C during irradiation could induce bleeding, so it is important that meticulous hemostasis is achieved.

The diameter of the cavity is now measured with a disposable tape measure cut to 4 or 5 cm. This and the judgement of how well the breast wraps around the applicator will determine the size of the applicator; actually, inserting the applicators in the wound and visualizing the apposition is very useful. The usual size of the applicator is 3.5, 4.0, 4.5 or 5.0 cm.

A purse-string suture is now taken with a no.1 silk (or prolene) mounted on a large needle (Fig. 5.5a). This step is very important and needs to be taken very carefully because the dose to the target tissues depends on how well it is taken. This suture needs to be skillfully placed: it must pass through the breast parenchyma and appose to the applicator, but at the same time it must not bring the dermis too close to the applicator surface. Since the Intrabeam device is not sterile, it is wrapped in a sterile polyethylene bag. A commercial device is available with pre-designed holes and tapes to cover the equipment. Once the applicator is in place (Fig. 5.5b), the purse-string suture is tightened carefully. Care is taken to ensure that all breast tissue in the cavity apposes and no part of skin is less than 1 cm from the applicator. For the edges of the wound, 3.0 Prolene stitches that slightly retract the skin away from the applicator are useful. If wound retractors are placed (Fig. 5.5c), then care should be taken to ensure that only the skin (and not the subcutaneous breast tissue) gets retracted, lest the very tissue that needs to receive radiotherapy will not be irradiated. For skin further away from the edge that cannot be effectively retracted for the fear of reducing the dose to the target tissues, a customized piece of surgical gauze soaked in saline can be placed deep to the skin. This allows the dermis to be lifted off the applicator, whereas the breast tissue just deep to it still receives radiotherapy. Before starting the therapy, a tungsten sheet covers the wound around the applicator (Fig. 5.5d). This blocks 95% of radiation and reduces the amount of radiation in the OR to very low levels and that in the corridor to near zero levels. The heart and the lungs are protected by the distance through which the radiation needs to travel (the chest wall) and do not need to be protected unless the chest wall is very thin. If the rib or the lungs are expected to be within 1 cm of the applicator surface as can happen in very medial tumours in thin women, a similar barrier can be placed between the pectoralis muscle and the rib/chest wall. The anaesthesiologist and the physicist, wearing a lead gown, sit or stand behind the patient or just outside the theatre close to the patients and the monitoring equipment. The surgeons and nurses unscrub and leave the theatre. Once the radiotherapy is complete, the sheet is removed, the purse-string suture is cut, and the applicator is removed. Hemostasis is reconfirmed and wound is closed.

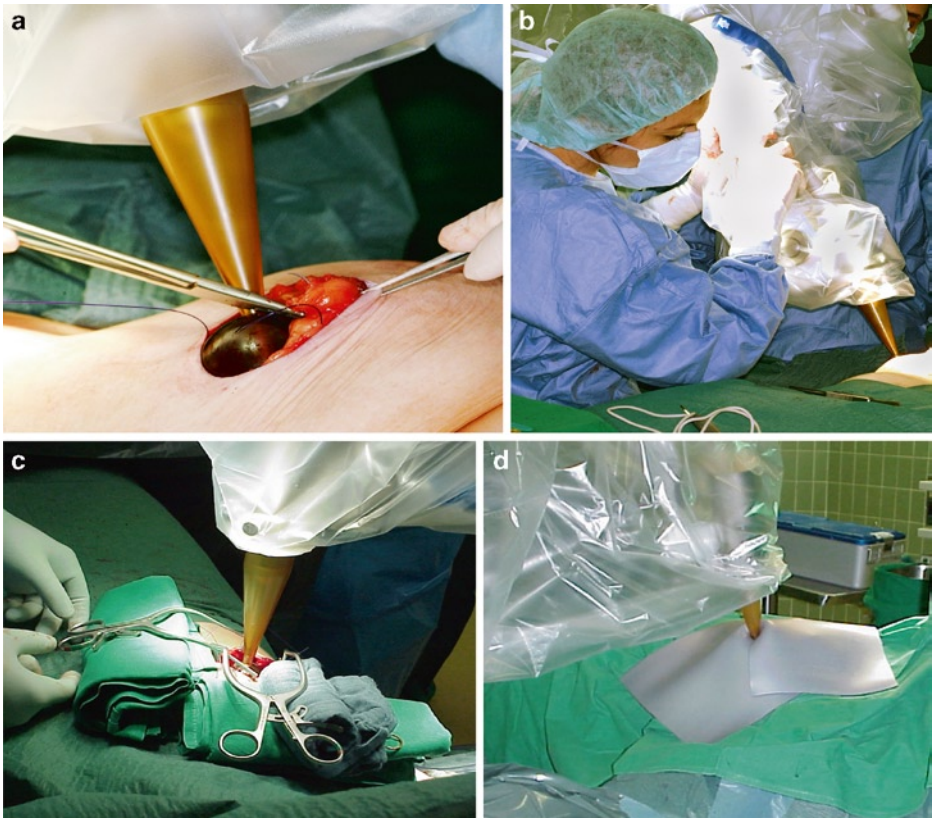

Fig. 5.5 (**a**) A purse-string suture is placed through breast parenchyma to improve apposition of the Intrabeam applicator. (**b**) The Intrabeam device is wrapped in a sterile polyethylene bag and the applicator is brought into the correct position. (**c**) Wound retractors keep the dermis away from the applicator shaft. (**d**) A tungsten sheet covers the treatment field.

Delivering IORT with Intrabeam increases the operating time by 45 min on average (range 34–60 min).

Axxent

The procedure for using Xoft has had very limited clinical experience. After completion of the partial lumpectomy for early-stage cancer of the breast, the surgical team must prepare the surgical bed for optimal placement of the balloon applicator. This process can be divided into the following important steps.

1. *Applicator balloon surface apposition to the circumferential surface of the surgical cavity.*
   An inflatable "sizer" is utilized to determine the optimal fill volume of the balloon applicator that will assure tissue to balloon wall conformance. Conformance can be checked both visually by the operating team in real-time or by utilizing intra-operative ultrasound. More sophisticated imaging techniques can be employed if desired. In addition, the final fill volume is used to determine the proper dosimetric calculations to deliver 20 Gy to the tissue/balloon surface. As an example, an applicator sized to a diameter of 4 cm delivers 20 Gy at the surface and ~7 Gy at 1 cm. The duration of treatment is a function of balloon applicator diameter and source output and can be calculated preoperatively on any number of possible surgical cavity diameters and loaded onto a flash drive. When the exact cavity diameter has been ascertained by the "sizer," the information can be easily and quickly up loaded into the controller by the radiation oncologist–physicist team prior to the start of radiation treatment.

2. *Shielding of the underlying pectoralis musculature, ribs, lung and heart from non-targeted radiation exposure.*
   The depth of the surgical excision of the cancerous lesion should extend to the retro-mammary fatty layer that separates the posterior surface of the breast from the fascia of the pectoralis musculature. Once the specimen has been sent off to pathology, this potential space is dissected in a circumferential fashion to a depth of approximately 2 cm to create a "lip" of breast tissue at the peripheral base of the surgical cavity. A flexible shielding material is used at the base of the excisional cavity to protect deeper structures. For example, a malleable sheet of lead, previously sterilized and approximately 5 mm in thickness, can be cut at the operating table to conform to the "sized" diameter of the surgical cavity with an additional 2 cm rim of shielding beyond the sized diameter. This shield is now ready for placement by its insertion at the base of the surgical cavity, i.e. positioned on the pectoralis fascia. The shield is inserted under the "lip" of mobilized breast tissue in a circumferential fashion so that the breast tissue will, upon the subsequent inflation of the balloon applicator, be in total apposition to the surface of the applicator with the shield lying beneath the applicator balloon. If needed, additional surgical techniques can be employed to facilitate this temporary adhesion. An added benefit to the mobilization of breast tissue at this stage is realized if an oncoplastic closure is required at closure.

3. *Protecting the skin from radiation overexposure.*
   Because the skin is sensitive to radiation overexposure, it must be protected. The Axxent system offers the surgical team flexibility in choosing how to best protect the skin. In one method, the applicator shaft can exit the incision. In this approach, any number of spacing methods can be employed to either shield the at-risk skin or distance the skin from the source of radiation. This method requires a somewhat vertical approach of the controller to dock the controller arm to the balloon applicator for insertion of the X-ray source and completion of therapy. An alternative method utilizes a percutaneous approach that permits the exit of the balloon applicator shaft in a 360 degree arc around the circumference of the breast and at any angle from the perpendicular. An additional therapeutic benefit with this approach is the complete circumferential treatment of all at-risk tissues. This approach also facilitates an unencumbered and rapid docking of controller to applicator shaft without any vertical overhang. By temporarily closing the incision over the balloon applicator, the surgical team can now measure the overriding skin and tissue bridge assuring that a safe minimal distance has been secured prior to the start of radiation therapy. This determination is done either by physical measurement or via intraoperative ultrasound examination.

   At this point, a sterile overdraping is placed over the operative field, an exit site is created through the drape for the applicator shaft, and this in turn is secured to the overdrape with a sterile adhesive sheet so that the distal portion of the balloon applicator can be handled in a non-sterile fashion by the radiation oncologist/physicist while delivering the treatment. The Axxent dose delivery time will add 17–25 min to the operating time, depending on the applicator balloon diameter. Once complete, the balloon is deflated and is removed in concert with the overdrape exposing the protected sterile operative field. Closure is then performed in the usual fashion.

Applicators

Intrabeam

The main applicators are spherical with the source placed at the center of the sphere; they range in outer diameter from 1.5 to 5.0 cm in steps of 0.5 cm. The spheres are made of a biocompatible polyetherimide material, trade name Ultem®, whose density ranges from 1.27 to 1.51 g/cm^3 and whose melting point is 350°C, making it acceptable for sterilization. The applicators are solid,

except for the cavity where the probe is inserted. The radius of this cavity is 2.8 mm, so a 4-cm diameter applicator will have a wall thickness of 17.2 mm. The small-size applicators (<3.5 cm) also have an aluminium "flattening filter" to produce a spherical flattening field. When the source is centered within the spherical applicator, the dose on the surface of the applicator is homogeneous (Fig. 5.3).

New applicators have recently been developed to expand the clinical indication spectrum. Now, it is possible to treat superficial skin tumours [33], the vaginal stump in patients with endometrial cancer [34] and vertebral bodies during kyphoplastic procedures for metastatic disease [35].

Axxent

The Axxent system has the capability of using three types of applicators (1) an inflatable balloon, similar to the Mammosite®[1] system, for accelerated partial breast irradiation, (2) vaginal cylinders that vary in diameter from 2 to 3.5 cm and (3) skin applicators, similar to the Leipzig®[2] applicators. Superflab applicators are in development which could potentially be used clinically in pelvic, abdominal or thoracic sites after marginal resection of malignancies.

Only the first type of applicator is discussed in this report. The inflatable balloons are either spherical or ellipsoidal. There are three spherical balloons, with 3–4 cm, 4–5 cm and 5–6 cm in diameter. The ellipsoidal applicators are 5×7 cm and 6×7 cm in size. A commissioning procedure for the breast applicators has been described by Hiatt et al. [29] that includes checks on well chamber constancy, beam stability, source positional accuracy, output stability, timer linearity, marker/source position coincidence, controller functionality and safety interlocks and treatment planning data verification of TG-43 parameters.

Safety Features

Intrabeam

One of the most important safety features for the Intrabeam® system revolves around the need to ensure that the probe tip, unless it is in the patient for treatment, needs to be shielded. This is the case for the pre-calibration alignment checks as well as for the in-air output check. For in-water measurements in the Intrabeam® water tank, there is sufficient water inside a tank whose walls are made of 8-mm lead glass (2 mm lead equivalent) and metal plates on top to ensure that the dose rate to the operator is below regulatory levels. The system knows that a protective cover or applicator is in place over the probe tip through an optical interlock system that is built into the end of each device, whether it be the spherical applicator, the stereotactic frame for intracranial lesions, the in-air calibration device or the diode-based beam alignment device. In addition, the interlock for the in-air calibration device requires that the ionization chamber also be present before the beam can be turned on.

[1]Cytyc Corporation, Marlborough, MA 01752.

[2]Nucletron, Columbia, MD 21046.

The second most important safety feature of the system is the monitoring of the output dose. Before explaining this, a brief description of the dose calibration check procedures carried out before each day's treatments is in order. After performing the mechanical beam alignment checks, an in-air calibration is performed. If the user has a water phantom, the in-air calibration is followed by an absolute dose measurement in water. In this case, the purpose of the in-air calibration is to provide a reference dose at the time of the operating procedure, since an in-water phantom cannot be done in the OR. Alongside this in-air calibration using an ionization chamber, a reading from an internal radiation monitor consisting of a scintillation detector [28] is recorded for each energy/current setting [25]. This device, therefore, acts as a back-up monitor. There is also a third monitoring device that is not calibrated, but can be used as relative monitor during treatments. This is an external radiation monitor that is placed at some arbitrary distance from the source, but at a close enough distance to give a sensible count. The count rate is determined for a short fixed time at the start of the treatment so, given the length of the treatment, the final count can be calculated and compared with the measured value. These safety features comply with IEC standards.[3] A detail description of large experience about the radiation physics of the Intrabeam system is expected to be published shortly.

Xoft/Axxent

The Axxent system has a number of safety features including a status indicator light to alert users that radiation is currently being emitted, an emergency-off button to turn the system off and a treatment recovery procedure to ensure that the treatment can be completed in case of power failure or emergency-off.

Quality Assurance

Intrabeam

Daily or Pre-treatment Checks

Pre-treatment checks involve mechanical checks on the probe straightness, verification of the symmetry of the dose in a plane orthogonal to the probe axis and calibration of both the internal and external radiation monitors. Importantly, for those users that have a water phantom, since an in-water calibration cannot be performed in the OR, both an in-water and in-air calibration are performed. Then, an in-air calibration in the OR, performed under sterile conditions, can be simply related to an in-water, or absolute, calibration. The straightness of the probe is verified by a device that attaches to the probe and can rotate around its axis, measuring the distance from a fixed radial point to the probe. If the variation in this distance exceeds a certain amount, a spring-loaded fixture in the side of the device can apply a small lateral force to improve the straightness, which is rechecked after each such manipulation. The symmetry of the dose distribution is checked with the aid of a device that contains five photodiodes, four arranged orthogonally at 90° intervals and one along the probe axis. They are all located at the same distance from the X-ray target. The software automatically adjusts the current in the steering coils to minimize the difference in the outputs to

[3]IEC 60601-1-1 International Electrotechnical Commission.

the diodes. The variation in outputs is usually around 5%. Similarly, the software checks the outputs of the internal and external radiation monitors by sequencing through each of the voltage and current settings for a fixed period of time. These are printed out and used as a reference for the treatment-time calculation.

Monthly Checks

There are no additional specific checks to perform on a monthly basis.

Annual Checks

For the annual checks, in addition to performing the daily or pre-treatment checks, the distance–dose curves should be measured for every voltage and current setting and compared with those taken at the time of the commissioning using the water phantom. For users who do not have a water phantom, the X-ray device can be shipped back to the vendor for a full calibration. Note that the output calibration from the vendor[4] is valid for one year unless some untoward circumstance indicates to the user that the calibration has changed, in which case, it would again have to be sent back to the vendor.

Axxent

Daily or Pre-treatment Checks

Pre-treatment checks are self-checks, much like those of a linear accelerator, that ensure that the system is operating in a normal manner. These self-checks ensure that the treatment-panel indicator lights operate correctly, that the source positioning and dwell times are accurate, and that the log file is saved appropriately to a USB drive. However, treatment parameters are not directly downloaded from the treatment planning system, so these parameters have to be transferred by hand and, therefore, double-checked by a qualified medical physicist.

Monthly Checks

The output of the X-ray device is checked by means of an on-board well chamber; this also serves to check source positional accuracy and timer accuracy and linearity.

Annual Checks

A more extensive set of tests is performed on an annual basis. Annual electronic brachytherapy QA requires more comprehensive tests of the source positional accuracy and timer accuracy/linearity over the practical treatment range. To further assess the source positional accuracy, the marker

[4]Carl Zeiss Surgical, 73447 Oberkochen, Germany.

catheters are checked for their overall condition and the reliability with which they indicate source positioning. The vendor recommends that the marker/source position procedure be applied to several applicators. A radiation survey should be performed for the areas at the controller during a simulated treatment.

Regulations

Regulations for electronic brachytherapy have been proposed by the conference of Radiation Control Program Directors (CRCPD/US) as a new subpart in their existing regulations governing therapeutic radiation machines. These regulations are similar to the current USNRC brachytherapy regulations for radioactive sources while recognizing the differences between radiation from sealed sources and machine-produced radiation. These regulations pertain to required safety features, misadministrations, certification of the device, training and education of the users and operators, conditions for use and acceptance testing, commissioning and calibration requirements. The CRCPD represents the radiation control programs of all the states, and these regulations are, therefore, a consensus view. However, these model electronic brachytherapy regulations are still in the proposal phase and have not yet been incorporated into the CRCPD's Suggested State Regulations for the control of Radiation (SSRCR). Currently (April 2009), these electronic brachytherapy regulations are being reviewed for adoption in several states, but this process has only been completed by the state of Florida.

Acknowledgements One of the authors (PJB) would like to thank Jessica Hiatt (Rhode Island Hospital) and Tom Rusch and Darius Francescatti (Xoft corporation) for useful comments on the Axxent system, Alan Sliski (Orbital Therapy) and Ken Harte for useful comments on the Intrabeam system and Bill Dundulis (Rhode Island Radiation Control Program) for his comments on regulatory matters.

One other author (UKT) wants to thank Frederik Wenz (University Medical Centre Mannheim, Germany) and Dietrich Wolf (Carl Zeiss Surgical) for their useful comments.

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Chapter 6
IORT with Electron-Beam, High-Dose-Rate Brachytherapy or Low-KV/Electronic Brachytherapy: Methodological Comparisons

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Keywords Methodological comparisons of IORT techniques - IOERT • HDR-IORT • Low-KV IORT

Introduction

Intraoperative irradiation (IORT) refers to delivery of a single dose of irradiation to a surgically exposed tumor or tumor bed while the normal tissues are protected from the irradiation either by retracting the mobilized tissue or by shielding the anatomically fixed tissues. IORT has traditionally been performed by using an electron beam as the source of irradiation.

A limitation of intraoperative electron-beam irradiation (IOERT) is that it can only be used in areas accessible to the nonflexible IOERT applicator. Narrow cavities, steeply sloping surfaces, or areas where treatment delivery requires turning a corner may not be accessible to the applicator. Therefore, IOERT may be less feasible in sites such as the skull base, paranasal sinuses, diaphragm, deep pelvis, and retropubic areas, which are frequent sites of residual disease after maximal surgical resection of cancers in those locations. Intraoperative high-dose-rate brachytherapy (HDR-IORT) may be technically more feasible in locations that are potentially inaccessible for IOERT, if the surgeon can accomplish a gross total or near gross total resection, thus extending the usefulness and applicability of IORT [1].

The terminology and abbreviations used in IORT literature can be confusing. In this chapter, IORT is used to define any radiation treatments delivered in a single dose while the patient is still under anesthesia. IOERT is used to refer to intraoperative irradiation delivered with electron

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_6,

beams, HDR-IORT refers to intraoperative HDR brachytherapy, and low KV-IORT refers to IORT with electronic brachytherapy or low-KV X-rays. Procedures in which the catheters are inserted in the operating room (OR) under anesthesia and the patient is recovered and later transported to the radiation department for fractionated HDR treatments are termed perioperative brachytherapy rather than intraoperative brachytherapy.

Treatment Factors

Shielded Facility in OR vs. Radiation Oncology

A shielded operating room (OR) is required for a dedicated fixed electron, fixed HDR, or mobile HDR IORT facility, either in the Radiation Oncology Department or in the hospital operating suite. The shielding can be accomplished by lining an existing OR with lead, using an existing shielded treatment room, or constructing a room with appropriately thick concrete walls.

The shielding requirements for HDR-IORT are slightly greater than those for IOERT. At the Ohio State University (OSU), therefore, a mobile lead shield is positioned between the HDR-IORT treatment site and the scrub room (where the surgical personnel wait), and personnel entry to the adjacent passageway is restricted during IORT treatments. Another option being used for HDR-IORT by some institutions, where completely shielded ORs are unavailable, is to treat the patient within a lead-lined box permanently placed in the OR (room within a room) after resection has been accomplished and the applicator for HDR-IORT has been positioned (Duke University).

Institutions not having a dedicated shielded OR can perform IORT by moving the anesthetized patient from the operating room to the radiation oncology department for either IOERT or HDR-IORT. A special transportation cart and strict procedural policy are required to facilitate the transfer of the patient. Another alternative is to build an OR (unshielded) adjacent to the shielded radiation treatment room. Hence, the patient will have to be moved only for a short distance for IORT treatment. The latter situation exists and has functioned well at Medical College of Ohio in Toledo and at Thomas Jefferson University and some other centers. However, it requires the institution to provide or at least consider the availability of OR services such as specimen transport, blood bank support, sterilization, pharmacy, etc., in a location remote from the routine ORs. Finally, the recent availability of mobile self-shielded IOERT machines (Mobetron®, Novac®, Liac®) or low-kV equipment (Intrabeam®, Xoft-Axxent®) allow IORT to be delivered in nonshielded ORs.

Operative Techniques

The radiation oncologist and the surgeon should interact before and during the operative procedure with regard to issues such as selective organ preservation and optimum exposure for both resection and IORT. When IORT procedures are being initiated in an institution, it is useful for the radiation oncologist to join the surgeon in the OR before tumor resection to allow visualization of the relationship of the tumor to the surrounding tissues for correlation with preoperative imaging studies. The radiation oncologist and the surgeon can then jointly discuss the volume of the tissue that optimally would be removed and which tissues may be able to be preserved. In general, a gross total resection with negative or only microscopically positive margins is preferable, if this can be accomplished without substantial destruction of functional tissues and if anatomic and/or functional reconstruction appears feasible.

In addition to accomplishing the tumor resection, the surgeon may need to optimize exposure for IORT treatment or shielding. This may include modification of the skin incision, resection/mobilization of surrounding tissues to better expose the tumor bed, and retraction of radiosensitive

structures (e.g., small or large bowel, stomach, heart, ureter, kidney) out of the irradiation field. It is possible to resect bone (e.g., maxilla) and regraft it after IORT, if this is required to gain access to the tumor bed.

The target area to be treated by IORT is the tumor bed, including microscopically positive margins, areas of close margins, and any gross residual disease as determined jointly by the surgeon and the radiation oncologist. The tumor bed or residual disease should be marked with radiopaque surgical hemoclips or fiducial markers to define the tumor margins on radiographs for future EBRT planning.

IOERT Technique

IOERT is usually delivered by a linear accelerator (linac) electron beam in the 4–20 MeV energy range (see electron isodose characteristics Chap. 3). The linac could be a fixed or mobile electron beam only unit in a dedicated OR or an existing linac, with photon and electron capability, in the radiation oncology department.

If a dedicated linac in the OR is used, the unit can be "warmed up," and the output checked before the patient is brought to the OR. If this cannot be accomplished because the patient is already in the room, the linac should be able to produce a very stable output under "cold start" conditions. Linacs should be calibrated and checked under "cold start" conditions to ensure their performance. If beam cannot be produced to check the linac, certain key operational parameters of the machine can be checked to get an indication whether the machine is operating normally.

The following is a description of the laser-guided "soft docking" technique in a dedicated operating room. There are some variations in the techniques employed, depending on whether a fixed or mobile unit is used. When the tumor bed is accessible to the IOERT applicator, an appropriate-sized electron-beam applicator is selected to cover the target area (Fig. 6.1). To maximize the possibility of being able to treat with IOERT, a wide assortment of applicator sizes and shapes is recommended. Applicator options available at Mayo Clinic Cancer Center-Rochester (MCCC-R), Massachusetts General Hospital (MGH), and Mayo Clinic Cancer Center-Arizona (MCCC-A) include circular applicators from 4.5 to 9.5 cm in 0.5 cm increments (flat, 15° and 30° bevel), and a variety of elliptical and rectangular applicators (flat and 20° bevel for elliptical, 20° bevel for rectangular). Madrid has an even wider range of circular applicators, in 1-cm increments, that include 12 and 15 cm diameters for large fields such as abdominal and extremity sarcomas.

The applicator is manually positioned over the area of high risk and attached to the table using a Buckwalter clamp assembly. Gauze packing or retractors are used whenever possible to displace normal tissues from the treatment field and, occasionally, to pull suspected tumor tissues (e.g., resected margin in base of tongue) into the treatment field. Custom pliable lead shields 1–2 mm thick can be used within the treatment field to protect critical normal structures. The patient is then positioned beneath the dedicated linac in the OR. With a fixed linac, the gantry angle is rotated ±90° as necessary for treatment of anterior pelvic structures such as the base of the prostate after an APR resection (Fig. 6.2a–f) or the retropubic region after pelvic exenteration (Fig. 6.2g–i). For pelvic sidewall (Fig. 6.2j–m), abdominal, or chest sidewall fields or distal presacrum (Fig. 6.2n), the gantry angle necessary to treat a patient can be 20–30°. The availability of both flat and beveled applicators, combined with gantry rotation and table angulation, provides some degree of freedom in treating accessible curved surfaces. For pelvic IOERT treatment, applicators with 30° bevel are used almost exclusively at MCCC-R. In Madrid, applicators with 45° bevel are commonly selected to encompass the presacral region in the adjuvant IOERT treatment of resected high-risk rectal cancers.

A mobile linac (Mobetron®) is the only current option available for IORT at MCCC-A and Ohio State University (OSU). With the Mobetron®, gantry motion is limited to 45° superior/inferior and 30° left/right, which is sufficient to treat most patients with indications for IOERT. If steeper angles

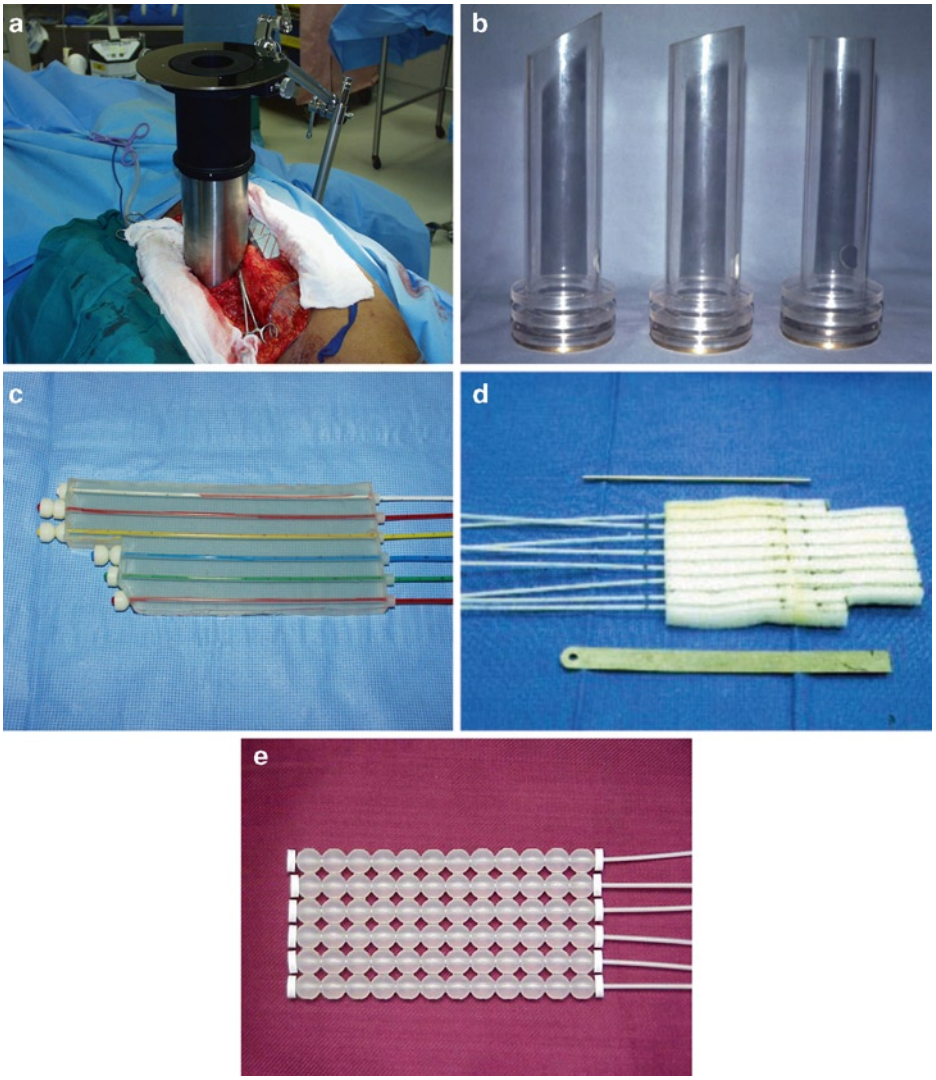

Fig. 6.1 Applicators for Intraoperative irradiation (IORT). (**a**, **b**) IOERT applicators (metal, lucite). (**c–e**) HDR-IORT applicators.

are required, the patient will need to be shifted or the OR couch rotated to make up the difference. For treatment of the inferior/anterior pelvis after abdominoperineal resection, the patient will usually need to be placed in prone position and treated through the perineal incision.

The applicator is aligned to the linac at OSU, MGH, and MCCC-A by moving the table under the guidance of a laser docking system. There is no physical contact between the linac and the applicator and hence the term "soft-docking" (see Chap. 3). Finally, the treatment field is suctioned to prevent any accumulated fluids from acting as a bolus. The staff then exits the OR, and the patient is observed with remote monitors while the IOERT is delivered. Other institutions, including MCCC-R and Madrid, use a "hard-docking" technique whereby the applicator is similarly positioned over the target volume with a Buckwalter retractor but is then physically attached to the gantry of the linac by adjusting the treatment couch height and location (see Chap. 3). For hard-docking

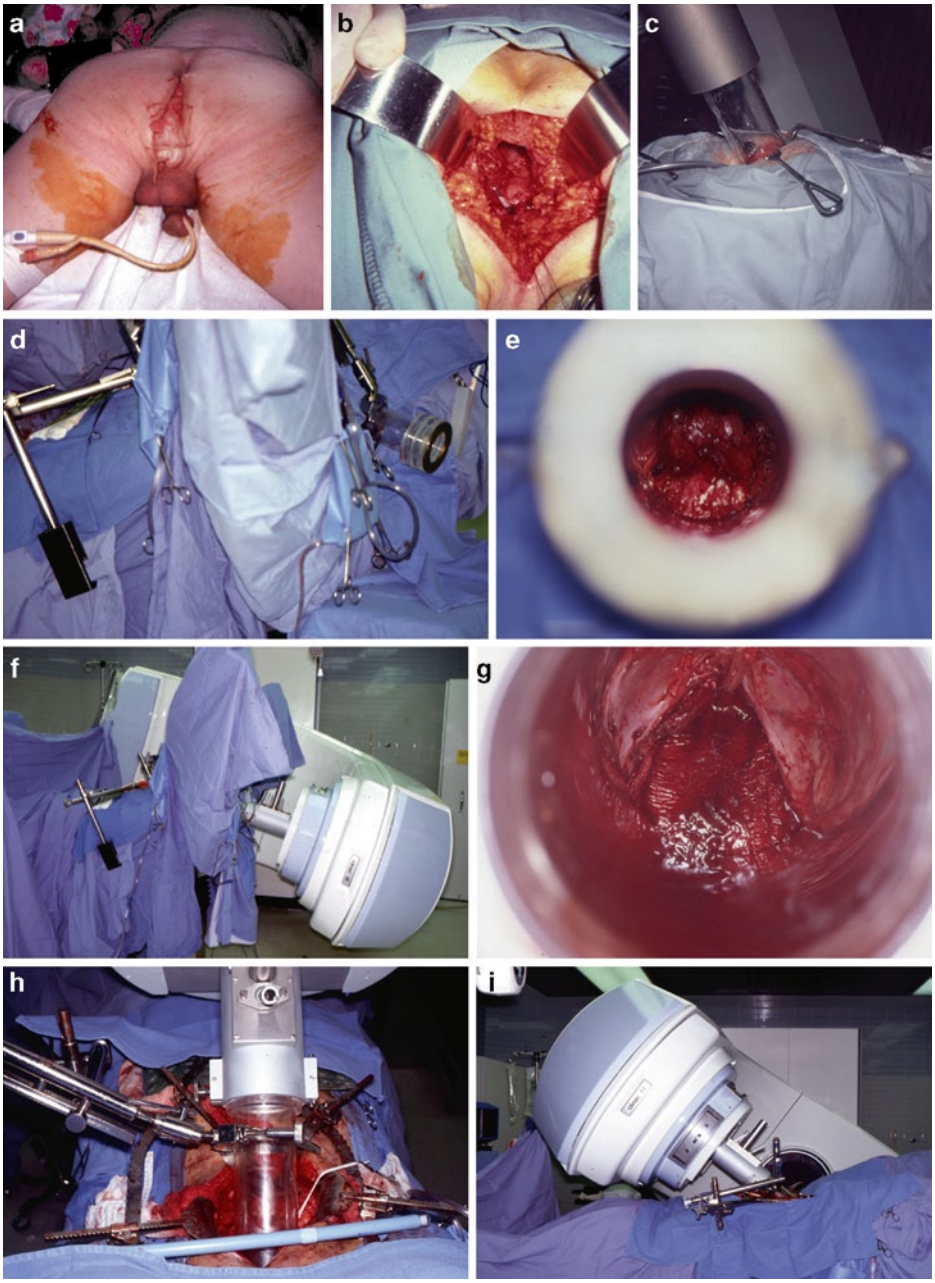

Fig. 6.2 Examples of abdominal or pelvic IOERT cases requiring gantry angle rotation of 30° to >90°. (**a–f**) Treatment of prostate ± base of bladder after abdominoperineal resection. (**a–c**) *Patient prone* – Sandbags under hips to produce flexion (**a**); exposure of prostate via perineal incision with TLD in place (**b**); applicator in patient and "docked" with accelerator (**c**). (**d–f**) *Patient supine* – applicator immobilized in position with Buckwalter retractor; patient is in Trendelenburg position with legs in stirrups and retracted (**d**); prostate visualized within IOERT applicator (**e**); linear accelerator in position for treatment with gantry rotation >90° (**f**); (**g–i**) treatment of retropubic region after pelvic exenteration. Applicator (8.0 cm with 30° bevel) in position with visualization of retropubic region including prostatic fossa (**g**); immobilization with Buckwalter retractor (**h**); linear accelerator in position with gantry rotation >45° (**i**). (**j–m**) Treatment of lateral pelvic sidewall. (**j**, **k**) Via abdominal incision. (**l**, **m**) Treatment of sidewall via perineal approach after abdominal perineal resection with patient in decubitus position. (**n**) Treatment of distal presacrum via perineal incision with patient in supine lithotomy position.

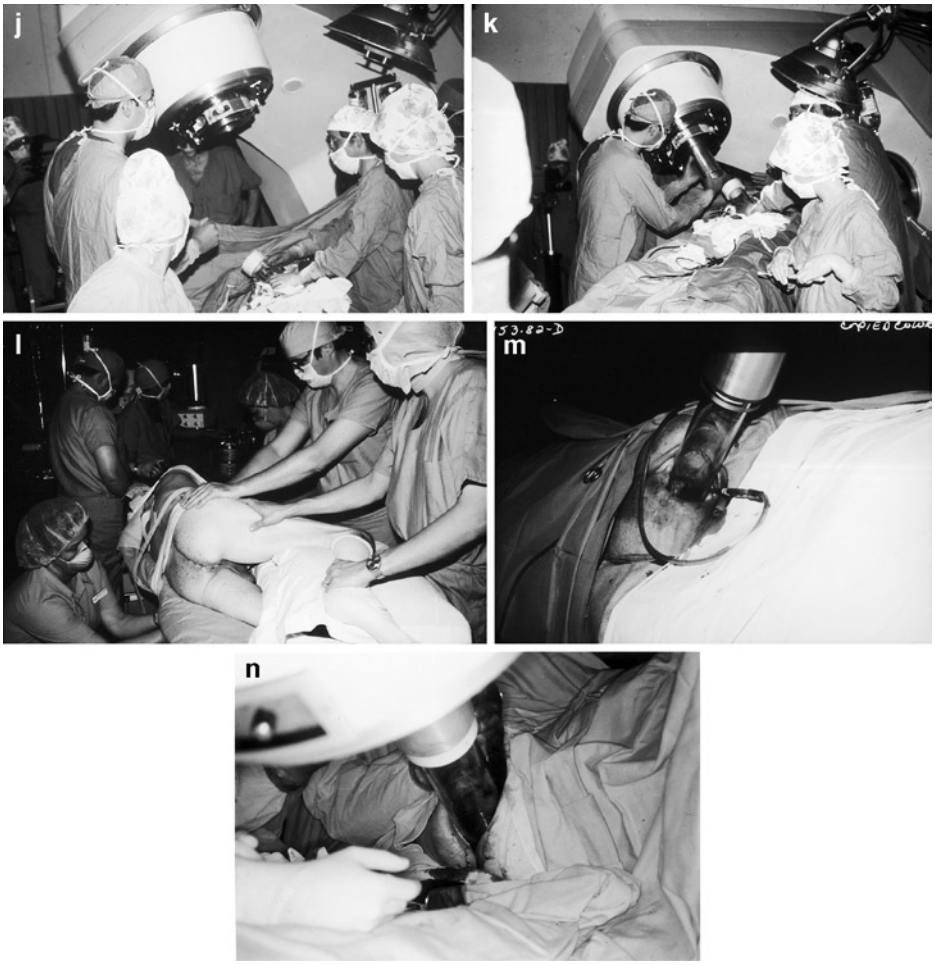

Fig. 6.2 (continued)

systems, the procedure is facilitated by the availability of a special OR table (Macquet, other) that has 5 cm of movement both in a superior/inferior and left/right modes. In addition, the aluminum adapter on the linac gantry has been modified from a fixed circular opening to a hinged system that opens to a half circle during the "hard-docking" procedure.

HDR-IORT Technique

HDR-IORT treatment is given with a HDR remote afterloader that has a nominal 10 curie iridium-192 source encapsulated in a small (4 mm × 1 mm) capsule attached to the end of a metal wire. This single source is moved by mechanically pushing the wire under remote control through transfer tubes into the hollow catheters that are placed in the tumor or tumor bed. In most departments, if an HDR afterloader is available, it is used and kept in the radiation oncology department. Since it is mobile, it can be transferred, as needed, to the OR. Such movement of the HDR unit requires modification of the user's license with the Nuclear Regulatory Commission. At OSU, Beth Israel, and MCCC-R, the HDR afterloader is transferred from the Radiation Oncology Department to the OR

for treatment, whereas at MSKCC a dedicated intraoperative suite is available in the Radiation Oncology Department. The MSKCC Suite has several rooms; the afterloader is moved from the procedure room to the OR, depending on the OR findings in a particular case.

In conventional brachytherapy, catheters are sutured onto the tumor bed, and then treatment-planning dosimetry is performed after obtaining orthogonal radiographs and digitizing the data. For HDR-IORT brachytherapy, since the patient is under anesthesia, the entire treatment must be performed rapidly, but accurately. To accomplish this, HDR-IORT surface template applicators and corresponding precalculated dosimetry tables have been developed at OSU [1, 2, 4]. Several types of HDR-IORT applicators (with catheters embedded parallel and 1 cm apart) are available in sizes suitable for various sites (Fig. 6.1c–e). After the tumor resection, an appropriate applicator is placed on the tumor bed, and localization radiographs are obtained using dummy sources. These radiographs are obtained for documentation and are not used for dosimetry calculations. The applicators can be easily cut or trimmed in the OR, if required, to fit into irregular or tapered tumor beds. In these circumstances, the preplanned dosimetry is modified by turning off the appropriate dwell positions and repeating the treatment plan before proceeding with the treatment. Hence, treating with modified, custom-made applicators requires an extra 10–20 minutes. At Beth Israel and MSKCC, Harrison–Anderson–Mick (HAM) surface applicators are used [3], and applicators made of "superflab" are used in Munich [5].

At MSKCC, a dosimetry atlas with several thousand plans is used to determine the plan and source loading for each case. The radiation oncologist determines the field size, total dose, prescription depth, and severity of curvature of the target surface. The physicist then can use the plan from the atlas that corresponds to the intraoperative situation. A similar atlas exists for volume implants and flexiguide needles. Many times, localization films are *not taken* because it is not possible to obtain accurate films with a C-arm unit. However, this has not limited the capability of delivering treatment. The remote control system has a video hookup, allowing the treatment site and delivery to be recorded for documentation purposes, if this is felt to be necessary.

Surface applicators are most suitable for treatment of tumor beds less than 0.5 cm thick. Tumors greater than 0.5 cm thick can be better treated by placing needles interstitially through a template into the gross tumor. The latter technique has been used to treat metastatic liver tumors at Georgetown University [8, 9]. At OSU, although a template is available for interstitial HDR-IORT, metastatic liver tumors are treated with permanent Iodine-125 brachytherapy, which involves a far easier technique [10, 11].

If HDR-IORT is found to be more suitable than IOERT at OSU or MCCC-R, the remote afterloading machine is transported by the physicist and brachytherapy technologist and cleaned with an antiseptic before entering the operating room. The preplanned treatment program is retrieved from the computer and transferred electronically to the treatment control panel. After the applicator has been secured on the tumor bed (packing with gauze, or suturing as indicated), radiosensitive structures are carefully displaced using retractors or are shielded with sterilized lead foils. Sterilized transfer cables are attached to the ends of the catheters. The catheters are checked for patency, and the proper length is confirmed by using a dummy source cable. A quality assurance check, which is mandated by the Nuclear Regulatory Commission, is performed with all personnel out of the room. The treatment plan is checked for accuracy. The transfer cables from the applicator are then attached to the treatment machine, and the treatment is performed with the patient still anesthetized. After the treatment, the applicator is removed from the treatment site, and the surgeon closes the incision.

Low-kV X-Ray Technology

New technologies using mobile devices producing low energy X-rays may now allow IORT to be delivered intraoperatively in nonshielded ORs [12–14]. The reduced radiation protection required for these devices due to limited penetration and steep dose gradient characteristics of low-kV X-rays

is a great advantage, but has restricted indications for use. These innovative devices include the Axxent® (Xoft Inc., Sunnyvale, CA) and Intrabeam® (Zeiss Surgical, Oberkochen, Germany) and are discussed in greater detail in Chap. 5.

The Intrabeam® system has a miniature X-ray source at the end of a 10-cm long probe, 3.2 mm in diameter. At its end, the accelerated electrons strike a gold target resulting in an isotropic X-ray distribution around the tip. The X-ray unit is small and lightweight and is combined with a floor stand with a balanced support that provides six degrees of freedom to gain access to target sites throughout the body. This flexibility enables radiation therapy in any operating theatre in any direction. Due to low-energy X-rays no special wall, floor, or ceiling shielding is required, and the treatment can be carried out in conventional ORs. It was initially used to perform radiosurgery on brain tumors. Applicators were then developed to treat recurrent rectal tumor beds. Intrabeam is currently being used primarily for IORT of lumpectomy cavities following breast-conserving therapy [12]. Forward firing applicators, suitable for IORT treatment of flat tumor beds (e.g., soft-tissue sarcomas), are being planned. A typical dose rate is 2 Gy/min at 1 cm from the center of the target in water with no applicator in place. Since the dose falls off almost as the inverse cube of the distance, for a lesion 3 cm in diameter that needs to be treated to 18 Gy, the treatment time would be approximately 30 min. A major limitation is that only small-sized tumor beds can be treated by this technique.

The Xoft-Axxent® system is an electronic brachytherapy device that can operate at energies between 20 and 50 kV. However, from a practical standpoint, only the highest energies are clinically useful. It differs from the Intrabeam® system in that it is a flexible device. The radiation is produced by a microminiature X-ray tube that travels inside a flexible, disposable sheath that permits water-cooling of the X-ray tube. This watercooling allows the device to be operated at higher dose rates than a similar aircooled device. The manufacturer quotes a nominal dose rate of 0.6 Gy/min at 3 cm in water. These dose rates are considerably higher than those for the Intrabeam system due to the watercooling of the X-ray target. Heavier filtration also means that the dose also falls off less slowly than the Intrabeam system. Note, however, that the typical source lifetime is about 2.5 h compared with the Intrabeam system that has a very extended lifetime. This new device currently has only a single channel and, therefore, has limited use. It is being used at a few centers in USA to treat breast cancer via a balloon device similar to the Mammosite® balloon, vaginal cuff with a single-channel cylinder applicator, and skin cancers with a surface applicator [13, 14]. Since a shielded room is not required, the Xoft-Axxent® system could be used in a regular (unshielded) hospital operating suite to deliver IORT by adding an indexer to treat multiple channels, mimicking HDR-IORT treatments. Like the Intrabeam® system, the Xoft-Axxent® system has the limitation of being able to treat only small-volume tumor beds with current applicators.

Intraoperative Irradiation: Methodological Alternatives

IORT vs. No IORT

The numerous *potential advantages of IORT* make it a useful addition to the radiation therapy armamentarium. The target volume can be visually defined with accuracy and directly irradiated, thus minimizing the risk of a geographical miss. Dose-limiting radiosensitive normal tissue can usually be retracted away from the volume to be irradiated. Tissues that cannot be retracted can often be shielded to reduce normal tissue toxicities, unless they are part of the target volume or are anatomically immobile or deep to the treatment field (peripheral nerve). Irradiation can be given during surgery and hence eliminating delay in treatment. IORT can be delivered as a supplement to tolerable moderate doses of EBRT (45–55 Gy in 1.8–2.0 Gy fractions), thus allowing delivery of a

Table 6.1 IORT equivalent of fractionated EBRT doses[a]

IORT dose (Gy)	Tumor effect[b] (Gy)	Late tissue effect[c] (Gy)	Late tissue effect[d] (Gy)
10	16.7	26	8
15	31.3	54	15.8
20	50	92	26
25	72.9	140	38.8

[a]Assume EBRT dose of 2 Gy per fraction in calculating equivalent doses
[b]Assume α/β ratio of 10, EBRT dose of 2 Gy per fraction
[c]Assuming no dose reduction to normal tissues, α/β ratio of 3
[d]Assuming a 50% dose reduction to normal tissues, α/β ratio of 3

higher total radiation dose to marginally resected or unresected tumor. In an adjuvant setting, the use of IORT may allow a decrease in the dose of the EBRT treatment component, thereby improving the integral tolerance of the irradiation program. Finally, the procedure is relatively brief (IOERT requiring an additional 45–60 min after maximal resection; HDR-IORT, 1–2 h).

However, *IORT does have its potential disadvantages*. First is the radiobiology of a large single dose that does not allow repair of sublethal damage. This disadvantage can be minimized, however, if a small dose of IORT is given as a boost to the immediate tumor bed to supplement modest doses of EBRT delivered to a larger target volume (Table 6.1). A practical disadvantage of IORT is that it requires a shielded OR for HDR-IORT or fixed-linac IOERT or transportation of an anesthetized patient, as previously discussed and hence limiting the widespread use of IORT until the mobile electron beam accelerators became available in the late 1990s.

IORT vs. Conventional Perioperative Brachytherapy

IORT has some similarities to conventional (permanent or removable perioperative) brachytherapy. Both techniques allow delivery of high-dose irradiation to the tumor or tumor bed while minimizing dose to the normal tissues. Both techniques require a surgical procedure, although in some cases perioperative brachytherapy can be given without exposing and/or resecting the tumor. In both cases, additional irradiation can be given to supplement a course of preoperative EBRT to an initially unresectable tumor at the time of subsequent planned resection without giving the tumor a chance to proliferate as may occur if further irradiation were to be accomplished with a postoperative EBRT supplement.

IORT differs from perioperative brachytherapy in the following respects. IORT (IOERT or HDR-IORT) is given in a short interval that does not allow for repair of sublethal damage or reoxygenation of hypoxic tissues. In contrast, conventional brachytherapy is typically given over a few days, thus allowing for repair of sublethal damage or reoxygenation of hypoxic tissues during the irradiation. Hence, IORT is preferably given in moderate doses of 10–20 Gy as a supplement to adjuvant doses of EBRT and not as the sole modality, whereas brachytherapy can be used either as a boost treatment with EBRT or as the sole modality. IORT has been used as the sole irradiation modality in previously irradiated patients but has its best potential value in that capacity if a gross total resection has been achieved, and a dose of 25–30 Gy is tolerable to normal structures.

Most clinical trials have shown greater benefit of IORT in the treatment of microscopic residual disease after maximal resection rather than for the treatment of gross residual disease, perhaps due to the radioresistance of hypoxic cells. Although perioperative brachytherapy does not suffer from this handicap, its efficacy in this regard is unclear. It can be used in the treatment of both gross and microscopic residual disease provided the implant is technically feasible and dose-limiting structures can be displaced away from the implant volume over the protracted time required for conventional brachytherapy.

The dose distribution of each technique is different. Electron-beam irradiation gives a more homogeneous dose distribution both to a large surface and at depth, whereas in perioperative

brachytherapy, the dose is highest at the center of the implant volume. This difference in dose distribution and the location of the normal and tumor tissue with the target volume must be remembered when selecting the technique. A potential (uncertain) advantage of the brachytherapy dosimetry is that of dose escalation within the target volume. The major disadvantage of perioperative brachytherapy is the potential for catheter movement and displacement (thus not delivering the planned dose), and the difficulty of displacing or shielding critical normal tissues from the high-dose region.

IORT with Electrons, HDR Brachytherapy, or Low-kV X-Rays

The potential differences (advantages and disadvantages) between IOERT, HDR-IORT, and low-KV X-rays are summarized in Tables 6.2–6.7. Factors including accessibility, depth of tissue at risk, field size, treatment time, and rationale for having more than one IORT modality, if feasible, are discussed here.

Accessibility

Although HDR-IORT can be used to treat both easily accessible and poorly accessible sites, at OSU and MCCC-R, IOERT is used for sites that are accessible to the electron-beam applicator because the treatment time and the setup time are both shorter, and a greater depth dose can be achieved, if required, when compared with the usual HDR-IORT surface applicator system. However, since the electron beam only travels in a straight line, and the electron-beam applicator has a finite diameter, IOERT may be unsuitable for treatment of sites deep in the inferior pelvis, subpubic locations, some lateral pelvic sidewalls, anterior abdominal walls, subdiaphragmatic areas, anterior ± anterolateral chest wall, and narrow cavities such as the paranasal sinuses. HDR-IORT, if available, usually becomes the modality of choice at OSU for these difficult locations. Most of the HDR-IORT coauthors in this chapter (S. Nag and L. Harrison) agree that there is literally no site or surface for which HDR-IORT cannot be used (Table 6.5).

If IOERT is the only available option for IORT and an adequate assortment of applicators exist, an innovative radiation oncologist and a surgeon can find a way to treat most sites. Modification of surgical incisions, gantry angle rotation (±90° or greater with fixed linacs, ±45° with Mobetron®), or change in patient position from supine to prone may be necessary to

Table 6.2 Potential differences between IOERT, HDR-IORT, and Low-kV IORT

	IOERT	HDR-IORT	Low-kV IORT
Actual treatment time	2–4 min	5–30 min	30–45 min
Total procedure time	30–45 min	45–120 min	45–120 min
Treatment sites	Accessible locations	All areas where depth at risk is ≤0.5–1.0 cm from surface of applicator[a]	Areas where depth at risk is ≤0.5–1.0 cm from surface of applicator; small target volumes only
Surface dose	Lower (75–93%)[b]	Higher (200%)	Highest (300%)
Dose at depth (2 cm)	Higher (70–100%)[b]	Lower (30%)	Lowest (20%)
Dosimetric homogeneity (surface to depth)	≤10% variation	≥100% variation	≥150% variation

IOERT intraoperative electron beam irradiation, *HDR-IORT* intraoperative high-dose-rate brachytherapy

[a]Precludes aortocaval region, mediastinum, and any unresected disease >0.5–1.0 cm. Gross tumors >0.5 cm thick in the liver have been treated by HDR-IORT using interstitially placed needles [8, 9]

[b]Based on electron energy of 6 MeV at OSU and energies of 6–18 MeV with 7 cm flat end lucite applicator at Mayo Clinic Cancer Center-Rochester (MCCC-R) [7] (see Table 6.3); add bolus to increase surface dose to 90%, as indicated

accomplish such (Figs. 6.2 and 6.3). At MCCC-R, although HDR-IORT has been available since 1999, HDR-IORT has been used for only 5 of the 2,090 patients treated with IORT from 1981 to August 2009, since the involved surgeons and radiation oncologists prefer IOERT when technically feasible (M. Haddock, personal communication).

Depth of Tissue at Risk

The dose-distribution characteristics for HDR-IORT, IOERT, and low-kV X-rays differ (Fig. 6.1 and Table 6.3). The percentage depth dose characteristics at OSU for HDR-IORT and IOERT with 6 MeV electrons are seen in Table 6.3. The dose is prescribed at 1 cm from the plane of catheters (0.5 cm from the applicator surface) for HDR-IORT, and at D_{max} for 6 MeV electrons for IOERT. The dose at the surface is higher for HDR-IORT than for IOERT. However, the dose at depth (for example, at 2 cm) is greater for IOERT than for HDR-IORT (usual single-plane surface applicator). Since HDR-IORT gives a far greater surface dose, investigators at OSU prefer to use HDR-IORT for treating small microscopic tumor beds (see subsequent section on field size). However, HDR-IORT (using surface applicators) is not suitable for treating residual tumors more than 0.5–1.0 cm thick. Gross tumors, thicker than 0.5 cm, have been treated by HDR-IORT at Georgetown University using interstitially placed needles [4, 8]. Low-kV X-ray devices (Axxent® and Intrabeam®) have even lower penetration and steeper dose gradient characteristics compared to HDR-IORT. Hence, the surface doses will be much higher with low-kV X-ray devices compared to IOERT or HDR-IORT while delivering the same dose at 0.5 cm depth.

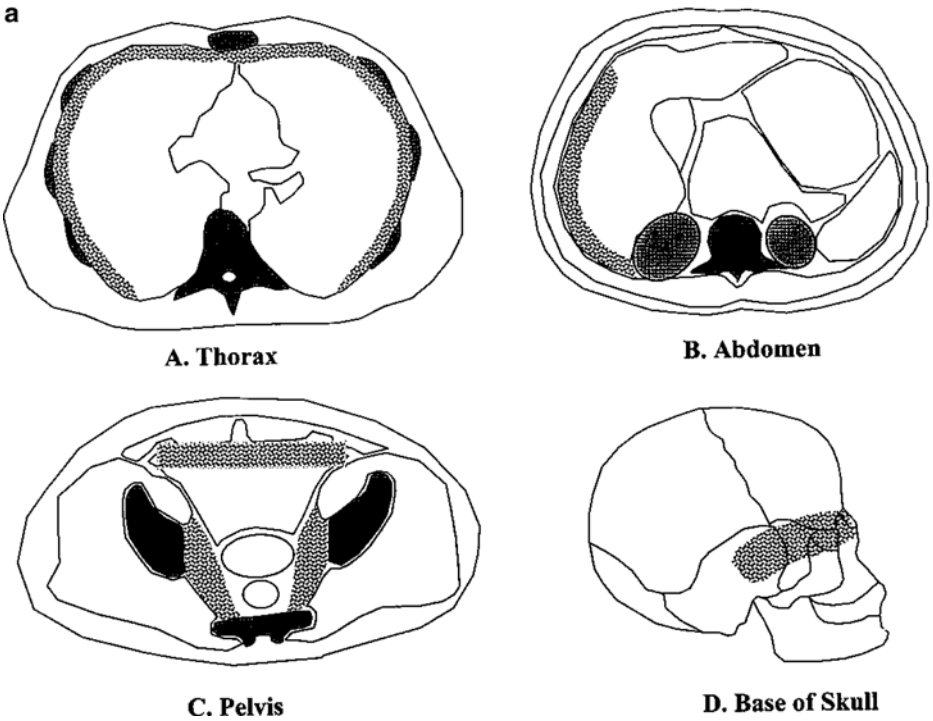

Fig. 6.3 (**a**) *Shaded areas* represent locations where HDR-IORT may be easier to use than IOERT if gantry angle rotation of linear accelerator is limited to ±25–30°. (**b**) If gantry rotation of linear accelerator is unlimited except for patient anatomy, *shaded areas* represent locations where IOERT may be difficult or impossible to use unless surgical incision is altered to yield different exposure (i.e., can treat posterior to sternum with a lateral thoracotomy approach).

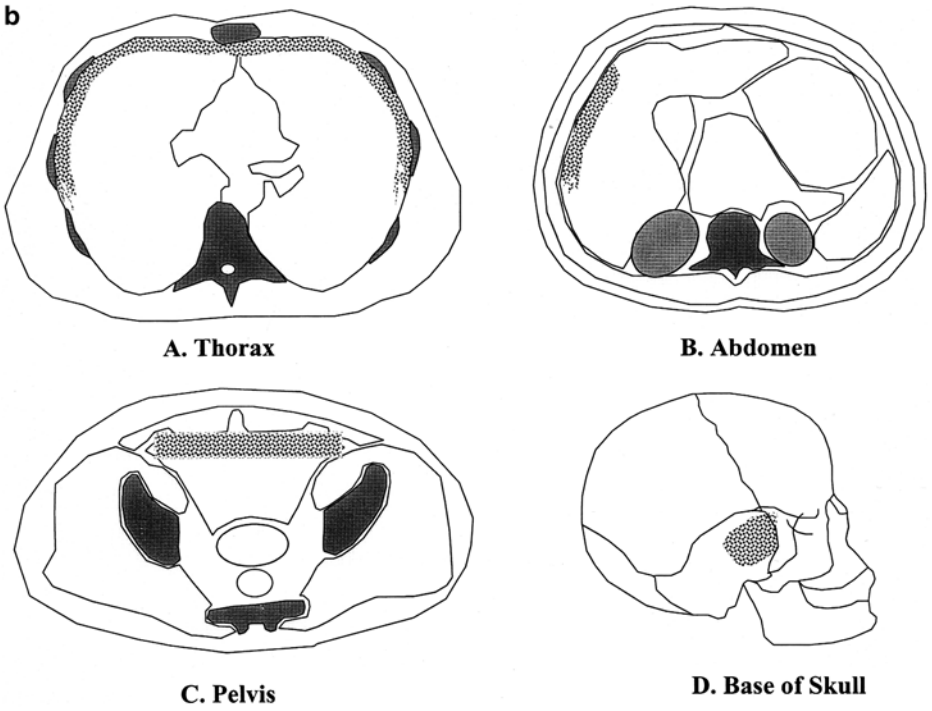

Fig. 6.3 (continued).

For purpose of comparison, Table 6.3 also contains data on depth dose characteristics of various energy electrons with the applicator system used at MCCC-R. The depth dose advantages of IOERT over HDR-IORT are demonstrated for tumor residual ≥1 cm depth.

For any IORT treatment approach, the radiation oncologist and the surgeon must address the issue of fluid buildup after resection, which could alter depth dose characteristics unless dealt with an appropriate fashion. It is necessary to maintain suction during the delivery of treatment when such risks exist.

Field Size (Table 6.4) and Treatment Time

For HDR-IORT, the treatment time depends on the total area to be treated and the activity of the source because a single source is used to treat the entire tumor bed. The actual HDR-IORT treatment time at OSU generally varies from 5 to 30 min because generally only small areas are treated with HDR-IORT. Larger tumor beds (up to 12 cm in diameter) are generally treated with IOERT at OSU. Extremely large tumor beds are less suitable for IORT treatments except in cases where gross total resection can be accomplished, as for large retroperitoneal and extremity sarcomas. In such instances, IOERT institutions (MCCC-R, MCCC-A, MGH, NCI, Pamplona, Madrid) have used abutting fields to cover the area at risk, and MSKCC, Beth Israel, and Duke use large HAM applicators for HDR-IORT, which may result in treatment times up to 145 min (median 44 min, range 17–145). Treatment time for the low-kV Intrabeam® device varies from 30 to 60 min for small target volumes of 3–5 cm diameter. Low-kV devices are currently not suitable for treating large tumor beds.

A comparison of applicator sizes available for IOERT and HDR-IORT at the authors' institutions is seen in Table 6.4. For HDR-IORT, there is basically no applicator-size limitation, and custom-made applicators can be constructed in the OR. However, it has to be noted that the prolonged treatment times will be required to treat large areas to high doses. IOERT applicators by definition

Table 6.3 Percentage depth dose for HDR-IORT brachytherapy and IOERT (6 MeV) at OSU; Variable Energy IOERT and Variable Applicator. Bevel Angle at MCCC-R

	OSU% Depth dose[a]		MCCC-R IOERT % DD, variable electron energy and applicator bevel[b]									
Tissue depth (cm)	HDR-IORT	6 MeV IOERT	6 MeV Flat	6 MeV Bevel	9 MeV Flat	9 MeV Bevel	12 MeV Flat	12 MeV Bevel	15 MeV Flat	15 MeV Bevel	18 MeV Flat	18 MeV Bevel
0	200	75	82	82	87	87	90	90	93	93	93	93
0.5	100	85	–	–	–	–	–	–	–	–	–	–
1.0	60	95	D_{max}[c] 1.2	90 (1.2)	–	–	–	–	–	–	–	–
1.5	40	100	90 (1.7)	75	D_{max}[c] 1.5	–	–	–	–	–	–	–
2.0	30	90	70	50	–	90 (2.1)	D_{max}[c] 2.0	–	D_{max}[c] 2.0	–	D_{max}[c] 2.0	–
2.5	20	50	30	20	90 (2.6)	80	–	–	–	–	–	–
3.0	15	20	10	10 (2.9)	70	60		90	–	–	–	–
3.5	–	–	–	–	45	40	90	77	–	–	–	–
4.0	–	–	–	–	20	20	77	62	90 (4.3)	90 (3.8)	–	–
4.5	–	–	–	–	10 (4.4)	10	60	48	82	75	–	–
5.0	–	–	–	–	–	–	40	30	68	62	90 (5.2)	90 (4.9)
6.0	–	–	–	–	–	–	10	10 (6.1)	37	38	74	68
7.0	–	–	–	–	–	–	–	–	10	10 (7.4)	50	48
8.0	–	–	–	–	–	–	–	–	–	–	23	28
9.0	–	–	–	–	–	–	–	–	–	–	10 (8.7)	10 (9.4)

[a]For OSU figures, dose of HDR-IORT is prescribed at 1 cm from catheter plane or 0.5 cm from applicator surface and for IOERT at 90% isodose for 6 MeV electrons

[b]At MCCC-R, IOERT doses are prescribed at d90 and the surface dose for most applicator sizes and beam energies is within 5% of d90. Figures listed are for 7-cm lucite applicator with flat and 30° bevel ends using a collimator jaw setting of 10 cm× 10 cm [6]

[c]D_{max} in cm

Table 6.4 Applicator size availability of IOERT and HDR-IORT

HDR-IORT applicators

OSU – Various sized from 2 cm×2 cm to 15 cm×12 cm. Custom-made sizes and shapes can be made in OR

Beth Israel – Any size or shape feasible

IOERT applicators (size in cm)	MCCC-R	MGH	Madrid	OSU	MCCC-A
Circular – flat and 22° bevel (4–12 cm diameter)	–	–	–	Y	–
Circular – flat, 15° and 30° bevel (0.5 cm increments, 4.5–9.5)	Y	Y	Y[a]	–	Y[b]
Circular 45° bevel	N	Y	Y	N	N
Elliptical (flat+20° bevel) 6×11, 7×12, 9×12, 8×15, 8×20	Y	Y	N	N	Y[b]
Rectangular (20° bevel) 7×9, 8×12, 8×15 cm	Y	Y	N	N	Y[b]

[a]Circular applicators in 1-cm increments include 12 and 15 cm size for large-field cases – i.e., retroperitoneal and extremity sarcomas

[b]Circular applicators – 3–12 cm; elliptical – 7 cm×12 cm, 9 cm×12 cm, 8 cm×15 cm; rectangular – 8 cm×15 cm

cannot be custom-made, although lead sheets can be custom-made for purpose of field shaping and protection of dose-limiting tissue or organs that cannot be surgically mobilized. For low-kV IORT with Intrabeam®, the spherical applicators are currently limited to 1.5–5.0 cm diameter in 0.5-cm increments.

Rationale for Having IOERT, HDR-IORT, Low-kV IORT, Perioperative Brachytherapy Available in the OR

A comprehensive IORT program should have combinations of IOERT, HDR-IORT, low-kV IORT, or perioperative brachytherapy facilities available to treat all disease sites and situations. For some institutions, this will mean IOERT, HDR-IORT, and perioperative brachytherapy (OSU, MCCC-R), HDR-IORT or IOERT and perioperative brachytherapy (Beth Israel, Duke, MCCC-A, Madrid), IOERT and low-kV IORT or HDR-IORT and low-KV IORT. A few institutions may have expertise in all four options. These modalities are not competitive, but rather complement each other. Tables 6.5–6.7 discuss the potential applicability of each method by both site and amount of residual disease after maximal resection.

IORT is preferred for the treatment of microscopic tumor beds (Table 6.6). At OSU, IOERT is preferred in accessible sites and HDR-IORT preferred for poorly accessible sites for the reasons previously discussed. The choice of IORT modality at other centers may differ as they may have IOERT, HDR-IORT, or low-kV IORT, but the overall concept and treatment outcomes are the same.

For the treatment of gross residual or unresectable tumor, interstitial brachytherapy (low-dose rate or high-dose rate) may be preferable to IORT if the residual disease can be uniformly implanted, and dose-limiting structures can be displaced for 3–7 days (Table 6.7). IOERT combined with EBRT and concomitant chemotherapy has been used quite successfully in the treatment of limited gross residual or unresectable disease, however, provided the volume can be encompassed within a single applicator. Results could potentially be improved with the addition of a dose modifier during IOERT (hypoxic-cell sensitizer, others).

Fractionated EBRT (±concomitant chemotherapy) should be used in adjuvant level doses of 45–54 Gy in 1.8–2.0 Gy fractions, whenever feasible, to irradiate the entire area of potential microscopic disease. For locally advanced primary or recurrent lesions where marginal resection would exist, preoperative EBRT ± chemotherapy is generally preferable over postoperative EBRT ± chemotherapy for reasons previously discussed. Depending on the volume and location of the tumor and the available expertise and equipment, IOERT, HDR-IORT, low-kV X-rays, and/or perioperative brachytherapy could be used along with EBRT and surgery for the optimal management of

Table 6.5 Potential applicability of IOERT, HDR-IORT, and perioperative brachytherapy by treatment site

	(LLG[a], CW[b], FC[a])		(SN[c])	Brachy (SN[c])		Brachy (LH)[d]	
Treatment site	IOERT	Brachy periop	IOERT	HDR-IORT	Periop	HDR-IORT	Periop
Pelvis							
Posterior	Y	+	Y	Y	Y	Y	Y
Lateral	Y	+	±	Y	Y	Y	Y
Anterior	+, ±	N	Y	Y	Y	Y	±
Abdomen							
Aortocaval	Y	N	Y	Y	Y	Y	±
Abdominal wall							
Posterior	Y	N	Y	Y	Y	Y	+
Lateral	±	N	±	Y	Y	Y	Y
Anterior	±, N	N	Y	Y	Y	Y	Y
Chest							
Mediastinum	Y	N	Y	Y	Y	Y	Y
Inner chest wall							
Posterior	Y	±	Y	Y	Y	Y	Y
Lateral	+, ±	±	N	Y	Y	Y	Y
Anterior	±, N	±	N	Y	Y	Y	Y
Head/neck							
Neck	Y	Y	Y	Y	Y	Y	Y
Oral cavity	Y	Y	Y	Y	Y	Y	Y
Base of skull	±	N	N	Y	Y	Y	+
Extremity (sarcoma)	Y	Y	Y	Y	Y	Y	Y
Brain	+, ±	+	±	+	Y	Y	±

The authors are aware that author's choices are to some degree operator dependent and reflect a combination of bias and other available treatment options in a given institution

Y = yes; N = no; + = possible; ± = may be possible (technically challenging situation); Periop = perioperative; brachy = brachytherapy

[a]Response of chapter coauthors, L. Gunderson and F. Calvo, who have availability of IOERT and periop brachy, but not HDR-IORT

[b]Response of C. Willett who had IOERT/periop brachy at MGH and has HDR-IORT/periop brachy at Duke

[c]Response of chapter primary author, S. Nag, who had availability of IOERT, HDR-IORT, and periop brachy at OSU

[d]Response of chapter coauthor, L. Harrison, who has both HDR-IORT and periop brachy (now Beth Israel, previously at MSKCC)

Table 6.6 Relative advantage or disadvantage of IOERT vs. HDR-IORT brachytherapy after gross total or near total resection (maximum thickness ≤0.5 cm)

IOERT potential advantage if technically feasible	
Better dose homogeneity[a]	
Faster treatment time	
Less shielding required in OR	
Can treat full thickness of organ or structure at risk with relative homogeneity[a] (i.e., aorta or vena cava, bladder sidewall)	
Potential disadvantages of IOERT	*Potential solution*
Surface dose <90% with 6 ± 9 MeV	Add bolus over tumor bed to improve surface dose; use HDR-IORT
If unable to include area at risk in single field within either abdomen or pelvis	Use abutting IOERT fields (difficult in pelvis); use HDR-IORT
Area at risk is technically inaccessible due to location	Use HDR-IORT; surgically displace small bowel or stomach with vascularized flap (omentum, muscle) and give postoperative EBRT boost or perioperative brachytherapy

[a]The chapter authors have different opinions with regard to the relative advantage or disadvantage of dose homogeneity with IOERT or inhomogeneity with HDR-IORT (i.e., authors S. Nag and L. Harrison feel dose escalation within a target may be advantageous rather than disadvantageous)

Table 6.7 Potential advantage or disadvantage of IOERT, HDR-IORT, low kV X-rays, and perioperative brachytherapy for unresected tumor or gross residual disease >0.5–1.0 cm thickness

Perioperative brachytherapy, potential advantages
Hypoxia and sublethal damage repair less of an issue due to longer treatment time (reoxygenation, repair of sublethal damage)
Higher central dose
Less risk to normal tissues
Perioperative brachytherapy, potential disadvantages
Unable to do homogeneous implant[a] (adjacent to vessels, curved pelvic surface)
Potential movement and displacement or extrusion of implant
Unable to displace dose limiting organs for prolonged interval
Inhomogeneous dose distribution with potential issues regarding both tumor and normal structures
Increased whole-body irradiation exposure
Radiation exposure to personnel

IOERT – potential advantages	*Over*	*HDR-IORT/Low kV X-rays*	*or Perioperative brachytherapy*
More homogeneous dose distribution[a]		Y	Y
Better displacement of dose-limiting structures		N	Y
IOERT/HDR-IORT/low kV X-ray disadvantages relative to perioperative brachytherapy		*Potential solutions*	
Hypoxia within unresectable tumors		Add dose modifiers (hypoxic cell sensitizers, other)	
Peripheral nerve risks		Evaluate radioprotectors	

[a]See footnote in Table 6.6 regarding dose homogeneity (IOERT) and inhomogeneity with target dose escalation (HDR-IORT)

malignancies. The best IORT results are obtained when used as a conformal boost to the tumor bed after maximal resection and incorporation with other modalities including EBRT and chemotherapy (concomitant with EBRT ± maintenance) or other systemic therapies (the future may include gene or immunotherapy, etc.).

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Part III
Normal Tissue Tolerance: IORT

Chapter 7
Normal-Tissue Tolerance to IOERT, EBRT, or Both: Animal and Clinical Studies

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Keywords Normal tissue tolerance • IORT animal studies • IORT clinical tolerance

Introduction

Early clinical investigations of intraoperative electron irradiation (IOERT) as an alternative to conventional external-beam irradiation (EBRT) were based on a limited number of preclinical studies to provide important information regarding the radiobiologic response of normal and surgically manipulated tissue to high, single doses of radiation. Since the overall goal of IOERT was to maximize the total radiation dose that can be safely delivered to the tumor, there was a strong need to establish tissue-specific guidelines for the clinical use of IOERT to minimize normal-tissue toxicity.

Similarities between humans and dogs to large, single IOERT doses greater than 10 Gy led investigators to conduct comprehensive experiments in a canine model [1, 2]. Guidelines for the clinical use of IOERT were largely established through a number of studies at two institutions, the National Cancer Institute (NCI) and Colorado State University (CSU). Two canine models, American foxhounds at NCI and beagle dogs at CSU, were used to assess acute and late normal-tissue response following a range of single doses of IOERT to various anatomic locations. The investigators designed the dog studies to mimic human thoracic and abdominal cavity surgeries where IOERT was utilized. Table 7.1 provides a list of experimental normal-tissue studies. The IOERT radiation parameters for the various studies are outlined in Table 7.2. An overall summary of the tolerance IOERT doses derived from these normal-tissue toxicity studies in intact canine tissues is found in Table 7.3, while a summary for surgically manipulated canine tissues is found in Table 7.4. A more detailed discussion of the design of these normal-tissue studies as well as the conclusions (or recommendations) for the maximum IOERT doses tolerated by a specific normal tissue is presented in the chapter.

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_7,

Table 7.1 NCI experimental normal-tissue studies

	Study name	Surgical procedure	IOERT field	Total dogs	No. IOERT	No. Sham
1.	Retroperitoneum	Laparotomy with exposure of unilateral retroperitoneum	Retroperitoneum, including portions of kidney and ureter	20	16	4
2.	Aortic anastomosis and small intestinal suture line	Laparotomy, transection aorta and reanastomosis, Roux-en-Y with formation of blind loop of small bowel	Aorta segment, blind bowel loop (separate field)	4	3	1
3.	Aortic anastomosis	Laparotomy, transection of aorta and reanastomosis	Aorta segment	11	10	1
4.	Small intestinal suture line	Laparotomy, Roux-en-Y with formation of blind loop of small bowel	Blind bowel loop	18	15	3
5.	Intact bile duct	Laparotomy, mobilization of biliary tree	Bile duct at lateral duodenum	7	6	1
6.	Biliary-jejunal anastomosis	Laparotomy, Roux-en-Y biliary-jejunal anastomosis	Biliary anastomosis	9	7	2
7.	Bladder	Laparotomy and cystotomy	Bladder trigone	18	15	3
8.	Lung and mediastinum	Right thoracotomy	Lung segment, atrium (separate field)	24	21	3
9.	Bronchial stump	Left pneumonectomy	Bronchial stump	15	12	3
10.	Esophagus	Right thoracotomy, mobilization of esophagus	Esophagus segment	13	12	1
11.	Peripheral nerve(high-dose)	Laparotomy, exposure of unilateral lumbosacral plexus	Lumbosacral plexus	27	21	6
12.	Peripheral nerve (low dose)	Laparotomy, exposure of unilateral lumbosacral plexus	Lumbosacral plexus	12	12	0
13.	Arterial vascular grafts	Laparotomy, segmental resection of infrarenal aorta and immediate grafting	Aorta segment including graft	30	24	6
14.	Spinal cord	Laparotomy, exposure of midline retroperitoneum	Lumbar vertebrae	25	22	3
Total dogs				227	196	31

NCI National Cancer Institute, *IOERT* intraoperative electron irradiation

Table 7.2 IOERT radiation parameters used in NCI studies

Study no.	Target tissues irradiated	IOERT field size/shape/ electron energy	Dose delivered, Gy (No. treated)
1.	Paravertebral soft tissues, aorta, vena cava, one ureter, lower pole one kidney	4 cm × 15 cm/ rectangle/11 MeV	0 (4), 20 (4), 30 (4), 40 (4), 50 (4)
2.	Paravertebral soft tissues, aorta, vena cava, blind end loop of jejunum	3.5 cm × 15 cm/ rectangle/11 MeV	0 (1), 20 (1), 30 (1), 45 (1)
3.	Abdominal aorta, vena cava, one ureter	3.5 cm × 15 cm/ rectangle/11 MeV	0 (1), 20 (4), 30 (3), 45 (3)
4.	Retroperitoneal soft tissues, blind end loop of jejunum	3.5 cm × 15 cm/ rectangle/11 MeV	0 (3), 20 (5), 30 (5), 45 (5)
5.	Extra-hepatic bile duct	5 cm dia./circle/11 MeV	0 (1), 20 (3), 30 (2), 45 (2)
6.	Extra-hepatic bile duct with anastomosis to jejunum	5 cm dia./circle/11 MeV	0 (2), 20 (3), 30 (2), 45 (2)
7.	Trigone of bladder (through cystotomy)	5 cm dia./circle/12 MeV	0 (3), 20 (3), 25 (3), 30 (3), 35 (3), 40 (7)
8.	Upper lobe right lung; Mediastinal soft tissues (right atrium large vessels, phrenic nerve, bronchi)	5 cm dia./circle/9 MeV	0 (3), 20 (7), 30 (7), 40 (7)
9.	Left bronchial stump, pulmonary artery and vein, esophagus, aorta, pericardium, segment of left atrium and ventricle	5 cm dia./circle/13 MeV	0 (3), 20 (4), 30 (4), 40 (4)
10.	Esophagus	6 cm dia./circle/9 MeV	0 (1), 20 (7), 30 (5)
11.	Lumbosacral nerve plexus (L4-S5)	9 cm dia./circle/11 MeV	0 (3), 20 (4), 25 (4), 30 (3), 35 (3), 40 (4), 50 (2), 54 (2), 70 (2)
12.	Lumbosacral nerve plexus (L4-S5)	9 cm dia/circle/9 MeV	10 (4), 15 (4), 20 (4)
13.	Graft of infrarenal aorta	3.5 cm × 15 cm/ rectangle/9 MeV	0 (6), 20 (8), 25 (8), 30 (8)
14.	Spinal cord	3.5 cm × 15 cm/ rectangle/11 MeV	0 (3), 20 (7), 25 (7), 30 (8)

dia diameter *cm* Centimeter

Since the greatest potential for IOERT is in treatment of abdominal and pelvic tumors, the majority of normal-tissue studies were related to the tolerance of retroperitoneal structures (aorta, vena cava, ureters, urinary bladder, peripheral nerves, bone, and muscle) and surgical anastomoses (small intestine anastomosis, biliary-enteric anastomosis, aortic anastomosis, aortic prosthetic graft). There are also reports of the effect of IOERT on other organs and tissues such as pancreas and duodenum, liver and bile duct, and thoracic organs.

Retroperitoneal Structures

Aorta and Vena Cava

Investigators at NCI administered IOERT (0–50 Gy in 10 Gy increments) in the American foxhound dog to a portal covering the retroperitoneum and encompassing the infrarenal aorta and vena cava to the bifurcation [3]. Over a 5-year follow-up period during which time contrast radiographic evaluations of the great vessels were regularly performed, no clinical or pathologic abnormalities of the

Table 7.3 IOERT tolerance for intact normal tissues in dogs, NCI studies

Tissue	Dose (Gy)	Maximum follow-up (months)	End point
Esophagus, full-thickness	20	60	Ulcerations and strictures above this dose
Esophagus, partial-thickness	40	60	No sequelae at this dose
Duodenum, lateral wall	20	60	Ulceration, fibrosis, and stenosis
Bile duct	20	60	Fibrosis and stenosis above this dose
Lung	20	60	Fibrosis at this dose
Trachea	30	60	Threshold for submucosal fibrosis
Aorta	30	60	Threshold for fibrosis, patency up to 50 Gy
Vena cava	30	60	Threshold for fibrosis, patency up to 50 Gy
Heart, atrium	20	60	Moderate fibrosis at all dose levels
Bladder	20	60	Ureteral stenosis and possible obstruction above this dose
Ureter	30	60	Threshold for stenosis and obstruction
Kidney	30	60	Threshold for complete intensified fibrosis
Peripheral nerve	15	60	Threshold for sensory-motor neuropathy
Spinal cord	20	18	Threshold for spinal hemorrhage and myelopathy

Table 7.4 IOERT tolerance for surgically manipulated tissues in dogs, NCI studies

Tissue or manipulation	Dose (Gy)	Maximum follow-up (months)	Endpoint or result
Intestinal suture line (defunctionalized)	45	60	Threshold for fistula formation
Biliary-jejunal anastomosis	20	18	Threshold for anastomotic disruption
Bronchial stump	40	60	Normal healing at this dose
Aortic anastomosis	45	60	Threshold for late fistula formation
Aortic prosthetic graft	20	60	Threshold for stenotic graft occlusion
Bladder, cystotomy	45	60	Normal healing with no changes in contractility at this dose

aorta or vena cava were observed in control sham-irradiated animals or dogs receiving up to 20 Gy [4]. Beginning 12 months following IOERT, dogs receiving 30 Gy showed minor pathologic changes of subintimal fibrosis. Animals receiving 40 Gy had developed mild to moderate intimal and subintimal fibrosis pathologically but showed no clinical or radiologic vascular abnormalities. Of four dogs receiving 50 Gy, three died of treatment-related complications to nonvascular structures within 6 months following IOERT. A single surviving 50-Gy dog showed aortic and caval patency at 5 years, with moderate fibrosis in the subintimal and medial regions of both the aorta and vena cava.

At CSU, investigators randomized adult beagle dogs into three treatment groups to compare normal-tissue tolerance to (1) single-dose IOERT, (2) fractionated EBRT, or (3) fractionated EBRT combined with an IOERT boost. The first group received single IOERT doses of 6 MeV electrons ranging from 17.5 to 55 Gy. IOERT was delivered through a 5 cm × 8 cm Plexiglas applicator inserted through a midventral celiotomy. The second group of dogs received fractionated doses of EBRT delivered in 30 fractions of 2, 2.33, or 2.67 Gy (a total dose of 60, 70, or 80 Gy) over a period of 6 weeks. Six MV photons were delivered to a 5 cm × 10 cm field through bilaterally opposed portals to the retroperitoneal tissue. A third treatment group included dogs receiving 50 Gy EBRT in 25 fractions over 5 weeks followed by an IOERT boost of 10–47.5 Gy. IOERT was given the week following completion of EBRT.

The CSU investigators found 35 Gy IOERT alone or 27 Gy IOERT plus 50 Gy EBRT corresponded to a 50% probability for developing aneurysms and/or severe thromboses of the aorta (Table 7.5) [5].

Table 7.5 Tolerance of canine retroperitoneal tissue to IOERT/EBRT, CSU studies

Tissue	End point	IOERT ED_{50}	IOERT + EBRT ED_{50}	Estimated MTD IOERT ± EBRT
Aortic wall [5, 6]	Aneurysms or thromboses	35.0 Gy (5 years)	27.0 Gy (5 years)	30 Gy IOERT
	Narrowing	38.8 Gy (5 years)	31.0 Gy (5 years)	20 Gy IOERT + 50 Gy EBRT
Branch arteries [7]	50% occlusion	24.8 Gy (5 years)	19.4 Gy (5 years)	
Ureter [7]	Radiographic abnormalities	32.5 Gy (5 years)	29.0 Gy (5 years)	25 Gy IOERT 17.5 Gy IOERT + 50 Gy EBRT
Muscle [7, 27]	Muscle fibers decrease	21.2 Gy (2 years) 33.8 Gy (5 years)	22.9 Gy (2 years) 25.2 Gy (5 years)	20–25 Gy IOERT + 50 Gy EBRT
	Vessel lesions	19.2 Gy (2 years) 25.8 Gy (5 years)	16.0 Gy (2 years) 18.0 Gy (5 years)	
Vertebral artery [26]	Fibrosis, hyalinization, necrosis	21.7 Gy (2 years) 27.0 Gy (5 years)	20.1 Gy (2 years) 20.0 Gy (5 years)	
Bone [26] (Lumbar vertebra)	Bone necrosis	38.2 Gy (2 years) 28.5 Gy (5 years)	32.5 Gy (2 years) 14.4 Gy (5 years)	15–20 Gy IOERT + 50 Gy EBRT

The estimates for maximum tolerated dose were based on those doses at which minor or no significant injury was observed

CSU Colorado State University, *MTD* maximum tolerated dose, *IOERT* intraoperative electron irradiation, *EBRT* external-beam irradiation, *Fx* fractions, *wk* weeks

Experimental design, CSU studies: (a) IOERT only, 17.5–55 Gy, (b) IOERT(10–47.5 Gy) plus 50 Gy/25 Fx/5 wk EBRT, (c) EBRT only, 60–80 Gy/30 Fx/6 wk

A significant risk of aneurysms or large thrombi was found with 30 Gy IOERT alone or IOERT > 20 Gy plus 50 Gy EBRT. This was determined at necropsy 4–5 years after treatment. The ED_{50} for aortic narrowing was 38.8 Gy IOERT alone and 31 Gy IOERT plus 50 Gy EBRT. The ED_{50} for branch artery injury was 24.8 Gy IOERT alone and 19.4 Gy IOERT plus 50 Gy EBRT. The ED_{50} for incidence of small thrombi in the aorta was about 29 Gy for IOERT alone and 23.5 Gy IOERT plus 50 Gy EBRT. In summary, the authors concluded that 20 Gy IOERT combined with 50 Gy EBRT might be near the MTD for the aorta and branch arteries and that IOERT doses in the range of 15 Gy had an effect roughly equivalent to that caused by an EBRT dose greater by a factor of five or more [6].

Most importantly, the canine experience suggested that large vessels can tolerate large, single radiation doses without clinical consequences. Since the canine vessels ranged from 5 to 10 mm in diameter, some caution must be exercised in extrapolating data to smaller vessels, where a relatively modest degree of mural fibrosis could result in a higher proportionate luminal narrowing than would be observed in larger caliber vasculature.

Ureter

The effects of IOERT on the intact ureter were investigated at the NCI in 20 dogs using doses of 0, 20, 30, 40, or 50 Gy delivered to an area extending from the renal vessels to the aortic bifurcation [3]. The portal included the inferior pole of one kidney and a segment of ipsilateral ureter. Doses up to 40 Gy produced few clinically apparent toxicities in the acute period, except for a single 30-Gy animal, which developed septic hydronephrosis 6 weeks postoperatively.

No significant clinical or histopathological changes were detectable in the NCI nonirradiated control or 20 Gy animals with up to 5 years of follow-up. Six months following treatment, one 30-Gy and one 40-Gy animal developed changes in the irradiated kidney on intravenous pyelography, which were consistent with radiation nephritis. Another 40-Gy dog developed ureteral stenosis with hydronephrosis at 6 months. Three of four animals that received 50 Gy suffered acute or chronic clinical complications: two experienced rectal perforation with purulent peritonitis due to bowel that was inadvertently irradiated, while another animal developed septic hydronephrosis and radiation nephritis. Two 30-Gy animals were humanely euthanized within 12 months of treatment: one animal developed septic hydronephrosis and had a stenotic ureter; moderate radiation nephritis was noted in another animal, which was clinically well. In two 40-Gy animals euthanized within 12 months postoperatively, moderate to severe radiation effects were noted in both the ureter and kidney, with edema and fibrotic inflammation. In all the three 50-Gy dogs, ureters in the irradiated fields showed significant stenosis, and both ureteral and renal fibrosis were prominent within 12 months.

Follow-up at 5-years of surviving NCI dogs revealed dense retroperitoneal fibrosis and encasement of the ureters in all dogs receiving doses of 30 Gy or greater [4]. A surviving 30-Gy dog developed an osteosarcoma within the radiation field. A 40-Gy dog had chronic right hydronephrosis which had persisted since 6 months following treatment. A 50-Gy dog required nephrectomy for ureteral obstruction and sepsis several months following IOERT. These studies suggested that ureteral tolerance to IOERT is 20–30 Gy. Significant fibrosis and resulting stenosis with the possibility of obstruction are likely at higher doses.

At CSU, investigators studied ureteral injury following IOERT with or without external-beam radiation therapy (EBRT) in beagle dogs. The follow-up time was 5 years [7]. The canine ureter appeared to tolerate 17.5 Gy IOERT with no evidence of injury and 25 Gy IOERT with a low probability for mild dilatation. Severe injury occurred at doses greater than 25 Gy IOERT. The ED_{50} for radiographic abnormalities was 32.9 Gy. The ureter tolerated 10 Gy IOERT combined with 50Gy EBRT. The ED_{50} was 29 Gy IOERT plus 50 Gy EBRT. Histologic evidence suggested that chronic injury of the ureter at 5 years had a vascular etiology.

Volume Effect on Ureter

The influence of ureteral volume to normal-tissue injury following IORT was assessed by a number of investigators over the past decade. In fractionated EBRT, ureteral volume irradiated does not significantly impact the probability for normal-tissue complications [8]. However, clinical investigators noted that increased ureteral volume irradiated may unduly influence normal-tissue response from IOERT. Thus, a number of studies were conducted in canines, which subsequently determined ureteral response to IOERT is strongly dependent on the total volume irradiated.

In CSU studies by Gillette et al., beagle dogs were given variable IOERT dose (12–54 Gy) to lengths of 2, 4, or 8 cm [7]. Ureteral strictures were evaluated with excretory urography. At 3 years, the ED_{50} for the 8-cm length was 22 Gy. The ED50 increased to 43 Gy for 4 cm and 85 Gy for 2 cm. Thus, the authors concluded that minimizing the volume of ureter within the irradiation field could reduce the incidence of ureteral stenosis [7].

The results from Van Kampen et al. in 2003 further confirmed Gillette's 1998 conclusions. In Van Kampen's study from Germany, 16 beagle dogs were randomized to receive 30 Gy IOERT to ureter volumes of 12, 8, or 4 cm [8]. The animals were followed up to 12 months following radiation exposure using magnetic resonance imaging, clinical examination, and resting sequential renography. These studies provided additional evidence detailing ureteral obstruction following IORT corresponds to the total volume irradiated.

Studies of ureters in human cancer patients showed a 50% incidence of obstruction following 10 Gy and 70% incidence after doses of 15–25 Gy IOERT [9]. The greater incidence of obstruction than that observed in young beagle dogs may have been due to greater age, surgical manipulation, and/or tumor-bed effects.

Bladder

Bladder tolerance to IOERT was investigated in a NCI study involving 18 dogs [10, 11]. After laparotomy and cystotomy, a 5-cm circular field was placed on the bladder mucosa and doses of 0, 20, 25, 30, 35, or 40 Gy IOERT were administered. The radiation portal included the trigone and both ureteral orifices. The dogs were followed closely up to 5 years with clinical evaluation, intravenous pyelography, and cystometry. No acute complications were observed in any animal. The likelihood of renal failure secondary to bilateral hydronephrosis at 2 years increased to 33% in animals receiving ≥25 Gy [10]. Obstruction occurred at the ureterovesical junction.

Among NCI animals followed for 5 years, one dog developed a rhabdomyosarcoma in the treatment field [11]. Distinct histopathologic differences between irradiated and unirradiated tissue, including mucosal inflammation, edema, and mural fibrosis, were seen within the IOERT portals. However, no dose–response relationship of severity of damage was noted for the irradiated tissues, with a similar histologic appearance at virtually all doses. On follow-up cystometry, no irradiated animal was noted to have marked changes in contractility from baseline or with respect to control animals.

In a Japanese study of 116 patients treated with IOERT for localized bladder cancer, only four patients developed significant complications [12]. Three patients had transient ureterovesical junction obstruction within the first few months following IOERT, and one patient developed progressive bilateral hydronephrosis.

Based on animal plus clinical findings, IOERT doses ≤20 Gy would be expected to contribute little to chronic toxicity. IORT doses >20 Gy carry the risk of ureteral obstruction and consequent renal damage unless ureteral stents are placed, as clinically indicated.

Peripheral Nerve

Clinical Studies: NCI

Numerous clinical studies have reported observation of peripheral neuropathies in patients 6–9 months following IOERT. Sindelar et al. [1] reported mild to moderate perineural fibrosis in 7 of 22 patients receiving IOERT doses of 20–25 Gy. In 1985, Kinsella et al. [14] observed clinically detected neuropathies with loss of sensory and motor function in 5 patients following combined excision with 20–26 Gy IOERT.

From 1980 to 1985, NCI conducted a randomized trial in which 35 patients with retroperitoneal sarcomas were randomized to receive EBRT ± IOERT [13]. Patients randomized to EBRT alone received 35–40 Gy to an extended field over 4–5 weeks and an additional 15 Gy over 2 weeks to a reduced field. The IOERT group received 35–40 Gy in 4–5 weeks to an extended field and an IOERT dose of 20 Gy to abutting fields (2–6 abutting fields) plus IV misonidazole. Neuropathy of any severity was seen in only 1 of 20 patients treated with postoperative EBRT alone vs. 9 of 15 treated with IOERT plus postoperative EBRT. Seven of 15 patients (47%) with 20 Gy IOERT as a component of treatment had moderate or severe neuropathy vs. 0 of 20 with EBRT alone ($p < 0.01$).

Animal Studies: NCI and CSU

In a subsequent study investigating peripheral-nerve toxicity following IOERT in an animal model, Kinsella et al [14] reported that paresis developed in foxhounds following single doses as low as 20 Gy delivered to the lumbosacral plexus and sciatic nerve while surgically exposed. No clinical injury was observed in the foxhounds following doses of 15 Gy or less. The main histologic observation was a loss of predominantly large myelinated fibers. They reported no evidence of vascular occlusion or thrombosis. Fibrosis was present in the endoneurium, but not in the perineurium.

The response to large, single IOERT doses reported from the NCI was comparable to findings in a study at CSU comparing peripheral-nerve tolerance in the retroperitoneal area with fractionated EBRT, IOERT, or EBRT to 50 Gy/25 fractions/5 weeks plus variable IOERT doses [15] (Table 7.6). No clinical signs of neuropathy were observed in the CSU study following EBRT to the lumbosacral plexus with doses of 60, 70, or 80 Gy delivered in 30 fractions over 6 weeks. Following single IOERT doses of 15 Gy, however, there were significant electrophysiologic changes. Clinical signs of neuropathy were observed at 20 Gy and higher. Histology revealed loss of axons and myelin and an increase in endoneural, perineural, and epineural connective tissue. In the CSU studies, definite vascular lesions were observed and included necrosis and hyalinization of medial small arteries and thrombosis and hemorrhage at high doses.

In a later CSU study, Vujaskovic et al. [16] reported response of surgically exposed and isolated right sciatic nerve in the midfemoral region and observed similar histologic changes to those reported earlier. That is, while no vascular thrombosis or occlusions were observed, there was histomorphometric evidence of a loss of small vessels. It appeared that a dose of greater than 20 Gy would cause some clinically significant peripheral-nerve injury as suggested earlier by Kinsella et al. [17]. Clinically significant neurologic or physiologic changes were not present in dogs given 20 Gy IOERT or less. It appeared that the isolated sciatic nerve irradiated in the

Table 7.6 IOERT-related dog neuropathy–electrophysiology abnormalities

NCI (foxhound)		Colorado State University (CSU, beagle)					
IOERT only		IOERT only		IOERT + 50 Gy EBRT[a]	External beam (EBRT) only		
Study 1	Study 2	Dose (Gy)	No.	No.	Dose (Gy)	No.	No. Fx/time
–	0/4	10	–	0/5	0	0/5	–
–	0/4	15	2/5	1/5	50	0/4	25 Fx 5 weeks
3/4	4/4	20	4/5	2/5	60	0/6	30 Fx 6 weeks
2/2	–	25	4/4	–	70	0/5	30 Fx 6 weeks
–	–	27.5	–	2/5	80	0/4	30 Gx 6 weeks
3/3	–	30	4/4	–			
3/3	–	35	2/2	5/5			
4/4	–	40	–	–			
–	–	42.5	3/3	5/5			
1/1	–	50	2/2	–			
1/1	–	65	–	–			
3/3	–	75	–	–			

EBRT external-beam irradiation, *IOERT* intraoperative electron irradiation, *No.* number, *Fx* fractions
[a]50 Gy in 25 fractions over 5 weeks

midfemoral region, distal to the lumbosacral plexus, was perhaps somewhat less sensitive to IOERT than the nerve or nerve roots irradiated in the lumbosacral plexus or retroperitoneal area. Vujaskovic et al. [16] suggested that the difference might be because neuropathies caused by IOERT of the lumbosacral region resulted from the direct effects of irradiation on nerve and effects of damage to regional muscle and vasculature on the nerve. It was also suggested that severe fibrosis that developed after IOERT to muscle could entrap the nerve and its vasculature, causing more severe nerve fibrosis and nerve-fiber loss secondary to the vascular damage. Single doses to the isolated sciatic nerve in the femoral region caused less damage to surrounding tissues and might have prevented some of the secondary effects of irradiation. There was also the possibility suggested that the sciatic nerve in the midfemoral area may be more hypoxic naturally or may be made hypoxic during the isolation procedure and, therefore, less sensitive to irradiation [18]. The main difference was likely to be the time of observation, which was only 1 year following irradiation of the sciatic nerve.

Kinsella et al. [17] reported time–dose relationships for paresis following experimental IOERT of the lumbosacral plexus and sciatic nerve of the dog. Although paresis was observed as early as 1 year, it is likely that smaller doses would require a longer period to cause paresis. Neuropathies have been reported to occur as late as 11 years after EBRT for breast cancer [19]. The time course for development of neuropathies after IOERT ranged from 1 to 32 months with a median of 15 months [9, 14].

It appears that injury to the vasculature is an important factor leading to damage to the nerves. Schwann cells and microvasculature are two critical structures associated with peripheral nerves, which are directly affected by irradiation. LeCouteur et al. [15] reported a 50% probability of severe damage to the small arteries and arterioles within 2 years following 19.5 Gy IOERT. Vascular lesions were not observed with EBRT alone. Vujaskovic et al. noted a decrease in small vessels 1 year after IOERT treatment in beagles [16, 18]. Clinical tolerance to peripheral-nerve injury in the dog appears to be ≤20 Gy IOERT.

Clinical Studies: Mayo Clinic

An initial analysis of nerve and ureteral tolerance with IOERT on a total of 51 patients who received IOERT at Mayo Clinic Rochester as a component of treatment for the management of primary or recurrent pelvic malignancies, initially unresectable for cure was published (Table 7.7) [10]. The treatment consisted of EBRT (median 50.4 Gy), maximal resection when feasible and IOERT boost (range 10–25 Gy) utilizing 9–18 MeV electrons. Fifty of the 51 patients were eligible for peripheral-neurotoxicity analysis. Complications were scored prospectively on a grade (gr) 1–4 basis utilizing criterion developed by the NCI IOERT contract group (NCI, MGH, Howard University, Mayo Clinic) [20, 21]. Sixteen of the 50 patients (32%) developed gr 1–3 peripheral neuropathy (unilateral pelvic or extremity pain, leg weakness, numbness, or tingling). Pain was severe (gr 3) in only 3 (6%). In the two patients with severe weakness (gr 3), the surgical option for cure was hemipelvectomy – 1 and hemicorporectomy – 1. Neuropathy incidence by IOERT location was pelvic sidewall – 15/32 (47%), presacrum –1/12 (8%), central pelvis – 0/6.

Colorectal Cancer: General

Mayo Clinic tolerance analyses of IOERT regimens in 178 patients with locally advanced, previously unirradiated, primary (55 evaluable patients) or locally recurrent (123 patients) colorectal cancer [22, 23] suggest a relationship between IOERT dose and the incidence of gr 2 or 3 neuropathy (Table 7.8; EBRT factors appeared constant). This trend is consistent with animal data that suggests a correlation between IOERT dose and the incidence of clinical and electrophysiologic neuropathy in dogs [1, 15, 17]. The incidence of gr 3 neuropathy was ~5% in both primary and locally recurrent patients, and the incidence of gr 1–3 neuropathy was ~32% as in the initial Mayo tolerance analysis by Shaw et al. [9].

Primary Colorectal

In the Mayo primary colorectal IOERT analysis, symptomatic or objective neuropathy was documented in 18 of 55 evaluable patients or 32% (10 of 18 or 56% had only gr 1 toxicity usually manifesting as mild or intermittent paresthesia and/or pain not requiring narcotics). Severe neuropathy (gr 3) was documented in only 3 of 55 patients or 5.5% (IOERT factors: dose of 15, 20, and 20 Gy; field size 7.0, 7.5, and 7.5 cm; energy 9, 12, and 18 MeV). One of the three had only microscopic residual after resection but received an IOERT dose of 20 Gy, since the EBRT dose was limited to 16.2 Gy in nine fractions because of prior pelvic EBRT. Grade 2 or 3 nerve toxicity was analyzed as a function of disease status and treatment factors (EBRT dose; IOERT dose, field size, and energy; amount of residual after maximal resection). Seven of the eight patients with gr 2 or 3 toxicity remained continuously free of disease within irradiation fields, which suggests their neuropathy was treatment-related. The remaining patient had a 6 cm × 5 cm × 4 cm nodal mass that could not be resected after preoperative EBRT of 50.4 Gy in 28 fractions over 5½ weeks. An IOERT dose of 20 Gy was given with 18 MeV electrons; the patient died 14 months from initiation of treatment with disease persistence within EBRT and IOERT fields. In the five patients with gr 2 neuropathy, most had pain requiring narcotics.

Of the seven patients with presumed treatment-related gr 2 or 3 nerve toxicity, incidence vs. IOERT dose was as follows – 57 fields in 55 patients (Table 7.9): 1 of 29 (3%) with ≤12.5 Gy, 4 of 19 (21%) with 15 or 17.5 Gy, and 2 of 9 (22%) with ≥20 Gy (both had a gr 3 neuropathy). These data suggest a relationship between IOERT dose and the incidence of gr 2 or 3 neuropathy (≤12.5 Gy, 1 of 29 or 3%, ≥15 Gy, 6 of 26 or 23%, $p = 0.03$). Of the five patients with gr 2 intolerance,

Table 7.7 Clinical peripheral neuropathy characteristics with pelvic IOERT, Mayo Clinic Rochester

				Time course (months from IOERT)			
		Severity		Onset		Resolution	
Characteristic	Incidence[a] [No. (%)]	Mild/mod [No. (%)]	Severe [No. (%)]	Range	Median	Resolved [No. (%)]	Range
Pain	16/50 (32)	13 (26)	3 (6)	1/2–18	15	6/14 (42)[b]	5–32[c]
Motor	8/50 (16)	6 (12)	2 (4)	3–22	7	1/8 (13)	20
Sensory	11/50 (22)	11 (22)	(0)	3–22	7	4/11 (36)	1,7,19,20

Modified from Shaw et al. [9]

[a]One patient excluded who died postoperatively

[b]Two patients excluded who were lost to follow-up

[c]Median 15 months

Table 7.8 Colorectal IOERT, Mayo Clinic – IOERT dose vs. neuropathy

		IOERT dose vs. incidence of neuropathy (grade 2 or 3)[a]		
		≤12.5 Gy	≤12.5 Gy	
Disease presentation	References	No. (%)	No. (%)	*p* value
Primary[b]	23	1/29 (3)	6/28 (21)	0.03
Recurrent, no prior EBRT[c]	22	2/29 (7)	19/101 (19)	0.12
Primary + recurrent		3/58 (5)	25/129 (19)	0.01
Recurrent (grades 1–3)[d]	24	23/269 (9)	70/337 (21)	0.0003

[a]Grade 2 neuropathy usually manifest as pain requiring narcotics
[b]57 IOERT fields in 55 evaluable patients
[c]130 IOERT fields in 123 patients
[d]607 recurrent colorectal cancer patients; no prior EBRT in field of relapse – 359 patients, prior EBRT – 248; neuropathy (≤12.5 vs. ≥15 Gy IOERT): grade 2, 4 vs 10%; grade 3, 1 vs 4%

Table 7.9 Primary colorectal IOERT, Mayo – IOERT dose vs. grade 2 and/or 3 neuropathy

	Grade 2[a] or 3 neuropathy		Grade 3 neuropathy	
IOERT dose (Gy)	No.	%	No.	%
≤12.5	1/29	3[b]	0/29	0
15 or 17.5	4/19	21	1/19	5
≥20	2/9	22	2/9	22
Total	7/57[c]		3/57[c]	

Modified from Gunderson et al. [23]
[a]Grade 2 neuropathy usually defined as pain requiring narcotics
[b]*p* value, log rank = 0.03 with ≤12.5 Gy vs. ≥15 Gy for grade 2 or 3 neuropathy
[c]Grade 3 neuropathy in 3 of 55 evaluable patients (5.5%) treated with 57 IOERT fields

one received 20 Gy for gross residual (5 cm × 4 cm × 1.5 cm), three received 15 Gy (negative margins – 2, microscopic residual – 1), and one received 12.5 Gy (negative margins). The relative incidence of gr 3 neuropathy by IOERT dose was 0 of 29 for ≤12.5 Gy, 1 of 19 (5%) for 15 or 17.5 Gy, and 2 of 9 (22%) for ≥20 Gy (Table 7.9).

Recurrent Colorectal

In the recurrent colorectal analysis, symptomatic or objective neuropathy was documented in 42 of 123 patients or 34% (21 of 42 or 50% had only gr 1 toxicity). Severe neuropathy (gr 3) was documented in 7 of 123 patients or 6%. Two of the seven had local relapse as a potential cause of their neuropathy (IOERT doses of 15 and 20 Gy). IOERT factors in the seven patients included a dose of 15 Gy in three and 20 Gy in four. Grade 2 or 3 nerve toxicity was analyzed as a function of disease status and treatment factors. All 14 patients with gr 2 toxicity had remained continuously free of disease within irradiation fields, which suggests that their neuropathy was treatment-related. Incidence of gr 2 or 3 nerve toxicity by IOERT dose was as follows (130 fields in 123 patients): ≤12.5 Gy, 2/29 (7%); ≥15 Gy, 19/101(19%), Table 7.8.

In the most recent MCR analysis of 607 patients with locally recurrent colorectal cancer, the incidence of gr 1–3 neuropathy was 15% (gr 1 – 32 pt, 5%; gr 2 – 43 pt,7%; gr 3 – 18 pt, 3%; Table 7.8) [24]. For IOERT doses of ≤12.5 Gy vs. ≥15 Gy, the incidence of gr 2 neuropathy was 4 vs. 10% and gr 3 was 1 vs. 4% ($p < 0.0003$).

Summary: Peripheral Nerve

Many patients who are candidates for IOERT present with pain from recurrent tumors due to neurologic tumor compression or invasion. While all patients are given an informed consent about possible nerve-related side effects, they are aware that with uncontrolled tumor they will often have similar side effects. On the basis of both human and animal data, when a full component of EBRT options exists (i.e., 45–54 Gy fractionated EBRT can be delivered), an IORT boost dose of 10–20 Gy should be used dependent on the amount of tumor remaining after maximal resection. If a marginal gross total resection can be accomplished after full-dose preop EBRT, the IORT dose can be limited to 10–12.5 Gy, with an associated decreased risk of neuropathy. IORT doses >20 Gy to ≤25 Gy are used in our institutions only when EBRT doses must be limited because of prior EBRT.

Spinal Cord

The maximally tolerable doses for spinal cord irradiation in beagles were discovered accidentally as a result of an oversight in dosimetry [25]. Twenty-two beagles were treated with nominal IOERT doses of 20 and 30 Gy. No bolus was used for the treatment to retroperitoneal fields. Because of the omission of bolus and the consequent lack of surface dose absorption with resulting deep penetration, the spinal cord was located at the depth of maximum dose in these dogs. Of 22 animals exposed to spinal-cord irradiation, 18 developed paralysis and incontinence. These animals were sacrificed for compassionate reasons between 6 and 13 months postoperatively. At necropsy, all animals had severe spinal hemorrhage in the irradiated segments, with consistent demyelination and leukomalacia. There was little surprise that single doses of 20–30 Gy caused significant spinal-cord toxicity. The addition of bolus with IOERT to subsequently treated animals decreased spinal-cord dose to approximately 10% of nominal levels and totally prevented cord toxicity. This experience emphasized that careful attention to detail and rigorous dosimetry is crucial to minimize potential toxicity to spinal cord.

Bone, Cartilage, and Muscle

Bone necrosis of the lumbar vertebrae was studied at CSU in dogs 2 and 5 years after IOERT, EBRT, or the combination of both [26]. Two years after irradiation, the dose causing significant bone necrosis, as determined by at least 50% empty lacunae in the vertebral cortex, was 38.2 Gy IOERT alone and 32.5 Gy IOERT plus 50 Gy EBRT/25 fractions/5 weeks (Table 7.5). Five years after irradiation, the ED_{50} was 28.5 Gy for IOERT only and 14.4 Gy for IOERT plus 50 Gy EBRT. The ED_{50} for the lesions of the ventral vertebral artery was 21.7 Gy IOERT only and 20.1 Gy IOERT plus 50 Gy EBRT 2 years after irradiation and 27.0 Gy IOERT only and 20.0 Gy IOERT plus 50 Gy EBRT 5 years after irradiation. The authors concluded that doses of 15–20 Gy IOERT combined with 50 Gy EBRT in 2 Gy fractions may be near the tolerance level for late-developing bone injury.

Powers et al. [27] also examined psoas muscle 2 or 5 years after IOERT. They found a 50% decrease in the percentage of muscle fibers after 21.2 and 33.8 Gy 2 and 5 years after IOERT alone, and 22.9 and 25.2 Gy 2 and 5 years after IOERT plus 50 Gy EBRT. The ED_{50} for severe vessel lesions was 19.2 and 25.8 Gy 2 and 5 years after IOERT alone and 16.0 and 18.0 Gy 2 and 5 years after

IOERT plus 50 Gy EBRT. Although it appeared from the study that the MTD of IOERT combined with 50 Gy of EBRT to sublumbar musculature and supporting vasculature was between 20 and 25 Gy, the determination of higher doses to observe a late effect at 5 years compared to 2 years is contrary to most of our understanding of radiobiology and should be interpreted carefully. This could reflect experimental variation, compensensatory muscular hypertrophy, or resolution of late effects by some other mechanism.

Surgical Anastomosis

NCI studies by Tepper et al. [28] investigating the tolerance of canine aortic and jejunum anastomosis to IOERT, showed that doses up to 30 Gy could be delivered to the anastomotic site with minimal risk of suture line breakdown or inadequate healing. However, the authors cautioned about possible late stenosis at the site of an irradiated vascular anastomosis. A study of cell turnover after IOERT in intact and surgically anastomosed aorta and intestine showed lowered cell proliferative capacity of irradiated tissue, but no significant effect on local inflammatory response. Radiation-induced depression of cell turnover rate decreases with time with the ability of intact and surgically manipulated aorta and intestine to recover from radiation-induced damage [29].

Small-Intestine Anastomosis

The NCI instituted large animal trials to determine the IOERT tolerance of defunctionalized anastomosed small intestine [2, 3, 28]. A jejunal blind loop was surgically constructed, with intestinal continuity maintained by an end-to-side jejunojejunostomy. Of 18 dogs treated with doses ranging from 0 to 45 Gy, three developed intussusception of the blind loop requiring surgical intervention. Alteration of surgical technique to include mesenteric fixation of the blind loop corrected the problem in subsequent dogs. One week postop, there were no histologic differences between irradiated segments and jejunum outside the IOERT field. However, animals receiving 45 Gy demonstrated reduced anastomotic bursting strength with some values less than 10% of those for animals receiving lesser doses. No major histologic differences were noted between 3 and 12 months of follow-up, except for moderate mural fibrosis in some 45-Gy animals.

After a 5-year follow-up, surviving animals which received 45-Gy IOERT developed internal interloop fistulas of the irradiated suture line [4]. Mucosal atrophy and hyaline necrosis of the intestinal wall was also present. Five-year follow-up of animals receiving 30 Gy showed varying degrees of hyaline degeneration of the muscularis, associated with submucosal fibrosis.

It, therefore, appears that while acute IOERT tolerance of defunctionalized intestinal anastomoses can be as high as 45 Gy, chronic complications render this dose excessive. A dose of 30-Gy IOERT appears to be well tolerated in the long term.

Biliary-Enteric Anastomosis

Additionally, IOERT (0–45 Gy) was delivered at NCI to dogs that had undergone biliary-enteric anastomoses [28]. After jejunojejunostomy with formation of a jejunal blind loop, the bile duct was transsected and anastomosed to the blind loop in an end-to-side fashion. One control animal remained clinically well through 18 months of follow-up. However, all irradiated animals died of complications of therapy. Five animals suffered anastomotic disruption within 3 weeks postoperatively.

One dog experienced fibrotic anastomotic obstruction after 20-Gy IOERT, which led to cholangitis. Another 45-Gy animal suffered bile-duct necrosis with subsequent bile peritonitis. These results suggest that IOERT to biliary-enteric anastomoses contributes to poor healing and should be avoided clinically.

Aortic Anastomosis

Aortic anastomoses were constructed in NCI animals by the transection of the midabdominal aorta and end-to-end resuturing [2, 28, 29]. IOERT doses of 0–45 Gy were delivered to a total of 11 animals. Mild medial thickening with elastic fiber destruction was noted in animals that received 30–45 Gy when sacrificed 7 days postoperatively. Out of the remaining animals followed through 14 months postoperatively, one animal developed anastomotic obstruction with collateralization after 20 Gy IOERT, and another animal developed an anastomotic arteriovenous fistula 2 months after 45 Gy. No suture line dehiscence was noted at any dose level, although the development of the vascular fistula was considered to be dose-limiting.

Aortic Prosthetic Graft

In another NCI study, a total of 30 animals underwent transection of the infrarenal aorta, with segmental resection and reanastomosis with a polytetrafluoroethylene prosthetic graft [30]. IOERT doses of 0, 20, 25, or 30 Gy were administered, after which half of the animals were randomized to 36-Gy EBRT in 10 fractions of 3.6 Gy over 4 weeks. Postoperative anticoagulation was provided with aspirin. The most frequent acute complication was thrombosis at the graft site, which affected seven of ten animals followed up to 6 months. Four dogs developed perioperative thrombi requiring emergent surgical thrombectomy; three had subsequent thrombus recurrence. Thrombosis was unrelated to IOERT dose and was considered to be a complication of surgical technique or manipulation.

Over a 5-year follow-up, anastomotic stenosis was the most frequent toxicity, although this was not symptomatic in any animal due to the formation of collaterals bridging the grafted segment. Graft occlusion occurred in three of 14 animals receiving IOERT doses of 20 Gy, while graft occlusion occurred in five of six dogs receiving 25 Gy or more. Incidence of graft occlusion was similar in both the IOERT alone and the IOERT + EBRT groups. Histologic changes were generally better correlated with total radiation dose (i.e., IOERT + EBRT) than with IOERT doses alone. Pseudointimal hyperplasia and thrombosis were the most commonly assessed changes on histopathologic review.

It can be concluded that IOERT may be administered to a fresh vascular prosthesis without fear of anastomotic dehiscence. Long-term patency of irradiated grafts, however, is questionable even with doses of <20 Gy.

Pancreas and Duodenum

Ahmadu-Suka et al. [31] studied the effect of IOERT on pancreas and duodenum in a total of 24 beagle dogs treated at CSU. They used IOERT doses ranging from 17.5 to 40 Gy in combination with 50 Gy EBRT given in 2 Gy fractions over 5 weeks. Dogs exposed to 32.5 and 40 Gy IOERT developed duodenal ulcers. Exocrine pancreatic insufficiency occurred in one dog given 25-Gy IOERT. Histologic results showed damage to the acinar cells, blood vessels, and ducts, and pancreatic

fibrosis. Following further study of pancreatic exocrine function, the authors concluded that doses less than 30-Gy IOERT plus 50-Gy EBRT could be tolerated for pancreatic carcinoma. The same study also showed that IOERT doses ≥20 Gy plus 50-Gy EBRT may result in serious long-term complications due to radiation injury of the duodenum. This is in agreement with a study of late effects of IOERT on rat duodenum [32, 33]. In those studies, the authors indicated that IOERT doses ≥20 Gy could cause unacceptable and irreversible late complications.

Liver and Bile Duct

Several IOERT studies of rat liver demonstrated that IOERT was a feasible adjunct to surgical resection of the liver with minimal functional and pathologic lesions [34–36].

Sindelar et al. [37] studied tolerance of bile duct to IOERT in a total of seven dogs. Using doses of 20, 30, and 45 Gy and a follow-up of 18 months, the authors concluded that IOERT delivered to the region of the common duct at these doses led to ductal fibrosis, partial biliary obstruction with secondary hepatic changes, and duodenal fibrosis if bowel wall was included in the field.

Intact Bile Duct

Intact canine bile-duct tolerance was investigated at the NCI [37]. Experimental dogs received IOERT to the subhepatic space and hepatoduodenal ligament at doses of 0, 20, 30, or 45 Gy with a follow-up of 5 years [4, 37]. No perioperative complications were noted in any animal. However, late duodenal obstruction developed in all doses because of inclusion of the lateral duodenal wall in the field. Latency varied from 6 weeks at 45 Gy to 8 months at 20 Gy. Bile ducts remained patent in all but a single 45 Gy animal, although pathologic ductal fibrosis was evident, which increased as a function of dose. In irradiated dogs at all doses, changes of periportal inflammation and early fibrosis that appeared within 3 months were considered to be a function of partial biliary obstruction caused by bile-duct fibrosis. Three of six irradiated animals developed frank biliary cirrhosis by 12 months, presumably from chronic partial biliary obstruction. However, one animal, which received 30 Gy to the bile duct, was followed for 5 years without clinical sequelae. Postmortem examination at the time of elective sacrifice revealed no evidence of obstruction of biliary cirrhosis [4]. Atrophy with mild fibrosis was noted in the bile-duct wall.

The potential acute toxicities and chronic partial biliary obstruction, which can lead to cirrhosis, limit IOERT doses above 20 Gy to the bile duct. However, some animals may remain asymptomatic for long periods at higher doses. Duodenal bypass should be considered if any portion of the duodenal wall must be included in the IOERT field because of the potential for fibrosis and subsequent stenosis or obstruction.

Thoracic Organs

The tolerance of mediastinal structures to IOERT doses of 20, 30, or 40 Gy was studied using adult American foxhounds [38]. There were no acute or late IOERT-related mortalities. After necropsy, the irradiated lung showed evidence of acute pneumonitis at 1 month with progressive fibrosis at 3 months and 1 year. Tracheal and esophageal reactions were minimal. Right atrial tissues showed signs of cardiac damage. The phrenic nerves showed evidence of perineural fibrosis. The 1- and

2-year results showed significant toxicity at doses over 20 Gy. Examination of tissues at 5 years suggested that IOERT in the mediastinum may be safe at dose levels ≤20 Gy [39].

Sindelar et al. [40] investigated tolerance of esophagus to IOERT. Dogs receiving 20-Gy IOERT showed transient mild dysphagia and mild esophagitis, but no significant clinical or pathologic complications. Dogs exposed to 30-Gy IOERT developed severe ulcerative esophagitis within 6 weeks of treatment and chronic ulcerative esophagitis with stricture formation by 9 months following IOERT.

Esophagus, Full-Thickness

Thirty-seven dogs underwent right thoracotomy with mobilization of the esophagus and IOERT on two NCI protocols [40, 41]. Segments of esophagus received full-thickness IOERT of 0, 20, or 30 Gy. Clinical examinations, barium swallows, and esophagoscopy were performed to assess toxicity for up to a 2-year follow-up period. No toxicities were noted in the first week postoperatively. No clinical toxicities were noted over the entire follow-up period in the sham-irradiated controls and in the 20 Gy animals. Endoscopic examinations were normal in all control and 20-Gy animals through 12 months of follow-up.

All 30-Gy IOERT animals suffered signs of dysphagia and weight loss, which were relieved by dietary modifications. These symptoms resolved within 3 months in all animals. One animal was noted to have circumferential esophageal ulcers 3 months after 30 Gy. This animal subsequently succumbed to exsanguination due to an esophagoaortic fistula, presumably IOERT-related. All animals receiving 30 Gy exhibited severe and progressive inflammatory changes between 6 weeks and 3 months postoperatively. By 12 months, all animals in this group had developed mucosal ulceration and strictures. These abnormalities also appeared on barium swallows and were confirmed at necropsy.

Five-year follow-up was obtained in five of 37 animals [39]. One control animal had an uncomplicated course. Two of the three animals treated with 20 Gy had no abnormalities, while the third developed achalasia without stricture necessitating a liquid diet. A single 30-Gy animal survived without clinical stigmata but did have an asymptomatic esophageal diverticulum and paraesophageal fibrosis on histologic review.

The data (acute plus chronic) suggest that full-thickness esophageal tolerance to single IOERT doses appears to be limited to 20 Gy.

Esophagus, Partial-Thickness

In a separate NCI study [38], dogs receiving mediastinal IOERT with partial-thickness esophageal treatment did not suffer severe clinical or radiographic sequelae at IOERT doses as high as 40 Gy. In many cases of mediastinal disease, esophageal shielding or partial-thickness esophageal inclusion may be possible, thus contributing to few complications at higher doses.

Lung and Bronchial Stump

IOERT delivery to the lungs and mediastinal structures were investigated at the NCI [38–41]. Following pneumonectomy, experimental dogs received IOERT in doses ranging from 0 to 40 Gy to the pleura, mediastinum, intact lung, and to the closed bronchial stump following pulmonary resection.

All irradiated animals developed pleural plaques at doses of 20–40 Gy within 12 months [38]. Fibrosis was pathologically evident in the pleura, and fibrotic pulmonary changes became evident in alveolar septa in the surrounding pulmonary vasculature and in bronchioles. Chronic concurrent pneumonitis appeared within 3 months in all IOERT fields that included the pulmonary parenchyma. The pneumonitis progressed pathologically to interstitial fibrosis and arteriolar sclerosis by 12 months.

After a 5-year follow-up, sharply marginated pulmonary fibrosis was the predominant pathologic change within the IOERT treatment portals [38, 39]. At pneumonectomy sites, all animals had wound healing of bronchial stumps with IOERT dose of 40 Gy [39].

Trachea

Among dogs receiving radiation to intact tracheal segments during IOERT to the mediastinum, gross specimens of the irradiated trachea revealed no changes [38–41]. Nine of 15 dogs receiving doses up to 40 Gy showed no significant histologic changes within the trachea. Three dogs had mild focal glandular atrophy with telangiectasia. One dog in each of the 30 and 40-Gy IOERT dose groups showed major tracheal changes at 12-month follow-up. Squamous metaplasia had replaced the normal columnar respiratory epithelium, widespread mucosal denuding was present, and submucosal fibrosis was prevalent. A 30-Gy animal experienced chondronecrosis of the tracheal ring. Another 40-Gy animal developed carinal necrosis with bronchial obstruction, which necessitated compassionate sacrifice 5 months following therapy [38]. Over a 5-year follow-up of four surviving dogs receiving 20 or 40 Gy, only minimal submucosal fibrosis was noted [38, 39].

Heart

In another NCI trial, the right atria of 18 dogs were irradiated with IOERT doses of 0, 20, 30, or 40 Gy using 5-cm mediastinal portals [38]. On necropsy at 3 and 12 months after treatment, dense fibrotic replacement of the myocardium was grossly noted after 30 and 40 Gy. Microscopically, changes ranged from mild medial hyaline degeneration to myocardial infarction and coagulation necrosis secondary to radiation vasculopathy. Myointimal proliferation and perivascular sclerosis contributed to epicardial thickening.

At 5-years of follow-up, moderate fibrosis at all dose levels was documented [39]. A straightforward dose–response relationship was not observed, although generally worsening histopathologic change occurred at higher IOERT doses [38, 39]. It appears reasonable to suggest minimizing cardiac inclusion in any IOERT field, but especially with doses >20 Gy.

Radiation-Induced Malignancies

Several authors have proposed requirements by which tumors may be identified as radiation-induced. The criteria adopted by Powers et al. [26] are valid for experimental model systems. These authors consider tumors arising in previously irradiated fields to be radiation induced using the following criteria: the tumors occurred in the radiation portal; they occurred after an appropriate latency period; they were histologically confirmed; they arose infrequently otherwise in the model species.

Tumor induction in dogs receiving IOERT in various NCI experimental trials has been described [42, 43]. Forty-six animals were followed clinically for at least 24 months post-IOERT. Ten tumors developed in nine animals with a median latency of 40 months. One dog, which had bladder IOERT, developed a breast tumor, which was determined to likely be a spontaneous neoplasm unrelated to radiation. In another animal, intraoperative trauma was believed to be a contributing factor to the development of a benign neuroma on a peripheral nerve IOERT portal. A neurofibroma, which was histologically benign but was grossly invasive, occurred in one peripheral-nerve animal. The remaining seven lesions were all malignant. Six of these lesions occurred in fields containing bone. The tumors were typically associated with bone necrosis in the IOERT portal. The seventh malignancy was a rhabdomyosarcoma occurring in a bladder IOERT field. All tumors were seen with IORT doses of 20–35 Gy.

Collectively, these data suggest that long-term survivors who receive IOERT may be at risk for a late-appearing radiation-induced malignancy, principally bone tumors. To date, human tumor induction has not been noted in available clinical trials of IOERT. However, orthovoltage radiation has higher bone absorption than electron beam irradiation; therefore, techniques for orthovoltage IORT should be specially designed to minimize the bone dose wherever possible to minimize the risk of late bone necrosis with the possibility of tumor induction.

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Part IV
Results of IORT Alone or Plus EBRT by Disease Site

Chapter 8
Central Nervous System Tumors

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Keywords Central nervous system tumors • IORT for CNS tumors • Malignant gliomas

Introduction

A heterogenous type of primary tumors arises in the central nervous system (CNS). Considering the natural history of the malignant pathologies, both low- and high-grade tumors show a similar behavior with an infiltrating pattern and a high incidence of local recurrence [1].

High-grade malignant gliomas (MGs) are the most common brain tumors of the adult life and account for about 30–45% of the primary brain tumors. Of these, nearly 85% are glioblastoma multiforme (GBM).

GBM and anaplastic astrocytoma (AA) are very aggressive tumors. The life expectancy of patients (pts) is rather short and only a few anecdotal cases diagnosed as GBM are reported as long survivors. The median survival time and the 5-year overall survival rates (OS) for AA are 36 months and 18% and for patients with GBM are 10 months and less than 5%, respectively [2].

Controlled clinical trials have identified tumor histology, age at diagnosis and Karnofsky performance status (KPS) as the best predictors of survival. Recursive partitioning analysis has allowed investigators to identify six groups of outcome based upon these prognostic factors [3].

Radiotherapy is the most effective adjuvant treatment modality to combine with surgical resection and is therefore a mandatory treatment after maximal gross tumor surgical resection in high-grade malignant gliomas [4]. Even though it improves survival, subsequent tumor persistence or

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_8,

local recurrence is the rule. The local tumor recurrence rate varies according to the primary pathological type, ranging from 10 to 40% for low-grade tumors and 80–100% for GBM [5].

A stepwise relationship between total radiation dose and survival in malignant gliomas was suggested by the Brain Tumor Cooperative Group (BTCG) [6]. Unfortunately, doses greater than 60 Gy produce unacceptable brain toxicity with conventional external beam radiation therapy (EBRT) [7].

Multi-institutional randomized trials have explored several treatment programs, including different adjuvant chemotherapy regimes in combination with conventional or alternative radiotherapy schemes. Although the addition of temozolomide (TMZ) to EBRT results in improved survival, the final results with regard to patient outcomes are not optimal [8].

Intraoperative radiotherapy (IORT) with high-energy electrons (IOERT) or low-energy photon beams (low KV-IORT) is a treatment modality designed to combine the efforts of surgery and radiation therapy to increase local tumor control rates in cancer management. During the last decades, the accumulated experience in the treatment of different solid tumors has been proved to be safe, feasible and is therefore very attractive as an intensified focal radiation which can be integrated into multidisciplinary protocols [9].

Malignant brain tumors, particularly high-grade gliomas, are considered a model of tumoral disease to be explored by IORT [10, 11]. The rationale for IORT in malignant brain tumors is based on several issues: (1) tumor unifocality, rarely multicentric, (2) pattern of recurrence "in" or very close to the primary tumor site, (3) radiation dose – tumor response relationship, and (4) possibility to deliver a high dose directly into the tumor or the tumor bed while sparing the normal brain tissue.

In the last decades, several institutions have reported their experience with IORT in intracranial tumors. They were able to show encouraging preliminary results compared to the historical controls [12–16].

Non-IORT Treatment of Malignant Glioma: Surgery +/– EBRT, Chemotherapy

The management of patients with malignant brain tumors requires a multidisciplinary approach and remains a challenge for neurosurgeons and oncologists. Surgery and postoperative radiation therapy or radiochemotherapy with TMZ is the standard of care for patients with malignant glioma [2]. A large prospective randomized phase III trial which compared chemoradiation with TMZ to radiotherapy alone in patients with GBM showed a significant survival benefit for patients who had received the combined treatment (2-year survival: 27% vs. 10%, $p<0.001$) [8].

Surgery

The goal of surgery in malignant glioma is to achieve the maximal tumor resection with the preservation of neurological function and without producing new neurological deficits. High-grade gliomas are diffusely infiltrating lesions without clear borders on neuroimaging studies or intraoperative direct vision, so the extent of the tumor is difficult to define.

Surgical debulking is essential in symptomatic patients to decrease the intracranial pressure, relieve symptoms, improve neurological deficits related to the mass effect and decrease steroid dependency, but this also reduces the number of cells potentially resistant to radiotherapy and/or chemotherapy and may thereby enhance the benefit of the adjuvant therapies.

The definitive role of extent of surgical resection is contradictory. The extent of resection has been based on subjective criteria which can result in either underestimating or overestimating the total amount of tumor removed. Although some have defined the extent of resection as a prognostic factor for survival [17, 18], there are no prospective randomized trials addressing this issue.

During the last decade, intraoperative MRI (iMRI) has been incorporated into operating rooms as a guide for neurosurgical procedures. Currently, the availability of the iMRI images and real-time neuronavigation allows more accuracy for the visualization of the location as well as the size of the tumor and the relationship to the close surrounding brain eloquent areas. The use of iMRI during surgery for brain tumors allows the surgeon to combine aggressive maximal tumor resection with safety and a good functional outcome.

In a series from the Tokyo Women's Medical University, 96 pts with intracranial gliomas underwent tumor resection with the use of iMRI in 50 pts compared to a control group of 46 pts. Higher resection rates (91 vs. 95%) and smaller residual tumor volumes (1.7 ml vs. 0.025 ml) were found in the iMRI group, whereas the rate of permanent morbidity did not differ significantly (13 vs. 14%) [19].

Awake craniotomy combining frameless computer-guided stereotaxis with intraoperative cortical stimulation and repetitive neurologic and language assessments may facilitate aggressive resection while minimizing postoperative neurologic dysfunction for tumors located in eloquent areas [20]. Despite these advances, the infiltrating edge of a neoplasm and the underlying tumor infiltration involving the cerebral edema are never amenable to a radical surgical resection.

Radiation Therapy: Techniques and Results

The beneficial effect of postoperative irradiation has been well documented in randomized clinical trials [6, 21]. The BTCG reported the results of randomized trial providing evidence that postoperative irradiation significantly improved survival over surgery alone both in median survival time (36 vs. 14 weeks) and 1-year survival (24 vs. 3%) in malignant glioma [22]. A randomized trial by the Medical Research Council confirmed a median survival benefit of 3 months (12 vs. 9 months) in patients with MG receiving a dose of 60 Gy when compared with 45 Gy [13] and Walker et al. [6] suggested a survival benefit for increasing the radiation dose from 50 to 60 Gy. Dose escalation with conventional radiotherapy techniques resulted in increased toxicity but no improvement in median survival, as shown by the RTOG/ECOG randomized trial comparing 60 Gy (9.3 months) vs. 60 Gy plus 10 Gy boost (8.2 months) [4].

Most malignant gliomas recur locally within 2–3 cm of the original contrast-enhancing tumor volume, although tumor cells are found at some distance on the surrounding edema. Accordingly, the accepted initial radiation treatment fields encompass tumor plus edema with a margin to 45–50 Gy in 1.8–2.0 Gy fractions/5 days per week followed by a boost to the enhancing gross tumor volume plus 2–3 cm margin to 60 Gy.

Many investigational approaches involving radiation therapy have been conducted for the purpose of improving the therapeutic index, including altered fractionation schemes and focal dose intensification. The latter is accomplished using brachytherapy (BQ), stereotactic radiosurgery (SRS), particle therapy or intraoperative radiation therapy (IORT). The results reported by an RTOG study of hyperfractionation (1.2 Gy twice daily to doses from 64.8 to 81.6 Gy) and accelerated hyperfractionation (1.6 Gy twice daily to 48–54.4 Gy) did not show a survival advantage compared with historical controls [23].

Dose escalation trials, including conformal fractionated stereotactic radiation (FSRT) or intensity modulated radiation (IMRT) techniques to 80–100 Gy in malignant glioma have been reported, but a benefit in survival has not been clearly demonstrated. A multicentric RTOG phase II trial with concurrent FSRT boost (4 weekly fractions of 5–7 Gy) during EBRT (50 Gy/25–28 Fx/5–5.5 weeks) in 76 pts with GBM, achieved a median survival of 12.5 months, which is not different from the RTOG historical results [24]. However, Baumert et al. [25] reported 1- and 2-year survival rates of 77 and 42%, respectively, in 17 pts with GBM treated with 20 Gy FSRT boost in four fractions after conventional EBRT, which was better than the historical group.

Using an even higher radiation dose, Chang et al. [26] did not find any advantage in survival of patients with high-grade glioma receiving a dose of 90 Gy with 3D conformal IMRT when compared with historical control, as the median survival and 2-year survival rates were 11.7 months and 12.9% (high-dose, 90 Gy) vs. 13.9 months and 25% (low-dose, 70 Gy), respectively. However, Tanaka et al. [27] did show an improvement in both median and 2-year OS of patients with GBM treated with 80–90 Gy vs. 60 Gy (median 16.2 vs. 12.4 months; 2-year OS 38.4 vs. 11.4%).

Select groups of patients with small tumors located in noneloquent areas have been treated either with radiosurgery or brachytherapy.

In the RTOG 93-05 randomized controlled trial, comparing SRS followed by conventional external beam radiotherapy (EBRT, 60 Gy) and carmustine to EBRT and carmustine in patients with GBM, the boost with SRS (15–24 Gy) failed to show a benefit in either median survival (13.5 vs. 13.6 months) or 2-year survival (9% vs. 13%) compared with conventional RT alone [28]. Overall, median survival ranged from 10 to 26 months in GBM and 9 to 28 months in AA [29].

Two randomized clinical trials comparing EBRT (50 Gy) with or without interstitial brachytherapy (60 Gy) as a boost technique also did not find any difference in outcome of patients with MG. Median survival times were 13.8 months (high-dose arm) vs. 13.2 months (low-dose arm) [30] and 68 weeks (high-dose arm) vs. 59 weeks (low-dose arm), respectively [31].

While several phase II trials have suggested benefit for increased local dose, all such studies are subject to selection bias. Evidence to date fails to confirm that RT dose escalation, regardless of method, leads to improved patient outcomes.

IORT Rationale and Treatment Factors

Intraoperative radiation using high-energy electron beams (IOERT) allows an optimization of the therapeutic ratio relative to conventional EBRT by exploiting the uniform depth dose distribution of the electron beam throughout the target volume with minimal normal brain tissue irradiation. The rapid fall-off of the radiation dose into the tissue allows sparing of structures beyond the target volume. During the surgical procedure, IOERT can be used to deliver a large single dose to the residual or unresected tumor or surgical bed that is directly exposed and visualized by the radiation oncologist. This procedure allows an improved therapeutic ratio, as the possibility of geographical miss is decreased while sparing the normal brain tissue from additional damage.

Because of the infiltrative nature of malignant gliomas, the difficulty in defining tumor borders is a critical problem. In GBM, a clear relationship between recurrence pattern and peritumoral edema has not been established, and this is a critical issue, taking into account the potential advantage to irradiate smaller volumes to a higher dose without increasing the risk of radiation-induced neurotoxicity.

The typical failure pattern of these tumors is local and a review of the published studies shows that recurrences are predominantly coincident with the primary site or within 1–2 cm of the enhancing edge of the original tumor. Studies using high doses of radiation in the range of 70–90 Gy with 3D conformal techniques showed that near 90% of tumor recurrences were “in field” within the prescription isodose [32, 33], leading to the conclusion that irradiation of the peritumoral edema does not seem to alter the pattern of failure in GBM.

In view of the local nature of relapses, IORT has been explored as an attractive treatment modality in brain tumors for selected patients. IORT should be considered in patients with malignant tumors, either primary or recurrent, unifocal not deep-seated lesions and located on an area of the brain accessible to a surgical procedure, mainly supratentorial. The tumor should not exceed a maximum diameter of 5–6 cm and not be located in or immediately next to an eloquent area.

The published data on IORT in the treatment of malignant gliomas are made up of a few small series of patients from single institutional series. No controlled randomized trials have been done to date.

In 1942, Dyke and Davidoff from Columbia University Hospital (New York, USA) were the first to communicate the use of IORT in intracranial tumors [34]. After removal, two patients with sarcoma of the brain received a single dose of 30 Gy by contact roentgen therapy, and the autopsy described brain edema and inflammatory changes related to the treatment in both patients.

The first report using IORT with high-energy electron beams (IOERT) in brain tumors was published by Abe et al. in 1971 [10] in two patients with recurrent brain tumors. One patient with bulky recurrence of fibrosarcoma previously treated with EBRT (59.6 Gy), received an IOERT dose of 35 Gy with 18 MeV electrons and an 8 cm IOERT applicator after subtotal tumor resection. The patient was free of symptoms for 5 months and died 189 days after IOERT. A second patient with recurrent glioblastoma after prior EBRT (59.4 Gy) was then submitted to subtotal removal and IOERT to a dose of 40 Gy with 12 MeV electron energy through a 4 cm field. The patient died after developing radiation necrosis requiring craniotomy 2 months after IOERT.

Thereafter, several institutions have considered IORT as a modality to be explored in the treatment of primary and recurrent brain tumors. IORT has been proven to be feasible and tolerable in different multidisciplinary programs, including surgery, radiation therapy, and chemotherapy [12, 14, 35–39].

IORT Procedure: Methodology and Quality Control

A precise maintained position of the cranium is a requisite necessity during the IORT procedure. Firm fixation must be achieved using a headholder, such as the Mayfield skull clamp.

It is not easy to determine the optimal position of the IORT applicator and the direction of the beam because radiation planning based on CT and MRI images on real time are not available. This step is critical in avoiding suboptimal dose because of geographical miss of the tumor or overdosing of the normal brain tissue.

In a dedicated facility with a linear accelerator directly in the operating room, the geographical miss can be easily minimized. In a nondedicated facility, the patient has to be transported to the radiotherapy department. Once there, it is difficult to adjust the beam direction from clinical considerations, as the patient is covered by sterile foil at this time. It is therefore better to define the optimal beam direction in the operating room and maintain it during transport. At the University of Muenster, a method for conserving the beam angle was developed, at the same time allowing post hoc treatment planning and quality control [40].

In the operating room, the intended beam direction is determined by means of the neuronavigation system provided by the neurosurgery department and, additionally, a special device called “beam direction indicator” (BDI). This way, it is possible to select the optimal beam direction directly in the operating room using clinical as well as imaging information from the neuronavigation system, taking into account the shape and depth of the resection cavity and the region presumed at risk of recurrence.

The neuronavigation pointer is adjusted to the selected direction using the three-dimensional neuronavigation display of the preoperative CT scan. This angle is transferred to the BDI device, a mobile arm with several joints mounted at the edge of the operating table. During patient transport, the intended beam direction is maintained by means of the BDI. At the end of the BDI, a cylinder with a central bore is attached which can be adjusted using the neuronavigation pointer. The joints are then locked, and the BDI maintains the determined direction of irradiation during transport to the radiotherapy department (for which the resection cavity is stuffed with saline-saturated cotton strips and the patient covered with multiple layers of sterile foil).

In the radiotherapy room, the gantry angle of the linear accelerator and the position and angle of the mobile operating table in the accelerator room are aligned with the previously determined optimal beam direction using a tray-mounted laser indicating the central beam axis. The operating table is

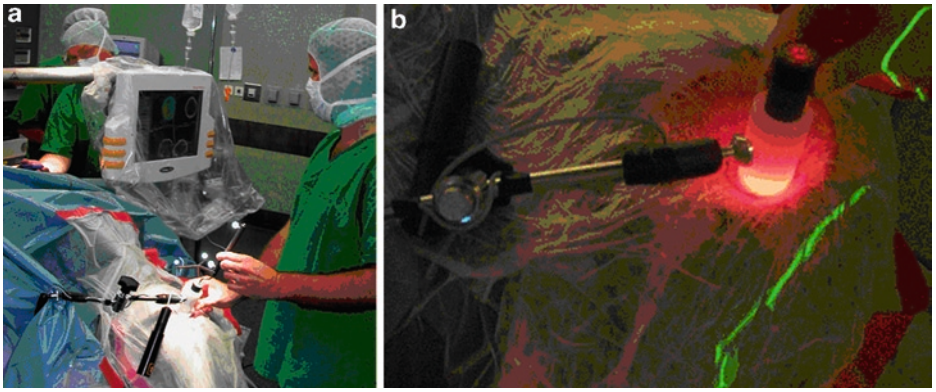

Fig. 8.1 (**a**) Alignment of the "beam direction indicator" (BDI) in the operating room, using neuronavigation. (**b**) Beam alignment at the linac according to the direction from neuronavigation by help of a central beam laser.

turned until the angle of the BDI device matches the gantry plane. The table position, height, and gantry angle are then adjusted until the central beam laser shines through the bore in the cylinder at the end of the BDI. When the angles match exactly, the laser tray is removed and the appropriate applicator inserted for irradiation (Fig. 8.1).

The IORT applicator size should include the diameter of tumor bed plus 1 cm margin and the electron beam energy is selected according to the depth so that the 90% isodose line encompasses the edge of the resection cavity and any remaining tumor by 1.5–2 cm if not limited by adjacent structures at risk.

When the patient returns for treatment planning of postoperative radiotherapy, the planning CT scan is done with the same head position and technical parameters as the preoperative scan for neuronavigation. This is facilitated by making the head mask for postoperative radiotherapy before the preoperative CT scan. When the two CTs are identical, it is possible to calculate a virtual gantry and couch angle relative to the neuronavigation CT by coordinate transformations. The craniotomy can be done virtually on the postoperative CT. This way it is possible to calculate an approximate post hoc isodose plan for the IORT electron field. The DVHs for structures at risk as well as for the target volume can be calculated.

IOERT Clinical Results

Several phase I–II clinical trials, most of them based on institutional experiences developed in Japan, the USA, or Europe, have published their results regarding the use of IORT in the management of brain tumors, either by using high-energy electrons from a megavoltage unit (linear accelerator) or low-energy photons produced by an X-ray generator (photon radiosurgery system, PRS) (Table 8.1).

A review of these published experiences is discussed, and special emphasis is put on toxicity, patterns of relapse, and survival of patients treated with IORT.

Europe IOERT Experience

Three major institutions in Europe, two University Clinical Centers in Spain and the University of Munster in Germany, have been involved in the development of clinical trials concerning IOERT in the management of solid tumors, and particularly for intracranial tumors.

Table 8.1 Intraoperative radiation therapy (IOERT) in primary high-grade brain tumors

Author	No. of patients	IORT dose	EBRT dose	Histology	Survival		
					Median (months)	1-year	2-year
Schueller et al. [39]	45	20 Gy	40–60 Gy	GBM	14.2	59%	6.8%
Ortiz de Urbina et al. [9]	19	15 Gy	50 Gy	AA/GBM	21	70.5%	36%
Goldson et al. [35]	10	15 Gy	0–55 Gy	AA/GBM	8	60%	20%
Gouda et al. [38]	11	10–20 Gy	50–70 Gy	AA/GBM	6	20%	–
Matsutani et al. [14]	30	18.3 Gy	58.5 Gy	GBM	26.4	97%	61%
Fujiwara et al. [43]	20	20–25	40–57 Gy	AA/GBM	14	43%	–
Sakai et al. [13]	32	26.7 Gy	50.6 Gy	AA/GBM	26.2	70%	57%
Nemoto et al. [36]	32	15 Gy	60 Gy	AA	24.7	81%	51%
				GBM	13.3	63%	26%

IORT intraoperative radiation therapy, *EBRT* external beam radiation therapy, *AA* anaplastic astrocytoma, *GBM* glioblastoma multiforme

Spanish Experience

The University Clinic of Navarra was the first in Spain to introduce IOERT in the treatment of brain tumors and describe the results of a small series of ten patients with primary (six pts) or recurrent (four pts) tumors and miscellaneous histologies, including GBM (two pts), AA (four pts), ependymoma (one pt), neuroblastoma, (one pt) oligodendroglioma (OA) (one pt), and meningioma (one pt). The median dose IOERT was 15 Gy (range: 10–20 Gy). Seven of nine patients developed local failure and died of tumor progression [11].

Ortiz de Urbina et al. [16] reported the preliminary results of 17 pts with malignant glioma (primary-8, recurrent-9) treated with IOERT at San Francisco de Asis Hospital in Madrid. The histology corresponded to six anaplastic oligodendroglioma, four AA, and seven GBM. After tumor removal, a single dose of 10–20 Gy IOERT was delivered to the tumor bed, and all the patients received EBRT either prior or after the IOERT. In primary gliomas, the 18-month survival rate was 56% (range 1–21 months). Patients with recurrent gliomas had 18-month survival rate and median survival of 47% and 13 months (range: 6–32 months), respectively. The median time to tumor progression was 9 months in primary (range: 3–14 months) and 11 months in recurrent tumors (range: 6–17 months), and a component of failure within or less than 1 cm to the IOERT field was observed in all these patients. No IOERT-related deaths were found.

A Joint IMO: SFA/CUN Clinical Experience

Subsequently, an updated analysis was performed of a joint experience from two major centers in Spain, including a total of 50 pts with intracranial tumors treated with IOERT (Madrid Institute of Oncology [IMO – SFA] and the University Clinic of Navarra [CUN]), using nearly identical IOERT protocols [9].

Prior to IOERT, histological diagnosis was mandatory, and patients with either supra or infratentorial tumors, but accessible to surgical exposure, were accepted. According to the pathological confirmation, anaplastic astrocytoma (21 pts), GBM (14 pts), anaplastic oligodendroglioma (eight pts), meningeal sarcoma (three pts), anaplastic ependymoma (two pts), anaplastic meningioma (one pt), and neuroblastoma (one pt) have been included. Nineteen patients (38%) had primary tumors and 31 (62%) had recurrence after surgery alone or plus EBRT.

Surgery, IOERT and EBRT procedures are previously discussed in detail [16]. A dose of 45–50 Gy with conventional fractionation EBRT was done either pre-IOERT (25 pts) or as adjuvant post-IORT (17 pts). Subtotal tumor resection was performed in 32 pts (64%) and total gross resection in 18 pts (36%). The IOERT applicator size was selected to include the tumor or surgical bed plus 1 cm radial

margin (3–9 cm, median: 5 cm). The electron energy was selected to encompass a depth of 1 cm beyond the deepest border of the tumor (10–20 MeV, median: 15 MeV) prescribing to the 90% isodose line. Primary and/or nonirradiated recurrent tumors received single fraction IOERT doses of 15–20 Gy, whereas in previously irradiated tumors a dose of 10–15 Gy was delivered.

Primary Tumors: Survival, Tumor Control, and Prognostic Factors

Nineteen IOERT patients had primary brain tumors and miscellaneous histologies (ten AA, five GBM, two OA, one meningeal sarcoma, and one neuroblastoma). After tumor removal (total: 8, subtotal: 11), an IOERT dose from 12.5 to 20 Gy (median: 15 Gy) was given as a single fraction with an IOERT applicator of 5–7 cm diameter. Post-IORT conventional fractionated EBRT (50 Gy) was given in 13 pts.

The 1- and 2-year OS were 70.5 and 36%, respectively, and median survival was 21 months (range: 1–65 months). At the date of evaluation, four pts (21%) had no evidence of tumor and 10 (52.5%) had tumor relapse in the IOERT site at 3–56 months after treatment (median: 17.5 months).

In this series, although no statistically significant differences were noted, the extent of surgery seems to have an impact on survival and local tumor control of the IORT patients with primary brain tumors. After total surgical resection, median survival was 22 months and 1- and 2-year OS were 87.5 and 58%, respectively, compared to a median survival of 10.5 months and 1- and 2-year OS of 53 and 39% ($p=0.18$) after subtotal tumor resection. This benefit has also been observed in local tumor control, with median time to progression (TTP) of 21 vs. 8 months after total vs. subtotal resection (Fig. 8.2).

Other factors, such as age, Karnofsky status, and tumor volume, were also analyzed, but they had no prognostic value.

University of Munster Experience

In 1997, the results with IOERT in 45 pts with malignant brain tumors were reported by Willich et al. [15], including primary and recurrent tumors, not only with different histologies but also with metastatic lesions. The IOERT procedure has been described in detail in a previous publication [41] as well as the methodology used for the treatment planning and the quality control in IOERT of brain tumors developed at the University of Munster [40].

At diagnosis of primary brain tumors, upfront treatment was surgery and an IOERT dose of 20 Gy to the tumor bed followed by conventional EBRT (40–60 Gy), whereas an IOERT dose of 25 Gy was given in pre-irradiated patients at time of recurrence. The recurrence free survival after 1 year was 52% in this series.

Rube et al. [41] reviewed the results by using the same IOERT protocol, including only patients with high-grade malignant brain tumors, 29 primary and 15 recurrent tumors, and the results compared favorably to the historical group of patients treated with surgery and EBRT. The 1-year survival rate was 64, 45, and 64% for AA, GBM and recurrent disease, respectively, and the 2-year survival for all 44 pts was 18%.

The performance status, extent of surgery and histology were prognostic factors in survival. The median survival time was 15 months in AA vs. 11.8 months in GBM ($p=0.04$). The 1-year survival of patients who underwent total vs. subtotal tumor resection was 66 and 18%, respectively, and the 1-year survival according to Karnofsky status >70 vs. ≤70 was 62 vs. 36%, respectively.

Recently, Schueller et al. [39] reported an up-date concerning the 12 years experience of the University of Munster with IOERT in 71 pts with malignant gliomas and compared the results to

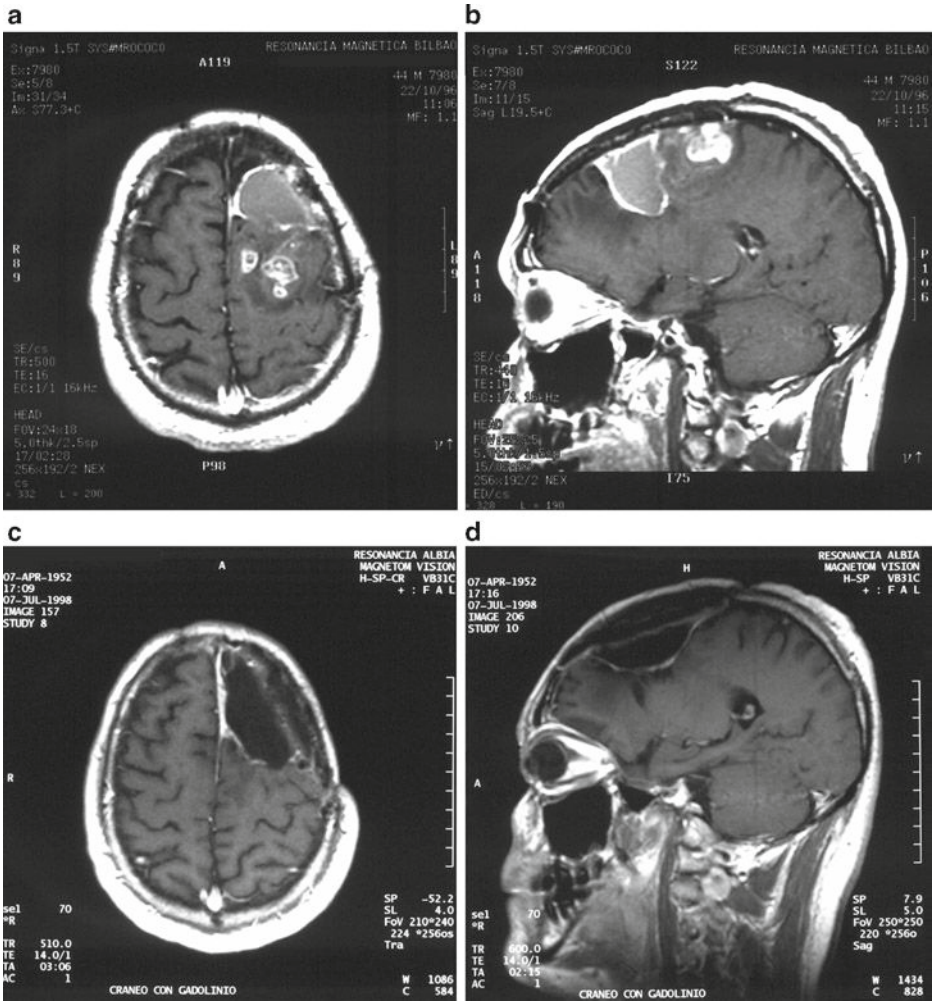

Fig. 8.2 Axial and sagittal MRI brain scan (T1-weighted with contrast) in a 44 year old patient with a left frontoparietal recurrent anaplastic astrocytoma treated with IOERT: (**a**, **b**) at diagnosis, before treatment, (**c**, **d**) at 20.5 months, after surgery and 15 Gy IOERT dose.

historical series. An IOERT dose of 20 Gy was delivered after surgical resection in addition to 60 Gy EBRT with conventional fractionation in primary tumors. For patients who presented at time of recurrence, IOERT alone was used to a single dose of 25 Gy or 15–20 Gy if time from primary treatment to relapse was less than 6 months.

The series included 26 pts with grade III glioma (glioma III) and 45 with GBM. In GBM, median survival was 12.2 months and 1-, 2-, and 5-year OS were 59, 5.8, and 0%, respectively, whereas in glioma III, median survival was 14.9 months and 1-, 2-, and 5-year OS were 65.4, 26.9, and 11.5%, respectively ($p = 0.02$). The median disease-specific survival in primary (14.9 months) and recurrent tumors (12.4 months) was almost the same. Median and 2-year freedom from progression (FFP) were 13.1 months and 11.8%, respectively, in glioma III, vs. 9.9 months and 4.4%, respectively, in GBM. Although the survival of patients with GBM in the IOERT group was better (median: 14.2 months, 1-year OS: 59%) than the historical group (median: 9.3 months, 1-year OS: 31.3%), this difference was not statistically different.

Japanese IOERT Experience

In the Matsuda study [42], 11 pts with glioma received 30 Gy preoperative EBRT plus 10–15 Gy IORT. Four of five patients with complete tumor resection survived more than 2 years.

Sakai et al. [13] reported a series of 32 pts with malignant glioma receiving IOERT as initial treatment after tumor resection and additional EBRT (median dose, 53.4 Gy) and a non-IORT control group of 41 pts. The median IOERT dose was 26.7 Gy (range: 10–50 Gy) prescribed to 1–2 cm deep to the tumor bed surface. The 2- and 3-year OS after resection/IOERT were 57.1 and 33.5%, respectively (median survival: 26.2 months), which is significantly better than the non-IOERT group (23.6% 2-year and 13.1% 3-year OS; median 20.7 months; $p<0.01$). A benefit for IOERT was also found in GBM patients with 3-year OS of 25.8 vs. 14.6% and median survival of 22.4 vs. 15.9 months, respectively (IOERT vs. non-IOERT). In 14 of 32 pts, IOERT was repeated because of tumor recurrence, and the survival was not significantly different between patients receiving one vs. two IOERT treatments without increased toxicity.

In a report of Matsutani et al. [14], 30 pts with GBM received IOERT after macroscopic total resection. The IORT dose was 10–25 Gy (mean dose: 18.3 Gy) and all patients received conventional EBRT (mean dose, 58.5 Gy). The 1- and 2-year OS were 97 and 61%, respectively, and median survival was 27.5 months. Two patients survived for more than 5 years without relapse and 87% were free of tumor for more than 1 year. In a control group of 19 pts treated with EBRT alone (mean dose, 62.5 Gy) after wide surgical resection, 1-, 2-year, and median survival were 79, 47, and 22.6 months, respectively (advantage to IOERT group), but 3-year OS was similar (33% IOERT vs. 37% non-IORT). Median TTP in the IORT vs. non-IORT groups was 16.9 vs. 17.6 months.

Twenty patients with supratentorial gliomas (11 GBM, 7 AA, and 2 low-grade astrocytomas) were involved in a clinical study developed by Fujiwara et al. [43] consisting of surgical resection, IOERT (dose: 20–25 Gy) and EBRT (dose: 40–50.7 Gy). The median survival time was 14 months, which was compared favorably with 10 months in the control group treated with EBRT alone.

A retrospective case-control study published by Nemoto et al. [36], including 32 pts with MG (AA-11 pts, GBM-21), did not find a difference in survival between IOERT patients and the control group treated with EBRT. After surgery, patients received an IOERT dose of 12–15 Gy (median: 15 Gy) followed by EBRT (dose, 60 Gy). In anaplastic astrocytoma, the 1-, 2-, and 5-year OS were 81, 51, and 15%, respectively, in IOERT patients vs. 54, 43, and 21% in control patients, whereas in glioblastoma the 1-, 2-, and 5-year OS were 63, 26, and 0% in the IOERT group vs. 70, 18, and 6%, respectively, in the control group. The median survival in IOERT vs. non-IOERT patients in AA was 24.7 vs. 33.6 months and 13.3 vs. 14.6 months in GBM, respectively. There were no treatment-related deaths.

US IOERT Experience

The US experience with IOERT in brain tumors is provided from two centers: Howard University Hospital [35] and the Medical College of Ohio [38]. Both published results of pilot studies using IOERT as intensification focal therapy during surgery in addition to EBRT either in primary or metastatic intracranial tumors.

Howard University Hospital

A pilot study using IOERT in brain tumors was developed at Howard University Hospital [35], including ten pts with high-grade gliomas and two with meningioma (primary and recurrent).

In gliomas, after surgical resection, a single fraction of 15 Gy IOERT was combined with EBRT doses of 50 Gy in 25 fractions whole brain EBRT plus a cone-down boost of 5 Gy in three fractions.

The survival of the three pts with GBM was 2.5, 15, and 15 months, respectively, and ranged from 8 to 13 months in anaplastic glioma (AA, OA, mixed). At the time of publication, four of ten pts with glioma and the two pts with meningioma were alive without evidence of disease 8–42 months after IOERT and the 1- and 2-year OS were 60 and 20%, respectively. Two pts with biopsy only died within 30 days after surgery due to massive brain edema and necrosis in one pt but unknown cause in the other patient because no autopsy was done. The authors suggested that surgical debulking is critical to decrease the risk of hazardous postoperative brain edema.

Medical College of Ohio

A total of 17 pts (12 primary, 5 metastatic) were treated with IOERT to a median dose of 15 Gy (range: 10–20 Gy) using applicator sizes from 2.5 to 9 cm (median: 5 cm). In 6 pts (glioma-5, metastasis-1), IOERT was given for the treatment of the primary lesion and at time of recurrence in the remaining pts (glioma-7, metastasis-4) [38].

In primary or recurrent brain tumors, median survival after diagnosis was 12 months (range: 2–22 months) and after IOERT was 6 months (range: 2 days – 14 months). Six of 12 pts survived more than 1 year after diagnosis. Five of 12 pts had infratentorial tumors with median survival of 9.4 months.

For patients with brain metastasis, the median survival time after diagnosis was 8.5 months (range: 4–13 months). The survival time from IOERT ranged from 2 to 11 months (median: 5 months).

Delayed bone flap necrosis was seen in three pts. Two pts with recurrent GBM died at 2 and 10 days after IOERT; postoperative CT scans did not find edema of the brain related to the treatment.

Intrabeam Low-KV IORT Experience

The PRS (PRS 400, Photoelectron, Lexington, MA) is a device for radiation therapy that can be placed in the surgical bed based on an X-ray source delivering up to 50 kV of energy, mounted on an Intrabeam floor stand (Carl Zeiss, Oberbochen, Germany). Spherical applicators 1.5 to 5.0 in diameter have been used for low-KV IORT of solid tumors since 1997.

Several clinical studies have evaluated Intrabeam low-KV IORT as intracavitary irradiation for primary brain tumors and brain metastasis.

Takakura and Kubo [44] reported 76 pts with malignant primary brain tumors and metastases treated with Intrabeam low-KV IORT. The survival rate for patients with glioma was significantly better than in the control group (89 vs. 77%), and the local tumor control rate for metastases was 82%.

In 2005, Curry et al. [45] reported the experience at the Massachusetts General Hospital (MGH) of 72 metastases in 60 patients irradiated stereotactically with Intrabeam low-KV IORT directly after biopsy. A mean dose of 16 Gy (10–20 Gy) was delivered to the tumor plus 2 mm margin. Local tumor control was achieved in 81% and the median follow-up was 6 months. Delayed symptomatic necrosis requiring surgery was seen in three patients (5%).

The Children's Memorial Hospital in Chicago [46] conducted a phase I study and published the preliminary results of Intrabeam low-KV IORT in a total of 14 children (13 ependymoma) with recurrent brain tumors. Six pts (43%) had subsequent tumor relapse in the IORT/surgical bed with

median time to recurrence of 11 months (5–18 months), and three pts had a marginal tumor recurrence adjacent to or beyond the IORT site with median time to relapse of 18 months (8–32 months). Local control in the IORT surgical bed with or without previous EBRT (≥50 Gy) was obtained in three of eight pts (38%) and in five of six pts (83%), respectively. Three pts (21%) developed radiation necrosis in the tumor bed at 6–12 months when the IORT dose of 10 Gy was prescribed to a depth of 5 mm, but was not seen if 10–12 Gy IORT was prescribed to 2 mm.

Intrabeam low-KV IORT seems feasible and tolerable in the management of brain tumors. Additional studies are needed to establish a definitive role in terms of improved local tumor control.

Prognostic Factors in IORT Series

The pilot study of Goldson et al. [35] identified favorable prognostic factors as age less than 38 years, Karnofsky status ≥70 and extent of surgery (biopsy vs. total or subtotal resection). Tumor histology was not prognostic.

Extent of surgery (total vs. subtotal resection) was an important factor in local control and survival of patients with primary and recurrent brain tumors treated with IOERT in the IMO-SFA/CUN Spanish Group series [9].

The University of Munster [39, 41] identified Karnofsky status (≥70 vs. <70), extent of surgery (total vs. subtotal resection) and histology (astrocytoma III vs. GBM) as determinant prognostic factors for survival in patients receiving IOERT.

Adequate volume coverage by IOERT treatment is a critical issue, as was reported by Schüeller et al. from the University of Munster at the ISIORT 2008 [47]. After quality control by dose reconstruction in 77 pts with MG, the median survival time between adequate and nonadequate volume coverage was 15.2 vs. 10.2 months, respectively, and the 2- and 5-year OS were 17.2 vs. 5.1% and 2.9 vs. 0% ($p=0.04$), respectively. This benefit was seen in GBM for median survival (15.2 vs. 9.3 months) and 2-year OS (9.3 vs. 0; $p=0.02$), and also trends in Glioma III median survival (17 vs. 12.5 months) and 2-year OS (33.3 vs. 21.4%; not significantly different, $p=0.9$).

As seen in brachytherapy series [47], longer survival was seen in GBM patients with radiation necrosis after IORT treatment. In the series of Matsutani et al. [14], the median survival in patients with post-IORT necrosis was 180 weeks vs. 116 weeks without necrosis ($p=0.04$) and 2-year OS was 80 vs. 51%, respectively.

Patterns of Failure: IORT Versus Radiation Boost Techniques

The predominant failure pattern using focal intensification techniques as a boost after conventional EBRT is local recurrence.

Clinical series have analyzed the patterns of local failure in patients with malignant glioma treated with interstitial brachytherapy, with categorization as either true local relapse (in resection cavity) or noncontiguous relapse (2 cm beyond resection cavity) as the predominant site of tumor recurrence. Sneed et al. [48] defined the predominant site of failure as within the treated tumor bed in 77% vs. 14% as a noncontiguous relapse, and Halligan et al. [49] found 70% local and 18% noncontiguous recurrences in 22 pts with recurrent high-grade glioma treated with I-125 implant (150–300 Gy). In contrast, Loeffler et al. [50] concluded that interstitial brachytherapy changed the pattern of failure because only 18% of GBM patients had true local relapse, but 82% had noncontiguous recurrences, and Aiken et al. [51] found that 63% of tumor recurrences involved sites more than 2 cm away from the surgical bed.

The RTOG 93-05 randomized trial, including 203 pts with supratentorial GBM, concluded that SRS boost followed by EBRT and carmustine did not change the pattern of failure and found local recurrence in 92.5% of patients. According to the site, the local, adjacent and mixed failures were 67, 5, and 21%, respectively, in the EBRT arm vs. 58, 3, and 25% in the SRS plus EBRT arm [28]. These results are consistent with other studies with SRS boost in GBM, with rates of local and marginal failures in excess of 80% [29].

Cardinale et al. [24] published the results of the RTOG 00-23 phase II trial and analyzed first sites of failure in 65 pts with GBM after FSRT boost in addition to EBRT. The local recurrence rate within the target volume was 88% (63% within alone and 22% within plus marginal).

Sakai et al. [13] found that 21 of 32 pts (65.6%) had tumor recurrence 12 months after the treatment with IORT (dose: 26.7 Gy; range, 10–50 Gy) plus EBRT (dose: 53.4 Gy). All the failures were within the original tumor site and a relationship between tumor recurrence and total radiation dose was not found. On review of the results of five autopsies in GBM IORT patients, the histological features in the primary lesion sites were necrotic changes in all cases, and tumor cells were found in the surrounding marginal area, distinguishing a well-defined border between, probably related to the IORT treatment.

At the Tokyo Metropolitan Komagone Hospital, 24 of 30 pts (80%) with GBM receiving 10–25 Gy IORT in addition to EBRT had a recurrence. In 96% of cases, the recurrence was within (17%) or immediately around (79%) the primary tumor site [14]. The median TTP was 73 weeks.

At the Institution of San Francisco de Asis in Spain [16], the median TTP after IOERT in primary gliomas was 9 months (3–14 months). A component of failure within and/or marginal to tumor bed was observed in all patients with tumor relapse.

Toxicity: IORT Versus Radiation Boost Techniques

Late effects on brain tissue related to radiotherapy are an important concern, and the frequency and severity of the neurotoxicity is associated with radiation dose as well as the irradiated volume. Radiation necrosis is the most severe complication because of the high risk of definitive sequelae. High-dose radiation provided by any technique of focal intensification, such as IORT, brachytherapy, or radiosurgery, often results in radiation necrosis, which is difficult to differentiate from tumor recurrence on MRI or CT brain scans.

The incidence of radiation necrosis is not easy to be defined due to lack of series addressing this issue by confirmation based on histopathological specimens, and also because GBM tumors are associated with large areas of necrosis, but is estimated from 4 to 14% after conventional EBRT [52] to 24% with accelerated EBRT plus chemotherapy [53]. However, the incidence of radiation necrosis almost surely exceeds the reported rates of reoperation because not all patients are symptomatic and the indications for reoperation are not uniform.

Symptomatic necrosis requiring reoperation after brachytherapy for patients with either primary or recurrent MG varies from 26 to 57% [54]. Published studies of temporary high-dose I-125 brachytherapy show reoperation rates of up to 40% for symptomatic radiation necrosis [55]. Radiation necrosis have also been reported in 38% of 106 pts with GBM treated with low activity I-125 implant delivering a dose of 52.9 Gy as a boost [56]. A large randomized trial by Laperriere et al. [30] comparing EBRT (50 Gy) vs. EBRT plus brachytherapy (I-125, 60 Gy) showed a reoperation rate of 33% with EBRT + brachytherapy vs. 31% with EBRT alone. In a small series of 15 pts treated with high-dose brachytherapy with low activity I-125 seeds (>250 Gy) plus EBRT (60 Gy), 70% of pts required reoperation for contrast enhancement and 47% had histological proven radiation necrosis [51].

Table 8.2 Primary glioblastoma multiforme: results with "boost" techniques of radiation

Author	No. of patients	Technique	Boost dose	Median survival (months)	% Reoperation
Cardinale et al. [24]	76	FSRT	5–7 Gy/fx×4	12.5	–
Baumert et al. [25]	17	FSRT	5 Gy/fx×4	20	6%
Laperriere et al. [30]	71	I-125 BQ	60 Gy	13.8	33%
Selker et al. [31]	133	I-125 BQ	60 Gy	16	50%
Scharfen et al. [56]	106	I-125 BQ	52.9 Gy	22	38%
Souhami et al. [28]	89	SRS	15–24 Gy	13.5	25%
Shrieve et al. [57]	78	SRS	12–15 Gy	19.9	50%
Mehta et al. [58]	50	SRS	12 Gy	11	10%
Sakai et al. [13]	32	IOERT	26.7 Gy	22.4	–
Matsutani et al. [14]	50	IOERT	18.3 Gy	11.9	33%
Nemoto et al. [36]	32	IOERT	15 Gy	13.3	12.5%
Schueller et al. [39]	45	IOERT	20 Gy	14.2	3%

FSRT fractionated stereotactic radiotherapy, *BQ* brachytherapy, *SRS* stereotactic radiosurgery, *IOERT* intraoperative radiation therapy with electron beam

The addition of SRS boost in primary malignant glioma is associated with an increased risk of toxicity, either symptomatic edema or radiation necrosis. Reoperation rates varied from 19 to 33% [29].

Souhami el al. [28] reported grade III late toxicity in 4 of 80 pts treated with SRS. Seven of 28 pts who underwent surgery as salvage therapy had necrosis only. Reoperation for symptomatic necrosis or recurrent tumor after SRS boost was reported in 39 of 78 pts with primary tumors by Harvard Medical School investigators [57], and in 4 of 29 pts in a study by Mehta et al. [58].

The accumulated experience based on clinical and histological results suggest the IOERT dose to be delivered as a single fraction must not exceed 30 Gy (Table 8.2). In an early report by Matsutani [59], two of three pts with large GBM treated by an IOERT dose of 30 Gy developed significant brain edema and neurological impairment in a few days, and the third patient with recurrent glioma treated with 25 Gy had brain edema at the irradiated site, but without clinical symptoms. When the IOERT dose was 15–20 Gy, neither intraoperative nor postoperative cerebral edema was seen in four pts with GBM, even those receiving additional EBRT.

No serious induced complications, defined as fatal cerebral necrosis, were observed by Sakai et al. [13] at the Gifu University after 10–50 Gy IORT (median: 26.7 Gy). In 5 of 32 pts (15.5%) marked peritumoral edema with midline shift on CT scan and mental deterioration was seen; four of the five patients received IOERT twice (20–30 Gy) in addition to more than 50 Gy with EBRT.

Delayed necrosis in the treated site was found in 10 of 30 pts (33%) with GBM treated at Tokyo Metropolitan Komagone Hospital, with a single dose of IOERT between 15 and 25 Gy combined with EBRT (mean dose, 58.5 Gy).The median time to diagnosis of necrosis was 14 months and the histological study performed in six pts showed wide coagulation necrosis with scattered heavily damaged tumor cells related to the radiation [14].

Nakamura et al. [60] reviewed 43 pts with brain metastases who underwent surgical resection and 18–25 Gy IOERT. Delayed necrosis in the treated area was seen in two cases (4.5%).

In a series of 32 pts with malignant glioma treated with IOERT (median dose: 15 Gy) plus EBRT (dose: 60 Gy) at Tohoku University, four pts (12.5%) developed CT and MRI brain scan findings suggesting brain necrosis [36].

Fujiwara et al. [43] found toxicity related to IOERT in 6 of 20 pts, consisting of radionecrosis – 1 pt, severe brain edema-3, convulsion-1, and abscess-1. The IOERT dose was 20–25 Gy prescribed to the 80% isodose line encompassing 2–3 cm below the tumor bed. The volume of tissue treated to a high single dose was too large which might explain the increased toxicity.

Three of 17 pts with malignant glioma included in a study published by Ortiz de Urbina et al. [16] had neurological impairment at 3, 3 and 4 months after IOERT and the enhanced CT and MRI brain scan suggested radiation necrosis at the treated site. The three pts received either pre- (50 Gy, two pts)

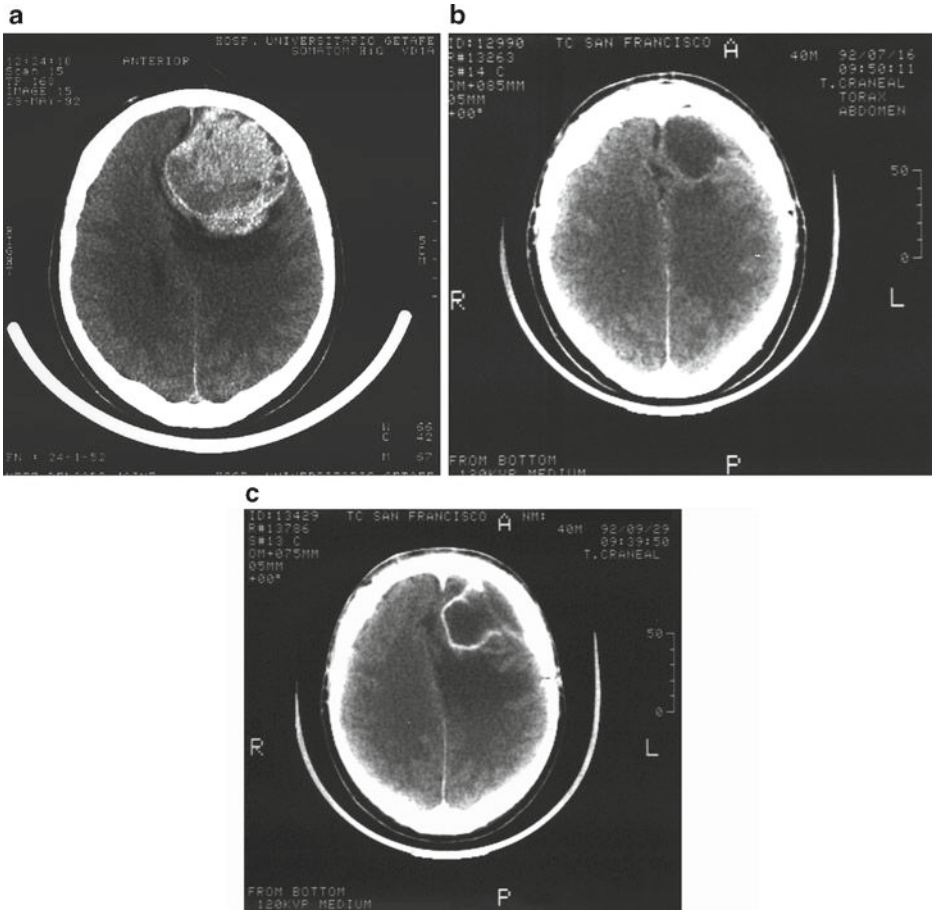

Fig. 8.3 Forty years, enhanced CT brain scan, left frontal metastatic malignant melanoma: (**a**) at diagnosis, (**b**) postoperative after total surgical resection and IOERT dose of 20 Gy, (**c**) brain edema and enhanced ring on CT image, corresponding to the treated surgical bed at 4 months after IOERT.

or post-IOERT conventional EBRT (46 Gy, one pt) and an IOERT dose of 20 Gy with 18 MeV electrons and applicator size of 5, 6 and 6 cm, respectively. After steroid therapy, two pts recovered completely and the other patient improved but with moderate neurological sequelae (nominal dysphasia). No symptomatic brain necrosis was seen with an IOERT dose < 20 Gy (Fig. 8.3).

As a result of the pilot study at the Howard University, Goldson et al. [35] concluded 15 Gy IOERT combined with EBRT (dose, 55 Gy) in intracranial tumors is tolerated, but they pointed out that two pts without surgical tumor resection developed severe post-IOERT edema, which was not observed in eight pts who underwent tumor removal. One patient with massive GBM and only biopsy, treated with IORT applicator size of 9 cm and dose of 15 Gy, had confirmed tumor necrosis and huge edema at autopsy performed after 82 days after surgery/IOERT. A brain CT found brain necrosis vs. tumor recurrence in two of four surviving patients with glioma, but no changes were found in two pts with meningioma at 33 and 42 months, respectively.

Neither long-term sequelae nor symptomatic radiation necrosis was observed in 50 pts with brain malignant tumors receiving EBRT + IOERT at the IMO – SFA/CUN Spanish Group, if the dose of IOERT was ≤15 Gy. According to the University of Munster, the IOERT treatment was well tolerated, with no increased rate of perioperative complications or fatal events related to the treatment in 71 pts receiving a dose ≤ 20 Gy. Two of the 71 patients, however, developed histologically proven brain necrosis [39].

IORT in Recurrent Tumors

There is little information concerning the treatment of brain tumor recurrences with IORT. Published data include small number of patients and just a few series address this issue. Focal radiation techniques show similar results in terms of median survival, whether using I-125 brachytherapy (range: 10.5–18.7 months), radiosurgery (range: 8–23 months), fractionated stereotactic RT (range: 11–21 months), or IORT (range: 8–12 months) (Table 8.3).

A large series using FSRT for reirradiation reported by Combs et al. [61] included 172 pts with recurrent glioma. Median survival was 8 months in GBM and 16 months in AA, after 36 Gy FSRT (range, 15–62 Gy). This was similar to median survival of 11 months obtained by Cho et al. [62] in 15 pts with recurrent GBM receiving 37.5 Gy.

The reported incidence of reoperation in recurrent malignant glioma treated with I-125 brachytherapy was 44–49%, due to radiation necrosis or recurrence [63]. In SRS series, the reoperative rate after reirradiation has been 22–31% [64–66].

IORT is an alternative to deliver a large dose focally into recurrent tumor in an attempt to improve local control with reasonable toxicity (Table 8.4).

Shibamoto et al. [37] from Kyoto University, reports long-term survivors in 17 pts with recurrent brain tumor and different histologies treated with IOERT. Nine pts had highly infiltrative tumors (GBM and AA) and eight pts had less infiltrative tumors (ependymoma, anaplastic ependymoma, and anaplastic astrocytoma) with previous EBRT (mean: 53 Gy). The IOERT dose ranged from

Table 8.3 Recurrent high-grade glioma: results with "boost" techniques of radiation

Author	No. of patients	Technique	Boost dose	Histology	Median survival (months)	% Reoperation/ necrosis
Cho et al. [62]	15	FSRT	37.5 Gy	GBM	11	12%
Combs et al. [61]	59	FSRT	36 Gy	GBM	8	0.5%
Gaspar et al. [63]	59	I-125 BQ	100 Gy	GBM	10.5	44%
Scharfen et al. [56]	66	I-125 BQ	64 Gy	GBM	11.7	46%
Leibel et al. [67]	45	I-125 BQ	70 Gy	GBM	18.7	49%
Hall et al. [65]	35	SRS	20 Gy	AA/GBM	8	31%
Shrieve et al. [64]	86	SRS	13 Gy	GBM	10.2	22%
Kong et al. [66]	65	SRS	16 Gy	GBM	23	24%
Matsutani et al. [14]	17	IOERT	17 Gy	GBM	9	–
Shibamoto et al. [37]	19	IOERT	23–40 Gy	AA/GBM	12	17.6%
Ortiz de Urbina et al. [9]	9	IOERT	15 Gy	AA/GBM	13	22%
Schueller et al. [39]	19	IOERT	20 Gy	AA/GBM	12.5	–

FSRT fractionated stereotactic radiotherapy, *BQ* brachytherapy, *SRS* stereotactic radiosurgery, *IOERT* intraoperative radiation therapy with electron beam

Table 8.4 Intraoperative radiation therapy in recurrent high-grade brain tumors

Author	No. of patients	IOERT dose	Histology	Median survival (months)
Shibamoto et al. [37]	9	23–40 Gy	AA/GBM	12
Matsutani et al. [14]	17	10–25 Gy	GBM	9
Willich et al. [15]	13	20 Gy	AA/GBM	21
Ortiz de Urbina et al. [9]	31	12–20 Gy	AA/GBM	15.5
Schueller et al. [39]	19	20–25 Gy	AA/GBM	12.5

IOERT intraoperative radiation therapy with electron beam, *AA* anaplastic astrocytoma, *GBM* glioblastoma multiforme

23 to 40 Gy. The median survival time was 51 months for patients with less infiltrative tumors and 12 months for the high-grade gliomas. The authors concluded that IOERT for recurrent tumors might be most effective in selected patients with less infiltrative tumors. Local tumor progression occurred in 12 pts (70%); five were outside the IOERT field, two in both unirradiated and irradiated areas, one had in-field recurrence, and four had no available information. Symptomatic brain necrosis in the IOERT volume was histologically proven in three pts and was fatal in one pt.

Matsutani et al. [14], treated 17 pts with recurrent GBM using 10–25 Gy IOERT (mean, 17 Gy). Median time to death was 36 weeks.

In San Francisco de Asis Hospital in Madrid [16], nine pts with recurrent glioma (GBM-3, AA-1, OA-5), received IOERT after tumor removal, including eight previously irradiated pts. The IOERT dose was 10–20 Gy (median: 10 Gy). The 18-month survival rate and median survival were 47.5% and 13 months (range: 6–32 months), respectively, and median TTP was 11 months (range: 6–17 months). Two patients developed neurological symptoms, and brain radiation necrosis was found on the MRI brain scan; both had an IOERT dose of 20 Gy.

The analysis at the IMO – SFA/CUN Spanish Group of 31 pts with malignant recurrent brain tumors who underwent surgery and IOERT (median: 15 Gy), in addition to planned postoperative EBRT, showed a median survival time of 15.5 months and 2-year OS of 37%. The main site of local failure was coincident to the treated IOERT site in the tumor bed (56.5%) and median time to tumor progression was 7 months (2–68 months). Extent of surgery was a determinant prognostic factor in both survival and tumor relapse. The median survival and TTP were 27 and 6 months with total resection vs. 11 and 7.5 months with subtotal resection, respectively.

Currently, there is not enough data to draw firm conclusions about the value of IOERT as a salvage treatment for patients with recurrent brain tumors. This technique should be evaluated further in controlled clinical trials on the basis of favorable results in small single institution series.

Discussion and Future Possibilities

EBRT + Boost

Two randomized trials of EBRT ± interstitial brachytherapy were performed for patients with malignant gliomas. In a series of 140 pts with malignant astrocytomas, Laperriere et al. [30] compared EBRT (50 Gy) vs. EBRT plus brachytherapy with Iodine-125 seeds (60 Gy) and found no benefit in median survival time in the high- vs. low-dose arm (13.8 vs. 13.2 months). The BTCG Trial 87 – 01 randomized a total of 270 pts with malignant glioma to surgery, EBRT and carmustine (BCNU) ± an interstitial brachytherapy boost and found no difference in median survival (68 vs. 59 weeks, respectively) [31].

The RTOG 93-05 randomized trial, did not find any survival benefit in GBM patients by adding SRS to EBRT and chemotherapy. Median survival in the SRS vs. control arm was 13.5 vs. 13.6 months, and 2-year survival was 9 vs. 13% [28].

IORT ± EBRT

The inadequate dose of radiation delivered to the tumor and the surrounding area of tumoral infiltration, as well as the wrong estimation of the volume to be encompassed by the prescribed dose, are two major factors conditioning the lack of local tumor control.

Focused on these aspects, IORT was thought to be an attractive treatment modality to be explored. However, only a few institutions have reported their IORT experience based on small phase I–II clinical trials and limited numbers of patients.

IORT has been used either alone or in combination with EBRT. One of the theorical advantages of combining EBRT with IORT is that coverage of the tumor bed would be better with fewer marginal recurrences.

Patient selection criteria could explain some encouraging results with select IORT series in patients with high-grade glioma, as patients with better prognostic factors (supratentorial, unicentric, good performance status, young patients) have been included in IORT studies. Unfortunately, the number of patients suitable for IORT is limited as found in the IOERT series by Matsutani et al. [14], which included only 30 of 123 pts (24%) with malignant glioma. As a result of the compiled data, IORT has not provided enough evidence of benefit in terms of survival of patients with high-grade brain tumors. Although several Japanese studies showed encouraging results, these have not yet been confirmed by other series.

Optimum IORT Dose and Volume

The optimum tumoricidal radiation dose with IORT remains unclear and the criteria to choose the dose has been done on the basis of the safety, in order to avoid unacceptable toxicity, rather than the antitumoral activity. Goldson et al. [35] found that an IOERT boost of 15 Gy is well tolerated, if previous surgical decompression is performed. Other authors feel that an IORT dose $\leq$ 20 Gy appears tolerable and have recommended such in clinical trials. Unfortunately, these IORT doses are not satisfactory to provide adequate local control; patterns of failure do not change, and relapses continue to occur in the tumor site within the treated volume.

A geographical miss is another reason of treatment failure. Direct visualization during surgery allows IORT to be more precise to deliver the radiation in the tumor bed by the correct selection of the target volume site. However, several parameters related to the IORT treatment can impact the ultimate outcome (IORT dose, energy of the electron beam, applicator size, and the angle of incidence of the IORT applicator). As the usual prior treatment planning is not possible to be done during the IORT procedure, the possibility to underdose the target volume and/or overdose the surrounding normal tissue is a particular concern to overcome.

The University of Munster has developed a method based on preplanning treatment by using a neuronavigation system, and thereafter a dose reconstruction is performed as a quality control of the IOERT treatment. As a result of this analysis, they found that inadequate coverage of the target volume to the prescribed dose had a significant impact in survival of patients with malignant glioma, and particularly in GBM.

Although reasonably tolerable, toxicity has been found with IORT, which is related to the dose of IORT as well as the volume of tissue irradiated. In some reports, treatment-related toxicity has been in excess of 30%. Some authors have found a single IORT dose of 25 Gy confined to a limited volume is safe but the accepted recommendation is 20 Gy as the maximum tolerable IORT dose since the rate of complications directly related to the IORT procedure appears to be low at this dose [42] in conjunction with EBRT and chemotherapy.

Histological studies from autopsies performed on patients with brain tumors treated with IORT, have shown extensive necrosis and complete absence of tumor cells in the irradiated volume, both in malignant glioma and metastatic brain tumors [68]. In 1980, Abe et al. [69] reported autopsy data from four patients with recurrent brain tumors who had previously received EBRT; completely destroyed irradiated areas with no viable cancer cells were found.

Conclusions

With regard to the efficacy of IORT in brain tumors, it is too early to draw definitive conclusions because the experience is based upon few series and small number of patients. While controlled randomized clinical trials could help answer this issue, they are unlikely to occur in view of the small number of institutions with interest in the use of IORT for brain tumors. Future research efforts evaluating IORT as a component of treatment for brain tumors are more likely to be prospective controlled single or multiple institution phase II studies that test optimal combinations of EBRT and IORT, the addition of biological dose modifiers with IORT/EBRT, optimization of IORT dose delivery and optimal patient selection criterion.

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Chapter 9
Head and Neck Cancer

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Keywords Head and neck cancer • IOERT series – head/neck cancer • HDR-IORT for head/neck cancer • Recurrent head and neck cancer

Introduction

Intraoperative radiation therapy (IORT) represents an attractive modality for treating head and neck cancers, an anatomic site in which a multiplicity of issues arise regarding total treatment package time, retreatment, organ function preservation, dosimetry of complex anatomic sites near critical structures, and integration with external-beam irradiation (EBRT) either in the primary setting or in the previously irradiated patient. Pioneered in the 1960s primarily by the Japanese for the treatment of gastrointestinal tumors [1] IORT has been investigated in USA and Europe as a way of "boost" dose in conjunction with conventional EBRT to treat malignancies with a high propensity for local recurrence such as locally advanced or recurrent colorectal, retroperitoneal sarcomas, and advanced gynecologic cancers. In the head and neck region, the major experience has been in the treatment of locoregionally recurrent cancers after a previous EBRT.

More recently, IORT has been integrated into the upfront treatment of newly diagnosed head and neck cancer focused on clinical scenarios considered at high risk for local relapse. IORT can be delivered using electrons (IOERT) or photons produced from a high-dose-rate gamma emitting radioisotope such as Ir-192 (HDR-IORT). The purpose of this chapter is to summarize over 25 years of experience with IORT in head and neck cancer and discuss new areas of potential applications.

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_9,

Results with Non-IORT Treatment Approaches

Approximately 45,000 new cases of head and neck squamous-cell carcinoma (SCC) occur annually in USA with about 12,000 deaths [2]. About two thirds present with local or regionally advanced disease (stage III or IV) and are usually treated with both surgery and radiation or by definitive chemoradiation, depending on the site of the primary and patient co morbidities. Oropharynx and many intermediate to advanced staged larynx/hypopharynx tumors are generally treated with an organ preservation regimen consisting of chemoradiation, most commonly using concurrent treatment but selectively with an induction chemotherapy approach in patients with very advanced disease [3–6]. With such approaches organ preservation and locoregional control are outstanding for larynx and oropharynx as well as selected early-immediate stage hypopharynx patients [3–8].

Definitive resection is most commonly used in the resection of tumors of the oral cavity, paranasal sinus, and very advanced hypopharynx/larynx cancers. Adjuvant radiation or chemoradiation is recommended depending on clinicopathologic factors that stratify patients according to the risk for recurrence [9–12]. Such factors include margin status, extracapsular nodal extension, perineural or lymphvascular invasion, number and level of nodes involved, T and N stage, subglottic extension, treatment delay, and primary site. Of these factors, the presence of a positive margin or extracapsular extension is the worst factor for locoregional recurrence of up to 30–50% and warrants intensive adjuvant treatment consisting of concurrent chemoradiation as demonstrated in two major randomized trials [12, 13]. Locoregional failure even after optimal multimodality therapy still occur in about 12–30% with either primary chemoradiation or definitive resection based on randomized data [3, 5, 7, 12, 13].

Strategies to salvage a locoregional recurrence usually require multidisciplinary evaluation. If patients have failed previous radiation, then they may be considered for salvage surgery with additional chemoradiation or chemoradiation alone. Locoregional control rates after salvage therapy using non-IORT based multimodality therapy ranges from 27 to 77%, and overall survival (OS) ranges from 9 to 35% [14–21]. Moreover, these programs are associated with severe complications including treatment-related mortality reported in 7–17%. Previously irradiated patients have a better chance for salvage if surgical resection is possible in combination with additional radiation. This scenario results in a doubling of locoregional control and overall survival compared to those undergoing chemoradiation [22, 23]. Surgical salvage for recurrent neck disease is most effective when disease is limited, and there has been no prior neck surgery. When there has been a prior neck dissection, however, surgical options alone are usually of limited value [24–28].

Given the limited tolerance to radiotherapy of multiple head and neck structures important for speech, swallowing, articulation, and general maintenance of quality of life, IORT represents an opportunity for reirradiation to the tumor bed without increasing exposure to normal tissue as well as minimizing total treatment package time when combined with external-beam radiation. This is particularly relevant in patients who have locoregional recurrence after a previous radiation. The approach may be strategically advantageous in addition as an upfront boost for those undergoing initial extensive resection.

IORT Rationale and Treatment Factors

Rationale for IORT

The goal of the IORT procedure in head and neck cancer is to deliver a large, single fraction of irradiation to the target area after maximal tumor resection, minimizing dose to surrounding structures including neurovascular and bony structures, as well as the suture line and anastamosis.

IORT offers several advantages. A large dose of radiation may be delivered to an area at greatest risk for residual microscopic disease. Simultaneously, dose-limiting structures may be maximally displaced with retraction and packing or protected with strategically placed shields. The ability to deliver radiation at the time of definitive resection is particularly relevant in head and neck cancer where the total treatment package time from the day of surgery to the end of radiation therapy is crucial to optimize locoregional control and survival [9, 13]. In addition, there may be radiobiological advantages that accrue from delivery of a large dose of radiation to overcome presumably radioresistant tumor clonogens that have been refractory to a previous EBRT.

Methods of IORT Delivery

With narrow cavities and complex surfaces, the head and neck region can present a challenging area to treat with IORT. Various strategies have evolved to deliver radiation intraoperatively. Two contrasting but complementary IORT approaches involve (1) electrons (IOERT) generated by a linear accelerator in a shielded room or a self-shielding mobile linear accelerator such Mobetron, LIAC or Novac-7 system and (2) photons delivered using a high-dose-rate gamma-emitting radioisotope such as Ir-192 (HDR-IORT) mounted on a mobile HDR afterloader.

HDR-IORT Versus IOERT

IOERT has been the mainstay of IORT delivery and requires the use of cylindrical applicators of various sizes and shapes that are adequate in many head and neck scenarios to treat a flat, planar surface but may be prohibitive in narrow, complexly shaped head and neck cavities or highly curved surfaces (Fig. 9.1). Beveled lucite or metal applicators, gantry rotation, table angulation, and patient repositioning are necessary to ensure proper tumor coverage. These maneuvers increase setup time and complexity. If the machine is not to be deployed in the OR, patients may be transported from the OR to the radiation therapy suite maintaining a sterile field and with monitoring under the care of the anesthesiologist and the surgical team. If the radiation suite is distinct from the OR, it must meet OR standards for decontamination, precleaning, and air flow and circulation. Electron applicators, bolus, docking equipment, and instruments should be sterilized, and radiation personnel should be scrubbed, gowned, and gloved.

IOERT electron energies for head and neck cancer patients typically range from 6 to 9 MeV with applicator sizes of 2.5–9.5 cm [29–33]. Flat applicator surfaces are preferred, but occasionally a beveled applicator is anatomically necessary. The mandible, carotid artery, and cranial nerves may be shielded as appropriate with 1–2 mm thick lead strips. A dose of 7.5–15 Gy is commonly delivered. If the tumor bed is large, the use of abutting electron fields may be necessary due to the size constraints of the applicators; either a hard or a soft docking system is needed to deliver the treatment. Setup and positioning require the majority of the time, while the actual treatment is for 5–10 min. After the procedure, patients who were transported from the OR return for closure of the surgical bed and defects with flaps as needed.

The HDR-IORT program offers the flexibility to treat narrow, complexly curved surfaces. Photon radiation is delivered with an HDR afterloader containing a nominal 10 Curie iridium-192 (Ir-192) encapsulated source (4 mm × 1 mm) mounted on a cable that is propelled into the hollow catheters of an 8 mm thick, flexible, translucent applicator [34, 35] (Fig. 9.2). HDR-IORT can treat virtually all tumor beds and offers the possibility to treat narrow spaces such as parapharyngeal space or paranasal sinus, as well as any curvilinear surface such as neck. The entire procedure takes place in shielded operating room.

Fig. 9.1 IOERT: A 71-year-old man with history of poorly differentiated squamous-cell carcinoma treated with left total parotidectomy and facial nerve sacrifice in May 1996. He then had full-course external-beam irradiation (EBRT) postoperatively. In routine surveillance, he developed a 1.5-cm left periauricular recurrence in the subcutaneous tissues. Needle biopsy showed recurrent squamous-cell carcinoma. The patient's tumor was resected en bloc with negative margins. While under anesthesia, the patient was brought to the radiation oncology department. The tumor bed was identified and measured within the open surgical wound. (**a**) A 1-cm bolus was placed over the target area and a 6 cm applicator was connected to the gantry and positioned over the tumor bed. Care was taken to avoid the mandible. (**b**, **c**) The total treatment was 15 Gy delivered to the 90% isodose line using 6 MeV electron therapy. After completion of treatment, the position of the applicator was reconfirmed, the applicator was disconnected from the gantry, and the surgical wound was closed. (**d**–**f**) No additional EBRT was given. As of last follow-up in December 2002, the patient remained without evidence of disease on examination or anatomic imaging (acknowledgment to Dr. I-Chow Hsu for providing clinical history).

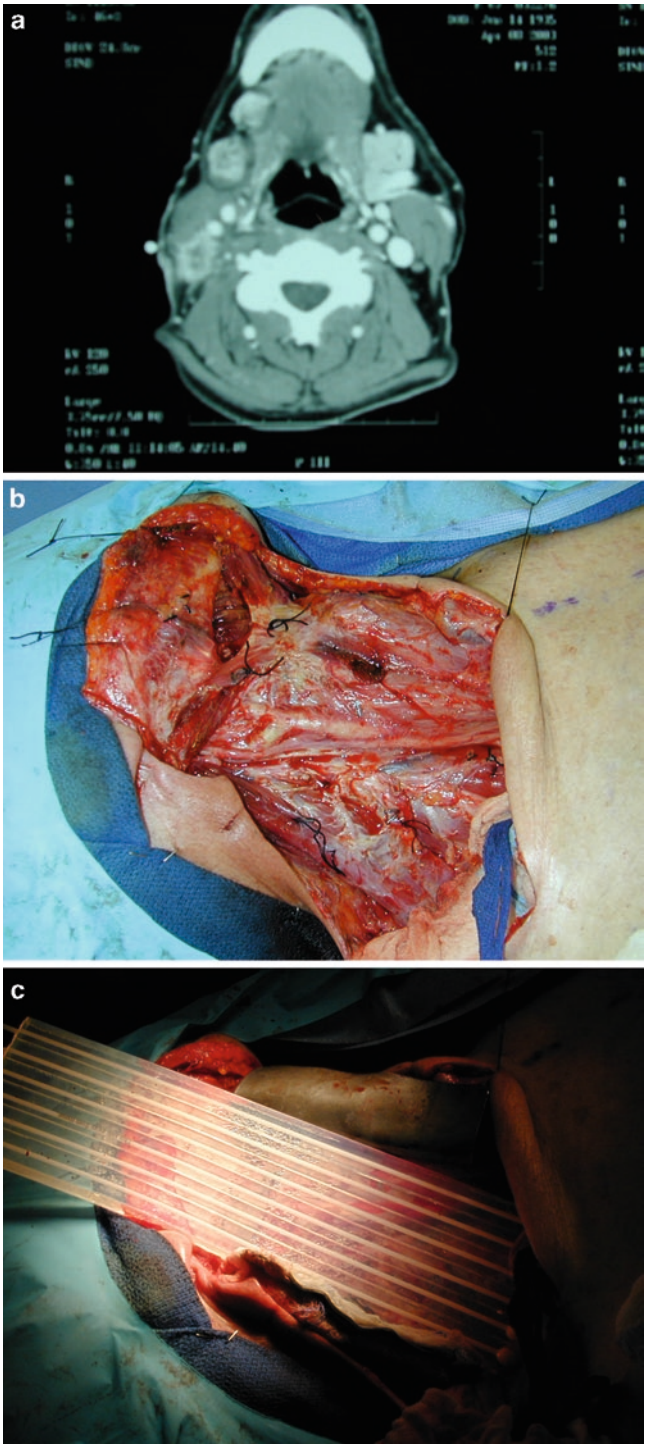

Fig. 9.2 Example of High-Dose-Rate brachytherapy IORT (HDR-IORT). The patient is a 58-year-old male s/p an isolated nodal recurrence after previous external-beam radiation (EBRT) for a oropharynx cancer. The occurrence appeared at the junction of the level II and III nodal station posterior to the jugular vein. (**a**) A gross total resection was achieved. The area of initial involvement was outline by surgical clips. (**b**) The larynx, carotid artery and vagus were not involved. A 6-channel applicator was selected to cover the treatment area, and a lead shielding was used to

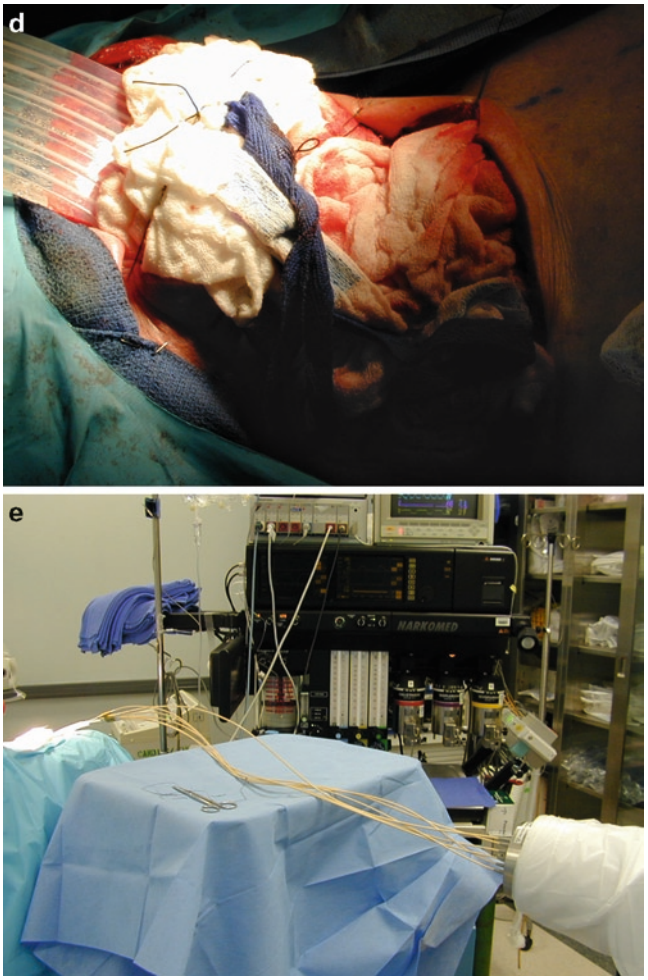

Fig. 9.2 (continued) protect the larynx. Packing was placed to maximally displace the overlying skin and suture line away from the applicator (**c**, **d**). Transfer tubes were then used to connect the applicator to the Ir-192 afterloader. The room was evacuated and the anesthetic equipment, patient and applicator were watched under surveillance cameras. (**e**) A total dose of 12.5 Gy HDR-IORT was delivered. Pathology revealed a nodal metastasis with extracapsular extension. The patient received an additional 5 Gy EBRT with concurrent platinum-based chemotherapy.

Compared to IOERT, the advantages of HDR-IORT are primarily as follows: (1) greater flexibility of the applicators facilitating treatment of more complex surfaces, (2) reduced dosimetry inhomogeneity in large fields and at the junction of abutting fields, (3) heterogeneity of dose distribution, facilitating the greatest dose to be delivered where the risk for microscopic residual disease is greatest [34, 35], and (4) target areas can be treated volumetrically, rather than only as planar surfaces. Disadvantages compared to IOERT include the "stepwise" delivery of radiation and increased treatment time; HDR-IORT introduces prohibitive hot spots when there is gross residual disease greater than 0.5 cm (Tables 9.2 and 9.3), while IOERT more homogenously covers gross disease and has shown to salvage a small percentage of patients.

At institutions with both capabilities, IOERT appears to be associated with total setup and treatment times that are about 30 min shorter compared to HDR-IORT (30–60 min vs. 60–90 min) and actual treatment time of 2–3 min vs. 5–20 min, and IOERT is often preferred for this reason. However, as the applicators can be unwieldy and inflexible for narrow spaces,

IOERT may be more limited than HDR-IORT for sites such as the skull base, paranasal sinuses, or highly complex curved surfaces that do not allow a homogeneous en face delivery of electrons [42].

Surgical Planning and Techniques

The first step in IORT is study of the preoperative MRI imaging to be sure that no more than microscopic margins are likely to be found intraoperatively. A careful assessment of the relationship of tumor to the carotid artery and the superior extent of tumor in areas inaccessible by the IORT technique envisioned is critical. A close interaction between the surgeon and the radiation oncologist is then critical for delineation of the irradiation target, adequate anatomic access for IORT delivery, and maximal protection of surrounding structures.

Modification in planned skin incision, mobilization of surrounding tissues, and protection and retraction of radiosensitive nontargets (vascular anastamoses, carotid artery, cranial nerves, bone) from the irradiation field may be necessary. Partial resection of the inferior border of the mandible or a temporary mandibulotomy may be required to obtain adequate exposure. Occasionally, suspected tumor-bearing tissues may be mobilized to bring them in close apposition to the applicator. The goal of retraction and packing during IORT is to maximize protection of normal tissue based on the principle that small changes in distance from the applicator surface result in several fold decreases in radiation exposure (proportional to the square of the distance). Specially prepared intraoperative lead disks orfoil shields normal tissues that cannot be mobilized outside the irradiation field. Particular attention should be paid to the skin around the incision site, peripheral nerves, the spinal cord, optic nerves, and the tissue near a vascular or mucosal anastamosis.

The target area to be treated by IORT is the at-risk tumor bed such as microscopically positive margins, areas of close margins, and any gross residual disease. The irradiated field may be defined with radiopaque surgical hemoclips or gold marker seeds to assist in subsequent EBRT planning.

IORT Treatment Planning and Dosimetry

After tumor resection, the tumor bed is reviewed by the surgeon, critical adjacent organs are identified, and precise measurements are taken of the target area. An appropriate sized applicator is placed on the tumor bed and secured into place (Figs. 9.1 and 9.2).

IOERT planning usually requires the selection of the appropriate energy and isodose curve along with the addition of bolus and determination of the need for beveled applicators to maximize the surface area to be treated. HDR-IORT treatment planning must use preplanned dosimetry atlases for various field sizes and curvatures of the tumor bed. Typically, the HDR-IORT dose is prescribed at 1 cm away from the source or 0.5 cm from the applicator surface. Localizing radiographs may be obtained using dummy sources for documentation.

Dosimetric Comparison of HDR-IORT to IOERT

Dose distributions are different when comparing a typical treatment prescription of 6–9 MeV electrons prescribed to 90% versus an Ir-192 prescription of treatment delivered 1 cm from the source and 0.5 cm depth into the tissue. The electron treatment has a buildup region of homogeneous dosing up to the prescription depth with a rapid falloff. In contrast, the dosimetry of the Ir-192 is 200% at the surface compared to that at prescription depth with more gradual falloff of dose beyond prescription depth. The dose inhomogeneity allows the greatest dose to be delivered

at the surface of the tumor bed but creates a greater dose gradient between the surface of the tumor bed and prescription depth in contrast to the markedly more homogeneous distribution between the surface under the bolus and treatment depth in IOERT. With a range of energies available, allowing delivery of homogeneous dose to depths of 1.5 cm (6 MeV) to 5.5 cm (18 MeV), IOERT is in theory better able to treat gross residual disease that are greater than 0.5–1 cm thick; however, results in such situations are poor regardless of modality. For grossly resected patients with no more than microscopic residual disease, either IOERT or HDR-IORT may be utilized. HDR-IORT may offer an advantage by giving a higher dose to an area of greatest tumor burden compared to the prescription depth.

IORT Results: Alone or Plus EBRT

Formulation of General IORT Principles from Early Experiences

Animal IORT Tolerance Studies

Animal studies done primarily in dogs were performed to determine the morbidity of IORT in critical structures of the head and neck area during a surgical procedure.

The morbidity of IORT was compared to low-dose-rate brachytherapy in a canine study evaluating differences in outcome after exposure to 4-cm segments of carotid artery, pharynx, or mandible [43]. Three groups of four dogs each were operated upon to widely expose bilateral necks. The pharynx was incised to the mucosa and mandible to the periosteum. For each animal, one side of the neck was exposed to radiation, while the other side was not irradiated and served as a control. The first group received 40 Gy IOERT, the second group received 60 Gy IOERT, and the third group received interstitial implant with afterloaded low-dose-rate brachytherapy to a total dose 60 Gy using Ir-192. Nine or twelve MeV electrons were delivered using a 3–4.4 cm applicator. At 2 and 4 months after radiation, two dogs were sacrificed and histopathologic examination of the carotid artery, pharynx, and mandible was performed. No statistically significant difference between treatment groups was found for carotid artery injury (perivascular fibrosis in the tunica media and inflammation), although a trend was noted for increasing fibrosis with higher dose and longer follow-up. No differences were noted for pharyngeal morbidity. The incidence for mandibular osteoradionecrosis was 18% and occurred in two animals, one receiving 60 Gy IOERT and the other 60 Gy Ir-192. Bone-marrow suppression was the most notable difference between irradiated and unirradiatied neck ($p=0.06$) and was increased in dogs receiving IOERT (4/7) versus Ir-192 (1/4) and was noted at both 40 Gy IOERT and 60 Gy IOERT.

Mittal evaluated dogs receiving IOERT doses of 25, 35, 45, and 55 Gy using 12 MeV IOERT and found increased collagen in the walls of irradiated carotids at 6 months, which was greater than that at 3 months [14]. Decreased density and cellularity of vagus nerve cells, as well as loss of nerve fibers, were also seen, which were worse at 6 months compared to that at 3 months postradiation.

Early Head/Neck IORT Clinical Series

The early experience with IORT in head and neck focused primarily on patients with recurrent cancer after previous EBRT to establish tolerability and efficacy of IORT treatment. The initial experiences with IOERT are summarized in Table 9.1. Much of the work is reported from a few US centers (University of California, San Francisco [UCSF], Methodist Hospital of Indiana, and Ohio State University) as well as from centers in Japan, Germany, and Spain. In general, patients with

Table 9.1 Single-institution IOERT experience in head and neck cancer

Institution/series	No. of Pts	Med F/U (mo)	Recurrent (%)	Prior EBRT (%)	Gross residual (%)	IOERT dose (Gy)	LRC (total) (%)	LC R0 (%)	LC R1 (%)	LC R2 (%)	OS 2 yr (%)
Methodist											
1987 [15]	28	14 (min)	57	61	23	10	66	87	75	0	67 (1 yr)
1988 [16]	67	NR	52	52	18	15–20	75	100	84	17	NR
1990 [17]	104	24 (min)	62	42	20	15–20	40	70	56	57	NR
1991 [27]	47	14	100	100	13	15–25	62	NR	NR	NR	55
OSU											
1998 [44]	38	30	100	100	8	15–20	4				
2001 [37]	37	40	0	0	0	7.5–10	97	NR	NR	NR	48
1999 [36]	43	45	0	0	0	7.5–10	93	NR	NR	NR	79
2007 [39]	123	62	0	0	0	7.5–10	91	NR	NR	NR	57
UCSF											
1997 [26]	44	20	77	72	2	14–18	62	NR	NR	NR	66
2007 [18]	137	41	83	83	0	15 (10–18)	67 (3 yr)	82	48	NR	36 (3 yr)
Pamplona											
1997 [19]	31	NR	74	47	52	10–15	33	NR	NR	NR	NR
Japan											
Toita [28]	25	19	68	33	23	10–30	54	82	55	0	45
Spaeth [46]	95	11	89	95	72	10–40	37[a]	73	57	17	NR
Marucci [31]	25	9	0	0	0	12	96	92	NR	NR	64

Pts patients, *Med* median, *F/U* follow-up, *EBRT* external-beam irradiation, *IOERT* intraoperative electron irradiation, *LRC* local regional control, *LC* local control, *yr* year, *OS* overall survival, NR not reported

[a]Pain relief in 74%

close margins, microscopic, or gross residual disease have local failure rates of 18–27%, 25–46% and 75–100%, respectively, after 15–20 Gy of IOERT [30, 40, 44, 47, 48]. Gross total resection is consistently a prerequisite to obtain the best outcome after IORT treatment [31–33].

Methodist Hospital of Indiana – IOERT

The experience at Methodist Hospital of Indiana was reported in a series of papers. The IOERT program was started in 1982, and a total of 355 patients had received IOERT as of September 1996 (R Foote et al., IORT for Head and Neck Cancer. IORT Techniques and Results, 1st Ed'n.).

Garrett reported the preliminary experiences from the Methodist Hospital of Indiana, demonstrating the importance of resection status in the success of IORT to control disease. Twenty-eight patients with head and neck SCC were maximally resected, and IOERT was given to 30 sites. The patients were transported intraoperatively to the radiation oncology suite. Once in the suite, the entire procedure took over 45 min with 15–20 min of radiation delivery time. Neck was the most common site of treatment ($N=17$), followed by pterygoid, maxilla, oral cavity, temporal region, and parotid. Previous EBRT had been given in 17 sites to a median dose of 60 Gy (50–82 Gy). Minimum follow-up was 14 months. Local failure occurred in 13% of those with close but negative margins (R0 resection margin), in 25% of those with microscopic residual cancer (R1 resection margin), and in all seven with gross residual disease (R2 resection margin). One year overall survival was 76% in those with microscopically positive margins and 86% in those with negative margins. Fatal carotid blowout occurred in two patients. One patient experienced mandibular osteonecrosis. Patients who received previous EBRT showed similar rates of local control and morbidity as those newly diagnosed without previous EBRT [15].

An update on a total of 67 patients (44 SCC and 19 salivary gland malignancies) was published in 1988, 35 with recurrent disease following prior EBRT (45–82 Gy) and 32 with initial presentation. An IOERT dose of 15–20 Gy (range 10–100 Gy) was typically given, and 27 of the 32 received additional 40–60 Gy EBRT. Irradiated sites were neck ($n=24$), parotid ($n=10$), skull base ($n=9$), pterygoids ($n=7$), mandible ($n=4$), temporal bone ($n=3$), floor of mouth ($n=3$), submandibular gland ($n=2$), and tongue ($n=2$). Gross residual disease was present in 12 patients, microscopic residual was present in 19 patients, and 23 had negative but close margins. All 13 parotid cancers had adequate margins, preserving the facial nerve. In-field failure was 25% for the entire group: 0% after adequate margin, 26% for a close margin, 16% for R1 resection, and 83% for R2 resection. There were four carotid blowouts. The four who developed osteoradionecrosis had received 50 Gy ($n=3$) or 100 Gy ($n=1$) of IOERT [16].

In 1990, a total of 104 patients, with longer follow-up, were reported by Freeman, 64 with recurrent disease and 40 with initial disease. The patients were treated with IOERT typically to doses of 20 Gy to the neck and 15 Gy to the oral cavity, salivary gland, or skull base. Histologies included SCC (74), salivary gland tumors (24), sarcoma (3), melanoma (2), and basal-cell carcinoma (1). Sites of IOERT were neck (38), skull base (21), parotid (19), oral cavity (22), prevertebral area (5), and temporal bone (5). The majority received 4 MeV electrons with applicator sizes of 4–6 cm in diameter. Minimum follow-up was 2 years in 50 patients. Local control was obtained in 54% (27/50). No obvious difference was noted in local control between neck and nonneck sites, (47% vs. 57%). Among the 74 patients with SCC, 35 had a minimum follow-up of 2 years, with local control of 40% independent of resection status. The patients with salivary gland tumors had 69% (9/13) local control at a minimum 2-year follow-up. Of patients with local failure who underwent autopsy, disease failure appeared to occur primarily outside the IOERT field, suggesting sterilization within field. Fistula developed in six patients, of whom three had previous EBRT to doses of 60–80 Gy. The three patients who developed carotid or innominate artery bleed had received previous EBRT. No apparent increase in wound healing complications was reported [17].

UCSF – IOERT

IOERT has been used at UCSF since 1991. Initially, the treatment was delivered by transporting the patient under general anesthesia to the linear accelerator; after 1997, a mobile unit within the OR suite has been available instead. Indications for consideration of IOERT include the following: persistent or recurrent tumors for which conventional salvage measures are judged to be inadequate, or extensive perineural or bony involvement with anticipation of close or microscopically positive margins. For recurrent tumors of the salivary glands manifesting high-risk features, IOERT may offer an improved opportunity for local control.

Between March 1991 and August 1995, 44 patients with head and neck cancer were treated with IOERT and maximal resection with or without EBRT [31, 37]. Two patients underwent IOERT twice. The majority of cases (78%) were chosen due to persistence of primary tumor after definitive therapy, or one or more recurrences despite aggressive salvage. The other cases were chosen for IOERT based on factors indicating high risk for local failure, such as neural, bone, or base of skull invasion. Over half (54%) of the patients had undergone previous surgery, and 72% had prior EBRT. Of 46 cases, 36 were SCC; other histologies were mucoepidermoid (3), adenocarcinoma (2), adenoid cystic carcinoma (2), and one each of poorly differentiated, anaplastic chordoma. An IOERT dose of 14–18 Gy was delivered to the 90% isodose line encompassing the tumor volume. Seventeen patients, including seven of ten patients with primary disease, received EBRT after IOERT. Twenty-five of the 29 cases which were not treated with additional EBRT had undergone prior dose-limiting radiotherapy. Four patients had chemotherapy after IOERT.

Table 9.1 summarizes the treatment results. Patients who were disease-free were followed for a median of 20 months. Two-year actuarial locoregional control and OS were 61.7 and 65.7%, respectively. Overall, 19 patients (43%) recurred, six locally, three with an associated regional out-of-field relapse. Eight regional relapses occurred outside the IOERT field, one patient had regional and distant failure, and four patients had distant metastases. The median DFS for patients who recurred was 4 months. Overall DFS at 2 years was 70.3%. There was no clear correlation between margin status and outcome, although among the 19 patients who remained free of disease, 89% had close or microscopically positive margins. All of the 17 patients who received postoperative EBRT remained free of disease.

Complications possibly attributable to IOERT and/or surgery were mucositis, supraglottic edema, abscess, cellulitis/osteoradionecrosis, and a 1-cm wound dehiscence (one of each). Three patients had facial nerve weakness. One patient had vasovagal symptoms referable to baroreceptors of the carotid bifurcation, and another patient developed a cerebrovascular accident; both were more likely related to surgery than to IOERT. One patient had a fatal carotid rupture 14 months after surgery–IOERT.

An update of the UCSF data has been published specifically examining persistent and recurrent head and neck cancers [18]. Between March 1991 and December 2004, a total of 137 patients were treated. This report excluded 40 patients who were treated at initial presentation, had multiple recurrences, had gross residual disease after surgical resection, received less dose than planned due to technical failure, or had metastatic disease at the time of IOERT. The majority of these patients (67%) were treated after 1997 with a specialized mobile electron unit (Mobetron) within the surgical suite. Applicator size ranged from 3 to 10 cm using electron energies of 4–12 MeV. Most patients (91%) were treated to a dose of 15 Gy. Only 35 patients had additional postoperative EBRT with or without chemotherapy.

With a median follow-up of 18 months (41 months among survivors), the 3-year actuarial in-field control rate after IOERT was 67% and 3-year OS was 36%. For patients with negative surgical margins, 3-year in-field control was 82%. Patients who had IOERT to the primary site had a distant

metastasis-free survival of 61% compared to 30% for those treated with IOERT in neck. Complications included four superficial wound infections, two orocutaneous fistulas, one flap necrosis, one trismus, and one facial neuropathy. There were no reported complications of osteoradionecrosis, bone fracture, brain necrosis, or carotid artery hemorrhage.

Japan and Europe: IOERT Series

Toita reported on a Japanese experience of 25 patients with recurrent or locally advanced head and neck cancer treated with resection and IOERT. A single dose of 10–30 Gy (median 20 Gy) was delivered to 30 sites using a median energy of 9 MeV (6–18 MeV) to a median area of 6 cm in greatest diameter (2.5–12 cm). Either pre- or postoperative EBRT was given for 20 sites to a mean dose of 41.2 Gy (10–70 Gy). Twenty-two sites consisted of recurrent disease and had been previously treated by surgery and radiation, while eight sites had been previously untreated. The site of treatment was the primary in nine patients and neck in 21. Margin status was R0 but close in 11, R1 in 12, and R2 in 7. 2-year control rate in the IOERT field was 54% for all patients, 82% for R0, 55% for R1, and 0% for R2 patients. At a median follow-up of 19 months, 2-year overall survival for all patients was 45%, with 70% for R0, 33% for R1, and 0% for R2. An overall 2-year cumulative complication rate was 33% with higher incidence at IOERT doses of 20 Gy or greater (5/12 vs. 0/11, respectively). Four sites developed osteoradionecrosis (hard palate, skull base, and cervical vertebra) and three developed carotid blowout. The complication rate was 0% if there was no prior therapy, 38% for recurrence after surgery, and 40% for recurrence after surgery and radiation [44].

Martinez-Monge reported the Pamplona/University of Navarra experience of a total of 31 patients treated with maximal resection and IOERT. Twenty-three patients presented with recurrence, while eight presented with primary disease (three larynx, two oral cavity, two oropharynx, and two with unknown primaries). For the patients with recurrent disease, tumor relapse occurred in the primary site in ten, neck in nine, and primary and neck in four. Squamous-cell carcinoma was the dominant histology in 83%. EBRT to a median dose of 50 Gy was given to 14 of 16 patients naïve to radiation, while 6 of 14 previously irradiated patients received additional EBRT (median dose of 30 Gy). After resection, there was gross residual in 52% and microscopic residual in 48%. The patients received an IOERT dose of 10–15 Gy using 6–9 MeV electrons to treat a 5–12 cm area. The treatment was given to the primary site in 42% of the cases and to neck in 58%. Locoregional control was achieved in 34% with better local control in patients newly treated versus those previously irradiated (46 vs. 19%, $p = 0.0049$). Overall median survival was 14 months with an 8-year actuarial survival of 20%. Patients with gross residual disease and those previously irradiated had worse survival (a median survival of 8 and 6 months, respectively, $p = 0.029$ and $p = 0.04$) [19].

HDR-IORT – Ohio State

Nag reported the initial Ohio State University (OSU) experience using HDR-IORT in a total of 29 patients with head and neck cancers, primarily in locations inaccessible to IOERT due to narrow cavities or complex curved surfaces especially paranasal-sinus and skull-base cancer. Customized surface applicators embedded with catheters spaced 1 cm apart to deliver Ir-192 based HDR-IORT with preplanned dosimetry were utilized to deliver HDR-IORT doses of 7.5–12.5 Gy. Median treatment time was 6.5 min (4–23 min). Twenty-three patients received additional EBRT to doses of 45–50 Gy, while six patients who recurred after previous EBRT (50–70 Gy) were treated with IORT alone to a higher dose of 15 Gy. At a median follow-up of 21 months (3–33 months), in-field control

Table 9.2 HDR-IORT outcomes in head and neck cancer

Institution	No. of Pts	Med F/U (months)	Recurrent (%)	Prior EBRT (%)	Gross residual (%)	IOERT dose (Gy)	LRC (total) (%)	LC R0 (%)	LC R1 (%)	LC R2 (%)	OS 2 yr (%)
OSU, 1996 [20]	29	21	21	21	0	7.5–12.5	67	NR	NR	NR	72
2005 [21]	65	65	17	18	11	7.5–20	69 (3 yr)	NR	64	33	63 (3 yr)
1999 [22]	7	59	100	100	0	10–15	57	NR	NR	NR	NR
Beth Israel 2008 [23]	49	13	84	84	0	12	61	77	47	NR	70 (1 yr)

Pts patients, *Med* median, *F/U* follow-up, *EBRT* external-beam irradiation, *IOERT* intraoperative electron irradiation, *LRC* local regional control, *LC* local control, *yr* year, *OS* overall survival, *NR* not reported

was 67% and crude survival was 72% for all patients. In 23 patients with primary presentation, local control was 78% and crude survival was 87%. For 17 patients who completed the planned EBRT and HDR-IORT, tumor control was 89% and survival was 100% (Table 9.2). In six patients who did not complete the planned EBRT, tumor control was 50% and survival was 50%. In six patients with previously irradiated recurrent cancers who received HDR-IORT only for microscopic positive margins, tumor control was 17% with a crude survival of 17%. No intraoperative complications occurred. Perioperative and acute morbidity included CSF leak with bone exposure ($n=1$), chronic subdural hematoma ($n=1$), septicemia, otitis media, and severe xerostomia [20].

An update discusses 65 patients with primary or recurrent locally advanced cancers treated at OSU with HDR-IORT [21].The local control and overall survival at 3 years was 69 and 63% respectively (Table 9.2). Of the 53 patients with primary disease 45% were alive at 3 years compared to 28% with recurrent disease. A survival difference was noted between patients who received EBRT and those who were treated with IORT only (48% vs. 28%, $p<0.05$). Forty-five percent of the patients with microscopic margin survived 3 years as opposed to 17% with gross residual disease. However, these differences were not statistically significant. Acute and long-term morbidity was acceptable, with xerostomia being the major complaint. Trismus, pharyngocutaneous fistula, soft-tissue necrosis, and hypoplasia of the orbit were noted in four patients.

Nag also reported long-term outcomes for seven patients with recurrent cancers that were previously irradiated (EBRT 60–104 Gy) and treated with HDR-IORT alone. Six patients received 15-Gy HDR-IORT, while one was treated to a dose of 10 Gy. At a median follow-up of 59 months (33–67 months), the crude in-field control was 57%. The median disease-free survival was 9 months with two patients alive and disease free at 28 and 30 months. Morbidity was considered acceptable and included subdural hematomas requiring surgical drainage in one patient, and orocutaneous fistula and necrosis of the mandible treated with HBO in another [22].

HDR-IORT: Beth Israel Medical Center

Hu et al. reported the preliminary Beth Israel Medical Center HDR-IORT experience in the recurrent head and neck cancer setting. From 1/01 to 2/08, a total of 49 patients with primary ($n=8$) or recurrent ($n=41$) head and neck cancer were treated with HDR-IORT after gross total resection to a median dose of 12 Gy (10–15 Gy) using the Harrison–Anderson–Mick applicator [23]. Six of the 49 patients received HDR-IORT to two separate sites. Patient characteristics were as follows: median age: 65 years, (range 41–88). Males: 65% ($n=32/49$). The sites of treatment were neck = 31, mandible = 5, parotid = 6, maxilla = 4, temporal region = 3, oral cavity = 3, and parapharyngeal region = 1. The median time of HDR-IORT delivery was 15 min (range 3–44 min) to a median field

size of (5 cm width (2–12 cm)×6 cm length (2–17 cm) at a depth of 1 cm (0.5–1 cm) from the source. Radical resection was performed in all patients with positive margins in 58% (28/48) and negative margins in 42% (20/48) of patients. Flap reconstruction was performed in 65% (32/49).

No intraoperative complications related to HDR-IORT ensued in any of the patients. Perioperatively, 3 of the 32 flaps required revision. Among the 37 patients available for detailed follow-up, 21 had positive margins, while 15 had negative margins and one unknown. Among these patients, crude rates of disease failure were noted in 57% (21/37) with failure occurring within the IORT treatment field in 35% (13/37) regional failure 24% (9/37) and distantly 27% (10/37) of patients. At a median follow-up of 13 months, the Kaplan–Meier estimate of 1 year OS was 70%, DFS was 48%, in-field local control was 61%, regional control was 80%, and distant metastasis was 29% for all patients. Margin status (negative versus positive margins) impacted on in-field local control (1 year 77 vs. 47%, $p=0.08$) and DFS (68 vs. 33%, $p=0.05$) in patients, respectively, but not OS (1 year OS – 73 vs. 63%, $p=0.78$), regional control (1 year 77 vs. 82%, $p=0.82$), or distant metastasis (25 vs. 33%, $p=0.70$), respectively. When stratified by HDR-IORT dose and margin status, 1-year local control among negative margin patients was 70% ($n=11$) vs. 100% ($n=4$) in those receiving ≤12 Gy vs. >12 Gy, respectively. Similarly, among positive margin patients, 1-year local control was 40% ($n=13$) vs. 55% ($n=8$) in those receiving ≤12 Gy vs. >12 Gy, respectively.

Morbidity

The reported morbidity from multiple single institutions is summarized in Table 9.3. The largest report focused on the morbidity of IORT originates from the OSU experience of a total of 53 patients with head and neck cancer treated with HDR-IORT ($n=20$) or IOERT ($n=33$). All patients received doses between 7.5 and 20 Gy and followed for at least 3 months. Patients who had been previously irradiated received 15 Gy for microscopic disease and 20 Gy for gross residual disease. Patients who were to receive planned EBRT to doses of 45–50 Gy received IORT boosts of 7.5–10 Gy for microscopic residual and 15 Gy for gross residual. IOERT ranged from 6 to 18 MeV. No perioperative deaths were reported, nor increase in length of stay (mean 13 days) compared to historic standards. The major complication rate was 17%: 9% medical and 8% surgical. The minor complication rate was 8%. Four patients had a major wound complication including flap necrosis in one patient, CSF leak from wound dehiscence in another patient, and two fistulae. Four other patients had superficial wound infections without tissue breakdown or fistula. In patients who had been previously irradiated, the major wound complication rate was 13% (2/16) versus 5% (2/37) in patients who had not been previously irradiated. The wound complication rate was considered similar to the historic experience without IORT at the same institution [24].

Summary: Early IORT Clinical Series

Based on these early experiences, some general principles can be derived establishing the optimal circumstances in which IORT may be useful. The need for gross total resection is clear: gross residual disease results in very poor in-field local control. The addition of EBRT to IORT appears to improve outcome, presumably primarily due to dose escalation but also possibly by treatment of a larger clinical target volume, especially in previously unirradiated patients. HDR-IORT doses of 10–15 Gy are recommended by the ABS in conjunction with EBRT doses of 45–50 Gy for previously unirradiated patients [25]. However, HDR-IORT alone achieves poor local control and is not recommended [22].

Patients treated at primary disease presentation also appear to have better outcomes compared to those with recurrent cancers, likely due to a combination of better tumor biology and ability to

Table 9.3 Morbidity IOERT and HDR-IORT experience

Series	F/U	No. of pts	IORT dose	Acute	Chronic	
IOERT-Methodist Garrett 1987 [15]	14 mo	28	10 Gy	CB 2/28	ORN 1/28	
1988 [16]	NS	67	15–20	CB 4/67	ORN 4/67	
1990 [17]	24 mo (min)	104	15–20	CB 3/104; FI 6/104	NS	
1995 [32]	NS	75	20	2.5% neurologic, CB 5%; FI 5%	NS	
IOERT – UCSF 1997 [26]	20 mo	44	14–18	CB (1/44) CN (3/44) WH(3/44)	ORN (1/44)	
2007 [18]	41 mo (among survivors)	137	15	WH (7/137) FI (2/137) CN (1/137)	No ORN or CB reported	
IOERT-Japan Toita 1994 [28]	19	25	10–30	CB (3/23)	ORN 4/23	Increased complications for doses of >20 Gy vs. <20 Gy (5/12 vs. 0/11)
IOERT – OSU 1999[36]	25	43	7.5–10	37% gr 4 acute toxicity STX 2/43	STX 2/43	
2001 [37]	40	37	7.5–10	WH (11/37) FI (5/37)	ORN (5/37) CN (1/37)	
2006 [38]	45	43	7.5–10	FI 14% WH4% PEG 11%	ORN 2/43 WH 7/43 ABS 1/43	6 mandibular plate exposure and 1 mandibular infection
2007 [39]	62	123	7.5–10	Mort 6% FI (15/123) WH3.4%	STX 1.6% MAND 9%	
2008 [31]	9	25	12	FI (3/25) WH (2/25)	NR	
HDR IORT-OSU Nag 1996 [20]	21	29	7.5–15	None reported	WH 5/29	All skull base
Nag 1999 [22]	59	7	15	FI (1/7) WH (1/7)	ORN (1/7)	
Nag 2004 [40]	72	34	10–20	WH 1/34FI (1/56)WH (1/56)	CN(2/34) BH(1/56) EPI(1/34)	All paranasal sinus
Nag 2005 [21]	65	65	10	CN 4/65, EPI 1/65,	ENO 1/65 TRI 2/65	

(continued)

Table 9.3 (continued)

Series	F/U	No. of pts	IORT dose	Acute	Chronic	
HDR-IORT & IOERT	3 (min) 59	20-HDR33-IOERT	7.5–20	WH (4/53)FI (1/7) WH (1/7)	NSORN (1/7)	
Nag [41] Nag [40] Haller [24]	6 yr	34	10–20	WH 1/34	CN 2/34 EPI 1/34	All paranasal sinus
HDR-IORT & IOERT [24]	3 (min)	20-HDR33-IOERT	7.5–20	WH (4/53)		

NS Not stated, *CB* carotid blowout, *ORN* osteoradionecrosis, *FI* fistula, *CN* cranial neuropathy, *WH* wound healing complication, *BH* benign hypoplasia, *PEG* feeding tube dependence, *STX* stricture, *MORT* treatment-related mortality, *MAND* mandibulectomy, *EPI* epiphora, *TRI* trismus, *ENO* enophthalmos, *ABS* abscess

receive higher doses of EBRT. However, patients with recurrent disease can tolerate IORT and be salvaged within the IORT field in a significant percentage of cases despite having been previously irradiated when the surgical resection can achieve clear or no worse than microscopically positive margins. Although the overwhelming experience is with squamous-cell carcinoma, patients with other histological types, such as salivary gland cancers, may also benefit from treatment. Patients appear to tolerate IORT doses up to 20 Gy with toxicities that do not overlap with those of EBRT, for which mucositis is the dose-limiting toxicity. A major toxicity associated with IORT is neuropathy, associated with dose of >15 Gy. Doses greater than 20 Gy are associated with carotid blowout and osteoradionecrosis, with time to development from 1 to 21 months for carotid blowout and 3–29 months for osteoradionecrosis [15, 17, 24, 26–28]. To minimize the risk of carotid artery rupture coverage associated not with direct carotid injury but with subsequent carotid exposure, the use of appropriate protective covering flaps (such as a pectoralis major myocutaneous flap or a microvascular free flap) is recommended [30, 36, 41].

IORT toxicity did not appear to significantly impair wound healing in the majority of cases compared to historical controls. Fistula formation has been consistently seen at several institutions, but not disproportionately compared to similar high-risk cases without IORT [29, 49]. Free-flap reconstruction failure after IORT is rare [30].

Integration of IORT to Decrease Total Treatment Time in Primary Cancers

For patients undergoing definitive surgical management and postoperative EBRT, Rosenthal and Ang demonstrated the importance of minimizing the total treatment package time to <100 days and 11–13 weeks, to optimize locoregional control [9, 13]. Integrating IORT during radical resection offers an important opportunity to decrease total treatment package time. Several groups have reported their experience exploring this concept.

The feasibility of combining IOERT with radical resection was reported for a total of 25 patients treated at the Regina Elena Institute in Rome. All patients underwent resection with negative margins, and 80% underwent subsequent EBRT. The sites of resection were oral cavity ($n=11$), skin ($n=6$), hypopharynx ($n=2$), larynx ($n=2$), and unknown primary ($n=2$). 17 patients underwent microvascular flap reconstruction. A dose of 12 Gy was delivered in all patients with IOERT energies ranging from 3 to 9 MeV (median 7 MeV), with a mean applicator diameter of 6 cm (range 4–8 cm). The mean time of setup and delivery was 20 min (range 15–30 min). The sites of delivery included the primary site in 17 patients, nodes in four with primary site, and node in four patients. One patient required flap removal due to flap necrosis, while three patients developed fistulas that did not require additional surgery. The total treatment package time for patients completing IORT and EBRT was 99.5 and 92 days (range 83–146 days) among patient receiving radiotherapy or chemoradiation, respectively. At a median follow-up of 9 months, 23 of 25 patients were controlled in the IOERT field. Two patients failed in-field. One patient developed an out-of-IOERT-field local failure that was salvaged with surgery and a second course of IOERT. Three patients died of disease: two of locoregional recurrence and one of systemic progression. Three patients died of nondisease related morbidity. The 2-year overall survival was 64% and disease-free survival of 51%. A flap complication rate of 23% (4/17) and surgical intervention rate of 6% (1/17) were reported to be within the institution's historical rate for flaps not treated with IORT [31].

Ohio State University Intensification Regimen

OSU has extensively reported a series of "intensification regimens" in which a short course of preoperative chemoradiation is integrated with IOERT and extensive resection followed by adjuvant

chemoradiation as a way to decrease the total treatment package time. The regimens differed by the type or dose of chemotherapy given.

In the initial report, a total of 37 patients with stage III/IV oral cavity, oropharynx, and hypopharynx were treated with a pre- and postoperative cisplatin-based chemoradiation with IOERT at resection [37]. Patients received preoperative EBRT BID to 9.1 Gy (1.3 Gy bid × 3 1/2 days with one cycle of cisplatin (80 mg/m^2/80 h) followed on day 4 with IORT of 7.5–10 Gy and resection followed 3 weeks later by postoperative EBRT (40–45 Gy) with two cycles of concurrent cisplatin. Total planned treatment package time was 8½ weeks. 89% achieved a negative margin, while 11% had a microscopically positive margin. Myocutaneous free flaps were performed in 76% ($n=28$) and osteocutaneous flaps in 5% ($n=2$). Compliance was 73%: reasons for noncompliance related to treatment toxicity (11%), on-treatment mortality (3%), patient refusal (8%), and patient comorbidity (5%). Delayed initiation of postoperative chemoradiation due to wound healing was noted in 30% ($n=11$) with a median delay time of 4 days. Forty-six percent had treatment interruption of 7 days or less versus 54% with a treatment delay of >7 days. At a median follow-up of 40 months, the local control, regional control, and distant metastasis rate were 97, 95, and 19%, respectively. 4-year OS was 48%. Late RTOG grade 3 or 4 toxicity was reported in 19% and consisted primarily of exposed mandibular plate or bone in 13% with neurologic complication in 3% ($n=1$ CN 10/12 palsy 7 months after treatment). Orocutaneous fistula was reported in 14% ($n=5$) requiring surgical repair in three of five patients.

Building on the initial intensification regimen demonstrating excellent locoregional control but a distant metastatic rate of 18%, high-dose taxol was added postoperatively to improve systemic disease control [36]. Forty-three patients with resectable oral cavity, oropharynx, or hypopharynx cancers were treated with a similar pre-and postoperative chemoradiation regimen with planned IOERT and definitive resection. However, three cycles of postoperative taxol given every 3 weeks (135 mg/m^2 q 3 weeks, day 25, 45, and 66 after surgery) was integrated with postoperative cisplatin-based chemoradiation. The total treatment package time was 12 weeks. The regimen was highly toxic with a 12% (5/43) rate of treatment-related mortality due to sepsis, myocardial infection, or dehydration and 42% hospitalization rate for infection-related complications. At a median follow-up of 25 months, among the 25 patients who received all treatments, locoregional control was 92% and distant metastasis rate was 8%. The 2-year disease-specific survival was 86% and overall survival was 65%.

To decrease toxicity, the dose schedule of postoperative taxol was changed to 9 weekly doses for 43 stage III/IV previously untreated carcinomas of the oral cavity ($n=15$), oropharynx ($n=20$), and hypopharynx ($n=8$) in a third-generation intensification regimen [38]. Protocol noncompliance was 47% due to toxicity (10%), mortality (2%), and patient noncompliance (21%). Grade 3 mucositis was reported in 39% and grade 2 xerostomia was reported in 20%. At a median follow-up of 45 months, the locoregional control was 93% and distant-metastasis-free survival was 91% with an overall survival of 79%. Flap reconstructions were performed in 56%, primary closure performed in 39%, and split thickness graft performed in 19%. Operative complications included pharyngocutaneous fistula in 14%, flap failure in 2%, flap dehiscence in 2%, and hematoma in 2%. PEG tube dependence was reported in 11%.

A pooled analysis of a total of 123 patients treated on the three intensification regimens was reported [39]. Treatment sites were hypopharynx (26%), oral cavity (30%), and oropharynx (44%). Compliance was similar at 61%. At a median follow-up of 62 months, locoregional control was 91%, distant metastases 14% and disease-specific survival 73% and overall survival 57%. Acute grade 3–4 toxicities were hematologic (35%), infectious (23%), gastrointestinal (17%), and mucositis (20%). Mortality during treatment occurred in 6%. Operative complications included pharyngocutaneous fistula (15), hematoma (1.6%), dehiscence (0.8%), and flap failure (0.8%). Late effects included mandibular complications (9%), esophageal/pharyngeal strictures (1.6%), and chronic aspiration requiring laryngectomy (0.8%). Thus, the intensification regimens appear to be optimized, achieving excellent disease outcomes but with high noncompliance rates.

Anatomic and Site-Specific Outcomes After IORT

Several institutions have reported outcomes for specific disease or anatomic sites as follows (Table 9.4).

IOERT for Borderline Resectable Nodal Disease

Freeman reported the Methodist Hospital experience using IOERT in 75 patients (70 SCC; 52 recurrent, of whom 46 had had prior EBRT) with N2-3 neck disease in which there was concern of borderline resectability due to invasion of prevertebral muscle or carotid artery [32]. Radical neck dissection was performed in 49, with about 1/3 involving the carotid artery. Carotid artery resection was required in 15, with adventitial stripping in 11. After resection, an average IOERT dose of 20 Gy was given (12–25 Gy) with median energy of 4 MeV (4–11 MeV) was used to treat areas of 4–10 cm^2. Extracapsular extension was found in 56% (42/75), surgical margins were close in 56% ($n=42$), microscopically positive in 33% ($n=25$) and grossly involved in 9% ($n=7$) with unclear margins in one patient. Postoperative EBRT was delivered in 25 patients including two patients who had previous irradiation. Major complications occurred in 25% (19/75) overall, and in 35% (9/26) of those with carotid artery involvement (carotid artery blowout – 4 patients [5%], neurologic complications – 2, pharyngocutaneous fistulas – 4). Six complications were attributed in part to IORT including two neurologic complications.

2-year in-field control rate was 68% and 2-year OS was 45%. Patients with close or positive microscopic margins had control rates of 76 and 73%, respectively, compared to 25% for those with gross residual disease ($p<0.05$). Two-year OS for all patients was 38%; 52% for patients with close or microscopic margins, and 15% ($p<0.05$) for those with gross residual disease. The outcomes with IOERT appeared particularly favorable for patients with carotid artery involvement as 2-year OS of 42% for such patients compared to the 13–28% reported by other groups without IORT [33–35].

Hypopharynx Cancer-IOERT

Outcomes for 32 patients with locoregionally advanced hypopharynx cancer treated on the OSU intensification regimens showed excellent locoregional control [50]. Patient compliance was 62% due to medical intolerance or patient refusal. At a median follow-up of 89 months, local control was 91%, OS 56%, and distant metastases 9%. Feeding tube dependence remained in 13%. The larynx was preserved in 53%. Flaps were used in 53%.

Base of Tongue-IOERT

A total of 15 patients with T3-4 tongue base cancer were treated in *Montpellier* with base of tongue resection combined with IOERT dose of 20 Gy (17.5–20 Gy) to the tongue base and neck dissection [43]. Thirteen of fifteen patients then underwent pectoralis major reconstruction. The patients received postoperative EBRT to a dose of 56 Gy in 28 fractions. Five patients received previous EBRT. IOERT energies of 6 or 9 MeV were used. Healing occurred in 14 of 15 patients after a mean delay of 15 days without dehiscence or necrosis. Two patients developed in-field recurrence in the tongue base, while two patients developed out-of-IORT-field relapse at the adjacent floor of mouth with tumor control in the tongue base.

Malone reported the outcomes of the *OSU intensification regimen* on 40 patients with stage III/IV base of tongue cancers [51]. Protocol noncompliance was 48% (19/40) with eight due to treatment toxicity or perioperative complications, six from patient noncompliance and five due to

Table 9.4 Site specific outcomes

Site/institution	No. of Pts	Med F/U (mo)	Recurrent (%)	Prior EBRT (%)	Gross residual (%)	IOERT dose (Gy)	LRC (all pts) (%)	LC R0 (%)	LC R1 (%)	LC R2 (%)	OS (%)
Neck-nodes [32]	75	NR	69	61	9	20 (12–25)	68	76	73	25	45
HPX 2006 [50]	32	89	0	0	0	7.5–10	91 (5 yr)	NR	NR	NR	56 (5 yr)
BOT 1989 [43]	15	6	33	33	0	20 (17.5–20)	100	NR	NR	NR	75
BOT 2004 [51]	40	32	0	0	0	7.5	100	NR	NR	NR	75 (2 yr)
FOM 1997[52]	42	NR	0	0	0	12–15 Gy	81	NR	NR	NR	NR
Skull base-IOERT											
Methodist [47]	25	12	56	44	11	15–20	64 (1 yr)	54	86	50	NR
Mayo Clinic [48]	25	NR	70	64	NR	12.5 (10–22.5)	62	NR	NR	NR	32
Skull base, HDR-IORT											
OSU [20]	29	21	21	21	0	7.5–15	67	NR	NR	NR	72
Paranasal Sinus (HDR-IORT) [40]	34	6 yr	7/34	7/34	0	10–20	65 (5 yr)	68	NR	50	44 (5 yr)
Salivary [45]	37	3.1 yr	100	82	0	15	82 (5 yr)	NR	NR	NR	NR
Thyroid [53]	5	34 mo	40	0	40	4–10 Gy	80	100	100	(1/2)	NR

Pts patients, *Med* median, *F/U* follow-up, *EBRT* external-beam irradiation, *IOERT* intraoperative electron irradiation, *LRC* local regional control, *LC* local control, *yr* year, *OS* overall survival, *HPX* hypopharynx, *BOT* base of tongue, *FOM* floor of mouth, *NR* not reported

treatment related deaths. At a median follow-up of 32 months, locoregional control was 100% and rate of distant metastasis was 8%. Two-year OS and DFS were 75 and 94%, respectively. Of the ten deaths, five patients died during treatment, two died of distant metastasis, and another two died of cardiopulmonary reasons 2–4 weeks after treatment. Seventy percent of patients underwent flap reconstruction, while 30% underwent primary closure. Transcervical resection was performed in 70% with mandibular resection in 30%. Partial or total laryngectomy was required in 50%. The performance status scale was obtained from 25 of the surviving patients. Mean PSS scores for eating in public, understandability of speech, and normalcy of diet were 55, 73, and 49, respectively. Scores for eating and diet were better in patients with early stage (78 vs. 42, $p=0.034$ and 77 vs. 33, $p=0.015$), respectively, and speech was better in those who did not have mandible surgery (86 vs. 39, $p<0.001$, respectively). Of the 25 patients, 36% (9/25) were feeding-tube dependent. The authors concluded that the high incidence of locoregional control justified the aggressive approach despite the ensuing functional disabilities.

Floor of Mouth Cancer-IOERT

Forty-two patients with floor of mouth carcinoma underwent resection and IOERT (6–21 MeV) [52]. Twenty-eight patients with T2-3 N0-1 cancers were treated with IOERT dose of 12–15 Gy followed by 50 Gy EBRT, while 14 patients with small tumors T1-2 received IOERT alone as the patients were unable to proceed with EBRT. No failure resulted in the IOERT field in the first group, but 25% (7/28) did fail locally outside of the IOERT field, while 0% (0/14) failed in the latter group. No reported complications were attributed to IOERT.

Skull Base/Neck-IOERT

Methodist Hospital of Indiana

A total of 25 patients (13 SCC, 8 salivary gland carcinoma, 3 sarcoma) underwent IOERT to the skull base following resection [47]. The sites of resection and IOERT were primarily anterior skull base ($n=11$), infratemporal fossa ($n=7$), and temporal bone ($n=6$). Indications included close but negative margins in 14 patients, microscopic residual in 9, and gross residual in 2. An IOERT dose of 15–20 Gy was delivered with 4 MeV electron to areas of 4–9 cm in greatest diameters. At a minimum follow-up of 12 months, 1 year local control was 64% for all patients and by margin status was 54% in R0 (7/13), 86% in R1 (6/7) and 50% in R2 (1/2). Tumor control was independent of whether the disease was newly diagnosed or recurrent (local control 67% (6/9) vs. 62% (8/13), respectively. Complications included osteoradionecrosis (outside the IORT filed) in two patients. No cases of peripheral neuropathy or major vessel bleed were reported.

Mayo Clinic Rochester

Pinheiro reported the Mayo Clinic Rochester experience using IOERT to the skull base ($n=25$) and neck ($n=19$) in 44 patients [48]. Seventy percent had recurrent disease, many having received previous EBRT (28/44) and surgery and 34/44 were squamous-cell cancers. IOERT was delivered to doses of median 12.5 Gy (10–22.5 Gy) with 6–15 MeV electrons. Mandibulotomy was required to access skull base and nasopharyngeal areas. At 2 years, tumor control in the IOERT field was 62% in patients with squamous-cell cancer and 61% in nonsquamous-cell histologies. Patients with R0 or R1 resection had better DFS ($p=0.03$) and OS ($p=0.09$) than those with R2 resection (gross residual).

Microscopic residual versus no microscopic residual did not impact on in-field local control nor did primary vs. recurrent presentation status. For all patients, 2-year OS and DFS were 32%/21% for SCC and 50%/40% for non-SCC, respectively. The only complication attributed to IOERT was peripheral neuropathy (brachial plexopathy) after 22.5 Gy; another patient developed a carotid artery bleed after 12.5 Gy IOERT and wound breakdown 5 days postoperatively.

Skull-Base: HDR-IORT

Nag reported a pilot study using HDR-IORT in the treatment of 29 patients with base of skull tumors [20]. All patients underwent gross total resection of the tumor and received HDR-IORT because the target area was inaccessible to IOERT. Patients were then treated with HDR-IORT (7.5–15.0 Gy) with ($n=17$) or without ($n=15$) EBRT (45–50 Gy) as part of the treatment plan. Concurrent chemotherapy was given with EBRT in five patients. At a median follow-up of 21 months, local failure was only 11% in patients receiving combined IORT and EBRT, but in patients treated with mainly HDR-IORT, local failure was 67% (8/12), 83% (5/6) in patients receiving previous EBRT, and 50% (3/6) if patients could not complete EBRT. Overall survival was 100, 17, and 50%, respectively, for patients treated with full dose EBRT+IORT, IORT alone, or IORT +incomplete EBRT. No major complications occurred during the delivery of HDR-IORT. Chronic complications were reported in five patients and included CSF leak with bone exposure, hematoma, septicemia, otitis, and severe xerostomia. No episodes of carotid blowout or osteoradionecrosis were reported.

Paranasal Sinus Tumors: HDR-IORT

Nag reported long-term follow-up on 34 patients with locally advanced paranasal sinus tumors treated with HDR-IORT and gross total resection. Histology consisted primarily of squamous-cell carcinoma ($n=16$), undifferentiated carcinoma ($n=4$), esthesioneuroblastoma ($n=3$), melanoma ($n=2$), and others. The primary sites irradiated were ethmoid ($n=23$), maxilla ($n=6$), and sphenoid ($n=3$) [40]. For 27 patients with new primary tumors, HDR-IORT doses of 10–12.5 Gy were delivered followed by 45–50 Gy EBRT. For seven patients with recurrent, previously irradiated tumors (EBRT doses of 45–63 Gy), HDR-IORT doses of 15–20 Gy were delivered without EBRT. At a mean follow-up of 6 years, 5-year local control and overall survival were 65 and 44%, respectively. Patients with R2 resection with gross disease had worse local control (5 years 17 vs. 60%) and survival (5 years 50 vs. 68%,) compared to those with R0 or R1 resection, respectively. The local control rates were similar between primary and recurrent patients (63% vs. 71%), although all patients with gross residual disease occurred in patients with primary tumors, thus biasing results against the primary patients. Acute toxicities included delayed wound healing and perioperative bacteremia in one patient while three patients experienced chronic toxicity including epiphora, diplopia and facial nerve paralysis. Based on these results, a prospective policy was instituted of delivering 60–65 Gy EBRT with 15 Gy HDR-IORT in patients with gross residual disease in previously unirradiated patients with a reduced dose of EBRT (50–54 Gy) in patients with microscopic disease. For patients with recurrent disease, 17.5 Gy HDR-IORT combined with 20–30 Gy EBRT is recommended [40].

Recurrent Salivary Gland Tumors: IOERT

A comparative subset analysis has been published based on UCSF data describing the management of recurrent salivary gland tumors consisting of reoperation with and without IOERT [45]. From January 1960 to December 2004, 125 patients were treated for locally recurrent salivary gland

cancers and 37 received IOERT. Excluded from analysis were 26 patients who were treated with radiation therapy alone, had subtotal resection, had a second or third local recurrence, had interstitial brachytherapy, and/or had metastatic disease. Of the remaining 99 patients, 81 had already undergone previous EBRT as part of their management at initial presentation. For management of their recurrence, 53 patients had reoperation only without EBRT or IORT and 23 failed locally. Nine had surgery followed by EBRT and three failed locally. Thirty-two patients had surgery and IOERT only and five failed locally. Five had surgery with IOERT and EBRT and one failed locally. At 3.1 years of follow-up, 3-year estimate of local control was 75%. The estimated 5-year local control rate was 60% in patients who did not have IOERT versus 82% in those who did. Distant relapse eventually occurred in 42 patients and comprised the first site of relapse in 34 patients. Despite excellent locoregional control after IORT, the risk for distant metastasis is high which prompted the authors to recommend integration of an effective systemic regimen.

Thyroid Cancer: IOERT

Thyroid cancer is a challenging site to treat with EBRT because of a concave dose distribution near the spinal cord and the rapidly changing body contours in the treatment volume [53]. Wolf reported on IOERT on five patients (three primary, two recurrent) with T4 follicular thyroid carcinoma with poor I131 uptake who were treated with IOERT, surgery, and EBRT. Microscopic residual disease was present in three patients, and two had close margins near major vessels or the trachea; three patients had involved neck nodes. A dose of IOERT of 4–6 Gy over a mean procedure time of 45 min followed by EBRT to a dose of 40 Gy was administered. Efforts were made to shield the vertebral body, while the carotid artery and trachea were exposed as needed. At a median follow-up of 34 months (20–48 months), all five patients were locally controlled. Three patients are tumor-free 34–48 months after treatment, while two developed mediastinal relapse. One patient with an infiltrative tumor into the hypopharynx developed a fistula. No aneurysm or neuropathy was noted up to 40 months of follow-up.

Palliation for Previously Irradiated Locally Recurrent Disease: IOERT

The major experience for the application of IORT for palliative intents was reported from the University Hospital of the RWTH at Achen Germany [46]. Palliative IOERT was used to treat 95 patients with recurrent disease in the head and neck after prior EBRT in 94% of all patients. A total of 120 IOERT treatments were delivered to a median dose of 20 Gy (10–40 Gy) with median energy 7 MeV (5–17 MeV) to an area ranging from 4 to 100 cm^2. Additional EBRT was given in 6%. The sites of treatment were primarily the neck in 76% (91/120) and primary site in 12% (15/120). Gross residual disease remained in 72% of patients after attempted palliative resection due to fixation to muscles or neurovascular structures; microscopically positive margins were reported in 6% and negative margins in 13%. At a median follow-up of 11 months, in-field control was 17% for patients with gross residual disease, 57% in patients with microscopically positive margins and 64% in patients with microscopically negative margins while overall tumor control was 6, 0 and 46%, respectively. Among 84 patients who complained of pain pretreatment, palliation was achieved in 74%. Complications included tracheostomy in 11 patients, necrosis in 8, and fistula in 3. No carotid blowout was reported. The authors report that the majority of patients were able to regain the ability to socially function during the final stage of their disease.

In a more detailed follow-up study, Schleicher reported the outcomes in 84 TWTH patients who had locoregional recurrence after prior EBRT at a median interval of 10 months [54]. The primary indications for palliation included tumor swelling, pain, asymptomatic recurrence and ulceration in 87% of cases. Patient tumors consisted primarily of hypo- and oropharynx as well as oral cavity and

larynx cancers. A total of 113 IOERT treatments were performed with 38 sites having previously received EBRT doses of <50 Gy previously to the IORT bed, 31 sites received 50–60 Gy, 29 sites had 60–80 Gy, and 15 sites received >80 Gy. Among the 113 treatment fields, gross residual disease (R2) remained in 67, microscopic residual (R1) in 17, negative microscopic (R0) margins in 10, and unknown (either R1 or R2) in 24. The median dose of IOERT was 20 Gy (10–20 Gy) with a median electron energy of 6–7 MeV to a field size of 34 cm^2 (6–196). The site of IORT was neck in 82% (88/113) of the cases. The median survival was 6.8 months, and median time to local tumor recurrence was 3.7 months. IORT was not reported to increase toxicity beyond expected postsurgical morbidity.

Tumor control within the IORT field was reported in 33% (37/113) with the majority of recurrences apparently originating from the outside and extending into the IORT area. The chance for tumor control was dependent on margin status and was 50% (6/12) in R0, 42% (5/12) in R1, and 24% (16/67) in R2 patients. Patients with R0 resections had a longer median overall survival time compared to those with R1/2 (15 months vs. 6.3 months, $p = 0.03$). No difference in recurrence-free or overall survival was reported between R1 and R2 patients. Palliation was achieved in 88% of patients including all patients with tumor swelling, bleeding, ulceration, fistula, dyspnea, and dysphagia. Pain relief was achieved in 71%. Wound healing complications occurred in 9% (10/113), infection in 4% (5/113), fistula in 4% (4/113), and necrosis in 2% (2/113). No reports of carotid bleeding were noted in any cases where tumor did not infiltrate major vessels.

Conclusion and Future Directions

When implemented with coordinated multidisciplinary interaction, IORT can be integrated safely into the treatment of locally advanced or recurrent head and neck cancers. Both HDR-IORT and IOERT represent effective means of delivering IORT treatment. In theory, IOERT may be more advantageous for treating gross residual disease due to potentially deeper levels of penetration with high-energy electrons; however, outcomes in this patient subset remain poor despite IORT. The flexibility of HDR-IORT facilitates treatment of large complex surfaces maintaining homogeneous dose distribution and allows large dose gradients of up to twofold between the applicator surface and prescription depth, which may allow for focused dosimetry if gross total resection is achieved.

Although the disease presentations and sites are diverse, general principles can be derived from the present data. These include the following: (1) the absolute preference for gross total resection with no worse than miroscopically positive margins; (2) an advantage derived from the addition of subsequent EBRT; (3) importance of a well-vascularized flap reconstruction (from outside the prior irradiation field) to reduce the risks of poor wound healing. Replacing previously irradiated mucosa or skin with new unirradiated tissue (free flap or myocutaneous flap) is recommended when feasible; (4) the primary dose-limiting toxicities of IORT appear to be tolerance of the carotid artery, mandibular osteoradionecrosis, vagus nerve damage, and fistula formation; (5) IORT is feasible as part of the initial treatment of patients undergoing extensive resection, with a potential advantage of minimizing total treatment package time.

In the recurrent setting, IORT is generally safe, can be useful for short-term palliation if gross residual disease is present, but long-term overall tumor control with IORT alone is significantly affected by relapse outside the irradiated field. This may be improved by IORT dose escalation or additional supplementation with EBRT, but that benefit is likely limited to in-field control.

With regard to specific disease sites and particularly challenging clinical scenarios, IORT appears to have promise when integrated into the treatment of advanced neck disease (particularly when the carotid artery appears to be involved), recurrent salivary gland cancers, locally advanced skull base and paranasal sinus tumors when combined with EBRT and in the reirradiation setting, and in the treatment of hypopharynx cancers. There are pilot experiences evaluating its use in thyroid carcinomas with poor I-131 uptake, as well as skin cancer with perineural invasion.

Future Directions to Consider Include

1. Coordinating multi-institutional studies to evaluate prospectively the promising outcomes at individual institutions (recognizing the statistical problems associated with surgical diversity and limited accrual)
2. Increasing the availability of mobile IORT units or developing technologies that reduce the need for expensive room shielding
3. Integration of image-guided treatment technology to define IORT treatment volume
4. Designing protocols to define the integration with EBRT
5. Refining clinical and eventually molecular criteria to select patients who will best benefit from IORT therapy

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Chapter 10
Breast Cancer

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Keywords IORT for breast cancer • ELIOT/TARGIT trials • BIO Boost • Pooled analysis

Introduction

Globally, breast cancer incidence rates are highest in North America and northern Europe, and lowest in Asia and Africa [1]. Incidence rates in Japan and urban China have been rising in recent years. In the USA, breast cancer is the most common female cancer, the second most common cause of cancer death in women, and the main cause of death in women aged 45–55 years. Breast cancer mortality rates have declined since 1975, attributed to the increased use of screening mammography and greater use of adjuvant treatments including radiotherapy. For locoregional treatment, breast-conserving therapy is regarded as standard of care, comprising breast-conserving surgery followed by ipsilateral whole-breast radiotherapy (WBRT) as an integral component.

Postoperative radiotherapy significantly reduces local recurrence rates. The more pronounced the achieved reduction, the more substantially it translates into improved survival. Four prevented local recurrences result in one avoided breast cancer death [2].

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_10,

Rationale for IORT

Clinical Rationale for a Dose Escalation in the Tumor Bed

Pathological analysis revealed that the greatest tumor cell density (up to 90% of microscopic remainders) is observed in an area of 4 cm surrounding the macroscopic tumor edge [3, 4]. As a consequence, after breast-conserving operation, the tumor bed represents the region with the highest probability of in-breast recurrences, which is confirmed in many clinical reports. Up to 80% of all tumor relapses within the breast are observed in the former index quadrant. [2, 5] Since tumor control probability is directly related to the applied radiation dose, numerous retrospective analyses described lower recurrence rates after an additional boost to the tumor bed following whole-breast irradiation with 50 Gy/25–28 fractions/5–5.5 weeks. This significant positive impact of a local dose escalation was confirmed in large randomized prospective trials. By the additional use of an electron boost of 10–16 Gy (5–8×2 Gy) or alternatively interstitial implants (HDR-brachytherapy) local recurrence rates were halved [6–8]. This effect could be observed in all age-classes, whereas the absolute gain was greatest in the group below 45 years [8].

Biologic Rationale for High Single Doses

Compared to squamous cell carcinoma, breast cancer seems to show a different sensitivity toward higher single doses. In 1989, Fowler postulated an alpha/beta ratio of 4 for breast cancer as its best approximation instead of 10 for most SCC [9]. This value was strongly supported by the clinical outcome of Canadian and British Hypofractionation Trials [10, 11]. A lower ratio results in higher sensitivity against higher doses per fraction, an argument clearly in favor of IORT. In the linear quadratic model, using an alpha/beta value of 4, an IORT dose of 10 Gy amounts to a BED of 35, hence being isoeffective to a boost of about 24 Gy when applied in single fractional doses of 2 Gy. However, the model was only tested for single doses below 15 Gy [12]. The prediction of isoeffects of doses above this level leaves open questions and has to be further evaluated.

Treatment Methods

Target Volume and Design of an IORT Boost

The work of Holland et al. [3] still builds the essential background for the boost design. Without detailed consideration of risk subgroups, which have been published extensively [4], microscopic disease can be expected in 40% of the cases outside a distance of 2 cm away from the macroscopic edge of the tumor. The larger the distance, however, the lower the probability: a safety margin of 3 cm will match over 80% of residual tumor cells, and a distance of 4 cm accounts for about 90% of possible residual disease.

The amount of tissue irradiated by IORT (or any other boost modality) should therefore also be chosen with regard to the width of free margins in all directions. A major advantage of an immediate boost during surgery is the close proximity of the walls of the surgical cavity due to the fact that no fluid will artificially enlarge the volume at risk by spherical distension, resulting in larger treated volumes and hence increased risk of late effects. Analysis of the IORT volumes treated by 85% of the maximum dose turned out to be comparable with those published for brachytherapy of clipped tumor beds, however, with more breast tissue at risk irradiated in the absence of postoperative hematoseroma [13].

General IORT Methods

The idea of IORT during breast-conserving surgery is the delivery of a single boost dose to the area at highest risk for subclinical tumor cell contamination with utmost precision, due to direct visualization [14]. The method was originally introduced by the Medical College of Ohio (MCO) in Toledo, OH, USA and the Centre Regional de Lutte Contre Le Cancer (CRLC) in Montpellier, France, based on reports of 72 patients [15–17] treated with an electron boost (IOERT) mainly with 10 Gy. In the late 1990s, a broad clinical IOERT application started at the European Institute of Oncology (EIO) in Milano, Italy [18] and the Paracelsus Medical University (PMU) in Salzburg, Austria [19]. Since then, IORT to the tumor bed during breast-conserving surgery has become a booming field of interest for partial breast irradiation, either as anticipated boost or as sole treatment strategy in limited-stage breast cancer (see below).

This has given rise to the development of different technical approaches, with the term "IORT" used for the following techniques: perioperative interstitial multicatheter brachytherapy (BT), endocavitary brachytherapy (MammoSite), a low-kV Orthovolt system (Intrabeam) and intraoperative radiotherapy with electrons on mobile or standard linear accelerators (IOERT).

Perioperative Brachytherapy

For both brachytherapy techniques only the applicators' positionings are true intraoperative maneuvers, with the irradiation being performed postoperatively, thus allowing for fractionated treatments. Perioperative multicatheter brachytherapy corresponds to classical interstitial BT by flexible needles, applied during open sight of the excision hole, with the implant's geometry usually following the guidelines of the Paris system [20, 21]. Endocavitary IORT (MammoSite) is performed by an inflatable balloon which is placed into the lumpectomy cavity and filled with sterile saline to a size that fills the cavity completely, typically 4 cm in diameter. A high-dose-rate source is guided into the balloon's center with the dose normally prescribed 1 cm from the surface of the balloon [22, 23].

Intrabeam Low-kV IORT

The Orthovolt system (Intrabeam) consists of a miniature electron-driven low-kV energy X-ray source, emitting an isotropic X-ray spectrum. For breast irradiations spheric applicators, chosen according to the excision cavity's size, are put at the top of the source, resulting in a similar configuration as for the MammoSite system: a point source at the center within a spheric applicator [24, 25].

IOERT and Surgical Methods

Finally, linac-based IOERT is possible with various electron energies (6–18 MeV). When breast-conserving therapy is likely, the tumor is excised and the surgical clearance confirmed by intraoperative pathological examination; in cases with close or positive pathological margins re-excison can be performed prior to IOERT. The tissue surrounding the excision cavity is then surgically mobilized and temporarily approximated by sutures in order to bring adjacent walls into reach of the electron beam (Fig. 10.1). The resulting tissue depth (i.e., distance to the anterior rib surface) is

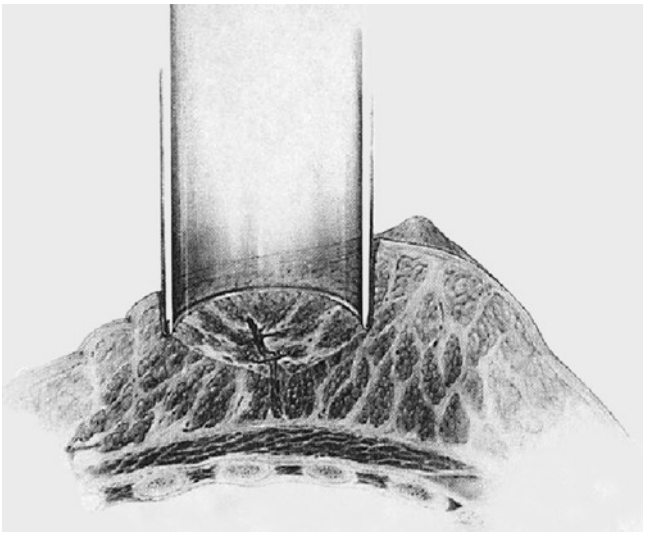

Fig. 10.1 From Battle et al. [17]. Idealized situs of an electron applicator placement for IOERT. The walls of the excision cavity are temporarily approximated by sutures to bring all tissue at risk into reach of the beam.

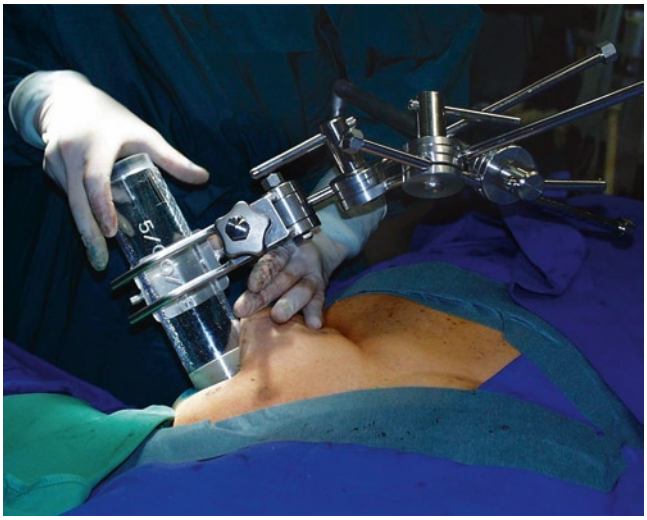

Fig. 10.2 IOERT applicator in situ. The tube is fixed on the operation table.

usually measured by intraoperative sonography or by scaled probes for depth dose prescription and choice of proper electron energies, respectively. Optionally, additional thoracic wall protection by lead shielding can be performed [18].

IOERT treatment is applied by circular applicators of different diameters [15–21] (Figs. 10.2 and 10.3). The applicator diameter should provide safe coverage of the PTV with the prescribed dose, accounting for transverse (cross-section) profiles of the selected electron energy. After IOERT, approximation sutures are removed and the breast tissue reconstructed including optional oncoplastic maneuvers. In the case of Boost IORT, complete wound healing should be achieved before the onset of WBRT (usually 4–6 weeks).

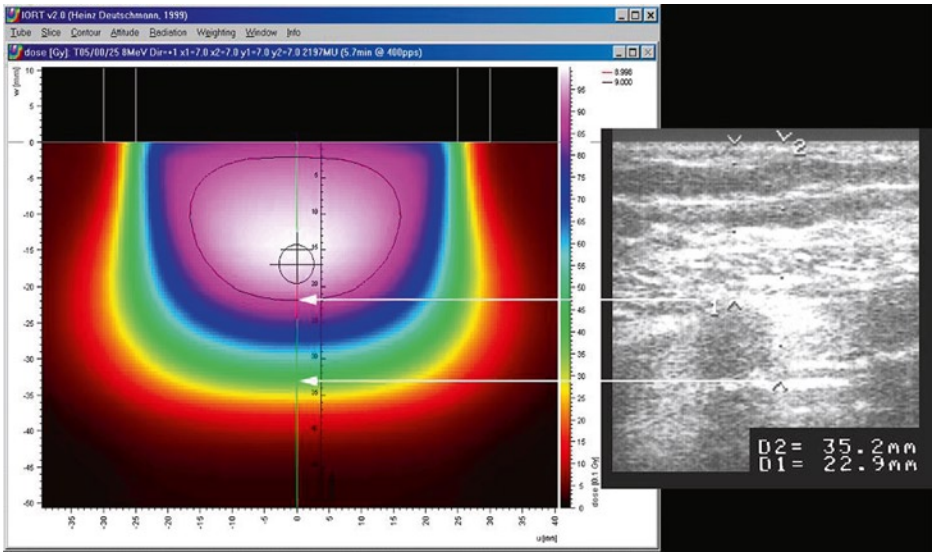

Fig. 10.3 Intraoperative sonography for proper electron energy selection and corresponding depth dose distribution. Rib surface is regarded as dose-limiting structure.

Summary: IORT Methods

The dosimetric properties of these four methods in terms of dose homogeneity, flexibility toward asymmetric PTV shapes and hence their ability to deliver a reliable dose to a given volume differ tremendously [13]. Outcome analyses of local control rates, as well as cosmetic results after "IORT," must strictly be performed according to the used technique.

In contrast to the brachytherapy techniques, only IOERT and Orthovolt low-kV treatments are intraoperative radiotherapies *sensu stricto*, where the boost dose is actually delivered during the operative maneuver. Reports on clinical evidence will therefore be restricted to the latter techniques.

IORT Boost vs. Single Modality

For both technical IORT approaches (electrons and orthovolt) two different treatment concepts are proposed (1) IORT as *anticipated boost* followed by WBRT ("BIO-Boost" = breast intraoperative boost) and (2) IORT as *full-dose partial breast irradiation* (ELIOT = electron intraoperative treatment) without further XRT:

- *Boost IORT* addresses the question whether this approach is an effective and/or superior alternative to conventional boost techniques. The advocates of a BIO-Boost emphasize the use of lower single doses compared to a full-dose concept, with dose ranges well understood in terms of tumor effects and late tissue reactions. Since IORT is followed by WBRT, the concept still accounts for the (unknown) risk of occult tumor burden in distant quadrants. Therefore, it is less vulnerable toward a possible underdosage in the periphery of the tumor bed (or outside) and remains applicable in every risk constellation. Although subsequent WBRT remains mandatory, a shortening of its duration can be achieved by total dose reduction and/or hypofractionated XRT-schedules according to the patient's individual risk.

- The rationale for *full-dose IORT* is based on the observation that tumor recurrences primarily occur in the close vicinity of the original tumor site. Therefore, investigation is focused on its potential to replace conventional postoperative WBRT especially in low-risk patients. The main advantage obviously lies in the substantial shortening of RT treatment duration. However, the sole use of IORT bears the risk of geographically missing parts in the periphery of a relevant target volume, though the tumor burden is smaller, but usually controlled by EBRT with doses around 50 Gy/25–28 fractions/5–6 weeks. Omission of EBRT might lead to a higher frequency of local recurrences in sites which are not reported up to now after "standard" treatment. Second, the α/β model does not give reliable information for dose levels in use during full-dose IORT.

To date, long-term outcome assessments are still scarce. Reports with follow-up data exceeding 5 years are needed to raise the level of reliability of the treatment concept (Boost or Full-dose IORT) and the applied technique (IOERT or low-kV), respectively. Both items are the subject of ongoing clinical research.

IORT Clinical Results

By May 2009, a PubMed Research revealed 274 publications on IORT in breast cancer, comprising informations on more than 1,900 patients with boost IORT and more than 700 patients with IORT alone.

Boost Concept

As to *Boost IORT*, evidence derives from

- One randomized trial [26]
- Ten reports on nonrandomized controlled studies and/or noncontrolled cohorts [15, 16, 25, 27–32]
- One multicentric pilot study [33]
- One pooled analysis [34]
- One sequential intervention study [35]

Reported local tumor control rates are outstanding in all reports, in the range of 0–1.5% vs. 1.7–4.3% in favor of the IOERT Boosts (Table 10.1). Interpretation of these studies' results has to account for partially overlapping patient cohorts. Despite its retrospective character, best data evidence is derived from the ISIORT Europe pooled analysis on IOERT (see below). Cumulative evidence on Boost IORT is high; however, at present there is only one randomized prospective trial with short follow-up.

The ISIORT Europe Pooled Analysis (BIO-Boost)

Starting in 2005, a collaborative pooled analysis on the outcome of a 10-Gy IOERT Boost prior to a 50 Gy/5–5.5 weeks WBRT has been repeatedly performed among six member institutions of the International Society of Intraoperative Radiotherapy, European Group (ISIORT Europe) [36]. Methods, sequencing and dosage in IORT- and postoperative EBRT during breast-conserving therapy were comparable. 1,220 patients were enrolled, 60% of them (655 patients) presenting with at least one adverse prognostic factor for local recurrence risk development in terms of tumor size >2 cm, high grade, young age <45, and/or positive lymph nodes.

Forty-three patients were referred to immediate secondary mastectomy due to massive margin involvement in the final histologic workup, which was not recognizable during frozen section

Table 10.1 Boost IORT followed by whole-breast radiotherapy (WBRT): selection of clinical studies

Author	No. patients (IORT/control gp EBRT boost)	Selection criteria	Technique	Median IORT dose, Gy (control gp EBRT boost, Gy)	Total WBRT dose, Gy (daily dose)	Median follow-up (months)	Local recurrence % (in-breast recurrence)
Merrick et al. [16]	21	T1–2	IOERT	10 Gy	45–50 (1.8–2)	71	0
Dubois et al. [15]	101 (51/50)	T1–2	IOERT	10 (n.s. for control gp)	45–50 (1.8–2)	24 min FU	0 (IORT) n.s. (control)
Lemanski et al. [30]	50[a]	T1–2	IOERT	10	50 (2)	109	4
Ciabattoni [26]	234 (122/112)	T1–2	IOERT	10 (5×2)	50 (2)	n.s.	0 (IORT) 1.7 (control)
Reitsamer [28]	378 (190/188)	T1–2	IOERT	9 (6×2)	51–56 (1.7–1.8)	25.8 (55.3)	0
Ivaldi [31]	204	T1–3	IOERT	12	37.05 (2.85)	8.9	n.s.
Sedlmayer[b] [34]	1,031 (pooled analysis)	T1–3	IOERT	10	50–54 (1.8–2)	51.5	0.6
Vaidya[c] [33]	300 (pooled analysis)	<4 cm	Low-kV	18–20 (surface dose)	45–50 (1.8–2)	n.s. (3–80)	2.6 (5–y actuarial)

n.s. not stated, *EBRT* external beam irradiation, *gp* group, *IORT* intraoperative irradiation, *EBRT* whole-breast irradiation

[a]Long-term follow-up from Dubois et al. [15]

[b]Includes patient cohorts from Ciabattoni et al. [26], Reitsamer et al. [29]

[c]Includes patient cohorts from Kraus-Tiefenbacher et al. [44], Joseph et al. [32]

assessments. No further follow-up data (>12 months) were available for 93 patients, leaving 1,107 patients for this analysis, who were repeatedly evaluated between 2006 and 2009. After a median follow-up period of 6 years (median follow-up: 71.53 months, range 0.8–129 months), the recent evaluation dated July 2009 shows a cumulative local recurrence rate of 1.2%, corresponding to an annual rate of 0.2 % (unpublished data).

Only 14 in-breast recurrences were observed, yielding a local tumor control rate of 99.0%. 1,008 patients are alive without evident breast disease at 6 years follow-up. One hundred and eight patients developed metastases. The actuarial disease-free survival (DFS) rates at 6 years amount to 88.7%, disease specific survival (DSS) and overall survival (OS) rates of 94.2 and 91.5%, respectively. In-breast recurrences (11 invasive cancer, three DCIS) occurred at median 57 (12.5–110) months after primary treatment. Seven of them accounted for true local recurrences within the index quadrant, the remaining seven were classified as out-quadrant relapse. Prolonged onset of WBRT after IORT was not associated with an increase in local failure, indicating the high value of a "tumor holding effect" of a single IOERT booster dose.

Sole IORT Concept

As to the use of *Sole IORT*, data of five prospective noncontrolled studies have been published so far [37–41]. For IOERT, reported local (*in-breast*) tumor relapse rates are 0–2.5% in series with short follow-up periods of 0.7–2 years. For tumor control analyses, the same restriction of lack of long-term observation still is true for two ongoing randomized prospective trials, although feasibility has been positively reported.

The issue of full-dose IOERT (ELIOT concept) is currently under investigation within the randomized prospective Milano ELIOT trial, comparing single-shot IOERT with 24 Gy to standard postoperative radiotherapy [42]. This study was initiated in 2000 and has meanwhile finished accrual.

The TARGIT trial (targeted IORT) stands for an international multicentric clinical study, where the potential of orthovolt-based IORT is tested prospectively [43]. Patients are randomly referred to either IORT with 20 Gy (surface dose) or WBRT (50 Gy). Only in case of specific risk factors, the IORT is complemented by WBRT.

ELIOT Series

The largest cohort published so far was treated in Milano at the European Institute of Oncology (EIO). Veronesi et al. reported their preliminary experience on 574 patients treated with full-dose IOERT (ELIOT) with 21 Gy, all patients presenting with unicentric tumors less than 2.5 cm size [41]. This cohort was treated apart from the ELIOT-study in a prospective noncomparative intent. After a median follow-up period of 20 months, six patients developed in-breast recurrences (three true local relapses, three elsewhere), resulting in an in-breast tumor recurrence rate of only 1.05%. Results on short- and middle-term toxicities were reported to be good.

Toxicity/Late Reactions/Cosmesis

In all studies, IORT maneuvers turned out to be safe and feasible, showing no treatment related mortality or excess acute local morbidity in terms of delayed wound healing or infection rates compared to conventional treatment [16, 25, 26, 29, 32, 44]. As to late reactions, cumulative incidences of fibrosis/sclerosis within the IORT volumes were slightly different according to the treatment

concept: for the boost patients, tolerance was excellent with incidences of 20–25% G1–2 and less than 2% G3 reactions [16, 30, 31, 44]. Following full-dose IORT, reported rates amounted up to 80% G1, 30% G2, and up to 6% G3 sequelae [37–39, 45].

Cosmetic outcome was analyzed in six reports, three for the boost strategy and sole IORT, respectively. In two trials, no difference was described for the boost patients in comparison to conventional groups: results were rated as 86/91% to be good or excellent for IORT Boosts and 81/96% for the control groups, respectively [26, 44]. Longest-term experience is provided by Lemanski et al. [30] who reported about late reactions in 42 recurrence-free patients after a median follow-up of 9 years. Six patients (14%) experienced Grade 2 late subcutaneous fibrosis within the boost area. Overall cosmesis was scored to be good to excellent.

In a salzburg analysis on 358 boost patients after a median follow-up of 47.2 months, patient self-evaluations resulted in a high 92% good/excellent rate, compared to 72% in the doctors' evaluation [34]. Based on their experience in 48 patients, Wenz et al. described inferior cosmetic results when time intervals between IORT and onset of WBRT fall below 30 days [46].

Three reports in cosmesis following full-dose IOERT described rates of 71, 72, and 95%, respectively, of good or very good results [38–40]. In all these studies, the authors used different standardized cosmetic scoring systems based on qualitative estimations. However, in comparison to conventional techniques, no negative impacts on cosmesis following IOERT have been reported so far in any concept.

IOERT During Nipple-Sparing Mastectomy

A novel indication for the use of IOERT during breast surgery was introduced by the EIO, Milano [47]. If breast conservation is not possible, nipple-areola complex (NAC) conservation can be proposed in order to reduce mutilation and to facilitate satisfactory results after subsequent plastic reconstruction. To cover the risk of retro-areolar recurrence, an IOERT-Boost of 16 Gy was administered. Between 2002 and 2007, 800 patients were treated. After a median FU period of 20 months, 14 breast recurrences were observed, providing a local recurrence rate of 1.4%. None of the recurrences occurred in the irradiated NAC volume, including a subgroup of patients characterized by a very close margin beneath the areola. The NAC necrosed totally in 35 cases (3.5%), partially in 55 (5.5%) and was removed in 50 (5%). Twenty infections (2%) were observed and 43 (4.3%) prostheses removed. Global cosmesis was rated in double evaluation (patient/doctor) and scored 8 on a scale ranging from 0 (worst) to 10 (excellent).

Discussion and Future Possibilities

Summary

IORT is currently used for various techniques, which show decisive differences in dose delivery. Reports on clinical outcomes have to refer strictly to the used method. So far, in most reports local recurrence rates are outstandingly low. Compared to other boost or PBI methods, an intraoperative treatment has evident advantages:

1. *Precision*: Direct visualization of the tumor bed during surgery guarantees an accurate dose delivery. While all other methods of a later reconstruction of the tumor bed's location (e.g., by clips) finally remain indirect, nothing compensates for a direct view to the tissue at risk. Furthermore,

a growing number of surgeons use primary reconstruction techniques after lumpectomy to optimize cosmetic outcome. IORT is performed before breast tissue is mobilized for plastic purposes.
2. *Cosmesis*: As a consequence of direct tissue exposure without distension by hematoseroma, IORT allows for small treatment volumes and complete skin sparing. Both should have a positive effect in late tissue tolerance.
3. *Patient comfort:* IORT marginally prolongs the surgical procedure, while shortening – or in selected cases maybe even replacing – postoperative radiotherapy.

Ongoing Trials

In 2010, a first interim analysis was published from the TARGIT trial at a median follow up time of 24.6 months [48]. The Kaplan Meier estimate of local recurrence at 4 years was 1.2% in the APBI arm and 0.95% in the WBRT group (ns) with a peak occurrence in the second and third year. The frequency of any complications and major toxicity was similar with both treatment modalities (3.3% TARGIT vs. 3.9% WBRT).

The ELIOT trial has reached its accrual goal, 651 ELIOT-patients were randomly compared to a cohort treated with standard EBRT. A first publication is awaited in 2011. Apart from this trial setting, another 1822 pts were treated according to the ELIOT concept [49]. After a median follow- up of 36 months, altogether 3.63% in- breast recurrences were observed. Predictive factors for LR were age <50y, tumor size, grading, involved nodes and negative hormone receptors.

Compared to results after "classical" WBRT, where especially incidences of out-quadrant recurrence rates rise over time, only adequate long term experience will reveal the potential of a sole IORT approach to replace WBRT in selected patient groups [50].

In addition to these ongoing trials, the ISIORT Europe started a multicenter single-arm prospective trial combining Boost IOERT with hypofractionated WBRT for stage I/II breast cancer. The design of the HIOB trial follows a sequential probability ratio test (SPRT), defining annual in-breast recurrence rates as benchmarks for successful treatment. Superiority of the intervention is defined by falling below the best published evidence in non-IORT cohorts along three differnt age groups (e.g. for patients > 50 a., local relapse rate of 0.44% per annum). A similar concept of IOERT plus short-term WBRT is being tested in a phase II design by the Milano Group [31].

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Chapter 11
Lung Cancer

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Keywords Lung cancer • Small-cell lung cancer • Non-small cell lung cancer • IORT for lung cancer

Results of Standard Treatment: Rationale for IORT

Small Cell Lung Cancer

Small cell lung cancer (SCLC) is considered as high-risk metastatic disease potential at the time of diagnosis, and combined modality therapy with chemotherapy and thoracic external beam irradiation (EBRT) is the treatment of choice. Surgery for patients with SCLC could probably be reserved for stage I disease. Patients with more advanced SCLC are not considered to be surgical candidates and early EBRT obtains acceptable thoracic control rates. Intraoperative irradiation (IORT) has not been reported in this tumor histology.

Non-Small Cell Lung Cancer

Radiation therapy has been the standard treatment in stage III disease. However, few patients can be actually cured, local control rates in the long term are modest and reported 5-year survival rates are only about 5% [1, 2]. In selected patients with a good performance status and without weight loss, the 5-year survival was only 7% [3].

The rationale to intensify the locoregional treatment for non-small cell lung cancer (NSCLC) is based on the observation that 30–40% of patients die with active locoregional disease [2, 4], and

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_11,

it is likely that the incidence of local failure is underestimated because most published series did not utilize CT or bronchoscopy for treatment planning and or restaging following EBRT. Histologic examination of bronchoscopic biopsy specimens in patients treated with irradiation or combined chemoirradiation documented a local failure rate of almost 80% [5]. Another reason for the underestimated local failure rate in patients with NSCLC is the development of distant metastases in the early follow-up period; local control is uncertain when assessed in patients surviving less than 1 year.

Several radiotherapy trials suggest that thoracic control in lung cancer is dose related [6, 7], but radiosensitive organs such as the lung, spinal cord, esophagus, and heart often limit the dose of EBRT to ≤60 Gy, a dose usually inadequate to sterilize large NSCLC. In an effort to improve local control and survival, new treatment strategies have seen explored, such as hyperfractionated [8, 9], accelerated fractionation irradiation [10], chemoradiotherapy [11], or surgery.

The standard of care for most patients with locally advanced (stage III) disease has become combined modality treatment, wherein the potential role of surgery with or without IORT remains controversial. Recently, two phase II multicentric trials [12, 13] have shown high resectability, locoregional control rates, and survival using a trimodality regimen consisting of induction based-platinum chemoradiotherapy followed by surgery in stage III patients without mediastinal lymph node involvement. In stage III patients with mediastinal lymph node involvement, surgery remains more controversial, and selected patients can benefit from this treatment [14–17]. There are accepted indications for surgery, as a part of combined modality treatment, in selected subgroups of patients with stage III NSCLC disease according to recent guidelines [18–22]. IORT is a technique developed to improve the therapeutic index of the combination of surgery and irradiation by increasing the maximum dose to the target volume while sparing adjacent uninvolved or radiosensitive structures [23]. IORT using electron beams permits the delivery of a high single dose of radiation during lung cancer surgery to high-risk areas of residual or marginally resected tumor in the mediastinum, chest wall, and hilum while normal tissues can be displaced or protected from the irradiation beam [24] (Fig. 11.1).

Other strategies are based on the sophisticated technologic advances in radiotherapy treatment planning and delivery occurring in the last years (three-dimensional conformal and intensity-modulated irradiation (3DCRT, IMRT), four-dimensional computed tomography (4DCT), image-guided radiotherapy, tomotherapy, proton beam therapy, image-guided adaptive radiotherapy, and stereotactic body irradiation [25]. The influence of technologic advances on outcomes in patients with locally advanced NSCLC treated with multidisciplinary outcomes has been recently published [26].

Technical Considerations for IORT

In properly selected patients for thoracic surgery, the only relative or absolute contraindication to IORT procedures using high energy electron beam is in the anterior chest wall region. A lateral thoracotomy incision is usually preferred for IORT exposure (Fig. 11.2). This approach permits the introduction of cylindric and beveled IORT applicators into the thoracic cavity to obtain the maximum inclusion of one side of the mediastinum or hilum after lobectomy, atypical resection, or pneumonectomy.

At the University Clinic of Navarra, investigators used custom-made cylindric, straight, and beveled, IOERT applicators with a fixed docking mechanism in a nondedicated accelerator to deliver an IOERT boost with electrons ranging from 6 to 20 MeV to selected regions including the hilum (Fig. 11.3), mediastinum (Fig. 11.4), chest wall, or thoracic apex (Fig. 11.5). If anatomically feasible and appropriate from the cancer treatment view, radiosensitive organs such as esophagus,

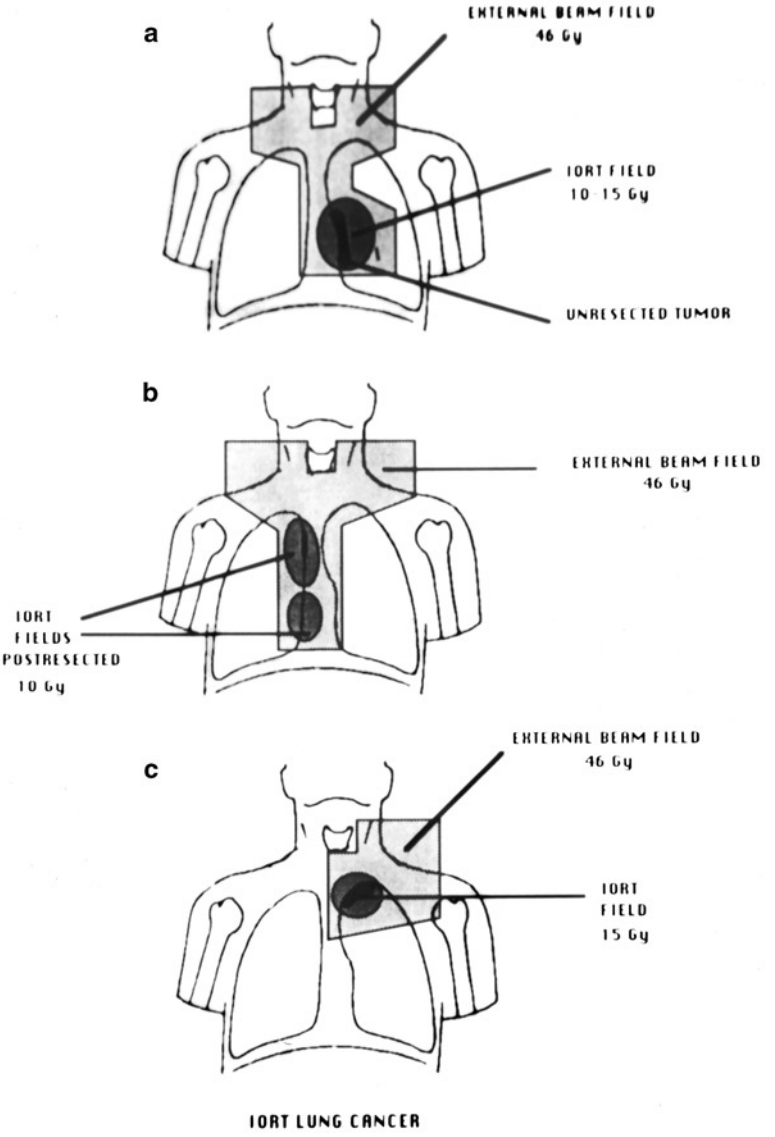

Fig. 11.1 Integration of external and intraoperative irradiation in lung cancer patients: (**a**) unresected left hilar tumor; (**b**) right post-lobectomy situation (two fields, non overlaping including bronchial stump and mediastinum); (**c**) Pancoast lesion.

spinal cord, and heart were protected with lead blocks. The bronchial stump is preferably protected with a vascularized flap to prevent suture dehiscence, after IORT treatment.

The IORT methodology used has been reported in detail in previously published articles [27, 28]. Macroscopic residual surgical masses, especially in Pancoast's tumors treated with preoperative chemoradiation may not contain viable tumor at the definitive pathology report. To properly select IOERT doses and electron energies, a biopsy of the surgical bed is informative. An IOERT boost to the medial aspect of the thoracic cavity apex in superior pulmonary sulcus tumors is frequently difficult to access, but through a trendelenburg position of the surgical coach, IOERT can usually be accomplished.

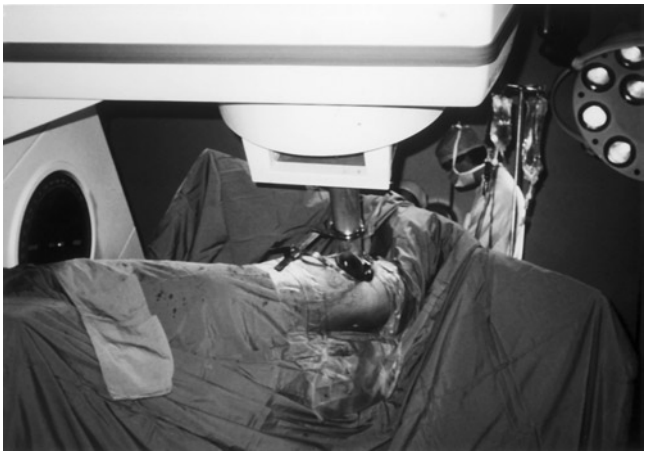

Fig. 11.2 General view of a thoracic IORT with electrons through left lateral thoracotomy.

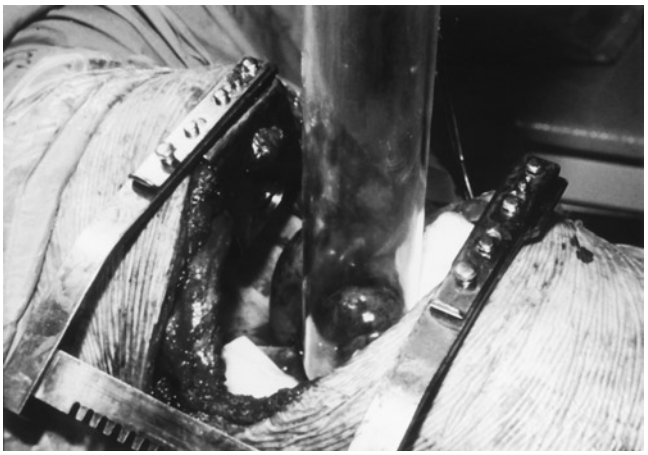

Fig. 11.3 IOERT applicator positioning during exploratory thoracotomy for an unresectable right lobe NSCLC. Notice that the tumor has been introduced in a 6-cm (0°) applicator, including normal lung parenchyma just around the tumor.

IORT Results: Animal Studies, Clinical Series

Tissue Tolerance: Mediastinal IORT

The tolerance of mediastinal structures to IORT has been prospectively analyzed in experimental animal studies. In a dose-escalation study [29] delivering 20, 30, and 40 Gy to two separate intrathoracic IORT fields, which included collapsed right upper lobe, esophagus, trachea, phrenic nerve, right atrium, and blood vessels, pathologic changes were observed at 30 Gy in the trachea and esophagus, with severe ulceration and peribronchial and perivascular chronic inflammation in the normal lung. A dose of 20 Gy produced minimal changes in the esophagus, trachea, and phrenic nerve, but major vessels and the atrium showed medial and adventitial fibrosis, obliterative endarteritis of the vasa vasorum, and severe coagulative necrosis. Acute pneumonitis was seen at all doses, and changes in the contralateral lung were detected using 12 MeV electrons.

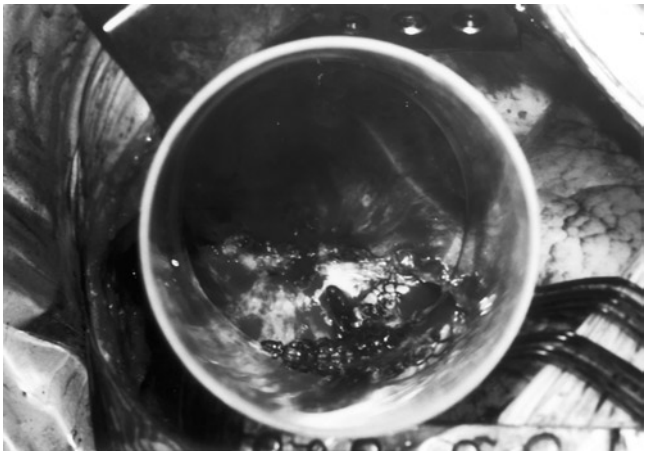

Fig. 11.4 Simulation for applicator selection (size, beveled angle, positioning, and maneuvers for normal tissue protection) after right superior lobectomy. The IOERT target volume includes right mediastinum and bronchial stump; remaining normal lung is mobilized out of the electron field.

Fig. 11.5 Postresection simulation for a Pancoast tumor. The target volume includes the tumor bed region (posterior and superior chest wall and paravertebral space), and remaining normal lung is mobilized out of the intraoperative field.

De Boer et al. [30] studied the effects of 20, 25, and 30 Gy in mediastinal structures of 22 adult beagles after left pneumonectomy. The bronchial stump healed in all dogs and there was no bronchial stump dehiscence or acute morbidity. Severe tissue damage was seen at all doses with six IORT-related mortalities due to bronchovascular (23%) and esophagoaortic (4.5%) fistulas and esophageal stenosis. Histopathological findings in surviving beagles showed marked myointimal fibrosis in the muscular arteries, submucosal fibrosis of the esophagus, and intersticial fibrosis of bronchial and lung tissue, especially in the higher dose group. The authors summarized that the mediastinal vascular, bronchial and esophageal structures are relatively sensitive to doses >20 Gy IORT.

At the National Cancer Institute [31] an experimental program evaluated the tolerance of surgically manipulated mediastinal structures to IORT in 49 adult foxhounds. Normal healing of the bronchial stump was found after pneumonectomy and IORT doses of 20, 30, and 40 Gy, but there were late changes with tracheobronchial irradiation damage at all doses (5–10 months after treatment). Two out of four dogs receiving 20 Gy developed esophageal ulceration at 6 months without late stricture. In dogs given 30 and 40 Gy, esophageal damage was severe (esophagoaortic fistula and stenosis)

Table 11.1 Clinical and pathologic findings observed in animal experimental models [27, 28, 31, 36, 38, 39]

IORT doses (Gy)	Bronchial stump	Esophageal damage	Lung damage	Pathologic changes in heart and vessels
20	Normal healing	Transient mild disphagia	Mild	Moderate
30	Normal healing	Chronic ulcerative esophagitis	Moderate	Moderate–severe
40	Normal healing	Esophageal perforation Esophageal stricture	Severe	Severe

and one dog developed carinal necrosis. The same institution reported the results of five dogs reserved for long-term studies and one stage II NSCLC patient alive at 5 years. They conclude that IORT in the mediastinum may be safe at dose levels that do not exceed 20 Gy [32].

Additional experimental analysis of canine esophagus tolerance to IORT has been reported by the NCI investigators [33]. After right thoracotomy with mobilization of the intrathoracic esophagus, IORT was delivered to include a 6-cm esophageal segment using a 9 MeV electron beam with escalating single doses of 0, 20, and 30 Gy. Dogs were followed clinically with endoscopic and radiologic studies and were electively sacrificed at 6 weeks or 3, 12, or 60 months after treatment. Transient mild dysphagia and mild esophagitis was observed in all dogs receiving 20 Gy, without major clinical or pathological sequelae except in one dog that developed achalasia requiring a liquid diet. At a dose of 30 Gy, changes in the esophagus were pronounced with ulcerative esophagitis and chronic ulcerative esophagitis inducing gross stenosis after 9 months.

Zhou et al. [34] analyzed the acute responses of the mediastinal and thoracic viscera in nine canines sacrificed after they received single IORT doses of 25, 35, and 45 Gy. No pathological changes were found in spinal cord and vertebra. Microscopic examination of trachea, esophagus, and lung showed mild or severe histological changes at 30 days at the level of 25 Gy vs. 35–45 Gy, respectively. Severe and unrepaired histological changes were found in heart and aorta receiving 35–45 Gy.

Morphofunctional changes in the bronchial mucosa were studied in 33 patients with stage III NSCLC treated with 15 Gy IORT with or without cisplatin [35]. No degenerative changes in the bronchial epithelium were found 2 weeks after IORT. Basal cell proliferation was observed, cells were reduced in size, and the basement membrane was thickened and twisted. Epithelial reparation due to pronounced local basal cell proliferation was observed 3 months later. A year later, the mucosa was covered with the multinuclear cylindrical epithelium and the cover of ciliated cells was preserved. The functional activity of goblet cells was in the normal range and scanty lymphoplasmocytic infiltration was found in the stroma. In patients treated with IORT without radiosensitization, the damaged epithelium was regenerated due to the reserved cells coming from the damaged margins with the formation of an epidermoid regenerative layer and subsequent cell differentiation. Moderate sclerosis occurred in the stroma. A year later, the bronchial epithelium was characterized by moderate goblet cell hyperplasia with preserved functional activity. The authors concluded that IORT caused mucosal damage as alteration, dystrophy, and desquamation of the epithelium. Subsequently, the bronchial epithelium recovered through reparative regeneration.

Based on these data, active clinical programs using thoracic IORT agree that 20 Gy is the upper single-dose limit that can be safely tolerated by mediastinal and thoracic viscera (Table 11.1) with IORT alone. There are no reported experimental normal tissue tolerance studies of IORT used in combination with EBRT.

Clinical IOERT Experience

The clinical experience of IOERT in lung cancer is still limited and the available data regarding treatment of NSCLC were obtained in phase I–II trials in small single institution series of patients. Abe and colleagues in the initial Japanese experience did not use IORT in lung neoplasms because of the early systemic dissemination pattern of the disease [36].

NCI Series

Based on a previous canine experimental model involving the use of pneumonectomy and IORT, a limited phase I NCI clinical trial was performed in 4 patients with stage II or III NSCLC delivering 25 Gy IOERT to two separate fields encompassing the superior and inferior mediastinum following pneumonectomy [37]. Only one long-term survivor is free from disease (more than 3 years). Early complications were described in three of four patients: one case of bronchial stump dehiscence, one bronchopleural fistula and one case of reversible esophagitis. Three patients with late complications showed one case of irreversible radiation esophagitis, one contralateral esophagobronchial fistula, and one case of reversible esophagitis. The retrospective analysis of toxic events detected overlapping of the fields in one toxic case. This study recognized the feasibility of IOERT during lung cancer surgery, but recommended a decrease in the IOERT dose to 15–20 Gy.

Graz University Experience

Combined IOERT (10–20 Gy) and postoperative EBRT (46–56 Gy) were initially used in 21 patients with inoperable tumors at the University Medical School of Graz (Austria) [38]. The analysis included 12 patients with N0 disease. The radiosensitive mediastinal structures such as heart, spinal cord, esophagus, and large vessels could be mobilized or protected from the IOERT beam by shielding maneuvers. The response rate in 14 evaluable patients 18 weeks after they completed IOERT and EBRT was excellent with three complete responses (21%) and ten partial responses (71%). Ten patients were alive and well at a period of 5–20 months (median 12 months).

Institutional results were updated in two consecutive publications [39, 40]. The IOERT procedure was generally well tolerated, but fatal intrabronchial hemorrhage related to IORT occurred in two cases with tumor involvement of the pulmonary artery. Local failure was seen in three patients and the 5-year overall (OS) and recurrence-free survival rates were 15 and 53%, respectively.

An expanded series from the University of Graz has been recently published [41]. Fifty-two patients with predominantly pathological stage I NSCLC (76%) with limited pulmonary reserve (median FEV1: 1,3) were treated with surgery, IORT (median dose 20 Gy), and EBRT (median dose 46 Gy). The actuarial overall survival and disease-specific survival at 3 years were 37 and 48%, respectively. Females had a significantly better disease-specific survival than males. Causes of death were unrelated to tumor in 17% and tumor related in 54% patients. Two patients died from second cancers and 25% are alive without evidence of tumor progression. Overall locoregional tumor control was 73% at 12 months and 68% at 24 and 36 months, respectively. IORT and EBRT were well tolerated without serious treatment-related acute or late side effects.

Montpellier Series

Patient Group

The Centre Regional De Lutte Contre Le Cancer in Montpellier (France), reported results in 17 patients with a median age of 56 years, 3 stage I, 7 stage II, and 7 stage IIIA [42]. The treatment protocol involved the use of IORT with doses in the range of 10–20 and 45 Gy EBRT in 20–25 fractions with or without a 3-week rest interval period following a complete surgical excision (4 patients underwent superior lobectomies and 13 underwent total pneumonectomies). Microscopic residual disease in the mediastinal nodes or pleura-chest wall was seen in 12 and 5 patients, respectively. The median follow-up time for the entire group of patients alive is 59 months, with follow-up ranging from 40+ to 120+ months.

Results

Disease control and survival results were as follows. Local control was obtained in 13 of 17 patients (76%) and central recurrence in the IORT field has been demonstrated in four patients. Three patients are alive without disease at 5.5, 8, and 11 years. Fourteen patients are dead, 7 from distant metastases, 4 from locoregional recurrence, 1 patient developed a second cancer, and 2 patients had a local recurrence in the EBRT field. The median survival time for the entire group was 36 months and OS rates were 80, 60, 27, and 20% at 1, 2, 3, and 5 years, respectively. The 10-year OS was 18% [42]

University of Navarra, Pamplona Experience

Patient Group

The largest clinical experience on the use of IORT in NSCLC is from the University Clinic of Navarra in Pamplona (Spain) [24, 27, 28, 43–45]. Between the period November 1984 and November 1993, 104 patients with histological confirmed stage III NSCLC were treated with IOERT as a treatment component of multidisciplinary management [46]. The retrospective analysis of the treatment programs in this period of time allows grouping of the patients into four categories. Between 1984 and 1989, 22 patients were treated with surgery, IOERT and postoperative EBRT. From 1989 to 1993, 82 patients received neoadjuvant chemotherapy. Responders or resectable patients after neoadjuvant chemotherapy (46 patients) were managed with surgery, IOERT, and postoperative EBRT. Nonresponders, unresectable disease (17 patients) or Pancoast's tumors (19 patients) received preoperative chemoradiotherapy, surgery, and an IOERT boost.

Treatment Techniques

Neoadjuvant chemotherapy. Neoadjuvant cisplatin (CDDP)-based chemotherapy consisted of two different protocols. The initial one (1985–1990) included CDDP 120 mg/m^2 6-h i.v. infusion on day 1, mitomycin C (MMC) 8 mg/m^2 1-h i.v. infusion on day 1, and vindesine (VDS) 3 mg/m^2 (maximum 5 mg) 3-h i.v. infusion on day 1 and 14 (MVP regimen). In 1990, a new chemotherapy regimen was evaluated in which CDDP and VDS were maintained, while MMC was omitted and intra-arterial carboplatin 150 mg/m^2 was added (MCP regimen). Chemotherapy was repeated every 4 weeks (MVP regimen) or 5 weeks (MCP regimen).

Surgery. Patients with an objective clinical response or stable disease considered resectable underwent surgical resection including the primary tumor and mediastinal lymphadenectomy 4–5 weeks after the last cycle of induction chemotherapy.

IOERT. Intraoperative electron irradiation (IOERT) dose and energy were dependent on the amount of residual disease. Total single doses ranged from 10 to 15 Gy. IOERT boosted a single anatomic site of residual disease in 79 procedures and two nonoverlapping fields were used in 25. The most common applicator diameters employed were 7, 8, and 9 cm (66%). The IOERT dose was 10 Gy (62%), 12.5 Gy (5%), 15 Gy (16%), and 18–20 Gy (17%) (generally administered for unresected tumors). Electron energies most frequently selected were 9 and 12 MeV.

EBRT. Thoracic EBRT was started 4–5 weeks after surgery. Treatment was delivered with a 15 MV linear accelerator employing AP-PA technique to encompass the treatment volume which included the bronchial stump, ipsilateral hilum, the bilateral mediastinal and supraclavicular lymph nodes. Patients were treated with daily fractions of 2 Gy, five times per week reaching a cumulative dose of 46 Gy in 23 fractions. A similar approach was used for preoperative irradiation.

Patient and Treatment Characteristics

Patients characteristics. Among the 104 treated patients, there were 101 males and 3 females, with a median age of 61 years (range 27–79 years). The median performance status was 80%. Squamous cell carcinoma was the predominant tumor type (63%) followed by adenocarcinoma, large-cell carcinoma, mixed histology, and undifferentiated carcinoma. Forty eight patients (46%) were classified as stage IIIA (60% N2 disease) and fifty six (54%) patients stage IIIB.

Treatment characteristics. A median of three cycles of chemotherapy were administered. Objective response to chemotherapy or chemotherapy plus preoperative EBRT was identified in 60 of 82 patients (73%). In the early part of this program, a large proportion of tumors were considered unresectable and tumor resection was not attempted. Poor prognostic patients were classified as nonresponders to neoadjuvant chemotherapy or considered unresectable.

Tumor resection was performed in 90 patients and the type of resection included 73 (70%) lobectomies, 8 atypical resections, 8 segmentectomies, and 1 pneumonectomy. Complete gross resection with microscopically clear margins was achieved in 73% of IIIA patients and 37% of IIIB patients. Differences between these parameters were statistically significant ($p = 0.0007$).

Treatment Results

Local control. Regarding the quality of resection, the local control rates observed in patients with ≤ microscopic residual disease (R0 or R1 resection) were 18/24 (75%), 4/14 (29%), and 11/12 (92%) for stage IIIA, IIIB, and Pancoast's tumors, respectively. Local control in patients with macroscopic residual disease (R2 resection) were 3/7 (43%), 7/30 (23%), and 5/5 (100%) for stage IIIA, IIIB, and Pancoast's tumors, respectively (Table 11.2).

Survival. At the time of this analysis, 16 patients (15%) were alive and free of disease. Five-year OS for the entire group was 40% for stage IIIA and 18% for stage IIIB patients ($p = 0.01$). Five-year disease-free survival (DFS) regarding amount of residual disease is as follows: 69 and 42% for microscopic (R1) or no residual disease (R0) for stages IIIA and IIIB, respectively, and 58 and 41% for macroscopic (gross) residual disease (R2) for stages IIIA and IIIB, respectively. Anecdotally, 19 patients survived more than 5 years after IOERT with a follow-up range from 64+ to 107+ months. Among patients surviving more than 5 years, there were three second tumors (colon, esophagus, and head and neck) and one cancer-unrelated death.

Treatment-related toxicities. Treatment toxicity and complications are outlined in Tables 11.3 and 11.4. IORT-related major toxicities according to treatment characteristics are summarized in Table 11.4. Four patients died in the postoperative period due to possible IOERT-related

Table 11.2 Patterns of failure according to disease stage and surgical residue, Pamplona analysis

Surgical residue	Local control	Distant
Micro/Absent		
IIIA	18/24 (75)	7/24 (29)
IIIB	4/14 (29)	4/14 (29)
Pancoast tumors	11/12 (92)	2/12 (17)
Macroscopic/Unresected		
IIIA	3/7 (43)	6/7 (86)
IIIB	7/30 (23)	12/30 (40)
Pancoast tumors	5/5 (100)	1/5 (20)

Local control = no local failure or distant
Distant failure = distant failure alone or distant and local failure

Table 11.3 Toxicity and complications for the entire group (104 patients) treated with combined modality therapy and an IOERT component (Pamplona analysis)

Toxicity and complications	Number of episodes
Postoperative period	
Pneumonia	4
Abscess-empyema	4
Pulmonary embolism	1
Peritonitis	1
Hemomediastinum	1
Pulmonary hemorrhage	2
Bronchopleural fistula	2
Acute vena cava syndrome	1
Short term	
Esophagitis grade III–IV	26
Symtomatic pneumonitis	6
Bronchopleural fistula	1
Pulmonary embolism	1
Pneumonia	2
Long term	
Transient neuropathy	6
Lung fibrosis	7
Bronchopleural fistula	1
Esophageal ulcer	2
Esophageal stricture	1
Instability of chest wall	1

toxicity: 2 bronchopleural fistula and 2 pulmonary hemorrhage. The first bronchopleural fistula occurred in a lobectomized patient, in whom the bronchial stump was not included into the IOERT field. Another patient died 3 months after surgery due to a bronchopleural fistula in a microscopically tumor-involved bronchial stump. One patient developed fatal massive hemoptysis at 2 months following IOERT because of pulmonary artery rupture. This latter patient had prior hemoptysis and a left hilar unresected tumor treated by tumor exposure and 15 Gy (20 MeV) IOERT plus 46 Gy postoperative EBRT. The autopsy study showed a necrotic cavity in the primary tumor with no viable residual tumor cells and a fistulous tract communicating between the pulmonary artery and the bronchial tree. A nonresected patient treated with three cycles of MVP regimen, preoperative EBRT (44 Gy), and IORT of 15 Gy died early in the postoperative period from pulmonary hemorrhage.

Esophagitis grade III–IV was noted in 26 (25%) patients and esophageal damage with ulcerated or necrotic tissue was observed in two patients (Fig. 11.6). One of two patients who developed esophageal ulcer died 8 months after surgery from fatal hemorrhage. This patient had a T4 tumor infiltrating the descending portion of the aorta and the esophagus. He was treated with three cycles of MVP chemotherapy regimen, preoperative EBRT (46 Gy), surgery (atypical resection plus chest wall resection), and 10 Gy IORT boost (12 MeV). No viable microscopic tumor was encountered in the resected specimen and the necropsy findings revealed a connection between the esophagus and the aorta without histological evidence of tumor cells.

Symptomatic radiation acute pneumonitis was observed in six patients (Fig. 11.7). Seven patients were diagnosed with severe long-term fibrosis and required chronic cortico-therapy administration.

Neurologic toxicity was noted only in patients treated with IOERT which included the thoracic apex or chest wall. Six patients developed transient neuropathy (4 Pancoast's tumors) with pain and paresthesia in the superior ipsilateral extremity or chest wall.

Severe infectious complications were seen in 11 patients. Six of these patients were diagnosed with simultaneous thoracic tumor progression coexisting with an abscess.

Table 11.4 Tumor treatment and IORT technical characteristics in patients with possible intrathoracic IOERT-related major toxicities. (Pamplona) analysis

Toxicity	Stage	Type of surgery	IOERT dose/energy/ tumor residue	IOERT target volume (applicator diameter)	Bronchial stump	EBRT	Surgery interval (days)
Bronchpleural fistula	IIIA	Lobectomy	11 Gy/9 MeV/ microscopic	Pulmonary apex + mediastinum (8 cm)	Suture	–	30
Bronchpleural fistula	IIIB	Lobectomy	10 Gy/12 MeV/ microscopic	Hilum[a] (9 cm, 7 cm)	Flap	Preop[b] (32 Gy)	45
Bronchpleural fistula	IIIA	Lobectomy	10 Gy/9 MeV/ microscopic	Hilum[a] (9 cm, 7 cm)	Suture	Postop (44 Gy)	270
Bronchpleural fistula	IIIB	Lobectomy	10 Gy/12 MeV/ macroscopic	Hilum + mediastinum (9 cm)	Flap	Postop[b] (6 Gy)	60
Pulmonary hemorrhage	IIIB	Tumor exposure	15 Gy/20 MeV/ macroscopic	Mediastinum (9 cm)	–	Postop (50 Gy)	60
Pulmonary hemorrhage	IIIA	Tumor exposure	15 Gy/18 MeV/ macroscopic	Hilum (8 cm)	–	Preop (44 Gy)	8
Esophageal ulcer	IIIA	Lobectomy	10 Gy/9 MeV/ microscopic	Hilum (6 cm)	Flap	Postop (46 Gy)	146
Esophageal ulcer	IIIB	Atypical resection	10 Gy/12 MeV/ microscopic	Mediastinum (10 cm)	–	Postop (46 Gy)	215
Esophageal stricture	IIIB	Lobectomy	15 Gy/12 MeV/ microscopic	Chest wall + mediastinum (9 cm)	Flap	Preop (46 Gy)	310

[a] IOERT multiple ($N = 2$) fields
[b] EBRT was stopped due to toxicity

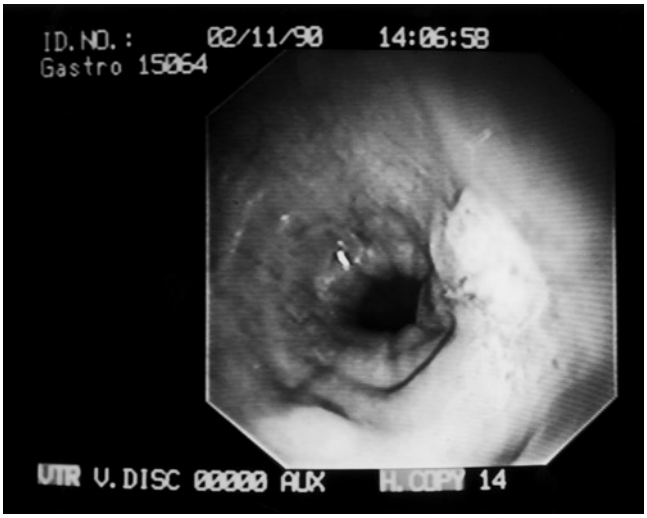

Fig. 11.6 Endoscopic view of an esophageal ulcer located in the internal portion of an IOERT field after lobectomy and treatment of the ipsilateral mediastinum. Symptoms were increased during the administration of adjuvant chemotherapy with radiopotentiating agents.

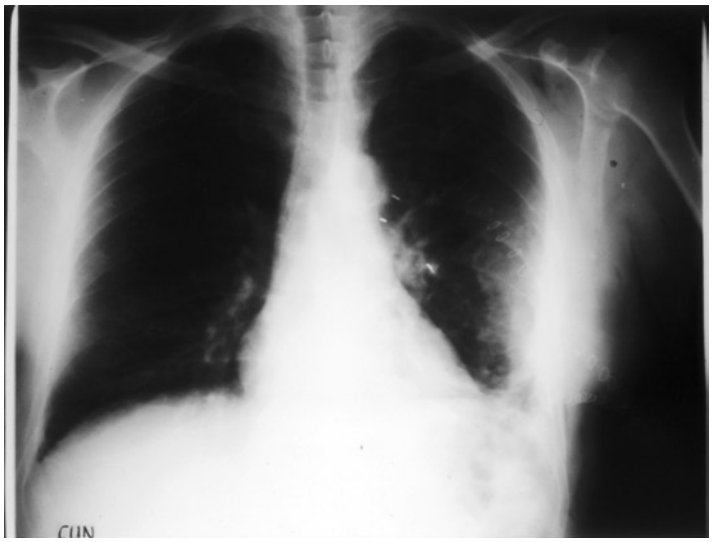

Fig. 11.7 An acute pneumonitis was identified in a patient treated with IOERT for an unresectable left hilar NSCLC on a 7 days postoperative chest X-ray showing a linear distribution of parenchymal increased density; resolution of pneumonitic changes was demonstrated after 15 days of steroid therapy.

The Allegheny University Hospital: Graduate Hospital of Philadelphia Experience

This unique experience in the USA was preliminarily reported in 1994 [46]. An update included 21 patients treated from June 1992 to September 1997 as part of a pilot feasibility experience for stage I ($N=1$), II ($N=2$), III ($N=18$) NSCLC patients managed by surgical resection, IOERT (10 Gy) and EBRT (45.0–59.4 Gy), 16 preoperatively and 5 postoperatively [43]. Chemotherapy was administered to all patients. The median survival time for surviving patients was 33 months and 5-year OS was 33%. Patterns of relapse included 3 (14%) thoracic and 12 (55%) systemic.

Instituto Madrileño de Oncología (Madrid, Spain)

From February 1992 to July 1997 18 patients with stage III NSCLC (11 Pancoast tumors) received IORT as a part of a multidisciplinary program including surgical resection in all cases, chemotherapy in 13, preoperative EBRT in 7, and postoperative EBRT in 7 [43]. Tumor residue at the time of surgery was macroscopic (gross) in 8 cases. The median survival for the entire series was 14 months. Intrathoracic relapse has been identified in two patients. Five-year OS was 22% (cause-specific 33%). Long-term toxicity observed has included neuropathy (2 cases) and esophageal stricture (1 case).

Summary

Disease control and survival outcomes for five IOERT series are in Table 11.5.

LDR- and HDR-IORT

Intraoperative brachytherapy using low-dose rate (LDR-IORT) or high-dose rate (HDR-IORT) is a radiation treatment alternative in lung cancer patients who are technically operable but cannot tolerate the operative procedure and the expected reduction in lung function after resection or conventional EBRT. LDR-IORT/HDR-IORT can be also used as a radiation boost technique in patients with residual disease after chemoradiation or in previously irradiated patients diagnosed with recurrent disease.

The LDR-IORT/HDR-IORT technique to be used depends on tumor location and the volume of residual disease after resection (R0, R1, and R2). Resectable but inoperable tumors, R2 resections and recurrent tumors may be treated by a permanent implant using Iodine-125 (I-125) or Palladium-103 (Pd-103) seeds. Unresectable chest wall lesions and R1 resections may be treated

Table 11.5 IOERT international clinical series in NSCLC

References	#	Stage	Treatment protocol	Local control	5-year survival
Smolle-Jeuttner[a] [40]	24	12 I 1 II 10 IIIA	IORT 10–20 Gy + EBRT 46–56 Gy	19/23 (83%)	15%
Dubois [42]	17	3 I 7 II 7 IIIA	S + IORT (10–20 Gy) + EBRT 45 Gy	13/17 (76%)	18%
Pamplona series [43]	104	19 IIIA (N0) 29 IIIA (N2) 56 IIIB	Multidisciplinary treatment with IORT 10–20 Gy + EBRT (46 Gy) ± CT (see text)	48/92 (52%)	40% (IIIA) 18% (IIIB)
Philadelphia series [43]	21	1 I 2 II 15 IIIA 3 IIIB	Neoadjuvant CT ± preop EBRT + S+IORT ± postop EBRT	18/21 (86%)	33%
Madrid series [43]	18	11 IIIA 6 IIIB 1IV	Neoadjuvant CT ± preop EBRT + S+IORT ± postop EBRT	16/18 (90%)	22%

CT chemotherapy
[a] Inoperable patients

intraoperatively by either a temporary Iridium-192 (Ir-192) implant (Fig. 11.8) or a permanent I-125 (Fig. 11.9) implant imbedded in absorbable polyglactin (vicryl) sutures and directly sutured onto the target area [47] or it may be treated by employing I-125 seeds imbedded into an absorbable gelatine sponge (Gelfoam) plaque [48]. Perioperative high-dose-rate brachytherapy (PHDRB) using Ir-192 administered over the immediate postoperative period has been mainly used in R0–R1 tumor resections. Intraoperative implantation of plastic catheters into the tumor bed after surgical resection for PHDRB has several theoretical advantages over other types of radiation boosting techniques,

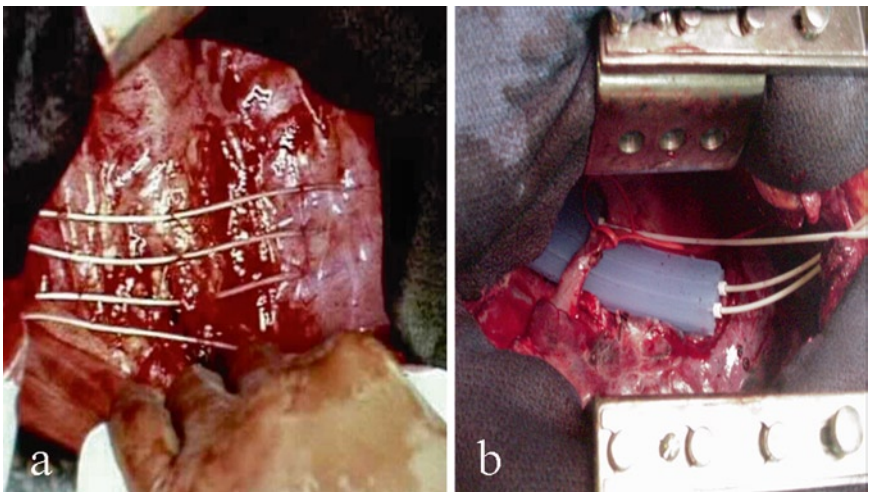

Fig. 11.8 Perioperative high-dose-rate brachytherapy (PHDRB) using Ir-192 in a resected NSCLC (**a**) and intraoperative brachytherapy using a silicone mold in which plastic catheters are inserted (**b**).

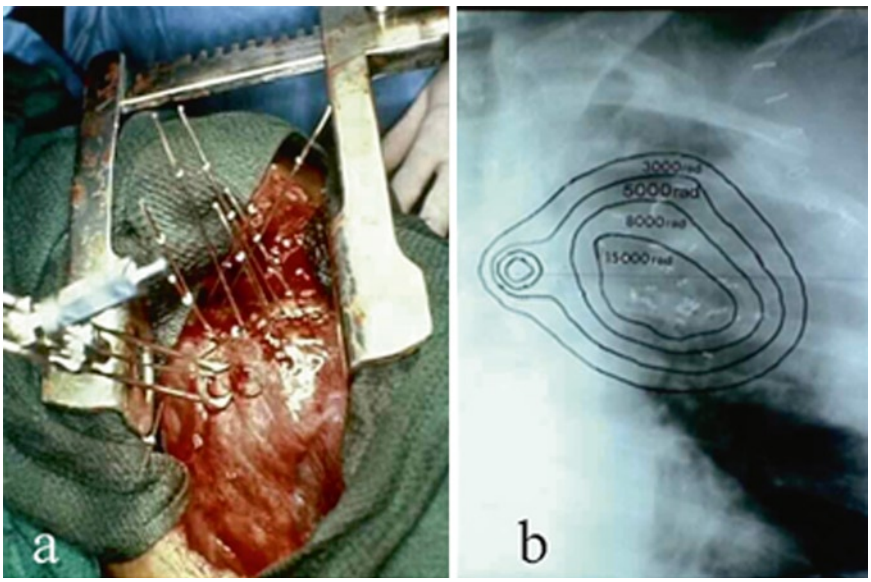

Fig. 11.9 Permanent LDR-IORT in a patient with inoperable NSCLC (**a**) and postimplant image obtained to confirm the seeds position (**b**).

including (1) accurate real-time definition of the clinical target volume (CTV) surrounding the tumor bed and other high-risk areas (with the assistance of the surgical team); (2) CT scan-based treatment planning; (3) risk-adapted brachytherapy dose selection based on the amount of residual disease described in the final pathology report; and (4) early delivery of fractionated radiation during the immediate postoperative period.

Stage I–II

The largest experience with IOBT has been published in patients with stage I–II lung cancer who are unfit for surgery and radical EBRT. The majority of the studies are retrospective and come from single institutions. The MSKCC experience has been reported by Hilaris et al. [49]. The study included 55 patients treated with thoracotomy, intersticial I-125 implantation ± moderate doses of EBRT. There were no operative or postoperative deaths. Locoregional control at 5 years was 100% in T1N0 lesions, 70% of patients with T2N0 tumors, and 71% in T1-2N1 tumors. The 5-year OS was 32% and DFS was 63%. The median survival was better in patients with cancer in the right lung but no difference in survival could be demonstrated among patients with squamous vs. adenocarcinoma, T1 vs. T2 tumors or those who did or did not receive postoperative EBRT.

Fleishman et al. [50] have published the results of 14 medically inoperable stage I patients treated with I-125 implantation at thoracotomy. Doses ranged from 80 Gy at the periphery to 200 Gy at the center. There was one operative mortality and two postoperative complications. With a minimum follow-up of 1 year, the local control was 71% and the median survival was 15 months.

A retrospective multicenter study of 291 patients with T1N0 disease was done comparing the outcomes after sublobar resection (124 patients) and lobar resection (167 patients) [51]. Brachytherapy (100–120 Gy to a 0.5-cm depth) was used in 60 patients with sublobar resection. With a mean follow-up of 34.5 months, brachytherapy decreased the local recurrence rate significantly among patients undergoing sublobar resection from 17.2 to 3.3%. There was no difference in survival between sublobar resection and lobar resection in tumors smaller than 2 cm. However, for tumor ranging 2–3 cm, median survival was significantly better in the lobar resection group.

Table 11.6 LDR-HDR-IORT international clinical experiences in stage I–II NSCLC

References	#	Stage	Treatment protocol	Local control	Time point
Hilaris et al. [49]	55	T1-2N0-1	S + I-125 (160 Gy) ± EBRT	100% (T1N0) 70% (T2N0) 71% (T1-2N1)	32% 5-year OS
Fleishman et al. [50]	14	T1N0	S + I-125 (80–200 Gy)	10/14 (71%)	MS 15.1 m
Fernando et al. [51]	291	T1N0	Lobar resection (LR) vs. sublobar resection (SR) ± I-125 (100–120 Gy)	96.5% (LR)[a] 95.6% (SR)[a]	MS 68.7 m (LR)[a] 50.6 m (SR)[a]
Lee et al. [52]	33	T1-2N0	Limited resection + I-125	31/33 (94%)	5-year OS 67% (T1N0) 39% (T2N0)
Voynov et al. [54]	110	T1-2N0	Limited resection + I-125 (100–120 Gy)	106/110 (96%) 5-year LC 90%	5-year OS 22% (T1N0) 12% (T2N0)

S surgery; *EBRT* external beam radiation therapy; *MS* median survival; *OS* overall survival
[a]Local recurrence and survival rates for the 2- to 3-cm tumors

The experience of the New England Medical Center in Boston is based in the implantation of radioactive I-125 seeds along the resection margin in 35 patients with stage I lung cancer treated with limited resection (not candidates for lobectomy) [52]. Two patients developed local recurrence at the resection margin and 6 patients developed regional recurrences in the mediastinun or chest wall. The 5-year OS was 67 and 39% for patients with T1N0 and T2N0 tumors, respectively.

Investigators of the University of Pittsburgh Cancer Institute reported a trial exploring the feasibility and outcomes of 125-I Vicryl mesh brachytherapy after sublobar resection (open or video-assisted thoracoscopic procedure) in stage I NSCLC patients with poor pulmonary function [53, 54]. The implant was introduced through the surgical incision and sutured to the visceral pleura. A prescribed dose of 100–120 Gy was delivered to a volume within 0.5 cm from the plane of the implant. There were four local recurrences in the 110 patients treated and the estimated 5-year local control, locoregional control, and OS rates were 90, 61, and 18%, respectively.

Stage III

University of Navarre investigators initiated a prospective, nonrandomized, controlled phase II clinical trial to determine whether PHDRB using Ir-192 administered over the immediate postoperative period is feasible and tolerable and may improve locoregional control rates in lung cancer patients with residual disease after chemoradiation or recurrent disease after previous radiation therapy [55]. In R0/R1 lung cancer resections the tumor bed was implanted with plastic catheters for PHDRB. The brachytherapy dose was 4 Gy b.i.d.×4–10 fractions (16–40 Gy total dose). Selected technically unfeasible cases for PHDRB were treated using a silicone mold in which plastic catheters are inserted and a single dose of 10–12.5 Gy was administered. Macroscopic residual unresectable tumors (R2 resections) were implanted with I-125 or Pd-103 seeds to deliver a minimum tumor dose of 90–110 Gy. From 2001–2006, 20 patients have been treated, 15 patients had residual disease and 5 patients had recurrent disease. Two patients developed grade 3 complication with thoracic abscess. Nine patients are alive, seven without disease, one without disease after radiosurgery for brain metastases and one patient is alive with disease. The local, locoregional and systemic control rates are 89, 84, and 70% respectively. After a median follow-up of 20 months (6–78 months) the 6-year OS and DFS are 36 and 27%, respectively.

The MSKCC treated 322 patients considered unresectable at thoracothomy and treated with brachytherapy [56]. Patients without mediastinal node metastases achieved 71% local control vs. 63% in patients with affected mediastinal nodes. The 2- and 3-year OS in N0 and N2 patients were 20/15% and 10/3%, respectively. A subgroup of 100 patients with positive mediastinal nodes were treated with surgical resection when feasible, brachytherapy (temporary Ir-192 implantation in patients with close or positive margins or I-125 implantation in patients with residual gross disease) and postoperative EBRT (median dose 40 Gy). There was no postoperative mortality and local control was obtained in 76% of patients (77% for patients with no residual disease and 72% in patients who had incomplete or no resection) [57, 58].

The same institution presented a later experience including 225 patients with thoracotomy and IOBT, when needed, in primary NSCLC invading only the mediastinum (T3-4N0-2) [59]. The authors encountered a positive correlation between prolongation of survival and extent of resection/IORT. Forty-nine patients had complete resection without IORT and fared no better than a cohort group of 33 patients who underwent pulmonary resection with simultaneous iodine-125 interstitial implantation or iridium-192 delayed afterloading to areas of unresectable primary or nodal disease. The median survival, 3-, and 5-year survival was 17 months, 21%, and 5%, respectively, with incomplete resection and 12 months, 22%, and 22% with incomplete resection and brachytherapy. One hundred and one patients underwent interstitial implantation without resection, with a median survival of 11 months, 3-year survival of 9%, and no 5-year survivors. The perioperative mortality was 2.7% and the nonfatal complication rate 13%.

Table 11.7 LDR-HDR-IORT international clinical experiences in stage III NSCLC

References	#	Stage	Treatment protocol	Local control	Time point
Valero et al. [55]	20	III	S + PHDRB (16–40 Gy) or IOBT (10.12.5 Gy) or I-125/Pd-103 seeds (90–110 Gy)	89%	36% 6-year OS
Burt et al. [59]	225	III	S ± I-125[a]/Ir-192	10/14 (71%)	MS 12 m[b] 22% 5-year OS[b]
Hilaris [56]	322	Unresectable	Thoracothomy + I-125 (160 Gy)	71% (N0) 63% (N2)	15% 3-year OS (N0) 3% 3-year OS (N+)
Hilaris [58]	100	IIIN2	I-125 (160 Gy)/Ir-192 (30 Gy) ± S + EBRT (30–40 Gy)	89% (R0) 53% (R1) 72% (R2)	22% 5-year OS (R0/R1) 22% 5-year OS (R2)
Nori et al. [48]	12	III (PSM)	± EBRT (45–60 Gy) +S+I-125/Pd-103 Gelfoam implant ± EBRT (45–60 Gy)	82%	45% 2-year OS

S surgery; *EBRT* external beam radiation therapy; *MS* median survival; *OS* overall survival; *PHDRB* perioperative high-dose-rate brachytherapy; *IOBT* intraoperative brachytherapy using a silicone mold in which plastic catheters are inserted; *PSM* gross of microscopic positive surgical margins

[a]125-I in patients with incomplete resections

[b]Patients with incomplete resection and brachytherapy

Researchers at the New York Hospital Medical Center of Queens in New York investigated the safety, reproducibility, and effectiveness of intraoperative I-125 or Pd-103 Gelfoam plaque implant technique in 12 patients as a treatment complement for resected stage III patients with positive surgical margin. All patients received preoperative or postoperative EBRT (45–60 Gy) and four patients received chemotherapy. There were no early or late complications due to brachytherapy or EBRT. The local control and 2-year OS and cause-specific survival were 82, 45, and 56%, respectively [48].

Superior Sulcus Tumors

The Erasmus Medical Center/Daniel den Hoed Experience in superior sulcus tumors (SSTs) has been recently reported [60]. Twenty-six patients with cytologically or histologically proven NSCLC (T3N0-1 or T4N0) arising in the pulmonary apex were treated with preoperative EBRT (46 Gy in 23 fractions, 2 Gy per fraction, 5 fractions per week), surgery and HDR-IORT using a flexible intraoperative template (FIT). FIT is a 5-mm-thick silicone mold in which afterloader catheters are inserted parallel to each other at a fixed distance of 1 cm and is used to deliver a homogeneous dose to a surface to which the shape of the mold is adjusted. A single radiation fraction of 10 Gy was administered specified in a plane parallel to the surface of the FIT at 1-cm distance with HDR Ir-192. EBRT (12 × 2 Gy) was indicated for unresectable tumors during thoracotomy. Three patients progressed during the preoperative treatment and were excluded. In 2 patients, HDR-IORT was not considered because the tumors had no chest wall invasion. Finally, 21 patients underwent the entire programmed treatment protocol. One patient (4%) died in the postoperative period due to a cardiac failure. Another patient died 7 weeks after surgery with a bronchopleural fistula and sepsis. Two patients had a prolonged hospital stay of more than 3 weeks because of ARDS and pleural empyema recovering after intensive conservative treatment. With a median follow-up of 18 months, 8 patients were alive (37%), of which 7 had no evidence of disease, and 18 patients (85%) were free from locoregional relapse. The median survival for patients without and with distant failure was 14 months and 6 months, respectively.

Hilaris et al. [61, 62] presented the results of 129 patients with SST treated with thoracotomy (in bloc excision of the involved lung and chest wall when feasible) interstitial IORT using either permanent implantation of I-125 seeds or temporary implantation of Ir-192, and postoperative EBRT in patients who had received no preoperative EBRT or when the implant presented unacceptable dose distribution requirements. The authors describe a 0.8% of postoperative deaths and 17 patients (13%) presented nonfatal complications including wound infection, empyema with or without bronchopleural fistula, bleeding, atelectasia or pneumonia, and phlebitis. The 5-year OS was 25% and patients with negative mediastinal nodes fared better than patients with positive mediastinal nodes showing a 5-year OS of 29 and 10%, respectively.

Discussion and Future Possibilities

The modern developments in the treatment of localized NSCLC confirm the oncology tendency to intensify systemic and local treatment to promote disease control. Although a large number of patients with stage III NSCLC die of systemic disease, local failure remains a substantial problem. CALGB reported patterns of disease failure in stage IIIA patients treated with induction chemotherapy, surgery, and thoracic irradiation [63]. The study found that of 52 of 74 patients had failures and the thorax was the first site of isolated or combined local failure in 36 patients (69%). Similarly, Le Chevalier et al. [5] reported that local control at 1 year documented by bronchoscopy was poor (15%) in the chemotherapy plus radiotherapy arm.

Unfortunately, less than 20% of stage III patients have disease that is resectable for cure at diagnosis and the optimal management of patients with unresectable disease remains controversial. In spite of improvement in resectability rates with neoadjuvant approaches, stage III NSCLC patients have a high incidence of local recurrence. Based on these observations, higher tumor doses may result in improved local control, and several trials have emerged in an attempt to promote thoracic control by escalating total radiation doses exploring altered fractionation or three-dimensional radiation planning [8, 9, 64, 65].

IORT/IOBT has been integrated into the multidisciplinary management of NSCLC in several small prospective single institution pilot trials as a sophisticated electron, LDR or HDR boost of radiation, confirming the feasibility of IORT procedure during surgical exploration of NSCLC patients. IORT doses between 10 and 15 Gy combined with EBRT (46–50 Gy), induces acute and late toxic events at a clinically acceptable level. Tables 11.5–11.7 shows summarized international IORT clinical trials regarding local control and survival data in NSCLC.

Definitive conclusions based on the available experiences discussed in this chapter cannot be established. In stage I or II NSCLC, IOERT and IOBT have been used for medically inoperable patients with excellent rates of local control (70–100%). Alternatively, stereotactic body radiotherapy (SBRT) has emerged as a well-tolerated technique in this subgroup of patients with high rates of local control [66, 67]. IOBT may be reserved to complex central T1-2 tumors or unexpected surgical findings.

Thoracic control seems to be related to tumor stage and location, surgical residue, and neoadjuvant treatment in locally advanced NSCLC (Fig. 11.10). Remarkable local control rates in Pancoast's and stage IIIA tumors with microscopic residual disease have been detected.

The effect of IORT on the group of patients presenting with stage IIIB appear to be favorable. This point is illustrated by the fact that patients with macroscopic residual disease or unresected disease achieved modest rates of local control (23%), but a few long-term survivors were identified. The high rates of metastatic disease in locally advanced NSCLC may conceal the definitive long-term local control, but the introduction of novel systemic agents generating more long-term survivors will clarify this question.

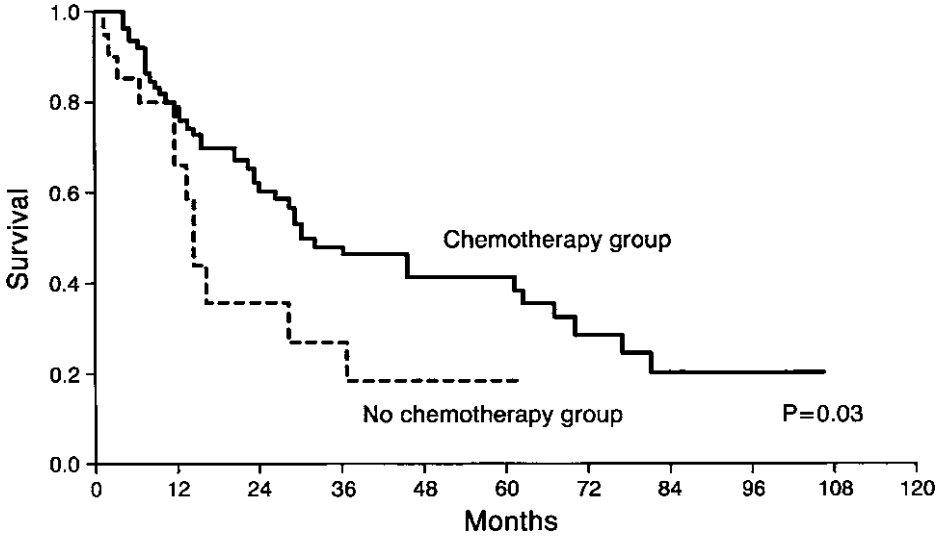

Fig. 11.10 Actuarial survival in patients treated with an IOERT component at the University of Navarra: chemotherapy contributed to survival prolongation ($p=0.03$).

Further confirmatory trials will be necessary to define the implication of IORT/IOBT in thoracic control and survival of patients with NSCLC. IORT/IOBT as a component of treatment can be integrated in phase III trials with treatment strategies that may include surgical thoracic exploration. This effort will require international cooperation among expert IORT institutions.

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Chapter 12
Gastric Cancer

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Keywords Gastric cancer • IORT for gastric cancer • Japan gastric IORT trials

Introduction

Epidemiology

Gastric cancer has experienced a marked change in prevalence during the last few decades. While in some countries, as in the Far East, gastric cancer continues to be a national health problem, the incidence in most Western countries has experienced a significant decline in both sexes. The causes of this decline are unknown [1]. Most importantly, while the overall incidence of gastric cancer has decreased in Europe and USA, there has been an increase in the relative percentage of proximal gastric adenocarcinomas (ACA) and ACA arising in the gastroesophageal junction (GEJ), especially in white males. With the exception of Japan, where mass screening programs have increased the number of patients diagnosed of early gastric cancer, diagnosis at an advanced stage is the rule. Approximately 50–75% of the patients who have gastric resection for cancer have serosal invasion and/or lymph node involvement. This helps to explain why cure rates have remained unchanged for decades in spite of improvements in oncologic therapy. Investigators should consider that both accrual and design of future trials in gastric cancer will probably be affected by these epidemiological trends.

Staging: AJCC vs. JSS

Japanese IORT trials for gastric cancer [2, 3] are reported according to the criteria of the Japanese Surgical Staging System (JSSS) [4]. The JSSS and the American Joint Committee for Cancer

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_12,

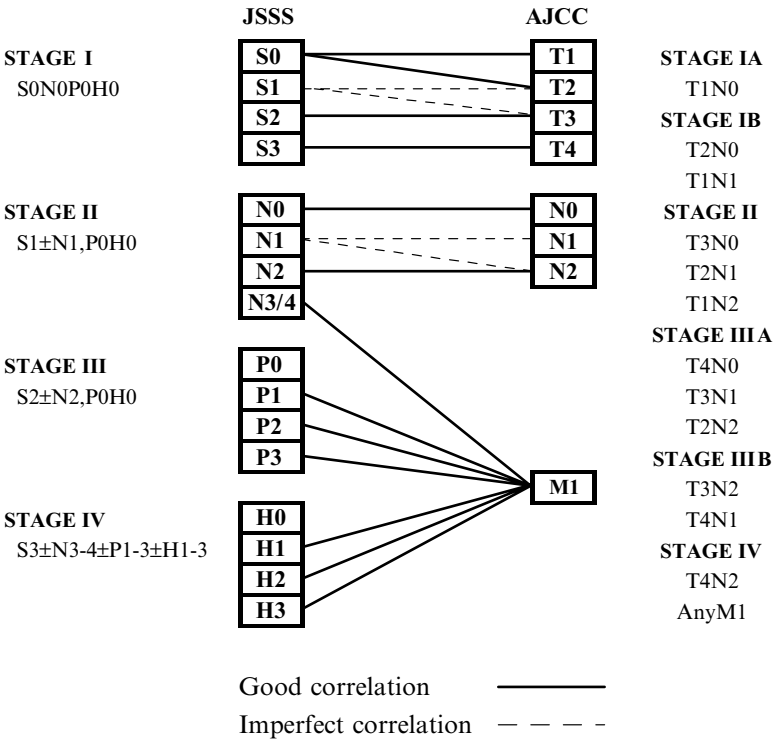

Fig. 12.1 Correlation between the Japanese Surgical Staging System (JPSS) and the AJCC Staging System.

Staging Classification (AJCC) [5], used in the Western countries, differ substantially. For that reason, the results for Japanese and Western IORT trials are not truly comparable. A comparison of the JSSS and the AJCC staging is provided to allow an easier comparison throughout the text (Fig. 12.1). This comparison contains important flaws, especially in the categorization of Japanese S1 (suspected serosal invasion), which is nonexistent in the AJCC staging and in the equivalence of nodal involvement for both staging systems.

Results with Non-IORT Treatment Approaches

Surgical Management of Gastric Cancer

Radical surgery remains the only curative option for gastric cancer. Patients with T1–2 tumors are best treated surgically with 5-year overall survival rates (OS) that range from 70 to 95%. T3 and T4 tumors have an increased risk of nodal metastases with resultant decreases in both disease-free survival (DFS) and OS (5-year OS of 20–30%).

Although no prospective randomized trials are available to define which should be the optimal extent of surgery for each disease stage and tumor location, subtotal gastrectomy is a reasonable alternative for most patients, especially those with distal lesions (this includes removing 80% of the stomach with the node-bearing tissue, the gastrohepatic and gastrocolic omenta and the first portion of the duodenum). Conversely, proximal tumors do functionally better with total gastrectomy, and this approach is therefore recommended.

The extent of lymph node dissection is controversial. In general, it varies from limited R2 dissection in Western countries to radical R2 dissection in Japan. In Japan, extended dissection prolongs survival in patients with deep tumors, even in the presence of lymph-node metastases [6], but this effect has not been reproduced in Western trials. Four Western randomized studies [7–10] have not demonstrated survival benefit for routine extended lymphadenectomy to date, but have demonstrated increased morbidity from the more aggressive approach. These trials have shown other important principles of lymph node dissection: by dissecting more areas and by being more compulsive in the lymph node evaluation, considerable stage migration occurs, with an apparent improvement in stage-specific survival without improvement in overall survival.

Patterns of Failure: Surgery Alone

Gunderson and Sosin [11] in their report of the University of Minnesota reoperative series demonstrated that truly complete resection of high-risk resected gastric cancers is difficult to achieve. In this study, 107 patients previously operated with "curative resections" for gastric cancer underwent programmed exploratory laparotomy (at 6–12 months after the previous surgery, 68 patients) or reoperation due to the development of symptoms suspicious of disease progression (39 patients). In the 105 patients evaluable for relapse patterns, the surgical pathology findings indicated recurrent or persistent tumor in locoregional areas in 70 patients (88% of the 80 patients who relapsed or 67% of the patients at risk) (Fig. 12.2). The rate of locoregional relapse increased by stage, with 43 out

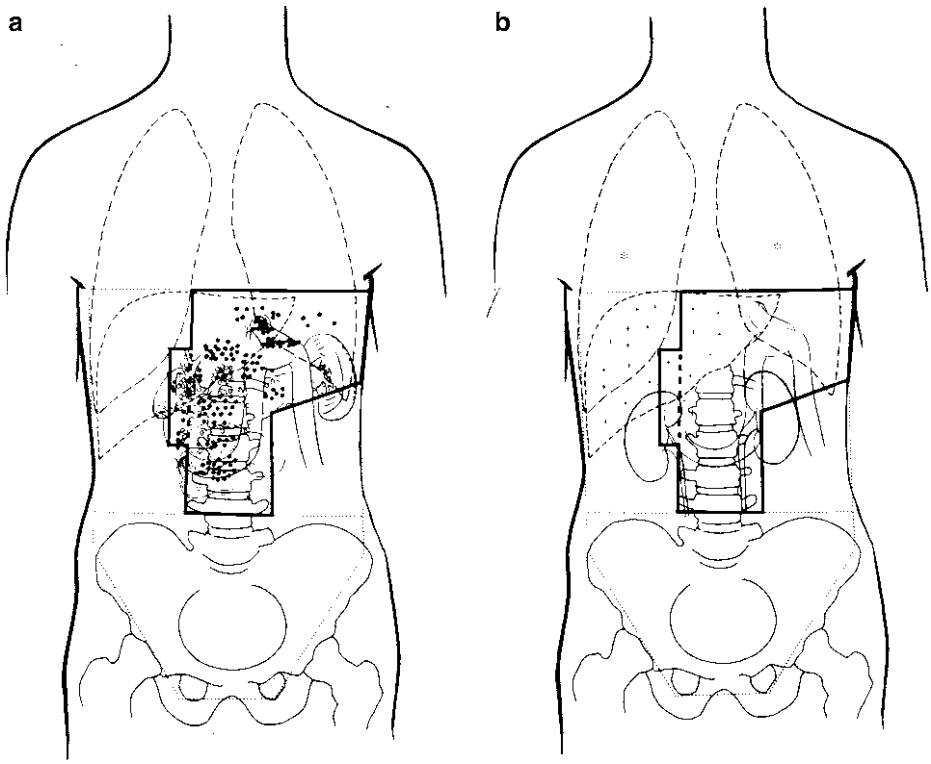

Fig. 12.2 Patterns of relapse in the University of Minnesota Reoperation Series with superimposed irradiation fields (modified from Gunderson and Sosin [11]). (**a**) Tumor bed and nodal relapses (*blackened circles* = tumor bed, 0 = nodal). (**b**) Distant relapses in liver and lung.

of 49 stage C2/C3 patients who developed disease progression relapsing in locoregional sites. Locoregional failure was the only manifestation of relapse in 24 patients (29% of those with relapse). Locoregional sites included the gastric bed in 55% of the cases, regional lymph nodes in 43%, anastomosis/gastric stump in 27%, and others in 5%. The locoregional relapses were located in more than one site in 60% of patients and were contained in one site in 38%.

These findings were reproduced in an autopsy analysis by Wisbeck et al. [12] of 38 patients with gastric cancer initially confined to the stomach (16 resected, 22 unresectable). Failure in locoregional sites was observed in 94% of the 16 patients with resected tumors.

However, when patterns of failure are documented by only clinical means, the reported figures are lower than those of reoperative or necropsy series. Landry and Tepper [13], reporting the Massachusetts General Hospital experience on the patterns of failure of completely resected gastric cancer, described an overall locoregional failure rate in 38% of the 130 patients at risk. In this series, patients were not routinely autopsied, but the failures observed were histologically documented in 69% of the cases.

The reoperation/autopsy series reported by Gunderson and Sosin provided a profound insight into the understanding of patterns of failure for gastric cancer. Two decades after their seminal publication, a combination of EBRT and fluorouracil–leucovorin chemotherapy (Int 0116 trial) proved to effectively decrease relapse rates and increase median and 3-year OS (see Adjuvant Therapy section). In spite of this favorable step forward, about 60% of the patients with resected high-risk gastric cancer will ultimately die of progressive disease, one third of them with localregional relapse as first site of failure.

Adjuvant Therapy in Gastric Cancer

Chemotherapy

Adjuvant chemotherapy for gastric cancer is needed based on the patterns of failure and survival results. Single-agent chemotherapy has been shown to produce clinical responses in the range of 20–30% for 5FU, MMC, or ADR. Chemotherapy consisting of 5FU-based combinations with ADR, MMC, VP16, and/or CDDP has yielded response rates of 15–55%. The regimen of epirubicin, cisplatin, and infusional fluorouracil (ECF), which was developed in the late 1980s, achieves response rates between 49 and 56% in randomized trials of the treatment of locally advanced gastric cancer [14, 15]. The ECF regimen improves survival and response rates among patients with advanced esophagogastric cancer [14], and these results are not improved by substituting mitomycin for epirubicin [15]. A recent meta-analysis found that in advanced disease, epirubicin and cisplatin contribute independently to the efficacy of combination chemotherapy.

In spite of its proven activity, the use of adjuvant chemotherapy has been controversial for decades [16], and a positive effect on overall survival has not been demonstrated until recently [17]. The MAGIC trial [17] demonstrated that the survival advantage observed with the use of ECF chemotherapy for advanced disease was also observed when ECF was used as in the perioperative setting in patients with resectable ACA of the stomach, distal esophagus or GEJ. This trial randomized 503 patients either to preoperative plus postoperative ECF chemotherapy or to a surgery-alone control arm. As compared with the surgery-alone group, the perioperative-chemotherapy group had a higher likelihood of overall survival [(HR for death, 0.75; $p=0.009$); 5-year survival rate, (36 vs. 23%)] and progression-free survival (HR for progression, 0.66; $p<0.001$). New chemotherapy agents have become available in the last few years, as the oral fluoropyrimidine prodrug capecitabine and the nonnephrotoxic platinum compound oxaliplatin. They appear to be as effective as fluorouracil and cisplatin, respectively [18].

Patterns of Relapse: Perioperative Chemotherapy

In the MAGIC trial [17], local recurrence was confirmed before death in 36 patients (14.4%) in the perioperative-chemotherapy group and in 52 patients (20.6%) in the surgery group, with distant metastases confirmed in 61 patients (24.4%) and 93 patients (36.8%), respectively. The patterns of disease progression confirm that distant metastases are a significant pattern of relapse even in the presence of active adjuvant chemotherapy.

Chemoradiation

Several randomized trials have demonstrated that EBRT ± chemotherapy improves local control in completely resected [16, 19], resected but residual [24–28], or unresectable gastric cancer [20, 21] when compared to observation or chemotherapy. In resected but residual or unresectable disease, EBRT + 5-FU prolonged survival when compared to either EBRT alone in a Mayo trial [21] or 5FU and methyl-CCNU in a GITSG trial [22] but was not clearly superior in terms of survival when compared to chemotherapy alone in additional trials conducted by the ECOG [23] and the GITSG [24]. Randomized trials on adjuvant EBRT ± chemotherapy for resected disease failed to improve overall survival in several studies reported in the past decades [16, 25], although a small percentage of patients with resected but residual disease were cured with chemoradiation.

The survival effect of chemoradiation has been finally elucidated by the results of the US GI Intergroup trial INT 0116 [26]. This study randomized 556 patients with completely resected high-risk gastric or GEJ cancer patients to postoperative 5FU-Leucovorin adjuvant and concurrent chemoradiation or a surgery-alone control arm. Chemoradiation patients received an EBRT dose of 45 Gy in 25 treatments over 5 weeks. Patients treated in the adjuvant arm had longer median and overall survival (median: 36 vs. 27 months; 3-year OS: 50 vs. 41%; $p = 0.005$) and a decreased risk of relapse (3-year DFS: 48 vs. 31%, $p < 0.001$). This adjuvant regimen is now an appropriate gold standard for completely resected but high-risk patients (RO resection with T3, T4 or N+ disease).

Patterns of Relapse: Postoperative Chemoradiation

In the INT 0116 trial [26], the rate of local recurrence decreased from 19% of patients at risk in the control group to 7% in the adjuvant arm. Regional relapse (usually in the form of abdominal carcinomatosis) was reported in 46% of those at risk in the surgery-only group and 27% in the chemoradiation group. Liver or extra-abdominal distant relapse was found in 12% of patients at risk in the surgery-only group and 13% in the chemoradiation group.

IORT Rationale, History, and Treatment Factors

Introduction/Historical Overview

Local relapse or disease remaining in the gastric bed and regional nodes after "curative resections" for patients with serosal invasion and/or lymph node involvement is a common event. Gunderson and Sosin [11] reported recurrent or persistent tumor in locoregional areas in 70 of 105 patients evaluated in the University of Minnesota reoperative series (88% of the 80 patients who relapsed or 67% of the patients at risk). Since then, a variety of adjuvant treatments including extended lymph-node dissections, chemotherapy, external beam radiation (EBRT), and intraoperative radiation (IORT),

alone or combined, have been tested extensively in an attempt to decrease locoregional failures and improve cure rates.

The pioneering work of Professor Abe of Kyoto University, Japan, in the 1970s fostered a renewed interest in the old idea of irradiating tumor-bearing areas under direct vision during laparotomy. Abe described the results of irradiating 14 gastric cancer patients with unresectable lymph nodes after gastrectomy and/or lesions invading the pancreas [27]. These lesions were irradiated at a dose of 30–35 Gy and no toxicity such as diarrhea, bloody stool, or abdominal pain was reported. Most interestingly, the lymph-node metastases that were smaller than 3 cm in diameter were eradicated. A dose of 40 Gy IORT to the unresected primary tumor was not able to eliminate it, although significant clinical regression was noted. Based on these results, Abe provided guidelines for treating gastric cancer with IORT alone [28]: (1) 30–35 Gy may be curative if the tumor volume is smaller than 3 cm in diameter. (2) For clinically undetectable lesions, a dose of 28 Gy may be optimal. (3) 40 Gy single-dose IORT is not effective in eliminating large primary unresected tumors.

The work by Abe and colleagues triggered gastric IORT trials around the world. Some investigators have followed the methodological approach proposed by Abe for gastric cancer [3, 29–34], while others have used IORT doses considerably lower than those advised by Abe because of fear of undue severe toxicity [35–43]. This has followed the tendency in the design of IORT trials for other anatomical locations, where IORT doses were in the 10–20 Gy range, based on the toxicity patterns of animal studies and preliminary human clinical trials. These latter studies have included the delivery of EBRT ± chemotherapy postoperatively or preoperatively. While this might compromise the total dose delivered by IORT, it was thought that a wider coverage of the stomach bed and surrounding nodal areas would result in a final advantage due to the knowledge of the patterns of local progression for gastric cancer rendered by the reoperation/necropsy studies.

In summary, IORT for gastric cancer has been used by many investigators after gross or complete macroscopic R0 or R1 resection to boost the surgical bed and/or lymph-node areas; others have also used IORT after R2 resection with gross residual disease. Some investigators have favored the use of IORT as the only adjuvant therapy after surgery [3, 27, 29–34] while others have incorporated IORT along with EBRT ± concurrent and maintenance chemotherapy [35–43].

Methodology

Candidates for IORT Programs

Although some patients with early gastric cancer have been included in IORT trials [27, 31, 33, 36, 37, 40, 44, 45] the excellent cure rates obtained with radical surgery alone do not make this group of patients a good candidate to be enrolled into adjuvant programs. The current NCCN guidelines [46] do not recommend adjuvant therapy in patients with resected pT1-2N0 gastric cancer. The use of postoperative 5FU-based chemoradiation for high-risk pT2N0 (high grade, LVSI+, PNI+ or age < 50 years) remains controversial and is usually reserved for patients with posterior wall lesions with extension beyond the muscularis propria [47].

Current knowledge on patterns of failure for gastric cancer after postoperative chemoradiation [26] or neoadjuvant and adjuvant ECF chemotherapy [17] suggests a 7–14.4% local failure rate after level 1 evidence adjuvant treatment. IORT could be an ideal supplement for these patients. It is imperative to identify subpopulations at a higher risk of local relapse to implement IORT programs. Patients most likely to benefit from the addition of IORT to resection and EBRT plus concurrent and maintenance chemotherapy include those with microscopic or grossly positive margins of resection (R1 or R2 resection; no hematogenous or peritoneal spread of disease) or with negative but narrow margins of resection and/or involved lymph nodes (R0 resection; T3-T4N0-N+).

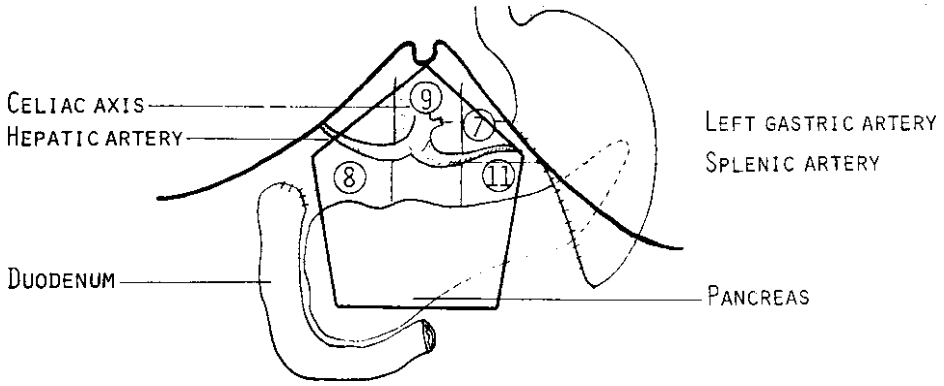

Fig. 12.3 Pentagonal IORT field preferred by Abe and colleagues in Kyoto (from Abe et al. Intraoperative radiotherapy of gastric cancer. Cancer 1974; 34:2034–41, with permission).

IORT Characteristics

Equipment and IORT Target Volume

Most of the research institutions where gastric IORT trials have been generated have used electron beams. However, there are major differences regarding the technology used. Both docking and nondocking applicators have been used. IORT has been delivered through circular [30, 33, 36, 37, 39, 40, 42, 43, 45, 48], pentagonal [27, 30, 31], elliptical [36, 48], hexagonal [48], or customized applicators [3]. Most institutions have treated a single target volume, while others have used multiple abutting fields [34].

A typical *IORT target volume* for gastric cancer contains the pancreas body and the celiac axis with its branches. Depending on the specific location of the gastric tumor, the head of the pancreas can also be part of the target volume. The distal biliary tract is usually dissected out to perform the biliary-digestive anastomosis, and it is not irradiated. Depending on the specific electron energy selected, the aorta, the extrahepatic inferior vena cava, and the anterior bodies of the underlying T11–L1 vertebrae are also irradiated.

Abe et al. [2] recommended the IORT applicator (pentagonal field) be positioned toward the residual tumor or the high-risk lymph node groups along the common hepatic, left gastric, and splenic arteries and around the celiac axis (Fig. 12.3). In cases where the posterior wall of the stomach was grossly adherent to the pancreas, this was included in the field. The electron energy was selected to encompass the tumor volume within the 90% isodose line.

Ogata et al. [3] used a custom-shaped applicator to conform a pentagonal-hexagonal field with 2-mm lead plates aiding to retract and shield radiation-sensitive organs. After 1992, they developed a new surgical technique that provides mobilization of the body and tail of the pancreas for patients with invasion of the pancreas or metastases to the lymph nodes along the splenic artery. Para-aortic nodes can also be included after the mobilization of the body of the pancreas. In general, most groups have used circular applicators [30, 33, 36, 37, 39, 40, 42, 43, 45, 48] centered on the celiac axis and covering a tumor bed of 6–10 cm in diameter. Electron energies ranged from 9 to 12 MeV (Table 12.1).

Implementation and Design

While the initial trials on IORT for gastric cancer called for high IORT doses as the only adjuvant therapy, most subsequent European and US trials have chosen to reduce the IORT dose and to incorporate EBRT ± chemotherapy in the adjuvant setting.

Table 12.1 Technical characteristics in IORT trials for gastric cancer

Author (reference), year, institution	IORT field shape	Energy[a] (MeV)	Applicator size[a] (cm)
Abe [27], 1980, Kyoto University, Japan	Pentagonal	Custom[b]	n/a[c]
Calvo [36], 1992, U Navarra, Spain	Circular/elliptical	12 (9–20)	8–9 (6–10)
Sindelar [34], 1993, NCI, USA	Abutting fields (2–4)	11–15	n/a
Avizonis [37], 1995, RTOG 85-04, USA	Circular	n/a	7.5 (5.5–9.5)
Ogata [3], 1995, Kochi Medical School, Japan	Lead shaped	12	n/a
Kramling [30], 1997, Munich, Germany	Pentagonal/circular	n/a	n/a
Coquard [40], 1997, Lyon, France	Circular	12 (9–20)	9 (6–11)
Martinez-Monge [39], 1997, U Navarra, Spain	Circular	12 (9–20)	8–9 (6–10)
Skoropad [45], 2000, Obninsk, Russia	Circular	12 (8–22)	6–10
Glehen [44], 2003, Lyon, France	Circular	9–12	7–11
Miller [43], 2006, Mayo, USA	Circular/elliptical	9 (9–18)	7 (5.0–9.5)
Qin [31], 2006, Shanghai, China	Pentagonal	6–16	n/a
Drognitz [33], 2008, Freiburg, Germany	Circular	6–15	4–12
Fu [48], 2008, Shanghai, China	Circular/elliptical/ hexagonal	12 (9–16)	6×5 to 10×11

[a]Median (range)
[b]That which encompasses the target volume thickness within the 90% isodose line
[c]Data not available

EBRT Field Design

EBRT is included in IORT trials on the basis that more than 60% of the locoregional relapses observed in the University of Minnesota reoperative series were multiple [11]. Also, the use of EBRT to cover a wide area in the upper abdomen follows the traditional doctrine of designing the radiation fields to treat uninvolved areas with a high probability of containing microscopic disease.

Gunderson, through the meticulous mapping of areas of relapse following "curative resection" [11] designed a comprehensive radiation portal for EBRT (Fig. 12.2) [36, 37] that was later incorporated into the design of the INT 0116 trial [26]. This portal design should be considered with the understanding that isolated locoregional relapses represent only about one third of all locoregional relapses, according to the Gunderson and Sosin report [11]. IORT alone could be inadequate in covering the whole extent of potential microscopic residual disease with a resultant geographical miss. EBRT portals should be designed according to the location of the primary tumor, and surgical findings and known patterns of nodal involvement generated from surgical series [47]. A clear example of the need for site-oriented field design is that for proximal gastric tumors that involve the esophagus, the lymphatic drainage places mediastinal nodes at risk. Wisbeck et al. in an autopsy series of 38 patients operated for gastric ACA demonstrated that 69% of the patients with tumors localized in the GEJ suffered relapse in extra-abdominal sites [12]. They recommended including mediastinal nodes in the EBRT fields.

Calvo et al. used 15 MV photon beams, AP-PA fields, and standard 1.8–2 Gy daily fractions to deliver a median total EBRT dose of 46 Gy after an IOERT dose of 15 Gy (Fig. 12.4) [36]. The idealized fields of Gunderson were modified according to the tumor location, lymph nodes involved in the resected specimen, and likely patterns of microscopic spread. The mean effective treatment area at midplane after customized blocking was 238.8 cm^2. This did not differ from a control subset of patients treated only with EBRT, with a mean effective area of 243.8 cm^2 [39].

Most authors reporting gastric IORT series have used standard fractionation and varied portals if they decided to treat with EBRT plus IORT. AP/PA ports have been more commonly used [36, 37],

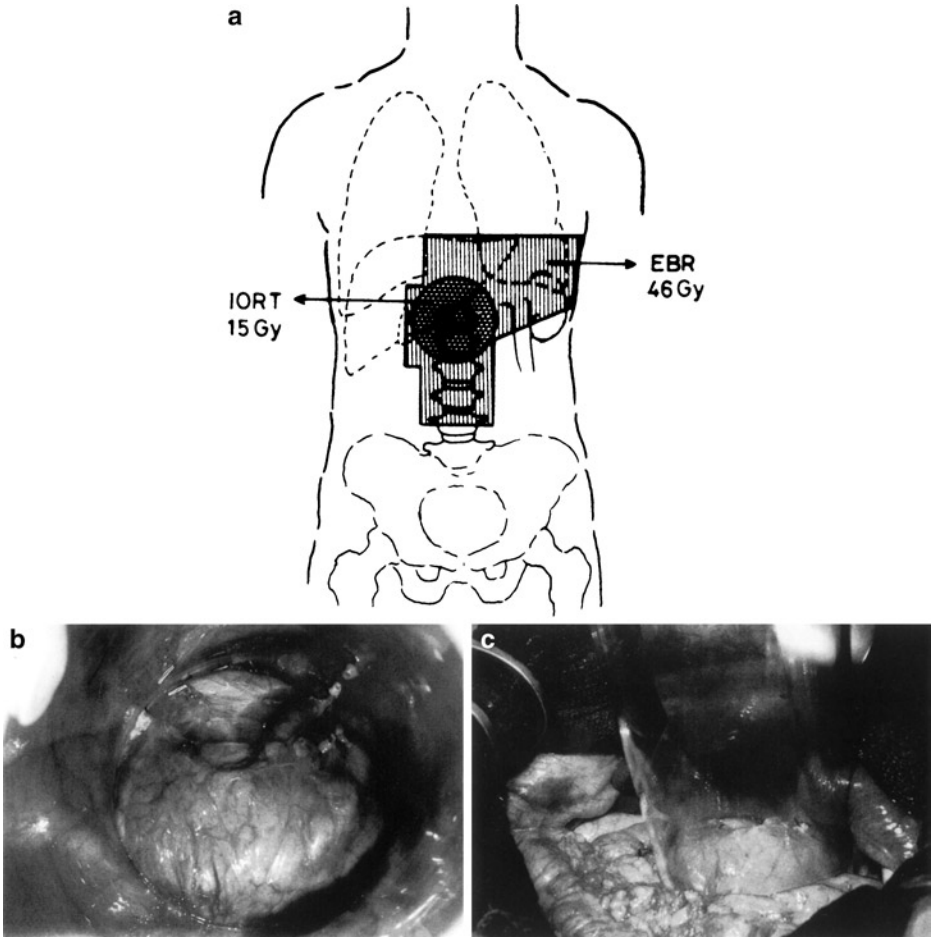

Fig. 12.4 Schematic representation of the intregrated program of IOERT (15 Gy) and EBRT (40 Gy) at Pamplona (from Calvo et al. [36] with permission). (**a**) Schematic representation of the integrated program of IOERT (15 Gy) and ERBT (46 Gy) at Pamplona. (**b–c**) IORT applicator in position over the gastric bed/body of pancreas and nodal regions.

although a four-field technique has also been reported [40]. As noted by Gunderson and Tepper [47], the use of multiple-field techniques, based on preoperative imaging and surgical clip placement, lessens treatment-related morbidity and is preferred whenever feasible.

Unfortunately, while the characteristics of the IORT part of the treatment are shown meticulously, the EBRT methodology is either omitted or not reported in detail. Another important characteristic of the combined approach (IORT + EBRT) is that some patients assigned to receive postoperative EBRT do not receive much because of postoperative complications, death, or refusal. Moreover, the planned EBRT dose is reduced in some additional patients due to gastrointestinal toxicity or due to the emergence of late postoperative complications. In general, only 40–90% of the patients included in early IORT trials completed the EBRT course as prescribed [36–38, 40], although in more recent reports, the rate of compliance has been much higher [41, 43, 45, 48, 49].

IORT Clinical Results

Survival Outcomes

Surgery + IORT (Table 12.2)

Abe et al. [27] reported a randomized study of 211 gastric cancer patients with JSSS stages I–IV randomized to either gastrectomy + IORT (admission on Friday, 101 patients) or gastrectomy alone (admission on Tuesday, 110 patients). The study was conducted between March 1974 and March 1984. IORT was delivered to high-risk (28 Gy) or residual tumor areas (30–35 Gy) in the stomach bed and/or upper abdominal nodes. No EBRT was given. The results were updated in 1988 [28] with the patients staged according to gross findings during laparotomy and indicated a 5-year survival advantage for IORT with stages II–IV (Table 12.3). However, when the results were further updated according to the microscopic findings [2], the differences observed were less and lacked statistical significance (Table 12.4). When the same analysis was performed based on histological features (serosal invasion, nodal station involved), survival trends favored IORT in patients with serosal invasion (S+) and N2/N3 involvement, although these differences were not statistically significant (Table 12.4).

Sindelar et al. [34] in a NCI randomized trial described a 5-year OS of ~10% for 15 patients with resected gastric cancer stages III–IV treated with radical surgery + IORT (data not stated in the text

Table 12.2 Treatment regimens and outcomes in IORT-alone trials for gastric cancer

Author (reference), year, institution	*N*, stage, resection	Radiation dose	LRC, time point	OS, time point
Abe [28], 1988, Kyoto University, Japan	101, JSSS I–IV, Gross findings	Phase III study: IORT 28–40 Gy vs. none	NR	5-year; stage II 83%, stage III 62%, stage IV 15%
Sindelar [34], 1993, NCI, USA	15, III–IV	Phase III study: IORT 20 Gy vs. EBRT 50 Gy[a]	56%[b]	MST 25 months; 5-year 10%
Farthmann [29], 1993, Freiburg, Germany	36	IORT 25–28 Gy	2-year 97%	2-year 50%
Abe [28], 1988, Kyoto University, Japan	94, JSSS I–IV, histological findings	Phase III study: IORT 28–40 Gy vs. none	NR	5-year; stage II 78%, stage III 60%, stage IV 33%
Ogata [3], 1995, Kochi Medical School, Japan	58, JSSS II–IV	IORT 28–30 Gy	NR	5-year; stage II 100%, stage III 55%, stage IV 14%
Kramling [30], 1997, Munich, Germany	51	IORT 28 Gy	NR	MST 26.9 months
Qin [31], 2006, Shanghai, China	106, I–IV	IORT 10–30 Gy[c]	NR	5-year; stage I, II 100%, stage III 60.4%, stage IV 14.3%
Drognitz [33], 2008, Freiburg, Germany	61, UICC I–IV	IORT 23 Gy	5-year 90%[d]	5-year 58%

[a]EBRT only given to stage III–IV patients

[b]Nonstandard criteria for definition of locoregional failure. The overall locoregional failure rate of 44% for the IORT arm and 92% for the surgery ± EBRT arm ($p < 0.001$)

[c]10–15 Gy if no clinically undetectable lesions; 20 Gy of microscopic residual nodes were suspected; 25 Gy if macroscopic residual nodes or direct invasion of adjacent structure were suspected; 30 Gy to one patient who had noncurative surgery because of incomplete excision of metastatic lesions

[d]Locoregional control data for non-IORT control group not shown in the chapter

N patient numbers, *LRC* local-regional control, *OS* overall survival, *NR* not reported, *MST* median survival time

Table 12.3 Abe/Kyoto University [28] survival results based on gross histological findings

	5-year survival rates	
Surgical stage	Surgery alone (%)	Surgery + IORT (%)
I	93.0	87.2
II	61.8	83.5
III	36.8	62.3
IV[a]	0.0	14.7

[a]In stage IV, patients with peritoneal or visceral metastases were not included (only stage IV H0P0 accepted, mainly patients with direct pancreas invasion, S3+ disease)

Table 12.4 Survival results based on histological findings, Kyoto University[a]

	5-year cause-specific survival	
Pathological stage	Surgery alone (%)	Surgery + IORT (%)
I	100	96
II	66	78
III	51	60
IV[b]	14	33
Pathology finding		
S–[c]	88.6	93.8
S+	50.6	60.2
N–[d]	97.4	100
N1+	67.2	63.4
N2/N3+	32.4	50.8

[a]Abe et al. [2]
[b]In stage IV, patients with peritoneal or visceral metastases were not included (only stage IV H0P0 accepted, mainly patients with direct pancreas invasion, S3+ disease)
[c]Serosal invasion
[d]Nodal invasion

Table 12.5 Ogata/Kochi Medical School survival results by stage [3][a]

	5-year survival	
Stage	Surgery alone (%)	Surgery + IORT (%)
II	63	100
III	42	55
IV	11	14

[a]Data not contained in journal article, but provided through a personal communication by the principal author (T. Ogata)

and obtained from figures). Median survival time for this subset of patients was 25 months. There were no differences between the IORT and the EBRT arms regarding survival. The median survival of the 25 patients in the surgery ± EBRT arm was 21 months, and the 5-year OS was ~20%. No stage III–IV patient in the control group survived after a median follow-up of 7 years, while 3 out of 15 in the IORT group were alive NED at the time of the analysis ($p = 0.06$).

Ogata et al. [3] reported a study from the Kochi Medical School, Japan, with 178 gastric cancer patients, JSSS stages II–IV treated with surgery alone (120 patients) or surgery + IORT (58 patients) during the time period of August 1983 to July 1992. The patients were not randomized. The surgery-alone group patients served as controls. The IORT group presented with more unfavorable features, but the difference was not significant. The results provided by stage demonstrated a slight survival advantage for IORT in stages III and IV that was not statistically significant (Table 12.5).

The best survival advantage for IORT was obtained in stage II patients, but this was not reported to be statistically significant.

Chen et al. [32] in Beijing reported similar results for stage III gastric cancer treated with IORT. The 5-year OS for the IORT-treated patients was 65 vs. only 30% in the surgical group ($p<0.01$). There was not a statistically significant difference in the survival rates for stage IV.

Kramling et al. [30] reported a study in which 115 patients with gastric cancer were randomized to 28 Gy of IORT or observation. Mean survival time was 26.9 months for the IORT arm and 30.8 months for the control group ($p=$ns).

Qin et al. [31] analyzed 106 patients treated with gastrectomy, D2–3 lymph node dissection, and 10–30 Gy of IORT. IORT dose was selected based upon the degree of surgical resection. A single dose of 10–15 Gy was given to 41 patients who had no clinically undetectable lesions, a single dose of 20 Gy was given to each 27 patients who were suspected to have microscopic residual nodes, 25 Gy was given to 37 patients who were suspected to have macroscopic residual nodes or direct invasion of adjacent structure, and 30 Gy was given to one patient who had non-curative surgery because of incomplete excision of metastatic lesions. To evaluate the effectiveness of IORT, 441 patients who were treated by operation alone during the same time period were classified histologically, and their survival rates were compared with those of patients treated by IORT. The 5-year survival rate for patients treated by operation alone was 92.8% for stage I, 80.6% for stage II, 45.1% for stage III, and 10% for stage IV. The 5-year survival rate for patients treated by IORT was 100% for stages I and II, 60.4% for stage III, and 14.3% for stage IV. There was no difference between the survival rates of patients in stages I and IV in the two groups, but the IORT procedure raised the survival of patients with stages II and III ($p<0.001$ and $p<0.005$, respectively).

Finally, Drognitz et al. [33] was not able to find differences in overall survival when a cohort of 61 patients treated with IORT of 23 Gy were compared with a similar group of 61 patients treated with surgery alone. Survival rates according to UICC stages were 71, 68, 14, and 0% for stages I–IV in the IORT group and 92, 47, 7, and 0% in the non-IORT group. Logrank analysis showed no significant difference between overall survival rates in the IORT group compared with controls (58 vs. 59%; $p=0.99$). Furthermore, univariate subgroup analysis of earlier stage carcinomas (UICC stages I and II), as well as advanced-stage carcinomas (UICC stages III and IV), showed no survival benefit with IORT.

Surgery + IORT + EBRT (Table 12.6)

Calvo et al. [36] described a 5-year OS of 39% for 48 patients treated with IORT + EBRT. This study included 16 patients with AJCC stages I–II and 8 patients with anastomotic or nodal recurrences. The percentage of patients with serosal involvement was 70, and 56% had nodal involvement. An update of this series [39] included 28 patients with serosal (89%) and/or lymph-node involvement (63%), and revealed a 10-year OS of 38%.

Avizonis et al. [37] reported on 27 patients treated with surgery + IORT 12.5–16.5 Gy and EBRT 45 Gy. 70% of the patients had AJCC stages III and IV tumors (90% had JSSS stages III and IV tumors). The 2-year OS was 47%, the 2-year DFS was 27%, and the median survival was 19.3 months. The 2-year OS for the JSSS stage III patients was 48%.

Coquard et al. [40] in a series of 63 patients treated with IORT ± EBRT in the Centre Hospitalier Lyon reported a 5-year OS of 47%, with a median survival of 47 months. Twenty-eight patients were in stages I and II, 29 in stages IIIa and IIIb, and six patients in stage IV. Serosal involvement, with or without adjacent organ invasion (T3 and/or T4), was found in 62% of the cases, and N1/N2 nodal involvement was found in 59%. Most patients were treated surgically with total gastrectomy and proximal (D1) node dissection. A complete resection was performed in 92% of the patients.

Table 12.6 Treatment regimens and outcomes in IORT+EBRT trials for gastric cancer

Author (reference), year, institution	*N*, stage, resection	Radiation dose	EBRT (%)	ChT[a] (%)	LRC, time point	OS, S+IORT
Dulce [35], 1991, Berlin, Germany	26, resectable	IORT 12–16 Gy; EBRT 24–38 Gy[b]	100	n/a	Not reported	Stage III 67%, 2-year
Calvo [36], 1992, U Navarra, Spain	48, AJCC I–IV, recurrent	IORT 15 Gy; EBRT 40–46 Gy[c]	89	27	90%	5-year, T3,4 33%, T1,2 56%
Avizonis [37], 1995, RTOG 85-04, USA	27, AJCC Ib–IV	IORT 12.5–16.5 Gy; EBRT 45 Gy[c]	85	0	63%	2-year 47%, MST 19 months
Chabert [38], 1996, CHU Bellevue, France	21, II–IV	IORT 15–20 Gy; EBRT 28–46 Gy	52	n/a	67%	5-year 32%, MST 19 months
Coquard [40], 1997, Lyon, France	63, I–IV	IORT 15 Gy; EBRT 44–46 Gy[b]	48	17	5-year 76%	5-year 47%
Martinez-Monge [39], 1997, U Navarra, Spain	27, S+ and/or N+	IORT 15 Gy; EBRT 40–46 Gy[c]	100[d]	4	89%	12-year 41%
Glehen [42], 2000, Lyon, France	87, resectable T1-4,N0-2M0	IORT12–23 Gy; EBRT 44–46 Gy	n/a[e]	16	5-year 79% in N+	5-year R0 60%; R0-pN0 90%; R0-pN+ 55%
Skoropad [45], 2000, Obninsk, Russia	78, resectable T1-4,N0-2M0	Phase III study: S vs. EBRT 20 Gy+S/IORT 20 Gy	100	0	Not reported	MST 21 months, 5-year 47%
Weese [41], 2000, Graduate H, USA	15, AJCC IIIA-IV	CAFL[f]+IORT 20 Gy; EBRT 45 Gy	100	100	2-year 93%	MST 21 months, 5-year 40%
Lowy [49], 2001, MDACC, USA	24, AJCC Tx-4	EBRT 45 Gy/F; IORT 10Gy	100	100	Not reported	Not reported
Glehen [44], 2003, Lyon, France	41, N1,N2	IORT 15 Gy; EBRT 45 Gy	86	16	5-year 79%	10-year 45%
Miller [43], 2006, Mayo, USA	50, G&E[g], R0 42%; R1 46%; R2 12%	IORT 10–25 Gy; EBRT 50.4 Gy	96	92	3-year local 90%; 3-year regional 85%	MST 21 months[h], 3-year 27%
Fu [48], 2008, Shanghai, China	97, AJCC T3,4 ±N+	Non-randomized comparison: EBRT 45 Gy/DPF[i] vs. IORT 12–15 Gy+EBRT 39.6 Gy/DPF	100	100	3-year 77%	3-year 56%, MST 38 months

[a]Neoadjuvant chemotherapy or concomitant chemotherapy during EBRT
[b]Four-field technique
[c]Field as derived from University of Minnesota reoperation data
[d]Only stages B2–C3 who completed the radiation course were included
[e]Only given to patients with T3 and/or N+ tumors
[f]Adriamycin, cisplatin, 5-fluorouracil, and leucovorin neoadjuvant chemotherapy
[g]Locally primary advanced of recurrent gastric and esophageal tumors
[h]Primary 3 years; recurrent 1.3 years ($p<0.05$)
[i]Docetaxel, cisplatin, 5-fluorouracil, and leucovorin chemoradiation
N patient numbers, *LRC* local-regional control, *OS* overall survival, *MST* median survival time, *S* surgery, *ChT* chemotherapy, *EBRT* external beam irradiation, *IORT* intraoperative irradiation

Thirty patients (48%) received postoperative EBRT through a four-field technique, to a total dose of 44–46 Gy, selected for the patients with poor pathological features in the surgical specimen (serosal and/or nodal involvement). Multivariate analysis demonstrated that the amount of residual disease, TNM stage, and pN and pT extent correlated with OS.

Glehen et al. [42] updated the results of the previous experience in the Centre Hospitalier Lyon including 87 patients T1-4N0-2M0 who underwent surgical resection for gastric ACA combined with IORT of 12–23 Gy. A R0 surgical resection was performed in 82 patients, and five underwent R1 resection. Patients with pT3 and/or pN tumors underwent EBRT with a standard dose of 44–46 Gy. The 5-year OS for all R0 patients was 60% (R0pN0 – 90%, R0pN+ – 55%).

Skoropad et al. [45] showed no survival difference among patients treated in a phase III trial that compared surgery alone with a combination of 20 Gy of preoperative EBRT in five treatments followed by surgery and 20 Gy of IORT ($p=0.311$). When selected subgroups of patients according to most important prognostic factors were compared, no difference in survival between the treatment groups was seen in N0 cases and T1–2 cases. In contrast, combined treatment had a survival advantage in more advanced stages: when lymph nodes were involved ($p=0.04$) and when tumor penetrated through the gastric wall ($p=0.04$). There was also a survival advantage when patients with stages II and IIIa were compared ($p=0.04$). Median survival was also better in the experimental group, 21.4 vs. 9.05 months, although the difference was not significant ($p=0.083$).

Miller et al. [43] reported the results of a group of 50 patients who received IORT for locally advanced primary or recurrent gastric or esophageal adenocarcinomas deemed unresectable for cure. IORT of 10–25 Gy was given after maximal tumor resection (R0 in 42%, R1 in 46%, and R2 in 12%). Forty-eight patients (96%) also received EBRT (median dose 50.4 Gy) and 46 (92%) had concurrent chemotherapy. Overall survival at 1, 2, and 3 years was 70, 40, and 27%. Median survival for patients with recurrent disease vs. primary disease was 3 vs. 1.3 years ($p<0.05$). There was a close to significant relationship between quality of resection and survival. Although no significant difference in OS was seen on the basis of extent of residual disease at the time of IORT ($p=0.09$), patients with R0 resection after preoperative chemoradiation had better survival. The median survival for patients with R0, R1, and R2 resections was 2.4, 1.2, and 1.1 years, respectively.

Fu et al. [48] reported on 97 patients with newly diagnosed stage T3, T4, or N+ adenocarcinoma of the stomach treated with gastrectomy and D2 lymph node dissection followed by either 12–15 Gy of IORT + EBRT 39.6 Gy with concomitant docetaxel, cisplatin, 5-fluorouracil, and leucovorin ($n=46$) or chemoradiation only with 45 Gy of EBRT with the same chemotherapy regimen ($n=51$). The use of IORT was determined by patient preference and availability of the facility at surgery without randomization. After a median follow-up of 24 months, the 3-year overall survival and disease-free survival rate was 47 and 36% in the EBRT group and 56 and 44% in the EBRT + IORT group, respectively ($p=$ ns), although multivariate analysis revealed that adjuvant IORT was an independent prognostic factor for overall survival ($p=0.04$). Multivariate analyses revealed that pN and pT categories were independent prognostic factors for overall survival ($p<0.05$).

Patterns of Relapse

Local-Regional

After Surgery + IORT (Table 12.2)

Sindelar et al. [34] in a NCI randomized trial described an overall locoregional failure rate of 44 vs. 92% for the IORT vs. surgery ± EBRT arms ($p<0.001$). The time to local failure was longer

in the IORT arm (25 vs. 18 months), but this difference was not significant. However, the time to overall failure was longer in the EBRT arm (16 vs. 12 months) with the differences again lacking statistical significance. The incidence of tumor bed recurrence was lower in the IORT group, 31 vs. 80%. These authors considered those occurring in the abdomen, retroperitoneum, thorax, and peritoneal surfaces as locoregional failures. All relapses were verified by biopsy or laparotomy, and all patients who died were autopsied unless a complete verification of the actual extension of the recurrent disease had been carried out within the three previous months. Three noncancer-related deaths in the IORT group at 1, 5, and 32 months were censored as free of local failure. However, even if these patients had ultimately relapsed, the advantage for the IORT arm would remain considerable.

Farthmann et al., Freiburg University [29], in a preliminary study, described only one case of local failure among 14 patients dead with disease in a series of 36 patients. The treatment was surgery plus IORT of 25–28 Gy.

Drognitz et al. [33] showed a 9.8% locoregional relapse rate in a cohort of 61 patients treated with IORT of 23 Gy who were compared with a similar group of 61 patients treated with surgery alone. Unfortunately, locoregional control rates were not evaluated in the non-IORT group.

After Surgery + IORT ± EBRT (Table 12.6)

Calvo et al. [36] described a locoregional failure rate of 10% of 48 patients included in the series of the University of Navarra. This report describes the whole institutional experience, including 16 patients with AJCC tumor stages I–II and 8 patients with recurrent disease (four anastomotic, four nodal). Martinez-Monge et al. [39], updating the previous series for only 28 patients with serosal and/or nodal involvement and treated homogeneously with IORT 15 Gy and EBRT 40–46 Gy, reproduced the same results, with a locoregional failure rate of 11% projected at 12 years.

Avizonis et al. [37] reported a local failure rate of 37% (isolated 15%, combined 22%) in the patients included in the RTOG trial 85-04. The relapses were documented mainly clinically. In this series, 70% of the patients had AJCC stages III and IV. Local failure appeared in 43% of the patients with serosal involvement, in 42% of the patients with positive nodes, and in 63% of the patients presenting with linitis plastica.

Coquard et al. [40] reported a 5-year local failure rate of 24% that was not improved with the addition of selective EBRT in patients with the high-risk pathological features of serosal and/or nodal involvement (62% of patients had serosal involvement [T3 or T4] and 59% had N1 or N2 nodal involvement).

Miller et al. [43] reported a 4% local failure rate and a 12% regional failure rate in a series of 50 patients who received IORT for locally advanced primary or recurrent gastric or esophageal ACA deemed unresectable for cure. Forty-eight patients (96%) also received EBRT (median dose 50.4 Gy) and 46 (92%) received concurrent chemotherapy. The use of concurrent chemotherapy showed a decrease in the rate of regional failure ($p < 0.001$), but not in the rate of central, local, or distant failure.

Fu et al. [48] reported a 23% locoregional failure rate in a cohort of 46 patients treated with 12–15 Gy of IORT after D2 gastrectomy, followed by postoperative EBRT to 39.6 Gy plus concurrent and maintenance chemotherapy with docetaxel, cisplatin, 5-fluorouracil, and leucovorin. The control group of 51 patients had a higher 3-year locoregional failure rate of 37% ($p = 0.05$). Multivariate analysis revealed that adjuvant IORT was an independent prognostic factor for locoregional control ($p = 0.02$). Other significant prognostic factors for locoregional control included the existence of residual disease (R0 vs. R1 resection; $p = 0.005$) and pN disease (pN0, pN1, pN2, pN3; $p = 0.03$).

Distant Failure

Calvo et al. [36] described a rate of distant metastases of 32% (peritoneal carcinomata was included under distant metastases) in a series of 48 patients treated with IORT in the University of Navarra. Martinez-Monge, in an update of the former study, reported a distant hematogenous metastases rate of 18.5% and an incidence of peritoneal metastases of 26%. Avizonis reported distant metastases in 48% of the patients (isolated 26%, combined 22%).

Farthmann et al., Freiburg University [29], described distant metastases or peritoneal dissemination as the main pattern of failure in a series of 36 patients treated with surgery + IORT 25–28 Gy. In this series, 13 of 14 patients who died of disease and 2 among 21 alive at the time of analysis had distant and/or peritoneal failure. A further analysis of this series [33] revealed the development of distant metastasis and peritoneal spread in 19.7 and 31.8% of the IORT-treated patients, respectively. Data on patterns of failure in the non-IORT control group was not shown in the chapter.

Coquard et al. [40] reported a 24% incidence of distant metastases in a series of 63 patients treated with IORT ± EBRT. Thirteen percent of the patients developed peritoneal carcinomata and 11% visceral metastases.

Glehen et al. [44] described the use of IORT + EBRT in a series of 42 N1–2 patients treated at Lyon. At 5 years, five patients had a local celiac recurrence (12%), and 12 had distant metastases with no evidence of celiac recurrence.

Miller et al. [43] showed that distant failure was the most common mode of failure (39 patients, 78%) in a series of 50 patients with locally advanced and recurrent gastric and esophageal malignancies treated with IORT + EBRT at the Mayo Clinic. The most common sites of distant failure were the peritoneum (39%), lung and pleura (32%), liver (37%), lymph nodes (12%), and other sites (34%). The use of concurrent chemotherapy did not decrease the rate of distant failure.

Preclinical Tolerance Studies

Pancreatic Function

Ahmadu-Suka et al. [50, 51] described an experiment in which the pancreas and duodenum of Beagle dogs were treated with IORT doses of 17.5–40 Gy. Fractionated EBRT was added postoperatively to 50 Gy. Only one dog experienced exocrine pancreatic insufficiency at an IORT dose of 25 Gy. On light microscopy, the number of surviving acinar cells and the degree of pancreatic fibrosis were proportional to the IORT dose.

Heijmans et al. [52] described an experimental protocol in which Beagle dogs were irradiated with IORT doses of 25.3 or 35 Gy to the upper abdominal structures. Applicators of 6–7 cm in diameter were used with 6–8 MeV electron beams. The irradiated structures included the pancreas and the medial wall of the duodenum. Two out of 15 dogs developed toxicity (13%). One had a common bile duct stenosis, and the other had an enterocolic fistula after 8 and 18 months of follow-up, respectively. None of the treated dogs developed exocrine insufficiency, diabetes, or pancreatitis. However, subclinical diabetes, manifested by decreased insulin plasma levels and lowered glucose clearance rates, was detected in the dogs irradiated at 30 and 35 Gy IORT ($p = 0.05$) doses without significant alterations at 25 Gy.

Vascular Tolerance

Johnstone et al. [53] reported a NCI study in which 30 dogs were treated with IORT doses of 0–30 Gy immediately after segmental resection of the infrarenal aorta followed by reconstruction

with a prosthetic graft. Half of the dogs received EBRT dose of 36 Gy. Anastomotic stenosis was observed in most of the animals followed for more than 6 months. This was correlated with the IORT dose. At an IORT dose of ≤20 Gy, 3 of 14 dogs developed graft occlusion, while at IORT doses >25 Gy, five of six dogs developed late graft occlusion.

Tepper et al. [54] studied the effect of IORT on aortic anastomosis in dogs. Animals were irradiated with IORT doses of 20, 30, and 45 Gy. There was no evidence of suture line weakening regardless of the IORT dose used, but some dogs developed anastomosis obstruction and arteriovenous fistula with IORT doses between 20 and 45 Gy during the first year of follow-up.

Gillette et al. [55] from the University of Colorado studied the response of intact aorta and its branches to IORT, EBRT, or combined IORT + EBRT. IORT doses were from 10 to 47.5 Gy when combined with 50 Gy of EBRT (25 fractions/5 weeks) and from 17.5 to 47.5 Gy when delivered alone. Dogs treated with EBRT alone received fractionated EBRT, 60–80 Gy in 30 fractions over 6 weeks (2–2.67 Gy/fraction). At 2 years, there was a high frequency of arteritis and necrosis of the media of branch arteries (only rarely obstructed) at IORT 20 Gy or IORT 15 Gy + 50 Gy EBRT. The ED50 for obstruction greater than 50% of the lumen at 5 years was 24.8 Gy with IORT alone or 19.4 Gy if IORT was combined with 50 Gy EBRT.

Gastric Mucosa Tolerance and Gastric Wall Healing

Kramling et al. [56] reported the tolerance of gastric mucosa to EBRT using a rabbit model in which animals received IORT to the celiac axis of 0–40 Gy. This was followed by EBRT dose of 32–52 Gy in 4 Gy fractions. The authors reported an earlier development of gastric ulcers with EBRT in the animals previously treated with IORT. They concluded that IORT to the celiac axis probably produced a reduction in the blood flow of abdominal organs that decreased the tolerance to EBRT.

Grab et al. [57], using the same model, reported the dynamics of wound repair in the stomach of rabbits treated with IORT + EBRT. At the time of surgery + IORT, the rabbits underwent full-thickness incision and *per prima* suture. The success of wound healing was measured using the wound breaking strength and the collagen types I and III content as end points. All the parameters were found to be lower in the IORT-treated rabbits. The authors concluded that IORT probably produced a reduction in the blood flow of abdominal organs that might be responsible for mucosal, vascular, or anastomotic complications.

Clinical Tolerance, Gastric IORT Series

Pancreatic Function

A short-term assessment of pancreatic function after IORT was performed by Abe et al. [27] at the Kyoto University. A temporary increase in the levels of pancreatic amylase and blood glucose was found after IORT, which returned to normal during the first week after the procedure.

Qin et al. [31] evaluated acute and late damage to the pancreas by assessing the changes in serum amylase and blood glucose levels after IORT. Temporary increases in both serum amylase and blood glucose occurred after IORT, but they returned to preirradiation levels within a week.

Pancreatic function has also been studied in long-term survivors after IORT. Aristu et al. [58] studied the pancreatic function of ten patients (minimal follow-up 2 years) treated at the University of Navarra with gastrectomy, IORT 15 Gy and EBRT 45–46 Gy. A healthy control group was used as baseline for comparison. A glucagon test and an intravenous glucose tolerance test were performed along with LDH, serum and urine amylase, and serum lipase determinations. Basal C-peptide levels were similar between groups, but the incremental and peak values were inferior in

the IORT group ($p<0.01$). Similarly, the basal glycemia and insulinemia did not differ between groups, but the 30- and 60-min glycemia were higher in the IORT group and the 30 and 60 min insulinemia were lower. However, exocrine pancreatic function in IORT patients remained similar to controls. These findings indicate that exocrine pancreatic function is not affected by IORT + EBRT, but endocrine pancreatic function appears to be impaired at the subclinical level.

Gastrointestinal Bleeding: Vascular Toxicity

Calvo et al. [36] reported six cases of gastrointestinal bleeding (GI) among 48 patients treated with gastrectomy + IORT at the University of Navarra (12.5%). Most received additional EBRT. In three of the cases, an arterioenteric fistula could be documented [59]. In a subsequent report of this series, where only patients with serosal and/or nodal involvement were included, the incidence of GI bleeding remained the same [39]. Sindelar et al. [34], in an NCI randomized trial, reported two cases of GI bleeding out of 16 patients (12.5%) included in the IORT arm. Kim et al. [60] reported three cases of GI bleeding in 53 patients (6%) treated with surgery + IORT + EBRT + chemotherapy. Coquard et al. [40] reported two cases (3%) of gastrointestinal bleeding at 3 and 6 months follow-up in a series of 63 patients treated with IORT ± EBRT. Both patients were treated with IORT 15 Gy and did not receive any EBRT. Only one of the patients was laparotomized, and no evidence of recurrent tumor was found. Japanese authors [2, 3] have never reported vascular toxicity in their series.

In a attempt to address the long-term status of upper abdominal vasculature after IORT ± EBRT, Aristu et al. [61] studied ten long-term survivors (minimal follow-up 2 years) treated at the University of Navarra with gastrectomy, IORT 15 Gy, and EBRT 45–46 Gy. The study was done performing selective and nonselective angiography of the celiac trunk, mesenteric artery, and renal arteries with late venous phases to visualize the portal vein and its branches. There were no significant changes attributable to IORT. However, six patients developed renal hypoperfusion and four left hepatic lobe hypoplasia. These lesions matched with the shape of the EBRT portal and were attributed to the delivery of EBRT (Fig. 12.5).

Fu et al. [48] reported that three patients (6.5%) treated with IORT12–15 Gy followed by 39.6 Gy of EBRT combined with docetaxel, cisplatin, 5-fluorouracil, and leucovorin chemotherapy developed grade 3 or 4 upper gastrointestinal hemorrhage. Peptic ulcers were found by endoscopic examination, and all 3 patients recovered after medical treatment. Surgical intervention was not required. No patient treated without IORT developed severe late toxicity.

Vertebral Toxicity

Calvo et al. [36] described six cases of partial vertebral collapse (vertebrae lying within the IORT/EBRT fields) in a series of 48 gastric patients treated with IORT at the University of Navarra. This clinical finding has also been described in some gynecologic series where the para-aortic region was treated with IORT due to nodal involvement. Previous clinical reports have also indicated the presence of mild hypocellularity in the vertebrae of patients treated with IORT for upper abdominal malignancies [62].

Soft-Tissue Toxicity

Sindelar et al. [62] reported the soft-tissue changes of an overall group of patients treated with IORT to the upper abdomen for miscellaneous malignancies, mainly gastric and pancreatic tumors. They

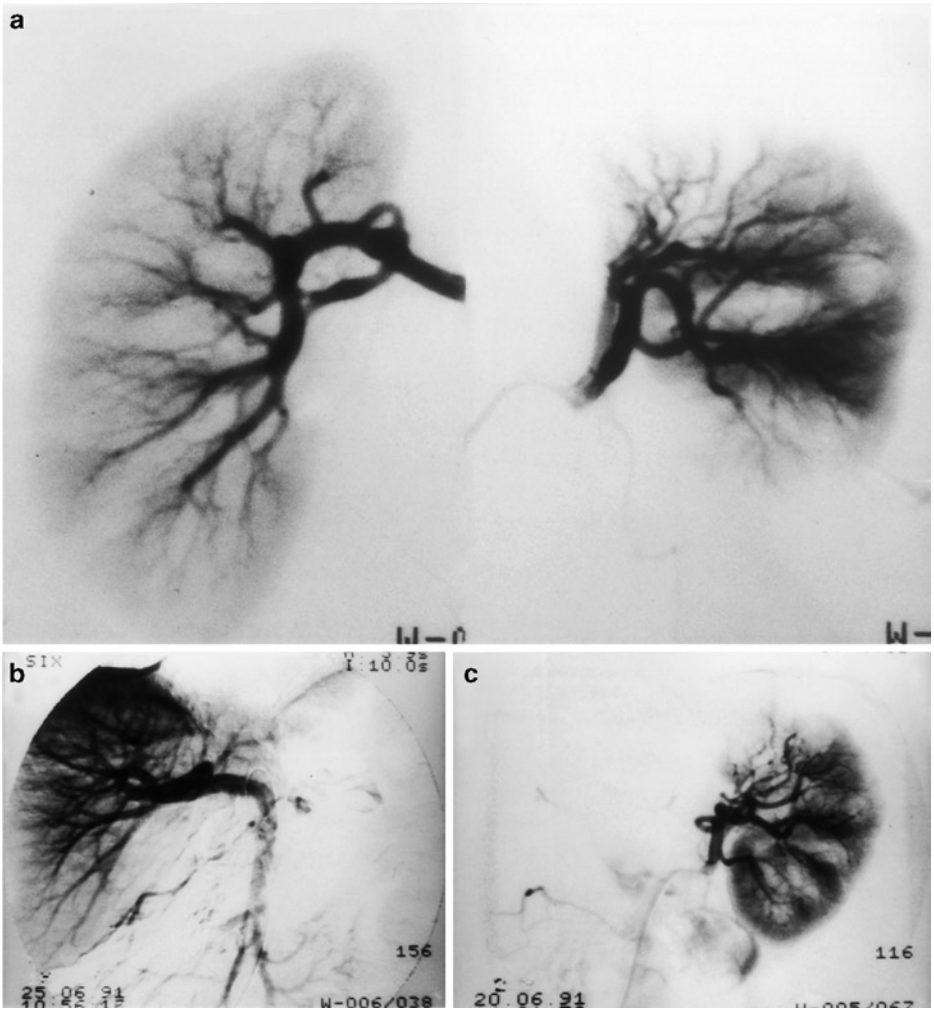

Fig. 12.5 Upper abdominal vasculature in long-term survivors after IOERT ± EBRT for gastric cancer at the University of Navarra, Pamplona. (**a**) Normal appearance of right kidney but abnormal vessels in the upper pole of the left kidney (within EBRT field). (**b**) Hypoplasia of the left hepatic lobe and left portal vein. (**c**) Hypoperfusion of the upper pole of the left kidney.

described mild fibrotic changes in the retroperitoneal soft tissues as well as fibrosis in the soft tissues around the porta hepatis and perineural fibrosis.

Small-Bowel Toxicity

Abe described three cases of small-bowel ulceration due to accidental movement into the IORT field during the procedure [2]. Small bowel should be always retracted away from the IORT target volume during the IORT procedure because of its limited tolerance. Calvo et al. [36] reported nine cases of enteritis in 48 patients treated with surgery + IORT + EBRT (19%). Five of them (10%) required surgery. Avizonis et al. [37] reported one case of small-bowel obstruction in 27 patients treated with IORT + EBRT (4%). Kim et al. [60] reported three cases of small-bowel obstruction in

53 patients treated with IORT + EBRT (5%). No small-bowel complications have been reported in series using IORT alone. The incidence of small-bowel obstruction requiring surgical intervention following surgery-alone procedures in the abdomen or pelvis ranges from 5 to 10%, which is similar to the results reported in series combining surgery + IORT/EBRT.

General Toxicity

In a randomized gastric trial comparing IORT vs. observation, Kramling et al., University of Munich [30], described enhanced mortality (8 vs. 2%) and morbidity (35 vs. 28%) in the IORT arm compared to the surgery-alone arm. These differences were not statistically significant. In the other randomized trial by Abe et al. [2], the toxicity results were only scarcely reported.

The NCI randomized gastric trial compared surgery + IORT 20 Gy with surgery ± EBRT [34]. The overall incidence of complications was 56%; included two fistulae, one mesenteric thrombosis, four abdominal abscess, four anastomotic strictures, and one biliary stricture. Four patients ultimately died of complications. However, the authors did not find a correlation between the observed toxicities and IORT. Moreover, the control group (in which most of the patients received EBRT) suffered a higher rate of complications (72%). This difference was not statistically significant.

Avizonis et al. [37], reporting the RTOG gastric trial 85-04, described the toxicity encountered in 27 gastric cancer patients treated with surgery, IORT 12.5–16.5 Gy (median 13.75 Gy) and EBRT (85% of the patients). Major postoperative complications were found in 15% of the patients, including one pancreatic fistula and one postoperative death resulting from necrotizing pancreatitis. Long-term complications were observed in 14% of the patients with one death probably related to necrotizing pancreatitis.

Ogata et al. [3] reported three cases of wound infection and two cases of suture leakage in a group of 58 gastric patients treated with surgery and an IORT dose of 28–30 Gy. Kim et al. [60] reported two cases of sepsis in a series of patients treated with IORT + EBRT (45 Gy) + chemotherapy.

Farthmann et al. [29] described a 5% perioperative mortality rate in a series of 36 gastric patients treated with surgery + IORT 25–28 Gy in the Freiburg University. The morbidity rate was 20%. Postoperative complications in the upper abdominal structures included five cases of anastomotic leakage/gastrointestinal bleeding, four cases of pancreatic fistula/necrosis, and one case of mesenteric vein thrombosis.

Chabert et al. [38] reported two deaths at 2 and 3 months after surgery due to anastomotic leak and sepsis in a series of 21 gastric patients treated with surgery + IORT 15–20 Gy ± EBRT. Other complications reported were pancreatic fistula, colic perforation, and sepsis in one patient each. One patient died at 6 months after sepsis and massive hemorrhage.

Coquard et al. [40] reported a 4.8% postoperative mortality rate in a series of 63 stage I–IV patients treated with 15 Gy of IORT ± 44–46 Gy of EBRT. An update of this series of 87 cases by Glehen et al. [42] revealed a postoperative mortality rate of 2.3% and a postoperative morbidity rate of 6.8%.

Drognitz et al. [33] found that overall major surgical complications were significantly more common in the IORT group than in the non-IORT group (44.3 vs. 19.7%; $p < 0.05$). This was mainly caused by an overrepresentation of pancreatitis (8.2 vs. 0%), abdominal or intestinal bleeding (8.2 vs. 3.3%), and anastomotic leakage (16.3 vs. 8.2%) in the IORT group, although none of these adverse events reached statistical significance individually. Perioperative mortality was similar in both groups (4.9 vs. 4.9%, p = ns).

Qin et al. [31] did not report significant late complications or deviation from the usual postoperative course in a series of 106 patients treated with 10–30 Gy IORT. There was no instance of delayed wound healing. One patient died from cardiac infarction, resulting in a death rate of 0.9% (1 out of 106). Recovery of gut function in all of the patients with IORT was delayed for 24 h.

Miller et al. [43] reported a 26% late toxicity rate of grade 3 or greater in a series of 50 patients with gastric or esophageal patients treated with 10–25 Gy of IORT and postoperative chemoradiation. Three grade-4 late complications were noted including pulmonary ARDS ($n=2$), vascular ($n=1$), and one grade-5 event due to small-bowel obstruction.

Skoropad et al. [45] reported complications in the immediate postoperative period in 15 (35%) patients of the experimental group and in 19 (50%) patients of the control group in a randomized study of preoperative EBRT followed by surgery and an IORT dose of 20 Gy vs. surgery alone. The difference was mostly caused by a higher incidence of postoperative pancreatitis after surgery. No statistics were performed to evaluate statistical significance.

Discussion, Conclusions, and Future Possibilities

Toxicity

EBRT is an appropriate component of treatment for resected high-risk gastric cancers. However, the total dose that can be delivered even with the most sophisticated EBRT techniques (3D conformal or intensity-modulated irradiation [3D CRT, IMRT]) is limited by the presence of surrounding organs or structures including the small bowel, stomach, liver, kidney, and spinal cord (also lung and heart for GEJ lesions). As a rule, an EBRT dose of 45–50 Gy delivered with standard fractionation and concurrent 5FU or capecitabine-based chemotherapy in the postoperative R0 resection gastric cancer setting achieves local control in 80–90% of the patients with a 5–10% risk of small-bowel or gastric complications. If residual disease is left after surgery (R1 or R2 resection), the increase in EBRT dose needed to achieve similar control rates will be accompanied by an increase in small-bowel or gastric complication rates. The INT 0116 gastric adjuvant trial [26] used EBRT doses of 45 Gy in 25 fractions over 5 weeks along with concurrent and maintenance 5FU/leucovorin chemotherapy following R0 resections and reported a 7% local failure rate. For gastric and other gastrointestinal (GI) malignancies, a delicate balance exists between the EBRT dose required for control of disease and the tolerance dose of small bowel and stomach.

EBRT portals for gastric cancer, as derived from the University of Minnesota reoperation series, encompass a significant volume of normal tissues (bilateral kidneys, liver [mainly left lobe], stomach, small bowel, spinal cord). With GEJ cancers, lung and heart are also within EBRT treatment fields. If multiple-field EBRT techniques are used with adjuvant doses of 45–50.4 Gy in 1.8 Gy fractions over 5–5.5 weeks, long-term risks to liver, kidneys, heart, lung, and spinal cord are minimal [47]. Small bowel and stomach (if present) are the main radiation dose-limiting structures in the postoperative target volume for gastric cancer.

The main advantage of using IORT during gastric cancer surgery is the ability to displace uninvolved stomach and small bowel out of the area to be irradiated. If EBRT doses in the range of 55–70+ Gy are needed to treat the gastric bed, because of residual microscopic or gross disease after an R1 or R2 resection, combined IORT plus EBRT is probably the only means of achieving local disease control with acceptable gastric and small-bowel tolerance.

As noted in the previous section, however, IORT alone or combined with EBRT and gastric resection has the potential for both acute and chronic toxicity. Investigators need to understand the tolerance of organs and structures that may be in an IORT field including pancreas and blood vessels. Anastamoses should be excluded from the IORT field if they involve the alimentary tract (esophagus, stomach, and small intestine) or bile duct.

Arterial stumps may be included in the IORT volume, but the radiation tolerance of arterial stumps (IORT alone or plus EBRT) has not been studied in the experimental setting. Animal studies

on large vessels suggest that IORT does not decrease the suture line strength of anastomosed aortas. Calvo et al. [36] reported six cases of GI bleeding among 48 patients treated with gastrectomy + IORT; most of them received additional EBRT. In three of the cases, an arterioenteric fistula between a vascular stump and the surrounding small bowel could be documented [59]. An update of this series included only the IORT patients that completed EBRT and a group of 35 patients treated with EBRT only that served as a control [39]. There were three cases of gastrointestinal bleeding in the IORT + EBRT group, but none in the EBRT only group. If vascular stumps have to be in an IORT field, they should be covered with omentum prior to surgical closure, to lessen the risk of adhesions between the vascular stump and intestine to decrease the risk of postoperative morbidity including arterioenteric fistulae.

In summary, there is no compelling evidence that patients entered in IORT trials are at a higher risk of perioperative morbidity and mortality than patients treated with surgery alone. However, preclinical and clinical data suggest that IORT treatment, alone or combined with EBRT and surgical resection, may produce postoperative complications. Well-conducted, controlled clinical trials are needed to address this issue.

Local Control

The average local or locoregional control rate reported in IORT-alone and IORT + EBRT trials ranges from 56 to 97% [29, 33, 34] and from 63 to 93% [36–41, 43, 44, 48], respectively. The results of the IORT series suggest that adjuvant IORT ± EBRT is superior to surgery alone in terms of local control. Although local control in IORT series can be overscored due to the inherent difficulty in diagnosing local failures in the upper abdomen after surgery and radiation, the number of patients free of local disease present in the IORT ± EBRT series clearly outweighs the same figures for the historical surgical series.

The series from Fu et al. provides some evidence that IORT + chemoradiation improves local control when compared with standard postoperative chemoradiation [48]. In this nonrandomized study, a 23% locoregional failure rate was found in a cohort of 46 patients (T3, T4, N+) treated with 12–15 Gy of IORT after D2 gastrectomy followed by postoperative EBRT to 39.6 Gy with concurrent docetaxel, cisplatin, 5-fluorouracil and leucovorin chemotherapy. This compared favorably with a 3-year locoregional failure rate of 37% ($p = 0.05$) in a control group of 51 patients treated with 45 Gy of EBRT and the same chemotherapy. Multivariate analysis revealed that adjuvant IORT was an independent prognostic factor for locoregional control ($p = 0.02$).

Survival

IORT-alone series report 5-year survival rates of 83–100% [3, 28, 31] in stage I–II patients, and of 10–62% [3, 28, 31, 34] in stage III–IV patients. Three randomized trials have studied the survival impact of IORT alone when added to surgical resection. An update of the University of Kyoto trial [2] continued to demonstrate a survival advantage for the IORT arm in the JPSS stages II–IV, although this was not statistically significant. The improved results with IORT were confirmed in a nonrandomized trial from the Kochi Medical School [3] in which the IORT patients were compared with a surgery-alone control group and in stage III patients from the Beijing trial [32]. In Western countries, the University of Munich trial [30] has not demonstrated any survival advantage between the IORT arm and the surgery-alone arm. In this study, the methodology used was similar to the Japanese trials. Similarly, the NCI trial [34] compared a surgery + IORT arm with a surgery ± EBRT

arm and did not find any survival differences. However, none of the stage III–IV patient in the control group survived after a median follow-up of 7 years, while 3 out of 15 in the IORT group were alive NED at the time of the analysis ($p = 0.06$).

More recently, Qin et al. [31] have compared 41 patients treated with gastrectomy and D2–3 lymph node dissection and 10–30 Gy of IORT with 441 patients who were treated by operation alone during the same time period. The 5-year survival rate for patients treated by operation alone was 92.8% for stage I, 80.6% for stage II, 45.1% for stage III, and 10% for stage IV. The 5-year survival rate for patients treated by IORT was 100% for stages I and II, 60.4% for stage III, and 14.3% for stage IV. There was no difference between the survival rates of patients in stages I and IV in the two groups, but the IORT procedure raised the survival of patients with stages II and III ($p < 0.001$ and $p < 0.005$, respectively). Drognitz et al. [33] was not able to find differences in overall survival when a cohort of 61 patients treated with IORT of 23 Gy were compared with a similar group of 61 patients treated with surgery alone.

IORT + EBRT series report 5-year results in the 10–60% range [35–38, 40, 42, 43, 45, 48]. All of these studies are nonrandomized institutional studies, and therefore only an indirect estimation can be made by comparing the survival results of these series with historical surgical results. This is complicated by the fact that some of these studies include patients with either early cancers or recurrent disease. These results are similar to historical surgical series that report 5-year survival results in the range of 10–40% for patients with serosal invasion and/or lymph node involvement (stages B2–C3) [13].

Conclusions

1. IORT is a feasible technique to be incorporated in gastric cancer surgery. There exists a worldwide experience generated over the last 40 years in Asia, Western Europe, and USA.
2. IORT improves local control if added to radical surgery. IORT ± EBRT trials report local failure rates of 3–44%, which are superior to historical surgical controls. IORT + EBRT may have superior local control vs. EBRT or IORT alone. There is indirect evidence from Fu et al. [48] that IORT combined with chemoradiation may improve locoregional control rates compared with chemoradiation alone.
3. IORT alone or combined with EBRT produces 5-year OS of 15–20% after incomplete resections for gastric cancer and may allow salvage of local-regional relapse of gastric cancer when combined with preop chemoradiation and resection (4-year OS ~20%, 5-year OS >10% in Mayo Rochester series).
4. Distant and/or peritoneal dissemination is a common pattern of relapse in IORT trials for gastric cancer and is present in 25–30% of the patients. A more effective form of systemic adjuvant therapy is needed.
5. IORT may produce severe vascular toxicity in the clinical setting of 15 Gy IORT plus 45 Gy fractionated EBRT or at a higher dose of IORT alone. A 3–12.5% GI bleeding rate has been reported in several IORT trials.
6. IORT needs to be studied in the context of recent gold-standard adjuvant chemotherapy (MAGIC trial) or chemoradiation programs (INT 0116).

Future Possibilities

The 23% local-regional failure rate with adjuvant chemoradiation + IOERT reported by Fu et al. is not ideal [48]. Further improvements in local control may be feasible with treatment intensification

or optimization. This might include an increase in adjuvant EBRT doses to the level of 45–50.4 Gy in 1.8 Gy fractions over 5–5.5 weeks, a decrease in the interval between resection/IOERT and EBRT (this interval was not stated in the Fu et al. manuscript), altered sequencing of IOERT and EBRT (i.e., give chemoradiation preop instead of postop with borderline resectable or unresectable disease based on preop imaging), and a change in concurrent chemotherapy or the addition of biologic dose modifiers.

In an attempt to decrease systemic failures, more routine use of neoadjuvant chemotherapy with ECF (or alternate chemo) should be evaluated in view of results seen in the MAGIC adjuvant trial [17]. For patients with locally unresectable or borderline resectable disease on the basis of preoperative imaging, evaluation of preop chemotherapy plus preop chemoradiation is reasonable.

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Chapter 13
Pancreas Cancer

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Keywords pancreas cancer • IORT for pancreas cancer • ISIORT-Europe pooled analysis

Non-IORT Results, Local Control, and Survival

Resectable Pancreas Cancer

Despite its infrequency, pancreatic cancer is the fourth leading cause of cancer death in USA with an estimated 42,140 new cases and 36,800 deaths projected in the USA for 2010 [1]. Although mortality rates have slightly improved in recent years, overall, outcomes after surgical resection remain poor despite attempts to improve survival through multimodality therapy including extended lymphadenectomies and novel biologic agents in addition to conventional neoadjuvant and adjuvant chemotherapy and radiotherapy. Surgery remains the mainstay of potentially curative therapy, although few patients, 10–15%, present with resectable disease. Figure 13.1 illustrates an unresectable head of pancreas carcinoma where resection is impossible because of vascular encasement. Survival in most large surgical series remains less than 20% for long-term survivors [2–5].

For the last four decades, radiochemotherapy- and chemotherapy-alone strategies have been employed as adjuvant therapies to surgery in an effort to improve survival. The optimal regimen remains strongly debated, with a combination of chemotherapy and radiotherapy being favored in USA, following the success of the Gastrointestinal Tumor Study Group (GITSG) trial in the 1970s and

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_13,

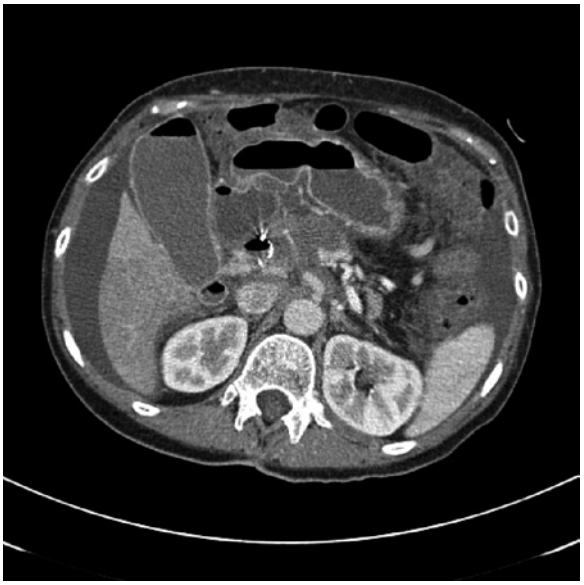

Fig. 13.1 Computed tomography image of encasement of the celiac axis.

the US GI Intergroup trial (RTOG 9704) in more recent years. Chemotherapy alone with gemcitabine (Gem) has become more popular in Europe in the last decade, following trials by the European Organization for Research and Treatment of Cancer (EORTC) and the European Study Group for Pancreatic Cancer trial-1 (ESPAC-1) that questioned the utility of radiotherapy in the adjuvant setting for pancreas cancer [6–9]. The Charité Onkologie trial demonstrated improved outcomes with patients receiving six cycles of Gem chemotherapy postoperatively in comparison to those receiving none following pancreatic carcinoma resection [10]. See Table 13.1 for a summary of recent major trials in adjuvant chemoradiation for pancreas cancer.

Patients undergoing potentially curative resection of pancreatic cancer are at high risk for systemic metastatic failure, with disease commonly spreading to the liver, peritoneal surface, and other organs. This pattern of failure has led many to focus on systemic aspects of adjuvant therapy to raise the low rate of survival following surgery [2, 11–13]. However, many patients also are at risk for concurrent or isolated local and regional failure of their malignancies [14–18]. Enthusiasm for extended lymphadenectomy, following early reports of success from Japanese investigators, has waned [16, 19–25]. Hiraoka has reported that extended resection did not reduce the risk of local recurrence without the addition of intraoperative irradiation (IORT) [21, 22].

Unresectable Pancreas Cancer

For decades, the standard approach in USA to treatment of locally advanced pancreatic carcinoma has been external-beam radiotherapy (EBRT) combined with concurrent 5-Fluorouracil (5-FU) chemotherapy. This approach has shown superior benefits to palliative interventions with median survival increasing from 3 to 6 months with observation or palliation to 9–13 months with definitive therapy. Local control with conventional EBRT with chemotherapy remains poor despite lengthened survival with only 30% having locally controlled disease in a series from Thomas Jefferson hospital [26–28].

More recently, combination of conventional EBRT with concurrent Gem in addition to Gem alone has demonstrated promise in improving outcomes. However, outcomes remain poor with even

Table 13.1 Adjuvant chemoradiation studies in patients with resectable pancreas cancer

Institution or Group (Ref no./year)	Adjuvant intervention	No. patients	EBRT dose (Gy)	Chemo agents	Survival			
					Median (months)	2-year	5-year	*p* Value
Postop EBRT ± 5-FU								
GITSG [6] (1985)	*RT/Chemo*	21	40	*5-FU*	20	43	19	$p<0.05$
	Observation alone	22	0	None	11	15	5	
GITSG (confirmation phase) [72] (1987)	RT/Chemo	30	40	5-FU	18	43	–	
EORTC [7] (1999)	*RT/Chemo*	107	40	*5-FU*	17.1[a]	37	20	$p=0.10$[b]
	Observation alone	103	0	None	12.6	23	10	
ESPAC-1 [8] (2001)	RT/Chemo + Adj Chemo	72	40	5-FU	19.9			
	RT/Chemo alone	73	40	5-FU	13.9			
	Adj Chemo alone	75	0	5-FU	21.6			
	Observation	69	0	5-FU	16.9			
Mayo-Hopkins Collaborative Study [73] (2008)	*RT/Chemo*	583	≥45/25*Fx*	*5-FU*	21.1	44.7	22.3	$p<0.001$
	Observation	509	0	None	15.5	34.6	16.1	
Preop EBRT ± 5-FU								
Fox Chase [74] (1998)	RT/Chemo	24	50.4/28Fx	5-FU, Mito C	16	–	–	
MDACC [75] (2009)	RT/Chemo	79	30/10Fx	Gem ± CDDP	18.7	–	–	

EBRT external-beam irradiation, *GITSG* Gastrointestinal Tumor Study Group, *5-FU* 5-fluorouracil, *Gem* gemcitabine, *MDACC* M. D. Anderson Cancer Center, *Adj chemo* adjuvant chemotherapy

[a]Pancreatic patients only

[b]1-sided $p=0.049$

this approach with progression-free survivals reported of 6.3 months and median survival times of 11.0 months with concurrent RT and Gem [29].

Stereotactic radiosurgery has been used in the experimental setting to obtain high rates of local control in patients with locally advanced and metastatic disease, but with no gains in survival when compared with standard chemoradiation (EBRT plus 5-FU or Gem). Stanford University has reported a median survival of 11.9 months with patients who received a single 25 Gy fraction of radiosurgery [30].

IORT Pretreatment Evaluation and Treatment Factors

Pretreatment Clinical Staging (Radiographic)

Tumors of the pancreas are unlike other solid tumors of the gastrointestinal tract in that accurate diagnosis, clinical staging, and treatment require extensive interaction and cooperation between physicians of different specialties (diagnostic radiologist, interventional upper endoscopist, surgeon, medical oncologist, and radiation oncologist). Accurate clinical staging requires high-quality (helical) multidetector computed tomography (CT) with advanced volumetric techniques to accurately define the relationship of the tumor to the celiac axis and superior mesenteric vessels in three dimensions. In the absence of extrapancreatic disease, the relationship of the low-density tumor mass to the superior mesenteric artery (SMA) and celiac axis is the main focus of preoperative imaging studies. The current availability of accurate preoperative imaging studies forms the foundation for two basic principles of clinical research when investigating new therapeutic strategies in patients with pancreatic cancer. Endoscopic ultrasound-guided needle biopsy is a preferred method of diagnosis. Endoscopic retrograde cholangiopancreatography may be of use in decompression of the biliary tract in patients with jaundice or pruritus [31].

First, local tumor resectability is most accurately assessed preoperatively; intraoperative exploration is an inaccurate means of assessing critical tumor–vessel relationships [32, 33]. Objective, reproducible radiographic criteria define potentially resectable disease as (1) the absence of extrapancreatic disease, (2) the absence of superior mesenteric vein (SMV) or portal vein encasement, abutment or distortion, or associated thrombi and presence of a patent SMV–portal vein confluence, and (3) distinct fat planes around SMA, celiac axis, and hepatic artery. The accuracy of this form of radiographic staging is supported by a report by Spitz et al., demonstrating a resectability rate of 80% (94/118) and a low rate of microscopic retroperitoneal margin positivity (17%) [34]. The accuracy of CT in predicting unresectability and the inaccuracy of intraoperative assessment of resectability are both well established [32, 35]. Pretreatment staging to exclude patients with locally advanced disease is critical to allow accurate interpretation of results from studies examining the value of multimodality therapy in patients with pancreas cancer. Borderline resectable tumors, which may benefit from neoadjuvant therapy, include tumors with (1) abutment or encasement of the SMV/portal vein without arterial involvement in which sufficient vessel is present proximally and distally to permit resection and venous reconstruction, (2) gastroduodenal artery encasement without extension to the celiac axis and with or without abutment or minor encasement of the hepatic artery, (3) abutment of less than 180° of the SMA [31].

Second, published data demonstrate that only patients who undergo a negative-margin pancreaticoduodenectomy receive a survival benefit from surgical resection of the primary tumor [32, 36]. The median survival of 8–11 months in patients who undergo pancreaticoduodenectomy and are found to have a positive margin of resection is not more different from the median survival reported for patients with locally advanced disease treated with definitive chemoirradiation without surgical resection of the pancreas. However, few studies differentiate between grossly positive and microscopically positive margins. The effect of IORT with or without EBRT on microscopically positive

margins is not known. The margin most frequently reported as positive in patients who undergo pancreaticoduodenectomy is along the SMV or proximal SMA. Studies that examine the use of IORT following pancreatic resection, in which survival and local control are analysis end points, should accurately document the pathologic status of the retroperitoneal margin of resection.

External-Beam Irradiation Factors

For patients with borderline resectable or unresectable cancers, pre-op EBRT plus concurrent chemotherapy is preferably given prior to exploratory laparotomy and possible surgical resection/IORT. EBRT is typically delivered through multiple fields (3D conformal irradiation or intensity-modulated irradiation [3D-CRT; IMRT]) on a daily basis over a period of 5–6 weeks at a dose of 45.0–50.4 Gy in 1.8 daily fractions along with infusional 5-FU, capecitabine or, more recently, weekly Gem. Imaged-guided radiotherapy now allows for accurate delineation of a planning target volume (PTV) that includes areas including the tumor itself and areas at risk for tumor involvement and for occult nodal metastases.

Nodal target volumes for head of the pancreas tumors include the pancreaticoduodenal, peripancreatic, porta hepatis, celiac, and suprapancreatic nodes. The portion of the duodenal loop at risk from involvement with extrapancreatic tumor extension is also included. For lesions involving the body and tail of the pancreas, the suprapancreatic, celiac, and splenic hilar nodes should be included in the PTV; inclusion of more medially placed lymph nodes (pancreaticoduodenal and porta hepatis) can be optional dependent on the ability to spare normal organs and structures.

Normal tissue tolerances should be carefully respected. Details regarding dose volume histogram parameters for treatment of pancreatic malignancies with radiotherapy have been published previously [37]. Figure 13.2 illustrates isodose distributions generated with this approach. The dose limits of the kidneys, liver, stomach, small intestine, and spinal cord will influence the choice of beam direction and weighting. Use of noncoplanar beams can allow for greater sparing of normal liver and kidney parenchyma. In the setting where IORT has been administered or is planned to be administered to a medial lesion over the vertebral column, the spinal cord dose should be limited to 35.0–40.0 Gy.

In the postoperative setting, planning principles are similar, with the operative bed and areas of potential residual tumor or microscopic extension taking the place of the former gross tumor volume in treatment planning. Current practice includes the incorporation of postoperative systemic Gem chemotherapy given the recent positive results of the European CONKO trial and other data suggesting a benefit to adjuvant chemotherapy, such as RTOG 97-04. The current sequence of postoperative adjuvant therapy at the Mayo Clinic for non-IORT patients includes restaging 1 month after surgery, two cycles of Gem chemotherapy, further restaging, concurrent

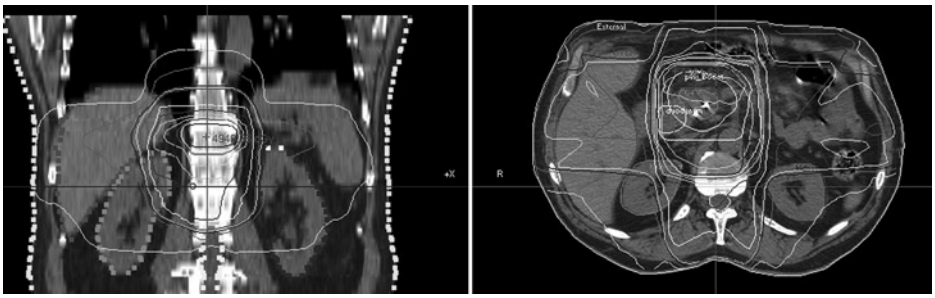

Fig. 13.2 Isodose distributions for external-beam radiotherapy of pancreas cancer.

EBRT and chemotherapy (infusion 5-FU, capecitabine, or weekly Gem), and then two further cycles of Gem chemotherapy [9, 10].

IORT Equipment and Doses

IORT for pancreas cancer has predominantly been delivered with megavoltage electrons produced by a medical linear accelerator (Fig. 13.3) [38]. The beam energy and dose of IORT is determined by the resection status and geometry of the treated field. Unresectable tumors often require energies of 12–18 MeV to achieve adequate coverage of the depth of the target tumor volume. After marginal resection of borderline resectable or resectable lesions, the tumor bed can be adequately treated with lower-energy electrons in the 9–12 MeV range. Intraoperatively, the radiation oncologist and surgeon consult regarding the unresectable tumor or retroperitoneal area at risk for residual tumor after maximal resection of the primary tumor, and the volume at risk is encompassed within a field defined by an IORT applicator with at least 1 cm margin (i.e., 5-cm unresectable tumor or tumor bed = 7-cm applicator). Figure 13.4 illustrates a Lucite IORT applicator in position for treatment of a pancreatic lesion. Figure 13.5 shows a typical operative field following resection. Figures 13.6 and 13.7 show the retroperitoneal structures at risk for microscopic tumor involvement appearing within the field defined by the IORT applicator. For tumors resected without identifiable residual gross tumor, doses in the range of 10.0–12.5 Gy are applied, depending on the extent of suspected residual microscopic malignant disease. For gross residual or unresected tumors, doses of 15–20 Gy have been employed. Intraoperatively, care must be taken to accurately identify the depth of the spinal cord beneath the IORT field using anatomic landmarks and a review of preoperative CT imaging. At both Mayo Clinic and Massachusetts General Hospital (MGH), a library of predefined isodose curves for a range of IORT applicator field shapes and electron energies is available for intraoperative consultation. An electron energy should be chosen to adequately encompass the target tissues within the 90% isodose curves, but limits the spinal cord dose to below tolerance [39].

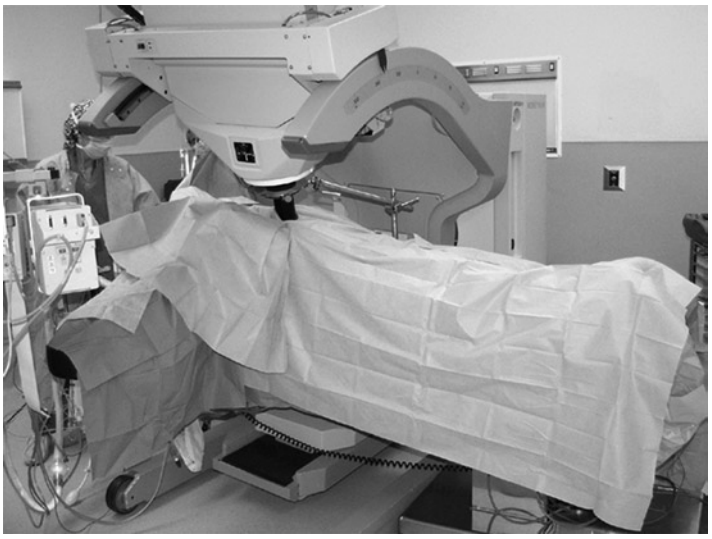

Fig. 13.3 Mobile linear accelerator (Mobetron®) in the operating suite in position to treat an intraabdominal IORT field.

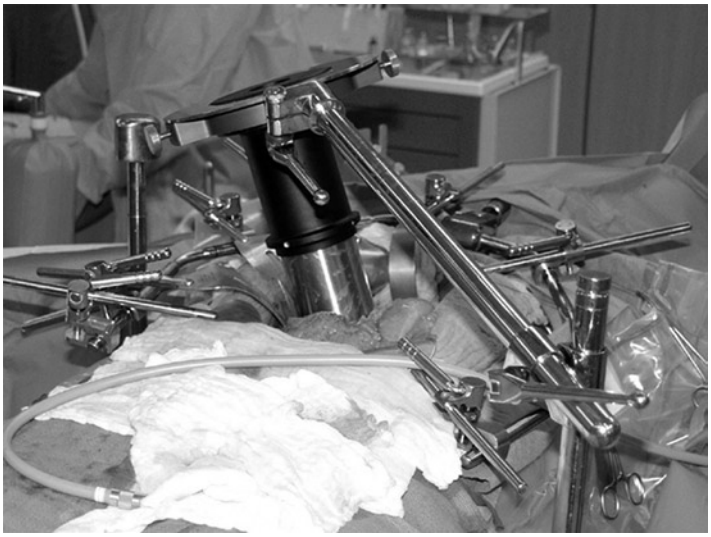

Fig. 13.4 IORT applicator in place intraoperatively for treatment of the tumor bed following resection of a pancreatic adenocarcinoma.

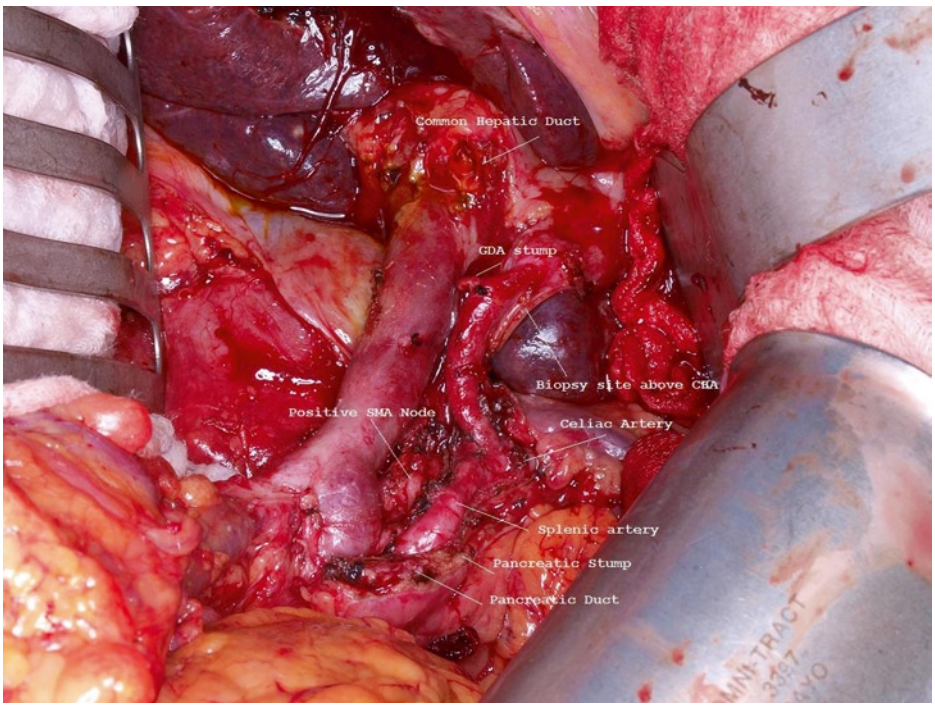

Fig. 13.5 Operative field following pancreatic carcinoma resection.

Fig. 13.6 The operative field receiving IORT seen through an IORT applicator.

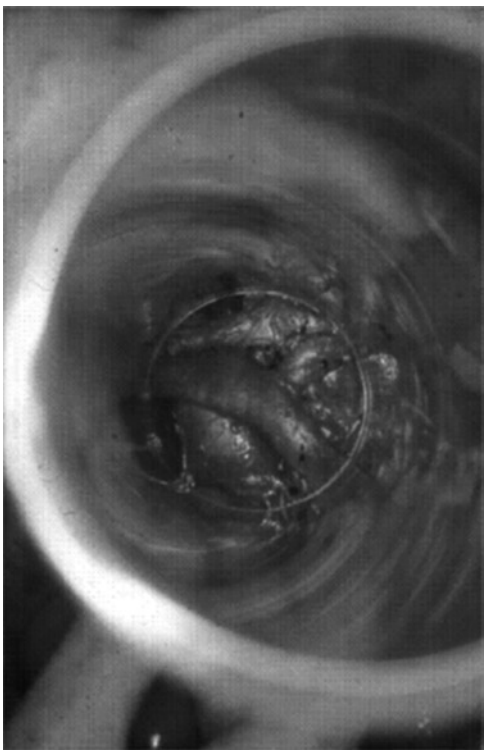

Fig. 13.7 A second view of an operative field receiving IORT seen through an IORT applicator.

Surgical Factors (Techniques): Pancreaticoduodenectomy

Pancreaticoduodenectomy involves the excision of the pancreatic head, duodenum, gallbladder, and bile duct, with or without removal of the gastric antrum. Access to the peritoneal cavity is obtained through a longitudinal midline incision, although many others prefer using a bilateral subcostal incision. Once in the abdominal cavity, all intra-abdominal organs and peritoneal surfaces are carefully inspected and palpated to exclude distant metastatic disease. Any suspicious lesions should be biopsied and sent for frozen-section examination, since presence of distant metastasis is a contraindication to proceed with resection. A wide Kocher maneuver is performed lifting all lymphatic tissue over the medial aspect of the right kidney, inferior vena cava and left renal vein. The gastrocolic ligament is divided, with special attention to preserve the gastroepiploic arcade if pyloric preservation is being entertained. The neck of the pancreas is then carefully dissected off the SMV. Dissection of the porta hepatis is usually initiated by excising the common hepatic artery lymph node to facilitate exposure. The gastroduodenal and right gastric artery are identified, ligated, and divided. The superior portion of the pancreatic neck is dissected off the portal vein. Cholecystectomy is then performed, and the common hepatic duct is divided. The gastric antrum or duodenum is divided using a liner gastrointestinal stapler. The jejunum is then transected approximately 10 cm from the ligament of Treitz with subsequent mobilization of its mesentery, as well as mobilization of the third and fourth portions of the duodenum. The pancreatic neck is transected. The pancreatic head and uncinate process are now dissected from the portal vein and SMV by ligating and dividing the often multiple venous tributaries that are encountered. Vascular resection of the SMV–portal vein confluence using either lateral venectomy or segmental venous resection and reconstruction should be performed when there is no tissue plane between the tumor and SMV and portal vein. With medial retraction of the SMV–portal vein confluence, the SMA is identified. All of the soft tissue along the right lateral aspect of the SMA should be excised. Special attention should be paid to this step given the high incidence of local recurrence. In spite of all efforts, a microscopically positive margin will occur in 10–20% of cases due to perineural invasion along the mesenteric plexus at the SMA origin and microscopic lymphatic spread beyond the extent of the palpable tumor [40, 41]. Although there are numerous reports showing that a positive margin of resection is an independent predictor of poor long-term survival, this concept has been recently challenged [42]. Prior to obtaining frozen-section histologic examination of the surgical margins, the specimen is appropriately oriented and areas in question are identified.

Reconstruction after pancreaticoduodenectomy starts with the pancreaticojejunostomy. We prefer a retrocolic end-to-side duct-to-mucosa technique using interrupted sutures. Then, distal to the pancreaticojejunostomy, the hepaticojejunostomy is completed in a single layer using either interrupted or running sutures depending on the caliber of the common hepatic duct. Approximately 40–50 cm from the hepaticojejunostomy, an antecolic, end-to-side duodenojejunostomy (or gastrojejunostomy if pyloric preservation has not been used) in two layers is then completed. The abdomen in then copiously irrigated prior to placing surgical drains and abdominal closure.

Perhaps one the most debated technical aspects of the pancreaticoduodenectomy is the extent of the associated lymphadenectomy (standard vs. extended). Using nomenclature by the Japan Pancreas Society (4), a standard lymphadenectomy (standard pancreaticoduodenectomy) commonly refers to the resection of gastric and pyloric nodes (groups 3, 4, 6), nodes to the right of the hepatoduodenal ligament (groups 12B1, 12B2, 12C), anterior and posterior pancreaticoduodenal nodes (groups 17A, 17B, 13A, 13B), nodes to the right of the SMA (groups 14A, 14B), and nodes anterior to the common hepatic artery (group 8A). An extended lymphadenectomy (extended pancreaticoduodenectomy) includes the skeletonization of the common and proper hepatic arteries (all group 8), celiac axis nodes (group 9), all nodes to the left and right of the hepatoduodenal ligament (all group 12), circumferential skeletonization of the SMA between the aorta and the inferior

pancreaticoduodenal artery (all group 14), all nodes in the anterolateral aspect of the aorta and the inferior vena cava, in continuity with Gerota's fascia, between the celiac axis and the inferior mesenteric artery.

To date, there have been three prospective randomized controlled trials that compare standard lymphadenectomy to the extended lymphadenectomy in patients undergoing resection of the pancreatic head for malignant disease. The largest of them by Yeo et al. [43] from Johns Hopkins University and another by Farnell et al. [44] from the Mayo Clinic have both failed to show any survival benefit of extended lymphadenectomy for pancreatic head carcinoma. The third study, by Pedrazzoli et al. [45], also demonstrated no difference in the overall survival, although patients with positive lymph nodes who underwent extended lymphadenectomy were noticed to have improved survival. More recently, Iqbal et al. [46] have published a meta-analysis comparing standard to extended pancreaticoduodenectomy. The authors concluded that extended pancreaticoduodenectomy offers no survival benefit and is associated with increased morbidity.

IORT Results

Rationale/General Results

IORT is a means of delivering a higher dose of irradiation to the pancreas in patients with locally unresectable disease and to the pancreatic bed and high-risk nodal groups in patients following pancreaticoduodenectomy. IORT was initially used in patients with locally advanced, unresectable adenocarcinoma of the pancreas in attempts to decrease pain and locoregional tumor progression and thereby improve survival. The experience with IORT and EBRT at MGH yielded a median survival of 12–16 months with improved pain control and decreased local failure [47, 48]. Initial studies at the Mayo Clinic involved an IORT dose of 20 Gy; after surgical recovery, patients received EBRT with or without concomitant 5-FU [39, 49]. Median survival was 13 months, and local failure as any component of failure was significantly less common with the addition of IORT.

IORT has also been applied to patients with resectable adenocarcinoma of the pancreatic head due to the high incidence of local recurrence with surgery alone. The experience at MD Anderson Cancer Center (MDACC) with preoperative 5-FU-based chemoradiation, pancreaticoduodenectomy, and IORT decreased locoregional recurrence to 11% [50].

Prognosis in pancreas cancer is dependent on a number of factors. Although it is a disease in which few long-term cures are achieved, survival is heterogeneous and strongly influenced by resectability status, lymph node involvement, tumor grade, and performance status [51]. Treatment strategy is decided by the fact whether tumors are resectable, unresectable due to locally advanced disease, or metastatic. Advances in imaging and staging such as the use of endoscopic ultrasound assessment of lymph node and vascular involvement have permitted better selection of patients for aggressive intervention [52]. Patients with metastatic disease have a short survival (3–6 months), the length of which depends on the extent of disease and performance status [35].

Patients who undergo surgical resection for localized nonmetastatic adenocarcinoma of the pancreatic head have a long-term survival rate of approximately 20% and a median survival of 15–22 months when surgery is combined with adjuvant chemotherapy and radiation [35]. Disease relapse following a potentially curative pancreaticoduodenectomy remains common, and local recurrence occurs in up to 85% of patients who undergo surgery alone. Locoregional tumor control is maximized with combined-modality therapy in the form of chemoradiation and surgery ± IORT. Patients with locally advanced (unresectable), nonmetastatic disease have a median survival of 6–12 months with chemoirradiation and up to 16 months with the addition of IORT. Some experiences seem to support better outcome when chemoradiation is given prior to surgery ± IORT [53].

IORT: Borderline Resectable or Unresectable Cancers

IORT for locally unresectable pancreas cancers was first reported in the English literature in the 1970s and 1980s by Abe [54, 55]. In 108 patients treated with IORT in this early experience, 80% experienced pain relief following treatment. Only a minority, 18 patients, received EBRT in addition. The doses employed, ranging up to 40.0 Gy, are higher than doses used in Western institutions in recent years. Doses in the ranges of 10.0–25.0 have predominated in reports from the last decade [56–60]. Since few patients are able to undergo resection at diagnosis, IORT is an attractive option to escalate dose in locally advanced, unresectable pancreas cancers and avoid treating large volumes of dose-limiting gastrointestinal organs.

In the published series of patients receiving IORT for locally unresectable pancreas cancer, the majority of patients treated report significant pain relief following IORT with or without EBRT. Median overall survival, depending on cohort size and the institution reporting, ranges from 3.0 months to 16.5 months, with most series reporting survivals after IORT for unresectable pancreas cancers in the 8.0–12.0 month range. Table 13.2 summarizes the medical literature to date for locally unresectable pancreas cancer treated with IORT.

US IORT Series

The combination of EBRT plus IORT has resulted in an improvement in local control in IORT series from MGH, Mayo, and TJUH [47, 49, 61–66] (Table 13.3). This has not, however, translated into major improvements in either median or 2-year survival. The delivery of EBRT plus concurrent chemotherapy prior to restaging and laparotomy plus IORT or resection plus IORT translates into improved patient selection and some improvement in median and 2-year survival [62, 67].

Massachusetts General Hospital

In the 1970s and 1980s, the treatment regimen at MGH was a combination of low-dose preop EBRT, IORT, and high-dose postop EBRT [47]. Patients with locally unresectable disease (no distant metastases) received 10–15 Gy of preop EBRT (pancreas and nodes). If metastases were not found and the primary tumor was unresectable, IORT was given (15–20 Gy with 15–23 MeV). After recovery from surgery, the patient received postop EBRT for an additional 35–39.6 Gy (4-field technique to clipped tumor ± LN) in conjunction with IV 5-FU (500 mg/m^2 3 days week 1 of EBRT).

Misonidazole, a hypoxic-cell sensitizer, was combined with IORT in a series of 41 MGH patients in an attempt to improve local tumor control; patients also received EBRT plus concurrent 5-FU [64]. Outcomes were compared with 22 IORT patients who did not receive misonidazole with 1-year local control of 67 vs. 55% and 2-year 45 vs. 31% (favoring misonidazole patients, $p > 0.05$). One-year OS was 50 vs. 77%, 2-year OS 20 vs. 33%, and median survival 12 vs. 16.5 months (favoring nonmisonidazole patients, $p > 0.05$); median survival in the total of 63 patients was 14 months. There was a bias toward larger tumors in those treated with misonidazole (15% of misonidazole/IORT patients with small tumors ≤4.5 cm vs. 50% in the control group of 22 patients).

In the most recent update of MGH results, 150 patients with locally unresectable pancreas cancer received IORT as a component of treatment from 1978 to 2001 in conjunction with EBRT and 5-FU-based chemotherapy [65]. Long-term survival was seen in eight patients, and five were alive at or beyond the 5-year interval. Actuarial 1-, 2-, 3-, and 5-year survival for the 150 patients was 54, 15, 7, and 4%, respectively, and median survival was 13 months. Survival was significantly related to the diameter of the IORT treatment applicator (surrogate for tumor size). In the 26 patients treated

Table 13.2 Intraoperative irradiation for locally advanced pancreas cancer

Author	Ref #	Year	No.	Dose of IORT (Gy)	No. receiving EBRT	Chemotherapy	No. treatment Related deaths	% Pain relief	Median survival (months)
Abe	[54]	1981	108	15–40	18	47	NA	80	NA
Wood	[48]	1982	12	15–18	11	6	0	NA	15
Shipley	[47]	1984	29	15–20	27	20	0	75	16.5
Tepper	[64]	1987	41	15–20 + Miso	41	41	NA	NA	12
Tuckson	[76]	1988	35[a]	15–30	14	2	8[b]	57	8.5[a]
Roldan	[49]	1988	37	20	37	24	0	NA	13.4
Manabe	[77]	1988	5	30–36.5	8	0	0	100	11.3[c]
Nishimura	[78]	1988	72	10–40	37	0	NA	76	8.8
Willich	[79]	1989	30[a]	15–20	11	8	NA	80	8[a]
Cromack	[80]	1989	29	25	25	25	1	NA	NA
Gilly	[81]	1990	14	12–25	9	0	0	89	8.9[d]
Abe	[82]	1991	69	25–40	20	0	1	80	12
Calvo	[83]	1991	25	15–20	25	0	NA	NA	10
Dobelbower	[84]	1991	27[a]	20–30	19	NA	1	NA	NA[a]
Kojima	[85]	1991	9	25–30	7	9[e]	0	80	8
Garton	[62]	1993	27	20	27	25	0	NA	15
Kasperk	[86]	1995	14	10–20	0	0	1	NA	3
Fossati	[87]	1995	21[a]	20–30	NA	21	0	85	8[a]
Mohiuddin	[63]	1995	49	10–20	49	49	0	NA	16
Shibamoto	[88]	1996	29	30–33	29	0	NA	NA	8.5[d]
Furuse	[56]	2003	30	25	28	28	1	NA	7.8
Okamoto	[60]	2004	65	15–30	65	11	0	51	10.9
Ihse	[57]	2004	37	20	29	29	0	11	7
Ma	[58]	2004	33	15–25	23	23	0	89	10.7-12.2
O'Connor	[59]	2005	24	12.5–20	18	NA	0	NA	11

IORT intraoperative irradiation, *EBRT* external-beam irradiation, *miso* misonidazole, *NA* not available

[a]Includes patients with metastases

[b]5 Delayed deaths

[c]Mean

[d]Survival of patients who received IORT/EBRT

[e]Mitomycin C used instead

Table 13.3 Pancreas: EBRT ± IORT for unresectable or borderline resectable cancers, select US series

			Survival overall (%)				Relapse (%)		
Series	Ref #	No. patients	Median	2-year	3-year	*p* Value	Local	*p* Value	Liver/PS
Thomas Jefferson									
EBRT ± CT	[28]	46	7.3 months	–	–		78%		–
IORT/5-FU-Leuc/EBRT[a]	[63]	49	16	22%	7%		29		55%
Massachusetts General									
EBRT ± 5-FU/IORT	[64]	22	16.5	33	20	>0.05	69(2 year)		–
EBRT ± 5-FU/IORT+Miso	[64]	63	12	20	–		55(2 year)	>0.05	–
EBRT ± 5-FU/IORT	[65]	150	13	15	7		–		–
Mayo Clinic Rochester									
EBRT ± CT	[49]	122	12.6	16.5	–		80(2 year)		56
IORT/Postop EBRT ± 5-FU	[49]	37	13.4	12	–	0.25	34(2 year)	0.0005	54
IORT/Postop EBRT ± 5-FU	[62]	56	10.5	6	0		35(2 year)		–
PreopEBRT ± 5-FU/IORT	[62]	27	14.9	27	20	0.001	[b]32(2 year)		52
Mayo Clinic Arizona									
EBRT + 5-FU or Gem/IORT	[67]	26	19	27	20		19		50
Resection after preop CRT		12	23	40	40	0.011	8	0.011	33
Unresectable		14	10	17	0		28.5		64

EBRT external-beam irradiation, *IORT* intraoperative electron irradiation, *CT* chemotherapy, *Gem* gemcitabine, *5-FU* 5-fluorouracil, *Leuc* leucovirin, *CRT* chemoradiation, *Univ* University

[a]Perioperative 5-FU leucovorin was given before, during and after EBRT

[b]2-year local relapse of 19% in the 23 patients with tumor diameter ≤7 cm vs. 75% in the 4 patients with >7 cm tumors

with a 5- or 6-cm applicator, 2- and 3-year survival were 27 and 17%, respectively; 0/11 patients treated with a 9-cm diameter applicator survived beyond 18 months, and those treated with a 7- or 8-cm applicator had an intermediate survival ($p < 0.05$).

Mayo Clinic

In the initial *Mayo Clinic Rochester* series, IORT usually preceded EBRT [49]. When results were compared with EBRT ± 5-FU, local control at 1 year was 82% for EBRT plus IORT ± 5-FU vs. 48% for EBRT ± 5-FU; at 2 years, it was 66 vs. 20%, respectively ($p = 0.0005$). This did not translate into a difference in either median or 2-year SR (13.4 months median SR with IORT vs. 12.6 months without; 12 vs. 16.5% 2-year SR). A higher percentage of patients in the non-IORT group received concurrent 5-FU during EBRT. The lack of survival improvement was related to a high incidence of abdominal relapse in both groups (20/37 IORT patients, or 54% developed liver or peritoneal metastases vs. 68/122 or 56% in non-IORT patients).

In an attempt to improve patient selection and survival, investigators from Mayo Clinic Rochester delivered the EBRT plus chemo before restaging and exploration [62]. In a total of 27 patients who received IORT after EBRT, local control was achieved in 21/27 (78%) with actuarial rates of 86 and 68% at 1 and 2 years, respectively. Median survival was 14.9 months with this sequence, and 2- and 5-year survivals were, respectively, 27 and 7%. These findings were compared with results in 56 patients who had IORT before receiving the high-dose EBRFT component at Mayo or elsewhere (median SR 10.5 months, 2 year SR 6%, $p = 0.001$). In an earlier analysis of 37 patients treated solely at Mayo with the latter sequence, median and 2-year survival were, respectively, 13.6 months and 12%. Although 2-year SR appeared to improve with the altered sequence of preop treatment followed by IORT, this was likely due to altered patient selection as the rate of liver plus peritoneal failure did not change (14 of 27 at risk, 52%).

Investigators from *Mayo Clinic in Arizona* have used only the sequence of preop chemoradiation followed by restaging, surgical exploration with resection/IORT, as indicated, for select patients with borderline resectable or unresectable pancreas cancer [67]. A series of 26 patients with no prior treatment have received IORT after preop chemoradiation; resection was performed in 12/26 before IORT (R0 or R1, 9; R2, 3). Median SR for the total group was 19 months, 2-year OS 27%, 3 year 20% (Table 13.3). Survival outcomes appeared to be improved in patients with resection after preop chemoradiation vs. those without resection (median 23 vs. 10 months; 2-year OS 40 vs. 17%; 3-year 40 vs. 0%; $p = 0.011$, logrank). Liver or peritoneal relapse has been documented in 13 of 26 patients (50%).

Japan IORT Series

Furuse, from the Japanese National Cancer Center Hospital East, has recently reported on a series of patients with locally advanced pancreas cancer treated on a Phase II trial consisting of 25.0 Gy of IORT, following conventional EBRT to 40.0 Gy with concurrent continuous venous infusion 5-FU. IORT was well tolerated, and 7 of 30 patients (23%) demonstrated a partial response radiographically to treatment. However, median survival was only 7.8 months with 2-year OS of 8.1% [56].

Sunumura, of Tohoku University in Sendai, Japan, conducted a small randomized controlled trial of the novel hypoxic radiosensitizer PR-350, in a total of 48 patients with unresectable pancreas cancer. The patients were randomized between intraoperative PR-350 vs. placebo infusion, followed by 25.0 Gy of IORT and later EBRT to 40.0 Gy. Survival was equivalent between groups with the PR-350 vs. placebo survival being 36.4 vs. 32.0% at 1 year. However, 4 of 22 PR-350 patients remained alive at 2 years vs. 1 of 25 from the control group [68].

Okamoto, in a large series of 65 patients with unresectable pancreatic tumors, found that 33 of 65 patients (51%) experienced pain relief after IORT followed by EBRT, with 21 patients (64%) of those patients experiencing complete pain relief. Of the patients experiencing complete pain relief, 10 of 21 were alive at 1 year [60].

Tolerance: IORT ± EBRT

Toxicity from IORT for locally advanced pancreas cancer is limited. Patient undergoing exploratory laparotomy and IORT for pancreas cancer may experience delayed gastric emptying, a common problem with gastrojejunostomy alone (with no IORT). Investigators from the MGH recommended performing a gastrojejunostomy at the time of IORT when the IORT treatment field for unresectable pancreatic head tumors includes the adjacent duodenum (most commonly the medial wall of part two of the duodenum), in view of the associated risk of duodenal stenosis [48]. Rare late complications include distal biliary stenosis, pancreatic insufficiency, epigastric discomfort, gastrointestinal hemorrhage, and nausea. Ma has recently reported a comparison between patients undergoing EBRT and either cholecystojejunostomy or choledochojejunostomy with and without IORT for locally advanced pancreatic cancer. No difference in late complications was noted between treatment groups [58].

IORT: Resectable Pancreas Cancers

Rationale for IORT

IORT after pancreatic resection was adopted following initial successes with treating unresectable tumors. Manipulation or shielding of organs at risk for injury at the time of surgery allows for exclusion of radiosensitive organs such as the stomach, small intestine, and biliary tree from the IORT field. IORT doses range from 10.0 to 25.0 Gy in most resected pancreas series. The retroperitoneal region at risk for persistent disease can be accurately identified at the time of surgery to delineate the IORT field. Typically, this would include the major vessels included as targets in the EBRT field such as the aorta, celiac axis, SMA and SMV, portal vein, and inferior vena cava. The pancreatic remnant has been included by some physicians in the treatment field, although the risk of pancreatic leak may be increased with the corresponding maneuver [69].

Table 13.4 summarizes the major publications of series of patients receiving IORT for resectable pancreatic cancer.

European Pooled Analysis

Recently, the European ISIORT group has published the final results of a pooled analysis evaluating IORT as a component of pancreas cancer treatment [53]. From 1985 to 2006, a total of 270 patients were treated with surgical resection and IORT ± EBRT in five European institutions (Istituto San Raffaele, Milan; Heidelberg Universität; Catholic University of the Sacred Heart, Rome; Hospital Universitario G. Marañon, Madrid; Paracelsus Universität, Salzburg), and data were pooled to investigate the contribution of IORT to the multidisciplinary treatment of pancreas cancer. Most of the patients had locally advanced disease, with tumor extending beyond the pancreas in 86.6% of cases. One hundred and seventy-six patients (67.4%) also had histologically confirmed lymph-node metastases, while 12 had liver metastases not identified during the staging procedures. These results are summarized in Table 13.5.

Table 13.4 Intraoperative irradiation for resectable pancreatic cancer

Author	Ref #	Year	No. patients	Dose of IORT (Gy)	No. receiving EBRT	Adjuvant chemotherapy	Treatment-related deaths	No. with local recurrence	Median survival (months)
Manabe	[77]	1988	4	25–30	4	None	1	2/4	9.5[a]
Nishimura	[78]	1988	11	10–40	11	None	NA	NA	5
Cromack	[80]	1989	10	20	0	None	4	NA	NA
Gilly	[81]	1990	8	12–25	0	None	0	NA	12.6[a]
Ozaki	[17]	1991	19	30	0	Mitomycin C	0	NA	28%[b]
Dobelbower	[84]	1991	11	12.5–15	7	5-FU	0	NA	10.5
Gotoh	[89]	1992	17	30	0	None	1[c]	NA	NA
Johnstone	[90]	1993	7	20	0	None	NA	NA	NA
Zerbi	[91]	1994	43	12.5–20	0	5-FU + epiadriamicin	1	10/37	NA
Fossati	[87]	1995	33	12.5–20	9	5-FU	1	7/33	19
Staley	[50]	1996	39	10–20	39	5-FU	1	4/38	19
Farrell	[92]	1997	14	12–15	14	5-FU	0	NA	16
Coquard	[93]	1997	25	12–25	20	5-FU	2	9/25	15
Hiraoka	[22]	1999	37	30	0	None	3	2/37	~16
Reni	[94]	2001	127	10–25	~36	Multiple regimens	0	50/112	15.5
Okamoto	[60]	2004	68	15–25	68	5-FU	0	6/68	14.6
Ihse	[57]	2004	18	20	10	5-FU	0	33%	9
O'Connor	[59]	2005	44	12.5–20	22	5-FU	0	NA	16.3
Valentini	[53]	2009	247	7.5–25	169 (63 pre-106 post)	32	4	NA	19

IORT intraoperative irradiation, *EBRT* external-beam irradiation, *miso* misonidazole, *NA* not available, *5-FU* 5-fluouracil

[a]Mean

[b]5-year survival

[c]Delayed death

Table 13.5 The ISIORT-Europe experience on IORT in pancreas cancer [53]

	No. patients[a]	%	Median LC (months)	5-year LC (%)	*p* Value	Median OS (months)	5 year-OS (%)	*p* Value
Whole series	270	100	15	23.3		19	17.7	
Tumor size								
pT1-2	35	13.4	n.r.	65.5	<0.0001	16	24.2	0.32
pT3-4	225	86.6	13	9.2		19	15.8	
Nodal status								
N0	85	32.6	53	54	<0.0001	18	22	0.097
N1	176	67.4	12	0		19	11	
Residual tumor								
R0-1	218	80.8	17	27.8	<0.0001	19	19.3	0.31
R2	52	19.2	6	0		18	6.3	
Radiotherapy								
Preoperative EBRT + IORT	63	23.9	n.r.	74	<0.0001	19	37	<0.0001
IORT + postoperative ERT	106	40.1	28	19		22	19	
Exclusive IORT	95	36.0	8	0		13	6	

LC local control, *OS* overall survival, *n.r.* not reached

[a]Data not available for all patients

Surgery was performed in a total of 247 cases (91.5%), with no residual tumor (R0 resection) in 53.4% of cases, microscopical residual disease (R1) in 27.4%, and macroscopical residual disease (R2) in 19.2% of cases. Overall, 4/247 patients died as a result of surgical complications. Surgery was complicated by adverse events in 23.8% of cases. All patients submitted to surgery received IORT, which was preceded by EBRT in 63 cases (23.9%), whereas 106 patients (40.1%) received further EBRT after surgery + IORT. Since the trial began in the mid 1980s, the use of concurrent chemotherapy with radiation therapy was optional; therefore, only 32 patients (11.8%) underwent concomitant chemoradiation before or after surgery + IORT.

EBRT was delivered to pancreas/tumor bed and regional lymph nodal stations with a multiple-field technique according to the single Institution policy. A median dose of 45 Gy was administered (range 18–61). IORT was delivered by electrons of 6–12 MeV, with a median dose of 15 Gy (range 7.5–25). Acute toxicity related to radiation treatment was slight, and no case exceeded grade 2.

Median follow-up was 96 months (range 3–180). Median local control (LC) was 15 months, whereas 5-year LC was 23.3%. LC was significantly associated with tumor size (median not reached for T1–2, 13 months for T3–4, $p<0.0001$), residual tumor (median 17 months for R0–1, 6 months for R2, $p<0.0001$), and positive lymph nodal status (median 53 months for N0, 12 months for N1, $p<0.0001$). A significantly greater LC was observed in patients undergoing preoperative radiotherapy (median LC not reached) compared to patients treated with postoperative EBRT (median LC 28 months) and to patients submitted to IORT exclusively (median LC 8 months) ($p<0.0001$). The Cox logistic regression revealed that tumor size, lymph node positivity, and timing and method of irradiation (preop better than postop EBRT or IORT alone) significantly affect local control with a hazard ratio (HR) of 1.8 (95% CI 1.06–3.2, $p=0.03$), 2.6 (95% CI 1.2–5.6, $p=0.0009$), and 3.3 (95% CI 1.8–6.2, $p<0.0001$), respectively.

Median OS was 19 months, while 5-year OS was 17.7%. The univariate analysis revealed that neither the tumor size, residual tumor after surgery, nor the lymph nodal status was significantly related to survival. In particular, median survival was 16 months for patients with stage T1–2 vs. 19 months for T3–4 cases ($p=0.32$), and 19 months for patients with R0/R1 resection vs. 18 months for patients with R2 resection ($p=0.31$). Median OS was 18 and 19 months, respectively, for N0 and N1 cases. Only the timing of EBRT was observed to affect survival, since a significantly longer OS was registered in patients undergoing preoperative EBRT (median OS 30 months) compared to patients treated with postoperative EBRT (median OS 22 months), or to patients submitted to IORT exclusively (median OS 13 months) ($p<0.0001$). The Cox logistic regression revealed that lymph nodal status and the timing of EBRT significantly affect survival, with a hazard ratio (HR), respectively, of 1.6 (95% CI 1.1–2.3, $p=0.008$) and 1.4 (95% CI 1.1–1.8, $p=0.008$). Interestingly, a prolonged survival was observed within the subset of patients who remained relapse-free for more than 2 years: in fact, in this group, the 3- and 5-year OS was of 31.9 and 28.4%, respectively, compared to 11.9 and 0% for patients who had a local recurrence within the first 2 years after IORT ($p=0.04$).

Tolerance

IORT in the setting of resectable pancreatic cancer is typically well tolerated. In the European pooled analysis, acute treatment toxicity was minimal and limited to grade ≤2. Surgical adverse events consisted of pancreatic fistula in 27%, delayed gastric emptying in 22%, hemorrhage in 18%, repeat laparotomy in 15%, abdominal abscess in 14%, sepsis in 3%, and perioperative mortality in 2% [53].

Summary

A trend seems to emerge from this study that EBRT may increase the effects of IORT in terms of local control and overall survival, since longer LC and OS were observed in patients submitted to EBRT + IORT. These findings, however, may be explained by a selection bias precluding surgery + IORT to patients progressing during preoperative EBRT, as well as excluding further EBRT patients in progression after IORT. However, the significantly greater LC and OS observed in patients undergoing preoperative radiotherapy compared to that of patients treated with postoperative EBRT, and to that of patients submitted exclusively for IORT, suggest that a preoperative treatment may act as a filter selecting patients who are already affected by occult metastatic disease at the moment of enrollment into the study and destined to progress during the time of induction therapy, sparing them of surgery and IORT.

Similar results have already been reported by Pisters et al. who obtained high survival rates in patients treated with preoperative chemoradiation followed by radical surgery and IORT at the MD Anderson Cancer Center [70]. More recently, this theory of the "filter-induction" has been explored on a wide retrospective study by Huguet et al. [71], who demonstrated a significant improvement in survival for patients submitted to chemoradiation after a period of induction chemotherapy. The significantly prolonged survival observed within the subset of patients who remained relapse-free for more than 2 years supports the idea that while metastasis still remains the main challenge for this disease, the improvement of local control by higher radiotherapy doses may have an impact on the survival of patients with lower trend to disease spread. The authors, therefore, conclude that IORT preceded by EBRT may have a positive impact on local control even if a more efficient strategy in the multimodality treatment is needed to control micrometastases and to select patients who could benefit from surgery and local therapies.

Conclusions and Future Possibilities

Long-term survival and disease control are achievable in select patients with borderline resectable or locally unresectable pancreas cancer, and survival appears to be better in patients with resection after full-dose preop chemoradiation. Accordingly, continued evaluation of curative-intent combined modality therapy is warranted in this high-risk population of patients. However, additional strategies are needed to improve both resectability rates after preop chemoradiation and disease control (local and distant).

IORT, as part of a multimodality treatment plan for pancreas cancer, either locally advanced and unresectable or resectable, has the potential to increase local control at the site of the primary tumor without a significant increase in treatment toxicity risk. Currently, the high risk of systemic failure outweighs risks of local and regional failure in determining patient mortality. For unresectable tumors, an upfront course of induction chemotherapy may identify the 20–30% of patients who experience early distant progression, allowing for EBRT and/or IORT in those with disease less inclined to systemic progression [71]. With advances in the ability of systemic therapy to treat occult systemic metastases, the importance of maintaining good long-term local and regional control may take preference. Strategies to select appropriate patients for aggressive local therapy in the resectable, borderline resectable, or unresectable settings will advance through improvements in imaging, biomarkers, and genetics or through the timing of when to administer IORT and/or resection.

The incidence of abdominal relapse must be decreased by utilizing either more aggressive or new regimens of systemic or regional therapy (intrahepatic and intraperitoneal). Targeted therapies

(i.e., epidermal growth factor receptor [EGFR] inhibitors, vascular endothelial growth factor [VEGF] inhibitors) and pancreas cancer vaccines are also being evaluated in an attempt to improve systemic disease control. As improvements are being made in distant disease control, the benefit of improved local control with IORT-containing regimens may become even more apparent.

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Chapter 14
Bile Duct and Gallbladder Cancer

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Keywords Bile-duct cancer • Gallbladder cancer • Tskuba IORT series for biliary cancer

Results of Standard Treatment

Surgical Considerations

Many patients with gallbladder and extrahepatic biliary duct lesions have either technically unresectable lesions or gross or microscopic residual disease after attempts at resection because of anatomic location and technical limitations [1–3]. Surgical removal of a malignant gallbladder lesion often necessitates blunt dissection from the liver with narrow or nonexistent margins unless a wedge of liver is removed.

A larger percentage of patients with proximal lesions are undergoing curative resections in modern series [2, 4–6]. In an early Mayo-Clinic analysis, only 5% of 78 patients with Klatskin tumors had curative resection, and there were no long-term survivors [1]. In a subsequent analysis of 171 patients with surgical exploration at Mayo Clinic from 1976 to 1985 for extrahepatic cholangiocarcinoma, the rate of curative resection with negative margins at the site of primary disease was 15% for proximal lesions, 33% for midductal, and 56% for distal lesions [6]. Five-year survival rates as high as 40% have been reported in patients with proximal lesions who have negative resection margins [5, 6]. Many patients with proximal lesions, however, are not candidates for standard resection because of both extent and location. For such patients, orthotopic liver transplantation is being evaluated in selected centers with 5-year survival rates of 15–20% [5, 7, 8].

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_14,

Lesions in the periampullary region or distal common duct have a uniformly better prognosis. Resection with a Whipple procedure is usually feasible and results in long-term survival in 30–40% of patients [5, 6].

Patterns of Relapse After Standard Surgical Resection

Local relapse in the tumor bed or regional nodes (LF–RF) is common in spite of "curative resection" for both gallbladder and extrahepatic biliary duct lesions [3, 5]. With mid and proximal bile-duct cancer, proximal and distal margins of resection are often narrow; radial margins are usually narrow if the primary lesion extends beyond the entire duct wall. With ductal lesions, locoregional relapse is a common cause of death. In combined series with "curative" simple cholecystectomy for gallbladder cancer, 95 of 110 or 86% of patients with early relapse died with or because of local recurrences, and 11 of 25 or 48% of patients alive at 5 years had local recurrence [9]. Twelve of 16 or 75% of patients with radical "curative" cholecystectomy died with or because of local recurrence [9]. Hepatic metastases can occur with gallbladder and ductal tumors, but with gallbladder primaries it may be difficult to differentiate liver metastasis from direct extension. Peritoneal involvement is more common with gallbladder vs. ductal primary tumors.

Kopelson et al. [3] analyzed patterns of relapse after curative resection in an MGH series of 28 patients with complete resection of gallbladder or ductal lesions. In the 25 postoperative survivors, distant metastases occurred in nine (36%), and locoregional relapse occurred in 13 patients (52%). Initial spread through the wall of the organ was the best predictor of locoregional relapse – (lesions confined to the wall, 4/11 – 36% vs. beyond the wall, 9/14 – 64%).

Willett et al. analyzed patterns of relapse in 41 MGH patients with ampullary carcinomas [10]. In 12 patients with low-risk pathologic features (limited to the ampulla or duodenum, well- or moderately differentiated histology, uninvolved resection margins and nodes), 5-year actuarial local control and survival rates were 100 and 80%, respectively, with surgery alone. In 17 high-risk patients treated with surgery alone, those rates were 50 and 38%, respectively, $p < 0.05$ (high risk was defined as tumor invasion of the pancreas, poorly differentiated histology, and involved nodes or resection margins).

External Irradiation ± Chemotherapy

Although areas of malignant obstruction can be decompressed with placement of percutaneous transhepatic catheters or retrograde endoscopic stents, or by performing a surgical bypass such as a segment-3 Roux-en-Y hepaticojejunostomy, none of these procedures actively treat the tumor. Therefore, the addition of EBRT ± chemotherapy to palliative drainage is reasonable. Significant palliation and occasional long-term survival can be obtained with EBRT to doses of 40–60 Gy in 4.5–7 weeks for unresectable or recurrent bile-duct cancers, but permanent local control is uncommon [9, 11–15] (Table 14.1). In view of the presence of multiple dose-limiting organs including liver, stomach, duodenum, kidneys, and spinal cord, EBRT doses higher than 40–45 Gy can be obtained with acceptable morbidity only if tumor extent is carefully defined with imaging studies and surgical clips, and the patient is treated with sophisticated, multiple field EBRT techniques that may include noncoplanar beams using 3D conformal irradiation (3D-CRT) treatment planning [11, 15] or intensity-modulated irradiation (IMRT).

Combinations of EBRT and chemotherapy need to be evaluated more extensively in view of survival trends seen in an early analysis by Kopelson et al. [9], and more recent series from Thomas

Table 14.1 Irradiation for locally advanced (usually unresected) primary bile-duct cancer – external beam +/– transcatheter irradiation +/– chemotherapy

Investigation [reference #]	No. pts	Median (months)	Survival 12 months no. (%)	18 months no. (%)	24 months no. (%)	36 months no. (%)	60 months no. (%)	Local relapse no. (%)	Septic death no. (%)
External irradiation +/– chemotherapy									
Buskirk et al. [12]	11	12.0	– (55)	0	–	–	–	6/11 (55)	0
Fields and Emami [13]	9	7.0	1 (11)	1 (11)	0 (0)	–	–	6/9 (67)	–
Hanna and Rider [14]	14	12.3	–	–	–	–	–	–	–
Alden and Mohuidden [16]	8	13.5	–	–	– (25)	–	–		–
Transcatheter + external +/– chemotherapy									
Fields and Emami [13]	8	15	5 (63)	–	2 (25)	1(13)	–	4/8 (50)	2/8 (25)
Alden and Mohuidden [16]	13	24	–	–	– (40)	–	–	–	–
Minsky et al. [17] (brachy boost 6 of 10)	10	16	– (80)	– (50)	– (50)	– (50)	NA	5/10 (50)	–
Hayes et al. [21]	8	13.4	4 (50)	2 (25)	1 (13)	–	–	–	1/8 (13)
Johnson et al. [22]	7	12.5	4 (57)	2 (29)	2 (29)	–	–	–	1/7 (14)
Foo et al. [23]	24	12.8	16 (67)	9 (38)	– (19)	– (14)	– (14)	8 (33)	–
Fritz et al. [24]	30	10	– (34)	– (20)	– (18)	– (18)	– (8)	14/27 (52)	–
Veeze-Kuypers [25]	42	10	– (46)	– (27)	– (18)	– (13)	–	–	–

no. = number, pts = patients

Jefferson [16], Sloan–Kettering [17], and the University of Pennsylvania and Fox Chase [18]. In the latter series, 1- and 3-year overall survival (OS) appeared to be better in patients with gross residual disease who received both modalities vs. EBRT alone (1-year OS 65% vs. 17%; 3-year OS 26% vs. 8%, $p=0.02$).

In bile-duct patients with subtotal resection and residual disease, an EORTC analysis suggests that the addition of EBRT may improve survival. The EORTC group [19] analyzed a series of 55 patients of whom 17 were treated with surgery alone and 38 received postoperative EBRT (52 of the 55 patients had pathologically positive margins). The EBRT patients had a median survival of 19 months vs. 8.3 months with surgery alone (1-year OS 85% vs. 36%, 2-year OS 42% vs. 18%, 3-year OS 31% vs. 10%; $p=0.0005$).

Investigators from Johns Hopkins reported a series of 50 patients with localized proximal bile-duct cancers who had exploration ± resection and were potential candidates for postoperative EBRT [2, 20]. A gross total resection with positive or negative margins was performed in 21 patients (42%), and partial resection was performed in 10 patients (20%). An additional 12 patients (24%) were unresectable and had stents placed. Twenty-three patients received postoperative EBRT to a mean dose of 46 Gy in 5 weeks for the 14 resected patients and 50 Gy for the 9 patients with unresected lesions (target volumes were not defined in the manuscript). Eight of 14 resected patients received a transcatheter iridium boost to an average dose of 13 Gy at an unspecified depth (Table 14.1). The addition of irradiation in this very mixed group of patients neither improved nor detracted from duration or quality of survival with similar duodenal and hepatic toxicity in irradiated and nonirradiated patients. Strategies suggested by the authors to improve outcome included adding 5-FU (5-Fluorouracil) ± cisplatin to irradiation, increasing dose of irradiation ± field size, and considering altered sequencing with preoperative irradiation ± chemotherapy instead of postoperative treatment.

In the MGH ampullary cancer series reported by Willett et al. [10], 29 of 41 patients had high-risk pathologic features (17 patients were treated with surgery alone, and 12 patients received postoperative EBRT ± 5-FU). Although the adjuvant treatment appeared to improve both 5-year local control and survival rates with values of 83% vs. 50% and 51% vs. 38%, respectively, these differences were not statistically significant in view of small patient numbers and distant risks (liver, peritoneum, and pleura).

Specialized Irradiation Modalities

The usual tumor-related cause of death after EBRT, with or without chemotherapy, for locally unresectable biliary tract cancers is local persistence of disease. In view of the proximity of dose-limiting organs and structures to the malignancy, improvements in local control may be feasible with the addition of specialized boost techniques including brachytherapy via transhepatic catheters or retrograde endoscopic stents or IORT with electrons, orthovoltage, or HDR brachytherapy (with or without irradiation dose modifiers).

Transcatheter Brachytherapy ± EBRT

The temporary insertion of sealed radioactive sources via transhepatic catheters or stents placed endoscopically can deliver localized high-dose irradiation. This method of boost treatment is attractive because of its potentially wide applicability (as opposed to that of IOERT). Deaths from sepsis are reported more commonly than in EBRT-only series, however, which is a reflection of the need for transhepatic catheters in all patients with the inherent risks.

There is a suggestion of improved survival in patients with unresectable bile-duct cancer treated with EBRT plus brachytherapy when compared with either method alone [11, 15, 21, 22], but no

randomized trials have been performed to test these possible differences (Table 14.1). In view of short follow-up and a low incidence of survival beyond 1 year, the exact incidence of locoregional failure is difficult to discern in published series.

In a Mayo-Clinic series [12, 23], 24 patients received EBRT to 45–50.4 Gy ± 5-FU (9 patients) followed in 2–4 weeks by a transcatheter iridium boost of 20–25 Gy (calculated at a 1.0-cm radius in 20 of the 24). Local failure was documented in 8 patients or 33% (Table 14.1). Five-year overall and disease-free survival were 14% in the total group (3 survivors ≥5 years; 5-year SR, 2 of 9 or 22% in patients who received 5-FU with EBRT vs. 8% in the 15 with no 5-FU during EBRT).

Data from a 48-patient single-institution analysis from Thomas Jefferson University Hospital (TJUH) [16] suggest a positive impact of increased irradiation dose on median and 2-year OS in 24 patients treated with EBRT ± chemotherapy ± transcatheter iridium. Higher doses were usually achieved by combining EBRT doses of 44-46 Gy with a brachytherapy boost dose of 25 Gy calculated at a 1-cm radius. Two-year OS for all 48 patients was 18% with a median survival of 9 months. Patients treated with irradiation vs. none had 2-year OS of 30% vs. 17% and a median SR of 12 months vs. 5.5 months ($p = 0.01$). Irradiated patients treated to a dose of >55 Gy vs. <55 Gy had 2-year OS of 48% vs. 0% and a median SR of 24 months vs. 6 months ($p = 0.0003$). Radiation dose response was also suggested by an increase in median survival with an increase in irradiation doses from <45, 45–54, 55–65, 66–70 Gy, respectively (4.5 months vs. 9, 18, and 25 months).

Results in two European series suggest a potential advantage of combining EBRT plus brachytherapy with noncurative resection (Table 14.1). In the Fritz et al. analysis of 39 patients treated at the University of Heidelberg with EBRT plus high-dose-rate bradytherapy ± noncurative resection [24], those with noncurative resection vs. no resection had a suggestive increase in survival (median – 12 months vs. 8 months; 3-year OS – 32% vs. 5%, 5-year OS – 32% vs. 0%, $p = 0.004$). In a Rotterdam series by Veeze-Kuypers et al. of 42 patients treated with EBRT plus Ir-192 alone or plus resection [25], the 11 patients with noncurative resection had improved median survival of 15 months vs. 8 months, and 3-year OS of 36% vs. 6% ($p = 0.06$) when compared to results in the 31 patients without resection.

Preop Chemoradiation, Brachytherapy, Transplant

Impressive results have been obtained when preoperative EBRT plus concurrent 5-FU-based chemo alone or plus transcatheter Ir^{192} preceded liver transplant in separate series from the University of Pittsburgh [26] and Mayo Clinic, Rochester (MCR; [27, 28]) (Table 14.2). Four and five-year survival was 53.5% in the University of Pittsburgh series vs. a 4-year survival of 22% when transplant preceded EBRT. In the highly selected MCR series, 3 and 5-year survival was 82% for the 38 patients who received an orthotopic transplant after preop EBRT + concurrent bolus 5-FU, Ir^{192} plus concurrent and maintenance protracted venous infusion of 5-FU.

Treatment Factors (EBRT, Surgery, IORT)

Preoperative Staging

Surgical unresectability of bile-duct cancer is based on a predetermined sequence of imaging studies obtained preoperatively in patients with obstructive jaundice. A chest X-ray or chest computed tomography (CT) is obtained to exclude pulmonary metastases. Once extraabdominal metastases are excluded, abdominal imaging is performed to assess the local and regional extent of the tumor. Abdominal ultrasonography is useful in defining dilated intrahepatic and extrahepatic bile ducts and

Table 14.2 Survival results with treatment intensification for biliary tract cancers, non-IORT and IORT series

Series/treatment method [references]	No.	Survival %						*p*-value
		Median (months)	12 months	18 months	24 months	36 months	48 months	60 months	
(a) Non-IORT Bile-duct cancer series									
Mayo Clinic Rochester									
Noncurative resection + EBRT +/− 5FU	6	12	50	0	–	–	–	–	–
Unresected									
EBRT ± 5-FU [12]	11	12	55	0		–	–	–	–
EBRT +/− 5FU + Ir-192 [23]	24	12.8	67	38	19	14	14	14	
EBRT + 5-FU + Ir-192	9	13	67	44	22	22	22	22	
EBRT + Ir-192	15	12	67	32	16	8	8	8	
EBRT/5-FU/Ir^{192} + transplant [27, 28]	38	60+	92	NA	NA	82	NA	82	0.02
Standard surgical resection [28]	26	35	82	NA	NA	48	NA	21	
Thomas Jefferson University Hospital [16]	48	9	–	–	18	–	–	–	
No Irradiation	24	5.5	–	–	17	–	–	–	
Irradiation + 5-FU + Ir-192	24	12	–	–	30	–	–	–	0.01
<55 Gy	9	6	–	–	0	–	–	–	
>55 Gy	15	24	–	–	48	–	–	–	0.0003
University of Pittsburgh [26]									
EBRT +/− 5FU +/− resection	55	9	32	20	10	6	4	–	
Transplant + EBRT +/− 5FU	9/55	12	50	32	22	22	22	–	
EBRT + 5-FU/CF; Bx or partial resection	38[a]	14	60	38	20	16	11	0	
EBRT + 5-FU/CF; transplant or total resection	23[a]	60+	82	74	68	53.5	53.5	53.5	0.0001

(b) IORT Bile-duct cancer series									
Iwasaki et al. (Japan) [40]									
Noncurative resection									
Alone	13	–	44	8	8	8	–	–	
Plus IORT	13	–	46	23	15	8	–	–	
Unresected									
Biliary drainage only	21	–	<5	0	–	–	–	–	
drainage + IORT	6	–	33	17	17	0	–	–	
Todoroki et al. (Japan) [43, 44]									
R1 resection + IORT	8	–	–	–	–	–	–	20.8	
R1 + postop EBRT	14	–	–	–	–	–	–	21.4	
R1 + IOERT/EBRT	27	–	–	–	–	–	–	58.8	0.01
Kaiser et al. (Essen) [46, 47]									
Unresectable, non-IORT	36	5.7	25	–	8.4	–	–	–	
Laparotomy + IORT	9	23.3	56	–	42	–	–	–	0.036
Laparotomy only, match-pair	9	9.4	33	–	0	–	–	–	
Mayo Clinic Rochester									
Noncurative resection + EBRT + 5-FU	6	12	50	0	–	–	–	–	
Unresected									
EBRT ± 5-FU [12]	11	12	55	0	–	–	–	–	
EBRT +/− 5FU + IOERT [32, 33][a]	14	18.5	71	43	29	14	7	7	
(c) IORT Gallbladder cancer series									
Todoroki et al. (Japan), Stage IV [34, 35]									
Surgery alone	43	6	–	–	4	–	–	4	
Surgery + IOERT/EBRT or both	50	13	–	–	22	–	–	13	0.0098

EBRT external-beam irradiation, *IOERT* intraoperative electron irradiation, *HDR Brachy* high-dose-rate brachytherapy

[a]Biopsy – 34, subtotal resection – 4; orthotopic liver transplant – 17, other total resection – 6. Single 5-year survivor died at 60 months with progression within EBRT field

pancreatic duct. Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTHC) are performed for complete visualization of both the right and left intrahepatic ductal systems, which is essential to assess bile-duct resectability and to demonstrate both the proximal and distal extent of the tumor. In general, multicentric tumors or tumors with bilateral intrahepatic segmental ductal extension preclude resection. If cholangiography shows only unilateral segmental extension or less proximal extension, resection is possible. A triphasic abdominal CT is performed alone or combined with position emission tomography (PET/CT) to rule out regional and intrahepatic metastases and assess for hepatic lobar atrophy [29]. Magnetic resonance imaging (MRI) of the liver is performed to determine the degree of intrahepatic tumor involvement. If metastases are excluded and the atrophy exists only on the side of the intrahepatic segmental extension, angiography is performed to assess vascular involvement. Angiography should demonstrate both the hepatic arterial and portal venous anatomy clearly. Bile-duct cancers are resectable if the blood supply to the liver can be maintained. If hepatic resection is undertaken, angiography should demonstrate the ability to preserve or at least reconstruct the vasculature to the postresection liver remnant.

Staging of proximal bile-duct cancers has been based on the Bismuth system. Bismuth classification of proximal bile-duct tumors is as follows:

Type 1: Confined to bile duct 2 cm or more below confluence.
Type 2: Ductal confluence involved but no intrahepatic segmental extension.
Type 3A: Ductal confluence involved with right unilateral segmental extension.
Type 3B: Ductal confluence with left intrahepatic segmental extension.
Type 4: Bilateral intrahepatic segmental extension.

In general, Bismuth Types 2 and 3 require hepatic resection. Implicit in all resections of bile-duct cancer is a thorough regional lymphadenectomy with skeletalization of the hepatic artery and portal venous systems. Bilioenteric continuity is restored via a Roux-en-Y hepaticojejunostomy.

Irradiation Techniques: EBRT

Dose-limiting structures. A major deterrent to improved results with EBRT ± bradytherapy for technically unresectable lesions is the limited irradiation tolerance of the liver, duodenum, stomach, and spinal cord and the lack of clear definition of the lesion's location and extent relative to the liver [30]. Although the superior and inferior extent of bile-duct malignancies can often be outlined by a percutaneous cholangiogram or endoscopic retrograde cholangiopancreatography (ERCP), the degree of extraductal invasion is poorly defined by current diagnostic imaging procedures. Both MRI and PET/CT imaging are useful in defining intra and extrahepatic disease extent and can be fused with treatment planning CT studies. Clip placement at the time of surgical exploration or resection is useful in outlining the extrahepatic component of ductal cancers and in defining the bed of the gallbladder. Shaped, multiple fields and shrinking field techniques should be used to spare as much normal tissue as possible [12, 21, 30, 31].

EBRT treatment volume and dose. The areas at risk for local relapse or progression include the tumor bed or unresected tumor and nodes along the porta hepatis, pancreaticoduodenal system, and celiac axis. An excretory urogram should be done at the time of CT simulation to confirm left renal function, as one half to two thirds of the right kidney is often included in the anteroposterior (APPA) component of treatment. Contrast is injected into the transhepatic catheter to define the extent of ductal tumor, and the location of pancreaticoduodenal nodes is determined with the contrast agent in the stomach and duodenum (nodes lie adjacent to medial wall).

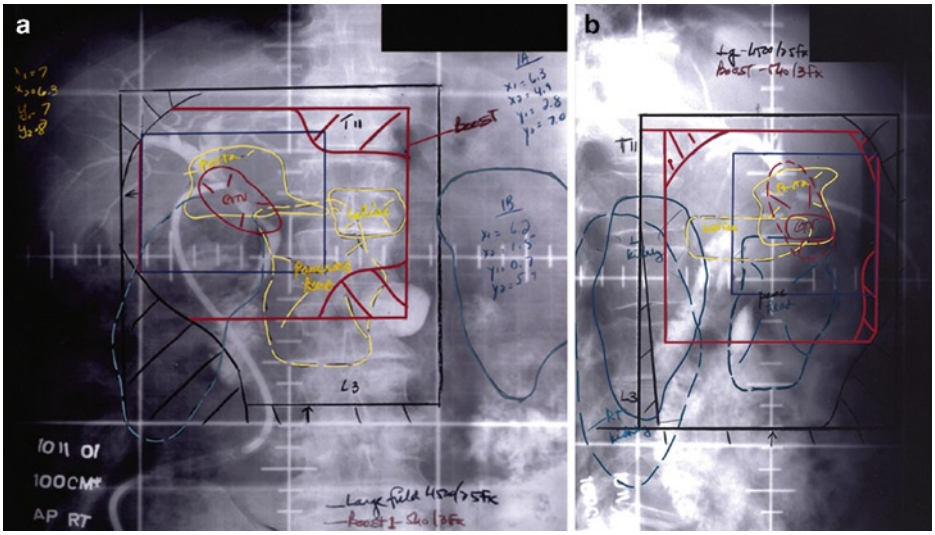

Fig. 14.1 (**a**, **b**) EBRT treatment fields. (**a**) APPA field with contrast in bile ducts and duodenum. (**b**) Lateral field.

The initial large-field treatment volume for EBRT fields can be treated to 40–45 Gy in 1.8 Gy fractions given 5 days a week via a 3D-CRT or IMRT multiple-field plan using shaped blocks to exclude unnecessary normal stomach, small intestine, kidney, and liver (Fig. 14.1) [12, 21, 30, 31]. Use of lateral fields for a portion of the treatment allows a reduction in dose to the spinal cord, right kidney, and portions of the liver. Liver intolerance to irradiation may necessitate an initial field reduction after 30–36 Gy and a second reduction after 45–50 Gy if unresected or residual gross disease exists. For bile-duct primary lesions, the preferred initial intrahepatic field margin beyond gross ductal disease is 3–5 cm because of the tendency for submucosal spread within lymphatics; these margins often need to be reduced to 2–3 cm after a dose of 30–36 Gy. The upper dose level within the second boost field is 55–70 Gy delivered over 6.5–8 weeks with EBRT alone. The higher doses are used only if the boost volume is carefully defined but could possibly be used more frequently with the advent of 3D-CRT and IMRT techniques [11, 15].

If boost dose irradiation is feasible with brachytherapy techniques, the tumor nodal dose is carried to 45–50 Gy with EBRT techniques and 20–30 Gy is delivered to a 1-cm radius with transcatheter Ir-192 [12, 21, 23]. If extraductal extent can ultimately be defined more precisely with transcatheter ultrasound, coil MRI imaging studies, or PET/CT, both 3D and brachytherapy boost techniques can be enhanced.

Surgical and IORT Factors

Unresectable bile duct. In most reported bile-duct series, IORT has been used as a supplement to EBRT for unresectable lesions. Exploratory laparotomy is performed to rule out occult peritoneal seeding, and intraoperative liver ultrasound is done to rule out undiscerned small liver metastases. The hilar component of the unresectable cancer is then surgically exposed, and titanium or small vascular clips are placed to mark the medial, lateral, and inferior extent of disease for purpose of postoperative EBRT field design. Duodenum and stomach can usually be mobilized out of the intended IOERT field.

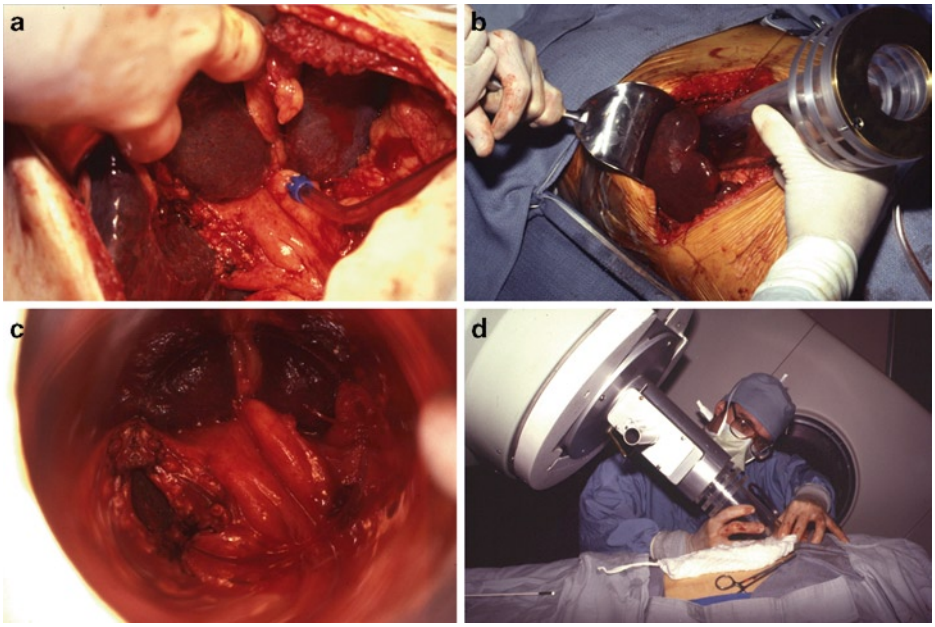

Fig. 14.2 (**a**–**d**): IOERT for unresectable bile-duct cancer (Mayo Clinic). (**a**) Definition of Klatskin tumor, (**b**) placement of IOERT applicator, (**c**) IOERT treatment field at liver hilum, and (**d**) IOERT applicator "docked" to accelerator.

The surgeon and radiation oncologist then determine the appropriate size IORT applicator to encompass both the palpable and radiographic tumor with at least a 1-cm margin (i.e., a 4 cm diameter lesion requires ≥6 cm diameter applicator) (Figs. 14.2 and 14.3). For unresectable lesions, the depth of the malignancy relative to the surgically exposed hilar lesion has to be estimated from preoperative imaging studies for purpose of determining IOERT energy (PTHC, ERCP, CT abdomen). In the MCR series [32, 33], IOERT energies ranged from 9 to 18 MeV. Since lesions are usually unresectable, IOERT doses commonly ranged from 15 to 20 Gy depending on the planned EBRT dose.

Major Resection Procedures and Indications, University of Tsukuba

In locally advanced biliary tract cancers, the extension mode of the tumor has a very wide range, and the surgical procedure should coordinate with the variety of tumor spread. Practically, liver resections of various extents, hepaticocholedocus resection with cholecystectomy, pancreatoduodenectomy, reconstruction of portal vein and/or hepatic arteries following resection, and systematic node dissection, are a basic component of resection surgery. For selecting resection procedures, tumor invasion to the (a) hepatic parenchyma, (b) intra- and extrahepatic bile ducts, (c) hepatic arteries, (d) portal veins, and (e) lymph-node metastasis will be taken into account based on preoperative imaging studies. Furthermore, a majority of patients with locally advanced disease require percutaneous transhepatic cholangio-drainage (PTC-D) for their associated obstructive jaundice to avoid unfavorable postresection complications. At Tsukuba University, PTC-D is performed to relieve jaundice for every patient with a serum total bilirubin level higher than 10 mg/dl or for patients with less than that level to clarify the exact location and pattern of the bile-duct obstruction. In order to predict the functional volume and conuration of the liver remaining after resection, the technology of 3D-functional liver imaging by GSA scintigraphy is applied routinely for patients with jaundice in whom extended hemilobectomy or hepatopancreatoduodenectomy would be inevitable.

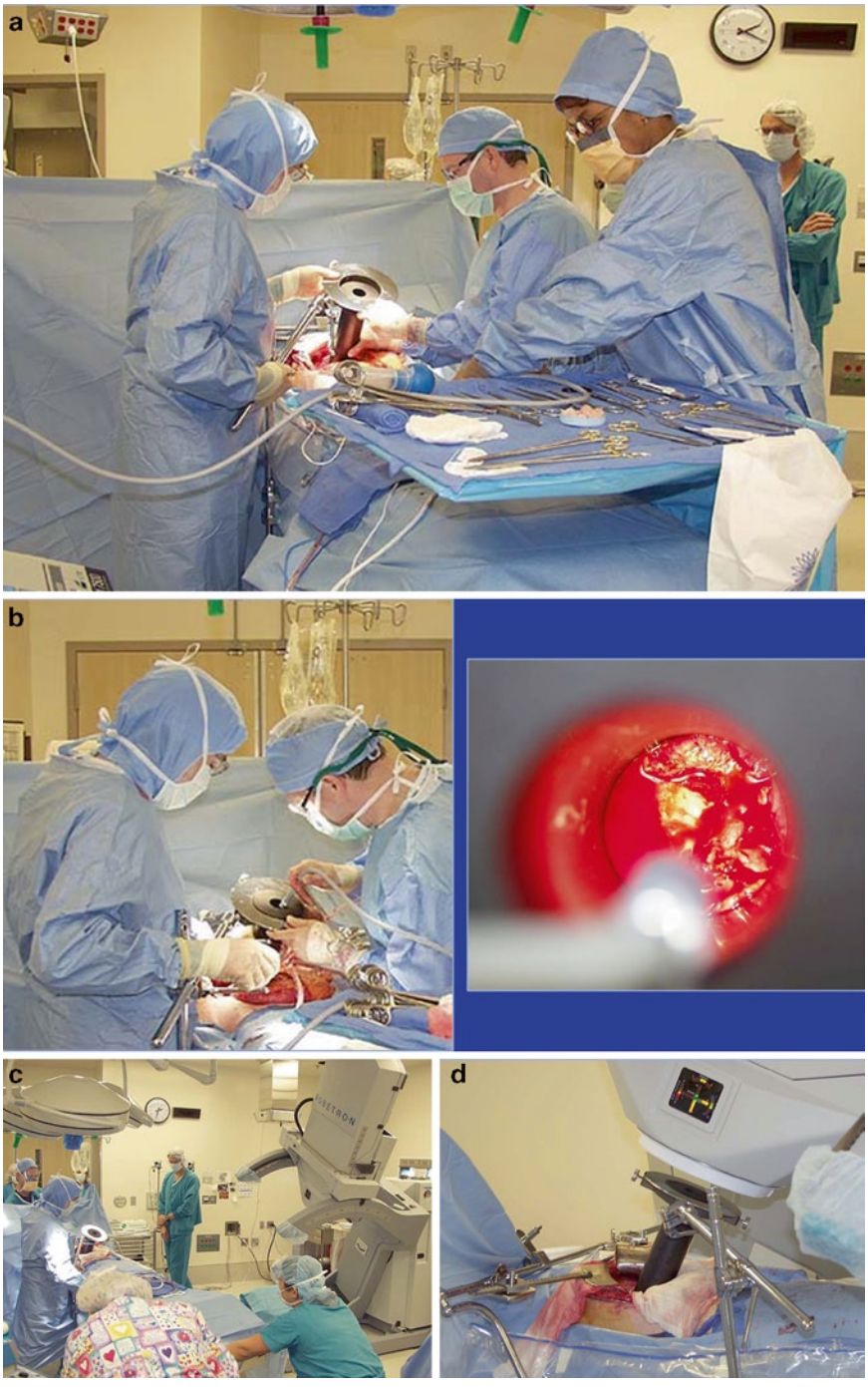

Fig. 14.3 IOERT for resected biliary tract cancer (Mayo Clinic Arizona). (**a**) Metal applicator placed over high risk surgical bed and clamped in position. (**b**) Applicator location checked with light source. (**c**) Patient moved adjacent to Mobetron x-band accelerator. (**d**) Mobetron alignment with applicator confirmed by laser light indicator.

The criteria for (1) hepaticocholedochus resection (HCR), (2) liver resection, and (3) systematic node dissection are as follows:

1. HCR is defined as a bile-duct resection of the main hepatic ducts up to above the primary bifurcation and down to the intrapancreatic portion. HCR is essential for patients with bile-duct cancer that has originated from or extends to the major hepatic bile ducts, or for patients with gallbladder cancer that extends to the bile duct. From a viewpoint of preoperative imaging studies, HCR should be considered when cholangiography reveals obstructive or narrowing changes of the main hepatic ducts and/or extrahepatic bile duct.
2. Liver resections of various extents – major hepatectomies, bisegmentectomies (S4 and S5), and wedge resections of the gallbladder fossa are performed alone, or with HCR according to the location of involved bile ducts. Furthermore, pancreaticoduodenectomy (PD) should be applied to patients with heavily metastasized peripancreatic lymph nodes and/or direct tumor extension to the head of the pancreas via the hepatoduodenal ligament. Hepatic bisegmentectomy will be carried out when the tumor extends less than 2 cm into the liver parenchyma in patients with gallbladder cancer, or when the tumor extends bilaterally to the main hepatic bile ducts with or without hepatic parenchymal involvement in patients with bile-duct cancer. Hepatic lobectomy should be done when the apparent tumor invasion extends beyond the scope of bisegmentectomy or, regardless of the extent of parenchyma invasion, when the tumor involvement in the portal vein precludes its reconstruction after resection. Resection of the Spiegelian lobe is essential when the tumor extension on the left hepatic duct reaches the bifurcation of the branch to the Spiegel lobe. Wedge resection of the gallbladder fossa is selected when the tumor is located on the fossa without evident invasion into the hepatic parenchyma.
3. The procedure of systematic node dissection is divided into three categories. The first category or grade involves dissection of nodes in the hepatoduodenal ligament including cystic duct, and pericholedochal and hilar lymph nodes. The second category includes nodes in the first-grade dissection, but in addition, lymph nodes of the right side of the celiac, around the common hepatic artery, periportal portion beneath the neck of the pancreas, and the right side of the superior mesenteric artery. The nodes of the right side of the aorta up to beneath the Spiegelian lobe and down below the bifurcation of the left renal vein are extirpated as a sample to check for metastasis. The third grade or category involves dissection of the paraaortic nodes together with the first- and second-category dissection.

Gallbladder. The largest experience using surgical resection and IOERT for locally advanced gallbladder cancers has been described by Todoroki et al. [34]. From October 1970 to May 1997, a total of 93 patients with stage IV cancers had surgical resection alone or in combination with EBRT, IORT, or IORT + EBRT at Tsukuba University. Resection procedures for stage IV disease varied due to the extent and mode of tumor invasion as previously discussed. Seventy-two of the 93 patients underwent some type of liver resection: major hepatectomy in 17 patients, hepatic bisegmentectomy (segment IV and V) in 43 patients, and wedge resection of the gallbladder fossa in 12 patients. Of the 72 patients with liver resection, 68 had additional hepaticocholedochus resection (HCR) as previously described. Pancreaticoduodenectomy (PD) was also performed in 31 of the 72 patients. Major vessels were reconstructed following resection of the portal vein and/or hepatic artery in 22 patients.

After en bloc resection of the cancerous lesion alone or combined with portal vein resection, IOERT was delivered to the liver hilum, including left and right intrahepatic ducts and Gleason's capsule in 40 of the 93 patients (mean dose 20.9 Gy, range 15–30 Gy). After IOERT delivery, lymphadenectomy was performed, as indicated, around the aorta and inferior vena cava. The irradiated intrahepatic ducts were then anastomosed to nonirradiated jejunum. Postoperative EBRT was given to 21 of the 40 IORT patients and an additional 10 received postoperative EBRT alone

without IORT. The mean EBRT dose was 40 Gy in 1.8–2.0 Gy fractions with a range of 12–54 Gy. The EBRT field included the periportal, celiac, and superior mesenteric nodal regions, as well as the IOERT field.

The rationale for combining maximum resection with IOERT ± EBRT in the Tsukuba series is based on an evaluation of X-ray sensitivity of human biliary tract cancer lines by investigators from the University of Tsukuba and Harvard School of Public Health [35, 36]. Although a number of clinical studies have indicated the efficacy of resection combined with IORT for advanced biliary tract cancer, the in vitro radiosensitivity of cells from this type of cancer has not been well described. The study from Tsukuba and Harvard Public Health was designed to examine both the sensitivity of human biliary tract cancer cells to ionizing radiation and the combined effects of radiation and 5-FU in these cells [36]. Five of the six cell lines examined that were derived from biliary tract cancers were significantly more resistant to radiation than two unrelated tumor cell lines, MCF-7 and Tera-2. The mean D_0, D_{10}, and SF_2 values for the five biliary cancer cell lines were 2.45 ± 0.23 Gy, 6.46 ± 0.41 Gy, and 0.60 ± 0.04, respectively. The sixth cell line was considerably more radiosensitive than the others (D_0 = 0.77 ± 0.02; D_{10} = 2.95 ± 0.06; SF_2 = 0.35 ± 0.03). The results suggested that bile-tract cancers as a group may be relatively radioresistant. Thus, tumor control may not be readily achieved by radiation alone. Combining IORT with maximal tumor resection can potentially improve tumor control and minimize the radiation dose to normal tissue, including grossly normal liver.

IORT ± EBRT Results

US Series: IORT ± EBRT

In the US series, both electrons and orthovoltage have been used as the method of IORT for primary biliary lesions. Many patients received both EBRT and IORT.

In the Rush Presbyterian IOERT series of nine patients, four had gallbladder cancer and five had extrahepatic bile-duct cancers. Five received EBRT, and four had chemotherapy. IOERT doses ranged from 15 to 22 Gy in the seven patients with unresectable lesions or partial resection with gross residual disease. Two of five bile-duct patients and one of four gallbladder patients survived ≥18 months [37]. Median survival for that group was 13 months with 1-year OS of 56%. The single disease-free survivor at 40+ months had bile-duct cancer and was the only patient in the series to receive concomitant chemotherapy during EBRT.

In a Joint Center analysis [38], a total of 15 patients received IORT doses of 5–20 Gy with orthovoltage for either primary (12 patients) or locally recurrent disease (3 patients). Thirteen patients also received postoperative EBRT. The median survival of the 12 patients with primary disease was 14.0 months, and local progression or persistence was documented in 50% of evaluable patients (five of ten). The three patients with locally recurrent cancers survived 2, 9, and 11 months.

MCR investigators reported an IOERT series of 15 unresectable patients at risk ≥1 year [32, 33]. Of 15 patients, 14 received EBRT doses of 45–50 Gy in 1.8 Gy Fx (before IOERT in 2 patients and after IOERT in 13) and 12 of 15 received IOERT doses of 20 Gy (15, 17.5, and 19 Gy in the other 3 patients). Median survival was encouraging at 16.5 months for the entire group and 18.5 months in the 14 patients treated with curative intent (one patient was a 5-year survivor). Five of the 14 curative patients (36%) were alive at 2 years. Local tumor persistence or relapse was diagnosed in 6 of 14 patients treated with curative intent (43%), but in 3 patients who died of noncancer causes, it was documented only at autopsy (15, 21.5, and 37 months). Only three patients received concomitant 5-FU during EBRT.

Japan IORT Series

In an early report of 11 patients treated in Japan at the Universities of Tsukuba and Chiba with 25–30 Gy IORT alone for biliary tract cancer (six gallbladder, five bile duct), Todoroki and coworkers [39] noted local persistence or progression in nine patients (82%). This was documented at autopsy in eight patients. Of the five patients with bile-duct cancers, the four postoperative survivors died with a local component of disease.

Bile-Duct Cancer

In a University of Tsukuba update by Todoroki et al. [40], a total of 81 patients were treated for bile-duct cancer from 1976 to 1986. Fifty patients had curative or noncurative resection (no further treatment, 33; IOERT boost, 14; EBRT, 3), and 31 patients had no tumor resection (biliary drainage alone, 21; IOERT, 6; EBRT, 4). Before 1983, IOERT doses ranged from 20 to 35 Gy, and no EBRT was given (12 patients – 9 with resection). Since 1983, the IOERT dose was limited to 20 Gy, and fractionated EBRT doses of 30–40 Gy in 4–5 weeks were usually added (seven patients received both; four patients had resection). Impact of treatment method on duration of survival in that series is seen in Table 14.2. There is a suggestive impact on survival at 18 and 24 months with the addition of IOERT. Only one patient (8%) with noncurative resection alone was alive at 18 and 24 months vs. 23% and 15% with IORT plus noncurative resection and 17% with biliary drainage plus IORT.

In a later analysis by Todoroki et al. [41, 42], 63 Tsukuba patients had surgical resection of Stage IVA Klatskin tumors and 47 of 63 had microscopic residual disease (R1 resection). 28/47 patients had adjuvant irradiation (17 both IOERT and EBRT), and 19 had surgery alone. Adjuvant irradiation resulted in higher 5-year OS than surgery alone in the 47 patients with R1 resection (33.9% vs. 13.5%; $p=0.014$), and the best results were with IOERT + EBRT (5-year OS, 39.2%). Locoregional control was also better in irradiated patients (79.2% vs. 31.2%).

At the 2008 ISIORT meeting in Madrid, Todoroki presented a Tsukuba series of 132 patients who underwent surgical resection of Klatskin tumors (Tis/T1 – 9 patients, T2 – 30, T3 – 72, T4 – 21) [43, 44]. Of the 93 with T3/T4 tumors, 83 had no distant metastasis (71/83 – R1 resection, 9/83 – R2 resection, 3/83 – R0 resection). In the 71 T3/T4 patients with R1 resection and no distant metastases, the treatment method was as follows: resection alone – 22 patients, resection/IOERT – 8, resection/postop EBRT – 14, resection/IOERT/postop EBRT – 27. Locoregional control was significantly better in patients who received some component of irradiation vs. resection alone (74% vs. 19%, $p=0.035$). The best 5-year OS was obtained in patients who received IORT and postop EBRT after R1 resection (IORT – 20.8%, postop EBRT – 21.4%, IORT + EBRT – 58.8%; $p=0.01$).

Gallbladder Cancer

Stage-IV gallbladder cancer has a distressingly dismal prognosis with a predominant locoregional failure problem after radical resection. The intent of Todoroki et al. in combining resection and IOERT at the University of Tsukuba [34–36] was to prolong survival by decreasing local relapse together with minimizing the sacrifice of normal tissues and structures surrounding the tumor. From October 1976 to May 1997, 93 patients with a Stage-IV gallbladder cancer underwent resection at Tsukuba University [35]. Resection procedures varied by the extent and mode of tumor extension and are discussed earlier in the chapter.

Survival results were compared in the various treatment groups [35]. For the 43 patients treated by resection alone, only one patient survived more than 26 months. Median survival was 6 months, and 5-year survival was only 4.4%. Of the 50 patients who received IOERT ± EBRT or postoperative EBRT alone, 5-year survival was 13.2% and median survival was 13%, $p = 0.0098$. Of the 52 patients with microscopic residual after resection, 22 had resection alone and 30 received IOERT ± postoperative EBRT. Median and 5-year survival rates favored those who received irradiation at 16 months vs. 8 months and 20% vs. 0% ($p = 0.005$). The surgical mortality rate as a whole was quite reasonable at 5.4%.

In an earlier analysis of 87 patients with Stage-IV gallbladder cancer, locoregional control rates in patients who were M0 at time of resection were 28.7% with resection alone [34]. When resection was combined with IOERT +/− postoperative EBRT, locoregional control was achieved in 73.6% of patients.

Summary

Although the method of treatment was not randomized in the Tsukuba series, their results indicate that aggressive resection combined with IORT + EBRT may be an efficient modality for improving the prognosis of locally advanced bile-duct and gallbladder cancer. Whether results could be improved further by delivering EBRT plus infusion prior to resection in patients with negative laparoscopy remains to be determined.

European Bile-Duct IOERT

Essen University Hospital Series

In 1997, Willborn et al. reported a series of 24 patients with carcinoma of the extrahepatic bile ducts including 17 patients with proximal third lesions who were treated by surgery and IOERT in the University Hospital in Essen, Germany [45]. IOERT was applied with energies of 6–15 MeV and total doses of 12–20 Gy. Resection was complete in 6 patients (R0), 11 had microscopic residual disease (R1 resection), and 7 had gross residual disease (R2). Ten patients received postoperative EBRT [eight to a total dose of 45 Gy/25 fractions/5 weeks in combination with continuous infusion 5-FU (300 mg/m^2/day), two received EBRT without 5-FU]. Two patients who were functionally inoperable were assigned to subsequent liver transplantation. In these two cases, IORT was applied to avoid tumor growth and tumor spread while the patients were awaiting transplant. Median survival of the 22 nontransplant patients was 8.6 months. Six patients were still alive at 1–18 months, four with no evidence of disease. Two patients received planned liver transplants and were alive with no evidence of disease (NED) at 38 and 43 months.

Many patients suffer from unresectable hilar cholangiocarcinoma, and palliative treatment is often the only therapeutic option. At Essen University Hospital, IORT is an additional option during surgery for patients found at laparotomy to have surgically unresectable cancers. An analysis by Kaiser et al. investigated the efficacy of IORT when compared with surgery alone in patients suffering from unresectable hilar cholangiocarcinoma [46, 47]. Palliative IORT (group 1) was performed on nine patients (four females and five males); surgery alone (group 2) was performed in a case-matched group of nine patients (four females and five males). The mean ages were 52.9 years (group 1) and 57.2 years (group 2). The two groups had comparable local tumor extension and stages of tumor disease according to UICC sixth edition. Group 1 was also compared to all 36 patients ($n = 36$) with unresectable cholangiocarcinoma treated without IORT (Group 3) in Essen.

The resectability rate at Essen University Hospital of patients operated on for hilar cholangiocarcinoma was 61%, comparable to most recently published investigations [48]. All patients tolerated the procedures well, no complications occurred during surgery or IORT. The in-hospital mortality rate was 0%. None of the IORT patients experienced complications in the postoperative hospital stay. One patient in group 2 developed an intraabdominal abscess treated successfully by drainage without reoperation and discharged 15 days after laparotomy. None of the IORT patients suffered from perioperative bile leakage or vascular thrombosis.

Patient survival was significantly increased after IORT compared to group 2 ($p=0.0359$) and group 3 ($p=0.0367$). The median survival time was 23.3 months (group 1) vs. 9.4 (group 2) and 5.7 months (group 3). One- and two-year OS were 56 and 42% after IORT, 33 and 0% – group 2, 25 and 8.4% – group 3. The survival benefit appeared to be related to improved local control, which resulted in less septic complications due to cholestasis and cholangitis.

Other German IORT Series

To analyze the actual clinical and scientific activity of IORT in Germany, questionnaires were sent to 102 centers in Germany [49]. The study focussed on indications in general surgery including bone tumors to evaluate the activity of IORT. Questionnaires were answered by 92% of the centers with the finding that 24 departments are working with IORT in Germany (16 are university hospitals). The main indications for IORT treatment are rectal carcinoma and soft-tissue sarcoma, but some IORT programs are also targeting head and neck malignancies, brain, gastric, pancreatic, and bile-duct malignancies. IORT was performed for bile-duct cancer in seven centers.

Sequelae of Treatment (Surgery, EBRT, and IORT)

Animal Studies

Liver and Bile-Duct Tolerance

Experimental data concerning normal tissue tolerance to IORT have been generated in both rabbits and dogs. Todoroki [50] studied the effects of large single doses of irradiation to the liver hilum in rabbits and found hepatic parenchymal atrophy, significant biliary fibrosis, and necrosis at doses greater than 30 Gy. Sindelar and coworkers [51] investigated the effects of IORT on the extrahepatic bile duct in dogs and noted dose-related fibrosis and duct stenosis at doses of 30 Gy or greater. Duct stenosis resulted in secondary hepatic changes of biliary cirrhosis, which developed with time. These studies used irradiation after performing the anastomosis, so both the jejunal and biliary part of the anastomosis were irradiated, resulting in healing insufficiency and anastomotic disruption.

In a recent study from the Essen IORT group, a total of 22 pigs underwent gallbladder and proximal bile-duct resection with or without IORT followed by Roux-en-Y hepaticojejunostomy [52]. There were no complications during surgery, and no anastomotic disrupture or bile leakage was diagnosed in the follow-up period of 56 days. In the control group, all the pigs survived well without jaundice, cholangitis, and gastrointestinal bleeding. Serum bilirubin levels and hepatic specific enzymes were within the normal range during follow-up. MR imaging demonstrated normal liver size without dilatation of intrahepatic duct. In the IORT group, one pig died after 20 Gy of gastrointestinal bleeding, which was considered as stress ulcer. Three 30 Gy pigs died of sepsis; one had typical obstructive purulent cholangitis due to stenosis of the biliodigestive anastomosis after irradiation. One pig after 40 Gy died of intestine obstruction that was not IORT related.

Serum bilirubin levels in the animals after 30 or 40 Gy of IORT were elevated from the second or third week after irradiation to the end of follow-up, which were consistent with the clinical findings. Findings on MR imaging at the end of follow-up also supported the existence of bile-duct obstruction. Postmortem examination confirmed the clinical evidence of stenosis in the biliodigestive anastomoses. Furthermore, the severity of the stenosis of biliary-enteric anastomoses was dose dependent, and higher irradiation dosage caused even more severe stenosis. However, when the hepatic duct is severely obstructed in humans, it needs endoscopic stenting or surgical drainage. But no anastomotic disruption occurred on the irradiated pigs. Additionally, after 40 Gy intraluminal sludge was found in the hepatic duct, while it was not found after 20 or 30 Gy.

The sequence of IORT and hepaticojejunostomy is an important factor influencing the healing of anastomoses. In previous studies on dogs, biliary-enteric anastomosis was performed prior to IORT. When the anastomoses receive IORT, irradiation will damage the capillaries in the anastomoses on both sides and prevent healing. In contrast, in the Essen animal studies, IOERT was given after resecting part of the extrahepatic bile duct as in the human procedure; after the completion of IOERT, hepaticojejunostomy was performed.

It has been proven that radiation has a number of effects on wound healing and angiogenesis [53]. However, if biliary-enteric anastomosis is performed after irradiation, only the blood vessels and tissue of the hepatic duct are damaged, while those of jejunum loop are intact. On the basis of these findings, we suggest that IORT should be given after bile-duct resection, but prior to hepaticojejunostomy.

The bile duct can tolerate IORT up to a dosage of 40 Gy without disruption of the biliary-enteric anastomosis. IORT with a dosage of 20 Gy on porcine biliary-enteric anastomosis is safe with acceptable complications. However, IORT will cause severe complications if the dosage is up to or more than 30 Gy. Stenosis of the biliary-enteric anastomosis is the most common IORT-related complication that occurs not only in the late postoperative period but also in the early postoperative period. Based on these experimental results, further studies in humans can be established with less fear for IORT-related complications up to a dose of 20 Gy.

Clinical Tolerance Studies

Severe complications are also well known in hepatobiliary surgery without IORT [48, 54]. Nevertheless, many surgeons are still afraid of IORT-related complications and, therefore, avoid this method in bile-duct cancer. Gastrointestinal bleeding, hepatic abscess, septicemia, stenosis, or obstruction of anastomoses have been found in clinical practice. Necrosis of the biliary tree wall after IORT was detected at the postmortem examination and reported in one patient by Kurosaki and colleagues after IORT [55]. Iwasaki and coworkers published the death of four patients after IORT of the biliary tract [40]. Their patients died within 6 months after IORT, and the cause of mortality was not cancer itself, but complications (gastrointestinal bleeding, hepatic abscesses or septicemia, or both) due to the multimodal therapy.

Gastric and Duodenal Tolerance

A good analysis of gastric and duodenal tolerance with EBRT exists in the biliary duct analysis from Mayo by Buskirk et al. [12]. For locally unresectable or resected but residual biliary cancer, three aggressive treatment regimens were used: EBRT alone or combined with 5-FU (45 Gy in 25 fractions in 5 weeks to a tumor and nodal field, with a reduced field boost for 10–20 Gy in 2 Gy fractions) or similar EBRT to a tumor and nodal field combined with IOERT or transcatheter brachytherapy.

The distal stomach and duodenal C-loop were usually within the EBRT field to a dose of 45 Gy. With brachytherapy, patients received doses of 15–30 Gy, usually calculated at a 1-cm radius from the transcatheter iridium. With IOERT patients, the duodenum and stomach were usually surgically excluded.

An analysis comparing dose with complications was performed for Mayo patients who received EBRT alone or EBRT combined with brachytherapy or IOERT. With EBRT doses of 55 Gy or less to the duodenum or stomach, the risk of severe GI complications varied from 5 to 10%, depending on which parameter was being evaluated. At doses greater than 55 Gy, one third of the patients developed severe GI problems. In patients who received EBRT plus iridium, the dose to the EBRT field was limited to 50.4 Gy, but most received additional radiation dose to duodenum and/or stomach from the iridium boost (higher doses with distal lesions). There was a 30–40% incidence of severe complications in the duodenum or stomach in this group.

Biliary Duct Tolerance

At radiation dose levels used in the aggressive treatment combinations at Mayo Clinic (EBRT plus transcatheter or IOERT boost), temporary fibrosis and duct stenosis have not been unexpected or uncommon [12, 30, 31]. Transhepatic catheters were previously left in place until the degree of stenosis had stabilized or lessened on serial cholangiograms, which usually occurs within 12–18 months of treatment. In view of stent-related morbidity, attempts are now made to remove transhepatic catheters or endoscopic stents within 3–6 months of the brachytherapy boost if imaging techniques of the biliary tree suggest that this is medically feasible.

Hepatic Artery Tolerance

In the series reported by Iwasaki and colleagues [40], the IOERT dose for bile-duct cancer was reduced to a maximum of 20 Gy following curative or noncurative resection because of an excessive incidence of severe complications. When IOERT doses of 20–35 Gy were used, four of seven patients with IOERT after surgical manipulation of the hepatic artery developed stenosis, obstruction, or aneurysm. In five patients treated subsequently with IOERT doses of 20 Gy or less after resection, no severe vascular complications occurred.

Summary and Future Possibilities

Summary

Treatment Intensification, IORT/Non-IORT

The potential impact of treatment intensification on duration of survival for patients with bile-duct or gallbladder cancer is seen in separate series from Japan, Mayo Clinic, TJUH, Rush Presbyterian, and the University of Pittsburgh (Table 14.2). Survival trends seen, however, may be due to patient selection rather than treatment method.

In the bile duct series from Japan by Iwasaki and colleagues [40], with biliary drainage alone (21 patients), survival at 6 months was only 20%, with a 1-year survival rate of ≤5% and no 18-month survivors. With noncurative resection ± IORT (13 patients each group) or biliary drainage plus IORT (6 patients), survival appeared to be better (1-year SR 44, 46, and 33%; 2-year SR 8, 15, and 17%).

In the Japan gallbladder analysis from the University of Tsukuba by Todoroki et al. [34, 35], with surgery alone for stage-IV disease ($n=43$), the median survival was 6 months and the OS at 2 and 5 years was only 4.4%. When surgery was supplemented by EBRT (10 patients) or IOERT ± EBRT ($n=40$), median and 5-year OS were 13 months and 13.2% ($p=0.0098$, log rank). Of the 52 patients with R1 resection, 5-year OS was better in the 30 patients who received IORT ± EBRT vs. those who received surgery alone at 20% vs. 0% ($p=0.005$).

In bile-duct cancer analyses by Todoroki of patients with R1 resection, those with irradiation had an improvement in both locoregional control and OS [41–44]. In the latest analysis [44], locoregional control was 74% in irradiated patients vs. 19% for surgery alone patients ($p=0.035$). Five-year OS was 58.8% with IOERT plus postop EBRT vs. 20.8% – IOERT only, 21.4% – EBRT alone ($p=0.01$).

In the Essen University Hospital series of 45 patients with unresectable hilar cholangiocarcinoma at surgical laparotomy [46, 47], patient survival was significantly increased in those who received IORT (group 1, $n=9$) compared to a match pair with laparotomy only (group 2, $n=9$; $p=0.036$) and the total non-IORT group of 36 patients (group 3, $p=0.0367$). The median survival time was 23.3 months (group 1) vs. 9.4 (group 2) and 5.7 months (group 3). One- and two-year OS were 56 and 42% after IORT, 33 and 0% – group 2, 25 and 8.4% – group 3. The survival benefit was felt to be related to improved local control with a resultant decrease in septic complications, including death, from cholestasis and cholangitis.

In data from Mayo Clinic [12, 23, 31, 33], survival ≥18 months was 0% with EBRT ± 5-FU for 11 patients with unresectable bile-duct lesions, 33% with gross total or subtotal resection before EBRT in 6 patients and 38 and 43%, respectively, in patients with unresectable lesions treated with EBRT plus a specialized boost with Ir-192 (24 patients) or IOERT (14 patients). There were four 5-year survivors in the latter group of 38 patients (10.5%). Nine of the 24 patients with an Ir-192 boost received 5-FU during EBRT and two (22%) were 5-year disease-free survivors vs. 8% 5-year survival in the 15 patients with no 5-FU during EBRT [22].

The TJUH series of 48 patients was previously discussed with regard to the suggested impact on survival of irradiation vs. none and increase in irradiation dose [16]. The 2-year survival was 48% vs. 30% with an increase in median survival of 24 months vs. 6 months with >55 Gy vs. <55 Gy, $p=0.0003$.

In the Rush Presbyterian analysis [37] treatment combinations of EBRT with IOERT or brachytherapy appear to have improved survival when compared to patients who received no irradiation. For the six patients with no irradiation, the mean and 1-year survival were respectively 4.6 months and 0% vs. 11 months and 46% in 13 patients who received EBRT ± Ir-192. For the nine patients who received IOERT ± EBRT, the median survival was 13 months, the mean survival was 17 months, and 1-year survival was 56%. Survival trends for patients without vs. with irradiation achieved statistical significance ($p=0.03$).

The most impressive results have been obtained when preoperative EBRT plus concurrent 5-FU based chemo alone or plus transcatheter Ir^{192} preceded liver transplant in separate series from the University of Pittsburgh [26] and Mayo Clinic Rochester (MCR – 26, 27) (Table 14.2). Four and five-year survival was 53.5% in the University of Pittsburgh series vs. a 4-year survival of 22% when transplant preceded EBRT. In the highly selected MCR series, 3- and 5-year survival was 82% for the 38 patients who received an orthotopic transplant after preop EBRT + concurrent bolus 5-FU, Ir^{192} plus concurrent and maintenance protracted venous infusion of 5-FU vs. 21% for 26 patients treated with standard resection for resectable proximal cancers ($p=0.02$).

IORT Dose and Indications

Based on experimental results and clinical experience, IORT is safe up to a dosage of 20 Gy [50–52]. Although the bile duct can tolerate IORT up to an absorbed dose of 40 Gy without disruption of the

biliary-enteric anastomosis in a porcine model, severe complications (i.e., anastomotic stenosis) can occur if the IORT dose is 30 Gy or more. Therefore, an IORT dose of ≤20 Gy is recommended when applied to the liver hilum in the clinical setting.

Since IORT and surgical exploration can be used effectively for tumor therapy by irradiation during the operation without additional risk, for patients with unresectable bile duct cancer, IORT offers a palliative therapeutic option with a potential survival benefit as shown in the Essen series by Kaiser et al. [46–48] and previously shown for unresectable pancreatic cancer by Willett et al. [56]. The procedure is safe for patients and maintains the possibility of prolonged survival in this desperate situation. Thus, IORT is a promising procedure for patients with proximal bile-duct cancer, who were intended for complete tumor resection but defined intraoperatively as unresectable.

Future Possibilities

In an attempt to improve survival and disease control for patients with biliary tract malignancies, it would be of interest to combine the various modalities that appear to impact those end points. For lesions that are unresectable with standard or extended surgical procedures, the options include EBRT, simultaneous ± maintenance chemotherapy, a specialized irradiation boost with transcatheter iridium or IOERT ± liver transplant. Improved imaging techniques would be helpful in defining both surgical resectability and tumor/target volumes for EBRT (standard and 3D conformal) and specialized boosts with IOERT or brachytherapy.

The increased utilization of simultaneous EBRT plus chemotherapy is indicated in view of results in single-institution studies in patients with bile-duct cancers and randomized single-institution and group trials in other GI sites (unresectable pancreas; unresected or residual gastric and large bowel; resected but high-risk rectal and pancreas ± gastric; unresected esophagus). The use of low-dose infusion 5-FU or capecitabine is preferred to bolus 5-FU or 5-FU/Leucovorin during EBRT as it is safer (less apt to result in severe leukopenia in a patient who is at risk for tube-related sepsis) and potentially more efficacious.

With regard to the use of IOERT vs. brachytherapy or stereotactic body irradiation (SBRT) for a specialized boost, this is dependent on whether the patient is a potential candidate for resection. If the primary lesion appears to be surgically unresectable on the basis of imaging studies and the specialized irradiation boost with brachytherapy or SBRT can safely be given, this is a more cost-efficacious method of delivery. If stomach or duodenum cannot be excluded from a brachytherapy or SBRT field, however, it may be reasonable to reoperate for the purpose of giving the boost with IOERT while displacing those structures.

For patients who present with surgically unresectable lesions, it would be reasonable to initiate treatment with EBRT plus infusion 5-FU or capecitabine and plan to reevaluate 3–4 weeks after completion of such for the option of attempted gross total resection ± specialized IORT boost. This approach is supported by results in bile-duct series from Heidelberg [24] and Rotterdam [25], which show a survival advantage for patients with resection vs. no resection and the excellent 5-year results with resection plus IOERT and EBRT in locally advanced gallbladder and bile-duct cancers demonstrated by Todoroki et al. in Tsukuba [34–36, 39–44]. Both Mayo Clinic [27, 28] and the University of Pittsburgh [26] performed studies in which patients with proximal lesions were candidates for liver transplant following preoperative EBRT plus concomitant 5-FU ± brachytherapy (Mayo) for lesions that are unresectable by standard surgical criterion with excellent 5-year OS (University of Pittsburgh – ~50%, Mayo Clinic – 82%).

For patients in whom microscopic or gross residual disease remains after an attempt at resection, the addition of EBRT ± chemotherapy seems reasonable on the basis of bile-duct analyses by Gonzalez et al. for the EORTC group [19] and Weiss et al. for Fox Chase/University of Pennsylvania

[18], and the use of IOERT (plus EBRT and resection) is supported by the excellent long-term results achieved in locally advanced gallbladder and bile-duct cancers in Tsukuba [34–36, 39–44]. The availability of IOERT or HDR-IORT may allow delivery of a localized boost dose of irradiation after resection but before reconstruction as in the Tsukuba gallbladder series by Todoroki et al. [34–36] (i.e., IOERT for positive radial or circumferential margins due to adherence to porta hepatis structures that could not be boosted with postoperative transcatheter iridium; HDR-IORT for microscopically positive ductal margins). It would be of interest to investigate sequencing issues in patients with potentially or borderline resectable lesions (give EBRT plus 5-FU before instead of after resection to alter implantability of cells that may be shed at the time of resection).

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Chapter 15
Primary Colorectal Cancer

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Keywords Colon cancer • Rectal cancer • Colo-rectal cancer • IORT for colorectal cancer

Introduction

Carcinoma of the rectum is a heterogeneous disease. At one end of the clinical spectrum, a small number of patients present with superficially invasive cancers who are well served by limited procedures, such as local excision or endocavitary irradiation. The great majority of patients with rectal cancer, however, have mobile but more deeply invasive tumors that require low anterior or abdominoperineal resection. At the other and less favorable end of the clinical spectrum, a subset

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_15,

of patients present with locally advanced tumors that are adherent or fixed to adjoining structures such as the sacrum, pelvic sidewalls, prostate, or bladder.

Within this last group of patients categorized as "locally advanced," there is also variability in disease extent with no uniform definition of resectability. Depending on the report, a locally advanced lesion can range from a tethered or marginally resectable tumor to a fixed cancer with direct invasion of adjacent organs or structures. The definition will also depend upon whether the assessment of resectability is made clinically or at the time of surgery. In some cases, tumors thought to be unresectable at the time of initial clinical or radiographic examination may be found to be more mobile when the patient is examined under anesthesia. With these caveats, a good working definition of a locally advanced tumor is a tumor that cannot be resected without leaving microscopic or gross residual disease at the resection site because of tumor adherence or fixation to that site. Figure 15.1 shows the CT scan of a patient with a "locally advanced" rectal cancer invading the posterior and left pelvic sidewall tissues. At surgery, it was adherent to the sidewall, and pathological review of the resection specimen showed that the radial soft-tissue margins were positive for carcinoma. Since these patients do poorly with surgery alone, irradiation and chemotherapy have been added to improve the outcome. This chapter summarizes the evolution of treatment and the role of intraoperative irradiation (IORT) in this group of patients.

Non-IORT Treatment Approaches

External Beam Irradiation

In the past, the management of locally advanced rectal cancer was variable. Some patients had incomplete surgical resections alone, while others had radiation alone or surgery combined with post- or preoperative irradiation. The results of high-dose external-beam irradiation (EBRT) as a primary curative treatment have been unsatisfactory with local failure rates of at least 90% or greater and 5-year survivals of less than 10%. Wang and Schulz reported that of a total of 58 patients with recurrent, inoperable, or residual rectosigmoid carcinoma treated at Massachusetts General Hospital (MGH) with 35–50 Gy in 4–5 weeks, six patients survived for 5 years disease-free [1]. O'Connell et al. noted that 37 of 44 patients with locally unresectable or recurrent rectal carcinoma treated at Mayo Clinic with 50 Gy in a split-course fashion over 7 weeks with and without adjuvant immunotherapy had progression of disease [2]. Median survival was ~18 months in both groups of patients. Of 31 patients assessable for sites of initial tumor progression, 17 had local progression only, 11 had concurrent local progression and distant metastases only, and three developed only distant metastases (28 of 31 or 90% had progression within EBRT field). Brierley and Cummings reported that of 77 patients with clinically fixed tumors who were treated at Princess Margaret Hospital with 50 Gy in 20 fractions over 4 weeks, local control was 3% and survival was 4% [3]. External-beam irradiation alone has no role as definitive treatment, unless the patient is not a candidate for surgery.

External-Beam Irradiation and Surgery

Postoperative EBRT

Combinations of EBRT and surgical resection have been used to improve local control and survival. When radiation therapy is given after subtotal resection, local control and survival are better in patients treated for residual microscopic disease compared to patients treated for gross residual disease.

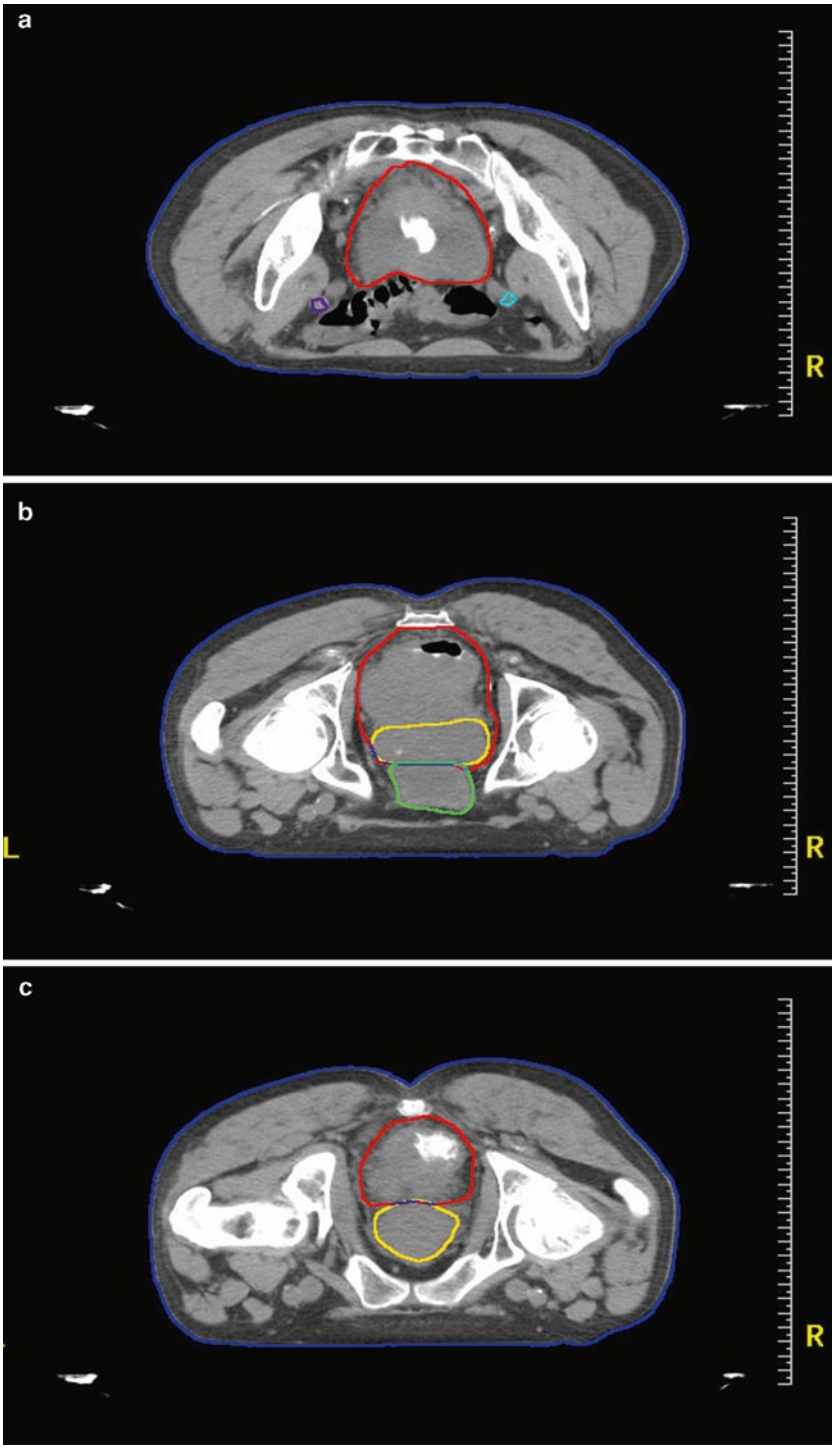

Fig. 15.1 EBRT techniques. (**a**–**h**) Conformal pelvic EBRT multiple-field technique for patient with locally unresectable cancer involving distal rectum and proximal sigmoid using CT-based treatment planning (**a**–**d**) CT images were used to define gross tumor volume (*red*; posterior tethering and loss of fat plane anteriorly relative to prostate), prostate (*yellow*), bladder (*green*), normal distal rectum (*blue*) and iliac vessels (*light blue*, *purple*). (**e**–**g**) Preoperative EBRT fields were designed using AP/PA (**e**, **f**) and lateral fields (**g**, **h**) with some lateral field reduction (**h**) after 45 Gy/25 fractions/5 weeks.

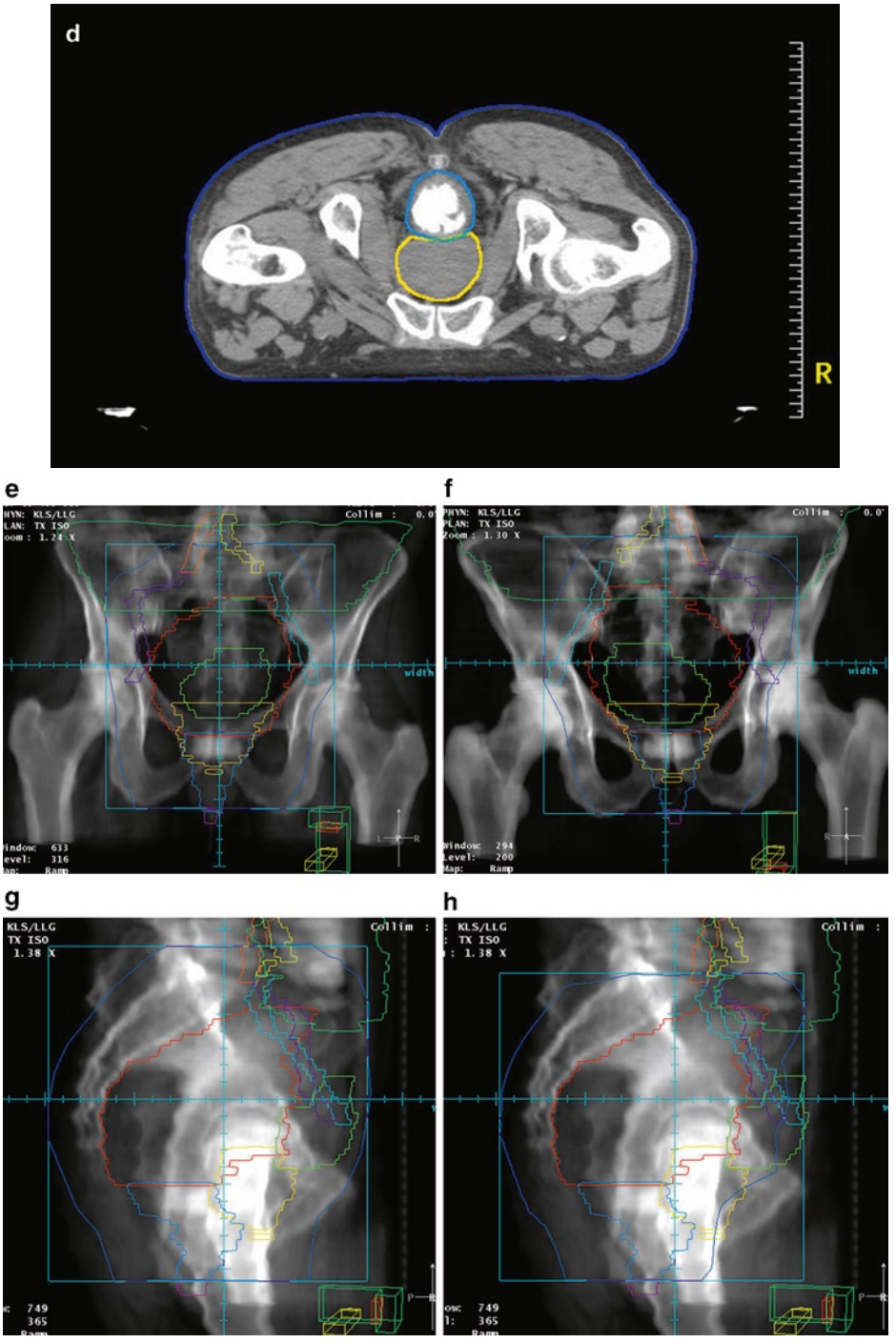

Fig. 15.1 (continued)

Allee et al. reported the results of 31 patients with residual microscopic cancer treated at MGH with 45 Gy in 25 fractions over 5 weeks followed by additional boost field irradiation to as much as 60–70 Gy if small bowel could be moved from the radiation field [4]. Local control and 5-year disease-free survival rates were 70 and 45%, respectively. In contrast, these figures were 43 and 11% for 25 patients treated for gross residual disease. A possible dose–response correlation was seen in patients with microscopic residual disease; the risk of local failure was 11% (one of nine) with doses of 60 Gy or greater versus 40% (8 of 20) if the boost dose was less than 60 Gy. There was no clear dose–response relationship in patients with gross disease.

Of a total of 17 Mayo Clinic patients receiving EBRT after subtotal resection, Schild et al. observed that local control was achieved in three of ten patients (30%) with microscopic residual cancer and one of seven patients (14%) with gross residual cancer [5]. Four of the 17 patients (24%) remained disease-free for more than 5 years, and median survival was 18 months.

Ghossein et al. treated patients at Albert Einstein to 46 Gy in 1.8 Gy fractions followed by a field reduction to the area of persistent disease that received 60 Gy [6]. The incidence of local failure and survival for patients treated with microscopic disease was 16 and 84%, whereas for patients with gross disease, these figures were 50 and 39%, respectively.

Preoperative EBRT

For patients presenting with locally advanced disease (unresectable for cure because of tumor fixation), the use of moderate- to high-dose preoperative EBRT (45–50 Gy in 1.8–2.0 Gy fractions) has been used to reduce tumor size and facilitate resection (Table 15.1). Emami et al. reported that the rate of resectability of 28 Tufts University patients after full-dose preoperative EBRT was 50% [7].

Dosoretz et al. reported MGH results in a total 25 patients with unresectable tumors in the rectum or rectosigmoid treated with 40–52 Gy preoperative EBRT [8]. Sixteen of the 25 patients underwent potentially curative resection, and the 6-year survival was 26% (with three postoperative deaths). Total pelvic failure after curative resection was 39% (5 of 13 patients).

Mendenhall et al. reviewed a total of 23 patients with locally advanced carcinoma who received 35–60 Gy of preoperative irradiation at the University of Florida [9]. Eleven patients were able to undergo complete resection with a 5-year absolute survival of 18% and a local failure of 55%.

As reported by Stevens and Fletcher, 28 of 72 patients (39%) with locally advanced carcinoma of the rectum or rectosigmoid who received 50–60 Gy preoperatively were resectable in a series from the University of Oregon [10]. However, tumor recurred locally in nine of 28 (32%) of these patients, and the 5-year survival was only 10%.

Of a total of 20 Brigham and Women's Hospital patients with unresectable rectal cancer undergoing 43–55.8 Gy preoperative irradiation reported by Whiting et al., 13 patients (65%) underwent

Table 15.1 Preoperative radiation and resection of locally advanced rectal cancer

	# of patients	Resectable for cure (%)	Local control resected pts (%)	5-year OS resected pts (%)
Tufts University [7]	28	50	–	41
Massachusetts General Hospital [8]	25	72	62	43[a]
University of Florida [9]	23	48	45	18
University of Oregon [10]	72	39	32	10
Brigham and Women's Hospital [11]	20	65	77	53

pts patients

[a]6-year survival rate of 26%

resection with curative intent [11]. Three of the thirteen patients (23%) subsequently developed a local failure. The 5-year survival was 40%.

There has been one randomized prospective study examining the merits of preoperative irradiation in patients with locally advanced rectal cancer. Under the auspices of the Northwest Rectal Cancer Group (Manchester, United Kingdom), 284 patients with tethered or fixed rectal cancer were entered into a prospective randomized trial between 1982 and 1986 assessing the effects of preoperative irradiation given 1 week before surgery [12]. One hundred and forty one patients were allocated to undergo surgical treatment alone, and 143 were allocated to receive 20 Gy in four fractions before surgery. This study showed a marked reduction in local recurrences in the irradiated group (12.8%) versus surgery-alone group (36.5%). Although there was no significant difference in either overall survival or cancer-related mortality between the two treatment groups, subset analysis of the patients who underwent curative surgery reveals an overall mortality of 53.3% for patients allocated to surgery alone and 44.9% for patients allocated to preoperative radiotherapy. This was a significant reduction in mortality.

In summary, following full-dose preoperative irradiation, most series report that one half to two thirds of patients with locally advanced rectal cancers will be converted to a resectable status. However, despite a complete resection and negative margins, the local failure rate depending on the degree of initial tumor fixation varies from 23 to 55%.

Preoperative EBRT with Chemotherapy and Surgery

Because of the efficacy of postoperative irradiation and 5-FU in the adjuvant treatment of rectal cancer, there has been interest in examining this approach preoperatively. These investigations have studied combinations of moderate- to full-dose preoperative irradiation (45–50.4 Gy) with 5-FU-based chemotherapy for patients with clinical T3 and T4 rectal cancer.

The most significant, practice-changing study with regard to preoperative EBRT with chemotherapy was the German Rectal Cancer study, which randomized a total of 421 patients with clinical T3 or T4 or node-positive rectal cancer to either preoperative or postoperative chemoradiotherapy [13]. Treatment consisted of preoperative 50.4 Gy in 28 fractions of EBRT with continuous infusion of 5-FU in weeks 1 and 5, surgery 6 weeks later, and then four 5-day cycles of 5-FU starting 1 month after surgery. The postoperative treatment arm was identical except for an EBRT boost of an additional 5.4 Gy. Five-year overall survival (OS) was not significant between arms (76 vs. 74%), but local relapse at 5 years was significantly lower in the preoperative chemoradiation arm, 6 vs. 13% ($p=0.006$). Preoperative treatment was more tolerable, with less Grade 3/4 acute toxicity (27 vs. 40%, $p=0.001$) and chronic toxicity (14 vs. 24%, $p=0.012$), and a higher percentage of patients were able to receive all the planned radiotherapy (92% vs. 54%) and chemotherapy (89% vs. 50%). Furthermore, preoperative treatment resulted in an approximately 10% higher rate of pathologic downstaging, had an 8% complete response rate (vs. 0% in the postoperative arm), and had significantly higher rates of sphincter preservation in patients judged by the surgeon pretreatment to require an abdominoperineal resection (39 vs. 20%, $p=0.004$). Owing to all these factors, preoperative chemoradiotherapy became the standard of care for patients with clinical T3 or T4 or node-positive rectal cancer.

Because several of the trials evaluating preoperative radiotherapy for locally advanced rectal cancer (including the German Rectal Cancer study) did not include patients with unresectable clinical T4 tumors, a Norwegian group conducted a phase III randomized trial examining concurrent preoperative chemoradiation plus adjuvant chemotherapy vs. preoperative radiation alone, among patients with unresectable T4 or locally recurrent disease [14]. Between 1996 and 2003, a total of 207 patients received either concurrent bolus 5-FU with 50 Gy in 25 fractions, surgical resection

5–8 weeks later, followed by adjuvant 5-FU for eight cycles or the same preoperative radiation alone. In resected patients, sphincter preserving-surgery was performed in 53% vs. 36% ($p=0.03$). An R0 resection was performed in 84% of the chemoradiation group vs. 68% in the radiation alone group ($p=0.009$). Pathologic complete response was found in 16% vs. 7%, respectively ($p=0.04$). After a median follow-up of 61 months, the chemoradiation with adjuvant chemotherapy arm had significantly improved 5-year local control (82% vs. 67%, $p=0.03$), time to treatment failure (63% vs. 44%, $p=0.003$), and cancer-specific survival (72% vs. 55%, $p=0.02$), with a non-significant trend to OS advantage (66% vs. 53%, $p=0.09$). Compliance with adjuvant chemotherapy was relatively low, as only 48% of patients started adjuvant chemotherapy, and only 20% of patients completed the planned eight cycles.

Comments in the rest of this section will be limited to analyses of patients with exclusively clinical T4 or tethered T3 tumors [15]. The end points of these studies have included not only resectability, local control, and survival but also pathological downstaging and sphincter preservation rates, as in the German Rectal Cancer study and Norwegian trial.

In a report from the MD Anderson Hospital (MDAH), a total of 38 patients with locally advanced rectal cancer (T4 or tethered T3) received 45 Gy in 25 fractions of preoperative EBRT with continuous infusion chemotherapy of 5-FU and/or cisplatin and surgery. Eleven of the 38 patients received an IOERT supplement to the site of adherence at time of resection. Three-year survival and local recurrence rates were 82 and 3%, respectively. These results contrasted to a 3-year survival and local recurrence rate of 62 and 33% for 36 similarly staged patients undergoing preoperative irradiation without chemotherapy or IOERT at MDAH. Although there was a higher rate of sphincter-preserving procedures in patients receiving chemoirradiation (35%) versus patients undergoing irradiation only (7%), there were no differences in rates of resectability or pathological downstaging between these groups of patients receiving chemotherapy versus no chemotherapy.

Other investigations, however, have reported higher resectability and pathological downstaging rates with the use of preoperative chemoirradiation schedules. In an analysis of 36 patients (30 primary and 6 recurrent) with locally advanced/unresectable disease who were treated with 50.4 Gy of pelvic irradiation and concurrent 5-FU and leucovorin at Memorial Sloan–Kettering Cancer Center (MSKCC), the resectability rate with negative margins was 97%, and the total complete pathologic response rate was 25% [16]. Similarly, a Swedish study reported an enhanced resectability rate in patients with unresectable rectal cancer who received preoperative irradiation, 5-FU, methotrexate, and leucovorin rescue compared with 38 patients who received radiation alone (71% vs. 34%) [17]. Investigators from Tom Baker Cancer Centre reported an 89% complete resection rate in 46 patients with tethered and fixed rectal cancer treated with 40 Gy and 5-FU infusion and mitomycin-C [18]. Of 31 patients receiving continuous 5-FU infusion throughout irradiation at Thomas Jefferson University, 29 patients (94%) underwent complete resection with negative margins [19]. Enhanced resectability is an important end point since patients with initially unresectable rectal cancer who have microscopic or gross residual disease have higher local failure and lower survival rates compared with those patients who undergo a complete resection.

Analyses of local control and survival following treatment programs of preoperative chemoirradiation and surgery for locally advanced rectal cancer are limited by small patient numbers and short follow-up. Nevertheless, preliminary results suggest improved outcomes in patients receiving chemoirradiation compared to prior studies evaluating patients undergoing irradiation only (Table 15.2) [15–20]. Based on this data, combinations of moderate- to high-dose preoperative irradiation with concurrent 5-FU-based chemotherapy appear to result in improved rates of resectability and possibly local control and survival.

Although the dose and techniques of irradiation are similar in these studies (45–50.4 Gy in 25–28 fractions to the pelvis via a three or four field arrangement), there is marked variability in 5-FU administration. Some studies employ a schedule of 5-FU administered as a bolus for 3 consecutive days during weeks 1 and 5 of irradiation, whereas other investigators have utilized a continuous infu-

Table 15.2 Preoperative chemotherapy, radiation therapy, and resection of locally advanced (T4 or tethered T3) rectal cancer

Study	# Pts	Drugs	EBRT dose	Complete resection	Local failure	Survival
MD Anderson [14]	38[a]	5-FU Infusion ±CDDP	45 Gy	84%	Crude – 3%	3 Yr – 82%
MSKCC [15]	36	5-FU/Leucovorin	50.4 Gy	97%	4 Yr Act. 30%	4 Yr – 67%
Tom Baker Cancer Centre [17]	46	5-FU/Mit-C	40 Gy	89%	2 Yr Act. 16%	3 Yr – 31%
Thomas Jefferson [18]	31	C.I. 5-FU	55.8 Gy	94%	Crude – 16%	3 Yr – 68%
Emory [19]	20	5-FU Bolus	50 Gy	N.S.	Crude – 10%	3 Yr – 82%

MSKCC Memorial Sloan–Kettering Cancer Center, *pts* patients, *EBRT* external-beam irradiation, *IOERT* intraoperative electron irradiation, *5-FU* 5-fluorouracil, *CDDP* cisplatin, *Mit-C* mitomycin-C, *CI* continuous infusion, *N.S.* not stated, *yr* year

[a]Tethered T3 and T4 tumors – 11 of 38 received IOERT supplement to site of adherence at time of resection

sion approach throughout irradiation. Additionally, several investigators have used other agents such as leucovorin, cisplatinum, and mitomycin-C in combination with 5-FU. Because of the US GI Intergroup trial showing a survival advantage for patients treated with continuous infusion 5-FU throughout irradiation compared to patients treated with bolus 5-FU in the postoperative setting [21], it would seem appropriate that this approach should be adopted for preoperative irradiation programs in rectal cancer. The value of additional agents such as leucovorin, levamisole, cisplatinum, and mitomycin-C in combination with 5-FU is under investigation. It is becoming clear from the adjuvant rectal cancer trials that more chemotherapy with irradiation is not necessarily better. In the adjuvant postoperative chemoirradiation rectal cancer trials, it appears that the three-drug combination of 5-FU, levamisole, and leucovorin is more toxic and no more efficacious than 5-FU only or the two-drug regimen of 5-FU and leucovorin [22].

At present, investigators at both MGH and Mayo Clinic are using a 5-FU schedule of 225 mg/m^2/24 h for 5 days (MGH) or 7 days (Mayo) per week throughout the 5½ week to 6-week course of preoperative irradiation (45 Gy to the pelvis followed by a tumor boost of 5.4–9.0 Gy in 1.8 Gy fractions). In our experience, this 5-FU schedule with preoperative pelvic irradiation has been well tolerated.

Treatment Factors

EBRT

Patients with locally advanced primary rectal cancer have been evaluated in aggressive local strategies including EBRT, IOERT, and maximal resection at MGH since 1978 [23] and at Mayo Clinic in Rochester (MCR) since 1981. Such patients currently receive full-dose preoperative EBRT with infusional 5-FU (225 mg/m^2/day 5 days per week throughout irradiation). Multiple-field techniques using 3D conformal or intensity-modulated irradiation (3D CRT, IMRT) are used to carry extended pelvic fields to 45 Gy in 25 fractions over 5 weeks, and boost fields to tumor plus 2–2.5 cm are carried to 50.4–54 Gy (Fig. 15.1a–e) If external iliac nodes are at risk due to tumor adherence or fixation to anterior structures (bladder, prostate, cervix, uterus), IMRT can be useful in decreasing small-bowel volumes in the EBRT field and thereby improving acute tolerance.

Surgery

Following a course of preoperative chemoirradiation, surgical exploration is undertaken 4–6 weeks later. The delay allows ongoing tumor shrinkage after the cessation of preoperative treatment as well as the resolution of treatment-induced acute inflammation.

Accurate *preoperative staging* is important because IOERT benefits primarily those patients who can undergo a grossly complete tumor resection. Ideal patients are in reasonably good health and are willing to undergo major surgery that may include stoma creation and possible pelvic exenteration. There should be no distant metastases to liver, lungs, or peritoneum, and no adenopathy of the para-aortic area, or groins. There should be no invasion of pelvic nerves or the sciatic notch (i.e., no sciatica or sacral/buttock pain) and no evidence of tumor invading or wrapped around the iliac vessels or ureters. In order to assess the extent of tumor, preoperative evaluation ordinarily includes the following: abdominal and rectal exam, sigmoidoscopy and/or colonoscopy, abdominal plus pelvic computerized tomography (CT) scan (Fig. 15.2a), and chest X-ray (sometimes chest CT scan). Transanal ultrasound usually adds little to the evaluation, since tumors appropriate for IOERT are large and advanced on clinical exam alone. PET-CT scans can give useful additive information with regard to nodal involvement or distant blood-borne metastatic disease. If there is any question of involvement of the urologic system, intravenous urogram, and possibly urology consult and cystoscopy, may be required. If a colostomy is possible, preoperative evaluation by an enterosomal therapist can be very helpful, not only to begin stoma counseling and teaching but also to mark the optimal site on the abdomen for the stoma.

Surgery is usually best carried out via a midline incision that allows extension as necessary and permits multiple stomas. Adhesions are completely taken down, and the abdomen is carefully evaluated for liver and peritoneal metastases. If metastases that are not resectable with curative intent are found (i.e., solitary liver metastasis), intraoperative irradiation is not performed, and treatment ends with palliative resection (or only EBRT).

If no metastases are evident, or are limited and can be resected for cure, the patient undergoes abdominoperineal resection, low anterior resection, or pelvic exenteration, depending upon the extent and location of the tumor (Fig. 15.2b–e). En bloc wide resection is the goal; at least, a grossly complete resection of the tumor is desirable, but if that cannot be done, as much of the cancer as possible is removed. Early intraoperative rectal irrigation with sterile water is helpful to eliminate residual stool and possibly exfoliated cancer cells from the rectal stump in preparation for anastomosis (usually with a circular stapler passed via the anus). Lavage is worthwhile even if abdominoperineal resection is planned, since the tumor may be fractured or the rectum is perforated during a difficult dissection. For any resection of locally advanced primary rectal or sigmoid cancer, mobilization of the tumor off the sacrum (Fig. 15.2b, c) and pelvic sidewall can be difficult. Sometimes a large periosteal elevator (e.g., Cobb elevator) functions well for this. Hemostasis after resection is important because pooled blood over the tumor bed could decrease the IOERT dose at depth.

If an anastomosis is to be done, it is completed after the delivery of IOERT. To minimize the likelihood of complications, it is preferable to mobilize the left colon completely and use unirradiated bowel (descending colon) for the proximal end of the anastomosis. Placement of pedicled omentum in the pelvis at the end of the procedure (Fig. 15.2d) is often beneficial; it may decrease the risk of a leak from an anastomosis, minimize the risk of malignant small-bowel obstruction if pelvic recurrence later occurs after abdominoperineal resection, keep small bowel out of the pelvis in case postoperative EBRT is necessary, and help prevent pelvic sepsis by eliminating dead space (which is a substantial risk especially after pelvic exenteration).

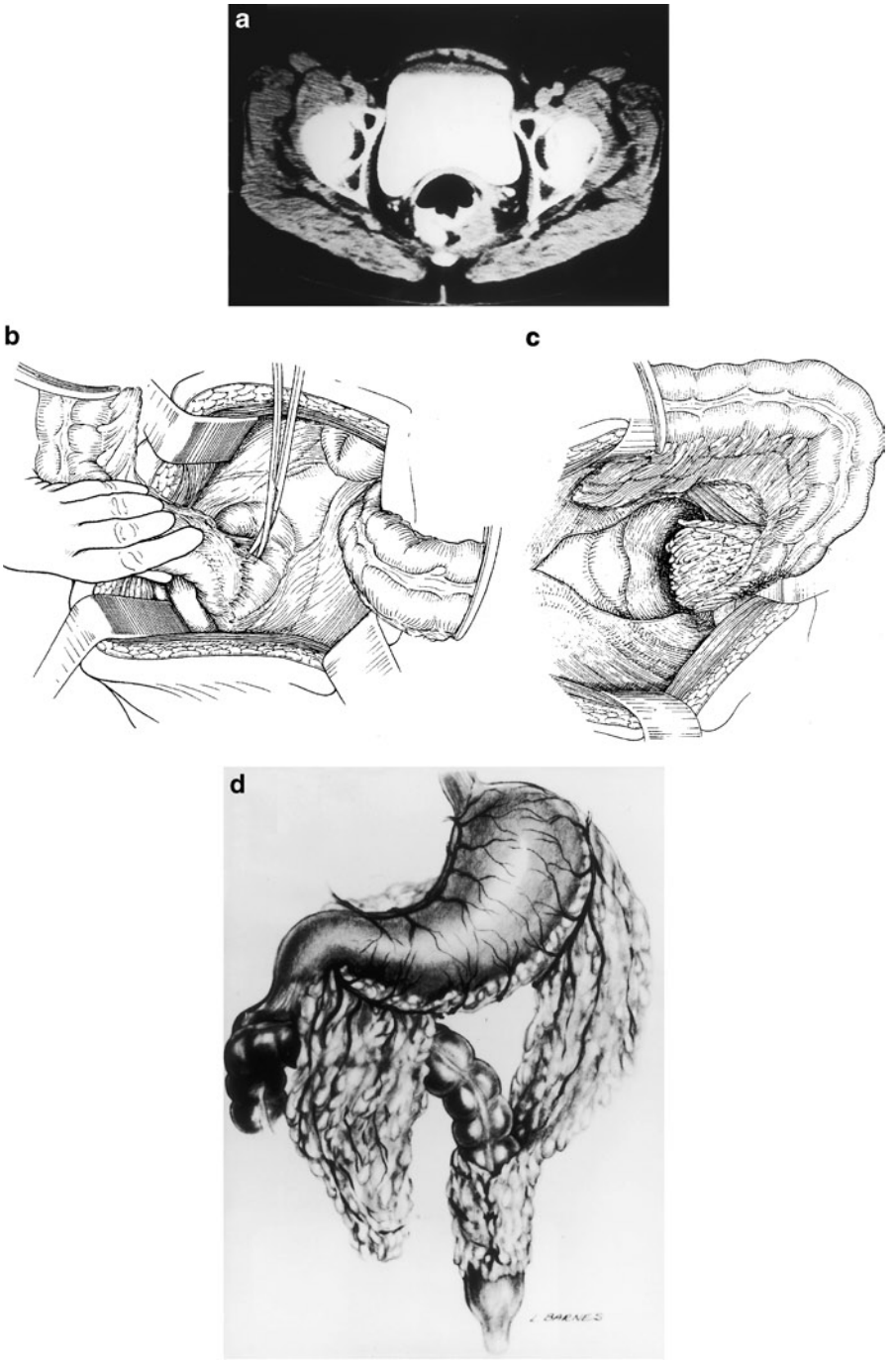

Fig. 15.2 Surgical techniques and preoperative staging. (**a**) Preoperative pelvic CT demonstrating mass in the left posterior lateral rectum with lack of free space posteriorly relative to pelvic structures. (**b**) Sharp dissection of rectum and tumor out of pelvis. (**c**) Rectal mobilization completed (mesorectal excision). (**d**) Placement of vascularized omental pedicle in the pelvis after rectal resection and reanastomosis.

IORT Factors

The decision to treat with IORT is based upon the operative findings, pathologic margin status, and pretreatment physical exam and imaging studies and is an intraoperative collaborative judgment made by the surgeon and the radiation oncologist. It is critical to define the area at highest risk for subsequent local relapse to determine the optimal position for the IORT field. Margins of resection are determined by frozen-section pathologic analysis of the surgical specimen and sometimes the tumor bed.

IOERT

If no tumor adherence exists after preoperative chemoirradiation and adequate soft-tissue radial margins are present (>1 cm), IOERT was often not delivered at MGH until a subsequent analysis suggested a high risk for relapse in patients with pretreatment adherence who had T3 or N(+) disease after preoperative treatment (see MGH results). Patients with gross residual cancer, with microscopically positive margins, or with close (≤5 mm) radial soft-tissue margins have always been candidates for IOERT. The tumor bed is marked with sutures to facilitate later positioning of the IOERT applicator and to direct the IOERT.

An IOERT applicator is selected according to the location and size of the area to be irradiated. The internal diameters of circular applicators range from 4 to 9 cm at MGH and from 4 to 9.5 cm at MCR. Applicator size is selected to allow full coverage of the high-risk area, which is generally on the presacrum or pelvic sidewall. Usually, the largest applicator that will fit into the area is the best. The applicator's shape is chosen so that the geometry fits the specific situation of tumor versus normal tissue. The applicator must abut the site being treated, which can be difficult if the high-risk area is located in an anatomically confined region such as the pelvis. Some have beveled ends of 15 or 30°, enabling good apposition of the applicator to sloping surfaces in the pelvis to maximize dose homogeneity (Fig. 15.3a, see also Chaps. 3 and 4). It is important that the applicator be placed so that the tumor or tumor bed is fully covered, that sensitive normal tissues are not included in the beam, and that there is no fluid buildup in the treatment area. The applicator not only directs the electron beam accurately to the high-risk area but also serves to retract sensitive normal tissues out of the way, especially small bowel and ureter. Visceral retraction and packing are also usually necessary. If a distal rectal stump remains for later anastomosis, it should also be excluded from the IOERT field by retraction outside the applicator with the applicator and packing or with the use of lead sheets, which can be cut out to block sensitive normal tissues that cannot be removed from the path of the beam. During treatment, suction catheters are positioned to minimize fluid buildup within the applicator.

Most IOERT treatments in rectal cancer are given via a transabdominal approach, since the area of concern is usually posterior presacrum or posterolateral pelvic sidewall (Fig. 15.3a–e, see Chaps. 3, 4, and 6). A perineal port is occasionally used after abdominoperineal resection to treat a very low-lying tumor involving the coccyx or distal presacrum, distal pelvic sidewall or portions of the prostate, and base of the bladder when an exenteration is not performed (Fig. 15.3g–i, see also Chaps. 3, 4, and 6). The perineal approach is technically more difficult. For institutions where IOERT is delivered with the X-band Mobetron accelerator (Mayo Clinic in Arizona, other US, European, and Asian institutions), the perineal approach is especially challenging if the tumor was adherent to or invading anterior structures. In such instances, the patient has to be rotated from supine to prone position following resection and prior to IOERT delivery (Fig. 15.3j, k). Rarely, it may be impossible to abut the applicator to the tumor bed if the lesion is located very low in the pelvic sidewall in an obese male with a narrow pelvis, and HDR-IORT would be a preferable option for IORT delivery, if available.

After positioning the IOERT applicator, it is docked to the linear accelerator, and IOERT is delivered. Typical doses of radiation delivered intraoperatively are in the range of 10–20 Gy with

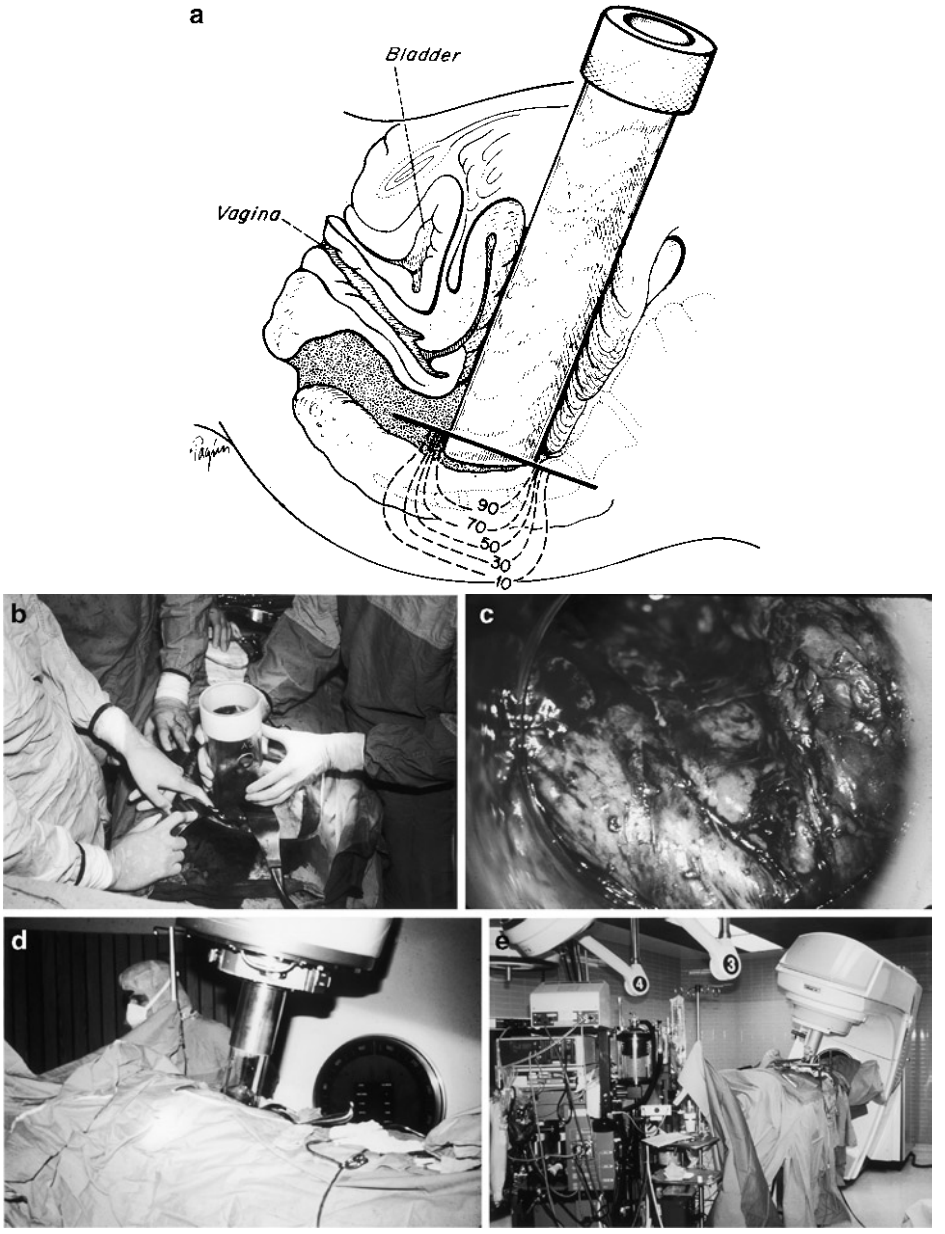

Fig. 15.3 *IOERT techniques*. IOERT to the *presacrum* via an *abdominal approach* (**a**–**d**) with both an artist's depiction (**a**) and actual patient treatment (**b**–**d**) showing applicator placement in the presacrum (**b**), view down the applicator (**c**) and applicator "docked" to the linear accelerator (**d**). (**e**, **f**) Treatment of the pelvic sidewall with either minimal gantry angle (**e**) or >45° (**f**). (**g**) IOERT treatment of the *distal presacrum* coccygeal region via perineal approach with gantry angle exceeding 45°. (**h**, **i**) Treatment of the *prostate*, *base of bladder* via the *perineal approach* with the *patient supine* (**h**). Note gantry angle exceeding 90° (**i**). (**j**, **k**) Treatment of the tumor bed overlying the prostate via the *perineal approach* with the *patient in prone position* for treatment with the Mobetron mobile accelerator in Mayo Clinic Arizona operating room. (**j**) Patient in prone position with head and chest support, (**k**) soft docking with laser light alignment and gantry angle of ~45°.

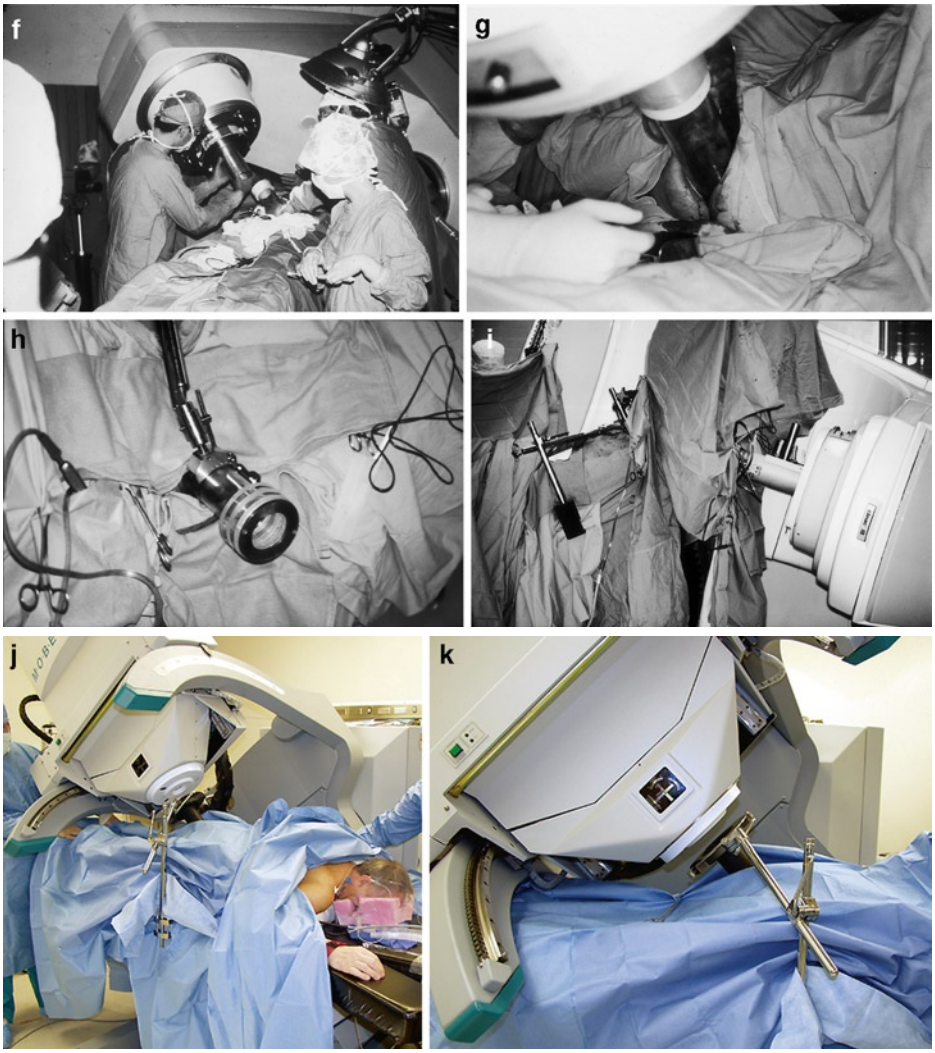

Fig. 15.3 (continued)

the lower doses being given for minimal residual disease (narrow or microscopically positive margins) and the higher doses for gross residual disease after maximal resection. For patients undergoing complete resection with negative but narrow margins (R0), the IOERT dose is usually 10–12.5 Gy, whereas for patients undergoing subtotal resection with microscopically positive margins (R1), the dose is 12.5–15 Gy. For patients with macroscopic or gross residual after resection (R2), the dose is 17.5–20 Gy. Typical electron energies used are 6–15 MeV, depending on the thickness of residual tumor. The dose is quoted at the 90% isodose.

HDR-IORT Factors

As with IOERT, the decision to treat with HDR-IORT is based on operative findings, margin status, physical examination and imaging studies, and collaborative judgment of the surgeon and the radiation oncologist. The decision to treat with HDR-IORT vs. IOERT is discussed extensively in

Chap. 6. A primary limitation of IOERT that could favor use of HDR-IORT for a given patient is the nonflexible IOERT applicator, which makes treatment difficult or sometimes impossible in narrow cavities, steeply sloping surfaces, or regions requiring treatment delivery to bend around a corner. The deep pelvis can sometimes present such a challenge. Other potential advantages of HDR-IORT include a higher surface dose. However these relative advantages must be weighed against HDR-IORT's lower dose homogeneity, longer treatment time, more shielding requirement, lower dose at depth, and inability to treat areas at risk with a depth greater than 0.5 cm from the surface of the applicator.

HDR-IORT treatment is given with a mobile HDR remote afterloader that has a nominal 10-Ci ^{192}Ir source encapsulated in a small (4 × 1 mm) capsule attached to the end of a metal wire, and this single source on the wire is moved mechanically via remote control through transfer tubes into hollow catheters placed on the tumor or tumor bed. There are several types of HDR-IORT applicators available in sizes suitable for various sites (see Chap. 5), and different institutions tend to use different materials. For flat tumor beds, a rigid Delrin applicator may be used, whereas for curved surfaces, flexible applicators made of various materials such as Silastic, silicone, supermold, Superflab, or foam may be employed. At MSKCC and Beth Israel (NYC), flexible Harrison–Anderson–Mick (HAM) surface applicators are used (see Chap. 5). HDR-IORT surface applicators are most suitable for treating tumor beds less than 0.5 cm thick. Once the applicator has been secured on the tumor bed with gauze packing or suturing as necessary, retractors or sterilized lead foils are used to shield or displace radiosensitive structures. Sometimes, localization films are not taken because C-arm units often cannot provide accurate films depending on anatomical constraints.

Institutions have various precalculated dosimetry tables or atlases that are utilized by the physics team, after the radiation oncologist determines the field size, total dose, prescription depth, and severity of curvature of the target surface. After the afterloading machine is transported into the operating room by the physicist and the therapist, the preplanned treatment program is retrieved from the computer and transferred on disk to the treatment control panel. Sterilized transfer cables are attached to the end of the catheters, catheters are checked for patency, and proper length in confirmed with dummy source cables. A quality-assurance check should be performed with the treatment plan checked for accuracy. Transfer cables from the applicator are attached to the treatment machine, and the treatment is performed while the patient is anesthetized and all personnel are out of the room. After treatment, the applicator is removed from the tumor bed, prior to surgical reconstruction and closure.

Results: IORT Alone or Plus EBRT

Despite full-dose preoperative irradiation and complete resection of locally advanced rectal cancer, local failure occurs in at least one-third of patients. These local failure rates are even higher in patients undergoing subtotal resection. At the Massachusetts General Hospital (MGH), Mayo Clinic, and other centers in USA, Europe, and Asia, intraoperative electron-beam irradiation (IOERT) has been used in combination with preoperative EBRT (with and without 5-FU) and maximal surgical resection for patients with gross residual cancer, microscopically positive resection margins, or simply a site of tumor adherence. HDR-IORT has been the available method of IORT delivery at various US (MSKCC, Beth Israel NY, Duke University) and European institutions (Rotterdam).

MGH Results (EBRT ± 5-FU, Resection, IOERT)

The IOERT program at MGH began in 1978 [23–25], and results have been reported in 64 patients with locally advanced primary rectal cancer who received full-dose preoperative irradiation (±5-FU)

and resection with IOERT. The 5-year actuarial local control and disease-specific survival (DSS) for 40 patients undergoing complete resection with IOERT were 91 and 63%, respectively (Table 15.3). For 24 patients undergoing partial resection, local control and DSS correlated with the extent of residual cancer: 65 and 47%, respectively, for microscopic residual disease, and 57 and 14%, respectively, for gross residual disease.

Local control and DSS of the completely resected patients are correlated to the post-EBRT pathologic findings (Table 15.4). Although there was a trend of improved local control in patients with intramural tumors compared to patients with transmural tumors after irradiation, these differences were not statistically significant.

Treatment Tolerance

The 5-year actuarial risk of complications of the 64 patients receiving IOERT was 16% (Table 15.5). Two patients developed osteoradionecrosis of the sacrum requiring surgical intervention. No deaths were seen as a consequence of these complications.

Table 15.3 MGH Primary Rectal IOERT Series – 5-year actuarial local control and disease-specific survival by degree of resection

Degree of resection	# Pts	LC (%)	DSS (%)
Complete resection	40 (12)	91	63
Partial resection	24 (5)	63	35
Micro residual (R1)	17 (4)	65	47
Macro residual (R2)	7 (1)	57	14

LC local control, *DSS* disease-specific survival
Number in parenthesis indicates number of patients at risk at 5 years

Table 15.4 MGH Primary Rectal IOERT Series – 5-year actuarial local control and disease-specific survival of completely resected patients by pathological stage

Pathologic stage	# Pts	LC (%)	DSS (%)
No tumor or intramural only	6 (3)[a]	100	63
Transmural, and/or lymph node positive	34 (10)[a]	88	64

LC local control, *DSS* disease-specific survival
[a]Number in parenthesis indicate number of patients at risk at 5 years

Table 15.5 Complications in MGH IOERT Series of 64 primary rectal patients

Pelvic abscess	1
Sepsis (from central line)	1
Wound dehiscence	1
Small-bowel obstruction	1
Small-bowel fistula	5
Delayed perineal wound healing	2
Sacral osteoradionecrosis	2
Ureteral obstruction	2
Total	15

Local Relapse vs. Stage of Disease After Preoperative EBRT; IOERT Selection Issues

An important issue in the use of IOERT in rectal cancer is the selection of patients for this modality. After moderate- to high-dose preoperative EBRT (45–50.4 Gy), tumor regression or pathological downstaging is frequently observed. The question arises whether patients with locally advanced rectal cancers exhibiting marked regression after preoperative treatment are at lower risk for local recurrence than patients with tumors not exhibiting this response. If so, IOERT would be of limited value in the subset of patients with downstaged tumors and probably should not be administered.

The incidence of local relapse as a function of stage of disease after preoperative irradiation ± concomitant 5-FU has been evaluated in three separate MGH analyses. For 11 patients with locally advanced (T4) rectal cancer treated with preoperative irradiation and curative resection in the original MGH series, five of eight patients (62.5%) that had persistent tumor extension grossly beyond the bowel wall failed in the pelvis versus none of three patients with tumor confined to the wall or only microscopic extrarectal extension [8]. In an analysis of 28 patients with *tethered* (T3) rectal cancers treated with preoperative irradiation and resection at MGH, the 5-year actuarial local recurrence and DFS was 24 and 66%, respectively. No correlation between local control and post-treatment extent of tumor penetration through the rectal wall and/or lymph node involvement was observed.

In another MGH analysis, the outcome of a total of 47 patients with locally advanced rectal cancer receiving 45–50.4 Gy preoperative irradiation and complete resection with clear resection margins by pathological stage was evaluated [26]. These patients did not receive IOERT because it was judged not indicated due to the favorable response to preoperative irradiation or IOERT was not technically feasible. For 24 patients with no residual tumor or tumor confined to the rectal wall after preoperative EBRT, the 5-year actuarial local control rate was 87%. In contrast, the 5-year actuarial local failure rate was 68% for 27 patients with transmural tumors and/or lymph-node metastases. Despite a favorable response to preoperative irradiation and no clearly defined indication for IOERT at the time of surgery (tumor adherence or compromised soft-tissue margins), local failure rates were high in this group of patients, especially for those with tumors exhibiting transmural penetration and/or lymph-node metastases. The extent of tumor regression after preoperative irradiation is no longer used as an absolute guide to the need of IOERT at MGH.

Mayo IOERT Series

At MCR, the treatment approach of primary locally advanced colorectal carcinoma has been similar to MGH combining EBRT (±5-FU) with surgery and IOERT to high-risk regions [27–29]. An initial analysis of a total of 56 patients with IOERT as a component of treatment was published in 1997 (Tables 15.6 and 15.7) [27, 28].

Results were recently updated in a series of 155 patients with primary locally advanced colorectal cancer who received IOERT at MCR from September 1981 through February 2007 [29]. The patients received an IOERT median dose of 12.5 Gy, usually combined with 45–55 Gy of fractionated preoperative EBRT and concurrent 5-FU based chemotherapy. Of the 146 evaluable patients with a minimum follow-up of 12 months, 131 patients (90%) received concomitant 5-FU delivered during EBRT, and 58 patients (40%) received adjuvant 5-FU-based chemotherapy. The amount of residual disease remaining at IOERT after exploration and maximal resection was negative margins in 100 patients (68%), microscopically positive margins in 28 patients (19%), and grossly positive margins in 18 patients (12%). Patients with close margins received 7.5–10 Gy, those with microscopically involved margins received 10–12.5 Gy, and those with grossly involved margins received 15–20 Gy.

Table 15.6 Primary colorectal IOERT: 5-year actuarial local control, distant failure, and OS by degree of resection and amount of residual, Original Mayo Analysis

		5-Year actuarial results		
Degree of resection, amount residual	# Pts	LC (%)	DF (%)	OS (%)
No tumor	2	100	0	100
Complete Resection (RO)	18	93	54[a]	69
Partial resection				
Micro residual (R1)	19	86	50[a]	55
Macro residual (R2)	16	73	83[a]	21
No resection	1	–	–	0
All patients	56	84	59	46

LC local control, *DF* distant failure, *OS* overall survival
[a]Three-year acturial DF of 43, 38, and 66% for complete resection, microscopic residual or gross residual

Table 15.7 Primary colorectal IOERT: impact of treatment and disease prognostic factors on disease relapse, Original Mayo Analysis

		Local relapse (EBRT) (%)			Distant metastases (%)			
Prognostic factor	# at risk	No. (%)	3 and 5 years	p[a]	No. (%)	3 years	5 years	p
EBRT ± 5-FU ($n=56$)								
EBRT + 5-FU	39	4(10)	11	0.54	14 (36)	35	41	0.013
EBRT	17	3(18)	24	–	13 (77)	66	83	–
Treatment sequence ($n=38$)								
Preop EBRT + 5-FU[b]	29	4(14)	14	0.37	10 (35)	32	39	0.18
Postop EBRT + 5-FU	9	0	0		4 (44)	53	53	–
Site of primary ($n=56$)								
Colon	18	1(6)	6	0.20	5 (28)	29	29	0.03
Rectum	38	6(16)	21	–	22 (58)	53	75	–
Grade ($n=56$)[c]								
1, 2	27	2(7)	4	0.09	15 (56)	43	43	0.83
3, 4	29	5(17)	32		12 (41)	45	45	
Nodal status ($n=51$, unk = 5)								
Negative	24	1(4)	4	0.11	12 (50)	50	62	0.95
Positive	27	5(19)	23		14 (52)	48	63	
Total group	56	7(13)	16	–	27 (48)	45	59	–

EBRT external-beam irradiation, *IOERT* intraoperative electron irradiation, *LF* local failure in EBRT field, *DF* distant failure, *5-FU* 5-Fluorouracil, *unk* unknown
Modified from Gunderson et al. [23]
[a]Log rank p-value
[b]Central failure in IOERT field occurred in only 1 patient (preoperative EBRT + 5-FU, rectal, no resection)
[c]Time to relapse by grade: Grade 2 – LF range 1.0–5.5 years, DF range 0.5–5.5 years; Grade 3 – all LF by 3 years, DF by 1.5 years; Grade 4 – all LF by 2 years, DF by 1.5 years

Disease Control and Survival

Median survival for the entire group of 146 patients was 3.7 years [29]. Estimated 3- and 5-year OS were 61 and 52%, respectively. Patients with microscopic or less residual fared better than those with gross residual with a 5-year actuarial overall survival of 56% vs. 22% ($p=0.0006$). Failures

within the IORT boost field occurred in only three patients (2%) at a median 3.7-years follow-up, 19 patients (13%) had a local failure in the EBRT field, six patients (4%) had a regional failure, and 68 patients (47%) had distant failure. The impact of other treatment and disease prognostic factors on disease control, in the original Mayo report [23], is seen in Table 15.7. Factors with statistical impact on distant relapse included EBRT + 5-FU (vs. EBRT alone, $p = 0.013$) and colon primary (vs. rectal, $p = 0.03$). Nodal status had no impact on distant relapse rates (nodes-negative – 50%; nodes positive – 52%). Because of the high rates of distant metastases in these patients, (absolute 48%; 3 and 5-year actuarial of 45 and 59%), more routine use of systemic chemotherapy was advised.

The influence of other prognostic factors on survival, in the Mayo update [29], is seen in Table 15.8 [29]. Age of 58 years or less was associated with improved DFS at 5 years (DFS: 52% vs. 33%, $p = 0.02$), as were clinical and pathologic M0 status (45% vs. 19% for M1 disease, $p = 0.02$). On multivariate analysis, only age remained significant ($p < 0.008$). Patient or treatment factors that were associated with OS at 5 years included age of 58 years or less (69% vs. 38%, $p = 0.001$), use of adjuvant chemotherapy (71% vs. 41%, $p = 0.002$), pathologic N stage (55, 51, and 43% for pN0, pN1, and pN2, respectively, $p = 0.004$), negative or microscopic margin status (56% vs. 22% for grossly positive margin, $p = 0.0006$), and preoperative EBRT (55% vs. 38% for postoperative EBRT, $p = 0.02$), although preoperative EBRT did not remain significant on multivariate analysis. Factors that were not found to be associated with improved DFS or OS include tumor location, number of fixed sites preoperatively, clinical N stage (though this was almost significant for OS), EBRT alone vs. with 5-FU, 5-FU vs. FOLFOX/FOLFIRI, or pathologic T stage.

Treatment Tolerance

An in-depth analysis of *peripheral nerve tolerance* following IOERT was also performed in the original analysis (Table 15.9) [28]. Symptomatic or objective neuropathy was documented in 18 of 56 patients (32%). Ten of 18 (56%) had only Grade 1 toxicity usually manifesting as mild or intermittent paresthesias and/or pain not requiring narcotics. Of the seven patients with presumed treatment-related Grade 2 (usually pain requiring narcotics) or Grade 3 nerve toxicity, the data suggested a relationship between IOERT dose and the incidence of Grade 2 or 3 neuropathy (≤12.5 Gy – 1 of 29 or 3%, ≥15 Gy – 6 of 26 or 23%, $p = 0.03$). The relative incidence of Grade 3 neuropathy by IOERT dose for 57 fields in 55 evaluable patients was 0 of 29 for ≤12.5 Gy, 1 of 19 (5%) for 15 or 17.5 Gy, and 2 of 9 (22%) for 20 Gy. In the Mayo update, the authors report that a total of 19% of the patients had evidence of peripheral neuropathy, including 3% with Grade 3 or 4 neuropathy [20].

The incidence of ureter-related side effects in the original MCR analysis is also seen in Table 15.9 [28]. The IOERT boost field encompassed ten ureters in nine of the 56 patients (solitary ureter: eight patients, bilateral ureters: one patient). Subsequent ureteral narrowing with hydronephrosis (Grade 2) or obstruction requiring a stent (Grade 3) occurred in five patients who had a ureter within IOERT fields (five of nine – 56%) and in five patients in whom the ureter was not included in the field (includes one patient with bilateral ureteral obstruction: one ureter was within the IOERT field, the other was surgically dissected). Pelvic relapse was the probable cause of ureteral obstruction in only one patient.

At the time of the updated results, 12% of patients had experienced ureteral obstruction, including 9% for whom this was Grade 3 or 4 [29]. Other late toxicities included in the updated results included small-bowel obstruction in 14% of patients, wound infection/breakdown in 9%, fistula with abscess in 8%, bladder dysfunction in 7%, sexual dysfunction in 6%, enteritis/proctitis in 3%, and abdominopelvic abscess in 3%.

Table 15.8 Primary colorectal IOERT – survival by prognostic factor, Mayo Clinic Rochester Updated Analysis

		Overall survival %					Disease-free survival %				
Prognostic factor	# at risk	Median (years)	1 year	3 years	5 years	p^a	Median (years)	1 years	3 years	5 years	p^a
Age											
≤58	72	7.6	90	73	69	0.001	6.7	77	59	52	0.02
>58	74	3.6	84	52	38	–	2.2	69	43	33	–
Sex											
Male	95	5.6	86	59	51	0.48	3.1	72	52	42	0.81
Female	51	5.2	86	66	54	–	3.4	73	51	44	–
Tumor location											
Colon	40	7.2	89	64	61	0.58	3.4	79	56	49	0.22
Rectum	106	4.9	87	60	49	–	3.0	70	49	40	–
Fixed sites preop (rectal, n = 106)											
≤1	85	4.8	87	56	45	0.15	3	70	49	38	0.15
≤2	61	7.4	88	69	62	–	4.2	76	55	49	–
Clinical N stage											
0	77	7.2	89	67	55	0.06	3.4	73	52	46	0.8
1	46	4.9	86	62	49	–	2.8	74	46	35	–
2	23	2.7	78	47	47		4.9	68	63	44	
Clinical M stage											
0	130	5.6	88	63	53	0.47	3.8	74	55	45	0.02
1	16	2.9	86	43	43		1.1	57	19	19	
Timing of EBRT											
Preoperative	124	6.3	88	65	55	0.02	3.4	75	53	45	0.28
Postoperative	20	2.2	85	43	38		2.8	58	46	33	

(continued)

Table 15.8 (continued)

Prognostic factor	# at risk	Overall survival %					Disease-free survival %				
		Median (years)	1 year	3 years	5 years	p^a	Median (years)	1 years	3 years	5 years	p^a
EBRT ± 5-FU											
EBRT alone	15	3.5	87	53	33	0.2	2.2	53	38	23	0.14
EBRT + 5-FU	131	6.3	87	62	54		3.4	75	53	45	
Adjuvant chemo											
No	80	3.9	84	54	41	0.002	3	69	49	39	0.49
Yes	66	9.4	93	74	71		3.4	77	55	49	
Type adj chemo											
5-FU ± leuc	53	7.8	92	69	63	0.21	3.4	77	57	47	0.88
FOLFOX/FIRI	13	Not reached	100	92	92		NR	92	58	58	
Margin status before IORT											
R0 or R1	128	6.3	90	67	56	0.0006	3.4	75	54	45	0.06
R2	18	1.8	72	22	22		1	55	34	26	
Path T stage											
3	52	6.6	90	74	62	0.08	4.2	78	64	48	0.28
4	94	3.9	86	54	44		2.2	69	45	40	
Path N stage											
0	67	7.2	91	66	55	0.004	4.9	71	54	49	0.22
1	40	5.6	92	64	51		3.1	84	51	38	
2	32	2.3	72	43	43		1.4	59	45	30	
Path M stage											
0	130	5.6	88	63	53	0.47	3.8	74	55	45	0.02
1	16	2.9	86	43	43		1.1	57	19	19	

EBRT external-beam irradiation, *IORT* intraoperative irradiation, *5-FU* 5-Fluorouracil, *preop* preoperative, *adj chemo* adjuvant chemotherapy, margin status: *R0* gross total resection with negative microscopic margins, *R1* gross total resection with microscopically positive microscopic margins, *R2* partial resection with grossly positive margins, *path* pathological[a]Log rank *p*-value, univariate). Modified from Mathis et al. [28]

Table 15.9 Primary colorectal IOERT peripheral nerve and ureter toxicities – treatment or tumor related, Mayo Analysis

	Grade of toxicity				
	1	2	3	4	
	No. (%)	No. (%)	No. (%)	No. (%)	Total $n=56$
Peripheral nerve	10 (18)	5 (9)	3 (5)[a]	0	18 (32)
Ureter	0	3 (5)	6 (11)	0	9 (16)

[a]IOERT dose (≤12.5 Gy – 0 of 29, 15 or 17.5 Gy – 1 of 19 or 5%, ≥20 Gy – 2 of 9 or 22%)

MD Anderson IOERT Series

In an MD Anderson series, 11 of 38 patients (29%) with primary locally advanced rectal cancer received IOERT to high-risk regions in the pelvis because of persistent tumor adherence or residual tumor following preoperative irradiation and infusional chemotherapy [15]. No local failures were seen in these patients although 7 of 11 patients developed distant metastases. One patient developed a sensory neuropathy following 20 Gy of IOERT.

Pamplona IOERT Series

In Europe, the Pamplona group has been investigating IOERT in a variety of disease sites, including rectal cancer [30]. From March 1986 to October 1993, 59 patients with primary locally advanced rectal cancer received IOERT as a treatment component in multimodal strategies including surgery and postoperative EBRT (13 patients, Group I) or preoperative chemoirradiation followed by planned surgery (46 patients, Group II). Pelvic recurrence has been identified in only one patient (simultaneously with lung and liver metastasis) and distant dissemination, as the only site of progression, in nine (42% in Group I and 9% in Group II). Cause-specific survival projected over a period of 80 months was 52 and 77% in Group I and II, respectively. Toxicity attributable to IORT consisted of pelvic pain (delayed neuropathy) observed in four patients (9%) and ureteral stenosis in five patients (11%).

Madrid IOERT Series

Another Spanish group, in Madrid, reported its single-institution experience with preoperative chemoradiation, surgical resection, and IOERT in locally advanced rectal cancer patients treated from 1995 to 2000 [31]. One hundred consecutive patients received preoperative 45–50 Gy EBRT plus oral tegafur or continuous infusion 5-FU, surgery, and a presacral IOERT boost with a mean dose of 12.5 Gy (range, 10–15 Gy), and 52 patients received adjuvant 5-FU/LV for four to six cycles. After a median follow-up of 23 months, among 94 patients who completed the treatment there was an estimated actuarial 4-year local control of 94%, DFS of 75%, and OS of 65%. The authors noted that of the three pelvic recurrences, one occurred at the anastomotic suture, one at the posterior vaginal wall, and one at the presacral region that was in the IOERT field.

The same group also analyzed predictive and prognostic factors for response to treatment among 115 patients with T3-4 or node-positive rectal cancer treated at its institution as above [32]. They found that increasing age (OR 1.04, 95% confidence interval [CI] 1.01–1.08) and use of tegafur (OR 4.25, 95% CI 1.79–9.98) were more likely to achieve a major histologic response with

persistence of only minimal residual microscopic disease. Male gender and persistence of macroscopic disease were found to be associated with worse disease-free survival on multivariate analysis. Patients who had 0, 1, or 2 of these risk factors had a 3-year DFS of 100, 81.3, and 53%, respectively ($p<0.0001$).

In a recently reported Madrid series at ISIORT 2008 of a total of 558 patients with T3-4 rectal cancer (66), 281 received preoperative chemoradiation (CRT) plus IOERT (50.5%) and 277 (49.5%) received postoperative CRT with no IOERT [33]. Outcomes appeared better in patients who received preoperative CRT plus IOERT in spite of higher stage disease at presentation (pelvic control 91.5 vs. 83.7%, $p=0.03$; DFS 65 vs. 56%, $p=0.05$, OS 68 vs. 58%, $p=0.016$).

German IOERT Series

The Heidelberg group evaluated 210 patients with locally advanced rectal cancers treated between 1991 and 2003 with TME, IOERT, and pre- ($n=88$) or postoperative ($n=122$) chemoradiation [34]. Chemoradiation was 5-FU based in 93% of patients, and median EBRT dose was 41.4 Gy in 1.8 Gy/fraction. At a median follow-up of 61 months, the 5-year OS, DFS, local control rate (LC), and distant relapse-free survival (DRFS) for all patients were 69, 66, 93, and 67%, respectively. Multivariable analysis showed that UICC stage and resection status were the most important prognostic factors for OS, DFS, and DRFS, while the only significant factor affecting LC was resection status. Their combined treatment approach was well tolerated, with 17% of patients having Grade 3 acute complications (no patients had Grade 4 acute effects), and 13% having Grade 3 or higher late complications at 10 years.

European IOERT Pooled Analysis

A pooled analysis of 651 IOERT patients from four major European centers was presented at ISIORT 2008 by Rutten et al.; 5-year OS was 67%, and 5-year LC was 88% [35]. Positive circumferential resection margins were a strong predictor for both OS ($p<0.0001$) and local relapse ($p<0.01$). Preoperative CRT seemed to improve OS (5-year OS of 70% vs. 64%, $p<0.05$).

MSKCC HDR-IORT Series

At MSKCC, HDR-IORT has been delivered using the HAM applicator for both primary unresectable and locally recurrent colorectal tumors [36]. From November 1992 to December 1996, a total of 68 patients were treated at MSKCC with HDR-IORT, including 22 patients with primary unresectable disease, and 46 patients with recurrent tumors. The primary unresectable patients generally received preoperative EBRT to 45–50.4 Gy with 5-FU/leucovorin, followed by surgery with HDR-IORT to a median dose of 12 Gy (range, 10–20 Gy) calculated at a depth of 5 mm in tissue. For the primary unresectable patients, actuarial 2-year local control was 81% overall and was 92% vs. 38% for those with negative vs. positive margins. The 2-year actuarial DFS was 69% overall for the primary unresectable patients, and was 77% vs. 38% for those with negative vs. positive margins.

Among all patients (primary and recurrent), 38% (26 of 68 patients) had Grade 3 or higher complications, including ten patients with wound complications, four patients with postoperative

infection/sepsis, four patients with bleeding, three with postoperative pain, and two patients each with hydronephrosis, neurogenic bladder dysfunction, and small-bowel obstruction/ischemia. The authors noted that most of these complications were multifactorial and manageable to complete recovery.

Dutch HDR-IORT Series

The Rotterdam group at Erasmus Medical Center published their experience with HDR-IORT for locally advanced or recurrent rectal cancer, which was only administered if resection margins were involved or close, specifically 2 mm or less [37]. Thirty-seven patients were treated from 1997 to 2000 with EBRT, surgery, and HDR-IORT with dose of 10 Gy. After a median of 3 years, the 3-year local failure rate was 19% for primary tumors (vs. 52% for recurrent tumors), and overall for the group was 37% for negative margins and 26% for positive margins ($p = 0.51$).

New England Deaconess Orthovoltage IORT Series

The New England Deaconess Hospital has analyzed their orthovoltage IORT experience for locally advanced rectal cancer [38]. Between 1982 and 1993, a total of 33 patients with locally advanced rectal cancer (primary – 22 patients and recurrent – 11 patients) received preoperative EBRT with 5-FU-based chemotherapy and curative resection. Intraoperative irradiation with a 300-kVp orthovoltage unit was given to 26 patients. The median dose of IORT was 12.5 Gy (range 8–20 Gy). The 5-year actuarial overall survival and local control rates for patients undergoing gross complete resection and IORT were 64 and 75%, respectively. The crude local control rate for patients following complete resection with negative margins was 92% for patients treated with IORT. IORT was ineffective for gross residual disease with all four patients progressing locally despite therapy. Seventeen patients (65%) developed pelvic soft-tissue complications and were treated successfully by posterior thigh myocutaneous flap. The incidence of complications was similar in the patients with primary or recurrent disease.

Conclusions and Future Possibilities

The treatment of locally advanced or clinical stage T4 primary rectal cancer has evolved over the past 30 years. In the 1980s, treatment programs of moderate- to high-dose preoperative EBRT followed by surgery were carried out at several centers in USA. These studies showed that a complete resection was possible in one half to two thirds of patients with locally advanced rectal cancer after full-dose preoperative EBRT. Despite irradiation and complete resection, local failure occurred in at least one third of these patients. Recent efforts to improve local control have included the administration of concurrent chemotherapy with preoperative irradiation and the use of IORT at resection.

Because of the efficacy of postoperative irradiation and 5-FU in the adjuvant treatment of rectal cancer, this approach was studied in a prospective manner preoperatively using modern chemotherapy. The German Rectal Cancer study demonstrated that for clinical stage T3/T4 or node-positive rectal cancer, preoperatively chemoradiotherapy was superior to postoperative treatment with regard to tolerability/compliance, pathologic downstaging, sphincter preservation, and local control, and as such became the standard of care for locally advanced rectal cancers. Various preoperative chemoradiation strategies continue to be studied. Overall, concurrent 5-FU-based chemotherapy should be utilized with moderate- to high-dose preoperative irradiation programs.

To further *improve local control* in patients with locally advanced rectal cancer, investigators from USA and Europe have studied IORT in combination with treatment programs of EBRT, surgery, and chemotherapy (preferably both concurrent and systemic). The data from these studies are compelling that local control is improved in patients receiving IOERT compared to patients not receiving this therapy. The result is most beneficial in patients undergoing complete resection versus patients undergoing partial resection. Disease persistence or relapse within the IOERT and EBRT fields is higher when the surgeon is unable to accomplish gross total resection. Therefore, it seems reasonable to consistently add 5-FU (infusion vs. bolus ± other drugs) during EBRT and to evaluate the use of dose modifiers in conjunction with IOERT (sensitizers, hyperthermia, and so on).

Patient selection for IORT following preoperative chemoirradiation for patients with pretreatment T4 lesions varies somewhat by institution and investigator. In both the initial MGH IOERT program and the current Mayo IOERT program, an attempt was made to reconstruct the site of pretreatment tumor fixation on the basis of pretreatment imaging and physical exam and treat the area with IOERT. In an attempt to exclude patients from the potential side effects of IOERT, Tepper and Willett appropriately attempted to exclude from IOERT those patients with lack of adherence following preoperative irradiation (± concomitant 5-FU) or with a good radial margin (≥1 cm). On the basis of a subsequent MGH analysis, it now appears that in any patient with T3 disease following preoperative treatment, an attempt should be made to define and treat the area of pretreatment fixation (i.e., using pretreatment physical exam and imaging studies in addition to operative findings). In patients with tumor regression to a T0-2 extent after preoperative treatment, it may be reasonable to withhold IORT on the basis of a 5-year actuarial local control rate of 87% in 24 patients followed at MGH. It will be of interest to have other institutions analyze their data in similar fashion.

The *treatment-related morbidity of IOERT* in patients with primary locally advanced rectal cancer has been minimal. It should be remembered, however, that the incidence of Grade 2 or 3 peripheral neuropathy appears to be related to an increase in the IOERT dose as seen in the in-depth analysis from Mayo investigators (≤12.5 Gy, 1 of 29 or 3%, ≥15 Gy, 6 of 26 or 23%, $p = 0.03$). These trends are consistent with animal data that suggest a correlation between IOERT dose and the incidence of clinical and electrophysiologic neuropathy in dogs (see Chap. 7 text and references). In spite of the potential for ureteral toxicity with IOERT-containing regimens (see Chap. 7 for animal data), ureter is not dose-limiting for IOERT because stents can be inserted to mitigate obstruction and preserve renal function as indicated. Therefore, when tumor is adherent to ureter, it should be included in the IORT boost. Animal studies at Colorado State University suggest that the incidence of IOERT-related ureteral changes is related to the length of ureter within the field [39].

In this disease site, IORT has been integrated successfully into treatment programs utilizing EBRT, chemotherapy, and surgery. However, in view of the *high metastatic potential* of ~50% in patients with locally advanced colorectal cancer, 4–6 months of modern systemic chemotherapy should be routinely given as a component of the aggressive treatment approaches discussed in this chapter [40–45].

Summary and Future Possibilities

Although encouraging trends exist with regard to improved LC and SR when IOERT or HDR-IORT is combined with standard treatment for locally advanced primary colorectal cancers, the incidence of systemic failure is ≥50%, and relapses within IORT and EBRT fields are significant if gross resection is not feasible. In attempts to improve LC, infusion 5-FU or other enhancing or additive agents should be given during EBRT, and studies should be performed to evaluate the use of dose modifiers with IORT (sensitizers, hyperthermia, etc.). In view of high systemic failure rates, maintenance chemotherapy should become standard and more modern chemotherapy regimens including biologics (Avastin and others) need to be evaluated after ± during EBRT (systemic FOLFOX/Avastin; add

Oxaliplatin to concurrent PVI 5-FU during EBRT). Most published data were accumulated prior to the availability of more effective multiagent systemic regimens and targeted agents.

While it would be of scientific interest to randomly compare standard treatment ± IORT, such trials did not accrue well in USA or Europe and were closed. Trials that are feasible will standardize the aggressive local treatment of EBRT, resection, and IORT with IOERT or HDR-IORT and randomize optimal chemotherapy/targeted agents during, as well as after EBRT, and the presence or absence of dose modifiers during IORT.

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Chapter 16
Recurrent Colorectal Cancer

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Keywords Recurrent colorectal cancer • Recurrent rectal cancer • IORT for recurrent colorectal cancer

Introduction

Aggressive, curative intent treatment approaches in patients with local or regional relapse after resection of primary rectal or colon cancers are often not considered. A growing body of evidence supports an aggressive approach combining external beam irradiation (EBRT) ± chemotherapy, resection, and intraoperative irradiation (IORT) in conjunction with systemic chemotherapy. Data will be presented in this chapter summarizing disease control and survival results with IORT-containing regimens from US and European institutions including the impact of prognostic factors on results and the results in previously irradiated patients. IORT tolerance and future potential as a component of treatment will be discussed.

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_16,

Results with Non-IORT Treatment Approaches

Surgery Alone

A majority of patients who develop local or regional recurrence after curative resection of primary rectal or colon cancers are treated with palliative intent in most institutions in the USA and worldwide. Exceptions include patients with a true anastomotic recurrence or female patients with a limited vaginal recurrence. In either instance, complete resection with negative margins may be feasible, and postoperative EBRT plus chemotherapy can be given as indicated. Five-year survivals in the range of 25 to >70% have been reported [1–3]. However, extension of disease beyond the anastomosis is common and less than 15% of patients with local relapse of rectal cancer will have disease confined to the anastomosis [3, 4].

Patients with prior resection of rectal or sigmoid cancers often present with pelvic pain, which is a manifestation of local recurrence involving nerve in the presacrum or pelvic sidewalls. Presentation with pain usually indicates that a surgical approach will be unlikely to yield negative resection margins. Distal sacrectomy with negative resection margins can occasionally be performed in patients with a central, distal pelvic relapse. If relapse develops after abdominoperineal resection, male patients may also require a pelvic exenteration in view of bladder or prostate involvement. Most patients, however, either have no surgical resection or a subtotal resection with gross or microscopic residual in view of tumor fixation to presacrum, pelvic sidewalls, or both.

After palliative resection of recurrent colorectal cancer, 5-year survival is generally in the 0–5% range. In a Mayo Clinic analysis of 106 patients with subtotal resection of a localized pelvic recurrence from rectal cancer, 12 patients were treated with surgery alone, and the remainder had some type of irradiation [5]. Of the 12 with no irradiation, 3- and 5-year overall survival rates were 8 and 0%, respectively. If eight patients who received EBRT with no planned spatial relationship to surgery are included, 3-year survival increases to 15% but 5 year was still 0%.

External Irradiation ± Chemotherapy

External irradiation ± chemotherapy has definite palliative symptomatic benefit for locally recurrent lesions but long-term survival is infrequent [6–14]. Relief of pain and/or bleeding is achieved in approximately 75% of patients with doses as low as 20 Gy in ten fractions over 2 weeks, but doses in most series vary from 40 to 60 Gy in 1.8 to 2.5 Gy fractions. Median duration of symptom relief is only 6–9 months, and long-term survival is infrequent (0–5% in most series).

Some data suggest a correlation between irradiation dose and duration of palliation [11, 15–17]. In an analysis by Wang and Schulz [11] for residual, inoperable, or recurrent lesions the percentage of patients who received palliation for 6 months or more increased with doses beyond 41 Gy (21–30 Gy – 3 of 24 or 12%, 31–40 Gy – 5 of 28 or 31%, 41–50 Gy – 7 of 12 or 58%). Correlation of response and irradiation dose level was also seen in series reported by Hindo et al. [15], Rao et al. [16], and Overgaard et al. [17] on groups of patients treated for palliation. In 110 patients, Hindo et al. reported successful response in 20% of patients treated with a nominal single dose (NSD) of 400–700 ret, 67% with 701–1,000 ret, and 82–89% in the other three dose divisions (1,001–1,300, 1,301–1,500, and 1,501–1,750 ret). Rao et al. treated 92 patients with successful palliation in only 12% with an NSD of 1,000 ret or less, 49% with 1,000–1,200 ret, 59% with 1,200–1,400 ret, and 87% with 1,400–1,700 ret.

Lybert et al. [18] published data from a group of 95 locally recurrent rectal cancer patients in the Netherlands treated with EBRT ± 5-FU for relapse after radical surgery. Seventy-six patients presented with locoregional relapse only (Table 16.1), and 19 presented with locoregional relapse and

Table 16.1 Locally advanced recurrent colorectal cancer survival and disease relapse with EBRT with or without IOERT, various series

Treatment	Patients at risk	Overall survival (%)			Local relapse (EBRT)		Distant relapse	
		Median (month)	2-year	5-year	No. (%)	3-year	No (%)	3-year
EBRT								
Netherlands – Lybert et al. [18]	76	14	25	5	43/63 (68)	–	26/63 (41)	–
EBRT <50 Gy	–	12	20	0	–	–	–	–
EBRT ≥50 Gy	–	20	40	10	–	–	–	–
Australian – Guiney et al. [19]	135	15	–	–	–	–	–	–
Low-dose palliative	16	9	13	–	– (94)	–	–	–
High-dose palliative (45 Gy/3 Gy Fx)[a]	80	15	26	4	– (94)	–	– (38)[a]	–
Radical (50–60 Gy/2 Gy Fx) [a]	39	18	31	≤9	– (82)	–	– (49)[a]	–
IOERT								
Mayo Clinic – Suzuki et al. [5]								
No IOERT	64	17	26	7 [b]	54 (84)	93	29 (45)	54
IOERT ± EBRT	42	30	62	19 [b]	16 (38)	40	24 (57)	60
Mayo Clinic – Haddock et al. [30]								
EBRT + IORT								
No prior EBRT	359	37	71	32	79 (22)	20	193 (54)	57
Prior EBRT	248	35	67	26	79 (32)	39	105 (42)	49

IOERT intraoperative electron irradiation; *EBRT* external beam irradiation; *DM* distant metastasis

[a] High-dose palliative patients had 1 week treatment break after 30 Gy in 10 Fx; incidence of metastasis underestimated as patients were only investigated as warranted by symptoms

[b] Survival advantage for IOERT vs. no IOERT, $p = 0.0006$ (log-rank univariate analysis)

concomitant distant metastases. The total dose of EBRT was, respectively, 44 Gy median (range 6–66 Gy) and 40 Gy median (range 6–50 Gy). Twelve of 76 with localized relapse received concomitant 5-FU with EBRT. In the patients with locoregional relapse only, recurrence-free and overall survival rates (RFS, OS) after EBRT were 23 and 61% at 1 year, and 6 and 13% at 3 years, respectively. Recurrent or persistent disease inside the EBRT volume was an important clinical problem in 43 of 63 evaluable patients or 68% (42 of 43 were diagnosed within 2 years). In the 76 patients with locoregional relapse only, using RFS as the endpoint, dose of EBRT was a significant multivariate prognostic factor ($p=0.01$); using OS as the endpoint, dose of EBRT (better survival with doses >50 Gy, $p=0.005$) and grade of tumor differentiation ($p=0.002$) were significant.

Investigators at Peter MacCullum Cancer Institute [19] retrospectively analyzed a group of 135 patients with locally recurrent, nonmetastatic rectosigmoid cancer treated from 1981 to 1990 with three different dose ranges of radiotherapy: 50–60 Gy ("Radical" group – 2 Gy fractions, no split), 45 Gy ("High-dose palliative" group – 3 Gy fractions with 1 week split after 30 Gy in ten fractions) and <45 Gy ("low-dose palliative" group). Symptomatic response rates of 85, 81, and 56% were achieved in the radical, high-dose palliative and low-dose palliative groups, respectively. Objective response rates were assessed only in the radical and high-dose palliative groups and were 44 and 37%, respectively. Estimated median survival times were 17.9, 14.8, and 9.1 months for the radical, high-dose, and low-dose palliative groups, respectively.

Mayo Analyses: EBRT ± Chemo or Immunotherapy

External irradiation has been used alone or in combination with chemotherapy, immunotherapy, surgical resection or IOERT at Mayo Clinic for locally advanced colorectal cancers. Early Mayo analyses did not analyze results separately as a function of locally recurrent vs. primary locally advanced cancers. Two of the analyses which included patients with locally recurrent lesions were small, single-institution randomized trials [9, 13].

In the first randomized trial, a group of 65 patients with locally unresectable or recurrent colorectal carcinoma was treated with 40 Gy in 2 Gy fractions over 4 weeks plus placebo or 5-FU (15 mg/kg on the first 3 days of EBRT) [9]. Median survival time was 10.5 months in the placebo group vs. 16 months in those receiving 5-FU concomitant with EBRT ($p<0.05$). Two-year survival was 24 vs. 38% and 3-year survival was 9 vs. 19% (Table 16.1).

In a later trial, 44 patients with locally advanced rectal cancer (unresectable – 7, resected but residual – 7, locally recurrent – 30) received 50 Gy split-course pelvic irradiation with or without adjuvant immunotherapy [13]. Site of initial tumor progression could be evaluated in 31 patients, and local progression within the radiation field was diagnosed in 28 (90%). In 17 (55% of evaluable patients), it was the only site of disease. Median survival time in both groups of patients was approximately 18 months. In this trial, 36 of 44 patients were experiencing significant pelvic or perineal pain prior to EBRT. Although 94% of patients experienced temporary improvement in pain following treatment, median duration of pain relief was only 5 months.

Patient Selection and Treatment Factors: IORT

Patient Selection and Evaluation

Appropriateness for an IORT boost should be determined by the surgeon and radiation oncologist in the setting of a joint-preoperative consultation, whenever feasible. This allows input from both

specialties with regard to studies that would be helpful for IORT and EBRT planning as well as whether IORT is appropriate. An informed consent can be obtained with regard to potential benefits and risks, and optimal sequencing of surgery and EBRT can be discussed and determined.

General criterion for evaluation and selection of patients with recurrent colorectal cancers have been detailed previously in publications from both Mayo Clinic and MGH [12, 19–30]. By definition, there must be no contraindications for exploratory surgery. Local control rates with surgery alone should be low and EBRT doses needed for local control following subtotal resection or with EBRT alone should exceed normal tissue tolerance. An IORT approach should permit direct irradiation of unresected or marginally resected tumor with single or abutting IORT fields while allowing the ability to surgically displace or shield dose-limiting normal organs or tissue. Small bowel should always be displaced out of the IORT field and other critical tissues, such as ureter and bladder, can often be displaced if not at risk for harboring residual disease. Patients with documented distant metastases are not often candidates because of limited lifespan. However, with increasing survival observed with modern systemic therapies, many patients will outlive the palliative effects of local therapy and aggressive locoregional therapy may be considered. In addition, patients with oligometastatic disease (limited liver or lung metastases) may be considered appropriate for curative intent treatment.

The pretreatment patient workup should include a detailed evaluation of the extent of the locally recurrent lesion combined with studies to rule out hematogenous (liver/lung) or peritoneal spread of disease. In addition to history and physical exam, the routine evaluation includes CBC, liver and renal chemistries, chest film, and CEA. If the rectum is still present, the local evaluation includes digital exam, and proctoscopy and/or colonoscopy. When low- or mid-rectal lesions are immobile or fixed or symptoms suggest pelvic recurrence following abdominoperineal resection, computed tomography (CT) of the pelvis and abdomen can confirm lack of free space between the malignancy and a structure that may be surgically unresectable for cure (i.e., presacrum, pelvic sidewall) in whom preoperative irradiation plus 5-FU-based chemotherapy should be given prior to an attempt at resection. Magnetic resonance imaging (MRI) often provides greater anatomic detail regarding local extension of disease. Extrapelvic spread to para-aortic nodes or liver and the pretreatment status of ureters with regard to presence or absence of obstruction can also be determined from a CT of the abdomen and pelvis. Positron emission tomography (PET) is very useful in evaluating potential metastatic spread of disease. If hematuria is present or findings on CT or MRI suggest bladder involvement, cystoscopy is done prior to or on the day of surgical confirmation. In patients with cutaneous or perineal fistulae, fistulography may be helpful in determining both size and depth for the purpose of treatment planning.

Sequencing of Treatment Modalities

For most patients with locally recurrent colorectal cancers, delivery of 45–55 Gy plus concomitant fluoropyrimidine-based chemotherapy preoperatively with reoperation in 3–5 weeks offers the following theoretical advantages over the sequence of resection and IORT followed by postoperative EBRT plus chemotherapy: (1) potential alteration of implantability of cells that may be disseminated intra-abdominally or systemically at the time of marginal or partial surgical resection, (2) deletion of patients with metastases detected at the restaging workup or laparotomy, thus sparing the potential risks of aggressive surgical resection ± IORT, (3) possible tumor shrinkage with an increased probability of achieving a gross total resection, and (4) reduction of treatment interval between the EBRT and IORT components of irradiation (if surgical resection and IORT are done initially and postoperative complications ensue, the delay to the EBRT plus chemotherapy component of treatment may be excessive). If patients present with locally recurrent colorectal cancer after

adjuvant treatment that included 45–50 Gy of EBRT, full doses of preoperative EBRT may not be feasible [29, 30]. In such instances, delivery of 30 Gy in 1.8–2.0 Gy fractions to conformal fields exclusive of small bowel, after a dose of ~20 Gy, may be followed immediately (1 day to 1 week) with surgical exploration and attempted resection (advantages #1 and 4 still exist).

There would appear to be no tumor-related advantages in having surgical resection, and IORT precede the EBRT component of treatment. For patients with locally recurrent pelvic lesions, the altered sequencing may, however, provide an advantage for normal tissue tolerance [6, 12, 31–34]. If fixed loops of small bowel were found at exploratory laparotomy, they could be mobilized out of the pelvis. Pelvic reconstruction could be performed with omentum or mesh to allow displacement of small bowel during subsequent EBRT plus chemotherapy. However, performing two surgical procedures may be difficult to justify (exploration and reconstruction; exploration, resection, and IORT after preoperative EBRT plus chemotherapy). An alternate approach would be to keep the planned preoperative dose at a level of 40–45 Gy, instead of a higher dose of 50.4–54 Gy, if fixed loops of small bowel were adjacent to the recurrent disease and could not be excluded after a dose of 40–45 Gy.

Chemotherapy should typically be instituted simultaneously with EBRT for locally recurrent colorectal cancers. The advantage of starting irradiation and chemotherapy simultaneously is that effective local and systemic treatment are instituted simultaneously [35–39]. There is less risk, therefore, that one component of disease will become uncontrollable due to progression during single modality treatment. The disadvantage of starting chemotherapy simultaneously with EBRT is that full-intensity chemotherapy may never be feasible. For tolerance reasons, the intensity of chemotherapy given during EBRT is usually less than the chemotherapy which precedes EBRT. If further cycles of chemotherapy are given after pelvic EBRT, full-intensity chemotherapy may not be feasible because of alterations in bone marrow reserve.

A potential advantage of altered sequencing of chemotherapy and EBRT (i.e., deliver two or more cycles of multiple drug chemotherapy before starting combined irradiation/chemotherapy) would be the ability to give full-intensity chemotherapy for at least two cycles. This may have increased impact on occult systemic disease and thereby improve the ultimate rates of systemic disease control. The risk of starting chemotherapy before EBRT, however, is that the local component of disease may continue to progress and subsequent resection may never be feasible. However, for patients with limited metastatic disease in whom resection with IORT is being considered, this may be the preferred approach.

Irradiation Factors

EBRT ± Concomitant Chemo

The method of EBRT in *previously unirradiated patients* has been fairly consistent in most single-institution and group colorectal IOERT studies. Doses of 45–55 Gy (100 cGy = 1 Gray; 1 cGy = 1 rad) may be delivered in 1.8 Gy fractions, 5 days per week over 5–6 weeks in previously unirradiated patients. For pelvic lesions, treatments are given with linear accelerators using ≥10-MV photons and multiple field-shaped external beam techniques [20, 23, 25, 27, 28]. With extrapelvic lesions, unresected or residual disease plus 3- to 5-cm margins of normal tissue are included to 45 Gy, usually with multiple fields [26, 28, 31, 40]. Reduced fields with 2- to 3-cm margins may be treated to 50–55 Gy. Intensity-modulated radiation therapy (IMRT) may be utilized to decrease dose to critical structures and boost the dose to the site of relapse. IMRT is particularly useful to decrease dose to small bowel for extrapelvic targets or for previously irradiated patients. When chemotherapy is given during EBRT, 5-FU is either given as a single drug in protracted daily venous infusion (225 mg/m^2/24 h-5 or 7 days per week or until intolerance [38]) or in combination with Leucovorin in bolus injections (5-FU 400 mg/m^2 plus Leucovorin 20 mg/M^2 intravenous push for 4 consecutive

days during the first week of EBRT and 3–4 days during the last week [34]). Alternatively, oral capecitabine may be delivered on days of radiation at a dose of 825 mg/M^2 twice daily.

In *previously irradiated patients*, only partial-dose EBRT can be given as a component of treatment [29, 30]. Since marginal resection is usually the surgical option, it is preferable that low-dose EBRT be given prior to an attempt at resection unless the patient presents with fixed small bowel loops within a prior high-dose EBRT field. The target volume is generally limited to the gross tumor volume with margin and small bowel is excluded from the fields after a dose of ~20 Gy. Initially, Mayo patients in retreatment situations received EBRT alone or EBRT plus bolus 5-FU ± Leucovorin. Currently, patients receive 30 Gy in 1.8–2.0 Gy fractions plus protracted venous infusion 5-FU (225 mg/M^2/24 h) or oral capecitabine (825 mg/M^2 twice daily). With concomitant bolus 5-FU plus EBRT, surgery would need to be delayed for ≥2 weeks after delivery of the bolus 5-FU to allow the WBC and platelet nadirs to have been reached. With infusion of 5-FU at 225 mg/M^2 or oral capecitabine at 825 mg/M^2 twice daily, patients can proceed directly to surgical resection after completion of the combined EBRT plus concomitant chemotherapy, thus shortening the overall treatment time and potential biological effectiveness of radiation.

IOERT

EBRT is supplemented by IOERT at the joint discretion of the surgeon and radiation oncologist as discussed previously. The radiation oncologist joins the surgeon at the time of surgical exploration or resection to help determine feasibility of a subsequent IOERT boost and size and shape of the IOERT applicator. If surgical exploration precedes EBRT and residual or unresectable disease remains after an attempt at resection, a similar intraoperative assessment for IOERT can be performed.

After abdominoperineal resection, optimal IOERT field exposure is determined with regard to an abdominal (Fig. 16.1a–d) vs. perineal approach (Fig. 16.1e), and prone vs. supine or lithotomy patient position [20, 23, 25, 27, 28]. If an exenteration is necessary, the prostatic fossa in the retropubic region can be treated through an abdominal (Fig. 16.1b–d) incision. Tumor adherence to anterior pelvic structures including the prostate or base of bladder can produce a technical challenge, as a perineal approach for IOERT is usually necessary. Patients can be treated in either the prone or supine position. Before the Maquet table became available at Mayo Clinic, patients were usually placed in the prone position for IOERT after colostomy formation and abdominal closure. With the availability of the Maquet table, patients remain in the supine surgical position for IOERT (Fig. 16.1e). The main technical challenge is the need for greater exposure and increased hip abduction. The small size of the pelvic inlet between ischial tuberosities in males can occasionally prevent use of an adequate-sized applicator. In patients with pelvic anatomy or anterior locations that cannot accommodate the IOERT applicator, HDR-IORT can often be used effectively for IORT delivery. In Mobetron institutions, prone position is necessary to treat anterior-inferior sites at risk (prostate, other).

Since April of 1989, both the operative procedure and delivery of IOERT at Mayo Clinic in Rochester are performed in a dedicated IORT suite within a hospital operating room and a similar facility became available at MGH in June 1996 (see Chap. 3). The operating rooms were designed to allow complete OR capabilities as well as delivery of IOERT ± dose modifiers. The linear accelerator at Mayo is a refurbished Clinac 2100C that provides variable electron energies from 6 to 18 MeV, and MGH uses the Siemens nonmobile dedicated IOERT linear accelerator with variable electron energies of 6–18 MeV.

The IOERT dose is calculated at the 90% isodose line and is dependent on the amount of residual disease remaining after maximal resection and the amount of EBRT that has or can be delivered as a component of treatment. For patients in whom 45–50 Gy of fractionated EBRT is feasible, the following IOERT guidelines apply: negative margins or microscopic residual (R0 or R1 resection), 10–12.5 Gy; gross residual (R2 resection) ≤2 cm in largest dimension, 15 Gy; unresected or gross

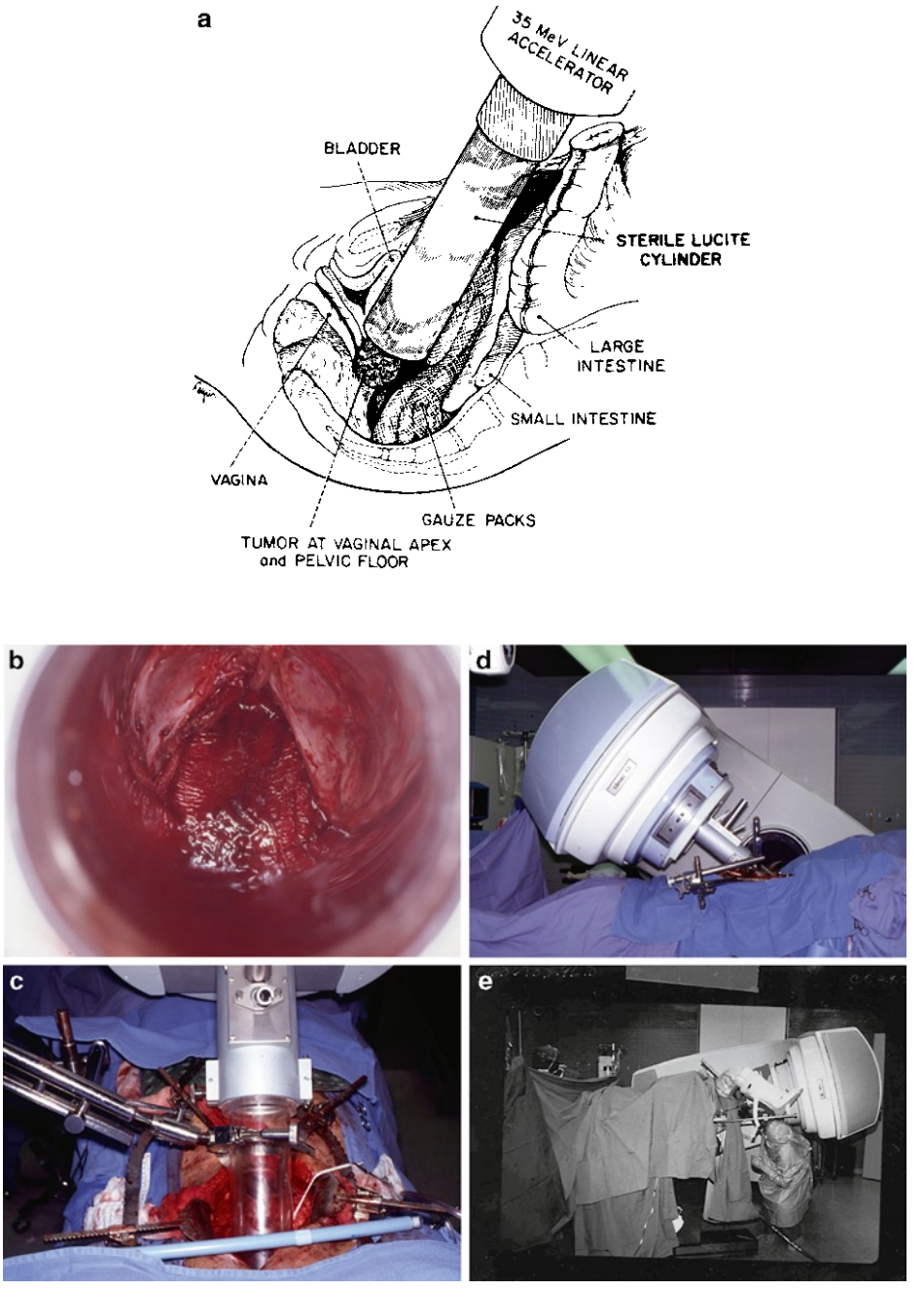

Fig. 16.1 IOERT techniques. (**a**) Artists idealized depiction of IOERT applicator in position to include relapse at vaginal apex and pelvic floor. (**b–d**) Prostatic fossa in the retropubic region is included in the IOERT field (8.0 cm applicator with 30° bevel) after an exenterative procedure – gantry angle exceeds 45°. (**e**) Treatment of low-lying pelvic tumor or tumor bed via the perineal incision with the patient supine – gantry angle approaches 90°.

residual ≥2 cm, 17.5–20 Gy. In retreatment situations where fractionated EBRT doses are restricted to 30 Gy, IOERT doses usually range from 15 to 20 Gy, but doses as high as 25 Gy have occasionally been delivered. Electron energies are chosen on the basis of maximum thickness of disease after maximal resection and the ability to achieve complete hemostasis after surgical resection. The lower energies of 6, 9, and 12 MeV are used after gross total resection or with minimal residual disease. If the 6 MeV energy is chosen, 0.5–1.0 cm of bolus material may need to be used to improve the surface dose. If surgical hemostasis is incomplete and suction drainage is not functioning properly, choice of either 6 or 9 MeV electrons could result in underdosage at depth. The 15–18 MeV energies and doses of 20 Gy are used more commonly in patients in whom gross residual or unresectable disease exists after attempts at resection.

The size and shape of the IOERT applicators used are dependent on tumor location. For pelvic tumors, circular applicators with 30° bevels are often needed to conform to the anatomy of the presacrum, pelvic sidewall, or anterior pelvis. With the 30° bevel, the depth of isodose curves is more shallow at the heel end of the applicator than the toe end [21] and should be considered when placing the treatment applicator relative to the tumor bed or residual tumor. For extrapelvic lesions, rectangular and elliptical applicators with flat or 20° bevel ends are occasionally used, in institutions where they are available, in addition to circular applicators.

IOERT Vs. HDR-IORT

Since February 1992, IOERT has been performed at Ohio State University using a dedicated Siemens linear accelerator with electron energies of 6–18 MeV [41]. In addition, sites that are nonaccessible for IOERT have been treated intraoperatively using a HDR afterloader (HDR-IORT) that is transported to the shielded operating room from the radiation oncology department (see OSU results for an expanded presentation of HDR-IORT technique). Investigators at Memorial Sloan Kettering Cancer Center (MSKCC) have utilized HDR-IORT for recurrent colorectal cancer in a dedicated HDR-IORT operating room [42]. This approach has also been utilized by investigators in Europe [43, 44]. HDR-IORT offers increased flexibility with regard to applicator placement as well as a higher dose in the superficial target without an increase in dose to displaced normal tissues. The HDR-IORT dose distribution is inadequate for treating targets greater than 1.0 cm deep and the OR time is significantly prolonged compared to IOERT.

Surgical Considerations

The intent of surgery is to accomplish a gross total resection if technically feasible and safe. Although palliation may be a secondary benefit from surgery for local recurrence, extensive surgical procedures are not advised for purposes of palliation alone, unless disabling complications of sepsis or bleeding are an issue. Patients should, therefore, be evaluated for the possibility of curative intent surgery, with the possibility of unresectable extrapelvic disease excluded and the potential resectability of local disease determined on the basis of preoperative imaging studies (Fig. 16.2a–d). Finally, with regard to preoperative selection, patients must be of suitable general health and must be counseled on the extensiveness of the multimodality therapy.

Pelvic recurrences are typically amenable to reresection if they are strictly posterior or anterior (Fig. 16.2a, c). Evidence of lateral pelvic sidewall involvement diminishes the chance of complete resection (Fig. 16.2b, d); however, operative assessment and at least an opportunity for resection and IOERT is warranted, providing no other contraindications are identified. Although locoregional

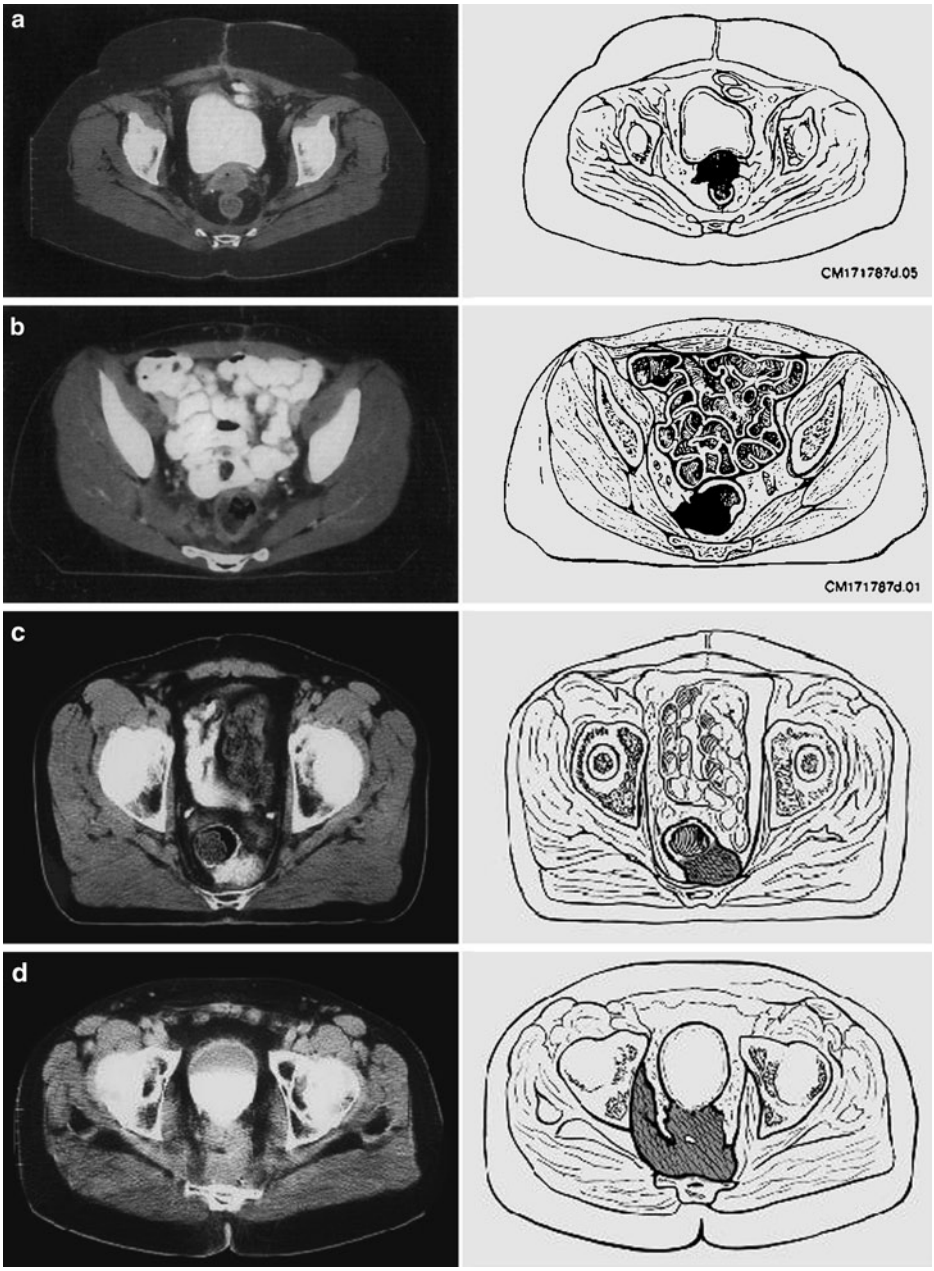

Fig. 16.2 (**a**–**d**) Potential resectability of locally recurrent pelvic lesions based on pretreatment imaging studies. (**a**) This case illustrates a fixed but resectable lesion involving *anterior* structures. The primary T3N0M0 rectal cancer was managed with low anterior resection, without postoperative chemotherapy or radiation therapy. The recurrence was fixed to the bladder and was treated with preoperative EBRT plus chemotherapy followed by resection and IOERT. (Reprinted with Permission from Churchill Livingstone.) (**b**) In this case, a fixed, but resectable *lateral* pelvic recurrence was diagnosed following a low anterior resection for a T2N0M0 primary rectal carcinoma. No adjuvant therapy had been administered, therefore a full course of EBRT plus chemotherapy was delivered followed by complete abdominal perineal resection, with negative margins, and IOERT. (Reprinted with Permission from Churchill Livingstone.) (**c**) *Posterior* recurrence involving the sacrum was diagnosed in this patient who had initially presented with a T3N0M0 lesion of the rectum, treated with resection and adjuvant chemoradiation. After a second course of external beam radiation plus chemotherapy, an en bloc resection of the tumor and sacrum accomplished negative margins. IOERT was administered to the surgical site at risk for recurrence. (Reprinted with Permission from Churchill Livingstone.)

recurrences that occur above or below S2 of the sacrum are amenable to resection using anterior table sacral resection or distal sacrectomy, respectively, the presence of tumor both above and below S2 precludes curative surgery. Similarly, although vascular tumor involvement of either the arterial or venous structures at or distal to the aorta may be resectable, involvement of both structures contraindicates curative surgery in most if not all cases.

At the time of surgery, careful assessment for extrapelvic disease is essential. If possible, it is preferable to determine resectability before critical structures are sacrificed or injured. Adjacent involved organs should be removed en bloc with the specimen if the associated morbidity is acceptable to the patient and physician. When the recurrent tumor is locally adherent to the prostate or base of the bladder (Fig. 16.2a, d), since the side effects of pelvic exenteration are excessive, it may be preferable to deliver preoperative EBRT with chemotherapy followed by gross total resection, with organ preservation, and supplemental IOERT to the site of adherence (may be able to spare the organ involved by adherence). However, in view of severe adhesions due to prior surgery and/or adjuvant EBRT, organ preservation is often not technically feasible in the setting of recurrent lesions, and exenterative procedures may be necessary in order to accomplish a gross total resection. The option to spare the bladder should be reserved for those cases where present function is good and there is minimal adherence, such that comparable local regional control could be accomplished with exenteration vs. organ-preserving resection plus IOERT.

In the setting of pelvic recurrence of rectal cancer, it is rarely possible or reasonable to restore intestinal continuity. Most often, a previous low anterior resection is being converted to an abdominal perineal resection (APR), or a previous APR to a sacrectomy or exenteration. In the face of local relapse, it is usually ill-advised to place another anastomosis in this heavily treated field which is at risk for subsequent local relapse. Rarely, in a highly motivated patient with good sphincter function and a very proximal anastomotic recurrence, it may be reasonable to perform a coloanal anastomosis. Following moderate doses of preoperative EBRT (45–50 Gy) ± 5-FU-based chemotherapy, anterior resection and primary anastomosis may be safely accomplished if an unirradiated loop of large bowel can be used for the proximal limb of the anastomosis. Temporary diverting colostomies are preferable in patients who receive preoperative EBRT or chemoradiation.

If at the end of resection it is decided that postoperative EBRT is indicated, small titanium or vascular clips should be placed around areas of adherence or residual disease for the purpose of boost field EBRT. The pelvic floor should be reconstructed after resection to minimize the amount of small bowel within the true pelvis, and primary closure of the perineum should be performed after APR to hasten healing (2–6 weeks vs. 2–3 months) and decrease the interval to postoperative EBRT and chemotherapy, if indicated. In patients who have been heavily pretreated or those with large defects, vascularized myocutaneous flap closure should be strongly considered. The muscle closes the dead space of the pelvis, which is typically fibrotic and prone to small bowel adhesion formation, and the fresh nonirradiated skin, ensures perineal healing. For posterior sacrectomy wounds, myocutaneous flap closure has become the standard at Mayo Clinic.

If patients develop locally recurrent disease following prior adjuvant EBRT, preoperative and postoperative EBRT options are limited at the time of retreatment unless pelvic reconstruction can be accomplished to displace small bowel (omentum, mesh, other). In previously irradiated patients, IOERT as salvage is usually feasible only in the setting of gross total resection of disease, and extended organ resection (anterior exenteration, distal sacrectomy, etc.) may be necessary in order to achieve total resection.

Fig. 16.2 (continued) (**d**) This case illustrates a locally recurrent lesion that is *fixed* and *not resectable*. The primary, a T3N1M0 tumor, was treated with abdominal perineal resection and a full course of adjuvant radiation and chemotherapy. Recurrent tumor was found to involve the bladder, sacrum, and lateral pelvic sidewall and was not amenable to resection. (Reprinted with Permission from Churchill Livingstone).

Results: IOERT ± EBRT, Previously Unirradiated Patients

US IOERT Series

Local Control ± Survival with IOERT Regimens

IOERT has been used at MGH for both locally advanced primary and recurrent colorectal cancers as a component of an aggressive combined approach with EBRT ± 5-FU and maximal resection [12, 20, 21, 24, 25, 27, 30, 45, 46]. Lindel et al. [46] reported 5-year actuarial survival of 27% in 49 patients who received EBRT (±5FU), IOERT, and maximal resection at MGH for locally recurrent rectal lesions. Prognostic factors which appeared to alter local control and survival are discussed in the next section.

In the Mayo Clinic analysis by Suzuki et al. [5], of 106 patients with subtotal resection of a localized pelvic recurrence from rectal cancer, 42 received IOERT as a component of treatment (41 of the 42 received EBRT; ≥45 Gy in 38). EBRT was the only method of irradiation in 37 patients, and 29 of the 37 received the EBRT in close approximation to subtotal resection in a planned adjuvant role. The 3-year survival rate was only 18% in the 29 adjuvant EBRT patients vs. 42.5% in patients with IOERT as a component of treatment, and 5-year survival was 7% (EBRT) vs. 19% (IOERT) ($p=0.005$ in a pair-wise comparison) (Table 16.1). Disease control within irradiation fields also appeared to be better in IOERT patients. In previous Mayo Clinic EBRT analyses that included both locally advanced primary and recurrent lesions and in the Suzuki analysis [5, 12], local progression was documented in 90% of EBRT patients vs. 40% in the 42 IORT patients in the Suzuki analysis. Although differences seen from series to series may reflect selection bias in nonrandomized series instead of treatment effect, it is possible that improvements in control of local regional component of disease with the addition of IOERT may translate into improved short-term, if not long-term, survival.

In the most recent Mayo analysis [30], 359 colorectal patients with local or regional recurrence and no previous EBRT for their large bowel cancer were treated with an aggressive multimodality approach including EBRT ± 5-FU, maximal surgical resection, and IOERT (Tables 16.2 and 16.3). Median survival and 5-year OS rates appeared better than two prior Mayo Clinic EBRT trials that contained a large percentage of patients with recurrence [9, 13] (IOERT median survival 37 mo., vs. 16 and 18 mo. with EBRT + 5-FU or EBRT + immunotherapy). Five-year OS was seen in 32% of patients in the current IOERT series vs. 5% [9] to 7% [5] in earlier Mayo Clinic EBRT analyses that noted 5-year results.

Prognostic Factors for Disease Control and Survival with IOERT Regimens

Both 5-year actuarial local control (LC) and disease-free survival (DFS) were improved in MGH analyses if the surgeon was able to perform a gross total resection prior to IOERT. In the initial analysis of 32 patients by Willett et al. [25], 5-year LC and DFS were 42 and 33% with negative resection margins after gross total resection vs. 11 and 6% with any degree of residual disease, microscopic or gross. In the most recent MGH analysis of 49 recurrent IOERT patients [46], 5-year actuarial LC and OS were 56 and 40%, respectively, in the 25 patients with R0 resection vs. 17 and 14% in the 24 patients with R1(microscopic residual) or R2 (gross residual) resection (Table 16.4). Five-year DFS in all 49 patients was 20% and the 5-year OS was 27%. Data from Rush-Presbyterian Hospital [47] RTOG [48] and the University of Navarra [49] also support the correlation between local tumor control and amount of residual disease after resection (Table 16.4). Patients with gross total resection and only microscopic residual had better in-field disease control than those with unresected or gross residual disease.

Table 16.2 Colorectal IOERT – locally recurrent, no prior EBRT disease relapse by prognostic factor, Mayo clinic Rochester

		Local (EBRT) (%)			Distant (%)		
Prognostic factor	No. at risk	No. (%)	3-year	P^a	No. (%)	3-year	P^a
EBRT ± 5-FU							
EBRT	63	13 (21)	18	0.98	35 (56)	59	–
EBRT + 5-FU	296	66 (22)	21	–	193 (65)	56	0.38
Systemic chemotherapy							
Yes	61	12 (20)	17	0.81	30 (49)	52	0.65
No	298	67 (22)	21	–	163 (55)	58	–
Site of primary							
Colon	150	28 (19)	17	0.14	73 (49)	52	0.09
Rectum	209	51 (24)	23	–	120 (57)	60	–
Volume of residual							
R2	102	32 (31)	30	–	66 (65)	65	–
R1	121	25 (21)	21	–	66 (55)	58	–
R0	136	22 (16)	12	0.007	61 (45)	50	0.02
Total Group	359	79 (22)	20		193 (54)	57	

R0 microscopically negative margins; *R1* microscopic residual; *R2* gross residual
Modified from Haddock, M.G. [30]
[a]Log-rank *P* value

Table 16.3 Colorectal IOERT – locally recurrent, no prior EBRT, survival by Prognostic factor, Mayo

		Survival %					
Prognostic factor	No. at risk	Median (month)	2-year	3-year	5-year	10-year	P^a
EBRT ± 5FU							
EBRT alone	63	29	66	43	24	15	–
EBRT + 5FU	296	39	72	53	34	17	0.09
Prior chemotherapy							
Yes	155	35	68	47	30	18	–
No	204	39	74	54	34	17	0.45
Primary site							
Colon	150	38	73	52	35	25	0.11
Rectum	209	36	71	50	31	13	–
Residual volume							
R2	102	28	60	38	17	5	–
R1	121	36	73	49	33	26	–
R0	136	50	80	64	47	23	<0.0001
Systemic chemo							
Yes	61	44	79	63	46	–	0.28
No	298	35	70	49	30	19	–
Treatment era							
Before 3/1997	151	30	66	42	22	10	–
After 3/1997	208	44	76	58	42	25	<0.0001
Total	359	37	71	51	32	17	

[a]Log-rank *P* value *R0* microscopically negative margins; *R1* microscopic residual; *R2* gross residual
Modified from M.G. Haddock [30]

Table 16.4 Colorectal IOERT – Tumor failure in IOERT (CF) or EBRT field (LF) vs. amount of residual

Series	Reference	Number of patients	CF or LF (%)		Residual vs. CF or LF (%)		
			Primary	Recurrent	None	Res(m) or none	Unresect or Res(g)
MGH (5-year act)							
Primary	[45]	42	23	–	12	31	50
Recurrent	[46]	49	–	65	44	54	88
Rush-Presbyterian	[47]						
Primary		9	33	–	–	14	100
Recurrent		35	–	54	–	39	64
RTOG – recurrent	[48]	37	–	62	–	33	89
Pamplona – recurrent	[49]	27	–	74	–	50	84

CF central failure (IOERT field), *LF* local failure (external beam field), *Res(m)(g)* microscopic and gross residual, *unresect* unresectable, *Act* actuarial

In an early Mayo IOERT analysis, volume of residual was not found to be statistically associated with disease relapse or survival [28]. In the most recent Mayo Rochester IOERT series of 607 patients with locally recurrent colorectal cancer, 359 had not received prior EBRT to the site of recurrence [30]. The volume of residual after maximal resection had a statistically significant impact on both disease control and OS ($p<0.007$, LC; $p<0.02$, distant metastasis, DM; $p<0.0001$, OS; Tables 16.2 and 16.3). Local disease relapse was not associated with use of 5-FU with EBRT, delivery of systemic chemotherapy or colon vs. rectum primary site. There was a trend toward higher distant relapse rates in patients with rectal vs. colon primaries (60% vs. 52% 3-year, $p=0.09$). Patients treated in the more recent era (after 1997) have improved survival (42% vs. 22% 5-year, $p<0.001$) although administration of systemic chemotherapy was not shown to impact survival. Advances in imaging technology and development of more effective systemic therapy regimens may have resulted in altered patient selection for IORT in the more recent era.

Distant Control: Implications for Chemotherapy

Since the risk of subsequent DM exceeds 50% in patients who present for IOERT at the time of local recurrence, effective systemic therapy will be needed as a component of aggressive treatment approaches including IOERT. In the most recent Mayo series [30], 193 of 359 previously unirradiated patients (54%) developed DM with a 3-year rate of 57%. Although 296 of the 359 patients (82%) received 5-FU-based chemotherapy simultaneously with EBRT, only 61 (17%) patients received maintenance chemotherapy after resection and IOERT. For patients who did or did not receive chemotherapy, the absolute rate of DM was 30 of 61 or 49% vs. 163 of 298 or 55%, respectively ($p=0.65$).

Tolerance of IOERT

Structures at major risk with the use of IOERT for recurrent colorectal cancers include primarily ureter and peripheral nerve [21, 23, 50–61]. Although ureteral narrowing or obstruction as a result of IOERT has been demonstrated in both animal [21, 23, 53–57] and clinical studies [23, 51–54], the ureter is not dose limiting for IOERT as stents can be placed to overcome obstruction. Peripheral nerve is the main dose-limiting structure for IOERT as judged from data generated from both clinical and animal studies [22, 51, 53, 54, 58–61]. In an early Mayo Clinic IOERT tolerance analysis by Shaw et al. [51], symptomatic or objective neuropathy occurred in 12 of 37 (32%) pelvic IOERT

colorectal patients at risk ≥12 months (pain in 12 patients, severe in 3 of 37 at risk or 8%; motor in seven patients, severe in only 1 of 37 or 3%; sensory in 8, nonsevere). When obtaining informed consent for IOERT, the potential for IOERT-related symptomatic neuropathy must be balanced against the likelihood that local persistence or relapse will result in tumor-related pain. Since many patients with locally recurrent colorectal cancers have moderate or severe pain at time of presentation, they can usually accept the risk of pain related to treatment given the high likelihood of tumor-related pain if local disease is not controlled.

In the recent Mayo analysis of 607 patients with IOERT as a component of treatment for locally recurrent colorectal cancers [30], the incidence of peripheral neuropathy of any degree was 15% (93 of 607 patients), lower than that observed in the analysis by Shaw et al. [51]. The incidence of severe neuropathy was 3% (18 of 607 patients had grade 3 toxicity). Thirty-two of 93 patients had only a grade 1 neuropathy (mild paresthesia or pain not requiring narcotics). Data in the updated Mayo analysis suggested a relationship between IOERT dose and grade 2 or 3 neuropathy. The incidence of grade 2 or 3 neuropathy by IOERT dose level was as follows: ≤12.5 Gy – 5% vs. ≥15 Gy – 14% ($p = 0.0004$). This trend is consistent with animal data that suggest a correlation between IOERT dose and incidence of clinical and electrophysiologic neuropathy in dogs [58–60].

The ureter can become narrowed or obstructed as a result of IOERT. In the prior published Mayo Clinic analysis of 51 patients with pelvic IOERT for primary or recurrent malignancies, 44% of previously unobstructed ureters became partially or totally obstructed when included in the IOERT field [51]. In the most recent Mayo analysis, ureteral obstruction was evaluated in 146 IOERT patients in whom 168 ureters were in the IOERT field [52]. Urinary obstruction due to any cause increased from 19% (no ureter in IOERT field) to 63% at 5 years and from 51% to 79% at 10 years. Increasing IOERT dose was associated with increased risk of ureteral obstruction with rates of 19, 35, 58, and 85% at 5 years for IOERT doses of 0 Gy, ≤12.5 Gy, 15–17.5 Gy, and ≥20 Gy. The ureter has also been shown to have IOERT-related toxicity in animal studies evaluating IOERT ± EBRT [53–57].

Ureter is not dose limiting for IOERT since stents can be inserted to overcome obstruction and preserve renal function as indicated. Therefore, when tumor is adherent to ureter, it should be included in the IOERT boost. In most institutions, ureteral stents are placed only if subsequent obstruction develops since stent-related problems are not infrequent. Animal studies from Colorado State University (CSU) suggest that the incidence of IOERT-related ureteral changes is related to the length of ureter within the IORT field [57]. Data concerning length of ureter within IOERT fields have not been correlated with subsequent intolerance in clinical series.

The issue of morbidity following aggressive treatment approaches is placed into perspective by an evaluation of tumor-related morbidity. As noted initially, when EBRT is used as the main treatment modality for locally recurrent rectal cancer, symptomatic pain relief is usually of short duration, >90% of patients have local persistence or progression of disease, most are deceased by 2–3 years, and 5-year survival is unusual.

On the basis of both human and animal data, when a full component of irradiation options exists (i.e., can deliver 45–55 Gy fractionated EBRT), IOERT doses of 10–20 Gy continue to be practical, dependent on the amount of tumor remaining after maximal surgical resection. For patients with local recurrence in a previous surgical bed, IOERT doses of 15–20 Gy have been used by many investigators even after gross total resection, because of concerns about hypoxia. However, in view of the suggestion of a lower incidence of grade 2 or 3 neuropathy with IOERT doses ≤12.5 Gy vs. ≥15 Gy in updated Mayo analyses, an IOERT dose of 12.5 Gy would be reasonable after R0 or R1 resection. IOERT doses >20 Gy to ≤25 Gy have been considered in the past only when external doses must be limited because of prior EBRT in view of an increased risk of neuropathy in animal studies [58–60]. As a debatable alternative to decrease the risk of IOERT nerve toxicity, the dose of EBRT may be increased (≥40 Gy) in previously irradiated patients if small bowel can be avoided allowing for an IOERT dose <15 Gy after R0 resection.

Norwegian IOERT Series

One hundred seven patients, 66 males and 41 females, with recurrent rectal cancer were treated between 1990 and 1999 with preoperative EBRT followed by attempts at radical surgery and IOERT [62, 63]. The preoperative EBRT dose was, in general, 46 Gy in 2 Gy fractions. Some patients received a boost of 4 Gy in two fractions. No chemotherapy was given either concomitant with EBRT or as maintenance therapy. IORT was considered indicated if margins were less than 5 mm. Forty-four patients had R0 resections, 39 had R1 and 12 had R2 resection.

IOERT was given to 59 patients (55%). In 48 cases, IOERT was not given for various reasons. In half of those not receiving IOERT, it was not felt to be indicated because of margins greater than 5 mm. IOERT was given to 41% of patients with R0 resection and 65% of those with R1 or R2 resection. A dose of 15 Gy at the 90% isodose line was used in patients with gross total resection and 17.5–20 Gy in those with gross residual.

Local recurrence in the true pelvis was observed in about 30% of R0 patients in both the IORT and non-IORT groups. For R1 patients local recurrence at 5-years was observed in 50% of non-IORT patients and 30% of IORT patients. Five-year OS was 30% in both IORT and non-IORT groups and was highly dependent on the volume of residual disease (5-year OS: R0, 60%; R1, 20%; R2, 0%). The effect of IOERT on survival cannot be determined in this study as the groups of patients given IOERT or not are not directly comparable.

European IORT Series

The current philosophy in Europe is closely related to the US concept which utilizes IORT as a segment of a multidisciplinary approach in cancer management. Either before or after surgery, a component of EBRT ± 5-FU-based chemotherapy is always attempted, if no previous EBRT has been delivered. Maintenance chemotherapy with FOLFOX or newer regimens incorporating targeted therapies is also recommended since local relapse is often the prelude of distant disease even after thorough staging is performed. Survival and disease control results from European series are summarized in Table 16.5.

Pamplona IOERT Series

Published results from Pamplona [49] are in concordance with the experience from US institutions. In an update of the Pamplona series [61], 37 patients have been treated with IOERT for locally advanced recurrent colorectal carcinoma with lesions fixed to the presacral space or pelvic side walls. In this set of patients, 12 were treated with an IOERT boost alone since they had received previous EBRT for their primary disease. Of 37 patients, 25 were treated with EBRT, 11 with post-operative EBRT and 14 with preoperative chemoradiation. In the preoperative approach, Carboplatin (55 mg/M^2) plus 5-FU (1 gm/M^2, maximum tolerated dose of 1.5 gm) were given as a continuous infusion for 3–5 days concurrently with the initiation and ending of the EBRT course. Current doses of EBRT are in the range of 40–50 Gy using standard techniques and fractionation schemes. IOERT doses of 10–15 Gy are used for microscopical residual disease and 15–20 Gy for macroscopic (gross) residual disease.

Results from the Pamplona update show local recurrence in 50% of the 34 evaluable patients. Among the three different treatment groups of IORT alone or with postoperative EBRT or preoperative EBRT plus chemotherapy, local relapse rates are almost identical at 55, 44, and 50%, respectively. The actuarial LC rate at 26 months was increased in patients treated with EBRT + IOERT vs. IOERT

Table 16.5 Summarized European results with IORT ± EBRT for locally recurrent colorectal cancer with regard to local control rates and actuarial 3-year survival

Institution	Reference	Number of patients	LC[a] (%)	Survival[b] (%)
Pamplona	[49, 61]			
IOERT alone		12	0	12
IOERT + EBRT		25	30	38
France	[64]			
IORT alone		30	0	24[c]
IORT + EBRT		16	61	68[c]
Heidelberg				
IOERT + EBRT	[65]	31	71	58[d]
R0		14	79	71
R1		9	61	33
R2		8	60	25
Eindhoven	[66]			
IOERT alone[e]		24	38	25
IOERT + EBRT		66	69	49
R0		84[f]	75	59
R1		34[f]	29	27
R2		29[f]	29	24

[a]LC: actuarial local control rates
[b]Survival: 3-year actuarial survival rates
[c]No long-term survivors beyond 42 months
[d]4-year actuarial survival and local control
[e]Previously irradiated patients
[f]Includes both previously irradiated and unirradiated patients

alone at 40 vs. 0% ($p=0.03$). Residual disease after surgery seems to be another factor related to local relapse. Crude rates decreased with a smaller amount of residual disease after surgery, being 56% after incomplete resections vs. 22% when microscopic residual remained after gross total resection ($p=$ns).

Systemic failure is also considerable, showing crude rates for the three treatment groups of 45, 56, and 29%, being slightly better for those patients treated with preoperative radiotherapy. However, this could be explained as the majority of the patients treated with the preoperative sequence regularly received concomitant chemotherapy.

Long-term survival in this group is poor, with a median survival time from initiation of treatment for patients treated with IORT alone of 15 mo. vs. 22 mo. for those treated with EBRT plus IOERT ($p=0.03$). In patients treated with adjuvant EBRT, the preoperative sequence seems to have better disease survival rates than postoperative EBRT at 23 vs. 10 months, respectively ($p=0.01$).

Toxic events related to the treatment consisted of neuropathy in 11 patients (30%); pelvic infection, four patients (11%); fistula, 11 patients (30%); severe hemorrhage, three patients (8%); and ureteral stenosis in seven patients (19%). Although toxicity seems to be increased in this group of patients, all patients had received previous treatment.

French IORT Group

Similar findings have been observed by investigators from the French IORT group as seen in Table 16.5 [64]. In 73 patients treated with an IORT boost, only 50 had localized pelvic relapse (36 of 50 patients had received prior EBRT). Long-term survival for the entire series is 30% at 3 years

with an actuarial local control rate of 31% at 3 years. In the 30 patients treated with IORT alone, no long-term survivors were found after 42 months vs. 70% for the 16 patients treated with IOERT plus EBRT. Actuarial local control was 60% for EBRT plus IORT vs. 0% with IORT alone.

Heidelberg Series: IOERT

Investigators in Heidelberg, Germany, treated 31 patients with recurrent rectal cancer with IOERT regimens [65] (Table 16.5). EBRT dose was 41.4 Gy preoperative with 5-FU and leucovorin in 22 patients. Nine patients received postoperative EBRT. IOERT doses ranged from 10 to 20 Gy. Four-year OS was 58% and DFS was 48%. Survival and local control were significantly higher in patients with R0 resection (4-year RFS 71% R0 vs. 29% R1/2 and local relapse 21% R0 vs. 35% R1/2, $P=0.019$).

Eindhoven Series: IOERT

Dutch investigators in Eindhoven treated 147 patients with pelvic recurrence of rectal cancer with IOERT regimens from 1994 through 2006 (Table 16.5) [66]. Seventy-nine had been previously irradiated. In those without prior EBRT, 50.4 Gy in 28 fractions was delivered. Chemotherapy with 5-FU and leucovorin was delivered concomitantly with EBRT after 1998. No systemic chemotherapy was utilized. IOERT doses of 10 Gy were used for R0 resection, 12.5 Gy for R1, 15 Gy for R2 with <2 cc residual and 17.5 Gy with >2 cc residual disease.

Survival at 3-years in patients without prior EBRT was 49% with 3-year LC of 69%. Including both previously irradiated and unirradiated patients, volume of residual was a significant predictor of survival and local control (Table 16.5, $P<0.001$). Stage of initial primary tumor was also a significant predictor of survival with risk of mortality three times higher for stage 2 or stage 3 patients compared to stage 1 ($P=0.012$ and 0.008). Metastasis-free survival was also significantly correlated with volume of residual with 3-year metastasis-free survival rates of 72, 31, and 19% for R0, R1, and R2 resections, respectively ($P<0.001$). The most common postoperative complications were urinary retention in 18%, abscess in 14%, and wound infections in 15%. Three-month mortality was 9%. Late complications included neuropathy in 24% and ureteral stenosis in 6%.

In an additional Eindhoven analysis of 170 patients treated from 1994 through 2008, the subsite of pelvic relapse was of prognostic significance [67]. Patients with presacral relapse were less likely to undergo R0 resection (26%) and had lower 5-year cancer-specific survival (19%) as compared to other pelvic subsites (posterolateral, anterolateral, anterior, or anastomotic). Patients with anastomotic relapse had the best prognosis with 77% R0 resections and 60% 5-year OS.

Asian Series: IOERT

Investigators in Saitama, Japan, treated 39 patients with recurrent colorectal cancer with IOERT regimens [68]. Two patients died of postoperative surgical complications and 11 had unresectable distant metastatic disease leaving 26 patients for analysis. Of these 26 patients, 8 received preoperative EBRT (50 Gy in 2–3 Gy fractions or 18–36 Gy in 2–3 Gy fractions) and 12 received postoperative EBRT (40–60 Gy in 2–2.5 Gy fractions). IOERT doses ranged from 15 to 30 Gy. Postoperative systemic 5-FU-based chemotherapy was given to 11 of 26 (42%) patients.

Five-year OS was 19% in the 26 patients without unresectable metastatic disease. Local relapse was observed in 45% of 17 patients with gross total resection (R0 or R1) at 3 years. Survival was higher in patients who presented without pain (59% vs. 0%, 3-yr OS; $p=0.0003$), patients with

R0 or R1 resection (59 vs. 22% 3-year, $p=0.0121$), patients with less than 2 sites of fixation (54% vs. 17% 3-year, $p=0.0125$) and patients treated with systemic chemotherapy (71% vs. 15% 3-year, $p=0.036$). Survival was also noted to be higher in patients treated with electron energies less than 12 MeV. This finding is attributable to the fact that patients with gross residual disease were treated with higher electron energies.

Summary

In view of the patterns of failure in recurrent colorectal carcinoma patients treated with IORT, additional efforts to increase the intensity of treatment strategies should be explored in order to improve disease control rates. As both local and distant relapse are important events in the clinical evolution of these patients, systemic therapy should routinely be integrated into the current management of locally recurrent colorectal carcinoma. Complete surgical resection is consistently reported as a prognostic factor for survival. However, IORT-containing regimens appear to improve the likelihood of local control for all three groups of patients (R0, R1, R2 resection). IORT alone without EBRT appears to be inadequate for achieving local control. In addition to IORT, EBRT with modern radiotherapeutic techniques (3D conformal or intensity-modulated EBRT) should be combined with concomitant and maintenance systemic therapy in all patients to achieve both radiosensitization and to decrease distant metastases.

Results: IOERT ± EBRT: Previously Irradiated Patients

Non-IORT Salvage Results

There is relatively little information in the literature regarding salvage therapy for patients with locally recurrent colorectal cancer who have previously received high or moderate dose irradiation. Previously irradiated patients who develop local recurrence have a worse prognosis than those with local recurrence following surgical resection who have not received prior irradiation in some series. In the series of Frykholm et al. [69], the 5-year OS rate following local recurrence was 6% in patients treated initially with surgical resection alone vs. 0% for previously irradiated patients. Nearly one-fourth (23%) of previously irradiated patients died with local disease and no known distant metastases. In a randomized Swedish study [70] comparing preoperative radiation to surgical resection alone, 15% of irradiated patients suffered local recurrence and were treated with a variety of combinations of surgery, radiation, and chemotherapy which resulted in a median survival time of 11 months compared to 15 months for locally recurrent patients treated initially on the surgery alone arm ($p=0.0002$). The 5-year OS rate was 5% among previously unirradiated patients, and there were no 5-year survivors in the previously irradiated group.

Salvage IOERT Without EBRT, US/European Series

Because of dose-limiting peripheral nerve toxicity, palliative resection + IOERT without additional EBRT is unlikely to result in acceptable local control in previously irradiated patients. In the updated Pamplona series of 37 patients discussed in a prior section of this chapter [49], 12 previously irradiated patients received IOERT without additional EBRT. The reported local recurrence

rate was 100% with 3- and 5-year OS of 12 and 0%, respectively. Similar results were reported in the French analysis [64] in which 30 patients received IOERT alone due to prior EBRT (100% local relapse, no long-term survivors beyond 42 months).

Ohio State investigators treated 80 patients with recurrent colorectal cancer, 53 of whom had been previously irradiated, with IOERT, HDR-IORT, or Iodine-125 brachytherapy [41]. Only four previously irradiated patients received additional EBRT. Five-year OS was 4% and LC 26%.

Merrick et al. reported the Medical College of Ohio experience with 38 patients who were treated for locally recurrent rectal cancer after prior adjuvant EBRT for the primary lesion [71]. Two patients had disease outside the pelvis at exploration and one had no evidence of local recurrent and did not receive IOERT. Thirty-five patients received IOERT doses of 10–25 Gy. The 3-year OS from the time of IOERT and surgical resection of recurrence was 20%. In the group of 20 patients in whom complete resection of gross disease was achieved, the 2-year OS was 45% and the 3-year OS was 30%; in the 15 patients with incomplete resection, the 2-year OS was only 27%. Ten of the 35 patients (29%) in this group again developed local disease. Most patients reported at least partial pain relief.

Salvage IOERT ± EBRT: Eindhoven Experience

In the Eindhoven experience discussed previously [66], 78 of 147 patients with locally recurrent rectal cancer had received EBRT as adjuvant therapy for treatment of their primary disease. Prior to 1997, no additional EBRT was given to these patients. In 1997, re-irradiation with 30.6 Gy in 17 fractions was initiated and 57 of 78 patients received EBRT in addition to IOERT for treatment of the recurrence. When compared to a group of 24 patients who did not receive EBRT (includes three patients without prior EBRT) survival was significantly improved (48% vs. 25% 3 year, $p = 0.043$). Local control (49 vs. 38% 3 year, $p = 0.038$) and metastases-free survival (59 vs. 18% 3 year, $p < 0.001$) were also improved. R0 resection was more common in patients who were reirradiated preoperatively (65% R0 resection) than in those who did not receive EBRT (29% R0 resection). Postoperative complications (61% vs. 62%) and late neuropathies (21% vs. 17%) were not more common in reirradiated patients as compared to patients treated with IOERT alone.

Salvage IOERT with EBRT: Mayo Analysis

IOERT following maximal surgical resection and moderate dose EBRT has been utilized as attempted salvage therapy at Mayo Clinic in patients with locally recurrent colorectal cancer following previous high or moderate dose irradiation [29, 30]. In the initial series [29] of 51 previously irradiated patients who received IOERT, additional EBRT ± chemotherapy was delivered to 37 of 51 (75%). The median EBRT dose was 25.2 Gy (range 5–50.4 Gy), and care was taken not to exceed small bowel tolerance doses. In the updated series [30], additional EBRT ± chemotherapy was delivered to 228/248 (92%) previously irradiated patients. The median EBRT dose was 27.5 Gy (range, 5–39.6 Gy). Since 1997, additional EBRT has been delivered to 138/140 (99%, preoperatively in 137) with a median dose of 30 Gy.

Survival and disease control data in the updated Mayo IOERT series of previously irradiated patients are presented in Table 16.6. The median survival was 35 months, with 3- and 5-year OS rates of 49% and 26%, respectively. These results are an improvement over the 23-month median survival and 28% 3-year and 12% 5-year OS reported in the initial Mayo publication. Subsequent local

Table 16.6 Locally advanced recurrent colorectal cancer in previously irradiated patients: survival and disease control in Mayo IOERT series by prognostic factor [30]

Prognostic factor	Number of patients	Overall survival (%)				Local relapse		Central relapse		Distant relapse	
		Median (month)	2 year	3 year	5 year	No (%)	Actuarial 3 year (%)	No (%)	Actuarial 3 year (%)	No (%)	Actuarial 3 year (%)
Residual											
Gross	54	21	49	28	12	17 (31)	44	8 (15)	21	24 (44)	68
≤ Microscopic	194	39	72	55	30	62 (32)	38	30 (15)	20	81 (42)	46
(+) margin	103	34	65	46	20	43 (42)	50	21 (20)	27	52 (50)	57
(−) margin	91	51	81	66	43	19 (21)	25	9 (10)	13	29 (32)	33
Primary site											
Colon	30	31	59	41	31	7 (29)	29	6 (20)	31	10 (33)	42
Rectum	218	36	68	50	25	72 (35)	39	32 (15)	19	95 (44)	50
Systemic CT											
Yes	46	49	86	67	32	16 (35)	39	5 (11)	14	20 (43)	48
No	202	34	64	45	25	63 (31)	38	33 (16)	21	85 (42)	49
Prior CT											
Yes	210	35	67	48	24	64 (30)	38	29 (14)	18	88 (42)	49
No	38	38	71	56	35	15 (39)	41	9 (24)	29	17 (45)	51
Treatment era											
Pre-march 1997	108	31	59	39	22	46 (43)	49	24 (22)	25	56 (52)	56
Post-march 1997	140	39	74	59	31	33 (24)	30	14 (10)	16	49 (35)	44
All patients	248	35	67	49	26	79 (32)	39	38 (15)	20	105 (42)	49

EBRT External beam radiation therapy, *IOERT* intraoperative electron irradiation, *CT* chemotherapy

re-recurrence was noted in 79 patients (absolute rate of 32%, 3-year Kaplan–Meier estimate 39%) and DM in 105 patients (absolute rate of 42%, 3-year Kaplan–Meier estimate 49%). Historically, nearly uniform disease relapse and death has been reported in this group of patients.

Prognostic Factors

In the most recent Mayo Clinic analysis [30] of 607 locally recurrent colorectal cancer patients, multivariate analysis identified volume of residual (R0 vs. R1 vs. R2), lack of prior treatment with chemotherapy, and treatment after March, 1997 (second half of the cohort) as statistically significant prognostic factors for survival. Although both central relapse (3-year, 16 vs 9%) and local relapse (3-year, 31 vs 17%) were more common in previously irradiated patients, prior radiation was not a prognostic factor for survival on multivariate analysis. For the 248 previously irradiated patients, residual disease volume, use of systemic chemotherapy, and treatment after March, 1997, were statistically significant prognostic factors for survival on univariate analysis. On multivariate analysis treatment era dropped out leaving only residual volume and systemic chemotherapy as prognostic factors for survival. Volume of residual and treatment after March 1997 were statistically significant prognostic factors for central, local, and distant control.

Distant Relapse

Although aggressive local therapy with EBRT, surgery, and IOERT may control local disease in a significant number of patients who develop local relapse in spite of adjuvant treatment, further improvements in long-term survival are limited by the high rate of distant relapse despite careful clinical staging at the time of local relapse in an attempt to detect occult distant disease. In the Mayo series [30], the actuarial rate of distant relapse was 49% at 3 years. Improvements in survival will require the addition of effective systemic therapy to aggressive local therapy.

Tolerance Issues with Retreatment

Aggressive salvage therapy is often not offered to previously irradiated patients with local recurrence because of the potential for severe treatment-related morbidity. Re-irradiation with EBRT can be accomplished with acceptable toxicity if small bowel tolerance doses are not exceeded. CT simulation with careful attention to small bowel location in relation to relapse is critical. In the Mayo Clinic series, small bowel was excluded or treated to very low doses in previously irradiated patients. Mohiuddin et al. [72] have reported the results of preoperative re-irradiation to a median dose of 36 Gy using lateral fields to exclude small bowel and reduce bladder volumes in a group of 39 previously irradiated patients with recurrent rectal cancer. Subsequent small bowel obstruction was noted in 15% of patients, gastrointestinal fistula in 8% and chronic severe diarrhea in 8%. In the Mayo IOERT series of previously irradiated patients [30], severe complication rates were similar to those seen in previously unirradiated patients [28] who received EBRT + surgery + IOERT.

Future Possibilities

Future studies in previously irradiated colorectal patients with advanced locally recurrent disease should focus on the addition of systemic therapies to aggressive local therapy which includes re-irradiation plus concurrent 5-FU-based chemotherapy, surgical resection, and IOERT. Through the 1990s, systemic therapy options were limited to 5-FU with leucovorin. In recent years, a number

of systemically active agents and regimens have been identified [73]. These include cytotoxic agents capecitabine (oral 5-FU prodrug), oxaliplatin, irinotecan and biologic agents such as bevacizumab, cetuximab and panitumumab. These advances have pushed median survival rates for metastatic colorectal cancer beyond 2 years. Choice of therapy depends on prior treatment and response as well as patient and tumor factors that are continuing to be defined. For example, agents targeting the epidermal growth factor receptor such as cetuximab and panitumumab have been found to be ineffective in patients with KRAS or BRAF mutations.

Although distant relapse has limited the number of long-term survivors, the palliative benefits of aggressive local therapy should not be overlooked. Nearly all patients with locally recurrent rectal cancer experience severe tumor-related morbidity. Nonaggressive local therapy is largely ineffective. Although EBRT may temporarily alleviate symptoms of local recurrence in 80–90% of patients, the median duration of pain relief is only 5–6 months and the average symptom-free interval is only one-third of the patient's remaining lifespan [74–76]. Further improvements in local and central disease control rates are necessary, and the use of tumor radiosensitizing agents and/or normal tissue radioprotectants during EBRT and IOERT should be explored.

Results with IOERT OR HDR-IORT ± EBRT: OHIO State Experience

Patient Group

Martinez-Monge [41] reported the Ohio State University (OSU) IORT experience with 51 patients (32 males, 19 females) ranging in age from 35 to 80 years (mean = 58 years) who were treated between March 1992 and December 1996. All had recurrent colorectal cancer in the pelvis or para-aortic lymph nodes. Thirty-two of 51 cases had prior EBRT, mostly 45–50 Gy at 1.8 Gy per fraction. Forty of 51 patients had been previously treated with chemotherapy.

Surgical and Irradiation Factors

The types of tumor resection at time of relapse included exenteration – 17, debulking surgery – 17, retroperitoneal resection – 7, APR/colectomy – 10. EBRT was delivered postoperatively to only 12 patients.

If the target area was accessible to the IOERT applicator, a dedicated Siemens linear accelerator installed in a shielded operating room was used to deliver IOERT (in 28 patients). An intraoperative applicator of 5–11 cm in diameter (to cover the entire tumor bed plus a 1–2 cm margin) was selected to deliver 6–15 MeV electrons (usually 6 or 9 MeV). Previously irradiated patients received 10–15 Gy prescribed at the 90% isodose level for microscopic residual disease and 17.5–20 Gy for gross residual disease. Patients who had not been previously irradiated and in whom postoperative EBRT (45–50 Gy) was planned received 10 Gy for microscopic residual and 15 Gy for gross residual disease.

HDR-IORT was used in 23 patients at OSU when the tumor bed was inaccessible to the IOERT applicator. The target area in the tumor bed was measured, and an HDR-IORT applicator that adequately encompassed the target area was selected. Various sized, presterilized applicators, made of silicone, foam, or Delrin were available to fit different-sized tumor beds. The rigid Delrin applicators were used for flat surfaces. Silicone applicators, having limited flexibility, were used on gently sloping surfaces. The very flexible foam applicators were used for irregular or curved surfaces. Hollow plastic catheters were inserted in parallel and 1 cm apart in the selected applicator. The applicator was then placed over the tumor bed and secured by gauze packing or suturing

to the underlying tissues. In unusual circumstances, the catheters were individually sutured (at two sites) to the tumor bed. Adjacent normal tissues (e.g., bowel) were displaced with a retractor and/or by packing with gauze. Tissues that could not be retracted (e.g., nerves or kidneys) were shielded by pliable lead sheets if indicated. With dummy sources in the catheters, a radiograph was obtained to verify catheter position. Various pre-planned treatment programs corresponding to each applicator and prescribed dose were available. Equal dwell times were used instead of an optimizing program since it was thought that the higher central dose achieved with equal dwell times was an advantage. Furthermore, errors were less likely using equal dwell times. The appropriate treatment program was then retrieved from the planning computer and transferred to the treatment control panel. The catheters were connected to a mobile high dose rate (HDR) remote after-loading machine that was brought to the shielded operating room from the radiation oncology department. Then, treatments proceeded without delay since new dosimetry was not required. The actual treatment time ranged from 5 to 30 min (median = 15 min) with the patient still under general anesthesia. The total procedure time was 45–120 min. HDR-IORT doses were the same as used for IOERT, prescribed at 0.5 cm depth.

Results

The 5-year LC rate was 40% for IOERT and 21% for HDR-IORT with no statistical difference. Local control in the various groups is given in Table 16.7. Local control was higher in patients with para-aortic relapse than in those with pelvic relapse. The median survival was 19 months following IOERT and 23 months following HDR-IORT, with 71, 12, and 8% OS at 1, 3, and 5 years, respectively, following IOERT and 86, 44, and 13% OS at 1, 3, and 5 years, respectively, following HDR-IORT. OS was higher in patients who received postoperative EBRT after IORT with either modality (5-year 20% vs. 5% IOERT and 50% vs. 0% HDR-IORT). The authors suggested there may have been a selection bias toward giving postoperative EBRT to patients with more limited disease.

Major morbidity occurred in 20 of 51 patients (39%) and grade 4–5 morbidity in 11(22%). The most common complication was enteric fistula in 8 patients, leading to death in 4. The incidence of complications directly related to IORT was relatively low. Painful neuropathy was observed in six patients (12%).

Future Possibilities

The experience of Ohio State University (OSU) is unique in that, while most institutions deliver IORT (to accessible sites) using IOERT, the additional availability of HDR-IORT at OSU allows the

Table 16.7 Local control with IOERT or HDR-IORT – OSU experience [41]

	HDR-IORT		IOERT	
	1-year (%)	3-year (%)	1-year (%)	3-year (%)
Overall	58	21	46	40
Post-op EBRT	50	50	40	20
No post-op EBRT	53	13	49	49
Previously irradiated	53	13	53	53
No prior EBRT	75	50	40	27
Pelvis site	n/a	n/a	33	33
Para-aortic site	n/a	n/a	83	56

delivery of radiation to sites (e.g., pelvic side wall, retropubic areas, etc.) which may be less accessible to IOERT. Ideally, both HDR-IORT and IOERT should be available for optimal management of patients with locally recurrent colorectal cancers.

Results with HDR-IORT

Rotterdam Series

Investigators at the Erasmus MC-Daniel den Hoed Cancer Center in Rotterdam began using HDR-IORT in 1997 in patients with recurrent rectal cancer and resection margins ≤2 mm [77]. Patients were treated with preoperative radiation to a median dose of 50 Gy in 2 Gy fractions (range, 25–60 Gy). No concurrent chemotherapy was delivered. HDR-IORT was delivered using a silicon template with 1.0 cm line spacing. HDR-IORT dose was 10 Gy at 1.0 cm depth.

Fifty-nine patients were treated from 1997 through 2003, 27 of whom received HDR-IORT. Local control at 3-years was 34% in the HDR-IORT group and 17% in the non-HDR-IORT group. There were 38 patients with R0 resection, 17 of whom received HDR-IORT for margins ≤2 mm. Local control at 3 years for R0 patients was 45% for HDR-IORT patients vs. 24% for non-HDR-IORT patients with wider margins. Twenty-one patients underwent R1 or R2 resection and ten received HDR-IORT. Local control at 3-years was 21% for HDR-IORT patients compared to 19% for non-HDR-IORT patients. Five-year OS was 24% for HDR-IORT patients and 11% for non-HDR-IORT patients. None of the differences were statistically significant.

Memorial Sloan Kettering Series

Memorial Sloan Kettering investigators have used HDR-IORT exclusively for delivery of IORT. Alektiar et al. [78] reported a series of 74 patients with recurrent rectal cancer treated from 1992 to 1998 using HDR-IORT as a component of therapy. Thirty-nine patients had been previously irradiated and did not receive additional EBRT. Twenty-nine of 35 patients with no prior irradiation received EBRT using a median dose of 50.4 Gy (range, 36–59.4 Gy). Concurrent chemotherapy with 5-FU and leucovorin was used in 27 of 29 EBRT patients (93%).

HDR-IORT was delivered using the Harrison–Anderson–Mick applicator, an 8 mm thick silicone rubber with 1.0 cm spacing between catheters. HDR-IORT was prescribed at a depth of 5 mm. Patients with no prior EBRT received 12.5 Gy if an R0 resection was accomplished and 15 Gy if margins were involved. Patients with prior EBRT received 15 Gy following R0 resection and 17.5 Gy if margins were involved.

Overall survival at 5-years was 23% and 2- and 5-year LC rates were 55 and 39%, respectively. Both survival and local control were better in patients following R0 resection (5-year OS 36% vs. 11%, $p=0.04$, 5-year local control 43% vs. 26%, $p=0.02$). Twenty-three of 60 (38%) patients without evidence of DM at the time of HDR-IORT subsequently relapsed distantly. There was a trend toward improved survival in patients who received adjuvant systemic therapy (5-year OS 45% vs. 19%, $p=0.11$). The main HDR-IORT related toxicity was neuropathy in 16% of patients.

In an updated series [79] of 100 HDR-IORT patients, median time to distant relapse was 68 months in R0 patients vs. 17 months in R1-2 patients ($p<0.01$). Vascular invasion was also identified as a prognostic factor for DFS (5-year DFS 27% for no vascular invasion vs. 8%, $p<0.01$) and local relapse (median time to local relapse 32 months for vascular invasion vs. 63 months, $p<0.01$).

Future Possibilities

Encouraging trends exist in colorectal IOERT analyses with regard to improvement in local control and possibly survival of patients with locally recurrent colorectal lesions when compared to non-IOERT series, and continued evaluation of IOERT approaches seems warranted. Disease persistence or relapse within the IOERT and EBRT fields is higher, however, when the surgeon is unable to accomplish a gross total resection. In the MGH analysis of locally recurrent rectal cancer, failure within irradiation fields was excessive even with gross total resections if margins were microscopically positive. Therefore, a protracted venous infusion of 5-FU (±other drugs) should consistently be considered during EBRT [37], and dose modifiers could be evaluated in conjunction with IOERT. To maximize the percentage of patients who can technically receive an IORT component of treatment, it would be reasonable for large institutions to have both IOERT and HDR-IORT capability in an OR setting, since certain technical factors can result in inability to treat with either method (inaccessible location for IOERT, residual disease >1 cm thickness for HDR-IORT).

Since the incidence of distant metastasis approaches 50% in patients with locally recurrent colorectal cancer in several series, 4–6 months of systemic chemotherapy should be evaluated as the systemic component of the aggressive treatment approaches discussed in this chapter. Most patients will have been treated with systemic therapy previously and the choice of systemic regiment depends on prior treatment and response, as well as host and tumor factors [73]. Molecular targeted therapies continue to be evaluated as a component of systemic therapy. Choice of targeted agents will need to be individualized given recent findings that subgroups of patients (KRAS or BRAF mutation patients) do not respond to EGFR inhibitors, for example. Given the improvements in survival observed in patients with metastatic colorectal cancer treated with modern systemic therapy [73], the importance of local control is increased as patients may live long enough to experience the severe symptoms associated with uncontrolled local disease in the pelvis. In this regard, even patients who are not ultimately cured may derive significant symptomatic benefit from an aggressive local approach.

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Chapter 17
Retroperitoneal Sarcomas

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Keywords Retroperitoneal sarcomas • NCI randomized series – EBRT vs. IOERT • HDR-IORT for retroperitoneal sarcomas

Introduction

Retroperitoneal sarcomas are rare, accounting for approximately 10–15% of all soft-tissue sarcomas with an estimated 1,500 cases occurring annually in USA [1, 2]. The most common histologic subtypes include liposarcoma, leiomyosarcoma, and malignant fibrohistiocytoma [3]. Approximately 33–50% of retroperitoneal sarcomas are low grade, in contrast to 19–26% of extremity and truncal

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_17,

sarcomas [4, 5], possibly explaining the lower incidence or delayed appearance of metastatic disease in these patients. In view of the expansile and invasive growth of retroperitoneal sarcomas, as well as the potential for asymptomatic tumor growth within the abdomen and retroperitoneum, patients frequently present with advanced tumors with local organ invasion. Approximately 71–94% of patients present with tumors >10 cm in diameter [2, 5]. In contemporary series, complete gross resection rates of retroperitoneal sarcomas range from 64 to 95% [6]. Even in resectable cases, the extent of disease frequently makes complete resection difficult, with microscopic or gross disease left intact in a high percentage of patients. Given these factors, the incidence of local recurrence following resection is high. Collective reviews of surgical series of retroperitoneal sarcomas have shown that local recurrence (as opposed to distant recurrence in extremity sarcomas) is the primary mode of failure, occurring in 41–82% of patients following gross total resection [7, 8]. Additionally, surgery-alone series describing long-term follow-up of patients undergoing gross total resection have demonstrated that relapses frequently occur many years following resection, with 10-year local recurrence rates of 82–91% [1, 9]. Further emphasizing this point, one series reported that in resected patients who are disease free at ≥5 years from initial surgery, 40% will recur by 10 years [10].

The avoidance of local failure is desirable, particularly given that the majority of patients experiencing local failure will again go on to relapse locally again. These further relapses often occur despite efforts of aggressive, "salvage" combined modality treatment with radiation therapy and complete gross resection. Additionally, resectability rates decrease with each subsequent recurrence [11]. Importantly, failure to achieve local disease control results in tumor-related morbidity including sepsis, gastrointestinal bleeding, bowel obstruction, perforation, fistula, biliary obstruction, and obstructive nephropathy, ultimately contributing to disease-related mortality in approximately 90% of patients failing locally [4].

Unlike extremity sarcomas, where it has been convincingly documented that complete resection plus radiation therapy can provide local control in 80–100% of cases and where two prospective, randomized trials have established the benefit of radiation therapy [12–31], data supporting the use of radiation therapy in sarcomas arising in the retroperitoneum are controversial [9, 32–35]. Based on the experience in extremity sarcomas, it is rational to expect external-beam radiation therapy (EBRT) would improve local control rates in resectable disease, provided an adequate radiation dose is delivered. In several small series using EBRT with resection, improved local control rates were seen in patients receiving >50–60 Gy compared to lower doses [33, 36, 37]. Similarly, in a large single-institutional experience of retroperitoneal sarcomas treated to an average dose of 49 Gy, most local recurrences were within the treatment field. Owing to the large size of these tumors, significant volumes of normal tissue (liver, small bowel, stomach, kidney, or spinal cord) may be within the EBRT field, and the treatment (using conventional techniques)is often limited to 45–50 Gy delivered at 1.8 Gy or 2 Gy per fraction. These doses of EBRT alone are generally insufficient to control the disease [5]. However, delivery of adequate doses of EBRT (>60 Gy) to most patients (as is routinely performed in the adjuvant setting of extremity sarcomas) would result in unacceptable toxicity given the proximity of normal organs, namely, abdominal viscera. This fact has made the delivery of therapeutic doses of postoperative EBRT problematic without causing excessive treatment-related toxicity. This is particularly relevant to the delivery of adjuvant radiation therapy, which results in irradiation of bowel that has previously been displaced by the tumor, allowing normal tissues to fall into the resection cavity and adhesion to the tumor bed. In an NCI randomized trial comparing EBRT alone versus lower doses of EBRT with intraoperative radiation therapy (IORT) (discussed below), patients receiving 54–55 Gy with EBRT alone experienced a 50% rate of chronic enteritis and 25% fistula formation rate [38]. Based on this and other reports, the efficacy of postoperative EBRT alone following resection is unclear. Given this inability to deliver satisfactory radiation doses, published series have demonstrated that most patients experiencing local recurrence will recur within the treatment field or as a marginal recurrence following EBRT alone [5, 9]. Clearly, better treatment strategies are needed.

In an effort to improve the local control and survival in patients with retroperitoneal sarcoma, therapy employing intraoperative electron-beam irradiation (IOERT), high-dose-rate intraoperative

irradiation (HDR-IORT) or orthovoltage IORT with preoperative or postoperative EBRT, and surgical resection has been explored. This chapter summarizes relevant data on the role of IOERT, HDR-IORT, and orthovoltage IORT in the management of patients with retroperitoneal sarcoma.

Surgery with and Without External Beam Irradiation (EBRT)

Surgery ± EBRT

Surgical resection remains the primary treatment modality for retroperitoneal sarcomas. Therefore, the majority of reports on retroperitoneal sarcoma are surgical series, with some describing the use of adjuvant EBRT. With advances in surgical techniques, there has been a steady decline in operative mortality and increase in resectability rates, but surgical resection alone is insufficient to control disease in the majority of patients. Cody et al. analyzed a total of 158 cases of retroperitoneal sarcomas treated at Memorial Sloan–Kettering Cancer Center from 1951 to 1977 with resection ± EBRT [32]. The patients were divided into two groups: 78 patients treated from 1951 to 1971 and 80 patients from 1971 to 1977. Over the entire time period, the distribution of tumors according to histology type and size remained relatively constant. However, the ability to achieve a gross total resection was 66% in the 1971–1977 group as compared to 49% over the entire time period. During the two time periods, the overall 5-year survival in the patients with gross total resection increased only minimally from 37% to 45% despite a marked decline in operative mortality from 21% to 2%. The 5-year local recurrence rate was 77% in patients who underwent a complete resection. Histologic grade influenced survival in this series: of the evaluable patients, the 5-year survival for 16 low-grade tumors was 80%, which was superior to 5% for 19 patients with high-grade tumors (values obtained from survival curves in paper). Of interest, the surgeon's intraoperative assessment of the resection margins frequently did not correlate with final margin status. Adjuvant EBRT after gross total resection resulted in an increase in overall survival from 30% to 53%, although this was not statistically significant.

In a follow-up report from Memorial Sloan–Kettering Cancer Center describing 198 patients treated between 1982 and 1990, the inability to achieve complete gross resection was the only factor significantly influencing tumor-related mortality, while the use of radiation therapy was the only factor significant ($p = 0.02$) for a reduction in the risk of local recurrence [10].

A Mayo Clinic surgical experience with retroperitoneal sarcomas was published in 1989 [39]. A total of 116 patients operated on between 1960 and 1982 and followed for a minimum of 5 years after operation were included. Total gross resection was possible in 54% of patients; 68% of those with gross resection experienced relapse with a median time to treatment failure of 1.3 years. Adjacent organ involvement was the strongest predictor of tumor relapse. Five- and ten-year survival for all patients was 40 and 22%, respectively (54 and 35% 5- and 10-year survival after complete resection). Survival was significantly improved if gross resection was possible for low-grade sarcomas, for sarcomas not fixed to adjacent organs, and if no metastases were apparent.

A follow-up Mayo Clinic report analyzing 97 patients undergoing primary resection between 1983 and 1995 showed that the cumulative 5-year probability for locoregional recurrence and distant metastases at 5 years was 44 and 29%, respectively. The actuarial 5- and 10-year survivals for patients who underwent gross total resection were 51% and 36%, respectively. The authors were unable to demonstrate a favorable impact of radiation therapy on local- and distant-disease relapse rates or overall survival (OS) [40].

A series reported by Karakousis et al. described 90 patients treated for retroperitoneal sarcoma with resection ± EBRT from 1977 to 1995 [41]. Resectability was 100% for 57 patients with primary

disease and 88% for 33 patients with recurrent disease. With a median follow-up of 32 months, the local recurrence rate for the entire group was 30% and varied with the extent of resection: 56% with local excision and 16% with wide or radical resection. With a minimum follow-up of 5 years, the overall local failure rates were 50 and 60% at 5 and 10 years, respectively. Local recurrence was lower, but not statistically different, with adjuvant radiotherapy use (33% vs. 22%). Survival was also influenced by the extent of resection: the 5- and 10-year survival rates were 72% and 61% for patients undergoing "wide" resection versus 55 and 23%, respectively, for "local" resection.

The importance of complete resection and resection margin status was also apparent in the University of Florida experience [42]. This study included patients with primary retroperitoneal sarcoma treated between 1970 and 1994. Patients with complete resection and pathologically negative margins (63% of patients with gross total resection) had a median survival of 68 months. In cases with positive, uncertain, or "close" margins, the median survival was 42 months. The median survival was 9 months in patients with gross residual tumor and 5 months in patients who underwent biopsy only. Tumor location within the retroperitoneum did not influence survival. Thirty-seven patients also received EBRT ± chemotherapy with no apparent survival advantage, although details on patient selection and dose factors were not specified. A follow-up report from the University of Florida confirmed the importance of resection-margin status and further detailed the experience with EBRT (see below) [43].

Evidence of improved survival with complete resection is also suggested in the Medical College of Virginia series reported by McGrath et al. in 1984 [44]. Forty-seven patients with primary retroperitoneal sarcoma were reviewed. Complete resection was defined as surgical removal of all gross disease with microscopically negative margins. Thirty-eight percent of patients had a complete resection by this definition. The disease-free survival (DFS) for this group was 50% at 5 years with an OS of 70%. The local relapse risk at 5 years was 55% in spite of negative resection margins. The remaining patients undergoing partial resection or biopsy only had a DFS of only 4% at 5 years.

A collective surgical review from the State University of New York at Buffalo analyzed 130 consecutive patients with retroperitoneal sarcomas. The gross total resection rate was 95% (99% primary tumors, 90% locally recurrent tumors). Local recurrence occurred in 41% of patients undergoing primary resection and 61% undergoing resection for locally recurrent disease. Actuarial 5-year survival was 65% for patients presenting with primary disease and 53% for those undergoing resection for local recurrence. As in other reported series, local recurrences tended to occur late, with a 10-year local recurrence rate in patients with resected primary disease of 66%. Overall, local recurrence rate for patients treated with surgery alone was 53% versus 38% for patients receiving postoperative EBRT ($p = 0.16$) [45].

A recent, large, single-institution experience from the Fondazione IRCCS Istituto Nazionale Tumori described outcomes of 288 primary or first-time locally recurrent sarcoma patients. These investigators reported that the adoption of a more aggressive en bloc resection (i.e., wider resection of adjacent normal tissues, including deep musculature) was associated with improved local control. Specifically, 5-year local recurrence rate was 48% for less aggressive resection (en bloc with adjacent organs only if directly involved) versus 29% for more extensive resection (en bloc resection of surrounding tissues and located within 1–2 cm from the tumor surface). Additionally, the use of radiation therapy with resection was associated with a significantly better local control and survival in patients treated with both less (crude LC 62% RT vs. 47% no RT) and more aggressive (crude LC 81% RT vs. 68% no RT) surgery [46]. An accompanying editorial pointed out that not all adjacent univolved structures were resected in this surgical experience and that not all retroperitoneal sarcomas were readily amenable to such an aggressive approach [47].

Similarly, a report by the French Cancer Federation Sarcoma Group addressing the role of postoperative EBRT showed that a 5-year actuarial local recurrence-free survival was 55% in 60 patients treated with adjuvant EBRT versus 23% in 34 patients who did not receive radiation therapy, which

was highly significant. The authors concluded that postoperative radiation therapy was associated with improved local control compared to surgery alone [37].

Storm et al. summarized the results of eight surgical series of patients treated between 1937 and 1987 [1]. Of 560 patients who underwent exploratory laparotomy, only half (53%) were able to have a complete resection, as defined by removal of all gross disease. Nineteen percent of the patients had a partial resection, whereas 21% of the patients underwent biopsy only. The survival rates at 2, 5, and 10 years of 410 resected patients from the combined series were 56, 34, and 18%, respectively. The survival was clearly influenced by the completeness of resection. The survival rate at 2, 5, and 10 years was 81, 54, and 46%, respectively, for completely resected patients. In contrast, these figures were 34, 17, and 8%, respectively, for patients undergoing subtotal resection. Even if a complete resection could not be achieved, patients undergoing partial resection fared better than patients who had biopsy only. The rate of local recurrence in patients with gross total resection was high at 72% at 5 years and ultimately 91% failed locally at 10 years. This study again emphasizes the high local failure rate in patients undergoing resection alone of retroperitoneal sarcomas. In summary, gross total resection clearly influences long-term outcomes and should be the goal of surgical approaches in this disease. Even in the setting of gross total resection, collective review of contemporary institutional experiences suggests that with surgery alone, at least one half of patients will develop local disease recurrence [4].

Surgery + EBRT

The use of EBRT may potentially benefit patients with retroperitoneal sarcomas. However, as demonstrated by a Surveillance, Epidemiology, and End Results (SEER) database analysis, the use and experience with radiation therapy in this disease is limited. In this evaluation of over 2,000 patients with resected retroperitoneal sarcoma treated between 1973 and 2001, the percentage of patients receiving radiotherapy was 26%, with the vast majority of patients treated adjuvantly (85.5%) and a small number treated neoadjuvantly (4.7%) and/or intraoperatively (5.1%). Whether these numbers apply to contemporary practice is unclear. Nonetheless, the authors concluded that prospective trials evaluating the use and timing of radiotherapy may require a significant change in current practice patterns, should higher level evidence support the benefit of radiation therapy [48]. Despite this, varying reports have described outcomes with EBRT combined with resection. However, exceeding standard EBRT of 45–50 Gy may result in difficulties with fistula formation and enteritis or bowel obstruction. Despite this, other series have suggested that a radiation-dose response exists in retroperitoneal sarcomas, with doses greater than 50–55 Gy resulting in superior local control relative to lesser doses [33, 36].

The results of adjuvant radiotherapy use in the management of patients with retroperitoneal sarcoma treated at the Fox Chase Cancer Center were reviewed by Fein et al. [36]. This series also included three patients who received IOERT. Between 1965 and 1992, 21 patients were treated with a follow-up ranging from 14 to 340 months. Of them, 19 patients were treated postoperatively, and two patients were treated preoperatively. EBRT doses ranged from 36.0 Gy to 61.2 Gy using fraction sizes of 1.5–2.0 Gy per day. The three patients who received IOERT were treated with total EBRT doses of 36–61 Gy, and two patients with IOERT doses of 10 Gy and one patient with 16 Gy. Two other patients received a brachytherapy boost with Ir-192. Two out of the three patients with IOERT achieved local control, as did the two patients with brachytherapy. For the whole group, the 5-year actuarial local control and overall survival was 72 and 44%, respectively. Local control rate was influenced by size, stage, grade, and histology of the tumor. A possible dose response was demonstrated in that patients receiving total doses of ≥55.2 Gy had a lower local failure rate (25%) than

that of patients receiving radiation doses <55.2 Gy (38%). The only reported complication was a small-bowel obstruction in one patient receiving an EBRT dose of 55.2 Gy.

Tepper et al. reviewed 23 patients treated at the Massachusetts General Hospital for retroperitoneal sarcoma between 1971 and 1982 [33, 49]. This series also included six patients who were treated with palliative intent for localized disease. Patients were classified as having a complete resection with histologic negative margins, a partial resection with gross or microscopic residual disease, or no resection. All patients received EBRT with megavoltage radiotherapy except for one palliative case receiving orthovoltage treatment. The stated intent was to deliver at least 50 Gy combined with maximal surgical resection. Doses ranged from 19.28 Gy to 69 Gy. A total of 17 patients were treated with curative intent. Of these, 6 patients received preoperative radiotherapy, 12 patients received postoperative radiotherapy, and 1 patient received pre- and postoperative treatment. Complete resection was achieved in seven cases, incomplete resection was achieved in seven, and no resection was achieved in three. The 5-year local control and survival rate for patients treated with curative intent was 54%. Analysis suggested that higher doses may increase the likelihood of local control. Four of six patients (67%) who received less than 50 Gy had a local failure, whereas none of the five patients receiving between 50 and 60 Gy and only one of six receiving more than 60 Gy developed local failure. There was no demonstrable correlation between tumor grade and recurrence rate. The complication rate was not reported.

An analysis from the University of Michigan evaluating 85 patients receiving EBRT for retroperitoneal and deep truncal sarcomas showed that, in addition to margin status, radiation dose significantly influenced local control (5-year local control rate of 58% in patients receiving ≥55.8 Gy vs. 34% in patients receiving lesser doses). Additionally, the delivery of postoperative radiation therapy was associated with an increased rate of local recurrence on univariate analysis compared to preoperative radiation therapy [50].

Similarly, a report from Wayne State described outcomes in 60 patients with nonmetastatic retroperitoneal and deep-trunk soft-tissue sarcomas treated with combined surgery and radiation therapy. Thirty-eight patients (63%) had retroperitoneal disease. Forty-six patients (76%) had primary disease, and 14 patients (24%) had recurrent disease. Resection margins were negative in 24 patients (40%), “close” in three patients (5%), and positive in 33 patients (55%; 18 microscopic and 15 macroscopic). EBRT alone was delivered in 44 patients (73%) to a median dose of 52.2 Gy and combined with brachytherapy (median EBRT and brachytherapy doses 42 and 16 Gy, respectively) in 16 patients (27%). Five-year DFS, local control (LC), distant-metastases-free rate, and OS rate were 53, 71, 58, and 56%, respectively. As in prior studies, surgical margin status was significant in predicting LC and OS [51].

A report from the University of Florida described 40 patients with retroperitoneal sarcoma treated with surgery with preoperative (15 patients) or postoperative (25 patients) EBRT. Of these, 35 patients had treatment for primary disease, and five patients had treatment for first local recurrence. In the postoperative group, most patients received 50.4 Gy using twice-daily fractionation (1.2 Gy per fraction). Two patients received postoperative interstitial brachytherapy to a dose of 24 Gy. Median overall follow-up was 2.8 years. Margin status was predictive for LC (5-year local control: 78 vs. 0% with negative vs. positive margins) and improved survival (5 year OS: 69 vs. 12%, negative vs. positive margins), regardless of EBRT treatment sequence. The use of postoperative radiation therapy was associated with significantly higher rates of acute reactions (primarily consisting of acute enteritis, 80 vs. 36%) and late complications (infection, hemorrhage, and bowel obstruction) as compared to preoperative radiation therapy. Local recurrence developed in 47% of patients treated with postoperative radiation therapy versus 16% of patients treated with preoperative radiation therapy, with a median time to local recurrence of 1 year in the postoperative group versus 2.5 years in the preoperative group [43].

In a multi-institutional review of two prospective trials encompassing 72 patients with intermediate or high-grade retroperitoneal sarcomas, 89% of patients were able to complete preoperative

radiation therapy as planned. Macroscopic complete resection was achieved in 95% of patients undergoing laparotomy. Patients receiving preoperative radiotherapy demonstrated a 5-year DFS of 46% and OS of 50%; patients completing preoperative radiotherapy and undergoing microscopic complete resection experienced a 5-year local-recurrence-free survival rate of 60%, comparing favorably to historical control data. The authors concluded that despite the large treatment volumes associated with EBRT for retroperitoneal sarcomas, preoperative EBRT is well tolerated and safe. Additionally, the authors concluded that their 5-LC rate of 60% compared favorably to similar patients treated in other series [52].

Investigators from the University of Alabama at Birmingham reported on the use of intensity-modulated radiation therapy (IMRT) for radiation-dose escalation in the preoperative treatment of retroperitoneal sarcomas. These investigators implemented a "simultaneous boost" technique, delivering 45 Gy to the primary tumor volume while concurrently delivering higher doses per fraction (2.3–2.5 Gy) to the margin deemed at risk for local recurrence to a total dose of 57.5–65 Gy. Although these investigators used a higher dose/fraction and overall dose delivered to the retroperitoneal margin, when compared to IORT (where doses of 10–20 Gy are often delivered in a single fraction, resulting in an estimated biologic equivalent dose of 25–60 Gy of conventionally fractionated EBRT), the effective radiobiologic dose remains lower. Nonetheless, they reported good tolerance with this dose-escalation technique. Whether EBRT alone approaches implementing technological advances will result in improvement in local control remains the topic of investigation [53].

In an effort to better define the role of EBRT, an international, randomized trial was initiated by the American College of Surgeons, randomizing patients with retroperitoneal sarcoma to preoperative EBRT to a dose of 45–50.4 Gy followed by surgery versus surgery alone, with a primary end point of comparing progression-free survival and local control. However, this trial was closed in 2006 owing to poor patient accrual. The lack of accrual in this study was likely due to physician/institutional bias and practice patterns. Arguably, without the use of radiation-dose escalation, data using EBRT alone (to doses lower than that used in the randomized NCI trial and other series), when analyzed collectively, have not suggested significant disease-related gains.

Prognostic Factors

Most patients with retroperitoneal sarcomas present with disease >10 cm. Although conflicting results have been reported, some series have described an increasing probability of local-relapse increases with increasing tumor size [46]. As in other sarcoma sites, grade clearly influences the ultimate development of distant metastases and overall survival. One series of 500 patients with retroperitoneal sarcoma demonstrated a median survival of 33 months in patients with high-grade disease versus 149 months in patients with low-grade disease [5]. The impact of grade and histology on local failure remains controversial, with some studies suggesting increased local failure rates with high-grade tumors; other studies have reported that the risk for local recurrence is influenced by liposarcoma histology [5, 7, 10]. Although low-grade tumors, when viewed collectively, have a very favorable prognosis, approximately 10% of patients with low-grade disease at any sarcoma site will die of their disease. This is particularly true for retroperitoneal tumors. Illustrating this, in a collective series from Memorial Sloan–Kettering Cancer Center of over 2,000 patients with low-grade sarcoma, 16% of tumors were in the retroperitoneum. Risk factors for death from this group included retroperitoneal site, larger tumor size, and inability to achieve negative margins (the latter factors characteristic of retroperitoneal tumors). Approximately 60% of deaths were due to uncontrolled local disease, with over half of all deaths occurring in the retroperitoneal group. Patients with low-grade retroperitoneal tumors experienced a mortality hazard ratio of 59 relative to patients with extremity

tumors. More than half of all deaths occurred >5 years following initial diagnosis, again with local recurrence/uncontrolled local disease progression dominating patterns of relapse. Frequent causes of death included bowel obstruction, renal failure, and failure-to-thrive symptoms [54].

Summary

The previously reviewed studies show that surgery remains the single most important treatment modality in the management of patients with retroperitoneal sarcoma (Table 17.1). Complete resection, i.e., removal of all gross disease, preferably with negative microscopic margins (R0 resection), offers the best chance for survival. Unfortunately, approximately one half of all patients undergoing laparotomy are not amenable to a complete resection. In the setting of gross total resection, margins are often involved microscopically (R1 resection), and even with a complete resection, local failure remains a substantial problem, with most of these patients developing local disease relapse.

The addition of EBRT to surgical resection is a common practice and may be beneficial in patients treated adjuvantly. However, using conventional radiation techniques, the delivery of adequate EBRT doses remains problematic. There is no high-level evidence that adjuvant EBRT alone significantly reduces the risk of local recurrence following gross total resection, although some experiences have suggested that there may be a delay in time to recurrence and clinical symptoms [9]. With documented microscopic residual disease or in patients with gross residual disease, a benefit for EBRT is less clear, although again such treatment may delay the onset of clinical symptoms. Some of the above trials and the NCI randomized trial presented later suggest no benefit of EBRT alone in patients with gross total but marginal resection. In terms of radiation timing, the use of

Table 17.1 Surgical series with and without EBRT: treatment method and results

Series/(ref. no.)	*N*	% Gross complete resection	EBRT	IORT (Gy)	Survival and local relapse after resection		
					DFS 5-yr	OS 5-yr	Local failure % (yrs)
Surgery ± EBRT							
Cody [32]	158	49	Some – no details	No	21[b]	40[b]	77 (5)
Karakousis [41]	90	96	Some – no details	No	47	63	50 (5)
Kilkenney [42]	63	87	37 pts – no details	No	–	48	–
McGrath [44]	47	38[a]	60% – no details	No	50[a]	70[a]	55[a] (5)
Storm [1]	560[c]	53	Some – no details	No	–	34	72 (5)
Stoeckle [37]	165	65[e]	56% – 25–90 Gy	No	–	46	–
Ferrario [45]	130	95	32 pts – no details	No	–	60	41 (crude)
Surgery + EBRT							
Fein [36]	21	–	36.0 – 61.2 Gy	3 pts-10,10,16	–	44	28 (5)
Tepper [33]	17	41	19.3 – 69 Gy	No	–	54	54 (5)
Zlotecki [43]	40	85	Most 50.4/ 1.2 Gy bid	No/2 pts brachytherapy	–	–	35 (5)
Feng [50]	85	72	7–73 Gy	No	30	34	42 (5)
Youssef [51][d]	60	75	Median 52.2/42 Gy in brachytherapy pts	No/16 pts with brachytherapy	53	56	29 (5)

[a]Microscopically negative margins
[b]Patients with complete resection
[c]Combined results of 8 series
[d]Retroperitoneal and deep truncal sarcomas
[e]Data not available for all patients

preoperative EBRT appears to be well tolerated and associated with fewer acute and chronic side effects relative to postoperative therapy. Because of the limitations of normal tissue to EBRT and the suggestion that there may be a radiation-dose dependence in terms of local control, optimal treatment is hampered with EBRT-only techniques, and IORT has been employed to dose-escalate specific regions in the retroperitoneum at risk for residual disease.

Treatment Factors

EBRT Factors

A current treatment approach at both Duke University and Mayo Clinic for patients with nonmetastatic retroperitoneal sarcoma is to utilize moderate-dose preoperative EBRT (usually 45–50 Gy in 1.8 Gy fractions over 4.5–5 weeks), surgical resection, and IORT (if technically feasible). The preoperative EBRT approach is favored for many reasons. First, a high-dose preoperative regimen sterilizes a large percentage of tumor cells and may minimize the risk of tumor implantation in the peritoneal cavity and tumor bed where a marginal resection may be performed. Second, partial regression obtained from EBRT may allow a more complete resection to be achieved. Third, these large tumors usually displace abdominal and retroperitoneal viscera to a degree that large volumes of radiosensitive organs such as the stomach and small bowel can be effectively excluded from the preoperative EBRT field, resulting in improved tolerance, which may not be feasible when carried out postoperatively. Exemplifying this, a prospective trial from Princess Margaret Hospital evaluated patients with primary or locally recurrent retroperitoneal sarcoma judged as resectable. Forty-one patients completed preoperative radiation therapy to a median dose of 45 Gy (range 42–50 Gy), and of these, 23 patients received postoperative brachytherapy. Although the toxicity associated with postoperative brachytherapy was substantial, the delivery of preoperative radiation therapy was well tolerated with acute toxicity scores of ≤2 observed in all patients [55]. Other series have similarly confirmed the good tolerance of a preoperative EBRT approach [43, 52, 53, 56]. Similarly, a primary disadvantage in delivering radiation therapy in the postoperative setting is the presence of small bowel adjacent to the resection bed, predisposing patients to radiation enteritis and chronic small-bowel injury. Finally, a preoperative approach also allows (1) patients with unfavorable biology to manifest evidence of metastatic disease, which may aid in selection of patients to surgery, (2) easier delineation of the primary disease during radiation planning, and (3) improved oxygenation (and therefore radiosensitization) of the tumor itself by treating with an intact vasculature. Using a neoadjuvant approach, collective review suggests that tolerance is good and that 78–95% of patients will achieve complete surgical resection.

When planning EBRT, the gross tumor volume with 3–5 cm margins is carried to 40–45 Gy, preferably with 3D conformal irradiation techniques (3D-CRT) and boost fields with 2–3 cm margins are treated to a total dose of 45–50.4 Gy. Dose-limiting organs/structures include the liver, kidneys, spinal cord, stomach, and small intestine. In some instances, oblique or noncoplanar beams are helpful in minimizing the dose to normal structures such as the spinal cord and kidney and the use of such is facilitated by the use of 3D treatment planning. The use of advanced radiation techniques, including intensity-modulated irradiation (IMRT), to selectively increase the EBRT dose to the margin at risk (i.e., treat an extended volume at 1.8 Gy per fraction, treat a reduced volume at 2–2.5 Gy per fraction) has demonstrated good tolerability and encouraging preliminary disease-related outcomes [53]. If irradiation of the tumor or tumor bed requires the inclusion of one kidney to doses beyond tolerance, function of the remaining kidney should be assessed with serum creatinine ± blood urea nitrogen levels and a contrast renal study (CT scan with IV contrast, renal scan).

Surgical Factors

Surgical resection remains the cornerstone for the treatment of retroperitoneal sarcomas. Despite technical and supportive advances, the surgical management of patients with retroperitoneal sarcoma remains a therapeutic challenge. As described previously, published series of surgical resection alone for retroperitoneal sarcoma have shown poor local control and survival rates, even in the setting of margin-negative radical excision. Because of the infiltrative nature of these tumors, large size and their anatomic origin, it is often difficult to obtain microscopically clear and not infrequently macroscopically clear resection margins. As described previously, in contradistinction to extremity sarcomas, contemporary series have suggested that locoregional recurrence is a predominant mode of failure and cause of death, occurring in a high percentage of patients, even following complete resection [2]. Therefore, optimization of local control is an important therapeutic end point.

As described previously, just over half of patients presenting with primary or recurrent retroperitoneal sarcomas are able to undergo gross total resection, and achieving gross total resection in either the primary or the recurrent setting is highly predictive of ultimate local control and survival. Even in situations where a gross total resection of a retroperitoneal sarcoma can be achieved, margins are likely to be very close, if not microscopically involved, with both microscopic and gross residual disease predicting for significantly worse disease-related outcomes [7]. The likelihood of obtaining margin-negative resection following local recurrence is significantly lower compared to patients presenting with de novo disease [5]. Because of local invasion, en bloc resection of surrounding viscera (including adjacent vasculature) is frequently required in efforts to obtain negative margins [57]. As described previously, recent reports have suggested that more aggressive resection may improve long-term disease-free outcomes [46]. Given that margin status influences long-term outcomes, the importance of aggressive surgical resection in retroperitoneal sarcomas should be emphasized. In subtotally resected disease, no survival difference has been observed between patients who are unresectable versus those who undergo subtotal resection leaving macroscopic residual disease [5]. While incomplete resection may alleviate some symptoms related to pressure (i.e., obstruction, pain) or invasion (i.e., hemorrhage, obstruction, and pain) of abdominal organs and structures, as well as provide constitutional improvements related to a massive tumor burden, these benefits are often short-lived. However, it has been suggested that patients with retroperitoneal liposarcomas, incomplete resection may improve survival compared to patients not undergoing resection, with palliation of tumor-associated symptoms achieved in the majority of patients [58]. This approach remains a topic of investigation. Surgical experience and volume of cases may also influence outcomes. A recent analysis of >4,000 patients with sarcoma, including retroperitoneal tumors, showed improved outcomes in patients treated at high-volume centers, suggesting that evaluation and management by an experienced, multidisciplinary team in this disease influences ultimate outcomes [59].

Preoperative Imaging

Preoperative planning is mostly aided by three-dimensional imaging of the abdomen, either with computerized tomography (CT) or magnetic resonance imaging (MRI) scans. The extent of the sarcoma, as well as likely involved normal structures, is generally readily apparent. Bilateral renal function must be documented because nephrectomy is commonly required to achieve total tumor extirpation. Arteriography, or more commonly venography, may be indicated if major vascular reconstruction is contemplated. A chest CT scan is sufficient evaluation for extra-abdominal metastases. Primary retroperitoneal sarcomas, unlike abdominal visceral sarcomas, are less likely to form peritoneal metastases; therefore, laparoscopy is not routinely used in these patients. In recurrent disease, this pattern of failure must be considered, especially if ascites is present on the abdominal scan.

Surgical Techniques

Four to six weeks following completion of EBRT, exploratory laparotomy is performed in the dedicated IORT suite in our institutions. At laparotomy, the abdomen and pelvis are carefully examined for metastases to the liver and/or peritoneal surfaces. If no metastases are found, the patient undergoes resection of the tumor, leaving as little residual sarcoma as possible. Every effort is made to resect the tumor and involved normal structures en bloc without violation or exposure of the tumor surface. Lateral mobilization of the tumor is generally easier because most vascularity arises from the medial aspect of the tumor. While normal tissue planes should be used whenever possible, it is easy to violate the sarcoma pseudocapsule, resulting in tumor enucleation and at least microscopic residual disease.

Figure 17.1a–c demonstrates the removal of a large, left-upper-quadrant sarcoma along with the distal pancreas, spleen, and left kidney (Fig. 17.1a). With the lateral location of most resectable retroperitoneal sarcomas, the kidney and colon are the most commonly resected organs [35, 60].

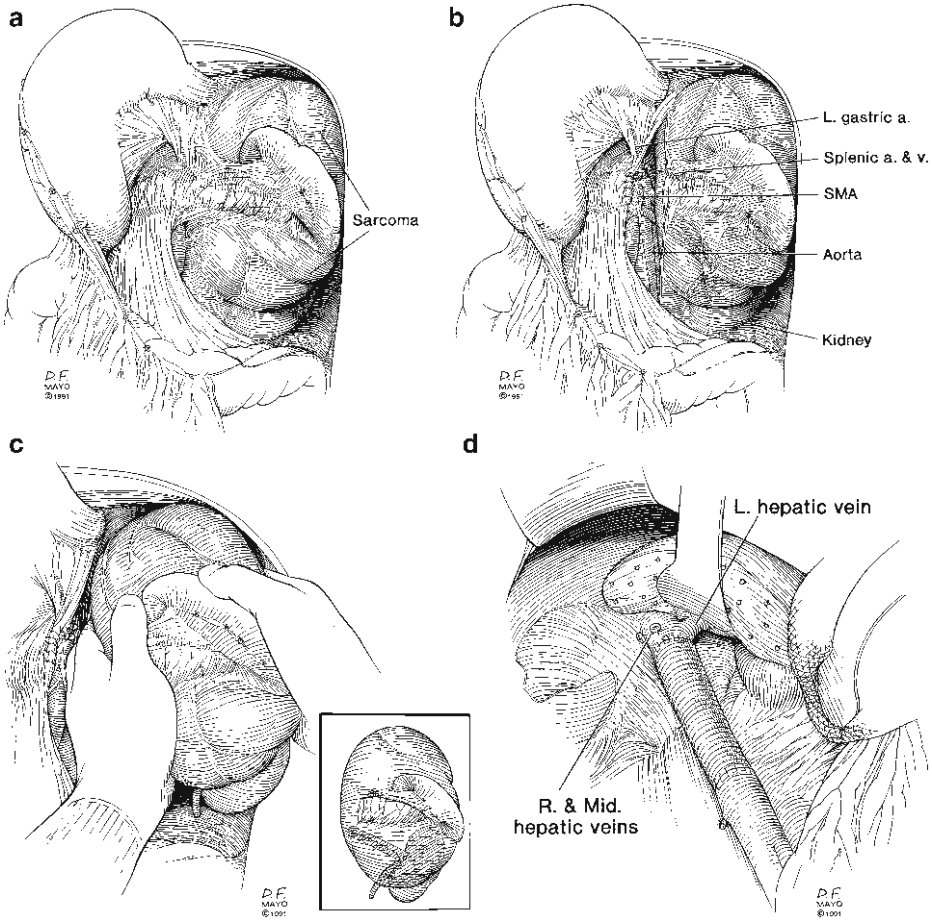

Fig. 17.1 (**a**) (32.6): A large left-upper-quadrant sarcoma is seen posterior to the spleen and distal pancreas. (**b**) (32.7): The medial border of the tumor has been dissected with ligation of the splenic artery and vein and division of the pancreas. The left renal vessels are dissected free in preparation for division, and the aorta has been dissected free with control of tumor vessels. (**c**) (32.9): After posterior and lateral dissection, the tumor and involved structures are removed en bloc. The *insert* shows the specimen that includes the distal pancreas, spleen, and left kidney. (**d**) (32.14): View of the resection field after removal of a large right-upper-quadrant sarcoma that involved the retrohepatic inferior vena cava and right liver. A ribbed tube vascular prosthesis has been used to replace the IVC.

Because the tumor was easily retracted away from the midline vascular structures, the splenic and renal vessels, along with a number of large tumor veins, were ligated early in the procedure, along with division of the pancreatic parenchyma (Fig. 17.1b). Once the tumor's blood supply was controlled, the lesion could be more safely mobilized with sharp and blunt dissection (Fig. 17.1c). Bowel anastomoses are usually completed after IORT has been utilized.

For sarcomas of the iliac fossa and central retroperitoneum, major vascular resections are more often necessary for achieving gross total resection. Vascular reconstruction is generally required, usually with prosthetic graft material. If the anastomosis is not within a high-risk area for local relapse, it can be excluded from the IORT field. The vascular anastomoses and large irradiated vessels should be shielded from adjacent bowel, particularly bowel anastomoses, using the greater omentum, peritoneal flaps, or other normal tissues. Figure 17.1d shows the postresection view of the right abdomen after combined extended right hepatectomy and inferior vena caval resection for a primary leiomyosarcoma.

If no gross tumor remains, frozen-section pathologic analysis is performed, focusing on the portion of the specimen at greatest risk for a positive margin. Biopsy specimens are obtained to examine for the presence of residual sarcoma in the tumor bed. The areas at highest risk for local tumor recurrence are defined by the surgeon and radiation oncologist and outlined with metallic clips or silk sutures for purpose of visualizing tumor bed through the applicator when IORT is used.

Intraoperative Radiation Therapy Factors

Intraoperative Electron-Beam Irradiation

To direct the IOERT, applicators (circular, elliptical, or rectangular) are used (Fig. 17.2). Applicator geometry and size are carefully selected to fully cover high-risk areas. For large sarcomas, abutting fields may be needed to assure that all high-risk areas are included.

The IOERT dose and energy are dependent on the amount of residual disease after maximal resection and the volume treated (i.e., length of peripheral nerve in IOERT field, amount of bowel circumference, etc.). For patients with completely resected tumors and negative margins, an IOERT dose of 10 Gy is usually selected whereas a grossly resected tumor bed with positive microscopic margins will receive 12.5–15 Gy (depending on the volume treated). For gross residual disease, doses will range from 15 Gy to 20 Gy depending on the extent of residual tumor and volume treated. The electron energy is selected according to the desired depth of penetration and ranges typically between 9 and 15 MeV.

High-Dose-Rate Intraoperative Irradiation

High-Dose-Rate Intraoperative Irradiation (HDR-IORT) units are remote afterloading devices that use an Ir-192 source. An advantage of using an HDR-IORT unit is that the device can be transported to the Radiation Oncology department for the treatment of malignancies in the outpatient setting, including gynecologic and prostate cancers.

The entire operative procedure (surgical resection, HDR-IORT) takes place in a specially designed operating room that is appropriately shielded for the delivery of the HDR-IORT using a high-dose-rate remote afterloading machine. The details of the design of this facility, applicator system, treatment planning algorithms, etc. have been previously reported [61, 62] and are discussed in Chap. 4 of this textbook. After maximal resection is accomplished, normal organs are displaced from the tumor bed, exposing the area to be treated, utilizing appropriate retractors. Metallic clips may be placed on the

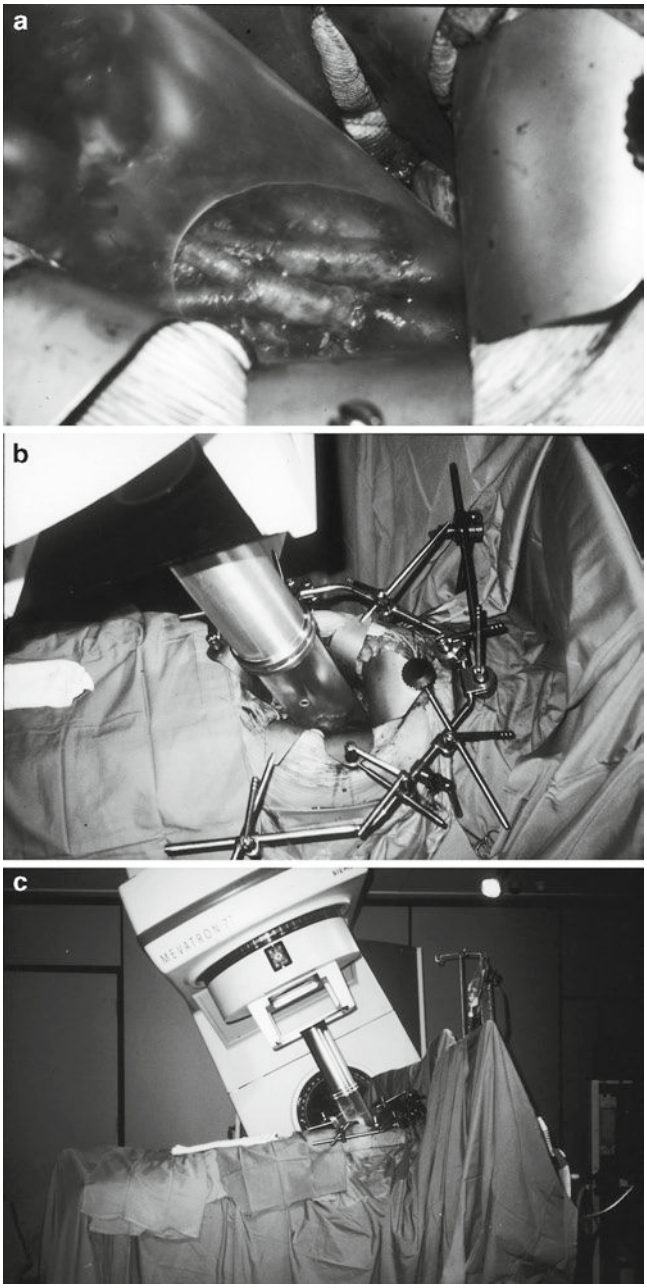

Fig. 17.2 IOERT treatment sequence after resection of retroperitoneal sarcoma. (**a**) Vena cava, aorta, and iliac bifurcation within IOERT applicator. (**b**) Applicator "docked" with linear accelerator. (**c**) Patient ready for treatment.

field to demarcate the target region. The target generally consists of the resected tumor bed plus a 2–3 cm margin. Note that irregular field shapes can be treated simply by varying the treatment length of individual catheters. The extent of margin is sometimes limited by obvious proximity of normal tissue such as spinal cord. With normal tissue maximally retracted, and the target area exposed, an appropriately sized Harrison–Anderson–Mick (HAM) applicator (Fig. 17.3) is placed onto the contour of the target area for the delivery of HDR-IORT [61, 62]. With appropriate packing and suturing

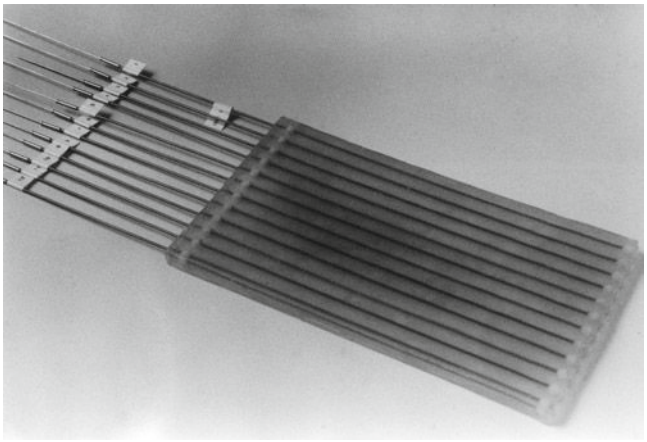

Fig. 17.3 Harrison–Anderson–Mick (HAM) applicator.

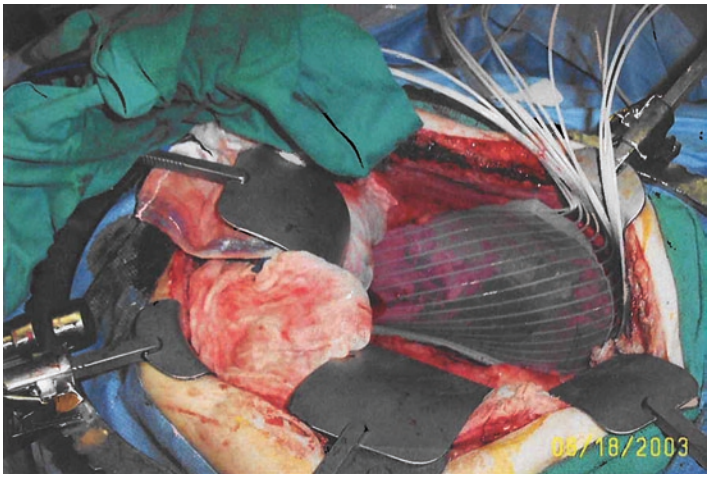

Fig. 17.4 HAM applicator in resection tumor bed following gross total resection of a recurrent left-sided liposarcoma. Note the individual channels emanating from the applicator which guide the I-192 source.

(when needed), the applicator is assured to be in good position. Because the HAM applicator is transparent, it is easy to make certain that the demarcated tumor bed is properly covered. Appropriate lead shielding discs can then be strategically interposed between the treated area and nearby normal tissue to enhance their protection. Figures 17.4 and 17.5 show clinical examples.

The setup procedure for HDR-IORT has also been extensively described [61, 62]. With the applicator in position, connection tubing is used to connect the applicator to the HDR remote afterloading machine. With the system in place, HDR-IORT treatment is ready to proceed. Using a prepared dosimetry atlas [61, 62], the dwell times of the sources are determined. A total dose of 10–20 Gy at tissue depth of 5–10 mm is delivered, depending upon the exact anatomical situation. The HAM applicator has a 5-mm thickness on the treatment surface, so the dose is prescribed to 5–15 mm from the sources. The treatment is delivered after everyone has left the room. The patient and the actual treatment delivery are monitored by remote-control cameras by the anesthesiologist, radiation oncologist, and surgeon. Once the treatment has been completed, the entire apparatus is dismantled, and the applicator is removed. The surgeon then completes the case and closes the incision.

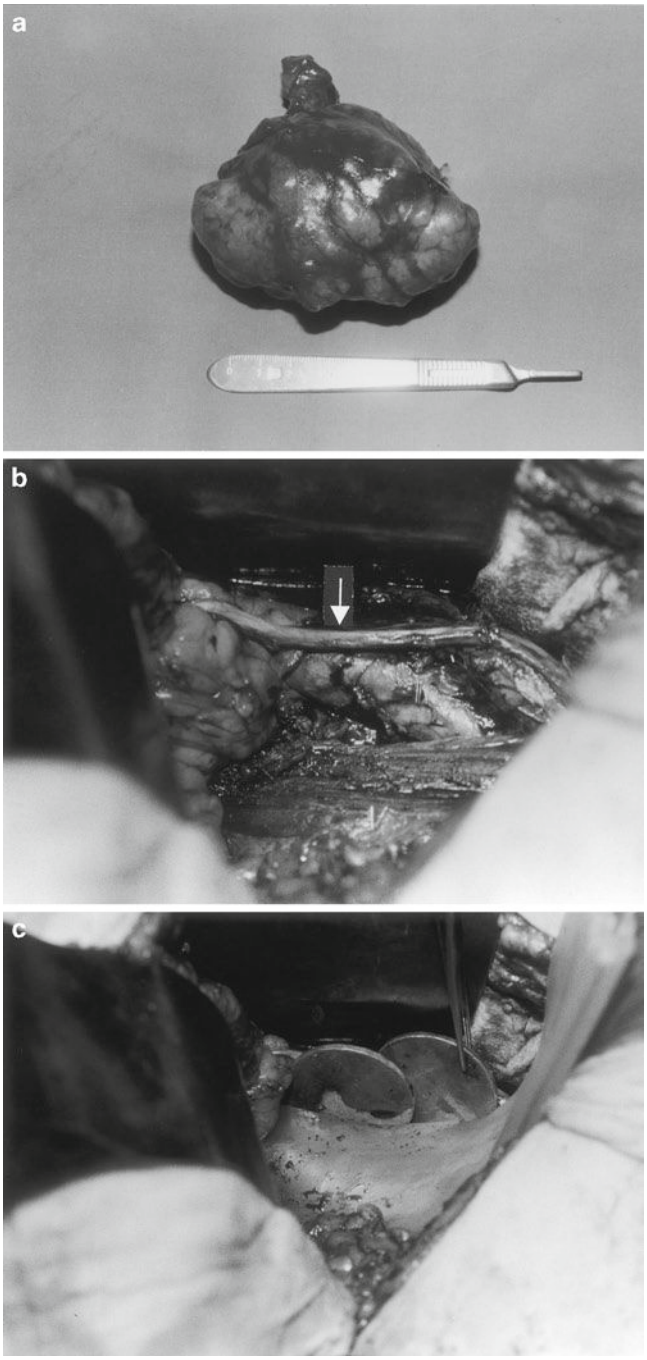

Fig. 17.5 (**a**–**c**) HDR-IORT after resection of retroperitoneal sarcoma. (**a**) Resected retroperitoneal sarcoma. (**b**) Tumor bed in the retroperitoneum (psoas muscle is the tumor bed). The liver and kidney are retracted superiorly (*left of figure*), and the bowel is moved inferiorly (*right of figure*). The ureter is seen medially (*top of figure*, *arrow*). (**c**) HAM applicator in place and lead discs protecting the ureter.

HDR-IORT vs IOERT

A detailed description of the relative advantages/disadvantages of Intraoperative Electron-Beam Irradiation (IOERT) and High-Dose-Rate Intraoperative Irradiation (HDR-IORT) has been discussed in Chap. 6 in this textbook and are beyond the scope of this chapter. In summary, treatment-procedure times are generally shorter with IOERT compared to HDR-IORT. Additionally, IOERT allows variation of electron energies and therefore treatment of both superficial and deeper-seated targets, whereas HDR-IORT is only appropriate for targets ≤0.5 cm in thickness. The flexible HAM applicator used in HDR-IORT may allow more conformal treatment along curved body surfaces (ex large pelvic sidewall fields, lateral abdominal wall, and thoracic cage), which may prove impossible with rigid IOERT applicators (Figs. 17.3–17.5). Separate, matching fields may be required to treat larger target areas with IOERT-based applicators, whereas this is seldom required with HDR-IORT given the large applicator sizes available.

Results with Intraoperative Irradiation

Intraoperative Radiation Therapy (IORT) was first used as early as the 1930s with the intent to either overcome the high skin doses that were commonly seen with the available low-energy X-ray machines or find an economical alternative to the costly radium at that time. Modern IORT began with clinical studies in Japan in the early 1960s. Initially, Co-60 was utilized, but soon IOERT was used with its more favorable depth-dose distribution. Several pilot studies in USA and in Europe and Japan, as well as a small randomized study by the NCI, evaluated IOERT for retroperitoneal sarcoma. Other series have evaluated HDR-IORT or orthovoltage IORT. Table 17.2 summarizes results from varying institutional IORT studies.

NCI Randomized Study: Adjuvant EBRT ± IOERT

Kinsella et al. first reported the preliminary results of a study conducted by the National Cancer Institute of 35 patients with resectable primary retroperitoneal sarcoma who were randomized to two different adjuvant treatments [63]. All patients had a gross total resection, but most had presumed or pathologically positive microscopic residual disease because of marginal resections. Fifteen patients received IOERT to a dose of 20 Gy, usually to abutting fields using high-energy electrons of 11–15 MeV, followed by postoperative EBRT to 35–40 Gy. Twenty patients received standard postoperative EBRT alone of 50–55 Gy (35–40 Gy to an extended field; 15 Gy within a boost field). All patients receiving IOERT also received misonidazole as a radiosensitizer. In the beginning of the study, a second randomization to adjuvant chemotherapy (doxorubicin, cyclophosphamide, and methotrexate) or no chemotherapy was carried out. This randomization was discontinued after the first 13 patients.

Outcomes – Disease Control, Tolerance

In the preliminary analysis by Kinsella et al. with a minimum follow-up of 15 months, there was no significant difference in DFS or OS [63]. There was a nonsignificant trend toward improved in-field LC for the IOERT group (78% vs. 30%).

Table 17.2 Retroperitoneal sarcoma resection ± IORT series: treatment method and results

Series (Author/ institution) (ref no.)	Resection no.	Resection Gross complete no (%)	EBRT (Gy) no., dose	IORT (Gy) no., dose	DFS (%) 5-yr	OS (%) 5-yr	In-field local failure % (yrs)
US series							
Sindelar, NCI**	15	15 (100)	35–40	20	–	38[a]	20[a]
phase III [38, 63]	20	20 (100)	50–55	no	–	44[a]	80
Hoekstra, NCI [66]	5	5 (100)	1 pt	5, 20–30	–	–	–
Willett, MGH [67]	20	14 (70)	40–50	12, 10–20	64 (4 yr)	–	19 (4)
Gunderson, Mayo [68]	20	–	45–52	20, 10–20[b]	–	48.5	15
Kiel, RTOG [71]	12	–	45–50.4	12, 12.5–20	–	–	–
Petersen, Mayo [92]	87	72 (83)	77, 45–52	87, 10–20	–	47	23 (5)[c]
Gieschen, MGH [56]	37	29 (83)	37, 45–50.4	20, 10–20	38	50	41 (5)[f]
Caudle, UNC [75]	14	13 (93)	14, 45–50.4	5, 12.5–15	–	74 (2 yr)	50 (2)
Zagar, Case [74]	31	26 (84)	31, 37–68	16, 10–12	–	70 (2 yr)	23 (2)
Ballo, MD Anderson [73]	83	–	82, 45–66	18, 10–15	39 (10)	–	60 (10)
Alektiar, Memorial [88]	32	30 (94)	25, 45–50.4	32, 12–15[g]	55	45	38 (5)
Pelton, Fox Chase [72]	41[d]	–	–	41, 10–20	–	–	–
Petersen, Mayo [70]	231	206 (89)	–	230, 5–30	–	50	29 (5)
Czito, Duke [93]	24	21 (88)	17	24, 12–18[g]	47	75	35 (5)
European series							
Bussièrs, Bergonié [76]	25	11	–	15–20	32 (2 yr)	60 (2 yr)	24 (2)
Dubois, Montpellier [90]	31[e]	30	28–56	31, –	–	64.5	31 (crude)
Willeke, Heidelberg [78]	25	55	8–40.4	11, 18	–	–	–
Calvo, Pamplona [80, 81]	30	21	39–50	10–20	–	36 (8 yr)	47
Bobin, Lyon Sud [85]	24	22 (92)	22, 45–50	24, 8–22	28	56	–
Gilbeau, Bergonié [77]	45	43 (96)	42, 41–59	17, 13–20	–	65	40[i]
Krempien, Heidelberg [79]	67	55 (82)	45, 20–59,4	67, 12–20	28	64	28
De Paoli, Aviano [82]	30	21 (70)	30, 45–50.4	23, 12–18	–	–	–
Alvarez, Madrid [84]	32	30 (94)	17, 39.6–51.2	32, 10–15	52 (2)	61 (2)	28 (2)
Dziewirski, Warsaw [89]	70	46 (66)	24, 50	46, 20[g]	–	55	51 (5)
Krempien, European pooled analysis [86]	122	–	75	122	28	64[h]	40 (5)[h]

Instit'n institution, *ref no* reference number

[a] From graphs, $p < 0.05$

[b] Dependant on amount of residual disease

[c] Local failure in only 3 of 43 (7%) with primary disease versus 17 of 44 (39%) with recurrent disease

[d] Includes patients with retroperitoneal sarcoma, colorectal and gastric carcinomas, and other disease sites

[e] Only 13 of 31 had retroperitoneal sarcomas

[f] 17% in IORT patients undergoing gross total resection

[g] HDR-IORT

[h] 10-year OS and LC in patients undergoing R0 resection with IOERT and EBRT 80 and 100%, respectively

[i] 15/23 local recurrences were within the EBRT planning target volume

** Randomized study: 35 patients: 15 with IORT, 20 standard treatment with EBRT

In the follow-up report of this study by Sindelar et al., with a minimum follow-up of 5 years and a median follow-up of 8 years, there was a significant difference in local control between the two groups [38]. In the IOERT group, only 3 of 15 patients (20%) experienced an in-field local recurrence versus 16 of 20 patients (80%) in the EBRT control group ($p<0.001$). The median survival was similar for both groups: 45 months for the IOERT group and 52 months for the control group. OS and DFS were correlated to stage of disease but were not significantly different between the two groups. There was no benefit from chemotherapy in this study.

The overall rate of treatment-related complications was similar in both groups but with marked differences in the types of complications. The treatment mortality rate was 9%, based on one death each in the control and study arm (postoperative pulmonary embolism in the IOERT plus EBRT group and hemorrhage from an aortic mycotic aneurysm in the EBRT-alone control group). Arterial occlusions developed in one IOERT patient and two control patients. Ureteral stenosis occurred in two patients of each group.

Both acute and chronic gastrointestinal complications were more common in the EBRT-alone control group. Severe acute enteritis occurred in 12/20 versus 1/15 patients ($p<0.001$), chronic radiation enteritis in 10/20 versus 2/15 ($p<0.05$), and fistulae in 5/20 versus 0/15 ($p=0.06$).

Peripheral sensory and motor neuropathy was more common in the IOERT group. This was observed in nine IOERT-treated patients (60%) and in only one patient (5%) in the EBRT control group. Manifestations of peripheral neuropathy were intermittent pain and motor weakness. The motor weakness resolved in all four affected patients within 6 months. The high incidence of peripheral neuropathy was likely related to both the 20 Gy IOERT dose [38, 64, 65] and use of abutting IOERT fields in most patients.

US Single-Institution and Group IOERT Series

NCI

Hoekstra et al. at the NCI, Bethesda, MD reported the results of five patients with extensive sarcomas in the pelvic girdle that underwent hemipelvectomy and IOERT with doses of 20–30 Gy [66]. The IOERT was directed to the resection margins and surrounding soft tissues using electron energies of 11–16 MeV. One patient also received postoperative EBRT, and one had postoperative chemotherapy. The treatment field sizes for the IOERT were 10×17 cm. Of these five patients, three developed metastatic disease within 3 months and died. Two were disease free at 43 and 53 months. Local control was reported in 4 of 5 patients. The only reported treatment complication was osteoradionecrosis at 7 month posttreatment in one patient.

Massachusetts General Hospital

Willett et al. initially reported on the Massachusetts General Hospital (MGH) experience of IOERT in the management of retroperitoneal sarcoma in a group of 20 patients with either primary ($n=14$) or recurrent ($n=6$) disease [67]. In contrast to other institutions, these patients standardly received preoperative EBRT that was followed by exploratory laparotomy and IOERT. Seventeen of the 20 patients underwent laparotomy, and 14 had a complete resection. Three patients had a partial resection and distant metastasis developed during EBRT in three patients. IOERT was given to 12 of the 14 patients. Irradiation doses used were 40–50 Gy EBRT at 1.7–2.0 Gy per fraction and 10–20 Gy IOERT with 9–15 MeV electrons. The time interval between EBRT and surgery was 4–6 weeks.

The 4-year actuarial LC and DFS of the 14 patients undergoing complete resection was 81 and 64%, respectively. Five patients developed complications: two with hydronephrosis, two with

sensory neuropathy, and one with a small-bowel obstruction. Based on this experience, the general treatment policy is to limit the IOERT dose to 10–15 Gy for microscopic residual disease and 17–20 Gy for macroscopic residual disease.

In a follow-up report from Massachusetts General Hospital, 37 patients (29 primary, 8 recurrent) received 40–50 Gy (median dose 45 Gy) of preoperative EBRT with 10–20 Gy of IOERT (20 patients) using 9–15 MeV electrons or preoperative RT alone (17 patients). Five-year OS, DFS, LC, and freedom from distant-disease rates were 50, 38, 59, and 54%, respectively. Comparison of these two groups demonstrated an improvement in OS (74 vs. 30%, $p=0.04$) with the use of IOERT with a trend toward improved LC (83 vs. 61%, $p=0.19$). Four patients in the IORT group developed significant complications including neuropathy, hydronephrosis, vaginal fistula, small-bowel obstruction as well as late occurrence of a ureteroarterial fistula requiring surgical repair [56].

A recent report from the same institution has described 103 patients with primary retroperitoneal sarcoma. Gross total resection was achieved in 62 patients, leading to improved survival compared to patients undergoing R2 resection or biopsy alone (5-yr OS 62 vs. 29%; 10-yr OS 52 vs. 20%) [8]. In patients with gross total resection, patients with high-grade tumors and/or involved margins were selected to receive EBRT ± IOERT. IOERT was given following tumor resection where a localized area of close margin or residual tumor was able to be identified. This study again demonstrated a trend for IOERT to further improve survival versus EBRT alone and significantly increased time to both local and distant relapse. Specifically, in patients undergoing complete resection, a trend toward improved survival with IOERT was observed compared to EBRT alone (5-yr OS 77 vs. 45%; 10-yr OS 77 vs. 30%, $p=0.13$). Additionally, pelvic tumors, leiomyosarcoma or liposarcoma histology, low-grade histology, decreasing tumor size, negative margins, and resection of less than or equal to one organ were all predictive of improved local- and distant-relapse rates. The authors concluded that gross total resection is important for curative therapy, with a potential beneficial effect of IOERT plus EBRT in high-risk patients following complete resection [8].

Mayo Clinic

In the initial Mayo Clinic experience reported by Gunderson et al., a total of 20 patients received IOERT plus EBRT: ten with primary tumors and ten with recurrent disease [68]. Nineteen of the 20 patients had retroperitoneal tumors. Six patients received planned preoperative irradiation with doses ranging from 45–52 Gy. In all other patients, a partial or gross resection was performed prior to any EBRT or IOERT. IOERT was delivered with 9–18 MeV electrons. IOERT doses were based on the degree of resection: 10–12.5 Gy for microscopic disease, 15 Gy for gross disease less than 2 cm, and 17.5–20 Gy for gross residual disease of 2 cm or greater. IOERT fields included the tumor with a margin of 1 cm, e.g., a 5-cm tumor requires a 7-cm applicator.

The actuarial survival for the initial group of 20 patients was 83% at 2.5 years and 48.5% at 5 years with equivalent survival for those with primary or recurrent disease. The local failure rate was 15%; only one patient recurred in the IOERT field and 3 patients within the EBRT field. Distant metastasis occurred in 25% of all patients but was limited to the group of patients with primary disease.

An updated analysis of the Mayo Clinic experience was reported by Petersen et al. [69]. This consisted of 87 patients with retroperitoneal or pelvic sarcomas who underwent resection plus IOERT at Mayo Clinic between 3/81 and 9/95 and had ≥1 year of follow-up (median 3.5 years). Many tumors were high grade (62%) and recurrent (51%). At the time of operation, all gross disease could be removed in 72 patients (83%). EBRT was delivered in 77 patients (all 43 with primary lesions and 34 of the 44 patients with recurrent disease).

Forty-nine patients had documented disease relapse with 20 of them (23%) experiencing local or central failure (central in 7 of 87 or 8%, local in 16 or 18%) (Table 17.3). Local or central failure occurred in only 3 of 43 patients with primary lesions (7%) versus 17 of 44 (39%) presenting with

Table 17.3 Mayo Clinic IOERT analysis: patterns of local failure in patients with retroperitoneal and intrapelvic sarcomas: primary versus recurrent and low versus high grade

Pattern of relapse	Primary $N=43$	Recurrent $N=44$	Low grade $N=33$	High grade $N=54$	Total $N=87$
CF	0	4	2	2	4
LF	2	11	8	5	13
LF and CF	1	2	1	2	3
Total # (%)[a]	3 (7%)[a]	17 (39%)	11 (33%)	9 (17%)	20 (23%)
Prior EBRT excluded[b]	3/41 (7%)	9/31 (29%)	6 (22%)	6 (13%)	12/72 (17%)

CF central failure in IOERT field, *LF* local failure in EBRT field or surgical bed (prior EBRT group)
[a]Patients with prior EBRT included in numerator and denominator
[b]Patients with prior EBRT excluded from numerator and denominator (primary $N=2$, recurrent $N=13$)
From Peterson et al. [69]

recurrent disease. If patients with prior EBRT are deleted from the analysis, the incidence of local or central relapse was 8 and 29% for the primary and recurrent disease patients, respectively.

Five-year overall survival (OS) was 48% with 46 of 87 patients (53%) alive. Five-year survival was unaffected by primary vs. recurrent status (52% vs. 42%) and low- vs. high-grade lesions (2-year 97% vs. 75%, 5-year 45% vs. 47%). Patients with R0 or R1 resection had improved local control (Fig. 17.6a, $p=0.04$) and a trend for improved OS vs. those with R2 resection (median – 4.7 vs. 3.2 years, 5 year – 49 vs. 36%, $p=0.08$, Fig. 17.6b).

Severe gastrointestinal intolerance was uncommon in primary-disease patients (2 of 43 or 5%), but 7 of 44 recurrent disease patients developed Grade 3–5 GI fistulae (16%) with one fatality. Grade-3 peripheral neuropathy developed in 4 of 43 patients (9%) with primary disease and 5 of 44 (11%) with recurrent lesions.

The influence of multiple prognostic factors on local- and distant-disease control and overall survival was analyzed separately for patients who presented with either primary (Table 17.4) or recurrent disease (Table 17.5). For patients with primary lesions, both initial lesion size ≤5 cm and the surgeon's ability to achieve a gross total resection prior to IOERT appeared to have a favorable impact on 5-year OS. Disease control appeared to be impaired only by the ability to achieve a gross total resection prior to IOERT. For patients who presented with recurrent disease, the amount of residual disease at the time of IOERT had less apparent impact on disease control or survival. Patients with low-grade lesions or recurrent tumor size ≤5 cm had more favorable trends for overall survival and disease control.

A further update of the Mayo Clinic experience evaluating patients treated from 1981 to 2008 was reported at ISIORT 2008 in Madrid [70]. Two-hundred twenty-six patients (52% primary) received IORT. Most (63%) had high-grade tumors. Thirty-six patients (16%) had received prior EBRT to a median dose of 47 Gy (range 20–70 Gy). In previously unirradiated patients, EBRT was delivered preoperatively in 78% of patients, postoperatively in 10%, and both ways in 10%. Neoadjuvant or concurrent chemotherapy with EBRT was delivered in 47 patients with an additional seven patients receiving chemotherapy postoperatively. Margin-negative (R0) resection was achieved in 90 (39%) patients and gross total but margin-positive (R1) resection in 116 (50%) patients. IORT was delivered to a median of 12.5 Gy (range 5–30) using IOERT in 225 patients and HDR-IORT in one. Five- and ten-year OS were 50 and 34%, respectively. Patients undergoing macroscopic complete resection had improved survival relative to subtotally resected patients. For the entire population, 29% experienced local failure at 5 years with distant metastases developing in 42% of cases in follow-up. Central failures within the IORT field occurred in only 10% of patients. The authors concluded that (1) retroperitoneal sarcoma patients undergoing gross total resection experienced improved local control relative to subtotal resection when treated with combined modality treatment including IORT, (2) improved outcomes were seen in patients with primary versus recurrent disease, and (3) the high rates of distant relapse suggest more effective systemic therapy is needed for patients with high-grade disease [70].

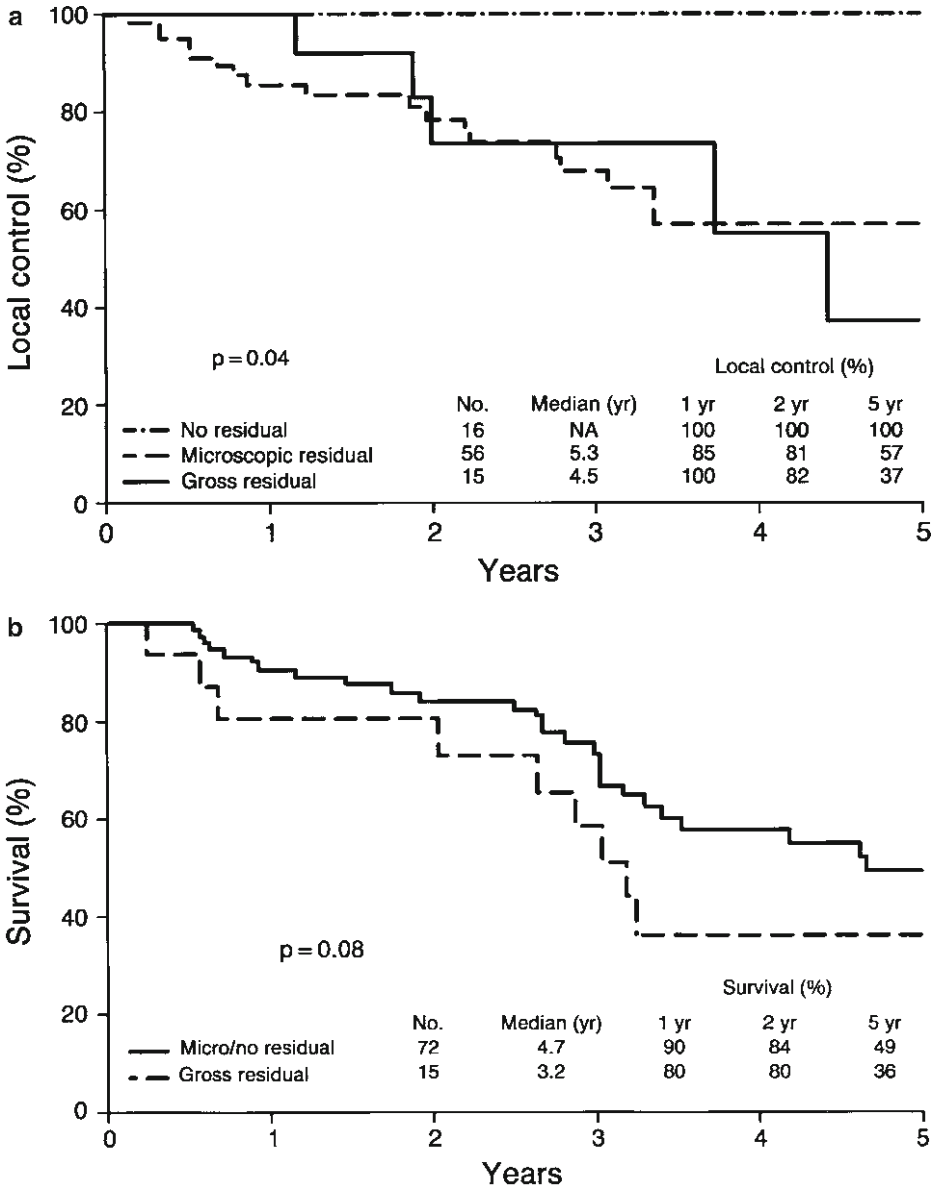

Fig. 17.6 Local control and overall survival by resection status, Mayo Clinic analysis ($n=87$). (**a**) Local control after maximal resection and IOERT with no residual disease (R0 resection) versus microscopic residual disease (R1 resection) or gross residual disease (R2 resection), $p=0.04$. (**b**) Overall survival after maximal resection with gross residual disease ($n=15$; R2 resection) versus ≤microscopic residual disease ($n=72$; R0 or R1 resection), $p=0.08$.

The Radiation Therapy Oncology Group

The Radiation Therapy Oncology Group (RTOG) provided information on their phase-II trial of IORT (RTOG 85-07). Preliminary results were reported by Kiel et al. at the Third International Symposium of Intraoperative Radiotherapy [71]. Twenty-eight patients were entered. Patients with resectable tumors received IOERT at the time of resection followed by postoperative EBRT. Patients with unresectable disease received preoperative EBRT followed by resection and IOERT if possible

Table 17.4 Primary retroperitoneal and pelvic sarcoma: influence of prognostic factors on disease control and survival, Mayo analysis

				Disease control			
		Overall survival (%)		Local (%)		Distant (%)	
Prognostic factor	No.	2 yr	5 yr	2 yr	5 yr	2 yr	5 yr
Residual at IOERT							
≤ Microscopic							
Margin (–) (R0)	11	91	62	100	100	71	53
Margin (+) (R1)	25	75	54	100	92	65	41
Gross (R2 resection)	7	71	29	80	60	43	29
Grade							
Low (1, 2)	9	89	42	100	100	88	25
High (3, 4)	34	75	54	96	84	55	43
Tumor size							
≤5	7	100	86	100	83	71	43
>5	35	76	45	96	92	62	46

Mo months, *Yr* year, *No* number, *Pts* patients, *preop* preoperative, *postop* postoperative, *EBRT* external-beam irradiation
From Petersen et al. [69]

Table 17.5 Recurrent retroperitoneal and pelvic sarcoma: influence of prognostic factors on disease control and survival, Mayo analysis

				Disease control			
		Overall survival (%)		Local (%)		Distant (%)	
Prognostic factor	No.	2 yr	5 yr	2 yr	5 yr	2 yr	5 yr
Residual at IOERT							
≤ Microscopic							
Margin (–) (R0)	5	80	80	100	100	60	60
Margin (+) (R1)	31	90	44	68	36	65	37
Gross (R2 resection)	8	86	45	100	67	50	33
Grade							
Low (1,2)	24	100	53	83	28	77	47
High (3,4)	20	75	35	70	58	42	27
Tumor size							
≤ 5 cm	10	90	58	80	50	60	50
> 5 cm	34	88	40	76	34	61	33

Yr year, *No* number
From Petersen et al. [69]

or IOERT alone. Sixteen patients received no IOERT and were excluded, mainly because of non-sarcoma or benign histology. Twelve patients were treated with IOERT using single doses of 12.5–20 Gy and EBRT with a range of 45–50.4 Gy.

With a median follow-up of 18 months, six patients were still alive, one with tumor relapse. Local control was achieved in 10 of 12 patients. This study has not been updated since the original report in 1991 (a personal communication with Dr. Kiel).

Fox Chase

Similar to other series, the importance of resection margins on local control was demonstrated in an IOERT series from Fox Chase Cancer Center, reported by Pelton et al. [72]. The outcome of 41 consecutive patients who underwent IOERT including patients with retroperitoneal sarcomas, colorectal

carcinoma, gastric carcinoma, and other disease sites were reviewed with attention to margin status. Many patients (73%) had failed previous multimodality treatment, and 44% had previous EBRT. The median IOERT dose given was 13.75 Gy, ranging from 10 to 20 Gy. Patients with prior EBRT had received a median dose of 49.65 Gy. Microscopic margin status was assessed in each case.

The 2-year OS for the entire group was 72%. In patients with negative vs. positive resection margins, 2-year OS was 100 vs. 59%, and LC was 79 vs. 48%. The only predictive prognostic factor was margin status.

MD Anderson

Investigators from MD Anderson Cancer Center reported the outcomes of 83 patients with localized retroperitoneal soft-tissue sarcomas (60 primary, 23 locally recurrent) treated with complete surgical resection and radiation therapy [73]. Radiation was delivered using EBRT alone in 63 patients (76%) or EBRT with IOERT in 18 (22%). One patient received a perioperative brachytherapy boost with EBRT, and one patient received brachytherapy alone. Fifty patients received preoperative EBRT to a median dose of 50 Gy (range 45–56 Gy) and 33 patients postoperative EBRT (median dose 55 Gy, range 45–65 Gy). Median IOERT dose was 15 Gy (range 10–15 Gy). Seventeen patients received concurrent chemotherapy with EBRT (continuous infusion Adriamycin or high-dose ifosfamide).

At a median follow-up of 47 months, actuarial disease-specific survival, distant-metastasis-free survival, and local control rates were 44, 67, and 40% respectively. Multivariate analysis indicated that histologic grade was associated with lower rates of disease-specific survival and that patients presenting with recurrent disease, involved margins and age greater than 65 experienced a significant increase in local failure rates. Ten-year actuarial LC was 40%. Of local failures, most were within the radiation field, two marginal and two outside. EBRT dose (≤50 Gy vs. >50 Gy) did not influence disease-related outcomes. There was no difference in LC with the use of IORT or concurrent chemotherapy, nor was there any difference based on the timing of EBRT. However, 5-year complication rates related to EBRT were 23% versus 0% in the postoperative versus preoperative groups. Median EBRT dose in patients developing radiation-related complications was 60 Gy. Despite these results, based on the collective body of literature evaluating the role of radiation therapy, the authors recommended preoperative radiation therapy followed by surgical resection, and if margins were close or positive, the use of IORT was recommended. [73]

Case Western Medical Center

A report from Case Medical Center described 31 patients with either primary or recurrent retroperitoneal sarcoma treated with resection and EBRT ± IOERT. Nineteen received preoperative EBRT and 12 postoperative EBRT to a median dose of 59.4 Gy (range 36.8–68.4 Gy). IORT using 6–12 MeV electrons was delivered to a median dose of 11 Gy in 16 patients. Eighty-four percent of patients were able to undergo gross total resection.

With a median follow-up of 19 months in all patients, 2-year locoregional control was 77% with no difference observed in pre- vs. postoperative EBRT patients, with similar rates of acute and late toxicities. Two-year distant-disease-free survival was 70% as was 2-year OS [74].

University of North Carolina

A study from the University of North Carolina evaluated a total of 14 patients treated with preoperative EBRT for either primary or recurrent retroperitoneal sarcoma to a planned dose of 45–50.4 Gy.

Thirteen of 14 patients underwent gross total resection, and seven had microscopically negative margins; five received IORT (12.5–15 Gy). Six patients experienced mild symptoms including nausea, diarrhea, and dehydration, requiring early cessation of EBRT in one patient. In patients undergoing gross total resection, 2-year LC was 50% and 2-year OS was 74% [75].

European Intraoperative Electron-Beam Irradiation Series

Institut Bergonié, France

A study by Bussièrs et al. at the Institut Bergonié, France reviewed a total 51 patients with either primary ($n=38$) or recurrent retroperitoneal sarcoma ($n=13$) referred to their institution [76]. Of these, 16 patients had already undergone resection without gross residual disease by CT prior to referral and were therefore not included in this study. Five patients were judged unresectable. Of the 26 patients who underwent resection after referral, 19 received IOERT. Reasons for withholding IOERT were: peritoneal seeding in 2 patients, negative frozen section in 1 patient, or technically not possible due to either bleeding, tumor size, or normal tissue tolerance in 3 patients. Of the patients who received IOERT, 14 had primary disease and 5 had recurrence. Median tumor size was 13 cm. Eleven of the 14 patients with primary disease had gross complete resections, which required en bloc resection of adjacent organs in seven cases. IOERT was delivered to the tumor bed or residual tumor with a median dose of 17 Gy, ranging from 15 to 20 Gy. EBRT was delivered postoperatively in 12 patients and preoperatively in one patient. The median dose was 50 Gy, ranging from 40 to 60 Gy at 1.8 to 2.0 Gy per fraction. EBRT was not added in three cases, because of no residual tumor in 1 patient, a second primary discovered at time of surgery in 1 patient, and postoperative complication in 1 patient.

The 2-year OS and DFS were 60 and 32%, respectively. In contrast to the Mayo Clinic experience, the five patients with recurrent disease did less well. Three patients died of their disease, and two patients were alive with disease. Twelve of the 14 patients with primary disease were alive and disease free. The local control rate at 2 years was 76%. Similar to other series, the actual failure rate within the field of IOERT was low with only one patient recurring. Distant metastasis occurred in three patients; all were in the group treated for recurrent disease. However, distant relapse was only recorded as the first site of failure, which underestimates the propensity for distant metastasis.

Postoperative complications were reported in four patients (21%), consisting of 1 CVA, 1 complex pelvic fistula, 1 anuria due to hematoma in single kidney patient, and 1 external pancreatic fistula. Late complications occurred in six patients (32%) resulting in one death (5%). The fatal complication was due to bleeding secondary to external iliac artery rupture. This patient had received 60 Gy of preoperative radiotherapy for a liposarcoma that had local extension to the iliofemoral area. IOERT consisted of 15 Gy dose with a field measuring 15×20 cm. This clearly demonstrates the risk of treating large volumes to high doses and in single fractions. Other complications were dehydration, lymphedema in the lower limb, temporary lumbar plexopathy, and two cases of chronic enteritis.

An updated report from the Institut Bergonié described outcomes of a total of 45 patients treated with combined radiation therapy and resection for retroperitoneal sarcoma. Seventeen (38%) underwent R0 resection, 26 patients (58%) underwent R1 resection, and two patients (4%) underwent subtotal gross resection (R2). Adjuvant EBRT was delivered to a hemiabdominal field to a median dose of 49 Gy (range 40.8–59.4) in 42 patients. Seventeen patients underwent IORT (median dose 15 Gy, range 13–20 Gy), and of these, three patients received IORT alone. Overall 5-year survival was 65%, 5-year locoregional relapse rate was 40%, and 5-year distant-relapse-free rate was 78%. On univariate analysis, margin status was the only predictor of overall survival and local control.

No survival or local control difference was seen in patients receiving IORT in addition to adjuvant EBRT. Two patients experienced significant late morbidity, with a peripheral neuropathy observed in 20% of patients receiving IORT. Despite the apparent lack of IORT benefit, the authors indicated a potential negative selection bias in patients undergoing IORT, as these patients were suspected to have involved margins at the time of resection, which was confirmed in 14 of 17 patients [77].

Heidelberg

Willeke et al. published the initial Heidelberg experience with IOERT in 25 patients with retroperitoneal sarcoma [78]. R0 resection was achieved in 55% of patients, R1 resection in 29% of patients, and R2 resection in 16% of patients. Only 11 patients received IOERT with a mean dose of 18 Gy. Eight of the 11 patients also received EBRT with a mean dose of 40.4 Gy.

Results were compared to a group of 14 patients treated in 3 years prior to IOERT use, who received EBRT alone after resection. In both groups, the predominant failure was locoregional, and there was no significant difference between the groups. These investigators concluded that there was no significant difference in the effectiveness of IOERT compared to conventional radiotherapy, although a decrease in toxicity was seen with the use of IOERT.

An updated Heidelberg experience reported by Krempien et al. described a total of 67 patients with retroperitoneal soft-tissue sarcoma (26 primary, 41 recurrent) treated with curative intent [79]. All patients underwent maximal resection in combination with IOERT to a median dose of 15 Gy. Additionally, 45 patients underwent adjuvant EBRT, while 20 had been previously irradiated. Five-year OS, DFS, LC, and freedom from metastatic disease rates were 64, 28, 40, and 50%, respectively. Emphasizing the importance of extent of resection, only one of 21 patients undergoing R0 resection and 8 of 34 undergoing R1 resection experienced relapse within the IOERT field versus 9 of 12 patients undergoing R2 resection. The only factor significantly impacting survival was margin status (87% 5-year survival R0 vs. 50% R1/R2). Five-year local control inside the IOERT field was 72%. In patients who completed both IOERT and EBRT following R0 resection, the 10-year overall survival and local control rates were 80 and 100%, respectively. These investigators concluded that IOERT resulted in excellent local control and survival in selected patients with acceptable morbidity and that following complete macroscopic resection, IOERT with EBRT appeared to compensate for minimal residual disease, whereas following incomplete resection, IORT did not improve locoregional control.

Pamplona

Calvo et al. reported the results of the Pamplona sarcoma series at the 1994 International IORT meeting in Lyon [80]. A total of 64 patients had received IOERT: 34 with extremity lesions (primary – 23, recurrent – 11) and 30 with central lesions. The results of IOERT for the 30 patients with soft-tissue sarcomas of central anatomical sites were presented separately [81]. These included tumor locations in the retroperitoneum in eight cases, pelvis in 5 cases, trunk in 10 cases, gluteus in 4 cases, head and neck in 2 cases, and scalp in 1 case. Of the entire group, 13 had recurrent lesions and 17 had primary tumors. Of the 13 retroperitoneal or pelvic tumors, six were recurrent tumors and seven were primary tumors.

All patients underwent maximum resection and received IOERT of 10–20 Gy with energies ranging from 6 to 20 MeV. EBRT was given to 23 patients (40–50 Gy at 1.8–2 Gy/fraction) excluding the seven patients who had received previous EBRT for the primary lesion. Patients with high-grade tumors also received chemotherapy consisting of ifosfamide, dacarbazine, and Adriamycin. Chemotherapy was given preoperatively to five patients and as maintenance treatment to 12. A gross

Table 17.6 Central sarcoma IOERT, Pamplona: disease relapse versus prognostic factors

		Local relapse		Distant metastasis	
Prognostic factor	No. Pts.	No.	(%)	No.	(%)
Disease status					
Primary	17	3	(18)	6	(35)
Recurrent	13[a]	11[a]	(85)	7	(54)
Size (max. diam)					
< 10 cm	18	5	(28)	7	(39)
≥ 10 cm	12	9	(75)	6	(50)
Residual disease					
≤ Micro	21	7	(33)	8	(38)
Macro (gross)	9	7	(78)	5	(56)

[a]Seven had EBRT for primary lesion to site of subsequent recurrence; no further EBRT feasible
Calvo et al. [80, 81]

total marginal resection was accomplished in 21 patients, and gross residual disease remained in the other nine patients.

Disease relapse as a function of various prognostic factors is seen in Table 17.6. Both local recurrence and distant metastases occurred with higher frequency in the 13 patients who presented with local relapse (7 of 13 had received prior EBRT and were treated only with maximal resection and IOERT at time of local relapse). Other factors predicting for an increased risk of local relapse were lesion diameter of >10 cm vs. ≤10 cm and gross (macroscopic) versus microscopic residual after maximal resection. Local control overall was 53% with better local control in patients with microscopic residual disease (67%) versus gross residual (22%). Local control also depended on tumor size: 72% for tumors ≤10 cm and 28% for tumors >10 cm. For the eight patients with retroperitoneal tumors, the median follow-up was 25 months. Of them, local recurrence was diagnosed in five patients, distant metastasis plus local recurrence in two patients, and no evidence of disease (NED) in three patients at 35, 38, and 63 months.

With a median follow-up of 25 months, the OS for the entire group was 36%. Five-year OS appeared better in the patients who presented with primary versus recurrent lesions at 53 versus 20%. The difference in survival between the Pamplona and Mayo series in patients with recurrent disease may be related to the fact that a higher percentage of patients in the Pamplona series had received prior EBRT.

Severe toxicity was experienced in 7 of 30 patients. Of the eight retroperitoneal patients, three had severe complications including acute enteritis, chronic enteritis, and neuropathy.

National Cancer Institute, Aviano

Italian investigators described 30 patients (15 primary, 15 recurrent) who were treated with preoperative radiation therapy using conformal 3D techniques to 45–50.4 Gy. Preoperative therapy was well tolerated with no grade 3–4 toxicity reported. Twenty-seven (90%) patients underwent resection (gross total in 70% of patients), and IORT was delivered in 23 patients to a median dose of 15 Gy (12–18 Gy). At a median follow-up of 27 months, local control rate of patients undergoing preoperative EBRT, complete resection, and IORT was 89% compared to 67% of patients who underwent partial resection and IORT. The overall distant-metastasis rate

was 20%. Given these results, the authors initiated a phase-II study consisting of concurrent preoperative EBRT and high-dose continuous infusion ifosfamide, followed by IORT or postoperative EBRT boost [82].

An updated report from the Aviano group described 52 patients with potentially resectable (25 primary) retroperitoneal sarcoma treated with preoperative EBRT (45–50.4 Gy). Fifteen patients received concurrent continuous infusion ifosfamide. In the patients receiving chemotherapy, 30% experienced grade-3 toxicity. Surgical exploration was performed in 49 patients (94%), with complete resection achieved in 33 (68%) of these. IORT was delivered in 39 of 40 resected patients. At a median follow-up of 52 months, 29 of 39 IORT patients (74%) were alive and disease-free. In patients undergoing complete resection and IORT, local control was achieved in 25 patients (76%). Two patients experienced bowel perforation following preoperative EBRT, and four patients (10%) developed neuropathy requiring medication. The authors concluded that preoperative EBRT, with or without concurrent ifosfamide, is feasible with acceptable toxicity and that IORT yielded excellent results in terms of tumor control and survival [83].

Gregorio Maranon Hospital, Madrid

A report from the University Hospital Gregorio Maranon in Madrid described a total of 32 patients with retroperitoneal sarcoma treated with maximal resection and IORT to a median dose of 12.5 Gy (10–15 Gy) using 4–18 MeV electrons. Two thirds of patients were treated for recurrent disease. Two patients (6%) had macroscopic residual disease and 13 patients had (41%) microscopic residual disease. Fifty-three percent of patients received EBRT to a median dose of 45 Gy (39.6–51.2). Two-year OS, LC, and DFS rates were 61, 72, and 52%, respectively. One patient died due to postoperative complications, and eight patients (25%) developed late toxicity including fibrosis, abscess, enteritis, hydronephrosis, and hernia development [84].

Lyon Sud Hospital

French investigators from the Lyon Sud Hospital reported on the results of a total of 24 patients with primary ($n=5$) or recurrent retroperitoneal sarcomas ($n=19$) [85]. Preoperative EBRT was delivered in 7 patients and postoperative EBRT was delivered in 15 patients. Median IORT dose was 15 Gy (8–22 Gy) using 6–20 MeV electrons (median 9 MeV). Six patients underwent R0 resection, 16 patients underwent R1, and 2 patients underwent R2. Five-year OS and DFS were 56 and 28%, respectively. Thirteen of 24 patients experienced local recurrence and three of 24 patients experienced distant-disease relapse. In 22 patients who received IOERT with EBRT, 11 developed local recurrence resulting in a 50% crude local control rate. Six of 24 patients developed neurotoxicity following IOERT, particularly with doses >15 Gy. However, severe chronic complications were only seen in 2 of 24 (8%) cases. The authors concluded that the combined EBRT with IORT is a promising technique for improving local control, particularly in association with margin-negative resection.

European Pooled Analysis

A pooled analysis on behalf of the European Working Party of the International Society of Intraoperative Radiation Therapy (ISIORT) from investigators at Heidelberg, Aviano, and Madrid described a total of 122 curatively approached patients treated with primary (41 patients) or recurrent (81 patients) retroperitoneal sarcomas undergoing maximal resection in combination with

Table 17.7 IORT for primary/recurrent retroperitoneal soft sarcoma: outcomes by prognostic factor in European Pooled Analysis

	2-yr	5-yr	*p*-value
Disease outcomes, total group			
Overall survival	81%	64%	
Disease-free survival	NA	28	
Local control	60	40	
Freedom from distant metastases	NA	50	
Central control in IOERT field	78	72	
Outcomes by type of resection			
Overall survival			
R0 resection	92%	83%	<0.05
R1/R2 resection	75	43	
Local regional control			
R0 resection	86%	76%	
R1/R2 resection	50	8	
Central relapse (in IORT field)			
R0 resection	5%	11%	<0.05
R1 resection	17	24	
R2 resection	52	65	

IOERT to a mean dose of 15 Gy [86]. Seventy-five patients received additional postoperative EBRT (40 patients were previously irradiated). Five-year OS, DFS, LC, and freedom from metastatic disease rates were 64, 28, 40, and 50%, respectively. The 5-year LC within the IOERT field was 72%. In patients who completed IOERT and EBRT following R0 resection, 5- and 10-yr OS and LC were 80 and 100%, respectively. Only 5% of patients experienced an in IOERT-field relapse after R0 resection, 23% after R1 resection, and 75% after R2 resection. Late complications ≥ grade 2 were seen in 21% of patients, although only 5% required surgical intervention for such. The authors concluded that in selected patients, IOERT results in excellent local control and survival with acceptable morbidity. Table 17.7 evaluates the impact of various prognostic factors with regard to survival and relapse outcomes.

Novel Approaches

As described previously, the Italian Sarcoma Group is conducting a phase-II study evaluating preoperative EBRT with high-dose continuous infusion ifosfamide, using IOERT or postoperative EBRT for radiation dose escalation following maximal resection. This trial has accrued approximately 50 patients and is scheduled to be completed in December 2010 (A. De Paoli, personal communication). Similarly, a phase-I trial combining EBRT with concurrent continuous infusion doxorubicin followed by resection and IOERT was reported by MD Anderson Cancer Center investigators [87]. Thirty-five patients with resectable primary or recurrent intermediate or high-grade retroperitoneal sarcoma were enrolled. Doxorubicin was administered weekly for 4–5 weeks as a 4 mg/m^2 bolus followed by a 4-day continuous infusion (4 mg m^2/day). EBRT dose escalation was performed to an ultimate dose of 50.4 Gy. Twenty-nine patients (83%) underwent laparotomy, and gross total resection was achieved in 90% of these patients. Among 6 patients undergoing radiation therapy at the 50.4 Gy dose level, two experienced greater than or equal to 90% tumor necrosis, three experienced 10–40% tumor necrosis, and one experienced less than 10% tumor necrosis. Twenty-two (76%) of the 29 patients underwent IORT.

High-Dose-Rate Intraoperative Irradiation Series

Memorial Sloan–Kettering

Between 1992 and 1996, a total of 32 patients with retroperitoneal sarcoma were treated at Memorial Sloan–Kettering (MSKCC) on a prospective protocol. Twelve patients presented with primary retroperitoneal sarcomas, while 20 patients presented with locally recurrent disease, having received prior surgery ± irradiation. With regard to histology, the majority of patients had liposarcoma (60%) or leiomyosarcoma (19%); 20 patients had high-grade lesions, and 12 had low-grade tumors. Thirty patients (94%) underwent grossly complete resections. Resection of contiguous organs was performed in 19 (59%) of the patients. Tumor size ranged from 5× 5×1 cm to 49×45×35 cm, with a median size of 20×12.5×11 cm. Therefore, by any criteria, this would be considered a challenging group of patients. Follow-up in these patients ranged from 1 to 77 months, with a median follow-up of 33 months.

Table 17.8 lists the various procedural and treatment-related parameters and time, including HDR-IORT delivery time, IORT procedure time, estimated blood loss from entire surgery/IORT procedure, entire procedure time, hospital stay, etc. As can be seen, depending upon the size of the region treated, activity of the HDR source, and complexity of the setup procedure, 30 min to over 4 h is added to the OR time due to the HDR-IORT procedure, with a median of 110 min. One patient received a permanent I-125 implant instead to three contiguous sites. In all the other cases, HDR-IORT was delivered as planned. In no instance did the treatment require interruption for anesthesiology problems or patent monitoring issues. Additionally, in no instance was the anatomy of the tumor bed unsuitable for the treatment using this technique.

For primary versus recurrent disease presentation, 5-year LC was 74 vs. 54% (overall 5-year LC of 62%), and 5-year OS was 75 vs. 30% (overall 5-year OS of 45%). The overall 5-year distant-metastasis-free survival rate was 82% (70% high-grade vs. 100% low-grade). The most common posttreatment complications were gastrointestinal obstruction (18%) followed by fistula formation (9%), peripheral neuropathy (6%), hydronephrosis (3%), and wound complications (3%). In one patient, an aortic fistula led to postoperative death [88].

Curie Cancer Center Series

Investigators from the Curie Cancer Center reported the results of 70 consecutive patients considered for curative intent resection plus HDR-IORT from 1998 to 2004. Sixty-four patients (91%) had

Table 17.8 HDR-IORT for retroperitoneal sarcoma: procedural and treatment-related parameters

Parameter	Number
Estimated blood loss	1342 cc
	Range 150–47,00 cc
Hospital stay	12 days
	Range 5–50 days
OR time	455 min
	Range 205–730 min
IORT procedure	124 min
	Range 32–250 min
IORT delivery time	60 min
	Range 17–165 min
IORT dose	14 Gy at 0.5 cm
	From the surface of the HAM applicator

locally recurrent tumors with six cases (9%) of primary disease [89]. Median tumor size was 15 cm. Twenty-four (34%) were deemed ineligible for HDR-IORT secondary to peritoneal spread, R2 resection, etc. Thirty-seven patients underwent HDR-IORT following resection along with nine patients who underwent delayed HDR-IORT within 1–3 days following the primary operation due to "poor intraoperative condition". In the HDR-IORT group, resection margins were R0 in 30 cases (65%) and R1 in 16 cases (35%). A total of 20 Gy was delivered to the treatment volume to a depth of 1 cm. HDR-IORT treatment duration ranged from 20 to 87 min (median 56 min). One patient died after surgery. Twenty-four patients (52%) underwent adjuvant EBRT to a total dose of 50 Gy.

With a median follow-up time of 20 months, actuarial 5-year overall and local-recurrence-free survival rates were 55 and 51%, respectively. The delivery of EBRT in addition to HDR-IORT resulted in a more favorable local control rate. Postoperative complications requiring reoperation occurred in ten patients following HDR-IORT, including abscess, fistula, dehiscence, ileus, and hemorrhage. Two patients (8%) developed chronic peripheral neuropathy. Overall 5-year survival was 55% in the HDR-IORT group, and 5-year local control rate was 51%. Predictive factors influencing overall survival in patients undergoing IORT included tumor grade and liposarcoma histology; predictive factors influencing local control included number of previous operations and delivery of EBRT. Three-year local control rates were 100% in primary tumors versus 68% in recurrent disease. In patients receiving adjuvant EBRT plus HDR-IORT, 3-year local control rate was 88% versus 58% in patients receiving HDR-IORT alone. The authors concluded that (1) their local recurrence rates compared favorably to those in the surgery-alone literature, notably in the context of the high percentage of locally recurrent cases in their series, (2) surgery with HDR-IORT was able to be delivered in the majority of patients with retroperitoneal sarcoma, and (3) the addition of EBRT to IORT improved local control, with high but acceptable complication rates in the setting of aggressive, extensive surgical resections.

Orthovoltage-IORT Series

Montpellier

Dubois et al. from Montpellier, France, reported on their experience with IORT in a total of 31 patients with soft-tissue sarcomas [90]. This series included 13 patients with sarcoma located in the retroperitoneum or pelvis. Sixteen patients were treated for primary disease and 15 were treated for recurrent disease; however, this information was not separately reported for the group of patients with retroperitoneal tumors. Patients with primary disease also received postoperative EBRT with doses of 28–56 Gy, with a mean dose of 41.8 Gy. Of the entire group, all but one patient had a gross complete resection. Local recurrence occurred in four patients (30.7%), all of whom had intrapelvic or intraabdominal disease. A 5-year OS of 65% was reported for the whole group.

Stanford

Investigators at Stanford University used orthovoltage IORT for treatment of 62 sites of disease in a total of 50 adult patients with locally advanced primary (30%) or recurrent soft-tissue sarcomas (70%) [91]. The primary sites included the retroperitoneum-pelvis (78%), extremities (8%), and others (14%). Prior EBRT had been given in 32% of the patients, and prior systemic chemotherapy had been given in 24%. Orthovoltage IORT was delivered after maximal resection with a mean dose of 11.6 Gy (range 6–16 Gy). Postoperative EBRT or chemotherapy was administered to 32% of the patients.

Actuarial 5-year in-field control, locoregional control, distant-metastasis-free survival, and disease-specific survival (DSS) probabilities were 55, 26, 51, and 25%, respectively. Significant prognostic factors on multivariate analysis were as follows: for locoregional control, disease-free interval and tumor size; for distant-metastasis-free survival, extremity location and leiomyosarcoma histological subtype; and for disease-specific survival, only prior disease-free interval was statistically significant. Post-IORT EBRT resulted in improved 5-year DSS (44% vs. 15%; $p=0.011$) but post-IORT chemotherapy did not significantly impact any clinical outcomes.

Conclusions and Future Possibilities

The natural history of retroperitoneal sarcoma after resection is characterized by a high rate of local recurrence, even following curative resection, clearly indicating the need for adjuvant treatment. On the basis of the NCI randomized trial, however, the use of adjuvant EBRT without IORT after marginal resection could be questioned, since the rate of tumor bed relapse with adjuvant EBRT in that trial was 80% [38, 63], which is similar to surgery-alone results. In addition, small-bowel toxicity was unacceptable in the EBRT-alone patients in that series. The excellent salvage of patients with recurrent disease in the Mayo Clinic-IOERT analyses further supports this stance. Although some institutional series have suggested improved outcomes using adjuvant EBRT-alone approaches, this approach has potential disadvantages.

A preferable approach for patients with locally advanced primary or locally recurrent disease is to deliver preoperative EBRT following biopsy and to resect the malignancy at an institution that has the capability of giving an IORT supplement with IOERT or HDR-IORT. Treatment programs of EBRT with surgery and IORT have been evaluated at a number of centers in USA, Europe, and Asia. The collective data suggests that local control in the retroperitoneum is improved when IORT is utilized as a component of treatment, particularly in patients undergoing gross total resection. This is an important end point in a disease where local failure dominates patterns of relapse. Its ultimate benefit in improving overall survival is unknown because of the small numbers of patients treated by this modality and the presence of only one small controlled trial (Table 17.2). Complications rates with the use of an IORT approach are relatively low but not insignificant; however, they appear acceptable given the complex and challenging patient population under study. Local, regional, and distant failures are still common in spite of combination treatment with EBRT, resection, and IORT, emphasizing the need for further improvement in local therapy and effective systemic treatment.

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Chapter 18
Extremity and Trunk Soft-Tissue Sarcomas

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Keywords Extremity sarcomas • Truncal sarcomas • IORT for extremity sarcomas • ISIORT-Europe pooled analysis

Background

Management of soft-tissue sarcomas of the extremities and trunk is optimally accomplished through a multidisciplinary team evaluation of each patient because of the diverse and complex nature of each clinical scenario. A team of orthopedic or surgical oncologists, radiation oncologists, medical oncologists, plastic surgeons, pathologists, and radiologists consider multiple issues including tumor stage, grade, location, and histologic type of tumor, as well as feasibility of a limb-sparing surgery, timing of radiation, and the patient's performance status and comorbid illnesses. The rarity of these tumors in combination with the variety of presentation in extremity and truncal soft-tissue sarcomas limits the amount of prospective data available to reliably outline the management of all situations, and hence, there is a range of approaches utilized around the world today.

Retrospective and prospective data indicate that surgical management remains the mainstay in the treatment of both localized extremity and truncal soft-tissue sarcomas [1, 2]. Currently, most

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_18,

surgical procedures are limb-sparing, allowing for excellent tumor control with good functional outcome [3]. It is the timing and indications for adjuvant therapies, specifically chemotherapy and irradiation, that are more variable.

The use of intraoperative irradiation (IORT) as a component of treatment in extremity and truncal soft-tissue sarcomas is a valuable tool in the management of these tumors using either electron beam (IOERT) or high-dose-rate brachytherapy techniques (HDR-IORT). Integration of IORT needs to be applied judicially to optimize local control and thereby improve the quality of life for the extremity and truncal sarcoma patient.

Prognostic Factors/Results with Non-IORT Approaches

Prognostic Factors

Multiple tumor criteria have an impact on the local control and metastatic risk in extremity and truncal sarcomas; these include tumor location, histopathology, tumor grade, and tumor size [4–8].

Tumor Location

Some locations in sarcomas of the extremities as well as the trunk may be at higher risk of local recurrence [9, 10]. In a series of 369 patients with high-grade soft-tissue sarcomas of the extremities, Alektiar found on multivariate analysis that upper extremity lesions were associated with a greater rate of recurrence compared to their counterpart in lower extremities, with 70% local control compared to 86%, respectively [10]. In addition, positive resection margins increased tumor recurrence risk, but the rate of margin positivity was not significantly different between upper and lower extremities. On univariate analysis, prior excision was also associated with lower tumor control. The ability to widely excise lesions in the upper extremities, especially in the setting of a prior contamination from an unplanned excision, puts these patients at high risk of local recurrence, especially if reexcision does not achieve negative margins. Princess Margaret Hospital also demonstrated that upper-extremity local control (82%) was compromised compared to lower-extremity local control (92%), but in that series the authors attributed this to the lower use of adjuvant irradiation in that population [11]. In another large series, the difference between upper- and lower-extremity tumor control was not significantly different with 81% 5-year local control in the upper extremities compared to 87% in the lower extremities [12]. The complexity of the upper extremities and its influence on function require detailed planning to optimize function without exposing the patient to increased risk of local recurrence.

Truncal lesions may also be sited as a higher risk location. In several series, the difference in local control is quite striking, yet others report no significant difference. See Table 18.1 for comparison of these studies. There may be some body-wall lesions that are more difficult to control, but a better way to identify them has not been reported.

Tumor location may not only be prognostic of outcome but may also play a role in the morbidity of the treatment. A series from Memorial Sloan Kettering (MSKCC) demonstrated that wound reoperation and edema problems were highest in the posterior and medial compartments of the thigh [13]. This is consistent with the data from Cleveland that saw the highest rate of wound problems in the thigh [14]. In addition, the MSKCC data indicated a 21% nerve damage rate in the posterior compartment compared to only 3.5% in anterior or medial locations, and most of these were in patients who had neurolysis. This high-risk location for morbidity should be carefully considered during the administration of IORT, with efforts to minimize the length of nerve irradiated and

Table 18.1 Truncal vs. extremity local recurrence risk

	5-year local control		
Study	Extremity	Trunk	*P* value
PMH [18]	84%	71%	<0.0001
MGH [9]	82%	41.7%	0.001
Finland [8]	78.6%	70.9%	0.147
MDACC [12]	81% UE; 87% LE	84%	ns
Korea [42]	64.3% UE; 77.8% LE	81.2%	ns

UE upper extremity, *LE* lower extremity

thereby keeping the intraoperative dose to the nerve at a minimum, if possible. Unfortunately, data on nerve tolerance in extremity sarcoma situations have not been demonstrated, and hence, the safe dose is not known. Data from other sites will need to be used to guide the treatment.

Tumor Histology

Even though there are a wide variety of sarcoma subtypes, most are grouped together for evaluation of treatment outcome. A few specific subtypes are classified separately by the AJCC staging system and are recognized as having different clinical behavior including desmoids tumors, dermatofibrosarcoma protruberans, rhabdomyosarcoma, and peripheral neuroectodermal tumors. Many authors often exclude these subtypes, endeavoring to create a more uniform patient population [9, 15, 16].

Despite this, some authors have reviewed the outcome of different histopathologies to aid in the understanding of the natural history of these tumors. Among these, it is clear that myxoid liposarcoma is a favorable type of liposarcoma with excellent local control of up to 97% at 5 years [5, 6]. Unlike most sarcomas, the tumor shrinkage seen with preoperative EBRT for higher-grade liposarcomas is often much more marked and can enhance local control. These tumors were also noted to have a more unusual pattern of spread, not just to the lungs but also a significant portion to the retroperitoneum, extrapulmonary soft tissues, bone, and liver. Local control and survival were significantly superior in this particular histology.

Tumor Grade

Pathologic aggressiveness has long been associated with the risk of distant metastases, but there is also evidence that it impacts the local control of the tumor. This datum has primarily been seen in a large retrospective study from MD Anderson Cancer Center where local control at 5 years is 88% with low- to intermediate-grade tumors compared to 80% with high-grade disease [12]. Unfortunately, this study includes sarcomas of all sites, so it is difficult to ascertain how much grade impacts extremity and truncal tumors specifically. Other authors have not found this correlation of grade to local control [9].

Tumor Size

Like grade, tumor size has long been identified as a prognostic factor for risk of distant metastases. Large series that include all sarcoma sites have identified an increased risk associated with larger size of the primary tumor, specifically tumors greater than 10 cm versus those smaller [12, 17]. A series from Finland showed size as a continuum of risk for local failure with small tumors less than 3.8 cm having a 87.4% local control compared to 74.2% for tumors 3.8–7.0 cm and 67% for tumors greater than 7 cm [8]. The author indicates, however, that with increasing size there was a

significant and corresponding decrease in the surgical margin. Given the strong association between margin and local control, it is possible that size is only a surrogate for margin status. This could explain why some authors have not found size a factor in local control [9, 18].

Results with Non-IORT Approaches

Radiation in combination with local tumor resection has been utilized in the treatment of soft-tissue sarcomas to optimize function outcome by limiting the use of amputation and other radical surgeries [15, 19–22]. Overall, the local control of extremity and trunk sarcomas with the combination of limb-sparing surgical resection combined with adjuvant irradiation has been highly successful as outlined in Table 18.2. These studies utilize a variety of approaches including preoperative and postoperative external-beam irradiation (EBRT) and brachytherapy. Local control of primary extremity and truncal sarcomas approaches 90% or better with these different techniques. The only potential exception is low-grade sarcomas treated with brachytherapy alone where local control was not significantly different from surgical management alone [23].

There are distinct advantages and disadvantages to each local treatment approach. Therefore, the employment of multidisciplinary teams can aid in determining the best approach for individual patients.

Perioperative brachytherapy requires a coordinated effort between the surgical and radiation oncology teams. Anatomical limitations may prohibit higher doses of irradiation with brachytherapy catheters adjacent to neurovascular and osseous structures. Furthermore, patients that are marginally resectable at presentation may not be offered limb-sparing surgery because of surgical concerns of resectability with negative margins. On the contrary, the advantage of brachytherapy is the direct understanding of the tumor bed anatomy in relation to the pathologic specimen, allowing potential tailoring of radiation delivery, especially if perioperative, high-dose rate (HDR) multifractionated brachytherapy treatment is employed.

With regard to the use of EBRT as a component of treatment, there are potential advantages to both preoperative and postoperative sequencing of EBRT. Preoperative irradiation is known to

Table 18.2 Outcome with radiation and surgical resection

Study (Ref)	Treatment approach	No. patients	Local control (%)	Overall survival	Years
MSKCC [2, 23]	Surgery (S) + brachytherapy				
	High grade	56	89	na	5
	Low grade	22	~73	~95%	
PMH [15]	S + pre/postoperative RT	190	92	85%	3.3
MGH [19]	S + preoperative RT	48	86	58%	5
	S + preoperative RT + neoadjuvant chemotherapy	48	92	87%	
NCI [37]	S + RT	73			
	Low grade	26	96	na	9.9
	High grade	47	100	74%	9.6
RTOG [60]	S + RT + MAID	64	89.9	75.1%	3
MDACC [4]	S + postoperative RT	246	72	na	5
	S + preoperative RT	271	83		
UCLA [20]	S + RT + doxorubicin	607	90	71%	5

Na not available, *MSKCC* Memorial Sloan Kettering Cancer Center, *PMH* Princess Margaret Hospital, *MGH* Massachusetts General Hospital, *NCI* National Cancer Institute, *RTOG* Radiation Therapy Oncology Group, *MDACC* MD Anderson Cancer Center, *UCLA* University of California, Los Angeles

increase the postoperative wound complication rate but allows for a more functional, less fibrotic extremity in the long term because of the smaller EBRT treatment fields and lower EBRT dose [4, 15, 24]. Postoperative irradiation results in fewer wound issues, and this may be important in patients with significant healing risks such as diabetic patients or patients with known vascular problems. The NCIC randomized trial also demonstrated that lower extremity locations are at particularly high risk of wound complications after preoperative irradiation [15]. Unfortunately, the trade-off for a higher wound complication rate (treatable/reversible) in preoperatively irradiated patients is the risk of persistent edema and fibrosis with high-dose, large-field, postoperative EBRT [24]. This could be reduced with use of IORT to decrease the total dose of postoperative EBRT, which even with shrinking-field techniques exposes large volumes of tissue.

Metastatic disease remains the major problem in the management of high-grade extremity and trunk sarcomas with hematogenous involvement of the lungs being the primary site of spread. More radical local treatment has not changed the problem with systemic relapse, but the value of routine adjuvant systemic therapy is controversial in its impact on these tumors.

Treatment Factors

With the currently available excellent results, it is important to determine which patients might be at highest risk for local recurrence or where IORT may be used to optimize therapeutic outcomes. Surgical and radiation factors in extremity and truncal soft-tissue sarcomas that have been associated with higher risk of local recurrence include positive or uncertain margins[9, 25–27], unplanned surgical procedure or intraoperative tumor violation [21, 26, 28–31], and radiation dose [9, 17, 21]; some of these risks are found in the same patient population. Each can be important for considering the addition of IORT.

Surgical Treatment Factors

Extent of Resection

With the use of a more conservative limb-sparing surgical approach, investigators have endeavored to define the adequacy of the surgery necessary to obtain good local control. Enneking categorizes the surgical procedures into four types: intralesional excision, marginal excision, wide excision, and radical excision [32].

Optimally, all patients with soft-tissue sarcomas will undergo a wide excision that entails removal of the tumor, the reactive zone, and a margin of normal surrounding tissue in continuity (see subsequent section on Margins). Unfortunately, different investigators use variable definitions of necessary distance from tumor to resection margin, and large prospective analyses correlating local control with the amount of radial margin are lacking. In addition, the necessary margins for patients receiving adjuvant irradiation are unknown. A wide excision may be unnecessary if adequate irradiation is administered, just as radical excision may eliminate or at least diminish the need for adjuvant irradiation [33, 34]. Wide excision alone is reported to have local relapses up to 50%, and marginal excision results in an even higher local recurrence rate of up to 90% [7, 35–37].

Despite adjuvant treatment, the type of surgical procedure remains important. Review of the Helinski University experience revealed a 3-year local control rate of 76% in patients receiving inadequate surgery despite the addition of irradiation as compared to 92% in patients having optimal surgery [38].

Surgical management of truncal sarcomas applies the same principles as that for extremity tumors. However, wide excisions are less frequent due to the approximation of vital organs or structures. Margins have also been important in the management of sarcomas at this site as well [39]. As a result, adjuvant radiotherapy should be considered for most soft-tissue sarcomas of the trunk.

Margins

Although margin status is consistently listed as a risk factor for local recurrence, what constitutes adequate surgical margins is not well defined. Enneking and Simon understood that local recurrence was directly related to the surgical resection. They originally described the use of wide surgical margins defined as removal of the tumor with a cuff of normal tissue within the anatomical compartment [36] (Fig. 18.1). The specific amount of normal tissue needed is not well known, and in situations where tumor abuts important structures such as a neurovascular bundle or bone, margins are often reduced to the overlying adventitia or the underlying periosteum [40, 41]. Fascial or periosteal margins have been upheld as representing more than just millimeters of tissue but constitute a barrier and imply a reasonable alternative to several centimeters of tissues [8, 41] (Fig. 18.2). In these studies, the results suggest this fascia margin as still within the definition of a wide excision as long as the fascia itself is not involved with tumor. In these situations, close margins are anticipated, and especially with utilization of preoperative irradiation, the risk of local failure has been reported as low as 3.6% [41]. Conversely, unanticipated positive margins represent a high-risk population for local recurrence [41]. Thus, there is a difference between intentional marginal margins and unintentional marginal margins. Some studies indicate that the positive margin can be managed with higher doses of irradiation [9, 42]. Table 18.3 summarizes data on studies that have evaluated margin status and the risk of local recurrence.

Unplanned Excisions

Sarcomas of the extremities and the trunk typically present as a painless mass, and therefore, it is not uncommon for these patients to undergo an unplanned excision of what was felt by the operating

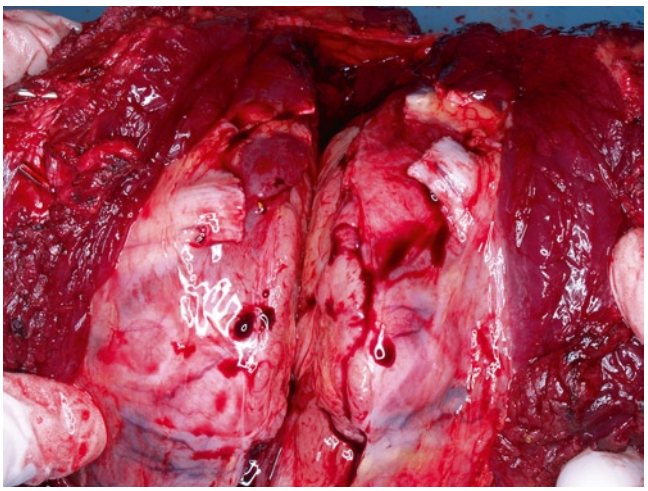

Fig. 18.1 The resected specimen includes the sciatic nerve. The nerve was intimately associated with the tumor. The cut edges of the specimen demonstrate the various possible margins: intralesional, marginal (with the reactive zone), and wide, the margin obtained here. Note the inflammatory edema in the reactive zone.

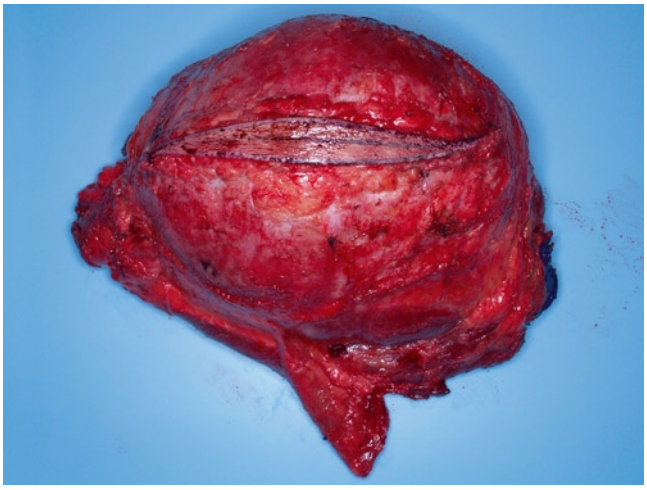

Fig. 18.2 Resected specimen with intact fascial layer. The tumor is immediately beneath the fascia. The margin here is considered wide because of the non-involved, intact fascial layer (see text).

Table 18.3 Impact of surgical margin

Study (Ref)	Population	Tx	Margins	N	5-year LC	5-year OS
MGH [9]	P, E, T	S + RT	Positive			
		Extremity		105	82.2%[a]	65.7%
		Trunk		9	41.7%	44.4%
Korea [42]	P, E, T	S + postop RT	Positive	94	75.5%[b]	79.5%
			Negative	56	78.6%	86.5%
MSKCC [61]	P, E, H	S + RT	Positive	91	74%	53%
		S		19	56%	
Finland [8]	P, R, E, T	S + postop RT	<0.4 cm	68	78.1%	na
			0.4–2.0	79	73.9%	
			>2.0 cm[c]	85	89%	
MDACC [29]	P, R, E, H, I	S	Positive	24	62%	70%
			Negative	71	91%	65%
Norway/Sweden [16]	P, E, T	S + RT	Intralesional	66	62%	na
			Marginal	285	81%	
			Wide	111	93%	
PMH [41]	P, E	S + RT	Planned positive	28	96.4%	na
			Positive after unplanned excision	19	68.4%	
			Unplanned positive	16	62.5%	

P primary disease, *R* recurrent, *E* extremity, *T* trunk, *H* high grade, *I* intermediate grade, *na* not available
[a]Higher external-beam irradiation dose impacted LC
[b]More patients with doses ≥65 Gy
[c]Only 5 of 85 received postoperative RT

physician to be a benign entity. In series where these patients undergo reexcision, residual disease is found in 35–63% of the cases [26, 28, 31, 43]. Local control can be achieved despite the high risk of recurrent disease, but as would be anticipated, high doses of radiation are needed to accomplish this. A series from Massachusetts General Hospital utilized a median radiation dose of 66 Gy to obtain an 88% local control [26]. The major difficulty with patients having a prior unplanned excision is often the lack of radiographic imaging prior to the initial surgery and the difficulty in

obtaining clear margins at reexcision. These patients often have incisions placed in awkward locations creating a soft-tissue problem that only increases the complexity of the reexcision. These patients are at significant risk of local recurrence, with a series from Canada demonstrating a 31.6% risk of recurrence [41].

Summary

It is clear that the quality of the surgical resection is paramount in the management of sarcomas with regard to both surgical/pathological margins and unplanned excisions. Although some data suggest that increasing irradiation dose can be helpful in controlling local disease, the data are not consistent, and therefore, optimizing surgical resection needs to be considered for determining the treatment approach to each patient.

Irradiation Treatment Factors

EBRT Sequence and Dose

In the postoperative setting with positive margins, higher EBRT doses are typically used [4, 15, 17, 21, 42, 44, 45]. Increased dose is often used to compensate for close margins, escalating doses to 70 Gy or higher [9, 16, 42]. Although the higher EBRT doses can result in good local control, the use of high-dose postoperative EBRT may also result in higher rates of fibrosis, edema, and poorer joint function in comparison to preoperative EBRT [15, 24, 46]. In addition, the volume of tissue irradiated either with a postoperative EBRT boost or when all EBRT is delivered after surgery is significantly larger, adding to the poorer functional outcome. The postoperative or positive margin setting is the ideal situation to consider for IORT as a component of treatment, as this modality can deliver the higher boost dose without exposing large amounts of normal tissue to high doses of EBRT.

In view of the problem with extensive fibrosis and edema when high-dose postoperative EBRT is used, the preference at Mayo Clinic is to use moderate-dose preoperative EBRT (alone or plus concurrent anthracycline or ifosfamide-based chemotherapy) combined with an IOERT or brachytherapy boost, as indicated. Preoperative EBRT or chemoirradiation also allows for smaller, more precise targeted treatment and has the potential to sterilize areas where close resection margins are anticipated.

For previously unirradiated patients, a dose of 45–50 Gy/1.8–2 Gy fractions/5–5.5 weeks is delivered preoperatively using 3D conformal irradiation (3D-CRT) to the gross tumor volume plus 3–5 cm margins or using intensity-modulated irradiation techniques (IMRT). In previously irradiated patients, the preference is to deliver low-dose preoperative EBRT (25.2–30.6 Gy in 1.8 Gy fractions) prior to an attempt at surgical resection. Use of IMRT in a previously irradiated patient may allow delivery of a higher additional dose of EBRT if sparing of other tissues is achieved.

IORT Treatment Factors

Preoperative EBRT alone or combined with concurrent anthracycline- or ifosfamide-based chemotherapy is followed by surgical resection in 2–5 weeks. For patients with narrow (R0 resection) or microscopically positive resection margins (R1 resection), the surgeon and the radiation oncologist make a decision in the operating room with regard to indications for and the preferred method of

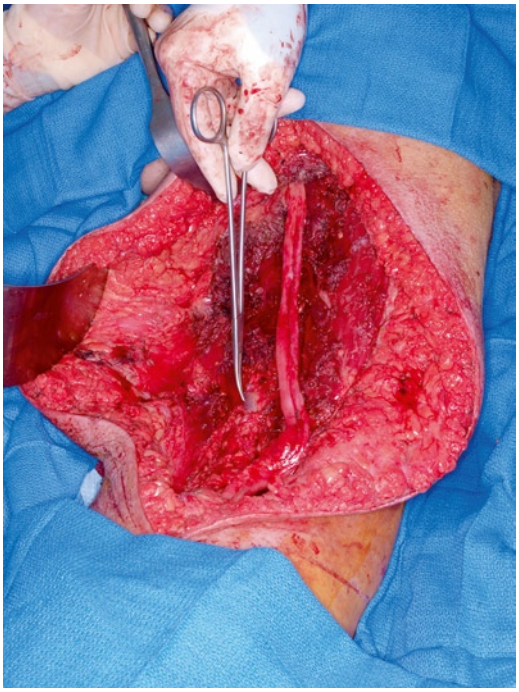

Fig. 18.3 The deep margin was felt to be "close" at the area where the femoral vessels were located. The posterior sheath of the femoral vessels was included with the resection. IORT was applied to this area. The sciatic nerve was not involved, but its sheath was resected with the tumor.

irradiation boost (IOERT, HDR-IORT, placement of catheters for perioperative brachytherapy, postoperative EBRT) based on surgical and pathological findings and technical/functional issues (Fig. 18.3). For both proximal extremity and trunk lesions, IOERT is often preferred to the placement of catheters for postoperative brachytherapy from a technical perspective, especially if skin grafting or muscular flap reconstruction is being performed at the time of resection (Figs. 18.4 and 18.5).

IORT is typically delivered using either IOERT or HDR-IORT to doses of 10–15 Gy for patients in whom preoperative EBRT doses of 45–50 Gy have been given. When the preoperative EBRT dose is restricted to 25.2–30.6 Gy in view of prior EBRT, the dose of IOERT, HDR-IORT, or perioperative HDR brachytherapy usually has to be higher (15–20 Gy) to compensate for the lower dose of EBRT if optimal local control with limb preservation is preferred by both the physician and the patient. In the latter situation, the patient needs to be informed of increased normal-tissue risks due to reirradiation, and the option of amputation should be discussed.

The delivery of IOERT or HDR-IORT to extremity or truncal locations is often easier technically than to deep body cavity sites because of the flexibility of the limb and the superficial nature of truncal sites. However, there are important aspects that need to be considered in these sites, such as proximity to skin edge, bone, joint, and body thickness, as well as underlying organs. Skin edges need to be carefully excluded from the IORT field. If HDR-IORT is being used as the mode of radiation delivery, the distance from the applicator to the skin should ensure that minimal dose is delivered to the skin edge so as not to affect wound healing. If the high-risk or marginal-resection site is subcutaneous but close to the dermis, then resection with reconstruction should be considered. Bone and joint issues are also important considerations in extremity IORT, especially with the potential for fracture in weight-bearing bones. Use of bolus or prescribing to the surface if using kilovoltage or brachytherapy may help minimize the impact to this normal tissue and restrict to only

Fig. 18.4 Tumor bed after resection of a large (8×10×11 cm) gluteal soft-tissue sarcoma, Pamplona. (**a**) Note that the sciatic nerve is in close contact with the surgical resection margin. (**b**) IOERT Lucite applicator in position to treat the high-risk tumor bed including the sciatic nerve (12-cm applicator, 30° bevel).

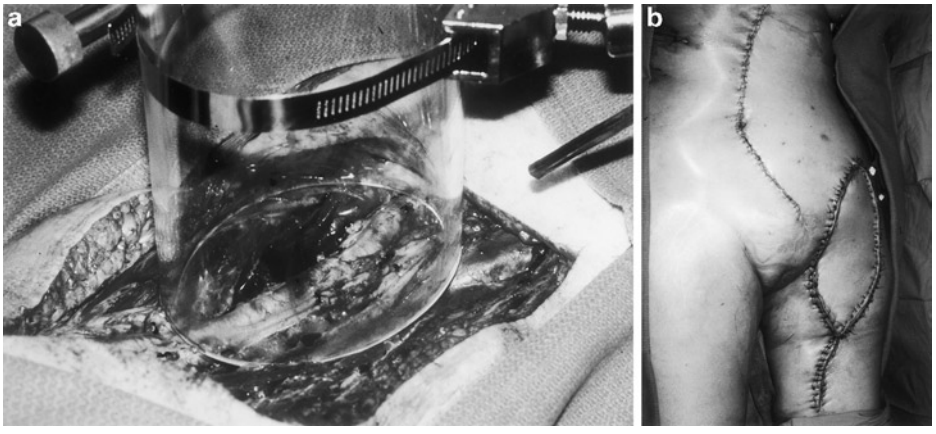

Fig. 18.5 Use of IOERT when myocutaneous flap is planned for wound closure after resection of soft-tissue sarcoma in left groin, Mayo Clinic Rochester. (**a**) IOERT lucite applicator in place over neurovascular bundle. (**b**) Rectus abdominus reconstruction of left groin defect.

the area(s) of highest risk. In addition when treating distal extremities, the thickness of the limb within the IORT field needs to be considered to avoid significant exit dose to the opposing skin. A similar issue occurs with truncal tumors where there may be underlying organs such as lung, bowel, or spinal cord. The total dose to these organs/structures from both EBRT and IORT must be judged appropriate and safe.

Results with Intraoperative Electron Irradiation

Intraoperative electron irradiation (IOERT) has been used in soft-tissue sarcomas in efforts to enhance local control and optimize function of the limb. Most studies include a significant population of patients with locally advanced primary or locally recurrent disease.

US IOERT Series

Mayo Clinic Rochester

Between June 1986 and September 1995, a total of 91 patients with limb-girdle or extremity soft-tissue sarcomas were treated at Mayo Clinic Rochester using IOERT as a component of therapy [47]. With a median follow-up of 2.9 years (range 0.5–10 years), the 3-year overall survival (OS) was 76%. The survival was better for patients with low-grade lesions with an 87% 3-year OS compared to 70% for the high-grade lesions ($p=0.06$). Size of tumor also predicted for outcome with patients with tumors ≤5 cm and >5 cm having a 96 and 65% 3-year OS, respectively ($p=0.009$).

Patient outcomes. Local control was comparable to series using EBRT and brachytherapy with a 92% local control at 3 years. The disease status of the patient impacted local control with a 95% local control in primary lesions vs. 81% in recurrent tumors ($p=0.014$). This local-control difference did not translate into a survival difference between these two populations. Although survival was influenced by the grade and size of the sarcoma, the local control was virtually identical. Local and/or central (within the IOERT field) failures were seen in six patients. Four of the six had concurrent failures in regional or distant sites. Toxicity was prospectively charted, as nerve tolerance was of particular concern in this population. Only two patients (2%) experienced severe peripheral neuropathy. Moderate neuropathy was seen in an additional nine patients (10%).

University of Kansas

Twenty-eight patients with soft-tissue sarcomas diagnosed between June 1987 and December 1989 were treated with wide local excision and IOERT [48]. Twenty-one of the 28 patients received additional EBRT. The primary site of tumor was in the extremities in 22 patients. The dose of IORT delivered ranged from 12.5 to 20 Gy calculated at the 90% isodose line. The energy of electrons ranged from 9 to 16 MEV depending on the thickness of tissue to be treated. EBRT doses ranged from 40 to 50 Gy.

Patient outcomes. Median follow-up at the time of presentation was 21 months. A total of six patients failed locally; three of the six failed within the IORT field (two despite EBRT), and three failed marginally or outside of the IOERT/EBRT fields. Five additional patients developed distant disease primarily in the lung. Nineteen patients were alive without evidence of disease. A total of five acute and

three chronic complications subsequently occurred. Four of the five acute complications were wound related. Two of the chronic complications were neurologic and felt to be directly related to the IOERT with or without surgical resection. The remaining chronic complication was leg edema.

Mayo Clinic Arizona

Callister et al. reported the results of the Mayo Clinic Arizona series at the ISIORT 2008 meeting in Madrid [49], and they are updated here. Between January 2002 and December 2007, a total of 80 patients were treated with preoperative EBRT with the intent of possible IOERT boost at the time of resection. Thirty-two patients did not receive IOERT due to the following: brachytherapy boost instead – 18 patients, widely clear margins – 9, distant metastases found on preoperative restaging – 2, other – 3, leaving 48 patients who received an IOERT boost (primary disease – 41, locally recurrent – 7). Tumor histologies included malignant fibrous histocytoma (22), liposarcoma (9), synovial (5), desmoid (4), chondrosarcoma (3), leiomyosarcoma (2), unclassified (2), extraosseous Ewing's (1). The lower extremity was involved in 33 patients, upper extremity – 14, trunk – 1. The median tumor size prior to therapy was 8.5 cm (range 1.3–29.6 cm). With regard to tumor grade, 32 tumors were classified as high grade, 6 as intermediate, and 10 as low. Seven patients (15%) were treated at the time of first local recurrence (no prior EBRT).

Treatment factors. All patients underwent preoperative EBRT to a median dose of 50.4 Gy (range 30.6–54.0 Gy). Neoadjuvant chemotherapy (prior to EBRT) was administered to 16 patients, and 20 patients received chemotherapy concurrent with EBRT. All patients initially underwent a limb-preserving surgical resection, with negative margins (R0) achieved in 40 patients, and microscopically positive (R1) in 8. The median IOERT dose delivered was 12.5 Gy (range 10–15 Gy) using energies of 6 or 9 MeV. The median applicator size was 8.0 cm (range 3.5–12 cm), with three patients requiring multiple fields.

Patient outcomes. With a median follow-up of 31 months (range 5–90 months), 11 patients had died (75% 3-year OS). Tumor relapse had occurred in 18 patients, with 5 local relapses (all in EBRT fields), 1 nodal, and 14 distant. The 3-year local control (LC) and distant metastatic control rates were 89 and 71%, respectively for the total group of patients. The 3-year LC for patients treated for primary vs. recurrent disease was similar at 89 vs. 86% (Table 18.4). Surgical margin status (R0 vs. R1), use of concurrent chemotherapy, tumor size and grade were not associated with a difference in local control. High-grade tumors were associated with a reduction in distant control at 3 years (93 vs. 58%, $p=0.014$ log rank). Significant postoperative wound complications were experienced in 16 patients.

European IOERT Series

Pamplona

Azinovic et al. and Calvo et al. reported a series of 45 patients with extremity sarcomas from Pamplona, originally presented at the IORT meeting in Lyon in 1994 [50, 51]. Twenty-six were in patients with primary disease and 19 were treated for isolated local recurrences. Fourteen of the primary lesions were grade 3. Lower extremity was the most common location (82%). Malignant fibrous histiocytoma and liposarcoma were the most common histologies.

Treatment factors. Surgery resection was considered wide in 28 cases, marginal in 13, and a compartment resection was performed in three cases. Close margins, defined as less than 5 mm, were

Table 18.4 IOERT in primary and recurrent extremity or trunk sarcomas, US and European series

				Primary		Recurrent	
Study	EBRT dose (Gy)	IORT dose (Gy)	FU time	No. patients	LC	No. patients	LC
US series							
Mayo Clinic MN, [47]	45–50.4	10–15	2.9-year median	74	95% 3-year	17	81% 3-year
Mayo Clinic AZ [49]	50.4 median, range 30.6–54[a]	12.5 median, range 10–15	2.6-year median	41	89% 3-year	7	86% 3-year
European series							
Munich, Germany [53]	50.6 median, range 30.6–60	14.5 median range 12–15	5 year	11	91%	17	74%
Pamplona, Spain [50]	40–60	10–15	5 year	26	88%	19	60%
Saar, Germany [57]	23–56	8–15	5 year	29	66%	9	50%
Austria [54]	50	15	2 year	37	100%	2	100%
Heidelberg, Germany [52]	43 median, range 40–50.4	15 median range 10–20	5 year	62	73%	38	69%
European pooled analysis [55]	43 median, range 40–50.4	15 (median)	5-year median	128	58%	192	15%

EBRT external-beam irradiation, *LC* local control, *FU* follow-up, *mo* months
[a]Dose of 30.6 Gy used for recurrent patients with prior EBRT

seen in eight patients, and positive margins were seen in seven. IOERT was done in a single field in 78% of the patients with a median dose of 15 Gy. External-beam irradiation was done postoperatively to all but nine patients, delivering doses of 40–50 Gy. Chemotherapy was utilized in 33 patients and was predominantly anthracycline-based.

Patient outcomes. Isolated local control was accomplished in 87% of the entire group, with a 5-year local control of 88% in the primary treatment group, compared to 60% in the recurrent population ($p=0.05$). Surgical margins correlated with local control with 87% having local control if the margins were negative/close compared to 57% with positive margins. In addition, the use of EBRT was suggested to impact local control with 85% control versus 74% where EBRT was not done ($p=0.09$). Seven-year overall survival with a median follow-up of 93 months was 75% compared to 47% for the primary and locally recurrent group, respectively ($p=0.01$). Acute dermatitis from the EBRT was noted in nine patients. Those with more than a year follow-up were assessed for late toxicity with neuropathy noted in five patients, developing at a median of 13 months. Four of these were grade 3–4, and the nerve was within the IOERT field in three of the four cases. Of the patients who had a nerve within the IOERT field, 25% (3/12) developed neuropathy compared to 11% (2/18) when the nerve was not included in the field. In four of the five who developed neuropathy, an IOERT dose of 15 Gy or more was utilized. Three of the five had some or complete recovery of nerve function.

Heidelberg

In a large series from Heidelberg, 153 patients were treated with combined IOERT and EBRT for soft-tissue sarcomas between 1991 and 2004 [52]. The majority of the sarcomas were primary

lesions (62%). In 16%, metastatic spread had occurred by the time of surgery. Two thirds of the patients were AJCC IIB, III with half of the patients having tumors over 10 cm in size.

Treatment factors. A wide-margin resection of over 1 cm was accomplished in 49%, and 37% had R1 resections. IOERT was delivered using a median energy of 8 MeV to a median dose of 15 Gy (range 10–20 Gy), treating the tumor bed with a 1–2 cm margin. External beam was delivered postoperatively to a median total dose of 45 Gy (range 36–50.4 Gy) in conventional fractionation using 5-cm longitudinal margins and 3-cm radial margins.

Patient outcomes. With a median follow-up of 33 months, the 5-year OS is 77% and LC is 78%. For 128 patients without metastatic disease, the 5-year OS and LC rates were 83%. Local control was significantly better in patients with an R0 vs. R1 resection (85 vs. 60%; $p=0.03$). In addition, patients receiving IOERT doses of 15 Gy or higher had an 85% local control compared to only 50% in those with less than 15 Gy ($p=0.003$). External beam dose, primary versus recurrent status, histology, tumor size, age, and grade did not influence local control. Resection status and IOERT dose also significantly influenced overall survival. Overall, extremity salvage was accomplished in 90% of the patients in this study with excellent limb function in 86%. Acutely, 17% had wound healing grade 2–4 toxicity. Late grade 2–4 neurologic toxicity was noted in 5% of patients.

Munich

Kretzler et al. evaluated a series of 28 patients with extremity soft-tissue sarcomas from Munich for outcome after IORT [53]. These patients were treated between June 1989 and June 1999 for localized sarcomas as part of an interdisciplinary treatment plan and were all felt to be at high risk for local relapse. The majority were locally recurrent (61%) with grade 2 or 3 (93%) T2 lesions (71%). The predominant histologies were malignant fibrous histiocytoma and liposarcoma.

Treatment factors. Tumor resection was microscopically positive (<2 mm) in 32% of patients and was microscopically negative in 61%. Intraoperative irradiation was delivered using either electrons (8–10 MeV) or with HDR-IORT using a high-dose rate afterloader and flab applicator. Mean IORT dose was 14.5 Gy (range 12–15). Twenty-five of the 28 patients had EBRT, all delivered postoperatively with a mean dose of 50.6 Gy (range 30.6–60). Two of the patients who did not receive EBRT had prior therapy, and the third had a compartment resection.

Patient outcomes. The 5-year OS and LC were 66 and 84%, respectively. Surgical margin and primary/recurrent status did not influence local control. Wound-healing problems were encountered in 18% (five patients), one resulted in discontinuation of EBRT. Grade 1–2 long-term complications were evaluated in 21 patients with one neuropathy case. Five patients (24%) had grade-3–4 toxicity with one grade-3 neuropathy and the other four were fractures and contractures.

Austria

Rachbauer et al. reported the use of HDT-IORT in a series of 39 patients for soft-tissue sarcomas between September 1996 and May 2002 [54]. Thirty-six of the 39 were in the extremity and trunk with three in the neck or retroperitoneum. Most were primary lesions (37) and half of the patients had liposarcomas. The most common stage was AJCC stage III in 22 patients with 11 having stage IIA.

Treatment factors. Patients underwent marginal resection as defined by Enneking [14]. A flexible tissue-equivalent slab with imbedded parallel plastic catheters was positioned into the target area and secured for each treatment, delivering a dose of 15 Gy to the surface of the applicator, delivering approximately 10 Gy to a 0.5-cm depth. This was reduced to 12 Gy when the applicator abutted a

major neurovascular structure. External-beam irradiation was delivered postoperatively in all the extremity and truncal patients to a dose of 50 Gy in 5 weeks to a volume covering the tumor bed with a 5–7-cm margin.

Patient outcomes. No local recurrences have been detected with a mean follow-up of 26 months (3–59 months), but seven patients (17.9%) have developed metastatic disease. All of them had tumors greater than 5 cm, and six of them were high-grade lesions. Two-year actuarial LC and disease-free survival were 100 and 84%, respectively. Extremity sarcomas had an excellent functional outcome with a Musculoskeletal Tumor Society score of 88.5%. No neurologic or vascular complications were seen.

European Pooled Analysis

Krempien et al. reported the results of a European pooled analysis at the ISIORT 2008 meeting in Madrid [55]. From 1991 to 2007, a total of 320 patients received IOERT as a component of treatment for extremity STS at three major European referral centers (University of Heidelberg; NCI CRO Aviano, Italy; University Hospital Gregorio Maranon, Madrid). Median IOERT dose was 15 Gy, and mean EBRT dose was 43 Gy (range 40–50.4 Gy, 1.8–2 Gy fractions).

Patient outcomes. Five-year OS and LC were 77 and 78%, respectively, with a median follow-up of 60 months. Resection status and IOERT dose were significant for LC, and resection status and grade were significant for survival. Tumor size, patient age, and EBRT dose did not significantly affect outcome. Extremity salvage until death or last follow-up was achieved in 90% of patients; 86% showed excellent limb function without impairment in daily-life activities. Acute toxicity grade 2–4 was observed in 23% of patients, and late toxicity grade 2–4 was observed in 17%.

Summary: Combined IOERT Series

In the series reporting outcome in primary disease, the local control is excellent despite the limited number of cases (see Table 18.4). The series from Heidelberg demonstrated an 82% local control when the EBRT dose was higher than 45 Gy. The lower control rate from Saar may be due to inclusion of secondary sarcomas and omission of EBRT in these patients, having significant impact on a small series. Both the Pamplona and Heidelberg series of patients were influenced by margin status and the use of EBRT.

Additional studies from Montpellier and Homberg have been reported, but the outcomes for primary vs. recurrent disease status or for extremity/trunk vs. retroperitoneal sites have not been separated. In both series, the local control was 87 and 63%, respectively, for 31 and 38 patients [56, 57].

Despite the aggressive therapy, the authors indicated that toxicity is generally limited with neuropathies seen in 0–11% of reports. This is despite a significant population of previously treated patients. Kunos et al. presented a series of 27 patients in whom the toxicity was specifically evaluated after IOERT with either preoperative or postoperative EBRT [14]. In this series, seven patients (26%) experienced wound complications, most commonly in the thigh tumors. Although not statistically different, no wound complications were encountered in 11 of the 13 (85%) postoperative patients compared to 6 of the 14 preoperative group (64%). Information on the functional status after the use of IOERT is limited and at best suggests no significant difference in outcome, although further evaluation is warranted [33, 50].

Local/Regional Relapse

Local recurrences of extremity and truncal sarcomas are in general uncommon with current combinations of surgery and irradiation as previously discussed, but patients who experience a local relapse can be challenging to manage. Data from several studies indicate that local recurrences are higher in patients who present with recurrent disease compared to primary-tumor situations [20, 58]. This is especially true in patients with more than one recurrence, where local control drops from 64.6% after one recurrence to 35.4% with two or more recurrences [59]. However, poor outcome with local recurrence is not a uniform finding, as other authors report similar local control [8, 18, 27]. In one case, the authors indicate that surgical margins influence the local control in these patients [58]. Table 18.5 indicates the different outcomes seen in these patients.

In series that have utilized IORT for the treatment of patients with recurrent disease, subsequent local control of the disease is not as optimal as the use of IORT for primary-disease patients. However, Table 18.4 demonstrates that aggressive approaches with second limb-sparing surgery and additional irradiation are worth considering. In patients with local recurrence who have had prior EBRT, the use of IOERT as a component of treatment becomes more appropriate due to the large volumes typically treated with EBRT as the sole component of irradiation.

Conclusions and Future Possibilities

Limb preservation and local-control rates are generally quite acceptable in patients with extremity and trunk sarcomas by virtue of combining surgical resection with both preoperative EBRT, IOERT (when indicated) and select use of concurrent chemotherapy during preoperative EBRT. Distant relapses, especially in lung, remain excessive in patients with high-grade lesions, however, and do not appear to be impacted by the use of neoadjuvant chemotherapy. While the latter conclusion may be based on small patient numbers, evaluation of more aggressive systemic therapy in patients with high-grade lesions is indicated. It is hoped that new and targeted agents will help improve this situation. The role of IOERT and HDR-IORT needs to be poised for a time when patients will have improved survival because of advancements in systemic disease management.

Table 18.5 Impact of disease status, non-IORT series

Study	Disease status	Number of patients	5-year Local control
UCLA [20]	Primary	607	90%
	Recurrent	146	81%[a]
MDACC [58]	Recurrent	62	51%
			73% – margin negative
			22% – margin positive
MSKCC [62]	Recurrent	161	73%
MGH [27]	Primary	93	96% – margin negative
		11	83% – margin positive
	Recurrent	23	91%[b] – margin negative
		5	80%[b] – margin positive
Finland [8]	Primary	230	75.5%
	Recurrent	40	82.4%[b]
PMH [18]	Primary	289	75%
	Recurrent	32	78%[b]

[a] p = significant
[b] p = ns

The benefits of a localized boost dose of radiation in high-risk patient populations while minimizing the potential late toxicity to bone, nerves, vessels, and musculature should be the goal of future IORT use. It has been well established that function after 2 years is better with preoperative lower-dose EBRT, allowing a more functional limb [24]. When this approach cannot be accomplished because of unanticipated positive margins, prior unplanned excision, or other patient issues, then IORT can be used to increase the radiation dose while keeping the volume of normal tissue irradiated to a minimum.

Future endeavors need to focus on the functional outcome and quality of life in patients with soft-tissue sarcomas when excellent local control of disease is achieved. EBRT can be tailored more using IMRT to focus on areas of highest risk and escalating dose in a limited fashion. Coordination of positron emission tomography (PET) response of the disease to preoperative treatment would be another way to focus the IORT to optimize the risk–benefit ratio for the patient. Currently, PET scans can show uptake in high-grade sarcomas, but their use in low-grade tumors is not as clear. Impact of local disease by chemotherapy or other systemic agents may also demand an evaluation of how EBRT and IORT are delivered. This requires detailed planning on the part of the surgeon, medical oncologist, and radiation oncologist with detailed input from the radiologist prior to surgery and from the pathologist at the time of resection. Finally, the optimal IORT dose is unknown. IORT doses are often delivered based more on tolerance of local structures than what is needed to control the disease. Dose de-escalation studies or methods to minimize normal tissue volumes within the IORT field should be considered.

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Chapter 19
Bone Sarcomas

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Keywords Bone sarcomas • Ewing's sarcoma • Osteosarcoma • Chondrosarcoma • Malignant fibrous histiocytoma • IORT for bone sarcomas • Extracorporeal irradiation

Introduction

Bone sarcomas are rare entities in clinical oncology, in which the histological subtype and site of involvement define the natural history of the disease and in particular the appropriate treatment strategy [1]. Ewing's sarcoma (ES) is a chemo- and radiation-sensitive disease in which combined modality therapy (more recently including a surgical component) is mandatory for radical management [2]. Osteosarcoma survival rates have been significantly improved by adjuvant chemotherapy and extremity preservation rates by neoadjuvant chemotherapy [3]. Other uncommon bone sarcomas, such as malignant fibrous histiocytoma (MFH) or chondrosarcoma, are considered marginally sensitive to chemotherapy or radiotherapy and the primary radical treatment modality is surgery [4, 5]. A universal feature in the natural history of bone sarcomas is the tendency to involve the extraosseous soft tissue and neuro-vascular structures once the tumor growth and infiltration acquires a certain size.

In extremity bones, amputation usually achieves a radical surgical margin in the circumferential and distal dimensions, and the only concern is to assure an adequate proximal margin distance [6]. Amputation is being replaced by extremity preservation surgical procedures. In the case of bone

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_19,

sarcomas, this requires bone resection and prosthesis replacement of the operated extremity which is in part related to the feasibility of muscle removal; the circumferential oncologic safe margin is compromised by more limited bone and soft tissue removal [7].

Intraoperative irradiation (IORT) with electrons or brachytherapy are available technologies to precisely treat the high risk or involved surgical margins after extremity bone sarcoma resection [8]. Both radiation modalities have a comparable accuracy in radiation dose-deposit for the treatment of less than 0.5 cm target volume thickness. Theoretical advantages are the use of a radiation component of treatment at the time of surgery, which after resection, may allow a decrease or deletion of the need for a fractionated external beam irradiation (EBRT) treatment component that would be given after the prosthesis or graft has been placed (potential detrimental effect on graft viability and/or dosimetric uncertainty due to the presence of metallic elements in the radiation field). Finally, IORT during sarcoma surgery, and in particular bone sarcoma resection, is a suitable situation for the use of *field-within-a-field radiation technique*, in which a larger area is treated with doses able to control microscopic disease (10–12.5 Gy) while not exceeding the tolerance dose for dose-sensitive structures (peripheral nerve), and a second reduced field to the target region at higher risk can be defined and treated with an additional dose (5–10 Gy) and either excluding or reducing the volume of dose-limiting tissues.

Bone sarcomas arising in central bones generally have less options for radical surgery, and the need to develop new therapeutic alternatives to promote local control is more evident [9]. In this situation, IORT is again a feasible technique to complement surgical exposure of unresectable bone tumors (protecting normal uninvolved abdomino-thoracic organs), postdebulked anatomic regions or a postcurettage surgical bed. The ability to locally control these patients is related to the integral treatment intensity able to be delivered with the available radiation therapy modalities (EBRT + IORT) and the chemotherapy programs integrated in chemosensitive tumors [10, 11].

In the last two decades, several reports have described and analyzed the technique of *extracorporeal IORT* as an alternative to postresection bone graft replacement in bone sarcomas [12, 13].

An overview of the IORT relevant experiences reported in the management of bone sarcoma patients is described, grouping the data by histological subtypes in which the treatment strategy is considered rather uniform, and the peculiarities of IORT technique and contribution to final results in special situations. The data regarding the experience at the University Clinic of Navarra is a 2009 update of the previously published Ewing's sarcoma and osteosarcoma results [14]. A new set of clinical information generated at the University Hospital Gregorio Marañón in the period 1995–2009 is reported involving Ewing's sarcoma, chondrosarcoma, and extracorporeal IORT.

Ewing's Sarcoma

Ewing's sarcoma is a malignant disease that requires multimodal treatment to obtain high cure rates [15]. Irradiation is an important component of the treatment of the primary lesion [16]. The reported rates of local control attributed to radiation therapy vary widely [17]. Tumor volume and the site of the primary tumor have been related to major differences in local tumor control. Thus, isolated local recurrences have been reported in 15% of patients with lesions of the extremities, in 47% with rib primaries, and in 69% with pelvic tumors [18]. The rate of local persistence/tumor recurrence, as evaluated by clinical and autopsy findings, was reported to be 35%, 25%, and 7% in patients treated with primary radiation therapy for central, proximal extremity, and distal extremity lesions, respectively [19]. Overall rates of local tumor control with radiotherapy are in the region of 90% for lesions less than 8 cm in maximum diameter, and 70% for those more than 8 cm in maximum diameter [20].

Surgical resection has attracted increasing interest in the management of Ewing's sarcoma. Several reports have described improvements in local control and survival with the addition of surgery [18, 21–23]. With reference to the clinical data available, it has to be noted that surgery in Ewing's sarcoma has been used in selected patients with positive prognostic factors, such as lesions of the extremities, small tumor volumes, and a good response to chemotherapy. The use of surgery in

the management of Ewing's sarcoma patients simultaneously provides an opportunity to consider the use of IORT as a radiation boost modality in areas of residual disease or at high risk for local recurrence. In a large (1,058 patients) prospective experience, local control was significantly improved by the use of surgery with or without pre- or postoperative radiotherapy compared to radical radiotherapy alone (local failure rates 7.5/5.3% vs. 26.3%, $p=0.001$). The analysis identified intralesional or marginal resection and poor histological response as risk factors in which radiotherapy improves local control. This seems an appropriate scenario for IORT exploration [24].

The conceptual advantages of the inclusion of IORT in the local treatment of Ewing's sarcoma include the accuracy with which the area at high risk for recurrence can be identified at the time of surgery, the ability to protect normal uninvolved tissues when lesions are located in central anatomic zones (pelvic bones, vertebra, etc.), and the possibility of reducing the total EBRT dose [25]. In the context of a randomized trial for combination chemotherapy comparisons, 75 patients with pelvic Ewing's sarcoma were analyzed in terms of local control outcomes after surgery alone ($n=12$), surgery and radiotherapy ($n=19$), or radical exclusive radiotherapy ($n=44$). The cumulative incidence of local failure was 21%, improved by the use of more intense chemotherapy (11% vs. 30%) and with equivalent control rates obtained by local treatment modalities [26].

HDR-IORT Experience, University Of Münster

Treatment Factors

In cooperation with the Department of Radiotherapy–Radiooncology and the Orthopedic Department of the University of Münster/Germany, the application of an HDR-IORT brachytherapy boost after preoperative radiochemotherapy was tested in patients, in whom the surgical margins proved to be close to the tumor. Generally, the brachytherapy applicators were introduced into flab applicators. In a few cases, intraosseous applicators were used. The flab applicator consisted of soft plastic material with a thickness of 1 cm. Parallel longitudinal channels penetrated the material at 1 cm distance from each other. In the channels, tubes were placed and the brachytherapy source could be introduced into these tubes. Different sizes of flab applicators were available depending on the extension of the tumor. Furthermore, the flab could be cut in the operating theater to the necessary size. Because of the flexibility of the material, it was possible to mould the applicator to the in situ structures. The fitting of the flab was done in the presence of the radiation oncologist and the surgeon (Fig. 19.1). In order

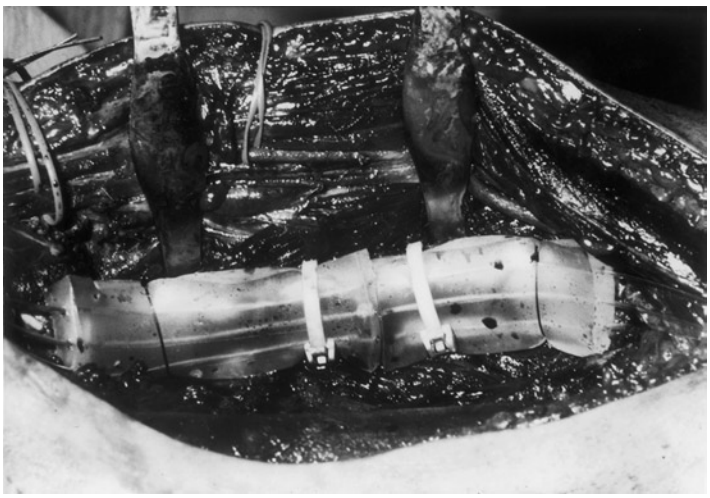

Fig. 19.1 Flab moulded to the high risk area in HDR-IORT procedures at the University of Münster.

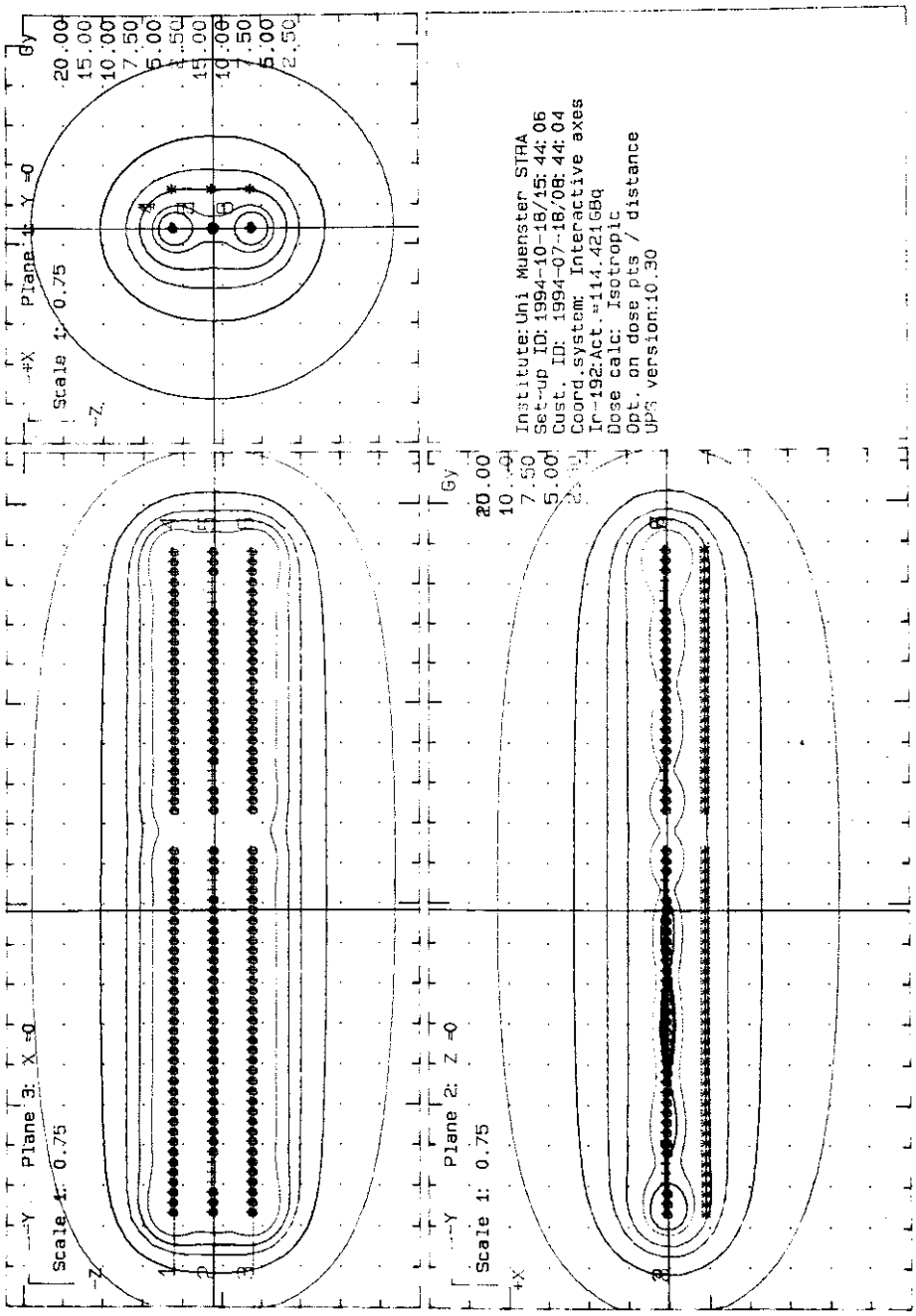

Fig. 19.2 Isodoses distribution with the inserted HDR-IORT brachytherapy applicators in a treatment procedure for a Ewing's sarcoma patient.

to avoid an overdose especially to nerves and vessels, they were distanced by ordinary cloth. No more than 10 Gy was allowed to these critical structures. After the flab had been positioned, the wound was provisionally closed. Perpendicular X-rays of the flab in situ were taken with markers in the tubes in order to identify the position of the applicators. The images were digitalized and the isodoses were calculated by the physicist (Fig. 19.2). For the radiation itself, the anesthetized patient was transported to the radiotherapy department. In general, 10 Gy was applied at a distance of 5 mm from the flab surface using an HDR-afterloading device. This was equivalent to a surface dose of about 20 Gy in unmoulded flabs. After the procedure, the patient was brought back to operating theater, the flab applicator was removed and the wound was closed.

Patient Group

From July 1992 to February 1995, twenty HDR-IORT brachytherapy boosts have been performed. The male to female ratio was 13 to 7. Four patients had tumors smaller than 100 ml, 16 patients had tumors larger than 100 ml. There were ten Ewing's sarcomas, five atypical Ewing's sarcomas, three PNET, and two extraosseous Ewing's sarcomas. Nine tumors were located in the pelvis, five in the femur, four in the humerus, one in the ulna, and one in the fibula. Six patients had initial metastases, one in the lung, three in the bone, and two with combined pulmonary and osseous manifestations. The tumor characteristics are summarized in Table 19.1. Eight patients received VAIA and 12 patients EVAIA chemotherapy. Two patients had an intralesional resection, five patients a marginal resection, and 13 patients a wide resection following the Enneking criteria [27]. The radiation doses applied ranged from 10 to 20 Gy with 16 patients receiving 10 Gy measured at 5 mm from the flab surface. The median follow-up of the patients was 24 months (range 14–46 months). The median operation time, including HDR-IORT, was 7 h 45 min (Min.: 5 h 45 min, max.: 10 h 35 min). On average, the brachytherapy procedure took 2 h 20 min (min.: 1 h 35 min, max.: 4 h 15 min). The median blood loss was 2,600 ml (min.: 200 ml, max.: 10,000 ml).

Table 19.1 Tumor and treatment characteristics of Ewing's sarcoma (ES) patients treated with HDR-IORT at the University of Münster (7/92 to 5/95)

Characteristics	#
Histology	
Ewing's sarcoma	10
Atypical ES	5
PNET	3
Extrasseous ES	2
Localization	
Pelvis	9
Humerus	4
Ulna	1
Femur	5
Tibia	1
Tumor volume	
<100 ml	4
>100 ml	16
Dose of HDR-IORT	
10 Gy	16
11 Gy	1
12 Gy	2
20 Gy	1

Table 19.2 Toxicity and complications observed with HDR-IORT in Ewing's sarcoma patients treated at the University of Münster (7/92 to 5/95)

Observations	#
Delayed wound healing	4
Wound infection	1
Hematoma	2
Thrombosis	1
Hemorrhagic cystitis	1
Edema	1
Abscess and proctitis	1
Paresis of the radial nerve	1

Results

There have been no intraoperative complications and postoperative complications have been observed in 40% of the patients (four cases of delayed wound healing, one wound infection, two hematomas, one thrombosis, one paresis of the radial nerve, one hemorrhagic cystitis, one case of edema, and one of proctitis and abscess; Table 19.2). Postoperative chemotherapy could be continued on average after 19 days (min.: 10 days, max.: 27 days). There have been three cases of surgical intervention due to complications: in two patients, a wound revision was performed; in one patient, an abscess was removed.

In an August 1996 analysis, 13 of 20 patients were in complete remission. Six patients had developed metastases and one patient had a combined local and systemic relapse.

Summary

The preliminary results show that an HDR-IORT boost in Ewing's sarcoma using the flab technique is a feasible method. There has been no event of an intraoperative complication due to the additional radiotherapy. In patients that have mostly large tumors with predominantly pelvic location, the complication rate of 40% is not increased when compared to patients that did not receive brachytherapy [28]. The early start of postoperative chemotherapy shows that the perioperative morbidity of the patients was not of major concern. So far local control is good with only one local failure combined with a systemic relapse.

Intraoperative high-dose rate brachytherapy in Ewing's sarcoma is a feasible method with a low perioperative complication rate. The operation time was longer in 20 patients treated by surgery and brachytherapy (7.9 h) compared to 40 patients treated with surgery alone (4.3 h, $p < 0.0001$). The average blood loss was comparable ($p = 0.3$), together with the surgical complication (30% vs. 31%) [29]. Especially in patients in whom limb preserving surgery is possible only with marrow resection margins, it offers the potential of increased local control. The follow-up in the present experience is too short to judge local control and the risks of accumulative late toxicity need to be evaluated in the future.

NCI IOERT Animal Data and Clinical Experiences

The use of IOERT for bone sarcomas has been reported in only a few series. At the National Cancer Institute (USA) IOERT was used in some patients with pelvic primary lesions including Ewing's sarcoma [30], but no conclusions can be drawn from this limited experience. Tolerance studies in normal tissue involving the use of surgery and IOERT alone or in combination with EBRT have suggested that the acceptable tolerated doses in peripheral nerves, muscle, large vessels, and bone are in the range of 15–20 Gy [31–36].

University of Navarra IOERT Clinical Series

Patient Group and Treatment Methods

At the University Clinic of Navarra from September 1984 to February 1996, 24 pediatric patients with Ewing's sarcoma have been treated with an IOERT component integrated in a multimodal program (Fig. 19.3). In patients with primary disease, preoperative, concurrent systemic chemotherapy, and EBRT were used. Alternating courses of two regimens were used, containing adriamycin, methotrexate, cyclophosphamide, actinomycin D, and vincristine (regimen 2), every 3 weeks. EBRT has been delivered to a volume encompassing the entire bone with a 3–5 cm margin beyond the known soft tissue extension. The total dose administered has been 45–50 Gy, 1.8–2 Gy per fraction, 5 fractions per week. Four to six weeks after the completion of preoperative EBRT, patients were considered for surgery and an IOERT boost (10–20 Gy) delivered to the residual tumor or tumor bed area. After surgery, alternating multiagent chemotherapy was maintained for 1 year according to the T_{11} protocol [37].

Patients with recurrent disease (four patients with local recurrence) received a reinduction course of systemic chemotherapy followed by maximal surgical resection plus a single IOERT dose of 20 Gy to the tumor bed. All patients had previously received a radical dose of EBRT. Systemic chemotherapy was given as adjuvant therapy for 1 year or until the development of disease progression.

In the group of patients with primary disease, there were three cases of protocol violation that have to be described in order to explain the types of toxicity later found. Two patients with large primary tumors in the lower extremities received a single dose of EBRT of 10 Gy the day before surgery (flash technique); the remaining EBRT was given postoperatively in a conventional program. One additional patient underwent surgical resection after 60 Gy of fractionated radical irradiation. Apart from these protocol violations, the primary disease group was consistently treated with moderate preoperative irradiation and IORT boost (10–15 Gy).

Patients characteristics showed: 16 male and 8 females, age ranging from 6 to 18 years old (median 12 years), patients were recurrent to previous therapy. Tumor characteristics are described in Table 19.3.

Fig. 19.3 General view of an IORT procedure for a femoral Ewing's sarcoma at the time of bone resection: 10 cm diameter applicator with a 15° beveled end; 9 MeV electron energy; 10 Gy total dose; one IORT field.

Results

The patterns of tumor progression revealed five combined local and systemic failures: 1 vertebral, 1 iliac, 1 rib and 2 humerus locations; 4 cases with a volumetric tumor size estimation over 300 cm^3: patients with recurrent disease to initial induction therapy. Three additional patients developed distant metastasis alone: one femur and one radius more than 300 cm^3 in size and one clavicle. Actuarial survival at 14 years is 63% for the entire group. There is a statistically significant relationship between risk of disease-relapse and initial tumor volumetry (>300 cm^3) ($p=0.04$).

Selective toxicity analysis for IOERT report of results purposes is focused on the description of local observations in the area of surgery and radiotherapy. Patients had several infectious and aplasia episodes as a result of the adjuvant chemotherapy program. In three patients, delayed wound healing and severe soft tissue necrosis were seen in the follow-up period. These three cases comprised the two treated with high-dose flash (10 Gy) preoperative radiotherapy and one additional case that was operated on after radical EBRT (60 Gy). Two had repair of their lesions with a myocutaneous flap. Two patients required amputation after the failure of conservative management.

Table 19.3 Tumor and treatment characteristics of Ewing's sarcoma pediatric patients treated at the University Clinic of Navarra with IOERT (Period 1984–2009)

	#	%
Sex		
Male	19	56
Female	15	44
Age		
Range: 2–30 years		
Median 15 years		
Follow-up		
Range: 5–288 months		
Median: 114 months		
Bone involved		
Femur	9	26.5
Tibia	8	23.5
Pelvis	3	8.8
Others	14	41.2
Response to neoadjuvant treatment		
Good (>90% necrosis)	24	72
Poor (≤90% necrosis)	10	28
Metastasis		
No	20	58.8
At diagnosis	14	41.2
EBRT		
Preoperative	27	79.4
Postoperative	2	5.9
Pre + postoperative	1	2.9
None	4	11.8
Total dose IORT (Gy)		
10	9	26
12.5	13	38
15	6	18
Undefined	6	18

IORT intraoperative irradiation, *EBRT* external beam irradiation

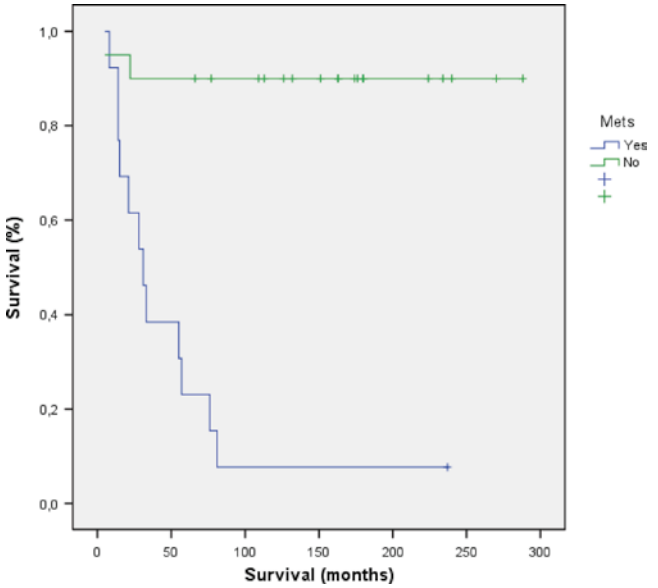

Fig. 19.4 Actuarial survival of Ewing's pediatric sarcoma patients treated with an IORT component at the University Clinic of Navarra (1984–2009): analysis by disease stage categories at diagnosis, localized versus metastatic ($p<0.0001$).

In seven patients, a minor to moderate degree of soft tissue fibrosis was evident during the follow-up period. Four developed a shortened extremity and one an articular retraction.

A 2009 update performed by Dr. Patiño and Dr. Sierrasesumaga of the experience identified 34 patients treated in the period 1984–2009, with a maximum follow-up time of 288 months. Patients and treatment characteristics are described in Table 19.3. Overall survival is 58% (Fig. 19.4) for the group, with significant differences by stage at diagnosis: 94% localized versus 5.9% metastatic.

Summary

An evaluation of the University Clinic of Navarra experience exploring IOERT in a pediatric radiosensitive tumor, such as Ewing's sarcoma confirms the preliminary observations that the local control and overall survival rates are encouraging, particularly in primary disease (OS, 94%) and actuarial disease free survival of 80% (median follow-up of 114 months). Surgery is now being considered more frequently in the overall management of this disease, and IOERT is an interesting modality that can be included in combined treatment programs [38]. The availability of IORT might decrease the total EBRT dose and enable a boost dose to be delivered to areas of residual disease or at high risk for local recurrence, with an accurate electron beam field. The complications observed in our initial series have been due to intensive local treatment. IOERT appears to be very attractive for the treatment of Ewing's sarcoma located in central bone (pelvis, vertebra, ribs, etc.), and it is already a well tested technique in lesions of the extremities.

University Hospital Gregorio Marañón (Madrid, Spain)

From 1995 to 2009 IORT was performed for selected indications in seven children or adolescents with Ewing's sarcoma who were candidates for surgical resection due to recurrent disease status or extensive initial primary disease volumetry. This has been an institutional protocol-based practice treated under the recommendations of major cooperative groups in pediatric oncology (SHIOP,

Table 19.4 IOERT Ewing's sarcoma experience at the University Hospital Gregorio Marañón (1995–2009)

Sex	Age	Stage	Rec	IOERT (Gy)	Site	EBRT	Follow-up	Status
Male	11 y	Disem	No	7.5	Tibia	25 Gy	CT 58m	NED
Male	15 y	Local	Yes	7.5+7.5	Rib	36 Gy (HFX)	CT 62 m	AWD (CR+D)
Male	15 y	Local	Yes	10	Iliac[a]	50 Gy	CT 37 m	DWD (LR+D)
Male	10 y	Local	Yes	10	Scapula	30 Gy	S+CT 17 m	DWD (LR+D)
Female	14 y	Local	No	10	Femur	NO	CT 13 m	NED
Female	16 y	Local	Yes	12	Scapula	45 Gy	167 m	NED
Male	16 y	Disem	Yes	10	Liver	NO	CT 13 m	AWD (D)

Rec Recurrent disease, *IOERT* intraoperative electron irradiation, *EBRT* external beam radiotherapy, *Disem* disseminated stage at diagnosis, *CT* chemotherapy, *NED* no evidence of disease, *S* surgery, *AWD* alive with disease, *DWD* dead with disease, *LR* local recurrence, *D* disseminated relapse

[a]Extracorporeal IOERT (bone resected)+IOERT (Tumor bed)

POG, etc.). Three of seven patients are long-term NED (13, 58, and 167 months), including initially metastatic (1 out of 2) and locally recurrent (1 out of 5, 2 more AWD 62 and 13 months after IOERT). The updated results (2009) are shown in Table 19.4.

Osteosarcoma

The treatment of osteosarcoma has changed dramatically in the past two decades [39]. Neoadjuvant and adjuvant chemotherapy have significantly increased both survival and tumor resectability rates [40, 41], and extremity preservation is an important goal of modern treatment [42]. Moreover, while osteosarcoma has historically been considered a "radioresistant" tumor type and there has been a lack of interest in exploring radiotherapy in the multidisciplinary approach to bone tumors [43]; in recent times, this treatment modality has been considered for the local treatment of osteosarcoma of the extremities [44].

In the era prior to adjuvant chemotherapy, the only alternative to amputation for the treatment of the primary lesion was local radiotherapy. The so-called *Cade technique* was an approach that delivered high-dose local EBRT to allow amputation to be delayed for 4–6 months while patients were observed to see whether pulmonary metastases would develop [45, 46, 47, 48]. In the modern practice of radiotherapy, the treatment modality has been reserved for lesions located in sites inaccessible to radical surgery [49, 50]. Several trials have explored the possible role of whole-lung irradiation as an adjuvant treatment for initially localized osteosarcomas [51, 52]. A systematic review does question its value due to the lack of studies using lung irradiation in addition to current standard chemotherapy regiments or in combination with metastectomy [53]. There have also been studies using high-dose preoperative EBRT and planned surgery [54], radical radiochemotherapy [55], and preoperative EBRT with local hyperthermic perfusion [56].

Kyoto University IOERT Series

Patient Group and Treatment Methods

The pioneering experience using IORT in osteosarcoma patients has been reported from Kyoto University [57]. Between 1978 and 1984, 21 patients with osteosarcoma received IOERT as a part of the treatment designed for their disease. Involved bones were femur – 12, tibia – 7, humerus – 1, and iliac – 1. The primary lesion was treated with IOERT alone in 11 cases while eight patients underwent prosthetic replacement 3 months after IOERT.

The IOERT technique was described as multifocal bilateral irradiation, using electron beams in the energy range of 6–12 MeV and delivering a total dose of 50–60 Gy to an area of the bone determined according to the CT findings. Skin and surrounding tissues were retracted to protect them from the radiation beam.

Results

Histologic changes were described in an initial report [58], and clinical results, published in a later update, showed several findings compatible with treatment efficacy, such as normalization of initially elevated serum alkaline phosphatase, a marked decrease in the uptake of contrast media in bone scintigrams, and complete necrosis of the tumor cells throughout the primary lesions that were resected and analyzed in serial histologic examinations. Two patients developed extensive skin necrosis apparently related to the surgical procedure.

The overall cumulative survival was 32%. This has improved since 1982 with the inclusion of chemotherapy in the treatment program; the estimated 5-year survival rate in ten patients treated with the new multidisciplinary program was 60% [59]. In the most recent update from this group, 2 out of 23 patients (9%) are reported to have developed a local recurrence, probably due to a marginal miss of the IORT fields. The most common complication has been fracture of the involved bone. The present recommendation for patients free of distant metastases 8–10 weeks after IOERT is reoperation for bone resection and prosthetic replacement [60].

In a 1993 update of the experience generated at Kyoto University [61], 17 patients treated with preoperative chemotherapy (Cisplatin and Doxorubicin) had a 5-year cumulative survival of 78% and no local recurrences (the IORT dose range delivered to the exposed bone was reported as 50–100 Gy).

The last institutional update available from 2001 reports the results in 39 patients with osteosarcomas of the extremities [62]. The IORT dose ranged from 45 to 80 Gy (electrons or photons). There were nine local progressions (4–29 months after IORT). No skin or peripheral nerve toxicity was observed (both structures were excluded from the IORT field). Cause-specific and relapse free survival at 5 years were 50% and 43%, respectively.

IOERT Experience: University Clinic of Navarra (1985–2009)

Treatment Methods

In the present experience, IOERT is used as a treatment component to boost the tumor bed area and surrounding tissues following bone resection. Moderate to high single doses of electrons were expected to sterilize residual osteosarcoma cells after surgical en bloc tumor resection. In addition, neoadjuvant chemotherapy was employed, since this induces even higher tumor necrosis rates (Fig. 19.5). On the other hand, it was elected to omit EBRT in those patients in whom metallic prosthetic devices would have been included in the field. This is the only instance in the IOERT program at the University Clinic of Navarra in which IOERT was not complemented by EBRT.
The treatment protocol was uniform in the patients reviewed. Once osteosarcoma was confirmed histologically, patients were entered in a treatment program comprising three major components:

Neoadjuvant chemotherapy: Three preoperative courses of neoadjuvant chemotherapy were given, commencing at 3-week intervals. Using the transfemoral Seldinger approach, cisplatin 40 mg/m^2 was administered intra-arterially on days 1, 3, and 5 of each cycle. On day 5 of each cycle doxorubicin 60 mg/m^2 i.v. was added to the program.

Surgery: Following the three neoadjuvant courses of chemotherapy, patients were considered for surgical en bloc tumor resection. The general aims of surgery were to remove all the involved bone and a margin of normal surrounding tissues if possible. Functional reconstruction of the extremity was done on an individual basis using endoprosthetic devices or bone graft. Before the reconstruction, the patient received IOERT to the tumor bed area, using a single dose in the range of 10–20 Gy. The electron beam energy selected was based on the thickness of tumor tissue left after surgery.

Systemic adjuvant chemotherapy: Three weeks after surgery, intensive adjuvant systemic chemotherapy was initiated using the following regime of cytostatic agents: cisplatin 120 mg/m^2 and doxorubicin 60 mg/m^2 in weeks 1, 5, 15, 25, 33, and 45; high-dose methotrexate 8 g/m^2 with folinic acid rescue in weeks 3, 4, 8, 9 13, 14, 18, 19 23, 24, 28, and 29; bleomycin 30 mg/m^2, cyclophosphamide 1,200 mg/m^2, vincristine 1.5 mg/m^2, and actinomycin D 1.2 mg/m^2 in weeks 10, 12, 36, 42, and 48.

External beam radiotherapy was not routinely used in this treatment program. Occasionally, patients with recurrent and/or macroscopic residual after maximal resection received additional fractionated EBRT.

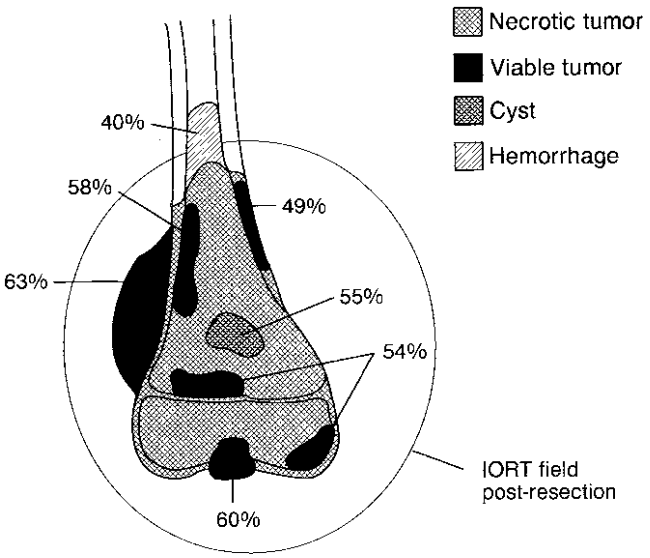

Fig. 19.5 Osteosarcoma of distal femur treated with neoadjuvant chemotherapy with diagram of pathologic findings following induction chemotherapy and definition of IORT target volume to include the soft tissues around the tumor.

Results

A recent update (2009) was performed by Patiño and Sierrasesumaga. In a 25-year follow-up period, 45 patients with osteosarcoma were treated with an IOERT treatment component (seven metastatic patients in CR following thoracotomy). Patients, tumor and treatment characteristics are described in Table 19.5: most frequent histological subtype was osteoblastic (65%) and close to half of patients had femur locations.

Actuarial survival rate projected to 25 years is 57% at maximum follow-up of 228 months (Fig. 19.6). Significant differences in survival are observed in nonmetastatic, initially metastatic but rescued and metastatic patients at follow-up. There has been observed six local recurrences (four in chondroblastic subtypes, $p = 0.0102$) (Table 19.6).

Toxicity and complications observed in these patients are related to surgical manipulation and adaptation of the anatomy to prosthetic devises. The contribution of IOERT to late normal tissue sequelae is not well established due to the multifactorial treatment-related tissue damage. In the literature reviewed, asymmetry (45%), graft necrosis (4%), graft fracture (15%), local infection (22%), and pseudoarthrosis (15%) have been complications observed in the follow-up period. A specific analysis of long-term normal tissue toxicity after IORT, including 195 patients alive more than 5 years after IORT identified bone sarcomas as the disease category with higher toxicity scores (60% grade 3–4) with BED estimations of 100.5 Gy [63]. An anecdotical case of skin "re-call" phenomenon during adjuvant high-dose methotrexate is illustrated in Fig. 19.7.

Summary

The goal of osteosarcoma treatment today is not only systemic disease control but also extremity preservation. In this context, the addition of IORT might improve local control rates as it has been achieved in extremity soft tissue sarcomas with conventional external irradiation [64–66]. EBRT might be more hazardous in osteosarcoma patients who have undergone resection because of the interaction of the radiation with metallic prosthetic reconstructive devices and the intensive chemotherapy programs

Table 19.5 Osteosarcoma characteristics in the IOERT experience at the University Clinic of Navarra (1985–2009)

	#	%
Sex		
Male	23	51.1
Female	22	48.9
Age		
Range: 5–19 years		
Median 15 years		
Bone involved		
Femur	20	44.4
Tibia	19	42.2
Humerus	5	11.1
Rib	1	2.2
Bone site		
Proximal	20	46.5
Medial	2	4.7
Distal	21	48.8
Histological subtype		
Osteoblastic	29	64.4
Chondroblastic	8	17.8
Other (telg, fibro, small c)	8	17.8
Response to neoadjuvant treatment		
Good (>90% necrosis)	24	53.3
Poor (≤90% necrosis)	21	46.7
Metastasis		
Never	19	42.2
At diagnosis	7	15.6
At follow-up	19	42.2
Follow-up		
Range: 3–290 months		
Median: 177 months		

required to cure these patients. As with soft tissue sarcomas, the tolerance of peripheral nerves to single high doses of electron irradiation is an important and still open question for radiobiology modulation.

IOERT Tolerance

The normal tissues at risk of receiving high to moderate single doses of IOERT for postresected osteosarcoma of the extremities are muscles, peripheral nerves, ligaments, and skin. Occasionally, structures such as cartilage and bone would be included in the IOERT field. These normal tissues have been extensively investigated to define their tolerance to escalating doses of IOERT alone or in combination with fractionated EBRT. In the case of osteosarcoma patients, the treatment program at the University Clinic of Navarra and Kyoto University did not include the addition of EBRT. The changes in normal tissues described in muscles, peripheral nerves, and bone following a 15–20 Gy single dose of IOERT alone are compatible with acceptable tolerance, although neurologic damage has been observed in a certain proportion of animals after 20 Gy [31, 33–36]. This dose by extrapolation is considered the upper dose limit in IORT trials in which nerves are included in the field.

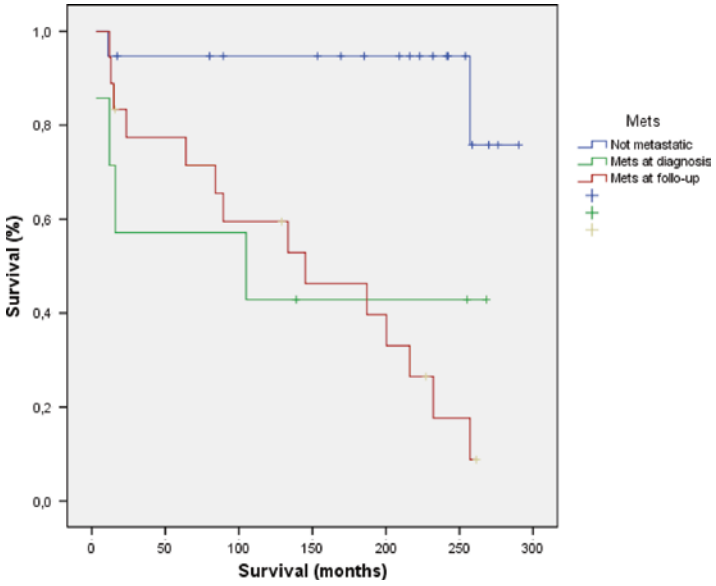

Fig. 19.6 Overall survival in Osteosarcoma patients treated with a component of IORT at the University Clinic of Navarra (1985–2009): categories of nonmetastatic, metastatic at diagnosis and metastatic at follow-up.

Table 19.6 Patterns of osteosarcoma relapse at the University Clinic of Navarra (1985–2009)

Histological subtype	#	Local alone	Local + distant	Distant alone
Chondroblastic	9	–	4 (44%)	3 (33%)
No Chondroblastic	36	–	2 (5%)	7 (20%)
Total	44	–	6 (13%)	10 (22%)

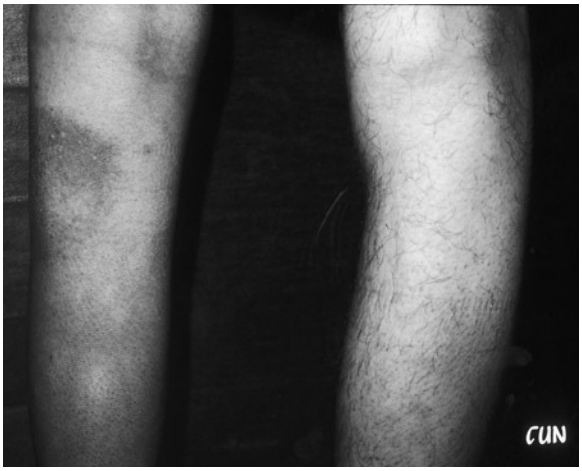

Fig. 19.7 "Re-call" phenomenon during adjuvant high-dose methotrexate in an osteosarcoma patient. Notice the circular skin erythema in the external region of the left leg, defining the IOERT beam exit site.

Malignant Fibrous Histiocytoma

MFH represents 0.7% of all malignant primary bone tumors, of relatively recent description, with a particular tendency to develop extraosseous tumor extension [67]. Extremity preserving yet radical surgical approaches have been recommended selectively for cases shown to have oncologic safe tissue margins on the preoperative imaging evaluation [68]. Transient remission of lung metastases have been reported with chemotherapy [69] and its role has been suggested to contribute to improved survival both in patients treated with amputation or conservative surgery [70]. IOERT has been used as definitive treatment in combination with surgical excision [71].

University of Navarra IOERT Series

Treatment Methods

The results of the experience at the University Clinic of Navarra with intense multidisciplinary therapy, including IOERT after resection are described in Table 19.7 (Fig. 19.8) [72]. Nine patients with bone MFH were treated with neoadjuvant chemotherapy (CDDP 40 mg/m^2 day 1, 3 and 5 of each induction week); and Doxorubicin (20 mg/m^2 i.v. days 2, 4, and 6 of each induction week; treatment was repeated every 21 days to a total of 3 cycles), surgical resection (with preservation of the extremity) plus an IOERT boost (10–20 Gy), followed by fractionated EBRT (40–50 Gy) and adjuvant chemotherapy (CYVADIC 6 cycles). Initial tumor size was >10 cm maximum diameter in four cases. Cortical bone was ruptured in all cases with radiological evidence of soft tissue involvement. Bone fracture was a presenting sign of disease in four patients. Pathologic positive margins in the resected specimen were identified in two cases.

A single IOERT field was used in eight procedures. The electron energy selected was 12 MeV or less in eight. Applicator size was 6–7 cm in three and 8–10 cm in six.

Table 19.7 IOERT experience description and results in MFH of bone at the University Clinic of Navarra (1984–1991)

Case	Site	IOERT dose	EBRT dose	Neuropathy	Status	Follow-up
1	Femur	10 Gy	50 Gy	Yes	NED	15+
2	Humerus	20 Gy[a]	50 Gy	Yes	DWD	37
3	Femur	20 Gy[b]	46 Gy	No	NED	50+
4	Ischium	15 Gy[a]	45 Gy	No	DWD	8
5	Femur	15 Gy[b]	40 Gy	No	NED	43+
6	Iliac	10 Gy 10 Gy	45 Gy	No	DWD	10
7	Femur	10 Gy	46 Gy	No	NED	2+
8	Femur	15 Gy[b]	60 Gy[c]	No	NED	49+
9	Femur	15 Gy[b]	38 Gy	Yes	NED	18+

NED alive with no evidence of disease, *DWD* dead with disease
Follow-up: months since IOERT
[a]Neuro-vascular structures protected or mobilized
[b]Neuro-vascular structures included in the IORT field
[c]Previous radiotherapy

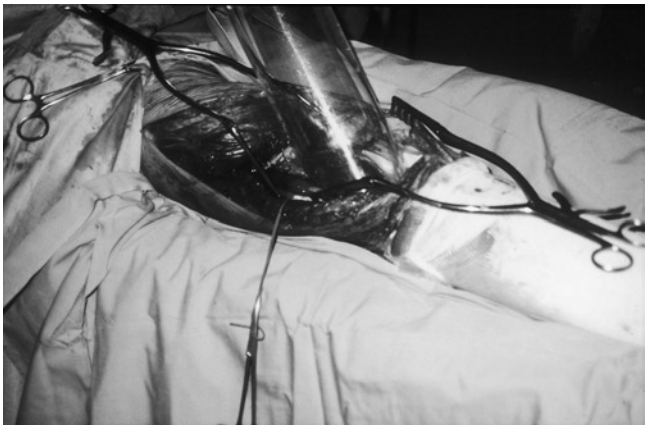

Fig. 19.8 IORT for femoral malignant fibrous histiocytoma after bone and soft tissues resection. Notice that the nerve have been dissected and mobilized out of the electron field (7 cm diameter applicator; 30° beveled end; 9 MeV electron energy; 15 Gy total dose).

Results

The median follow-up time at publication was 19+ months (range 20+ to 50+ months). One local and systemic progression had been observed in an iliac partially resected patient 8 months after surgery. Actuarial survival is projected as 63% at 5 years. Three patients developed symptomatic neuropathy, one of whom has a permanent motor and sensory deficit.

Chondrosarcoma

Chondrosarcoma is considered a radioresistant bone tumor able to be controlled by surgery only if radical margins are able to be achieved [1, 5, 11]. In the IORT literature, there are reports of results with this histological subtype [60, 73], including a long-term surviving patient after internal hemipelvectomy [74].

Kyoto University

Up to 1991, three chondrosarcoma patients were treated with "radical" IOERT (50–100 Gy). No local recurrence had been observed at the time of publication [60].

University Clinic of Navarra

In the experience up to December 1990, three cases of chondrosarcoma were treated with surgery plus IOERT and EBRT. Table 19.8 describes characteristics and results. The information should be interpreted as anecdotal, but of relative value for patients with tumor rupture of the bone cortex, candidates with extremity preserving procedures with close surgical margins or unresectable lesions for cure.

Table 19.8 IOERT case report description in chondrosarcoma patients treated at the University Clinic of Navarra (1984–1992)

Case	Site	IOERT dose	EBRT dose	Neuropathy	Status	Follow-up
1	Sacrum	20 Gy[a]	50 Gy	Yes	NED	72[c]
2	Tibia	15 Gy[b]	50 Gy	Yes	NED	49[c]
3	Femur	10 Gy	50 Gy	No	NED	20[c]
		10 Gy				

NED alive with no evidence of disease
Follow-up: Months from IOERT procedures
[a]Neuro-vascular structure protected or displaced
[b]Neuro-vascular structure included in the IOERT field
[c]Previous radiotherapy

Table 19.9 IOERT chondrosarcoma experience (1995–2009) at the University Hospital Gregorio Marañón

Sex	Age	Stage	IOERT (Gy)	Site	EBRT	Rec	Follow-up	Status
Female	30 y	T2b (Primary)	12.5	Pubis	45 Gy	No	53 m	NED
Female	30 y	T2b (Primary)	10	Gluteus	45 Gy	No	115 m	NED
Male	57 y	T1b (Recurrent)	10	Supraclavicular	No	Yes (LR + D)	21 m	DWD
Male	67 y	T2b (Primary)	12.5	Inguinocrural	No	No	37 m	NED
Male	72 y	T1b (Recurrent)	12.5	Inguinocrural	46 Gy	Yes (D)	103 m	AWD (lung)

Rec recurrence, *IOERT* intraoperative electron irradiation, *EBRT* external beam irradiation, *NED* no evidence of disease, *AWD* alive with disease, *DWD* dead with disease, *LR* local recurrence, *D* disseminated recurrence

University Hospital Gregorio Marañón (Madrid, Spain)

From 1995 to 2009, IOERT has been used as a boost technique in resected chondrosarcoma patients with high risk for relapse or involved resection margins not amenable to radical surgery with free margins. Five patients with pubic, gluteous (sacroiliac), supraclavicular, and inguinocrural locations were treated with IORT (10–12.5 Gy) and additional EBRT (3 patients). Four patients are alive (follow-up range 37–115 months and 3 are NED; Table 19.9).

Extracorporeal Intraoperative Radiotherapy

Several reports have described in animals the feasibility of delivering a high-massive single dose of radiotherapy to bone sarcomas after they were resected and extracted from the animal body and reimplanted in the original anatomic area, generally in the extremities for a limb-sparing policy [75]. Limb function was judged good or excellent in 10/13 dogs after dose of 70 Gy single fraction. Fractures and infection were complications observed. Three tumors recurred locally [76].

Experiences in humans have reported feasibility in the treatment of osteosarcomas [77], Ewing's sarcomas [78, 79] and miscellaneous histologies, including MFH and adamantimomas [12, 13]. Complications in the surgical area (infection) and occasional recurrences were reported in this small pilot experience. Figure 19.9 describes an extracorporal IORT procedure performed at the University Hospital Gregorio Marañón.

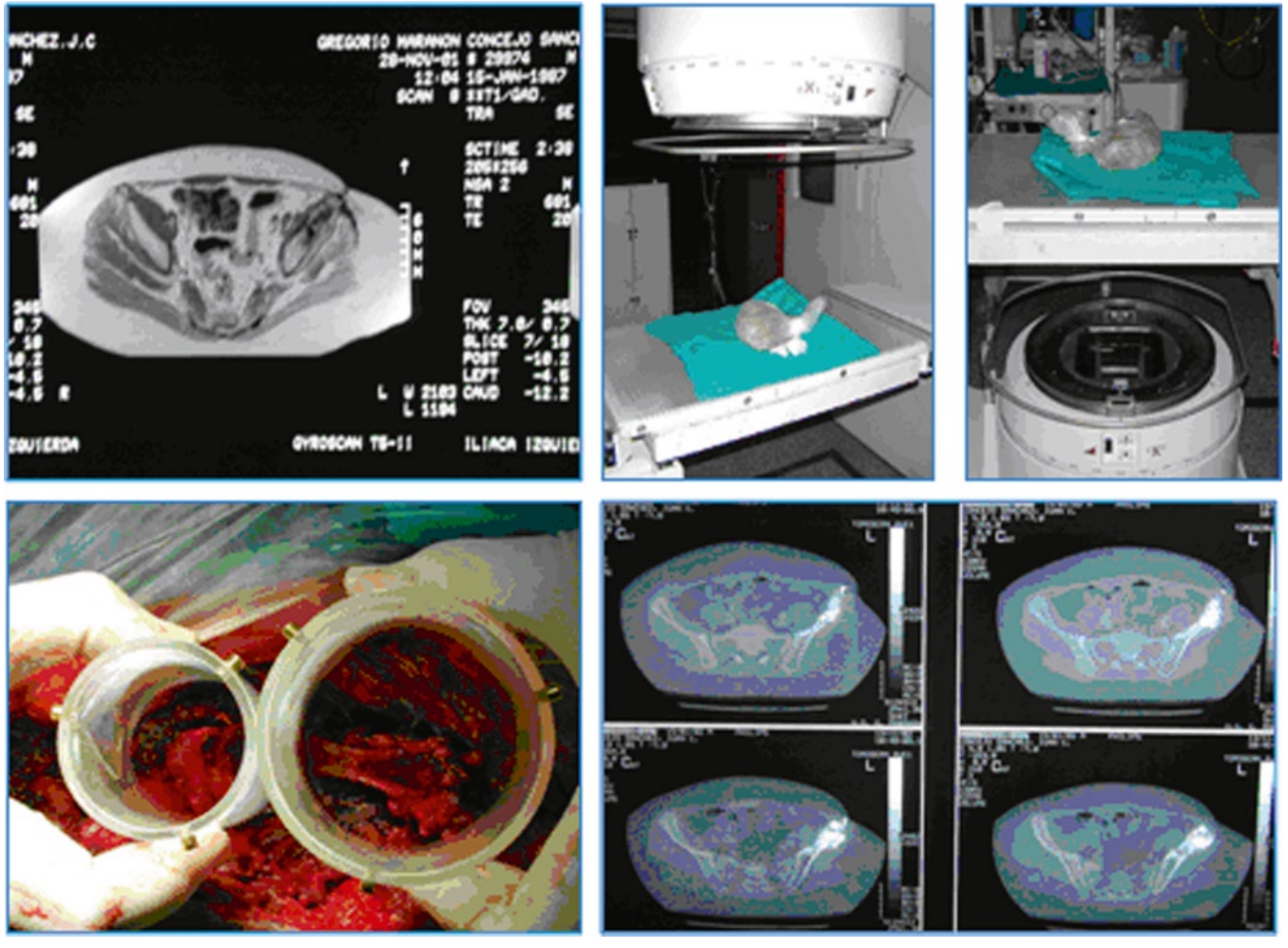

Fig. 19.9 Extracorporeal IOERT procedure in an Ewing's sarcoma patient involving the iliac bone. (**a**) Primary lesion after induction chemotherapy; (**b**) Extracorporeal resected bone irradiation; (**c**) IOERT fields treating the surgical resection margins; (**d**) reconstruction after bone reimplantation in the follow-up (University Hospital Gregorio Marañón).

Conclusions and Future Possibilities

Bone sarcoma patients require an optimized combination of surgery and radiation therapy to maximize local control. In pediatric bone sarcoma patients, the combination of IOERT and EBRT seems to reduce the risk of local recurrence after incomplete resection: 1 local recurrence in 18 children treated at the University of Heidelberg (60.5 months median follow-up) [80]. This clinical model (≥R1 resection + pediatric patients) allows investigators to explore both the sustainability of the local effects after IORT-guided dose-escalation in terms of sarcoma control and normal tissue toxicity risk, due to the long-term follow-up availability of this group of patients and the particular normal tissue sensitivity in developmental ages. Clinically significant late morbidity was observed, including neuropathy, ureteral stenosis, kidney hypotrophy, and soft tissue necrosis [81]. Advanced-technology is available for individualized treatment and research initiatives, including IMRT, protons, IORT brachytherapy, and electrons [82]. Radiation tolerance in pediatric sarcoma patients is of concern regardless of the type of precise radiotherapy technique employed [63, 83]. Emerging options, such as extracorporeal IORT, are developmental techniques to be explored. Systemic treatment is a priority part of treatment in bone sarcoma histologies with a dominant metastatic pattern.

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Chapter 20
Gynecologic Malignancies

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Keywords Gynecologic (gyn) cancer • Cervix cancer • Ovarian cancer • IORT for gyn cancer

Introduction

The prognosis for women with locally advanced gynecologic tumors with direct tumor extension to pelvic sidewall structures or gross lymphatic spread to pelvic or para-aortic nodes is poor. Although high-dose external-beam radiation (EBRT) with or without brachytherapy is often utilized to treat primary locally advanced malignancies with some success, aggressive local therapy is often not considered in patients with locally advanced recurrent disease in whom standard radiation or surgical therapy has failed. This chapter summarizes the results of standard therapy for locally advanced gynecologic malignancies and presents data from series of patients treated with IORT containing regimens. The future potential of IORT in the management of locally advanced gynecologic malignancies is discussed.

Results with Non-IORT Treatment Approaches

Primary Gynecologic Malignancies

Management of the Primary Cervix Tumor

Patients with early cervical cancer that has not spread beyond the cervix (stage I) or upper vagina (IIA) may be effectively treated with either radical hysterectomy or EBRT + brachytherapy with

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_20,

5-year overall survival (OS) rates ≥90% with either approach. A randomized trial by Landoni et al. demonstrated that definitive radiation was equivalent, in terms of disease free survival (DFS) and OS, to radical hysterectomy in patients with stage IB-IIA cervical cancer [1]. Tumor extension into the lateral parametrial tissue precludes a curative attempt with surgical resection alone; standard therapy is EBRT + brachytherapy. Because of the relatively high normal-tissue-radiation tolerances of the upper vagina, cervix, and uterus, very high central-tumor doses may be safely delivered with intracavitary brachytherapy. EBRT + brachytherapy is highly effective for cervical carcinomas that have not spread to the pelvic sidewall with 5-year tumor control rates >90% for stage I cancers and 75–90% for stage II cancers [2]. However, when the tumor extends beyond the zone of high-dose irradiation achievable with intracavitary brachytherapy, the minimum tumor dose becomes a function of the maximum EBRT dose and tumor control rates fall [3]. Five-year pelvic control rates for patients with involvement of the pelvic sidewall (stage III) treated with EBRT + brachytherapy range from 50 to 65% in most series; the corresponding 5-year control rates for those with bladder or rectum invasion (stage IVA) are in the 25–35% range [2].

A number of strategies have been explored to attempt to improve tumor control rates in stage III patients including altered fractionation schemes, concomitant radiation and chemotherapy, hypoxic cell sensitization, and neoadjuvant chemotherapy followed by radiation or surgery. A summary of survival and pelvic control rates in stage III cervical cancer treated with EBRT + brachytherapy ± chemotherapy is presented in Table 20.1.

The addition of concurrent cisplatin-based chemotherapy has resulted in significant improvements in survival ± disease control when compared to that achievable with radiation therapy alone for patients with locally advanced disease (stages IIB-IVA). The superiority of concurrent chemoradiation over radiation alone was demonstrated in an RTOG randomized trial reported by Morris et al.

Table 20.1 Survival and pelvic control in stage III cervical carcinoma: external-beam radiation ± chemotherapy

				Overall survival	Disease-free survival	Pelvic control
Series	Ref. no.	No. Pts	Chemotherapy	5 yr (%)	5 yr (%)	5 yr (%)
Fyles, PMH	[108]	329	None	–	41	–
Komaki, 1978 POC	[109]	115	None	39	33	49
1983 POC		24	None	47	39	69
Petereit, Wisconsin	[110]	61	None	46	–	63
Teshima, Osaka	[111]	82	None	45	–	54
Mitsuhashi, Gunma	[112]	148	None	52	–	86
Ito, Keio U.	[113]	366	None	47	–	68
Patel, India	[114]	114	None	50	–	76
Montana, Duke	[115]	107	None	–	36	55
Perez, Wash. U.	[9]	259	None	–	40	61
Jones, ACS	[116]	630	None in 92%	38	–	–
Horiot, France	[117]	482	None	50	–	57
Souhami, Brazil	[67]	52	None	39	–	46
		39	Neoadjuv BOMP	23	–	50
Brunet, Barcelona	[118]	31	Neoadjuv BMP	49	47	–
Benedett-Panici, Rome	[119]	70	Neoadjuv CDDP, bleo[a]	49	–	–
Pras, Groningen	[120]	18	Conc. CBDCA, 5-FU	47	–	–
Fields, Einstein	[121]	28	Conc. CDDP	67[b]	67[b]	77[b]
Stehman, GOG	[122]	53	Conc. hydroxyurea	47	48	–
Thomas, PMH	[123]	89	Conc. 5-FU ± mito C	43 (3-yr)	–	52 (3-yr)

conc concurrent, *CBDCA* carboplatinum, *5-FU* 5-fluorouracil, *CDDP* cisplatinum, *mito C* mitomycin C, *BMP* bleomycin, methotrexate, cisplatinum, *BOMP* bleomycin, vincristine, mitomycin, cisplatinum

[a]Chemotherapy followed by surgery or radiation therapy

[b]Crude survival and disease control

In it, a total of 403 patients with stage IIB-IVA or stage IB or IIA cancer (tumors > 5 cm or positive pelvic lymph nodes) were randomized to definitive RT or chemoradiation. The dose of external-beam radiation (EBRT) was 45 Gy in both arms, but the volume of RT differed; it was limited to the pelvis in the chemoradiation arm but included the para-aortic region as well in the RT alone arm. Both arms included low-dose-rate intracavitary brachytherapy to 40 Gy given in 1 or 2 insertions. The chemotherapy included CDDP (75 mg/m^2 on days 1, 22, and 43), and 5-FU (5-Fluorouracil) (1,000 mg/m^2/day as a 96-h infusion each cycle) for three cycles. Patients in the chemoradiation arm had significantly better rates of locoregional control, distant control, DFS and OS [4]. Rose et al. reported the results of a GOG randomized trial comparing three different chemotherapy regimens with definitive RT for patients with stage IIB-IVA cervical cancer. These include the following: hydroxyurea (3 g/m^2 twice weekly), CDDP (40 mg/m^2/weekly × 6 weeks), or CDDP/5-FU/hydroxyurea (CDDP 50 mg/m^2 on days 1 and 29 with 5-FU as a 1,000 mg/m^2/day continuous infusion over 96 h and hydroxyurea 2 g/m^2 twice weekly for 6 weeks). With a median follow-up of 35 months, both cisplatinum-containing regimens were significantly more effective than treatment with hydroxyurea alone ($P < 0.001$). The relative risk of progression and death were also reduced, compared with hydroxyurea with radiation alone (0.57 for CDDP, 0.55 for combination chemotherapy). In the two cisplatinum-containing arms, the toxicity was less for the weekly cisplatinum arm [5]. Whitney et al. reported on another GOG randomized trial comparing 5-FU plus CDDP versus hydroxyurea in addition to definitive RT [6]. Both progression-free survival (PFS) and OS were improved with CDDP/5-FU ($P = 0.033$ and $P = 0.018$, respectively). These three randomized trials established the role of concurrent chemoradiation as the standard of care for patients with locally advanced cervical cancer in USA, and due to a low-toxicity profile and ease of administration, weekly cisplatinum (40 mg/m^2 × 6) became the preferred treatment regimen. Interestingly, the benefit of chemoradiation over RT alone still exists in patients with stage III-IVA, but the magnitude of difference was less than that seen for stage II disease, indicating that more work is still needed in this group of patients [7].

Retrospective studies have suggested a radiation dose response for pelvic control in patients with stage III cervical cancer. Perez et al. [8] reported improved pelvic control rates with point A doses (combined brachytherapy and EBRT) > 60 Gy (38% pelvic recurrence vs. 72%, $p \leq 0.01$) and pelvic sidewall doses > 40 Gy (39% pelvic recurrence vs. 71%, $p \leq 0.01$). In another Washington University analysis [9], the pelvic failure rates were 58% for point A doses ≤ 60 Gy, 43% for 60–75 Gy, and 32% for 75–90 Gy. Pelvic failure rates in this series were also correlated with pelvic sidewall doses: 65% local failure in stage III patients who received ≤45 Gy to the sidewall vs. 35% for >45 Gy [9]. Other investigators have reported similar results. Chism et al. [10] reported pelvic failure rates for stage III cervical cancer of 80% for <60 Gy, 63% for 60–80 Gy, and 50% for >80 Gy total point A doses. Hanks [11] reported the results of a national practice patterns of care survey (PCS), which showed improved pelvic control rates in patients who received PCS paracentral point doses greater than the PCS lower limit (75 Gy for stage IIIB disease).

The use of higher radiation doses to improve tumor control rates results in an increase in severe complications. Kottmeier and Gray reported improved survival with higher radiation doses in women with locally advanced cervical cancer at a cost of increased severe bladder and rectal complications [12]. In the 1973 PCS survey of five major centers, Hanks reported severe complications (required hospitalization) in 15% of all women and 26% of survivors with stage III cervix cancer. An increase in major complications was noted in patients who received >85 Gy to the PCS paracentral point and >45 Gy to the pelvic sidewall [11]. Other investigators have reported similar results. Perez has reported increased small bowel complications in patients who received >50 Gy to the pelvic sidewall [8, 13].

The likelihood of severe complications has been associated with the EBRT dose in several retrospective reports. Hanks reported that for a given dose, EBRT was more likely to produce complications than brachytherapy [11]. Nearly all the severe complications reported in the series of Unal et al. [14] occurred in patients who received >35 Gy EBRT in addition to brachytherapy. In another

report from MD Anderson, Hamberger et al. [15] analyzed complication rates in patients with locoregional control of disease as a function of the whole-pelvis EBRT dose: severe complications were seen in 3% with 40 Gy, 11% with 50 Gy, and 20% with 60 Gy.

Summary and Future Possibilities

The minimum tumor dose in cervix cancer patients with pelvic sidewall extension is largely a function of the whole-pelvis or split-pelvis EBRT dose as the radiation dose to the pelvic sidewall from intracavitary brachytherapy is minimal. It is likely that currently utilized EBRT and brachytherapy doses are at or near maximum tolerated levels. Given the sharp increase in complications seen as EBRT doses are escalated above the 45–50 Gy range, increasing the EBRT dose above 45–50 Gy to improve the poor local/regional control rates in stage III patients is not advisable.

Preoperative EBRT plus concomitant cisplatin-based chemotherapy followed by surgical resection and pelvic sidewall IORT is a potential management strategy that may result in increased effective pelvic sidewall doses and tumor control without excessive toxicity. This strategy has not been fully explored.

Management of Nodal Disease in Primary Cervix Cancers

Standard therapy for patients with metastases to pelvic or para-aortic nodes is EBRT to the pelvis ± para-aortic node regions. Potish [16] reported on the results of surgical staging followed by extended field EBRT in patients with involved pelvic or para-aortic lymph-node metastases. Relapse-free survival (RFS) was 57% in women with grossly involved but resectable pelvic nodes and 0% in women with unresectable pelvic nodes. Pelvic failure was noted in 20% of those with resected grossly positive nodes and 56% of those with unresectable pelvic nodes. Because of adjacent bowel, the dose that may be safely delivered to pelvic nodes is in the range of 50–60 Gy [16]. Although doses in this range may control microscopic nodal metastases in about 90% of cases, the control rate for grossly involved nodes would be expected to be less than 50% [17].

In a multivariate analysis of prognostic variables in patients with cervix cancer treated on Gynecologic Oncology Group protocols, nodal status was the most significant variable associated with tumor relapse; patients with involved para-aortic nodes had the worst prognosis [18]. Microscopic or limited-volume macroscopic para-aortic nodal metastases can be controlled with tolerable EBRT doses. Komaki [19] treated 15 patients with microscopic or limited-volume macroscopic para-aortic nodal metastases with 40–58 Gy (median 50 Gy) EBRT. Control of para-aortic disease was obtained in 11/15 (73%), the small-bowel obstruction rate was 14%, and actuarial 3- and 5-year DFS were 60% and 40%, respectively. Others have reported long-term survival in 25–50% of patients with positive para-aortic nodes (usually microscopic or limited volume macroscopic disease) using doses of 45–51 Gy [20–22].

Doses necessary to control macroscopic para-aortic nodal metastases exceeds small-bowel tolerance doses. Para-aortic EBRT doses up to 45 Gy are well tolerated in patients who are not surgically staged, but severe small-bowel complications occur in as many as 14% of patients who receive doses of 50–55 Gy without surgical staging and 19% of patients who receive 43–55 Gy with surgical staging [23]. Piver et al. [24] treated a total of 31 women with para-aortic metastases; intestinal complications were seen in 62% of those who received 60 Gy compared to 10% of those who received 44–50 Gy. A total of 16% of the women in this series died of complications of radiation without evidence of disease relapse. Wharton [25] also reported a fatal intestinal complication rate of 14% in a group of surgically staged patients who received extended field doses of 55 Gy if they were found to have positive nodes. Despite the relatively high EBRT doses, only 10% were alive without evidence of disease at 5 years (all survivors had microscopic nodal disease at the time of EBRT), and on postmortem examination 9/14 (64%) had recurrent disease in the para-aortic region [24].

Primary Endometrial Cancer

Unlike cervical cancer, the majority of patients with endometrial cancer present with early-stage disease, and the primary treatment is often surgery rather than definitive radiation. The role of RT is mainly adjuvant, and for most patients with early stage, it consists of intravaginal brachytherapy [26].

Although endometrial cancer is commonly confined to the uterus at diagnosis, clinically detectable extension beyond the uterus is present in 5–10% of cases [27]. In patients with tumor extension to the pelvic sidewall who are unresectable for cure, survival is poor, and EBRT + intrauterine brachytherapy is associated with a high rate of pelvic failure. Danoff [27] treated 19 patients with clinical evidence of extrauterine tumor extension confined to the pelvis with EBRT ± brachytherapy; the 5-year OS was 12%, and 37% suffered local relapse. There were no 5-year survivors among the group of patients with extension of tumor to the pelvic sidewall [27]. Others have also reported poor results in patients with macroscopic extra-adnexal spread [28, 29] and/or tumor extension to the pelvic sidewall [30]. Pelvic recurrence or persistence of disease has been reported in 90% of women with clinical stage III endometrial cancer after treatment with EBRT + brachytherapy [30, 31]. Local failure occurs in 30–40% of patients with clinical stage III endometrial cancer treated with surgical resection and adjuvant radiotherapy [29, 31].

As is the case with cervical cancer, microscopic or limited-volume macroscopic nodal metastases from endometrial adenocarcinoma may be controlled with tolerable doses of EBRT, but the EBRT doses necessary to control gross adenopathy exceed normal-tissue tolerance. Komaki [19] treated seven patients with para-aortic nodal metastases (microscopic or limited volume) with 40–58 Gy and achieved local control in the para-aortic nodes in 6/7 (87%); the 3- and 5-year DFS were 60%. Several investigators have reported 5-year OS in the range of 40–60% after extended field EBRT for endometrial cancer with para-aortic nodal metastases [32, 33]. However, most long-term survivors have only microscopic nodal disease, and nearly all patients with macroscopic nodal disease suffer disease relapse after doses of 50-Gy EBRT [32, 34].

Recurrent Gynecologic Malignancies

Recurrent Cervix Cancer

Salvage therapy for *recurrent cervical cancer* with surgery or radiation is historically unsuccessful. Early studies of salvage therapy reported 5-year OS of 2–4% with the majority of long-term survivors having recurrent disease confined to the central pelvis [35, 36]. In 39 patients selected for attempted curative therapy from a group of 193 with recurrent cervix cancer, Calame reported a salvage rate of 21% (8 of 39) [36]. Perez reported 5-year OS in only 5% of stage III patients treated for pelvic recurrence [9]. Approximately 60% of women who die of cervical or endometrial cancer have local failure as the major cause of death [37].

Successful salvage of patients with pelvic recurrence of cervix cancer following primary radiation therapy is rare with most investigators reporting 5 year OS of ≤5% [9, 38], but selected patients with locally recurrent disease that is confined to the central pelvis may be cured with exenterative surgery. Fatal complications have been reported in up to 10% of patients with 5 year OS in the 25–50% range [39–42]. Subsequent pelvic recurrence has been reported in around 30% of patients [40, 41]. Factors that have been shown to predict for survival include negative margins, small tumor size (<3 cm), interval from initial radiation therapy to exenteration > 1 year, and lack of sidewall fixation [40].

Shingleton et al. [40] performed pelvic exenterative procedures in 143 women with recurrent cervical cancer; the 5-year survival was 0% after anterior exenteration with positive margins and 63% after anterior exenteration with negative margins. After total exenteration with positive margins, the 5-year OS was 10% versus 49% with negative margins. In addition, all nine patients who were noted

preoperatively to have some degree of pelvic sidewall fixation subsequently died. Hatch reported 5-year OS of 70% after exenteration when the tumor was confined to the cervix versus 24% for patients with any degree of extension beyond the cervix (most commonly to the bladder in this series) [41].

Some patients with recurrent cervix cancer following radiotherapy may be salvaged with radical hysterectomy instead of exenterative surgery, but this approach has been associated with a high rate of complications. In the series of Coleman [43], 50 patients with recurrence [32] or persistence [18] of cervical carcinoma following primary radiation therapy were treated with radical hysterectomy. Although the 5-year OS was 65% in 32 recurrent patients, subsequent locoregional failure was noted in 42%, and severe complications were noted in 42% including bladder dysfunction in 20%, ureteral injury in 22%, vesicovaginal fistula in 24%, and rectovaginal fistula in 20%. The salvage rate was 22/33 (67%) for patients in whom the disease was confined to the cervix, 4/11 (36%) for those with vaginal extension, and 0/6 for those with parametrial extension.

Successful salvage therapy for patients with locally recurrent cervix cancer may be more likely in patients treated with primary surgery than in patients who recur following radiotherapy. Shingleton reported a 5-year OS of 10% in a series of 67 women with local recurrence; the 3-year OS was 14% for those who recurred after primary radiation therapy and 27% for those who recurred after primary surgical therapy [44]. The 5-year OS with salvage EBRT ± brachytherapy in previously unirradiated patients ranges from 15 to 50% [44–49].

The likelihood of successful salvage radiotherapy for patients with cervical cancer who have locoregional recurrence following radical hysterectomy is dependent on the extent of the recurrent disease. Small-volume central recurrence limited to the vagina is adequately treated with EBRT + brachytherapy in many instances, and 5-year salvage rates of 40–80% have been reported [46, 48, 50, 51]. Local control and survival are poor in patients with extension of disease beyond the vagina; 5-year OS of 4–27% has been reported with local control achieved in only 20–30% of patients [42, 45, 46, 48, 50, 52]. When peripheral relapse is limited in volume with only unilateral sidewall extension, 15–30% may be salvaged with radiotherapy; salvage rates for those with massive peripheral relapse involving both sidewalls are less than 5% [50, 52]. Patients who recur within 6 months of surgery have been reported to have a worse prognosis with a median survival of 6 months versus 12 months in patients who were diagnosed with recurrence after a longer interval [45].

Interstitial brachytherapy alone has been used for salvage therapy in patients with recurrent cervix or other gynecologic malignancies. Nori et al. [53] treated 75 patients with recurrent cervix cancer and reported a 10% 5-year DFS with a median survival of 11 months; 5-year OS in women with disease confined to the central pelvis was 31%. The median survival in 21 women with noncervical primaries was also 11 months with 1 of 21 surviving 5 years (5%). The majority of patients in this series had been previously irradiated. Better results were reported by Monk et al. [54] who treated a total of 28 locally recurrent patients (18 cervix, 10 corpus) with interstitial brachytherapy ± EBRT; long-term DFS was reported in 36%, and local control (LC) was reported in 54%. None of the patients with sidewall involvement were salvaged [54].

Patients with locally advanced recurrent cervix cancer may respond to chemotherapy in as many as 2 of 3 cases, but chemotherapy with currently available drugs has no potential for a long-term cure [55]. Fifteen patients with locally recurrent cervix cancer were treated with chemotherapy alone in the series of Potter [49], and all died of disease. Chemotherapy given concomitantly with radiation therapy for salvage of local recurrence may improve salvage rates, however. In a preliminary Princess Margaret Hospital study, a total of 17 patients with recurrent cervix cancer were treated with EBRT and concomitant 5-FU ± mitomycin; 8 of the 17 patients (47%) were rendered disease-free and remained alive for a median of 34 months (range 21–58 months) following salvage therapy [38]. The need for effective systemic therapy in patients with recurrence apparently limited to local sites is evidenced by the fact that 50% of patients treated for local recurrence develop distant metastases [9].

Recurrent Endometrial Cancer

The results of salvage therapy for local recurrence of *endometrial cancer* following primary surgical therapy are similar to those reported for cervical cancer with prognosis dependent upon the extent and location of the recurrence. In women with isolated vaginal recurrences, treatment with EBRT + brachytherapy results in long-term disease control and survival in 25–60% [56–61]. Salvage therapy is less effective if the vaginal recurrence extends into the pelvis; Kuten [59] reported a 5-year DFS in 40% and pelvic control in 59% of women with recurrences limited to the vagina versus 20% 5-year DFS and 17% pelvic control in those with extension of disease into the pelvis. Survival rates for women with pelvic recurrence with or without vaginal recurrence range from 0 to 20% at 5 years [56, 58–60]. Local failure has been reported in 100% of patients with lateral pelvic recurrence treated with EBRT alone [56] or EBRT ± brachytherapy [59].

Patient Selection and Treatment Factors for IORT

Patient Selection

Potential candidates for IORT should be jointly evaluated by the radiation oncologist and the gynecologic oncologist. A thorough history should be taken and a detailed examination is performed; pelvic examination under anesthesia may be required in some cases to accurately determine the extent of pelvic tumor. Staging studies should be directed toward the most common sites of distant metastases; these would include liver-function tests, imaging of the abdomen and pelvis with computed tomography (CT), and imaging of the chest (chest X-ray or CT). Magnetic resonance imaging (MRI) may be useful to delineate tumor extent within the pelvis. In patients with known para-aortic adenopathy, consideration should be given to biopsy of scalene lymph nodes prior to proceeding with exploration and IORT. Positron emission tomography (PET) combined with CT (PET/CT) may be useful in excluding metastatic disease that has not been demonstrated with CT alone.

General criteria for selection of patients with gynecologic malignancies for IORT have been detailed in publications from Memorial Sloan–Kettering Cancer Center (MSKCC) and Mayo Clinic [62, 63]. Patients should be able to tolerate a major operation and have local or nodal disease that would not be adequately controlled with surgical resection alone; EBRT doses needed for local control should exceed normal-tissue tolerances, and there should be no evidence of distant metastases. Candidates for IORT would include those with locally advanced primary or recurrent gynecologic malignancies (most commonly cervix or corpus origin) with direct extension to the pelvic sidewall, or those with gross nodal metastases to pelvic or para-aortic lymph nodes [64]. Although patients with ovarian cancer are not routinely considered for IORT because of the high rate of generalized intra-abdominal metastases, those with localized recurrent disease are appropriate candidates.

Sequencing of Treatment Modalities

Radiation-naïve patients with primary locally advanced gynecologic malignancies in whom surgery + IOERT are being considered should receive preoperative EBRT and concomitant cisplatin-based (CDDP) chemotherapy to increase the probability of achieving a gross total resection. Doses in the range of 45–50 Gy in 1.8 Gy fractions can be safely delivered over 5–5.5 weeks to the pelvis or para-aortic nodal regions.

Although the benefit of concurrent CDDP-based chemotherapy during EBRT has been well defined in phase III trials [4–6], the role of systemic chemotherapy has been in question. Studies of neoadjuvant chemotherapy in locally advanced cervical cancer have either been negative or favored irradiation alone [65–68]. Postoperative chemotherapy has not been fully evaluated; one randomized study of postoperative radiotherapy ± cisplatinum, vinblastine, and bleomycin in node-positive cervix cancer patients following radical hysterectomy showed no benefit to adding chemotherapy [69]. There is emerging data on adjuvant chemotherapy following chemoradiation. In an intergroup trial reported by Peters et al., a total of 268 patients with stage IA2, IB, and IIA cervical cancer underwent radical hysterectomy and pelvic lymphadenectomy. These patients had high-risk features (positive pelvic lymph nodes, positive surgical margins, or parametrial invasion) and were randomized between postoperative RT and postoperative chemoradiation. The radiation dose was the same for both groups (49.3 Gy administered in 29 fractions to a standard pelvic field). The chemoradiation group received four cycles of cisplatin (70 mg/m^2, day 1) and 5-FU (1,000 mg/m^2/day as a 96-h continuous infusion). Two cycles were given concurrently with RT and two cycles after RT completion. The chemoradiation arm was superior to the RT arm in terms of DFS and OS [70].

Preoperative EBRT plus concurrent CDDP-based chemotherapy is also the preferred treatment sequence in patients with locally recurrent disease. In previously irradiated patients, however, full-dose EBRT is not feasible and the preoperative EBRT dose depends on the prior radiation dose, the time interval from initial treatment to recurrence, and the location of the recurrence with respect to normal dose-limiting structures such as small bowel. Investigators at Thomas Jefferson University [71] demonstrated that retreatment doses of 30–36 Gy to the posterior pelvis via lateral fields that exclude small bowel are tolerable in patients who have previously received 45–50 Gy when given in conjunction with low-dose continuous infusion 5-FU for patients with recurrent rectal cancer.

Preoperative chemotherapy should be considered in patients with limited EBRT options to increase the probability of gross total resection. In a phase II study using the MVAC (methotrexate, vinblastine, doxorubicin, and cisplatinum) regimen in women with recurrent cervical or vaginal malignancies, an objective response rate of 66% and a clinical complete response rate of 21% was reported [72]. For those with fixed small-bowel loops in the pelvis, which prevent preoperative EBRT, chemotherapy followed by maximal resection + IOERT and pelvic reconstruction with omentum or mesh to exclude the small bowel from the tumor bed may allow postoperative chemoradiation to be delivered and is the preferred sequencing of modalities.

Irradiation Factors

EBRT

In previously unirradiated primary or recurrent patients, EBRT doses of 45–50 Gy (± concomitant chemotherapy) should be delivered to the pelvis or para-aortic regions in 1.8-Gy fractions. For pelvic lesions, treatment should be delivered on a linear accelerator with ≥10 MV photons using 3D conformal irradiation (3D-CRT) or intensity-modulated irradiation (IMRT). In women with cervix or uterine primaries, the external and internal iliac lymph nodes should be included in the treatment field. In patients with involved pelvic lymph nodes, consideration should be given to the inclusion of the lower para-aortic nodes in the EBRT field. If there is disease extension to the lower one third of the vagina, techniques to include the inguinal lymph nodes should be utilized. For patients in whom inguinal, external iliac, or periaortic nodes are included in the EBRT field, IMRT techniques often will have dosimetric advantages over 3D-CRT with regard to sparing of normal organs and structures (pelvis: small bowel, bladder, femoral heads; abdomen: small bowel, spinal cord, stomach, kidney).

EBRT treatment of para-aortic nodal metastases should also be done using 3D-CRT or IMRT techniques and ≥10 MV photons with the patient immobilized in either prone or supine position. Use of a false tabletop technique and prone patient position for the lateral fields often results in anterior displacement of small bowel and stomach away from nodal regions and may result in better target volume coverage with less small-bowel dose. This has the potential for improving both acute and chronic tolerance. The dose contribution from lateral fields should be limited to 18 Gy so that kidney tolerance is not exceeded. If IOERT to the para-aortic region is contemplated, the spinal cord dose should be limited to 35–40 Gy as additional spinal cord dose may be delivered with IOERT.

External-beam treatment of previously irradiated patients must be individualized. The target volume is usually limited to the gross tumor recurrence with a 2-cm margin. If small bowel can be excluded from the target volume, doses of 25–30 Gy may be delivered preoperatively. If the treatment planning CT scan shows fixed loops of bowel adjacent to the target volume, preoperative EBRT may need to be limited to 20 Gy or less in 1.8 Gy daily fractions or 1.5 Gy bid. Alternatively, EBRT could be delivered postoperatively after surgical exclusion of the small bowel from the tumor bed.

IOERT Factors

Dose and Energy

IOERT is delivered at the time of surgery after maximum surgical resection. At Mayo Clinic Rochester, a refurbished Clinac 2100C® is located within a dedicated IORT suite in the operating rooms, and electron energies from 6 to 18 MeV are available. The choice of electron energy depends on the depth of the target volume and the location of critical deep structures such as spinal cord. The IOERT dose is calculated at the 90% isodose line; if 6 MeV electrons are used, bolus material may be placed over the IOERT field to compensate for the lower surface dose of low-energy electrons. If abutting fields are indicated, silk sutures should be placed to mark the edge of the initial field (inner portion of the applicator) to facilitate accurate matching of the subsequent field.

The IOERT dose depends on the amount of residual disease and the amount of EBRT that has been delivered preoperatively or is planned postoperatively. If EBRT doses of 45–50 Gy have been delivered or can be delivered postoperatively, 10–12.5 Gy is used for narrow or microscopically positive margins, 15–17.5 Gy for gross residual ≤2 cm in diameter and 17.5–20 Gy for gross residual >2 cm in diameter. When the EBRT dose is limited to 20–30 Gy because of prior treatment, higher IOERT doses of 15–20 Gy may be used even for microscopically positive margins; however, IOERT doses higher than 20 Gy are rarely given.

IOERT Applicators

A variety of shapes and sizes of lucite applicators are necessary to conform to the anatomy of the presacrum, pelvic sidewall, anterior pelvis, and para-aortic lymph node regions. In the pelvis, circular applicators with 30° bevels are usually selected. Elliptical or rectangular applicators with flat or 20° bevel ends are often utilized in the para-aortic region (Fig. 20.1). The availability of a variety of applicator sizes ensures optimal coverage of the resected tumor bed or residual disease while minimizing normal-tissue risks. At Mayo Clinic, circular applicators are available in 0.5-cm increments from 4.5 cm to 9.5 cm. Elliptical applicator sizes include 7×12 cm, 9×12 cm, 8×15 cm, and 8×20 cm; rectangular applicator sizes include 8×9 cm, 8×12 cm, and 8×15 cm.

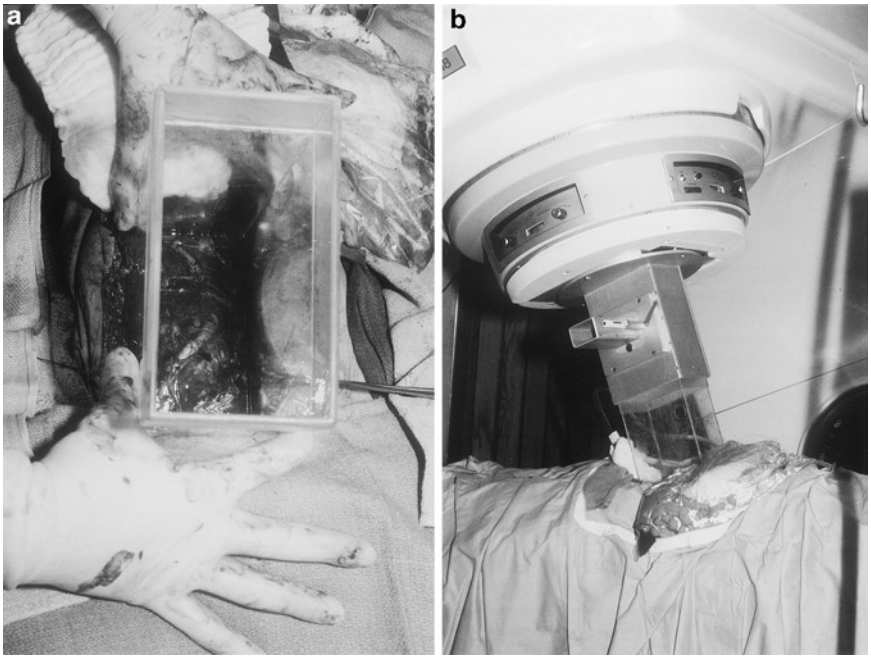

Fig. 20.1 Treatment of para-aortic region with IOERT, Mayo Clinic Rochester. (**a**) Rectangular applicator 8 × 15 cm with 20° bevel positioned to cover the para-aortic region after mobilization of the small bowel. (**b**) Applicator "docked" with linear accelerator and patient is ready for treatment.

HDR-IORT Factors

Intraoperative brachytherapy is usually delivered by using high-dose-rate (HDR) technique. The HDR-IORT is delivered using the Harrison–Anderson–Mick (HAM) applicator. The HAM applicator consists of a flexible pad of material called silicone rubber that is 8 mm in thickness with an array of catheters that traverse it spaced 1 cm apart. Once the applicator is positioned, an Iridium-192 source is programmed to deliver a uniform dose to the area at risk at a dose rate similar to that used for electron-beam IORT.

Because of its flexibility, the HAM applicator easily conforms to the shape of most tumor beds to which it is applied (Fig. 20.2). This represents a technical advantage of brachytherapy in that there are virtually no clinical situations in which, due to anatomic or technical constraints, HDR-IORT cannot be delivered. The dose of HDR-IORT is usually 15 Gy when used in combination with EBRT and 17.5 Gy when used alone. The dose is prescribed to a depth of 0.5 cm from the surface of the applicator. One potential disadvantage of HDR-IORT is that for patients with residual gross disease, the dose coverage may not be as good as IOERT.

Surgical Considerations

The addition of IORT to the surgical procedure has not resulted in increased acute surgical complications compared to that seen with EBRT + surgery without IORT [73–75]. Tepper reported complications in 35% of patients who received preoperative EBRT without IOERT and 32% in patients who received IOERT in addition to EBRT and surgical resection [74].

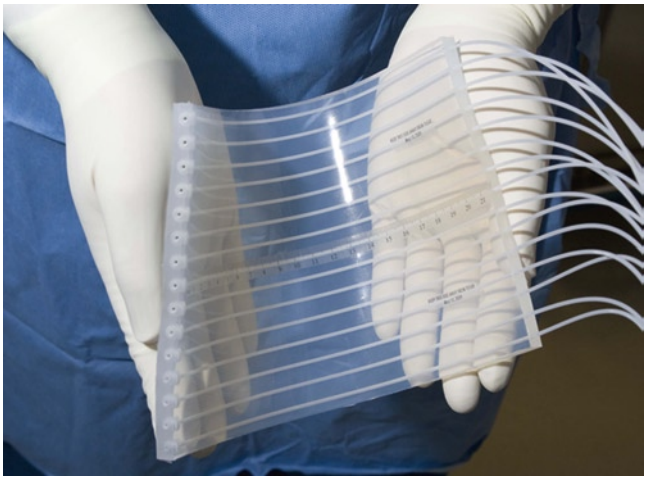

Fig. 20.2 HAM applicator.

A midline incision is usually necessary to achieve adequate exposure for resection and IORT in the abdomen and pelvis. The incision may need to be more extensive than usual to allow for placement of the IOERT or HDR-IORT applicators. When both abdominal and perineal incisions are necessary for resection of low-lying pelvic lesions, the tumor bed may be visualized and treated more appropriately through the perineal incision [73].

A thorough exploration of the abdomen and pelvis should be performed to detect clinically occult hematogenous distant metastases (i.e., to the liver) or peritoneal spread of disease, which would be a contraindication to aggressive local therapy unless the metastasis is solitary in nature and can be resected with negative margins. Patients with locally advanced cervix or endometrial cancer should undergo pelvic lymph-node dissection, and if positive lymph nodes are reported on frozen-section analysis, the para-aortic nodes should be dissected. In patients with known para-aortic lymph-node metastases, consideration may be given to scalene lymph-node biopsy prior to laparotomy.

The goal of the surgical procedure is gross total resection if it can be safely accomplished. Maximum resection of the tumor should take place before IORT. The availability of frozen-section pathology analysis is critical to allow for identification of the limits of gross and microscopic tumor extensions. Patients with invasion of the bladder or rectum or those with recurrence in the pelvis after previous irradiation usually require anterior or posterior exenteration. Reconstruction should be done after IORT (i.e., reanastomosis of the rectum) to allow for full exposure of the tumor bed and to avoid irradiation of the anastomosis. However, if a vascular reconstruction is required, this should be performed prior to IORT [64]. Inclusion of large-vessel anastomoses in the IORT field appears to be safe; arterial anastomoses have been shown to heal adequately after IORT doses as high as 45 Gy in dogs [76].

If postoperative EBRT may be indicated, a number of surgical options exist to optimize tumor volume reconstruction and displacement of dose-limiting organs. Placement of clips to mark the borders of the IORT field is helpful for follow-up evaluation and for design of postoperative EBRT fields, if indicated. When postoperative pelvic EBRT is planned, reconstruction of the pelvic floor and mechanical exclusion of the small bowel from the pelvis (using omentum if available versus tissue expanders or absorbable mesh) may improve EBRT tolerance and decrease the risk of treatment related small-bowel complications. In patients with a history of prior EBRT in whom aggressive re-treatment approaches include additional EBRT, maximal resection and IORT, pelvic reconstruction with a vascularized rectus abdominus flap may be useful in improving healing and displacing small bowel if an omental flap is not feasible.

Results: IORT ± EBRT

US Series: IOERT

IOERT has been used at Mayo Clinic Rochester [62, 63, 77] for both locally advanced primary and recurrent gynecologic malignancies and at the University of Washington [78, 79] for recurrent cervical cancer. Survival and disease control with IORT containing regimens from these two institutions are summarized in Tables 20.2 and 20.3. None of the patients in either series were considered potentially curable with surgery and/or EBRT alone. The 5-year OS of 27% and 32% and 5-year LC of 50–55% are encouraging given the historical poor results with standard salvage therapy.

Primary Disease

There is very little information in the literature regarding the use of IORT in primary locally advanced malignancies in US series. Patients with primary cervix or uterine malignancies with disease extension to the pelvic sidewall or locally advanced nodal metastases are those with the potential for benefit from the addition of IORT to the treatment program.

Table 20.2 Locally advanced gynecologic malignancies, survival results: US IOERT series

Series, patient group	No. Pts.	Median (mo.)	Overall (%)			Disease-free (%)		
			2 yr	3 yr	5 yr	2 yr	3 yr	5 yr
Mayo Clinic, All [76]	63	15	44	30	27	36	27	21
Primary[a]	8	12	14	14	14	14	14	14
Recurrent	55	20	48	32	29	38	29	21
Cervix	36	15	40	25	25	30	24	21
Endometrium	10	56	80	57	38	60	50	17
Other[b]	9	14	44	33	33	44	22	22
Univ. Washington, Rec. cervix [79]	21	22	–	–	32	–	–	–

[a]4 cervix, 2 vagina, 1 endometrium, 1 uterine sarcoma
[b]3 vagina, 4 uterine sarcoma, 2 ovary
Rec. recurrent

Table 20.3 Locally advanced gynecologic malignancies, disease relapse: US IOERT series

Series, patient group	No.	Local	Relapse	(%)	Central	Relapse	(%)	Distant	Relapse	(%)
		No. (%)	3 yr	5 yr	No. (%)	3 yr	5 yr	No. (%)	3 yr	5 yr
Mayo Clinic, All [76]	63	23 (37)	45	45	16 (25)	33	33	25 (40)	43	47
Primary[a]	8	4 (50)	62	62	3 (38)	43	43	2 (25)	36	36
Recurrent	55	19 (35)	43	43	13 (24)	31	31	23 (42)	44	48
Cervix	36	14 (39)	50	50	11 (31)	40	40	17 (47)	52	58
Endometrium	10	2 (20)	22	22	0	0	0	3 (30)	33	33
Other[b]	9	3 (33)	50	50	2 (22)	42	42	3 (33)	33	33
Univ. Washington, Rec. cervix [78]	22	10 (45)	52	52	–	–	–	6 (27)	–	–

[a]4 cervix, 2 vagina, 1 endometrium, 1 uterine sarcoma
[b]3 vagina, 4 uterine sarcoma, 2 ovary
Rec. recurrent

Some of the earliest results with IOERT in the treatment of gynecologic nodal metastases in USA were reported by investigators at Howard University [80]. Delgado et al. [81] treated a total of 16 patients with locally advanced cervical cancer with IOERT to the para-aortic region; 11 patients had para-aortic metastases, and five were treated prophylactically. IOERT doses ranged from 15 to 20 Gy, and only two patients received para-aortic EBRT. Four of the 11 patients with nodal metastases were alive for 10–36 months following IOERT, and two patients were without any evidence of disease.

In addition to the Mayo series (Tables 20.2 and 20.3) [77] and the Howard University series [81], two other small series using IOERT for patients with primary gynecologic malignancies have been reported. Yordan reported the results of IOERT in a total of five women with primary gynecological malignancies (2 cervix, 3 corpus) at Rush or Pamplona [82]. Four of the five women were without evidence of disease at the time of publication, and there were no local failures. IOERT doses were 10–15 Gy for microscopic disease and 15–26 Gy for macroscopic disease. Konski et al. [83] reported treating a total of eight patients with cervix cancer with IOERT to the para-aortic region. IOERT doses ranged from 10 to 25 Gy (median 20 Gy), and no patient received EBRT to the para-aortic region. Two patients had bulky para-aortic metastases, five patients had microscopic disease, and one was treated prophylactically. The median survival was 27 months and the 2-year OS was 63%. Para-aortic nodal recurrence was diagnosed in three of the eight patients (38%).

Recurrent Disease

IORT has been more frequently utilized in patients with isolated nodal or locally recurrent gynecologic malignancies than in primary malignancies. Preliminary results from Howard University [81] and Massachusetts General Hospital (MGH) [84] suggested that IOERT was feasible in locally recurrent patients. Konski et al. [83] treated a total of six patients with para-aortic nodal recurrences of gynecologic malignancies (2 endometrial, 2 cervix, 1 uterine sarcoma) with IOERT doses of 10–25 Gy following surgical debulking. Four of the six patients received 45-Gy EBRT to the para-aortic region in addition to IOERT. Two of the six patients were alive at the time of publication, one at 11 months with no evidence of disease and one at 19 months with para-aortic recurrence.

The largest US series of IOERT in recurrent patients are from Mayo Clinic and the University of Washington. Results are summarized in Tables 20.2 and 20.3.

University of Washington

In the *University of Washington series* [78, 79] of patients with recurrent cervical cancer, IOERT was combined with either preoperative or postoperative EBRT in 13 of 22 (59%) patients. Nine of 15 previously irradiated patients received no additional EBRT, while six were reirradiated using conformal fields to doses ranging from 26 to 50 Gy. The median IOERT dose in all patients was 22 Gy at the point of maximum dose. In all cases, surgery alone was inadequate to address tumor extent. From the time of IOERT, 5-year OS was 32% with a median survival of 22 months. LC at 5 years was 46% (R2 resection with gross residual – 36% LC at 5 years; R0 or R1 resection – 55% LC at 5 years).

Mayo Clinic Rochester

In the *Mayo Clinic Rochester series* [62, 63, 77], IOERT was combined with preoperative or postoperative EBRT in 7 of 8 (88%) primary patients and 36 of 55 (65%) recurrent patients. Nine of the 28 (32%) patients with recurrence in a previously irradiated field were reirradiatiated with EBRT

doses ranging from 9 to 50 Gy. The median IOERT dose in all patients (dose prescribed at 90% isodose line) was 15 Gy for microscopic residual tumor and 20 Gy for gross residual tumor. Eleven of the 28 patients with recurrence in a previously irradiated field received preoperative MVAC chemotherapy in an attempt to increase the probability of gross total resection, which was achieved in 7 (64%) patients. 5-year disease outcomes for the total group of 63 patients included OS – 27%, LC – 55%, distant relapse – 47%.

In an updated analysis, a total of 148 women with gynecologic cancers received IOERT at Mayo Clinic Rochester from January 1983 to January 2005 after maximal surgical resection [85–88]; 125 of them had local or regionally recurrent tumors (site of origin: cervix – 66, endometrium – 31, corpus – 6, vagina – 6, ovary – 16), and 23 of them had locally advanced primary cancers (site of origin: cervix – 11, endometrium – 1, corpus – 4, vagina – 3, female GU – 4). At the time of IOERT and after maximum surgical debulking, 115 patients had microscopic residual or less (R0 or R1 resection), and 33 (22%) had gross residual (R2 resection). Of the 148 IOERT patients, 113 also received EBRT as a component of treatment (median 48.6 Gy; range 0.9–75.4 Gy; 85/148 patients had prior EBRT). Concurrent chemotherapy during EBRT was given in 31/148 (22%). The median IOERT dose was 20 Gy in previously irradiated patients versus 15 Gy in previously unirradiated patients. Systemic chemotherapy was given to 42 patients (28%) before or after resection (MVAC [$n=29$] or CDDP based in 39/42). The 5-year OS for the total group was 27%; 5-year actuarial central (within IOERT field), local, and distant relapse rates were 28, 40, and 51%, respectively.

In a Mayo Clinic analysis of patients with recurrent endometrial cancer treated with IOERT regimens from 1986 to 2002, 25 patients were evaluated [89]. Five-year OS was 47% and was dependent on residual volume at time of IOERT (close margins 71% 5-yr OS vs. 40% microscopic residual and 0% gross residual). The local control rate within the IOERT field was 84%. Two patients in the series developed enteroarterial fistula with associated pelvic abscess or recurrent small-bowel obstruction and died of septicemia without evidence of disease relapse at 57 and 92 months.

Summary

The reported 5-year survivals of 27 and 32% in the Mayo Clinic and the University of Washington series of patients are encouraging as none of the patients in either series were considered potentially curable with surgical resection alone. Local control was reported in 60% of patients in the Mayo series and 48% in the University of Washington series, an apparent improvement compared to historical controls. Despite careful staging to rule out distant metastatic disease, subsequent distant relapse was a significant problem in both series (Table 20.3).

European Series: IOERT

There have been three major published European series of IOERT for locally advanced gynecologic malignancies [52, 90, 91]. Survival and disease control rates from these series are summarized in Tables 20.4 and 20.5.

Lyon

Gerard et al. [91] reported results in a total of 54 patients treated in Lyon for either primary or recurrent disease. Twenty women with locally advanced primary cervix cancer (7 stage IIB, 12 III, 1 IV) were treated with 44 Gy EBRT + 1 cycle 5FU/CDDP + IOERT. At a median follow-up of 18 months

Table 20.4 Locally advanced gynecologic malignancies, survival, and disease control: European IOERT series

Series	Patient group	No. Pts.	Median survival	Overall survival	Local relapse (%)	Central relapse (%)	Distant relapse (%)
U. Navarre [90]	Recurrent cervix, prior EBRT	14	7 mo.	7% 4 yr	6/10 (60)	2/9 (22)	2/10 (20)
	1° or recurrent cervix, no prior EBRT	24	38 mo.	47% 4 yr	3/19 (16)	1/19 (5)	2/19 (11)
	Miscellaneous[a] recurrent	10	19 mo.	30% 4 yr	4/9 (44)	3/9 (33)	6/9 (67)
France [52]	Recurrent cervix	70	11 mo.	8% 3 yr	50/67 (75)	–	22/67 (33)
Lyon [91]	Primary cervix	20	–	15/20 (75%)[b]	4/20 (20)	–	2/20 (10)
	Recurrent cervix/ uterus	34	–	32% 4 yr	–	6/34 (18)	–

EBRT external-beam radiation therapy, 1° primary, *yr* year
[a]4 endometrium, 4 ovary, 2 vulva
[b]Crude survival, follow-up 12–34 months, median 18 months

Table 20.5 Locally recurrent gynecologic cancer IORT series: Survival and disease control by amount of residual disease

Series	Residual[a]	No. Pts.	Median survival	Survival 5-yr	Local failure (%)	Local failure 5-yr	Distant mets (%)
U. Washington [79]	Micro	10	25 mo.	40%	–	45%	–
	Gross	12	18 mo.	29%	–	64%	–
France [52]	Micro	30	13 mo.	–	19/30 (63)	73% 3 yr	9/30 (30)
	Gross	37	10 mo.	–	31/37 (84)	89% 3 yr	11/37 (30)
Spain [92]	Micro	7	–	71%[b]	–	–	–
	Gross	19	–	5%[b]	–	–	–

[a]Micro = microscopic residual disease, gross = macroscopic residual disease
[b]Crude survival

(range, 12–34 months), only four pelvic relapses (20%) had occurred. Fourteen of the 20 women (70%) were without evidence of disease, and 15 of the 20 women (75%) were alive at the time of publication. An additional 34 patients with pelvic recurrence (28 – cervix, 6 – endometrial; sites of recurrence – central pelvis in 4, sidewall in 25, para-aortic lymph nodes in 5) were treated with IOERT; 16 of the 34 patients received EBRT in addition to IOERT. Gross residual tumor was present in the 22 of the 34 patients at the time of IOERT. The 4-year OS was 32%, and central failure occurred in 6 of 34 (18%) patients.

French IORT Group

The largest European series of IOERT for recurrent cervix cancer is from the cooperative French IORT Group who reported results of IOERT (18–19 Gy) alone or combined with EBRT and chemotherapy for a total of 70 recurrent cervix cancer patients treated in seven French institutions [52]. Median survival was 11 months; OS at 1, 2, and 3 years were 47, 17, and 8%, respectively. Subsequent local relapse was noted in 79% of the patients. Forty of the 70 patients in this series received no EBRT, and some of the 37 patients with gross residual had no resection of tumor.

University of Navarre, Pamplona

At the University of Navarre in Pamplona, a total of 48 women with locally advanced gynecologic malignancies have been treated with IOERT [90]. Survival results were poor in women with locally recurrent cervix cancer who had been previously irradiated with a median survival of 7-month and 4-year OS of 7%. Local relapse was reported in 60% of re-treatment patients, but only 22% relapsed within the IOERT field. Better results were seen in women with primary or recurrent cervix cancer without prior EBRT with a 38-month median survival and a 5-year OS of 47%. The local relapse rate was only 16%, and the central relapse rate was 5%.

Results at the University of Navarre were updated in 67 patients with locally advanced primary or locally recurrent cervical cancer (Table 20.6; ref. [92]). Previously unirradiated patients were treated with preop chemoradiation prior to resection and IOERT, but those with prior EBRT either proceeded directly to resection and IOERT or received preop chemotherapy. As seen in Table 20.6,

Table 20.6 Gynecologic cancer: IORT ± EBRT, US and European results by prognostic factor analysis

			Survival	Overall survival (%)			Relapse: 5 yr, %		
Treatment group	References	#Pts	Median	2-yr	5-yr	*p*-value	Local	Distant	Central
Mayo Clinic Rochester[a]	[85–88]	148	19 mo	41	27		40	51	28
Residual									
≤Micro		115	21	44	31	0.01	42	49	29
Gross		33	15	31	13		26	58	19
Prior EBRT									
None		63	22	47	35	0.01	37	46	26
Yes		85	15	33	15		45	58	32
DFI									
>2-yr		81	29	56	35	0.002	34	41	23
≤2-yr		44	15	19	14		58	68	36
University of Navarre	[90]	67							
Primary disease		31	–	–	67	<0.001	21	16	7
Recurrent		36	–	–	14		58.5	58	53
No prior EBRT		5	–	–	33 (4-yr)		23	–	6
Prior EBRT		31	–	–	7 (4-yr)		67	–	61
Residual disease									
None (R0 resection)		50	61	–	45 (10-yr)	<0.001	–	24	12
Microscopic (R1)		11	11	–	9 (10-yr)		–	82	79
Gross (R2)		6	8	–	0 (10-yr)		–	83	100
Stanford, orthovoltage[b]	[94]	36	22	46	42		56	49	–
Rec cervix-IORT salvage									
Univ Washington	[78, 79]	22	26	–	32		52	–	–
French IORT group	[52]	70	11	17	8 (3-yr)		79	–	–
Mayo Clinic Rochester[a]	[88]	66	17	–	19		51	–	–
Rec Gyn, HDR-IORT									
MSKCC	[96]	17	–	–	54 (3-yr)		33 (3-yr)[c]	46 (3-yr)	
Recurrent ovarian							# (%)	# (%)	
Mayo Clinic Rochester[a]	[88]	16	78	61	54		–	–	–
Stanford	[100]	22	26	–	22		5 (32)	12 (55)	–

DFI disease-free interval, *EBRT* external-beam irradiation, *IORT* intraoperative irradiation, *Rec* recurrent

[a]Modified from M. Haddock et al., ISIORT 2005; primary – 23 pts, recurrent – 125; Multivariate analysis: Gross residual, $p=0.02$; Prior EBRT in-field, $p=0.05$; DFI > 2-yr, $p=0.0004$

[b]Stanford series – 89% treated for recurrent disease

[c]LC @ 3-yr with R0/R1 resection – 83% vs. 25% with R2 resection, $p=0.0005$

the best outcomes were achieved in patients who presented with locally advanced primary lesions (5-yr OS, 67%; 21% local relapse) or previously unirradiated recurrent disease.

Orthovoltage-IORT Series

Roswell Park

Orthovoltage IORT without EBRT was utilized in a Roswell Park series [93] of 23 recurrent patients. Median survival was 7 months with 2- and 3-year OS of 20% and 13%, respectively.

Stanford University

Investigators at Stanford University Medical Center [94] have used orthovoltage IORT as a component of treatment in a total of 36 patients from September 1986 to November 2005 (prior EBRT – 72%; recurrent disease presentation – 89%). The primary sites were cervix (47%), endometrium (31%), vulva (14%), vagina (6%), and fallopian tubes (3%). Maximum cytoreductive surgery was accomplished in 84% of patients, including 18% exenterations, and mean IORT dose was 11.5 Gy (range 6–17.5 Gy). EBRT (mean dose 44 Gy, range 10–79 Gy) and chemotherapy were given to 53 and 24% of the patients, respectively, after IORT.

The 5-year locoregional control, distant metastases-free survival (DM-free), and disease-specific survival (DSS) probabilities for the entire group were 44, 51, and 47%, respectively (Table 20.6), and for those with cervical cancers the same were 45, 60, and 46%, respectively. On multivariate analysis, the prognostic factor that predicted locoregional control was disease-free interval, whereas for DM-free survival, it was tumor size, and for DSS, the prognostic factors were cervical primary, previous surgery, and locoregional relapse. The actuarial 5-year grade 3–4 complication-free survival rate was 72%; exenterative surgery was an independent predictor of grade 3–4 complications ($p \leq 0.05$) on multivariate analysis. The post-IORT treatments including EBRT and/or chemotherapy did not statistically significantly affect clinical outcomes. The series included three patients with positive margins after pelvic exenteration for recurrent cancers who remained alive after IORT (198, 187, and 14 months at the time of analysis).

HDR-IORT

Intraoperative irradiation may be delivered with a high-dose-rate brachytherapy source (HDR-IORT) after placement of temporary catheters along the tumor bed. German investigators have reported preliminary results of postoperative HDR brachytherapy using catheters placed at the time of operation for women with recurrent gynecologic malignancies that involve the pelvic sidewall [95]. While this approach has the advantage of allowing for fractionation of the radiation dose, normal tissues such as small bowel cannot be displaced to the same degree achievable with true HDR-IORT.

MSKCC Series

From November 1993 to June 1998, a total of 17 patients with recurrent gynecologic cancer had radical resection and HDR-IORT at MSKCC (Table 20.6; [96]). The primary lesion was treated with

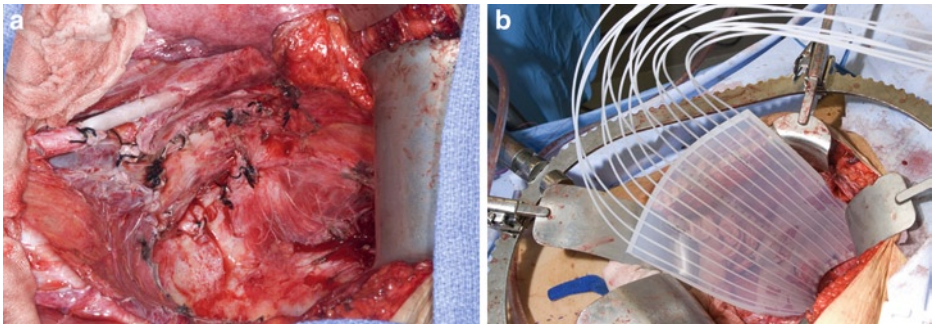

Fig. 20.3 (**a**) Left pelvic sidewall extended resection. (**b**) HAM applicator conforming to left pelvic sidewall tumor bed.

definitive irradiation in 3/17 patients, and 14 patients had surgical resection alone ($n=3$) or plus adjuvant irradiation ($n=11$). The site of the primary was cervix in 9 (53%), uterus in 7 (41%), and vagina in 1. Surgery for local relapse was exenteration in 10 (59%) and tumor resection in 7 patients (41%). Gross total resection (R0 or R1) was achieved in 13/17 patients (76%). The mean HDR-IORT dose was 14 Gy (range 12-15). I-125 implants were done in three of four patients with an R2 resection as a supplement to HDR-IORT. No patient received EBRT at the time of local relapse. With a median follow-up of 20 months (range 3–65 months), 3-year actuarial results demonstrate a LC for the entire group of 67% (R0/R1 resection – 83% vs. 25% for R2 resection; $p<0.01$), a distant control of 54%, and an OS of54%.

In an update of MSKCC data [97] reported by Aubey et al., a total of 56 patients with recurrent gynecologic cancer were treated with radical resection and HDR-IORT. With a median follow-up of 11.4 months, the 2-year survival rate for patients with R0 or R1 resection was 60%, compared to 20% for those with R2 resection/gross residual disease ($P<0.01$). Major postoperative complications were as follows: pelvic abscess, 6 (11%); intestinal obstruction requiring re-exploration, 2 (4%); complex fistula, 2 (4%); cerebrospinal fluid leak, 1 (2%).

The increased use of HDR-IORT at MSKCC has also impacted the extent of surgical resection in patients with recurrent gynecologic cancers (Fig. 20.3). Caceres et al. reported on 14 patients with recurrent cervical/uterine cancer who had undergone attempted curative resection of pelvic bone, pelvic sidewall muscle, major blood vessels, and/or nerves. R0 resection was attained in 11/14 (78%) patients, and seven patients received HDR-IORT. With a median follow-up of 26 months (range, 5–84 months), ten patients (71%) are alive and four patients (29%) have died of disease at 8, 13, 33, and 42 months postoperatively [98].

IORT for Recurrent Ovarian Cancer

Limited numbers of patients with recurrent ovarian cancer have been treated with IOERT. Konski et al. [99] treated a total of five patients with recurrent ovarian cancer with surgical debulking, IOERT, and postoperative whole-abdomen EBRT. Two of the five patients had gross residual tumor at the time of IOERT; median survival was 14 months (range 8–46).

Excellent results have been found with the use of IORT as a component of treatment for select patients with recurrent ovarian cancer at both Mayo Clinic Rochester [87, 88] and Stanford University [100] (Table 20.6). The Mayo Clinic Rochester series of 148 patients included 16 with recurrent ovarian cancer [87, 88]. In this select group of patients, median survival was 78 months with a 2-year OS of 61% and a 5-year OS of 54%.

Twenty-four patients had maximal resection of recurrent disease followed by orthovoltage IORT at Stanford University, and 22 were evaluable for analysis [100]. Most had undergone cytoreductive surgery plus chemotherapy at the time of initial diagnosis; the mean DFI was 48.2 months prior to resection/IORT. After maximal resection, only microscopic residual disease or <0.5 cm residual remained. The median IORT dose was 12 Gy (range 9–14 Gy). Postoperative EBRT (14 pts) or chemotherapy treatment (6 pts) was given to 20/22 patients and was individualized based on the site of relapse and prior therapy (EBRT – abdominal/pelvic – 9, pelvic – 4, inguinal – 1). With a median follow-up of 24 months, five patients remained free of disease. The 5-year OS was 22% with a median survival of 26 months from the time of IORT. Five patients recurred within the radiation fields for a locoregional relapse rate of 32%, and 12 patients relapsed at distant sites. Nine patients (41%) experienced grade 3 treatment-related toxicities.

Prognostic Factors for Disease Control and Survival

Amount of Residual Disease After Maximal Resection; Extent of Resection

Improvements in survival and local control have been reported in both US and European IOERT series when the surgeon is able to perform a gross total resection prior to IOERT. A summary of survival and disease control according to the amount of residual disease is summarized in Tables 20.5 and 20.6. Five-year OS was 40 vs. 29% for recurrent patients with microscopic versus gross residual disease in the University of Washington series [79]. In the updated Mayo Clinic series of 148 IOERT patients [77, 85–88], 5-year OS for the total group was 27%, but patients with R0 or R1 resection at the time of IOERT ($n=115$) had a significantly higher survival than patients with R2 resection (median SR 21 vs. 15 mo, 5-year OS 31 vs. 13%, $p=0.01$; Fig. 20.4a, Table 20.6).

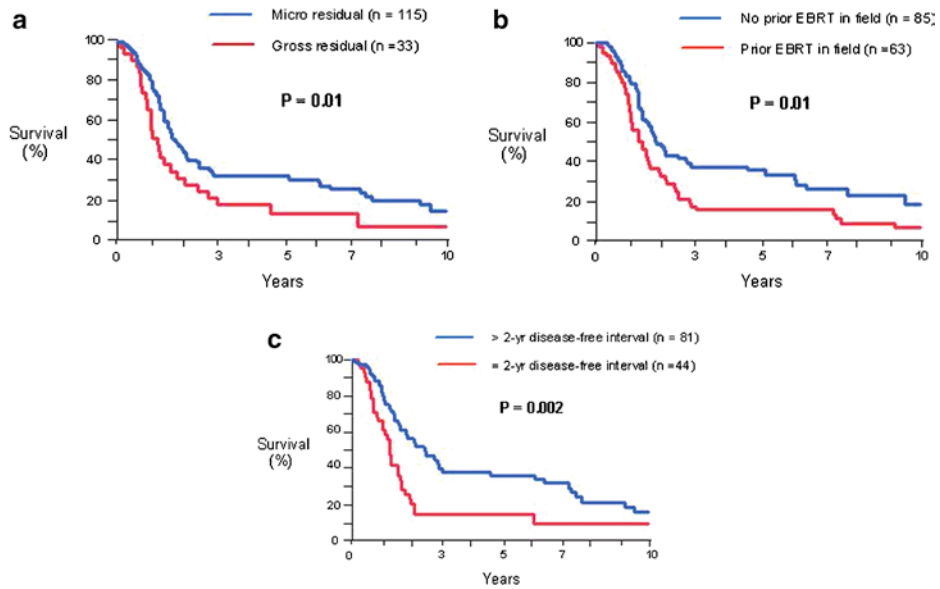

Fig. 20.4 Mayo Clinic Rochester analysis on impact of various prognostic factors on overall survival after maximal resection+IOERT. (**a**) Microscopic vs. gross residual. (**b**) No prior EBRT in IOERT field vs. prior EBRT (**c**) DFI≤2-yr vs. >2-yr.

In the Mayo series of 25 recurrent endometrial cancer patients, 5-year OS was 71% for R0 resection vs. 40% for R1 and 0% for R2 [89].

The rate of distant metastases in the Mayo series [77, 85–88] was increased in patients with R2 vs. R0/R1 resection (5-year, 58 vs. 49%), but local failure at 5 years was noted in 42% of patients with microscopic residual or less versus 26% of patients with gross residual disease. The low local-failure rate in Mayo patients with gross residual disease may be partially attributable to the high rate of distant failure and subsequent death before local relapse was clinically evident. In contrast to the Mayo experience, there was no difference in distant metastatic rates in the French series [52]. However, the rate of local failure in the group with gross residual was 84% (some of these patients had no resection, only biopsy of disease), and it is likely that many of these patients died of their local disease prior to manifestation of distant metastases. When a gross total resection is not possible, tolerable doses of IORT without EBRT is unlikely to result in local control of tumor. In the Roswell Park series, nine patients with recurrent cervix cancer were treated with 15-Gy orthovoltage IORT without EBRT; all four patients with gross residual disease had central recurrence of disease [93].

The extent of the surgical procedure, pelvic exenteration versus less extensive surgery was evaluated in the University of Washington series. No difference in disease-specific survival was reported [78].

Prior EBRT

The prognostic significance of prior EBRT is uncertain; some have reported inferior results in previously irradiated patients, while others have found no difference. A summary of results from the Mayo series [77, 85–88] and the University of Navarre series [90, 92] is presented in Table 20.6. The University of Washington group [78] reported similar disease-specific survivals for previously irradiated and unirradiated patients with recurrent cervical cancer. In the updated Mayo series, however, patients with no prior in-field EBRT ($n=63$) had improved survival when compared to patients with prior in-field EBRT (median 22 vs. 15 months, 5-yr OS 35 vs. 15%, $p=0.01$; Fig. 20.4b, Table 20.6), and there was a slight improvement in disease control in previously unirradiated patients (5-yr: LC 63 vs. 55%, central control 74 vs. 68%, distant control 53 vs. 42%). In the Pamplona/Univ Navarre experience, 4-yr OS was only 7% in previously irradiated patients vs. 33% for those who recurred following surgical therapy; for the 31 IOERT patients with primary cervix cancer, 5-yr OS was 67%.

Disease-Free Interval

In the updated Mayo Clinic analysis [85–88], recurrent disease patients with a disease-free interval >2-years (DFI > 2-yr; $n=81$) had improved survival relative to those with DFI ≤ 2-yr ($n=44$; median SR 29 vs. 15 month, 5-yr OS 35 vs. 14%, $p=0.002$; Fig. 20.4c, Table 20.6).

Irradiation Dose: EBRT, IOERT

The dose of EBRT or IOERT has not been consistently associated with outcome. In the initial Mayo Clinic series of 63 patients [77], there was no association of EBRT dose or IOERT dose with survival, local control, or distant control. In a small combined Rush Presbyterian/Pamplona series of 10 recurrent gynecologic malignancy patients, the EBRT dose did not correlate with local control using a dividing point of 40 Gy. However, they did note improved local control for those in whom the sum of the EBRT dose and twice the IOERT dose (effective IOERT dose is two to three times

fractionated EBRT dose) was >70 Gy with 4/7 patients controlled locally versus none of three with effective doses <70 Gy [82].

Distant Control

Distant failure is a significant problem, especially in the group of patients with gross residual disease at the time of IOERT. In the updated Mayo Clinic series [77, 85–88], the 5-year distant relapse rate was 51% for all patients ($n=148$) and 58% for recurrent patients with gross residual disease ($n=33$).

Improvements in survival in patients with locally advanced gynecologic malignancies will require effective systemic therapy. The most effective single agent for the treatment of squamous cell carcinoma of the cervix is cisplatinum with an objective response rate of about 30% [55]. The duration of response in patients with relapse following radiation or surgery is in the order of 4–6 months, and few patients survive longer than a year [55]. Salvage chemotherapy with currently available agents is largely ineffective [55].

Patients with unresectable recurrent disease after previous irradiation may be considered for combination chemotherapy to increase the likelihood of a gross total resection and decrease the distant metastasis rate. The MVAC regimen has been shown to have significant activity in advanced cervical cancer with a response rate of 66% (21% complete response, 45% partial response) [72]. There was a trend toward reduction in distant metastases in the Mayo series with the use of chemotherapy (largely MVAC) with 5-yr distant relapse rates of 54 vs. 27% ($p=0.09$) (Fig. 20.4), but the administration of chemotherapy did not appear to impact on survival.

More recent GOG trials in patients with advanced/recurrent cervical cancer have also shown that combination chemotherapy might be better than single-agent cisplatin. When cisplatin was compared with cisplatin plus paclitaxel, the combination therapy resulted in a higher response rate and longer PFS, but not OS [101]. In another GOG study, a survival benefit was demonstrated with the addition of topotecan to cisplatin but at the expense of significantly higher toxicity [102].

In similar fashion, a series of GOG randomized trials established that combination chemotherapy was superior to single-agent cisplatin in patients with locally advanced/recurrent endometrial cancer [103–105]. The combination chemotherapy of highest activity with cisplatin, doxorubicin, and paclitaxel (TAP) is available to date, with a response rate of 57% and an overall survival of 15 months. GOG 209 is comparing TAP to carboplatin/paclitaxel in a randomized trial.

Tolerance of IORT

Peripheral nerve is the dose-limiting structure for IORT in the pelvis and para-aortic lymph-node region. Painful neuropathy has been reported in 5–30% of patients who receive IORT [63, 78, 90, 106]. In the University of Washington IOERT series [78], 9 of 22 (41%) women developed painful peripheral neuropathy (minor motor deficits in addition to pain in two patients) following IOERT doses ranging from 14 to 27.8 Gy (median 22 Gy) calculated at the depth of maximum dose. In two cases, the neuropathy was due to recurrent tumor rather than IOERT. The risk of neuropathy was not related to IOERT field size or dose. There was an association noted with cumulative EBRT dose; neuropathy developed in 4 of 4 patients with cumulative EBRT doses >75 Gy and 3 of 18 patients with <75 Gy. Reirradiation with EBRT doses of 26–50 Gy (median 30.6 Gy) was done in 6 of 15 previously irradiated patients. Four patients had resolution of neuropathy after 6–18 months; the remaining three patients had neuropathy that persisted until death.

The risk of peripheral neuropathy has been associated with IOERT dose in patients with recurrent colorectal cancer. In the Mayo Clinic analysis, the risk of grade 2 or 3 neuropathy was 7% with IOERT doses ≤ 12.5 Gy versus 19% with higher doses [107]. In the initial Mayo Clinic series of 63 patients with locally advanced primary or recurrent gynecologic malignancy, only 2 (3%) developed grade 3 neuropathy [77].

Grade 3 or higher toxicities of any nature related to IOERT were diagnosed in 11 (17%) of 63 patients in the Mayo Clinic gynecologic series [77]. Toxicities other than neuropathy included intestinal fistula or obstruction in 8%, soft-tissue injury in 3%, and ureteral obstruction in 3%. If tumor is adherent to the ureter prior to resection, the ureter should be included in the IORT field with a stent placed either prophylactically or if subsequent obstruction develops to prevent loss of renal function.

Conclusions and Future Possibilities

In patients with recurrent gynecological cancer in the pelvic sidewalls, para-aortic or pelvic lymph nodes, the use of aggressive surgery and IORT ± EBRT appears beneficial when compared with standard EBRT salvage, even with recurrent ovarian cancers. Although the potential for complications is not insignificant, IORT-containing regimens offer potential cure in selected patients with locally recurrent disease who are otherwise poor candidates for salvage. Research efforts should concentrate on efforts to improve the likelihood of gross total resection given the poor results seen in patients with gross residual disease. Preoperative concomitant chemoradiation should be explored where feasible. For patients in whom gross total resection cannot be accomplished, use of dose modifiers at the time of IORT needs to be evaluated (sensitizers and others).

Further evaluation of IORT in unresectable locally advanced primary malignancies is warranted in view of the excellent results in the Pamplona series. Long-term control of locally advanced gynecologic malignancies is possible in a significant number of carefully selected patients with aggressive multimodality local therapy that includes IORT.

Owing to the high incidence of distant metastases, especially for patients with gross residual disease at the time of IORT, the search for effective maintenance chemotherapy is warranted. In view of survival advantages found with concomitant chemoradiation versus irradiation alone in multiple positive US randomized trials for cervix cancer patients, concomitant chemotherapy will need to be fully incorporated in IORT trial designs, and the value of maintenance chemotherapy needs to be evaluated with cisplatin- or mitomycin-based regimens.

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Chapter 21
Genitourinary Cancer

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Keywords Genitourinary (GU) cancer • Renal cancer • Prostate cancer • Bladder cancer • IORT for GU cancer

Bladder Cancer

Results with Non-IORT Approaches

Radical cystectomy, with a pelvic lymph-node dissection, is considered the standard treatment for invasive bladder cancer. The optimal goals of treatment for any invasive bladder cancer should include long-term survival, prevention of both pelvic relapse and development of metastases and an excellent quality of life. This treatment has achieved excellent oncological results with 7% local relapse rates and 5- and 10-year disease-free survival rates of 68 and 60%, respectively [1]. However, radical cystectomy results in erectile impotence, infertility, and involves the problem of urinary diversions compromising the quality of life.

In order to avoid these adverse effects, bladder-preserving treatments have been evaluated as a viable option in selected patient candidates to radical cystectomy. Bladder preservation strategies for muscle-invasive bladder cancer have evolved from single modality to multimodality treatment

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_21,

Table 21.1 Intraoperative irradiation for bladder cancer

Author	#	Clinical stage	Treatment	5-year local control (%)	5-year survival (%)
van der Werf-Messing et al. [3]	328	T2	EBRT, Ra-226	77	56
Batterman et al. [5]	85	T2	EBRT, Ra-226	74	55
Mazeron et al. [4]	24	T2	Resection, Ir-192, EBRT	92	58
Matsumoto et al. [2]	28	T2	IOERT, EBRT	82	62
Nieuwenhuijzen et al. [20]	108	T1–T2	EBRT, Ir-192	73	62
van Onna et al. [13]	111	T1–T2	EBRT, Ir-192	–	70
van der Steen-Banasik et al. [12]	76	T1–T2	EBRT, Cs-137, Ir-192	70	57
Blank et al. [10]	122	T1–T2–T3	EBRT, Ir-192	76	73

EBRT external beam radiation therapy; *Ra-226* brachytherapy, radium needles; *Ir-192* brachytherapy, afterloading iridium; *IOERT* intraoperative electron irradiation

approaches (transurethral resection and chemoradiation). Promising results in terms of organ preservation were achieved in the past using sophisticated radiotherapy techniques such as brachytherapy or IOERT in combination with EBRT [2–13] (Table 21.1).

Contemporary approaches in patients with clinically staged muscle-invasive bladder cancer can achieve complete response rates of 60–85%, 5-year survival rates of 50–60%, and survival rates with an intact bladder of 40–45% [14]. The approach to organ preservation trails including radiotherapy should be based upon strict selection criteria: only those patients who exhibit a complete tumor response after initial chemotherapy induction therapy are candidates for high-dose EBRT + cisplatin in an effort to preserve the bladder [15]. Within this frame work, IOERT is an attractive boost modality, as it can accurately treat tumors located in the lateral and posterior bladder walls while avoiding irradiation of small bowel and rectum [16, 17].

Although randomized trials comparing radical cystectomy with combined therapies for bladder preservation are not available, literature data show that overall and disease-specific survival rates in patients clinically T2–T4a treated with radical cystectomy are comparable to those of bladder-preserving protocols [14].

Treatment Factors

Surgical

Different surgical approaches have been described to perform intraoperative brachytherapy or IOERT. A baseline pretreatment transurethral bladder resection should be performed prior to treatment with neoadjuvant chemotherapy or chemoradiotherapy in order to determine clinical stage and characteristics of the lesion (number, size, location, exophytic vs. ulcerative). Three to five weeks following completion of neoadjuvant chemotherapy or chemoradiation (chemoRT), patients should be re-evaluated cystoscopically for the assessment of the primary tumor response to chemotherapy or chemoRT.

Both the re-evaluation cystoscopy and the open surgical procedure for IORT should be at least two and no more than 5 weeks following the completion of chemotherapy or chemoRT. A midline longitudinal incision from the pubis to the umbilicus is performed. Patients should undergo a pelvic lymph node dissection by an extraperitoneal approach, if possible. The intent is to retrieve lymph nodes around the external and internal iliac vessels and from obturator fossa, bilaterally. Both ureters are dissected free over the extravesical part of their length to ensure that they are excluded from the IOERT field. The bladder should be opened with an incision that is not directly adjacent to the original tumor

site and that is judged to give good exposure for IOERT. The extravesical tissue deep to the primary tumor should be palpated and biopsied to assist determination of electron energy selection. Following IOERT, bladder closure and bladder catheter drainage will be managed conservatively with an anticipation that the healing of the cystotomy may be compromised by prior chemotherapy and EBRT. This surgical approach could be questionable because of the risk of tumor seeding following the bladder opening which would be minimized by the delivery of preoperative chemoRT. Alternatively, the IOERT applicator can be introduced through the anterior laparotomy incision and the whole collapsed bladder included in it. The small bowel is mobilized out of the pelvis with fixed retractors.

Finally, outside the organ-preserving approaches protocol, IOERT could be also useful in order to improve local control in locally advanced disease where surgery is not able to obtain negative margins. In this setting, IOERT could be delivered to the surgical tumor bed after removal of the radical cystectomy specimen. The target volume is represented by macroscopic residual tumor or area at risk of tumor relapse. Until now, only preliminary and unpublished studies report this approach.

With intraoperative or perioperative brachytherapy, a median suprapubic laparotomy approach is performed and the iliac lymph nodes are exposed and biopsied in order to ascertain the pathological stage. The bladder is then opened at some distance from the tumor location. After accurate tumor inspection and palpation, the geometry of the implant is decided and curved needles are inserted to cover the clinical target volume (CTV) and then substituted by plastic guide wires. The plastic loops are fixed by stitching on the skin.

EBRT

A four-field box or 3-D conformal irradiation (3-D CRT) technique is usually employed with ≥10 MV photons to perform the external beam component of irradiation for bladder cancer. Irradiation fields are typically designed with CT-based planning. Treatment volume should include the entire bladder, the bladder tumor volume with any extravesical components, the prostate and prostatic urethra in male patients, and the regional lymphatics, i.e. hypogastric, external iliac, and obturator lymph nodes (Fig. 21.1a). Typically, the treatment volume should extend inferiorly to at least the superior aspect of the obturator foramen (≥2.5 cm beyond bladder mucosa) and superiorly to just below the sacral promontory. Field width should extend 1.5 cm lateral to the bony pelvis. For lateral fields, the anterior boundary of the fields should be 2 cm anterior to the most anterior portion of bladder mucosa as demonstrated by imaging study (CT or air contrast cystogram). Posteriorly, the fields should extend at least 2.5 cm posterior to the most posterior portion of the bladder or tumor mass seen on CT. The lateral fields should be shaped with corner blocks inferiorly to shield the tissues outside the symphysis and the anal canal. Intensity modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) techniques by conventional linac or helical tomotherapy may be implemented to improve dose distribution while sparing surrounding normal tissues.

Concomitant Administration of Chemotherapy with EBRT – Cisplatin and/or other drugs (5-fluorouracil, paclitaxel, gemcitabine) should be administered during the course of EBRT to improve tumor response. A typical treatment schedule consists of administration of cisplatin 100 mg/m^2 given as a 30- to 40-min infusion 2 or more hours after EBRT on days 1 and 21.

IOERT

IOERT applicator size, bevel angle, and beam energy should be chosen so that the total target volume (the pretreatment tumor volume) is enclosed within the 90% isodose line. Typically, the applicators are between 5 and 7 cm in internal diameter and should allow a 1.0- to 1.5-cm margin around the entire initial tumor volume (in responders, the margin should be larger with regard to the residual

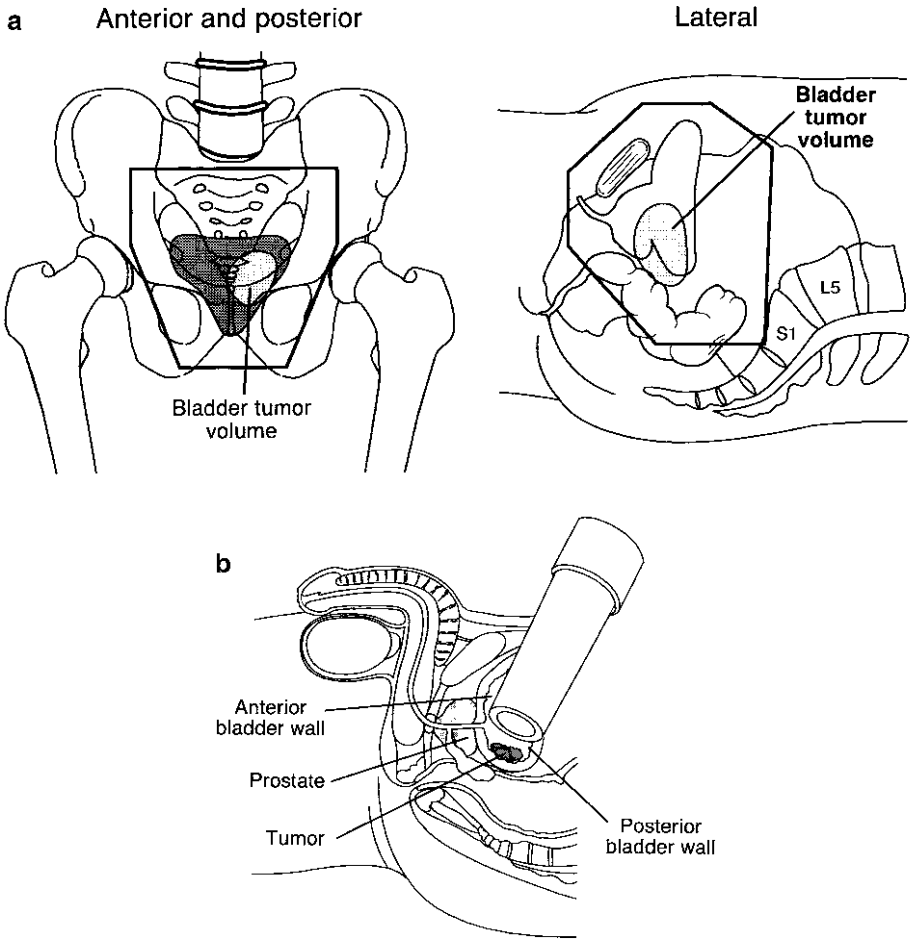

Fig. 21.1 Idealized artist's depiction of irradiation techniques for bladder cancer. (**a**) EBRT four-field technique. (**b**) IOERT treatment (modified from Shipley [16, 17]).

lesion). Electron beam energies can range between 9 and 18 MeV but should be adequate to assure coverage at the appropriate depth. There should be protection of the rectum and/or rectosigmoid by angulation of the treatment beam and/or by packing posterior to the target volume with either lead or laparotomy pads to prevent penetration behind the tumor target volume into the structures. Bolus material may be needed to improve the dependency of surface dose on the chosen electron energy. A suction catheter should be used to assure that excess urine does not collect over the surface of the tumor during treatment. If the peritoneal cavity has been opened for exposure, the use of omentum to cover either the perivesical biopsied site and/or the irradiated site should be considered.

A sagittal schematic of IOERT applicator placement for the treatment of a patient with locally advanced – stage T3b – bladder cancer is seen in Fig. 21.1b. The bladder has been opened superiorly and the treatment applicator is angled laterally to avoid irradiating the right ureteral orifice and the rectum.

Perioperative Brachytherapy

Brachytherapy may represent a curative treatment for selected high-risk superficial and solitary muscle-infiltrating tumors. Typically, this technique can be performed in T1–T2 tumors, 5 cm or

less in diameter. Brachytherapy may be combined with partial cystectomy depending from the response after previous EBRT and/or chemotherapy.

The CTV should include macroscopic disease or the tumor bed with a safety margin of 1 cm including the full thickness of the wall. During the procedure, the bladder tumor is implanted by plastic tubes that are fixed to the skin. Usually, dummy sources are loaded to check the position of the plastic tubes under fluoroscopy and perform a CT scan to calculate the dose distribution. Iridium-192 wires are inserted 4–5 days after the surgical procedure with low dose-rate (LDR), pulsed dose-rate (PDR), or high dose-rate (HDR) technique. The prescribed dose depends on the previous preoperative EBRT dose and fractionation and on the dose rate of brachytherapy. Usually, it may range from 25 to 30 Gy (after 40 Gy EBRT/2 Gy/fx) up to 60–65 Gy after lower-dose EBRT when using LDR.

Results with IORT

Japan IOERT Series

Historically, the largest reported series using IORT in bladder cancer patients were from Japan [2, 18]. The characteristics of the treatment program tested were preservation of the bladder in combination with a high-dose IOERT boost of 25–30 Gy and fractionated EBRT, starting 3–4 weeks postoperatively, to moderate total doses of 30–40 Gy in 15–20 fractions over 3–4 weeks. Other technical aspects of interest were the use of low-energy electron beams (4–6 MeV) and the size of the applicators (4, 5, and 6 cm in diameter).

In a 13-year period from 1965 to 1978, 116 patients were treated. Tumors were generally located at the ureteral orifice (36 patients – 44%), the posterior wall (18 patients – 22%), or the lateral walls (15 patients – 19%). Tumor diameter was less than 3 cm in most cases. Pathologic tumor stage was Ta, T1, and T2 in 94 cases.

The cumulative total relapse rate in these early tumor stages was 29% within 6 years of follow-up. There was a significant difference in recurrence rate between the group with solitary tumors (8%) and the group with multiple tumors (27%). Cystectomy was performed in five cases as rescue treatment for recurrences. Thirteen local tumor recurrences were documented in the period evaluated.

The survival rate for patients with Ta, T1, and T2 tumors was 72%. No long-term survivors were seen among T4 patients, but there were some long-term survivors among T3 patients.

The complications related to the treatment program included three cases of flank pain for several days after irradiation, presumably due to acute obstruction of the ureteral orifice, which was included in the irradiation field. No serious late complications were observed except in one patient who had a contracted bladder after 30 Gy IOERT and 21.5 Gy EBRT, requiring urinary diversion 12 years later because of progressive bilateral hydronephrosis. Radiation proctitis or other bowel damage was not experienced. Obstruction of the bladder neck or ureteral orifice did not occur.

French and Belgium Series

Various IORT modalities have been used for the treatment of urinary bladder cancer over time.

IOERT

At the Centre Hospitalier Lyon Sud [19], a phase I–II study was performed using IOERT boost in the combined bladder preservation treatment of muscle-invasive bladder carcinoma (Table 21.2). In

Table 21.2 Lyon and Pamplona IOERT results in bladder cancer

Author	#	Stage	Downstage	Local relapse	Survival
Gerard et al. [8]	27	22 T2 5 T3	24/24 (100%) CCR	4 (15%)[a]	53% (5 years)
Aristu et al. [unpublished data]	40	7 T2 17 T3 11 T4	27 (67%) pT0	3 (7%)[b]	46% (7 years)

CCR clinical complete response
[a]Bladder preserved
[b]Bladder removed

a 4-year period (4/1990–4/1994), 27 patients (median age 63, male 23) were treated with IOERT and bladder preservation treatment modalities with the restriction criteria of having a solitary tumor lesion, located in the fixed portion of the bladder and size of less than 6 cm in maximum diameter. Tumor histology was transitional cell in 25 and squamous cell in two cases. Clinicopathological stages were T2 ($N=22$) or T3 ($N=5$) N0 M0. Following lymphadenectomy, four patients pN1 were detected. In 19 cases, patients were deemed ineligible for radical cystectomy due to severe comorbidity or refusal of bladder mutilation.

The treatment program included the administration of preoperative chemoRT (small pelvis four-field technique, 18 MV photons, 48 Gy/24 fractions/35 days and two concomitant courses of cisplatin 30 mg/m^2/days 1–3 and 28–30 continuous intravenous infusion). In 13 patients, two cycles of methotrexate, vinblastine, cisplatin (MVC) chemotherapy were given before irradiation and one patient pN1 received two adjuvant MVC courses. IOERT was performed with a 6- to 7-cm diameter applicator, selecting in all procedures 9 MeV electron energy and a total single dose of 15 Gy. A limited iliac lymphadenectomy was performed in 20 patients.

Cystoscopic evaluation following the preoperative chemoRT treatment (3 weeks after completion of EBRT plus cisplatin) showed all patients in complete clinical response. Local recurrences were proven in four patients (two treated by salvage cystectomy) and distant metastasis were observed in ten patients. Five-year survival was 53% for the entire group.

With a follow-up of 10–15 years, no grade 4 complication was observed in the surviving patients. Grade 3 late toxicity was noted in three patients: bladder wall and pubic bone necrosis after treatment of an anteriorly located tumor – 1 patient, bladder necrosis – 1, and ureteral stenosis – 1. There was no operative mortality.

Intra- or Perioperative Interstitial Brachytherapy

Interstitial brachytherapy can be applied in the management of invasive bladder cancer in a bladder-sparing intent. This approach was popularized in the 1980s by van der Werf-Messing. For invasive non-metastatic bladder cancer, she proposed preoperative EBRT (10.5 Gy in 3 fractions) immediately followed by a partial cystectomy combining an intraoperative placement of radium needles [3]. More recent Duch series report excellent results [3, 10, 12, 20] (Table 21.1).

Van Poppel et al. [21] treated 28 selected patients, with different stages of invasive bladder cancer, with preoperative EBRT followed by surgical exploration with or without partial cystectomy and insertion of source carrier tubes for afterloading with iridium-192. Sixteen patients (57%) were alive with no evidence of disease. Five patients (18%) died of non-cancer-related causes without evidence of recurrent tumor. Tumor progression was seen in seven patients (25%).

De Crevoisier et al. [22] recently reported excellent long-term results of conservative treatment of bladder cancer using peri-op iridium HDR brachytherapy with an afterloading technique. During

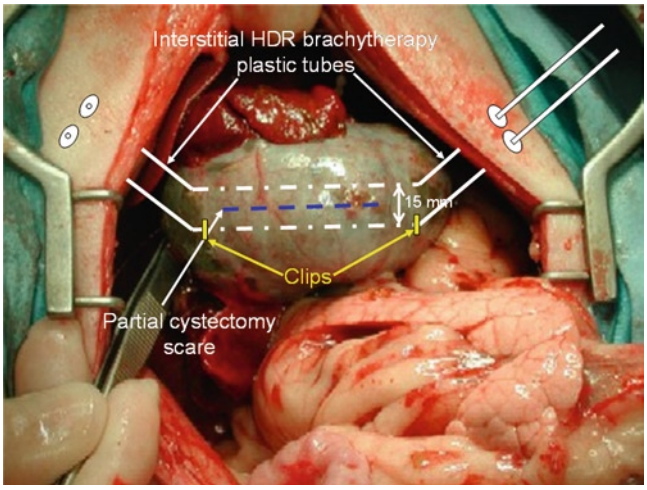

Fig. 21.2 Intraoperative high dose rate interstitial brachytherapy procedure.

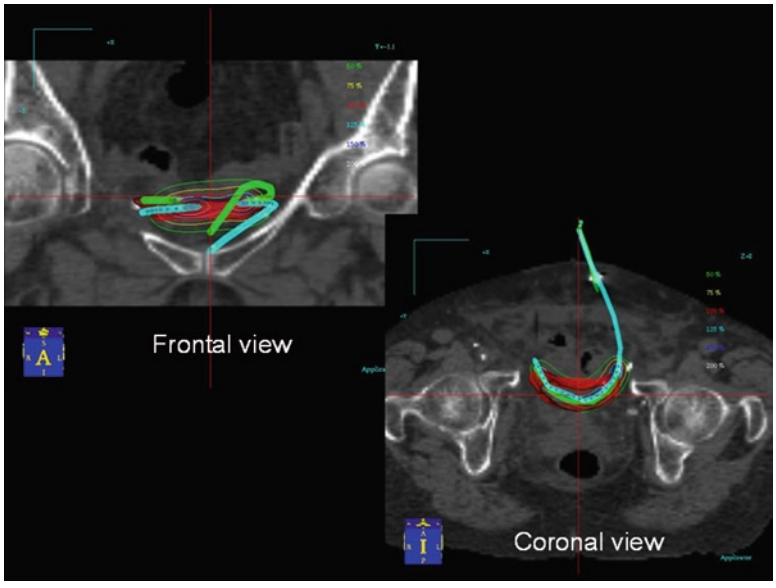

Fig. 21.3 3D reconstruction of HDR interstitial brachytherapy and dose distribution.

the surgical procedure (after partial cystectomy of the mobile part of the bladder), the radiation oncologist placed into the bladder wall two plastic tubes spaced at 10- to 15-mm distance (Fig. 21.2). Based on a CT scan performed 3–4 days postoperatively, the target volume was outlined with the help of the clips placed intraoperatively on the partial cystectomy scar. The optimization of the dose distribution was performed manually according to the modification of the dwell-time position of the HDR iridium source (Fig. 21.3). The total prescription dose was 34 Gy in ten sessions of 3.4 Gy twice a day with a 6-h interfraction interval. After completing the HDR brachytherapy procedure, the plastic tubes were removed in a painless manner.

At the Centre Antoine Lacassagne in Nice, five patients were treated with this technique between 2006 and 2008 presenting a T2-3 N0 M0 carcinoma of the dome of the bladder. After 1–3 years follow-up, all the patients were in complete remission with a good urinary and bladder function. These results are equivalent to those achieved in Paris or Lyon with low dose rate iridium intraoperative technique [9, 22].

Spanish IOERT Series

The University Clinic of Navarra (Pamplona, Spain) explored the integration of IOERT in a multidisciplinary treatment program for locally advanced bladder cancer using preoperative EBRT and more recently a combination of neoadjuvant chemotherapy and preoperative EBRT [6]. An important aspect of that experience has been the possibility it has afforded to analyze the cystectomy specimen and to correlate the pathologic findings with the previous treatment program. This information is of particular value for the development of clinical trials using IOERT as a boost modality in organ preservation protocols [7].

The treatment protocol is outlined in Fig. 21.4. An IOERT dose of 15 Gy was delivered in most patients (range 10–20 Gy) with electron energies of 9–12 MeV. EBRT started 4 weeks after the IOERT. The treatment consisted of a four-field box technique, including in the target volume the bladder and the pelvic nodal areas. A CT treatment planning system was available in all cases. The daily dose was 2 Gy, and the total dose delivered to the volume was 46 Gy in 5 weeks. Radical cystectomy was performed 4–6 weeks after completion of preoperative EBRT. Chemotherapy administered in the neoadjuvant group consisted of: cisplatin 15 mg/m^2, 24 h i.v. infusion days 1–3; 5-fluorouracil 1,000 mg/m^2 (maximum 1,500 mg/24 h), i.v. infusion days 1–3; doxorubicin 35 mg/m^2, i.v. day 1; hexamethylmelamine 150 mg/m^2, p.o. (maximum dose 200 mg/day) days 8–17. Three courses of

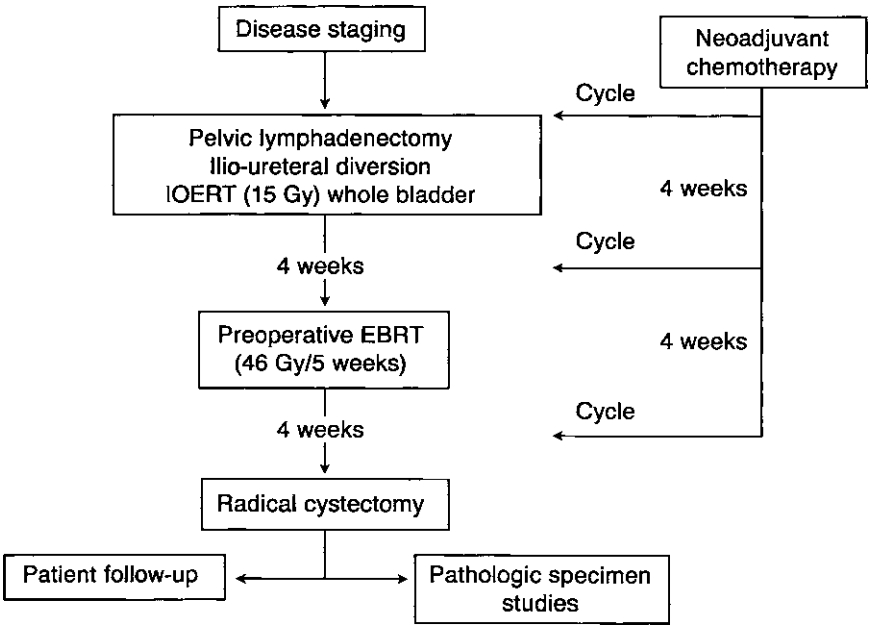

Fig. 21.4 Multidisciplinary treatment protocol for bladder cancer which integrates IOERT, University Clinic of Navarra (Pamplona, Spain).

Table 21.3 Pathologic downstaging (primary and nodal) and patterns of relapse – Pamplona series

Stage	#	Local	Mixed	Distant	Unknown
pT0N0	18	0	1	3	1
pT+N0	7	0	0	3	1
pT0N+	9	0	0	4	0
pT+N+	6	1	1	1	0
Total	40	1 (2%)	2 (5%)	11 (27%)	2 (5%)

the above-described chemotherapy were given, commencing every 4 weeks. The initial cycle started just after the transurethral resection and the confirmation of invasive bladder cancer. The second chemotherapy course was given after the laparotomy for ureteral diversion, IOERT, and lymphadenectomy. The third course started upon the completion of preoperative EBRT, 4 weeks before the second surgical intervention for cystectomy.

The unpublished analysis of these data (study period 11/87–10/93; analysis performed in 12/95) showed 40 patients treated with the complete program: median age 60 years old (range 44–74), 35 males; 34 patients with Karnofsky index >70%. Clinicopathologic tumor stages were: 7 T2, 17 T3, 11 T4, 5 N+. Posttreatment pathology showed 27 pT0 (67%) and 15 pN+ (37%). The follow-up period for the entire group ranges from 2 to 96 months (median 35 months).

Patterns of tumor relapse show 24 patients NED, 1 local recurrence alone, distant sites of relapse – 11 patients, mixed local and distant failure – 2 and unknown relapse status – 2. Local recurrences have been observed in 2 of 22 pT + or N+ patients (33%) and 1 of 18 pT0N0 (5%) (Table 21.3).

Cause-specific survival at 7 years was projected at 46% for the entire group. Actuarial survival was 52% in pT0N0 vs. 38% for any pathology-positive patients. Survival at 7 years by initial tumor stage was 85% T2, 48% T3, and 10% T4.

Renal Cancer

Results with Non-IORT Approaches

The standard therapy for renal cell carcinoma is radical nephrectomy. Local control and survival rates after surgery alone are satisfactory for T1–T2 N0 (LC = 90–100%; 5-year OS = 80–90%) but are poor for locally advanced and N+ disease (LC = 70–80%; 5-year OS = 0–40%) [23, 24]. The isolated local recurrence after radical nephrectomy is uncommon (0.7–3.6%) but it is associated with a poor prognosis. An aggressive surgical approach seems to prolong survival when the mass is completely resected with negative margins.

Randomized trials testing preoperative or postoperative irradiation failed to demonstrate an advantage either for local control or overall survival [25–28]. In these studies from a few decades ago, inadequate patient selection, low-radiation doses, and poor radiation technique may have negatively influenced the results also in terms of toxic effects in the surrounding organs.

More recent nonrandomized series have shown that resectability and local control in locally advanced disease can be substantially increased by using radiotherapy with CT-based technique for treatment planning and total doses of about 50–60 Gy [29]. Moreover, recent data about the implementation of high dose per fraction by stereotactic technique seem to show high percentage of local control rate even in unresectable cases [30].

Treatment Factors

Surgical

The surgical approach to cytoreductive surgery associated with IOERT has to reconcile the two goals of this treatment program; namely, the right approach to the tumor mass to be resected and a similar satisfactory approach for the placement of the applicator for the use of IOERT. Open surgical approaches (anterior and flank/thoracoabdominal) are determined by tumor location, body habitus, and prior surgical history. A flank approach in obese patients can provide optimal exposure and minimize morbidity associated with a larger midline incision. A flank approach can also avoid adhesions in patients with prior abdominal surgery. Anterior incisions (midline, paramedian, and subcostal) provide transperitoneal and intraperitoneal exposure. By entering the posterior peritoneum via a midline incision the renal pedicles are easily accessed and controlled. Radical nephrectomy involves the en bloc removal of the affected kidney, adrenal gland, perirenal fat, proximal ureter, and Gerota's fascia. Vascular control is a priority in dealing with larger renal tumors. In all the preparations around the arterial vessels, great emphasis is given to avoid removing the adventitial tissue. This is done to avoid a spontaneous perforation following the EBRT, resection, and IOERT.

All efforts are made to remove all visible cancer. This is facilitated, particularly in renal cell cancer, through the use of preoperative EBRT which seems to involve the cancer in a capsule which is then easily dissected out from the retroperitoneal area, particularly around the large vasculature of the vena cava and aorta. Patients may suffer from prolonged ileus following the surgical treatment program plus IOERT. Nasogastric suction is usually necessary for a more prolonged period of time.

EBRT

EBRT can be delivered either before or after the surgical procedure by using CT-based 3D conformal techniques to optimize the radiation dose distribution by maximizing target volume coverage while minimizing the dose to normal structures such as bowel, liver, spinal cord, and contralateral kidney. Total radiation doses of 45–50 Gy in 1.8- to 2-Gy daily fractions to the tumor or to the nephrectomy bed and regional lymph nodes are appropriate. Treatment plans should be designed to keep no more than 30% of the liver from receiving doses >36 to 40 Gy. The contralateral kidney dose should not exceed 20 Gy in 2–3 weeks. The spinal cord dose should be limited to 45 Gy in conventionally fractionated doses of 1.8–2 Gy per day. IMRT may be a reasonable treatment option due to the sensitivity of adjacent surrounding structures. Uncertainties in target localization such as gating or breathing control should be taken into account especially if IMRT is planned. Patients with systemic metastases do not proceed to exploratory laparotomy or IOERT except for the situation of a solitary resectable metastasis.

IOERT

Intraoperative irradiation with 6–12 MeV electrons can usually be delivered to the para-aortic or caval region and/or renal fossa (tumor bed). The dose of IOERT, as calculated at the 90% isodose curve, varies from 10 to 20 Gy depending on amount of residual disease remaining after maximal resection and the dose of EBRT that has been given preoperatively or is feasible postoperatively. Small vascular or titanium clips should be placed around areas of adherence or residual disease, before wound closure, to facilitate the identification of target volume of postoperative EBRT, if indicated and the follow-up studies.

IOERT Clinical Results

Mayo Clinic Series

IOERT has been utilized since 1983 at Mayo Clinic as a component of therapy for 49 patients with locally advanced genitourinary malignancies deemed unresectable for cure [31, 32]. The patient population included 16 females and 33 males with a median age of 62 years (range, 7–77). Nine patients had advanced primary disease while 40 (80%) had recurrent disease diagnosed with a median of 2.3 years after primary treatment. Site of primary origin was kidney – 28, bladder – 8, prostate – 7, ureter – 2, female genitourinary tract – 3, and urethra – 1. Tumor histology was as follows: adenocarcinoma – 28, transitional cell – 11, squamous cell – 5, mesoblastic nephroma – 3, and sarcoma – 2. Sixteen patients (33%) had been previously irradiated to a median dose of 45 Gy (range, 10–70 Gy). Maximum resection with IOERT was preceded or followed by EBRT in 42 patients (median dose 49.90 Gy; range, 5–56 Gy). Electrons ranging in energy from 6 to 18 MeV were utilized to deliver a median IOERT dose of 15 Gy (range, 7.5–30 Gy) (Fig. 21.5). Six patients received chemotherapy concurrently with EBRT and four patients received additional systemic chemotherapy. All patients were followed until death or for a median of 3 years for the 15 surviving patients.

Actuarial survival and disease relapse data are presented in Table 21.4. Survival was significantly better for kidney patients (5-year 37 vs. 16%, $p=0.05$) and for patients without gross residual at the time of IOERT (5-year 41 vs. 0%, $p<0.0001$). Central failure was higher in patients with gross residual (3-year 28 vs. 7%, $p=0.03$). Grade 3 toxicity related to IOERT was observed in two patients (4%). Neuropathy was observed in six patients including one with grade 3, four with grade 2, and one with grade 1 neuropathy.

Pamplona Series

Feasibility and early clinical results using IOERT at the time of surgical management of recurrent or locally advanced renal cancer was reported at the University Clinic of Navarra [33]. In a 20-month period, 11 consecutive patients with stage III (five patients), IV (three patients) or lumbar fossa recurrence (three patients) were treated with a combination of surgical tumor resection, IOERT to the tumor or tumor bed region and postoperative EBRT (not given in four patients). Histology was confirmed as clear cell adenocarcinoma in all surgical samples, except for one recurrent patient in which histology was consistent with transitional cell carcinoma. Age ranged from 40 to 76 years old (median 60). Macroscopic postsurgical residual disease was evident in four cases; close margins or microresidue was assumed in the remaining seven cases.

The IOERT target volume was encompassed by an applicator size of 10 cm diameter in four procedures, 7 cm in 3, 8 cm in 2, 9, and 12 cm in 1 each. The electron energy selected for treatment was 9 MeV – 6, 12 MeV – 1, 15 MeV – 2, 18 MeV – 1, and 20 MeV – 1. Total single IOERT dose was 15 Gy – 8, 10 Gy – 2, and 20 Gy – 1. EBRT was added in seven patients, ranging from 30–45 Gy (five patients).

With a follow-up period at the time of publication of 2–33 months (median 8 months), patterns of tumor progression showed three patients with a distant relapse (three lung metastases together with two liver metastases). One of the three had a local relapse at 7 months follow-up from IOERT (no EBRT was administered in this particular case, IOERT dose was 20 Gy, residual disease was microscopic and the applicator size and electron energy were 7 cm and 9 MeV, respectively). An interval analysis of the reported group of patients identified long-term survivors without evidence of recurrent disease (three patients with more than 3 years follow-up). No early or late relevant toxicity related to the local components of treatment was detected.

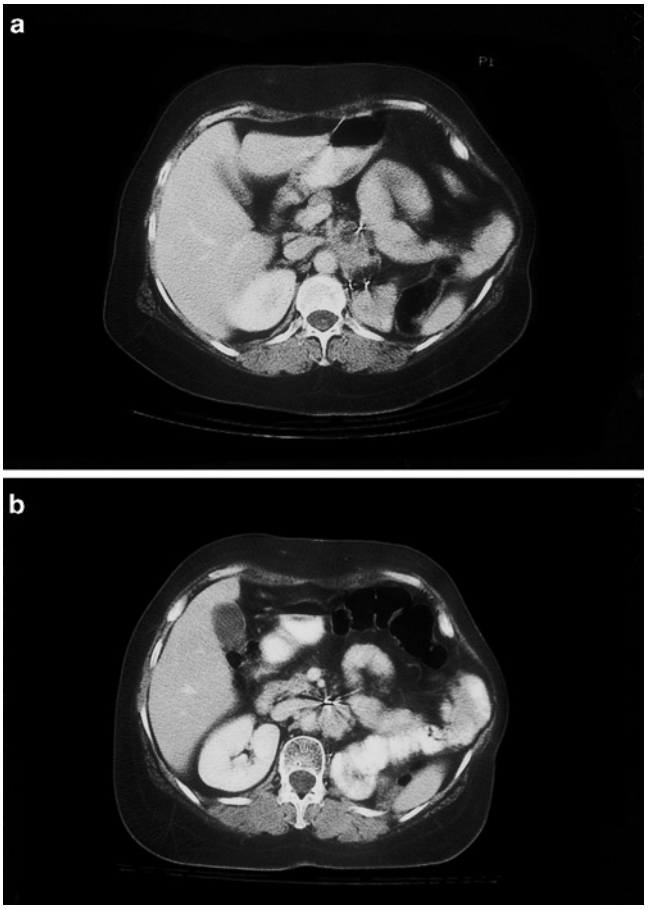

Fig. 21.5 Tumor regression in a patient with recurrent renal cancer who received preoperative EBRT before resection and IOERT at Mayo Clinic Rochester. (**a**) Preirradiation CT scan with bulky left para-aortic adenopathy and lack of fat plane adjacent to aorta. (**b**) Postirradiation scan 4 weeks following completion of 45 Gy/25 fractions/5 weeks and 2.5 months after initial scan; note shrinkage of mass with improved fat planes relative to aorta. An IOERT dose of 12.5 Gy was given after a marginal gross total resection.

Table 21.4 Survival and patterns of relapse in 49 IOERT patients with locally advanced genitourinary malignancies deemed unresectable for cure at the Mayo Clinic [32]

	#	Median S (months)	5-year OS	3-year LR	3-year CR	3-year DM
Primary vs. recurrent						
Primary	9	31	48%	24%	24%	25%
Recurrent	40	20	25%	19%	10%	79%
P value	–	–	0.06	0.59	0.23	0.002
Primary site						
Kidney	28	29	37%	10%	12%	72%
Non-kidney	21	13	16%	35%	12%	63%
P value	–	–	0.05	0.03	0.95	0.72
All patients	49	20	29%	20%	13%	70%

IOERT intraoperative electron irradiation, O*S* overall survival, *LR* local relapse (external beam irradiation field), *DM* distant metastasis, *CR* central relapse (IOERT field)

Heidelberg Series

A series of 11 patients with renal cancer (primary – 3, locally recurrent – 8) treated at the University of Heidelberg with maximal resection, IOERT (15–20 Gy) with 6–10 MeV and postoperative EBRT (40 Gy in 2 Gy fractions, 5 days per week) was reported by Eble et al. [34]. With mean follow-up of 24 months, all patients were controlled locally, but distant metastases occurred in 5 of 11 (lung – 3, bone – 2). Local tumor control in the entire group was 100%. Overall and disease-free survival rates at 4 years were 47 and 34%, respectively.

UCSF Series

At the University of California, San Francisco (UCSF), 14 patients underwent resection of recurrent renal cancer and 10 also received IOERT [35]. Mean time to relapse was 40 months. Nine of 14 subsequently died of disease (mean 17 months) and five were alive (mean 66 months; range 14–86 months). Survival was 40% at 2 years from surgery and 30% at 5 years.

Prostate Cancer

Results with Non-IORT Approaches

The results of the treatment for prostate cancer are quite favorable for low-risk patients with relapse-free survival rates of 80–92% at 5 years and of 76–92% at 10 years either using radical prostatectomy or curative radiotherapy but are less satisfactory for intermediate-risk and even more for high-risk cases where combined treatments including hormone therapy, radiotherapy, and/or surgery can achieve only 37–62% and 44% or less of RFS at 5 and 10 years, respectively [36]. Local failure occurs in more than 40% of patients with locally advanced disease after radical prostatectomy and biochemical relapse in 24–72% after radiotherapy and hormone therapy [23].

Treatment Factors

IOERT without prostatectomy was used at Kyoto University and at Saitama Cancer Center in Japan as a single treatment or combined with lymphadenectomy or EBRT to pelvic lymph nodes [37–40]. A perineal approach was mainly used to deliver doses of 25–35 Gy in a single fraction by electrons of 8–14 MeV energy. The IOERT dose was limited to 20–25 Gy when combined with pelvic EBRT (Table 21.5).

A different treatment approach was more recently adopted by three Italian centers that selected high-risk patients based on preoperative risk factors such as PSA level, Gleason score, clinical stage, and number of positive biopsy cores. The selection criteria were oriented to the intermediate-risk patients in the Saracino's series and to the high-risk patients in the other two studies [36, 41, 42].

In these centers, IOERT was combined with retropubic radical prostatectomy and pelvic lymphadenectomy. Saracino et al. described 34 cases treated after radical prostatectomy to total IOERT doses of 16–22 Gy by 7–9 MeV electrons; no EBRT was given. In vivo dosimetry for urethra and rectum was performed [36]. Orecchia et al. and Krengli et al. reported on series of 11 and 38 patients, respectively, treated in a similar fashion before prostate removal to total doses of 10–12 Gy prescribed to the 90% isodose using 9–12 MeV IOERT [41, 42].

Table 21.5 Treatment factors of the series of locally advanced prostate cancer treated by IOERT

Author	#	Approach	Surgery	IOERT energy/dose	EBRT
Takahashi et al. [37]	14	Perineal	No prostatectomy	10–14 MeV/28–35 Gy* (single dose) 20–25 Gy* combined with EBRT	50 Gy to pelvic nodes
Abe et al. [38]	21	Perineal	No prostatectomy	8–14 MeV/28–35 Gy* (single dose) or 20–25 Gy* combined with EBRT	50 Gy to pelvic nodes
Kojima et al. [40]	30	Perineal/ retropubic	Lymphadenectomy No prostatectomy	–	–
Higashi et al. [39]	35	–	No prostatectomy	25–30 Gy	30 Gy
Orecchia et al. [41]	11	Retropubic	Before prostatectomy	8–10 MeV/12 Gy*	45 Gy, 1.8 Gy/fx
Saracino et al. [36]	34	Retropubic	After prostatectomy	7–9 MeV/16–22 Gy	No
Krengli et al. [42]	38	Retropubic	Before prostatectomy	9–12 MeV/10–12 Gy*	46–50 Gy, 2 Gy/fx

*dose prescribed to the 90% isodose

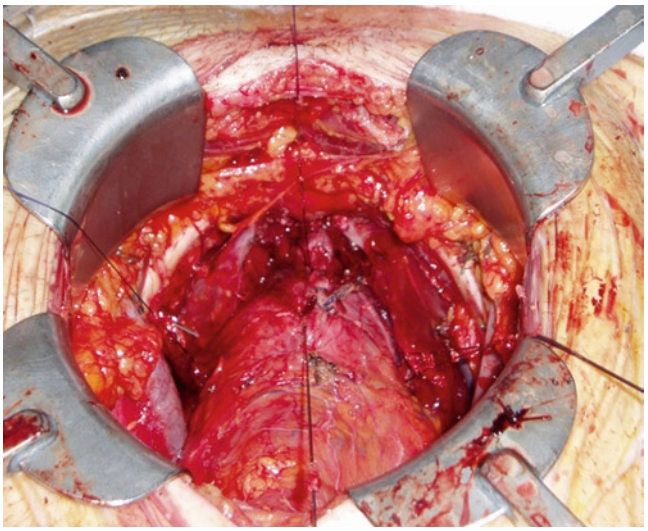

Fig. 21.6 Prostate exposure for IOERT procedure for high-risk, locally advanced prostate cancer.

From the surgical point of view, retropubic space was approached by a midline subumbilical-pubic incision. The pelvic fascia was prepared and the IOERT procedure started after exposure of the anterior aspect of the prostate, section of the pubo-prostatic ligaments, and control of the deep dorsal vein plexus (Fig. 21.6). The apex of the prostate and the endopelvic urethra were visualized. A stitch is placed as a marker of the bladder neck. First, the anterior–posterior prostate diameter and the distance from prostate surface to the anterior rectal wall were measured by intraoperative ultrasound (Fig. 21.7). Based on clinical and ultrasound parameters, the appropriate collimator and beam energy were chosen in order to include the prostate gland and the surrounding soft tissues with a suitable margin for subclinical disease of 0.5–1 cm. Rectal dose was measured "in vivo" by radio-chromic films placed on the surface of a rectal probe.

All cases with evidence at pathology examination of extracapsular extension and/or positive surgical margins were scheduled for postoperative EBRT delivered to prostate bed about 3 months

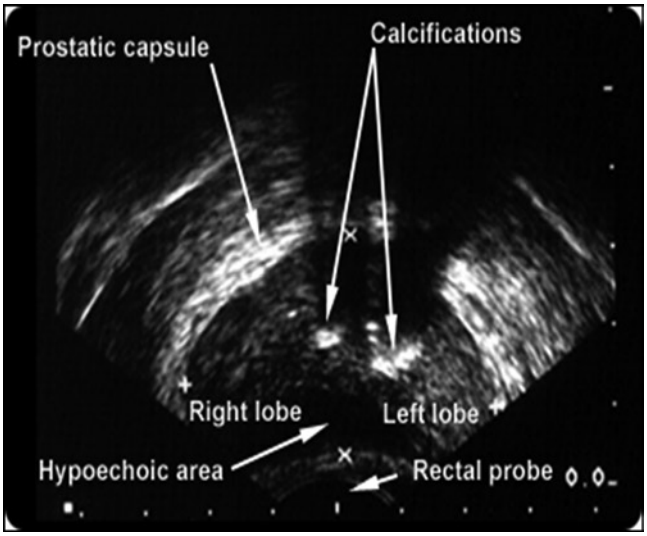

Fig. 21.7 Intraoperative ultrasound examination preliminary to IOERT procedure in prostate cancer.

after surgery by using three-dimensional conformal radiotherapy with 4–6 customized beams or dynamic arcs to a total dose of 45–50 Gy in 25 fractions (2 Gy/fraction). Adjuvant hormonal therapy was administered in patients with pT3-4 disease or positive nodes.

IOERT Results

Japan Series

The series reported in the literature consist mainly in pilot and feasibility studies on a relatively small number of patients (Tables 21.5 and 21.6). Local control was obtained in more than 80% of cases without prostatectomy in the Japanese studies with OS rates ranging from 43 to 72% at 5 years with 92% for the subgroup with stage B. These studies using high single dose report no severe toxicity, apart from very high rate of hematuria and some urinary complications including chronic cystitis and urethral stricture. The authors [39, 40], however, preferred to switch from a perineal to retropubic approach because of the potential risk of rectal damage, impossibility to perform lymphadenectomy and discomfort of the patient who cannot maintain the seated position for a longtime after the procedure.

Italian Series

The Italian studies report a relatively low rate of IOERT toxicity with most intolerance related to the surgical procedure than to the IOERT itself and mainly consisting of lymphocele, hematoma, and anastomotic leakage [41, 42]. Favorable results in terms of LC and BRFS were observed in the Saracino's study after a median follow-up of 41 months [36]. In this series, unfavorable prognostic factors were stage >T3, PSA >10 ng/ml at univariate analysis and surgical positive margins at both univariate and multivariate analyses. Postsurgical T2 stage was detected in 53% of cases in the Saracino's series and 36% in the Orecchia's series, and 37% in the Krengli's series. In these cases, postoperative EBRT was not performed (Tables 21.5 and 21.6).

Table 21.6 Results of the series of locally advanced prostate cancer treated by IOERT

Author	Local control	Survival	Early toxicity	Late toxicity	Prognostic factors
Takahashi et al. [37]	86%	–	No severe IOERT related	No severe IOERT related	–
Abe et al. [38]	81%	72% OS at 5 years	100% hematuria 10% pollakiuria	1 chronic cystitis, 1 urethral stricture	–
Kojima et al. [40]	–	43% OS at 5 years	–	–	–
Higashi et al. [39]	–	92% (stage B), 87% (stage C) OS at 5 years	No critical cystitis, proctitis, anal bleeding	No critical cystitis, proctitis, anal bleeding	–
Orecchia et al. [41]	–	–	Perioperative: 1 lymphocele, 3 anastomotic leakage	–	–
Saracino et al. [36]	91%	77% BRFS at 3 years	No toxicity	No toxicity	UA: T-stage >3, PSA >10, positive SM MA: positive SM
Krengli et al. [42]	98%[a]	100% OS[a]	Perioperative: 5 (16%) lymphocele, 2 (6%) hematoma EBRT: 11% G2 (rectal), 4% G2 (urinary)	6.8% bladder neck stricture[a]	–

IOERT intraoperative electron irradiation, *OS* overall survival, *BRFS* biochemical relapse-free survival, *UA* univariate analysis, *PSA* prostate-specific antigen, *SM* surgical margins, *MA* multivariate analysis, *OS* overall survival, *EBRT* external beam irradiation

[a]Unpublished data on 44 patients after 24 months mean follow-up

Testicular Cancer (Retroperitoneal Disease)

Testicular cancer either in the seminomatous or in the nonseminomatous variety is a very sensitive tumor to chemotherapy and radiation; however, IORT as potential dose escalation treatment modality has not extensively been tested. Controversy exists regarding the management of residual disease following chemotherapy with options of simple observation, surgical resection, or irradiation. Surgery is usually preferred in case of residual mass from nonseminomatous tumor or seminomatous tumor with residual mass ≥3 cm which are often not radically resectable and may contain viable tumor cells in up to 50% of cases making the risk of relapse not negligible [43]. In this situation, IOERT can deliver a high radiation dose to the high-risk region while sparing the surrounding radiosensitive structures such as bowel, ureters, and kidneys.

A case of unresectable retroperitoneal recurrence of a nonseminomatous testicular tumor treated by IOERT was described by Cromheecke et al. [44]. IOERT was given to a dose of 20 Gy followed by EBRT to a total dose of 46 Gy in 23 fractions. Local control of the lesion was obtained for a period of about 2 years after which tumor progression into the spinal canal developed.

In a series of four patients affected by advanced seminoma, IOERT was used to treat retroperitoneal residual disease following chemotherapy and incomplete surgical resection [43]. Total dose was 20 Gy to the area at risk delivered with energies of 12–15 MeV through rectangular lucite applicators positioned in the abdomen after retracting the ureters and small bowel away from the irradiation field and shielding the ureters with customized lead plates. No IOERT-related complications were observed after treatment. All four patients were alive and disease free after a mean follow-up of 19 months.

Tolerance Issues

IOERT tolerance for intact or surgically manipulated GU organs/structures in animals is seen in Table 21.7.

Bladder

Both clinical and laboratory data indicate that single doses of 20–25 Gy to a portion of the bladder (<1/3) is very well tolerated with infrequent compromise of lower urinary tract function [2, 45]. In the 116 patients treated by Matsumoto et al. only 4 complications related to IOERT were reported,

Table 21.7 Normal genitourinary tissue tolerance to IOERT in animals (usually dogs)

Tissue	MTD (Gy)	Tissue effect	Dose (Gy)
Intact structure			
Bladder	30	Contraction and ureterovesical narrowing	≥25
Ureter	30	Fibrosis and stenosis	≥30
Kidney	<15	Atrophy and fibrosis	≥20
Surgically manipulated			
Bladder	30	Healing but contraction	≥30

MTD maximum tolerated dose

even though a ureteral orifice was included in 44% of patients and the bladder neck, or trigone, in 11 patients [2, 18]. Three patients had transient ureterovesical junction obstruction, felt due to local edema. In one patient, bilateral hydronephrosis developed requiring urinary diversion. Only 1 of the 57 patients followed more than 5 years developed a clinically significant bladder contracture.

A NCI study of IOERT bladder tolerance in foxhounds showed relatively few acute or late harmful effects [45]. After cystostomy, IOERT was delivered using a 5-cm circular applicator and a 12-MeV electron beam to an area including the trigone, one ureteral orifice, and proximal urethra, with escalating single doses of 0, 20, 25, 30, 35, and 40 Gy. No fractionated EBRT was delivered. Dogs were electively sacrificed at 1 and 2 years. With follow-up to 24 months, all dogs given ≤25 Gy to the bladder neck and to one ureteral orifice in the NCI study had normal renal function, no abnormalities shown by serial IVP and no major loss of bladder volume or contractility by serial cystometric studies. Obstruction of a ureteral orifice and renal failure secondary to bilateral hydronephrosis was seen in 3 of 15 dogs that received 25, 35, and 40 Gy. At autopsy, histologic changes comprising mucosa thinning and telangiectasia with submucosal fibrosis were confined to the IOERT field and appeared to be dose related. The bladder epithelium remained intact at all doses. The ureterovesical junction in animals receiving 20 Gy showed mild fibrosis of the lamina propria and moderate chronic inflammation. Above 20 Gy the histologic changes at the ureterovesical junction were pronounced, with gross stenosis in three animals. The authors concluded that the bladder trigone can tolerate 20 Gy IOERT without major clinical sequelae.

In a report by Hoekstra et al. [46], an interesting new observation has been described in one of four dogs kept for long-term evaluation. This animal developed a bladder tumor 3 years after an IORT dose of 30 Gy. Microscopic study of the tissue after resection showed a hemangiosarcoma of the bladder within the IOERT field.

Ureter

In an early Mayo analysis of 51 IOERT patients with pelvic malignancies, 44% of previously unobstructed ureters became partially or totally obstructed when included in the IOERT field [47]. Ureteral tolerance was reanalyzed in a recent Mayo publication utilizing IOERT as a component of treatment in 146 patients with locally advanced or recurrent pelvic and abdominal malignancies where a portion of one or both ureters (168 ureters) was within the IOERT field [48]. IOERT dose ranged from 7.5 to 30 Gy and was associated with EBRT (50.4 Gy) in 132 cases. Follow-up ranged from 0.01 to 19.1 years (median, 2.1 years). The rates of clinically apparent type 1 ureteral obstruction (from any cause) after IOERT at 2, 5, and 10 years were 47, 63, and 79%, respectively. The rates of clinically apparent type 2 ureteral obstruction (occurring at least 1 month after IOERT, excluding ureteral obstruction caused by tumor or abscess and patients with stents) at 2, 5, and 10 years were 27, 47, and 70%, respectively. Multivariate analysis revealed that the presence of ureteral obstruction before IOERT ($p<0.001$) was associated with an increased risk of clinically apparent type 1 ureteral obstruction. Increasing IOERT dose was associated with an increased risk of clinically apparent type 2 ureteral obstruction ($p<0.04$). Obstruction rates in ureters not receiving IOERT at 2, 5, and 10 years were 19, 19, and 51%, respectively.

The ureter is a dose-sensitive structure relative to IORT but is not dose-limiting, since stents can be inserted to overcome ureteral obstruction and preserve renal function as indicated. Accordingly, when tumor is adherent to ureter, it should be included in the IOERT boost field rather than excluded in an attempt to prevent treatment-related toxicity.

Discussion and Future Possibilities

Bladder Cancer

The integration of an IOERT boost to the whole bladder in a multidisciplinary protocol combining neoadjuvant systemic chemotherapy, preoperative radiotherapy, and planned cystectomy has proven to be feasible in the Pamplona series. The sterilization rate of invasive bladder cancer, confirmed in pathologic studies of the cystectomy specimens, is high (in the range of 65%) and seems to be increased by the addition of neoadjuvant chemotherapy to the treatment program [49–51]. These findings are of importance with respect to the development of new protocols with the aim of bladder preservation. In the Lyon series, excellent bladder preservation rates were achieved with the combination of preoperative chemoRT followed by IOERT, and it would be of interest to attempt to repeat their results in other IORT institutions. IORT might have a role also in case of radical surgery for locally advanced disease in order to improve local control rates. IORT is a very attractive radiotherapy boost modality to be considered also in the future in this cancer site.

Renal Cancer

Aggressive IOERT-containing approaches appear reasonable for locally advanced renal cancers on the basis of small series from Mayo Clinic Cancer Center – Rochester, Pamplona, the University of Heidelberg and UCSF. The addition of IOERT to surgery and EBRT is associated with a high rate of local and central control and acceptable toxicity. The best candidates are untreated patients with large tumor volume and risk of positive margins after radical nephrectomy and patients with local recurrences. Distant relapse is common, especially in patients with recurrent disease. Accordingly, future treatment strategies should evaluate a systemic component of treatment (new targeted therapies).

Prostate Cancer

Longer follow-up and further clinical trials are needed to assess the real efficacy of IOERT in locally advanced prostate cancer but preliminary results are quite promising. Recent radiobiological data about the low alpha/beta value of prostate cancer cells seems to support the delivery of large dose per fraction and therefore the use of IOERT [52].

Since patient selection is preferably based upon risk category, IOERT could results in overtreatment if performed prior to prostatectomy, since a percentage of patients may be pT2 after surgery. In this sense, the best candidates for IOERT would be pT3N0 and positive margins patients, for whom the addition of EBRT after surgery improves outcomes [53, 54].

In the future, multicenter studies should be designed to clarify a number of questions: (1) Which patients could benefit from IOERT? (2) Which technique is preferable – retropubic or perineal? (3) Is single-dose IOERT safe and adequate for tumor control or should IOERT be combined with EBRT; if so, could the interval between IOERT/EBRT be shortened to 4–6 weeks? (4) Radical nephrectomy involves the en bloc removal of the affected kidney, adrenal gland, perirenal fat, proximal ureter, and Gerota's fascia. (5) Could IOERT be extended to disease stages besides locally advanced?

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Chapter 22
Pediatric Malignancies

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Keywords Pediatric malignancies • Neuroblastoma • Wilm's tumor • IORT for pediatric malignancies

Standard Treatment Results

Rationale for IORT

Outcomes in many pediatric tumors have improved dramatically over the last few decades. Eighty percent of all children diagnosed today with childhood malignancies are expected to be long-term survivors [1]. The number of long-term survivors in almost every disease site and histology has increased with advancements in combined modality therapy such that a new era in cancer therapy, treatment de-intensification to reduce late effects, has emerged. Many emerging cooperative group protocols are trying to determine the minimal amount of therapy necessary to maintain the excellent outcomes in order to minimize the morbidity of treatment. Reduction in the use of external beam irradiation (EBRT) as well as the dose when used is an attractive choice secondary to the known detrimental effects of EBRT in the developing child, including growth disturbance and secondary malignancy.

Currently, high-dose EBRT is primarily used as a part of multimodality therapy for pediatric central nervous system tumors and bone and soft-tissue sarcomas (including Ewing and rhabdomyosarcoma). Soft-tissue and bone sarcomas typically present in areas that are either difficult or morbid to resect and radiotherapy plays an important role for local control in these tumors.

The problem of achieving local control with a suitable therapeutic ratio is especially difficult in the pediatric population. The exquisite radiosensitivity of pediatric tissues results in a very narrow therapeutic window in which to balance benefits and late effects. In addition to the kidney, liver, spinal cord, stomach, and bowel, which are known to be radiosensitive organs in both adults and

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_22,

children, the morbidity of irradiating developing bones and soft tissues adds to the morbidity in the pediatric population. Neuhauser et al. [2] were the first to describe the relationship between growth compromise, radiation dose, and age in children. A significantly greater tendency toward vertebral body deformation with doses in excess of 20 Gy and age under 2 years was identified. Modern series have confirmed these effects [3].

Because of dose-limiting organs in the abdomen and pelvis, adequate local control with acceptable treatment morbidity remains a problem in the treatment of malignancies of these locations as well. IORT is an attractive option for tumors in the abdomen and pelvis because immediately adjacent radiosensitive organs can be physically displaced away from the target or mechanically shielded from the treatment beam.

Because of the dramatic improvements in survival, more data as to the type and severity of late effects after cancer therapy are emerging. Second malignancy is a serious issue after treatment for pediatric cancers with an incidence as high as 18% [1]. Modern advances in radiotherapy, such as intensity-modulated radiotherapy (IMRT), have dramatically improved the therapeutic ratio for early and late effects but are associated with a dramatic increase in the irradiated volume [4]. This has led to concerns over the increased risk of second malignancies in long-term survivors.

Proton, or charged particle, radiotherapy is another advance in external beam treatment delivery that has resulted in improved therapeutic ratio, especially for tumors requiring high-dose radiotherapy immediately adjacent to a radiosensitive critical structure (e.g., base of skull, spine). Proton radiotherapy has the additional benefit of a greatly reduced irradiated volume (generally 60–70% lower than photon plans) [5]. Proton radiotherapy is extremely attractive in pediatric malignancies for this reason, but proton facilities are very limited at this time.

Electrons are charged particles and have a rapid dose fall-off similar to protons. Thus, IORT with electrons (IOERT) should be considered as a method to limit the irradiated volume, especially in facilities without charged particle capabilities.

Other possible situations for the use of IORT in pediatric malignancies include those in which surgery and/or chemotherapy would not be expected to result in local control or in which EBRT doses in excess of 50 Gy would be necessary [6]. IORT should be considered even for low-dose radiation in an infant or small child. In addition, there are cases in which the substitution of IORT for a part of the EBRT dose would decrease the dose to normal structures and, therefore, minimize damage to these tissues. Consideration should be given to the use of IORT as a component of treatment in the primary management of Wilms tumor, neuroblastoma, rhabdomyosarcoma, and other soft-tissue sarcomas, as well as bone tumors such as Ewing and osteosarcoma.

Wilms Tumor

In Wilms tumor, the standard flank dose of 10.8 Gy has acceptable acute morbidity. Radiation volumes are generally large relative to the small size of these patients, and recent reports from long-term childhood cancer survivors show a 4.6-fold increased risk of second malignancy in patients receiving radiation [1]. IORT could be used in place of EBRT in an attempt to minimize treatment morbidity, especially in patients with residual disease after maximal resection who require a boost. Patients with bilateral Wilms tumors not suitable for partial nephrectomy or with local recurrence pose a difficult problem. One is faced with the possibility of bilateral nephrectomies followed by hemodialysis and/or renal transplantation and a poor survival rate. DeMaria et al. [7] reported a 29% survival in bilateral Wilms tumor patients undergoing transplantation. The excess death rate was related to a higher incidence of sepsis thought to be due to the use of radiotherapy, chemotherapy, and the resulting immunosuppression in these patients. The use of IORT in combination with nephron-sparing surgery may permit obliteration of both gross and microscopic tumor, while preserving maximum residual renal function.

Neuroblastoma

Neuroblastoma is the most common extracranial pediatric solid tumor, accounting for approximately 10% of all pediatric malignancies. Prognosis is poor even in modern trials with progression-free survival just over 30% [8]. Treatment principles for high-risk patients include myeloablative systemic therapy with radiotherapy to areas of disease remaining immediately prior to definitive surgery. Although the irradiation dose is generally low (21.6 Gy), there is a potential role for IORT in the management of neuroblastoma due to the young age of the patients and EBRT dose restrictions of adjacent radiosensitive organs such as kidneys [9]. Most children are less than 4 years old and the median age at diagnosis is 21 months. 30% of cases occur in infants less than 1 year of age. Toxicity after EBRT in this very young group of patients includes second malignancy, hematologic, renal, gastrointestinal, musculoskeletal, and hepatic [10, 11].

Although for a number of years controversy existed surrounding the role of radiotherapy in the setting of myeloablative chemotherapy, evidence is accumulating supporting a role of consolidative radiotherapy for advanced-stage neuroblastoma [12–14]. In one of the earlier studies showing an improvement in outcomes with the addition of EBRT, Castleberry et al. [14] performed a randomized comparison of chemotherapy with and without irradiation in a high-risk patient group (older than 1 year with Pediatric Oncology Group Stage C disease). Differences in complete remission rate, event-free and overall survival in favor of the group receiving irradiation were significant ($p = 0.013$, 0.009, and 0.008). More recently, data in patients undergoing local radiotherapy and transplant showed a benefit for those receiving total body irradiation (TBI) as part of the transplant regiment suggesting a dose–response effect for neuroblastoma [13]. Based on this data, current recommendations for radiotherapy in neuroblastoma are 21.6 Gy to all disease present after chemotherapy but before delayed surgery. IORT is a potential way to administer all or part of the irradiation.

Soft-Tissue Sarcoma

Rhabdomyosarcoma is the most common pediatric soft-tissue sarcoma. Survival after therapy for localized rhabdomyosarcoma exceeds 70% [15]. Most patients present with Group III disease, that is, disease that is not completely resected at the time of initial surgery. Thus, definitive radiotherapy plays an important role in local control and cure in this disease. Complete surgical resection with pathologically negative margins is accomplished in a minority of patients with pelvic and retroperitoneal sarcomas, and despite such aggressive surgical approaches, the local recurrence rate may exceed 50% [16]. Nearly a third of patients are very young (less than 3 years of age) at diagnosis. Because of the concern for radiotherapy late effects in this very young population, some European study groups have recommended reserving radiotherapy for salvage therapy. This unfortunately results in a compromise in event-free survival (EFS) of approximately 20–30% with a subsequent effect on overall survival [17, 18]. Radiotherapy clearly is an important component of treatment for these tumors and improvements are necessary to minimize late effects, especially in the youngest patients.

Because of the radiosensitivity of rhabdomyosarcoma, morbid surgeries are not generally recommended and organ conservation approaches are favored. For example, results from the Intergroup Rhabdomyosarcoma Studies (IRS-IV) show an EFS of 77% at 6 years for Group III bladder/prostate rhabdomyosarcoma patients who were treated with the intent of bladder preservation. Of the event-free survivors, 55% had normal bladder function, indicating favorable long-term outcomes after primary radiotherapy [19]. Despite these encouraging results, local failure after radiotherapy is still the predominant form of relapse in Group III patients. Local failure is significantly associated with overall survival in rhabdomyosarcoma, reiterating the importance of local control in curing these patients and suggesting an area for potential improvement in radiotherapy techniques, including the use of IORT as a component of treatment.

Bone Sarcoma

Local control is an essential component of the successful management of bone sarcoma patients. Certain bone tumors, such as osteosarcomas, are relatively radioresistant [6]. Outcomes with EBRT alone are generally poor and used only in inoperable disease [20]. The addition of IORT to neoadjuvant chemotherapy, conservative surgery, and EBRT may allow dose escalation and facilitate en bloc tumor resection with functional reconstruction, sparing the patient amputation or other debilitating surgery.

Treatment Factors for IORT

Children are small relative to adults. The issue of size challenges the tenets of IORT because of the close proximity of critical structures, internal organs, and the need to treat physically small (or occasionally relatively large) areas in these patients. High dose rate brachytherapy IORT (HDR-IORT) has a benefit in this regard as it has an applicator or delivery system designed to treat confined spaces which may restrict or prevent the introduction of a rigid IOERT applicator.

The use of this modality in children requires extraordinary communication and planning between the pediatric oncologist, the surgeon and the radiation oncologist. Each operation is planned with the intent of complete excision of the tumor. However, the extent of resection attained is determined at operation and is not necessarily predictable by tumor biology, histologic subtype, response to therapy or preoperative imaging. For most pediatric tumors, the strategy involving IORT considers two points in time: an immediate surgical procedure at diagnosis and a subsequent secondary operation or delayed primary resection after biopsy of the tumor and chemotherapy +/− EBRT.

The primary objective of an immediate operation is to confirm the histologic diagnosis, provide adequate tissue for prognostic and biologic specimens and evaluate the site and extent of disease. The safest procedure necessary to accomplish this is generally recommended. However, if the tumor is localized, more extensive operative exposure may be carried out to determine resectability and accomplish a complete resection, if feasible. If the tumor location, friability, invasion of adjacent organs or other factors suggest excessive risk of resection, the procedure should be abandoned with no consideration of the use of IORT at the initial operation. A definitive secondary procedure will be delayed until chemotherapy response (alone or in combination with EBRT) allows for more effective local tumor control at a subsequent time. IORT may be employed during the initial operation after complete gross tumor resection, but where a high suspicion of microscopic residual disease exists such as with an inflammatory pseudocapsule containing viable tumor cells or a difficult marginal surgical dissection. If a nearly complete resection is attained and minimal gross disease is left in surgically inaccessible areas, IORT is a reasonable adjunctive measure to utilize during initial operation but would need to be supplemented by postoperative EBRT +/− simultaneous chemotherapy.

The most common utilization of IORT in children occurs during the delayed primary or second-look procedure after initial chemotherapy [21, 22]. The delayed operation is carefully planned based on imaging studies and is appropriately timed within the patient's overall treatment regimen since this approach generally provides the best opportunity for complete local tumor resection. Patients with initially unresectable disease, residual tumors or local recurrences who have demonstrated any response to chemotherapy are reasonable candidates for IORT. Extensive tumor progression is a contraindication except in the most extraordinary circumstances. Because of the limited experience with these techniques in children, the use of hemodilution, regional hyperthermia and circulatory arrest with cardiopulmonary bypass would currently also eliminate the possibility of IORT.

Because of the potential magnitude of this procedure, preoperative monitoring of the patient's hematologic coagulation status is mandatory. Adequate red blood cell and platelet transfusion is accomplished before operation, and all blood components including fresh frozen plasma must be available for intraoperative infusion [23]. The anesthetic management requires invasive monitoring of arterial

pressures, urine output, and central venous pressures in anticipation of sudden hemorrhage, fluid sequestration, ventilatory restriction, or major vascular compression. Obviously, adequate large bore peripheral venous access may be critical depending on which body cavity is being operated upon.

Fortunately, in pediatric patients, most uninvolved structures can be adequately mobilized so that IOERT applicators from 3–7 cm (or larger) in diameter or in length along outside edges can be comfortably placed even in the deepest body cavities without cumbersome lead shielding. In the Mayo pediatric patient series, applicator sizes used varied from 4.5 to 9 cm for circular applicators and from 6×11 cm to 8×15 cm for rectangular or elliptical applicators. If necessary, the use of multiple but nonoverlapping fields may be planned in the operating room before patient transport. In one 3½-year-old Mayo patient with marginal resection of a 17×10×8 cm retroperitoneal ganglioneuroblastoma, five IOERT fields were required to cover the areas at risk (two abutting fields for the under surface of the liver and three abutting fields to cover the right retroperitoneum) [22, 24].

Bench surgery for renal tumors such as bilateral Wilms tumors offers the advantages of careful palpation and dissection of the tumor, avoids tumor spillage into the field and permits extensive renal resection. For the management of recurrent bilateral Wilms tumors, the substitution of ex vivo irradiation for ex vivo surgical excision in appropriately selected patients may offer the advantage of delivering a large radiation dose to a precisely localized tumor while avoiding damage to uninvolved renal structures and leaving neighboring structures unirradiated. This is especially beneficial for patients who have small renal lesions unsuitable for resection or who have had previous abdominal irradiation.

Logistical considerations aside [25, 26], HDR-IORT may be more advantageous than IOERT when treating certain pediatric patients. The size of the patient and the geometry of the site may allow flexible HDR-IORT applicators to be more functional than rigid lucite or metal IOERT applicators [27, 28]. Solid tumors most likely to benefit from HDR-IORT are the same as for IOERT as previously discussed. Specific locations that may benefit from the more flexible HDR-IORT applicators include anterior or lateral chest wall and anterior or anterolateral abdomen or pelvis.

The potential advantage of HDR-IORT over conventional brachytherapy is not specifically related to the radiobiologic or invasive characteristics of HDR-IORT (the subject of a far more reaching debate and companion chapters in this book). It is related to the rapidity of treatment while normal dose-limiting organs are surgically displaced and logistical considerations that make the use of indwelling catheters for conventional brachytherapy difficult. Indwelling catheters and sources are problematic for the pediatric patient, their parents, and caregivers. Small patients require prolonged immobilization or specialized care when afterloading catheters and high photon energy sources such as iridium are used.

IOERT Results

Denver Children's: General Results

Limited data exists in the literature to assess the role of IOERT in the management of pediatric malignancies. The largest single institution series from the Children's Hospital of Denver (Table 22.1) suggests efficacy of IOERT in children [21]. They reported 59 pediatric patients with a variety of tumor types treated since 1984. IOERT doses of 10–17 Gy were delivered with 5–11 MeV electrons to 84 fields in 64 procedures. Some patients also received EBRT. The local control rate in 11 patients with histologically benign but locally aggressive lesions was 91%. In the 48 patients with malignant tumors, local control was reported in 75%, and survival was 63% at a mean of 51 months after diagnosis (range 14–104 months). Results in the 24 patients with neuroblastoma and 6 patients with osteosarcoma will be reported in the subsequent results sections dealing with those pediatric disease sites.

Table 22.1 IOERT general results

Author/institution (ref)	Patients (*n*)	Local control (%)	Survival (%)	Follow-up (months)
Haase – Denver Children's [21]				
Benign	11	91	100	51 mean
Malignant	48	75	63	51 mean
Schomberg – Mayo Clinic [22, 24]	11	91	73	99 median
Stauder – Mayo Clinic update [22, 24]	20	85	70	139 median
R0 or R1 resection	17	88	76	118 mean
R2 resection or unresectable	3	67	33	79 mean
Nag – Ohio State University [29]	13	72	26	42 median

Mayo Clinic Series

Patient Group and Treatment Method

A smaller series of 11 patients with locally advanced primary or recurrent abdominal-pelvic tumors was reported by Schomberg et al. from the Mayo Clinic [22]. This data was updated recently and now includes long-term follow-up on 20 patients [24]. The tumor histologies include 4 neuroblastomas, 2 paragangliomas, 1 Wilms and 13 sarcoma-family tumors, including 3 synovial cell, 2 neurofibrosarcomas, 2 rhabdomyosarcomas, and 1 each of the following: fibrosarcoma, spindle cell, clear cell, epithelioid, malignant fibrous histiocytoma, and desmoid. The patients with desmoid tumor and embryonal rhabdomyosarcoma were treated at the time of recurrence. All patients received EBRT (median dose, 45 Gy; range, 10.8–51.3 Gy). Multiple field techniques were used in all patients. The EBRT was given prior to surgical resection and IOERT in six patients, after the resection and IOERT in four patients, and both before and after the procedure in one patient.

Maximal surgical resection was attempted in all patients prior to IOERT. Seventeen patients underwent gross total resection (GTR) but had adherence of tumor to normal structures and were presumed to have microscopic residual tumor. In two patients, the surgery was a debulking subtotal resection (STR), leaving gross residual disease, and in one patient the lesion was unresectable.

IOERT with 6–15-MeV electrons was delivered to the tumor or tumor bed using a linear accelerator. The IOERT dose, as calculated at the 90% isodose curve, varied from 7.5 to 20 Gy in 19 patients. In the remaining patient, a dose of 25 Gy was given because the EBRT dose had to be limited to 33 Gy in 19 fractions due to prior EBRT. The number of IOERT fields treated per patient ranged from 1 to 5 depending on the anatomic location and size of the tumor bed. A total of 28 fields were treated in 20 patients with a mean dose of 11.9 Gy per field. Applicator size ranged from 4.5 to 9 cm for circular applicators and 6 cm × 11 cm to 8 cm × 15 cm for elliptic or rectangular applicators. The applicators were either flat or beveled to 15, 20, or 30°.

Thirteen patients received multiagent chemotherapy as part of their treatment. Agents differed on the basis of tumor histology. Chemotherapy was given prior to, and concomitantly with EBRT and as maintenance treatment for systemic effect in all patients receiving chemotherapy.

Survival and Disease Control

At last follow-up, 13 of 20 patients (65%) were alive and without evidence of disease; median follow-up measured from the date of the IOERT procedure was 139 months (range 25–306 months). The Kaplan–Meier overall survival (OS) at 5 and 15 years for all patients was 70%. In patients who underwent GTR, 5- and 15-year OS was 76% compared to 33% in those where GTR was not achieved. Patients who underwent an STR had a median survival of 6 months while median survival has not yet been reached in GTR patients.

Overall local control and 15-year actuarial control for all patients were 85% (17/20 patients) and 83%, respectively. One child was deemed unresectable at the time of surgery, received IOERT and EBRT, and had subsequent central and local failure. This child eventually died from progressive local and metastatic disease 6 months after surgery. There were two other children who had a local recurrence. One child with recurrent rhabdomyosarcoma had only a debulking procedure and died 2 months after surgery from lung metastasis. Another patient with neurofibrosarcoma had a local failure in the EBRT field after GTR, developed distant metastasis in the lungs and died of disease 41 months after surgery. All other patients had their disease controlled locally. Similarly, local control was achieved in 15 of 17 patients (88%) who underwent GTR compared to two of three patients (67%) who did not. The estimated Kaplan–Meier local control at 15 years in patients who underwent GTR was 87% compared to 50% in those where GTR was not achieved.

An additional four patients developed distant metastasis (total – 7/20 or 35%). One of these patients with Wilms tumor is alive with stable lung metastases at 86 months after surgery. Another patient diagnosed with spindle cell sarcoma underwent GTR, subsequently developed lung and mediastinal metastasis 1 month after surgery and died of disease at 8 months. Bilateral lung metastasis were seen in a patient with rhabdomyosarcoma of the prostate 2 months after surgery and the patient ultimately died of disease at 20 months after surgery. Lastly, one patient undergoing GTR for neurofibrosarcoma developed bone metastasis and died at 18 months after surgery. Of the six patients who died after developing metastatic disease, the median survival was 13 months (range 2–41 months).

Ohio State University Series

Nag and colleagues reviewed their results using IOERT for 13 patients treated at Ohio State University [29]. Histologies included two patients each with Wilms tumor, Askins tumors, and PNET and six soft-tissue sarcomas. The group included five patients receiving palliative treatment for metastatic disease, as well as IOERT alone in eight patients. IOERT dose ranged from 10 to 15 Gy and in the five children who received EBRT, doses ranged from 35.4 to 45 Gy.

After a median follow-up of 42 months, four patients were alive and without evidence of disease. Actuarial 3-year survival was 26% in this unfavorable population and crude local control was 72%. Both patients with Wilms tumors achieved local control with IOERT alone (100% local control), however, overall, the use of EBRT was associated with improvement in local control. The authors conclude that EBRT is necessary for successful local control and disease-free survival, especially for soft-tissue sarcomas.

Disease-Specific Pediatric IOERT Results

Wilms Tumor

Experience with the use of IOERT in the management of Wilms is limited. Halberg et al. [30] utilized IOERT either in situ or ex vivo in the management of two patients with recurrent bilateral Wilms tumor. This use of IOERT produced tumor control and maximized preservation of residual renal function in these patients with a traditionally poor prognosis with commonly available treatment methods. Ohmuna et al. [31] reported four cases of Wilms tumor treated with multimodal therapy combined with IOERT (usually 15 Gy) to the tumor bed and lymph node regions at Chiba University between 1979 and 1990. Three patients were alive and disease free at more than 9 years following treatment. The fourth patient had bilateral Wilms tumor, underwent nephrectomy on one side and partial tumor resection on the other. Surgery was followed by IOERT and chemotherapy

but the patient succumbed to metastatic disease. Similarly, Nag et al. reported on two patients with Wilms tumors, one of which had bilateral disease. IOERT (15 Gy) was given to the remaining partial kidney to avoid nephrectomy. Not unexpectedly, the patient did develop kidney failure in the remaining kidney. Both patients remained locally controlled with IORT alone and were alive at last follow-up [29]. The Mayo Clinic series included one patient with Wilms tumor who was controlled locally but developed lung metastasis and was alive with stable disease more than 7 years after surgery.

Neuroblastoma

Because of the radiosensitivity of neuroblastoma, young median age at diagnosis, and current treatment algorithm which includes a delayed resection, IORT has a logical role and has frequently been used in the treatment of neuroblastoma (Table 22.2).

Ohnuma et al. [32] utilized either IOERT or EBRT as a component of a multimodality treatment approach for advanced-stage neuroblastoma. Thirty-six patients were treated with high-dose chemotherapy, surgery, and an autologous bone marrow transplant followed by 13-*cis*-retinoic acid. Local irradiation was administered in 27 of the patients (IOERT [$n = 18$] or EBRT [$n = 10$]). IOERT was utilized except when it was prohibited by technical factors. No local failures were observed in the 27 patients who received local irradiation. One-third of patients who did not receive some form of local irradiation failed locally as at least a component of their failure. The 65% 3-year disease-free survival in this series compares favorably with other auto-transplant series (30–40%) [8]. No increase in toxicity was reported in those patients receiving IOERT.

Sugito et al. [33] reviewed outcomes of 13 patients treated with IOERT for high-risk neuroblastoma. No local recurrences were documented within the IOERT field, however, in a patient in whom securing the IOERT field was difficult, disease recurred at the margin of the field around the superior mesenteric artery. In two subsequent cases in which there was difficulty securing the IOERT field, adjuvant EBRT was administered. Nine of the 13 patients are long-term survivors.

Kunieda et al. [34] recently reported outcomes of 27 patients treated between 1988 and 2006 for advanced-stage neuroblastoma. Patients received between 8 and 15 Gy with IOERT at the time of delayed resection with no additional EBRT. Two- and 5-year OS for Stage III patients was 78% with Stage IV patients faring predictably worse (71 and 21% at 2 and 5 years, respectively). Six local recurrences were observed, three in an area adjacent the margin of the field and three that were either anterior or behind the electron ports. The authors conclude that adjuvant EBRT may be valuable to improve local control.

In another report from Japan, Kuroda et al. [35] report on a series of 33 patients with Stage III and IV neuroblastoma, including high-risk patients with n-myc amplification, treated with surgery and IOERT. In all but four patients, GTR was achieved. Three patients had loco-regional tumor relapse; all were outside the IOERT treatment volume. In patients with GTR, DFS was 51.7% at nearly

Table 22.2 IOERT neuroblastoma results

Author (ref)	Patients (*n*)	Local control (%)	Survival (%)	Follow-up (years)
Ohnuma et al. [32]	18	100	78	3
Sugito et al. [33]	13	92	69	2
Kunieda et al. [34]	27	78	71–78[a]	2
Kuroda et al. [35]	33	91	60	3
Zachariou et al. [36]	13	92	84	1.5
Oertel et al. [45]	9	100	78	5
Leavey et al. [37]	24	54	50	4.5
Gillis et al. [9]	31	85	60	3

[a]Stage III–IV

7 years, including five of nine patients surviving with n-myc amplification (55.9%). In contrast, none of the children who underwent STR were long-term survivors. IOERT doses in this trial ranged from 10 to 15 Gy; no adjuvant EBRT was administered. Interestingly, local control was obtained at the treated sites in all patients with macroscopic residual disease. The authors propose that macroscopic residual may result in dissemination of viable tumor cells before the tumor has been destroyed by IORT. Alternatively, this may reflect a poor response to chemotherapy resulting in tumors that are less likely to be resectable [9]. Toxicity in this series was minimal with only two patients having maldevelopment of an irradiated vertebral body [35].

Zachariou et al. [36] from Germany reported on their initial results with 13 patients all of whom had macroscopic residual disease at the time of IOERT. IOERT doses ranged from 8 to 10 Gy. Only one patient progressed locally. One patient developed sepsis 9 months after surgery and died; the remainder were without evidence of disease at last follow-up.

Leavey et al. [37] updated the Denver series which included 24 neuroblastoma patients, 12 of whom were long-term survivors with median follow-up of 54 months after IOERT. Seven of 12 Stage III and three of nine Stage IV patients survived. DFS correlated with local control in both Stage III and IV patients.

In the USA, the largest series reported to date is from the University of California at San Francisco (UCSF). Building on their early experience in IOERT at recurrence or progression [38], they recently reported on a series of 31 patients with newly diagnosed high-risk neuroblastoma were treated with IOERT as a part of multimodality therapy [9]. IOERT doses ranged from 7 to 15 Gy (median 10 Gy). Patients with involved lymph nodes or gross residual disease after surgery were selectively given adjuvant EBRT (ten patients; 6–41.4 Gy) based on the results of their previous series [13]. Six patients received TBI as a part of the conditioning regimen for BMT. The 36-month LC, PFS, and OS from the time of diagnosis was 85, 47, and 60%, respectively. Only 1 of 20 patients with a GTR recurred. In contrast, three of nine patients recurred after STR. Use of EBRT was not associated with improvement in local control in this series, likely due to the selective use in only the highest risk patients. Toxicity in this group was significant with seven patients developing hypertension or vascular stenosis after treatment and two patients with potential treatment-related death. One patient with tumor involving the aorta and inferior vena cava developed massive ascites and died 3.9 months after surgery. Another patient with preoperative hypertension developed middle aortic syndrome and mesenteric ischemia and died of bowel necrosis. Three separate IORT fields were utilized in this patient suggesting radiation-field overlap as a possible contributing factor. Based on these results, the authors suggest IORT alone is an acceptable treatment option for patients with GTR (95% local control in this series) provided the great vessels can be shielded from radiotherapy and the disease can be encompassed in a single radiotherapy field. For all other patients, additional EBRT should be administered to a total dose of 21.6 Gy in compliance with current pediatric treatment protocols. This algorithm will minimize the toxicities of EBRT as well as IORT in this vulnerable population.

Bone sarcoma

Local treatment of osteosarcoma is surgical and is generally surgical and requires an en bloc resection of the involved tumor and bone. In the USA and Europe, reconstruction with either a prosthesis or allograft is generally used, when possible, to avoid amputation. In Asian cultures, bone is not typically donated for religious reasons. Reports of high-dose radiotherapy to avoid amputation and resection of bone have demonstrated that radiotherapy may have a role in the definitive local therapy for osteosarcoma.

Oya et al. [39] reported their experience with IOERT for osteosarcoma in Japan. Since 1978, they have used IOERT in combination with chemotherapy for treating primary and metastatic malignant bone tumors in 39 patients in an attempt to preserve the affected limb. Doses of 45–80 Gy were given to involved bone after soft tissues have been dissected away from the treatment plane.

Treatment was administered with opposed fields and photons if needed. With a median follow-up of 124 months, nine patients developed local recurrence, all but one were in the soft tissue retracted away from the radiotherapy field. Five-year cause-specific survival and relapse-free survival were 50 and 43%, respectively. Fractures developed in 13 early patients, but none of the six patients treated recently who received preventive nailing developed fractures. With long-term follow-up, 13 patients eventually required prosthetic replacement, eight patients underwent amputation, internal stabilization was performed in three patients, and no further surgeries were required in only nine patients [40]. Functional outcomes were best in patients who underwent internal stabilization and worst in patients with no further surgery secondary to limitations on weight-bearing required to prevent fracture. Based on these results, the authors felt that local control and functional outcome were suboptimal. Internal stabilization is recommended for all patients receiving IORT, but further research is necessary to determine the role of IORT in osteosarcomas of the extremities [39–41].

In a similar report also from Japan, Araki et al. [42] report on 20 patients in whom the tumor and involved bone was removed with a wide en bloc resection, 50 Gy extracorporeal radiation was given to the isolated bone, and the bone was then reimplanted into the patient with fixation devices. Non-union (20%) and infection (15%) were the two major complications. Functional outcomes were good and no local recurrences were detected with a mean follow-up of 45 months. However, nine of the 20 patients required a second surgery to either manage complications or late toxicity and one for local recurrence outside the irradiated graft. Despite the significant complications, the authors felt that extracorporeal radiation provides additional treatment options when bone allografts are not available or when existing prosthetic options are not satisfactory (i.e., elbow, wrist, or ankle).

More recently, extracorporeal radiation was adopted by a group in Australia who has treated 50 patients with bone tumors without local recurrence. [6, 43, 44] The authors reviewed a modern series of 16 patients received extracorporeal irradiation during limb-salvage surgery for femoral tumors which confirmed their excellent results. All patients were disease-free for a minimum of 2 years after surgery (mean 49.7 months). Good to excellent functional results were achieved in 88% of patients. In this series, no deep infections were noted and only one patient experienced fracture in the irradiated bone. The authors feel these results are comparable to allograft outcomes and may even be functionally superior in the femur, although longer-term follow-up is necessary [6].

In the USA, IOERT for bone sarcomas typically involves EBRT with an IORT boost for close margins or macroscopic residual disease. In the Denver series [21], six patients with Ewing or osteogenic sarcoma were treated with IOERT. Local control was achieved in five of six patients; three were long-term survivors. One patient died of infection with no evidence of local disease at autopsy and another died of disseminated disease without detection of local recurrence.

The German series [45] also included six patients with either Ewing or osteosarcoma. One of the two osteosarcoma patients experienced local recurrence but was eventually salvaged with further chemotherapy and surgery. None of the Ewing patients experienced local recurrence and all six patients were long-term survivors.

Nag et al. treated two patients with Askin tumors (poor prognosis Ewing of the chest wall) both of whom died within 2 years of surgery with recurrent disease within the chest cavity [29].

IOERT Toxicity

In the Mayo series, seven of the 20 patients analyzed (35%) reported grade 3 toxicity as sequelae of treatment-related side effects. All of these patients had abdominopelvic tumors. Among the seven patients, there were a total of 11 grade 3 toxicity events reported due to treatment-related complications. These events include four bowel obstructions, two each neuropathy and obstructive uropathy, and one each vascular, acute renal failure, and osteomyelitis. There was no reported grade 4 or 5 toxicities or second malignancies observed during the follow-up period.

All seven patients that reported grade 3 toxicity events are alive at last follow-up except for one patient with synovial cell sarcoma who developed lumbosacral plexopathy. The femoral nerve and vein were included in this patient's initial IOERT field. The patient had a subsequent regional relapse outside the EBRT field, received an additional course of EBRT and was subsequently found to have metastatic disease in the pancreas. The patient received palliative whole abdomen EBRT and died 200 months after surgery and IOERT.

Genitourinary toxicity was seen in three of the seven Mayo patients. One patient with a 9 cm pelvic paraganglioma had bilateral ureteral obstruction that was related to IOERT, EBRT, and surgery. Both ureters were within the IOERT and EBRT fields, and a portion of the wall of the ureter was also excised with the tumor at the time of surgery. These urinary complications eventually resulted in chronic kidney disease and a subsequent surgical procedure to create bilateral ileal conduits from the kidneys to the bladder. Renal failure developed in a patient who had her kidney and ureter included in the IOERT and EBRT treatment fields for treatment of a 20 cm retroperitoneal ganglioneuroblastoma. Bilateral hydronephrosis was seen on follow-up CT scans and abdominal ultrasounds in another patient with inclusion of the left ureter in the IOERT field. This patient, however, had complete resolution of hydronephrosis without any specific intervention. Although the current Mayo Clinic practice is to exclude the ureter from IOERT fields when not at risk for tumor involvement, ureteral problems can also occur with surgical manipulation of ureters that have received EBRT but no IOERT.

Lumbosacral neuropathy and osteomyelitis of the sacrum developed in a Mayo patient with an 11.5 cm recurrent desmoid of the left false pelvis/hemi-abdomen following left hemi-pelvectomy. He was treated with preoperative EBRT, subtotal resection (gross residual) and IOERT. The sciatic nerve and portions of the lumbar spine were included in the IOERT field. Despite undergoing only a STR, the patient is alive, disease-free at 228 months follow-up.

Two other Mayo patients experienced grade 3 toxicity requiring subsequent surgical intervention following GTR plus IOERT for intra-abdominal malignancies. One was diagnosed with renal vascular hypertension and another had small bowel obstruction. In both patients, the primary etiology of toxicity is unknown but presumably multifactorial (EBRT, surgery, IOERT) [22, 24].

In a German series, 6 of 15 patients (40%) alive at a 60.5 mo. median followup treated with a combination of IOERT and EBRT had clinically significant late morbidity [45]. These include loss of limb due to hypoplastic vessels, fibrosis, and thrombosis after IOERT for thigh sarcoma, kidney atrophy after combined IOERT and EBRT, ureteral stenosis 8 years after IOERT and 32 Gy EBRT, pes equines deformity, neuropathy in a patient who received 15 Gy IOERT to a long length of pelvic nerve, and bone fracture in a patient later found to have tumor recurrence which may have partially contributed to the complication. Out of 13 patients treated for neuroblastoma in a separate report [36], one patient developed superior mesenteric artery occlusion 1 week after surgery resulting in extended bowel resection due to ischemia. The patient developed short-bowel syndrome and became dependent on total parenteral nutrition. An additional patient required dilation of renal artery stenosis.

In the Ohio State series, morbidity was observed in 4 of 13 patients. One patient with scoliosis was extensively treated with EBRT and IOERT to her posterior and lateral chest wall, retroperitoneum, lumbar and sacral spine, and bilateral hips. The patient died of uncontrolled disease. A second patient developed right kidney failure after hemi-nephrectomy and 15 Gy IOERT to the remaining right kidney to treat scattered gross disease. Lip deformity was observed in a patient treated for multiple recurrences of rhabdomyosarcoma. The final patient experienced chest-wall deformity after rib resection and IOERT for Askins tumor [29].

Haase et al. [21] reported no increase in operative morbidity or mortality in their IOERT patients and no problems with intracavitary infections related to the patient transport or treatment applications. One of their 64 patients did develop a superficial wound complication, but this was easily treated with local care and antibiotics and did not adversely impact the patient's overall treatment or outcome. There were no manifestations of acute intestinal injury. There were no differences in operative morbidity or mortality in patients where IOERT was employed compared to a matched group who underwent tumor resection alone. In a subgroup of neuroblastoma patients in this series, one patient whose pancreas was

within the IORT field experienced transient pancreatitis and two patients developed postoperative intussusception. One child developed scoliosis after laminectomy and IORT [37].

As discussed previously, the UCSF group reported a small number of significant toxicities in their neuroblastoma series. Toxicity in this group included seven patients who developed hypertension or vascular stenosis after treatment, two of which also suffered potential treatment-related vascular death. One of the deaths may have been due to field overlap in a patient requiring three adjacent IOERT electron cones to cover the tumor bed. Based on these data, the group recommends EBRT for patients requiring more than one field or for patients whose tumor encompasses the great vessels [9].

High doses of IOERT in osteosarcoma patients have been associated with poor functional outcomes and a high risk of pathologic fracture, as previously discussed [39, 40]. In one of the largest series reported, nearly 75% of patients required at least one additional surgical intervention for either local control or to manage long-term toxicity [39]. Current reports in which patients received preventive intramedullary nailing after IOERT to prevent pathologic fracture have reduced fracture rates and improved functional outcomes [6, 39, 42].

HDR-IORT Experience: USA and Europe

Ohio State University

The group at Ohio State University has a treatment algorithm in which IOERT is generally preferred for patients requiring IORT, but HDR-IORT is used if the tumor site is inaccessible with an electron applicator. Thirteen patients in their series received HDR-IORT, median dose ranged from 10 to 15 Gy for minimal gross residual disease, generally in combination with 27–30.6 Gy EBRT postoperatively. Eleven patients were alive without evidence of disease at 47-month median follow-up (4-year actuarial OS 77%). Of the patients who died, one had Stage III pulmonary blastoma with sacral recurrence; the other had an undifferentiated synovial sarcoma, experienced local and distant failure (lung metastasis) and died 34 months after treatment. Local control in this series was 95% (Table 22.3) [27, 28].

Memorial Sloan-Kettering

Patient Group and Treatment Methods

The largest series in the literature is from the group at Memorial Sloan-Kettering who updated their initial pediatric series [46] to report on long-term outcomes [47]. Sixty-six patients with solid tumors were treated with HDR-IORT brachytherapy via a remote afterloader. The study included patients with Ewing sarcoma, rhabdomyosarcoma, synovial cell and undifferentiated sarcomas,

Table 22.3 HDR-IORT results

Author/institution (ref)	Patients (*n*)	Local control (%)	Survival	Follow-up (years)
Nag – Ohio State [28]	13	95	77	4
Goodman – MSKCC [47]	66	56	54	1.3
Ozaki – Munster [50]	20	95	85	2

MSKCC Memorial Sloan-Kettering Cancer Center

Wilms tumor, neuroblastoma, desmoid tumors, and other rare pediatric tumors including osteosarcoma and immature teratoma. HDR-IORT was used in the initial management of 31 patients and at the time of recurrence in the remainder. GTR was obtained in 60 patients but only 24 patients were found to have negative surgical margins. Sixty-two patients received chemotherapy as a part of treatment and 29 received EBRT as a component of therapy (median 35 Gy, range 10–53 Gy). HDR-IORT ranged from 4 to 15 Gy (median 12 Gy) single-fraction treatment which was prescribed to a depth of 0.5 cm from the surface of a multichannel tissue-equivalent applicator.

Results

With a median follow-up of 16 months, the actuarial rates of local control and overall survival were 56 and 54%, respectively (Table 22.3). Use of postoperative EBRT was significantly associated with improvement in local control (83% vs. 29%, $p=0.002$). Patients treated for recurrent disease appeared to have worse local control (43% vs. 74%) but the difference was not significant ($p=0.19$). Patients with negative margins had a local control rate of 61% compared to 56% for positive margins, but again, the difference was not significant ($p=0.09$).

Recently, the authors have updated their findings in some specific patient populations [48]. HDR-IORT was used as a component of therapy in 8 of 20 infants (median age 17 months) treated with radiotherapy for rhabdomyosarcoma. HDR-IORT doses ranged from 8 to 12 Gy in a single fraction at the time of delayed resection generally following 36 Gy EBRT. Six of eight patients were locally controlled and alive at the time of last follow-up [48].

MSKCC investigators also reviewed their results specifically in 41 patients with recurrent neuroblastoma [49]. Median age at the time of surgery was 5.6 years and median follow-up after HDR-IORT was 12 months. All patients had high-risk neuroblastoma, 12% Stage III and 88% Stage IV. All had received prior chemotherapy or surgery, 88% had been treated with EBRT with a median dose of 21.6 Gy and 37% had tumors with MYCN amplification. The rate of gross total resection of the recurrent/persistent primary tumor was 95%, and there were no operative or postoperative deaths. The median dose of HDR-IORT was 15 Gy (range, 8–20 Gy). Postoperative surgical complications occurred in seven patients, including five cases of hydronephrosis, one bowel fistula, and one perforation. Sixty percent of patients had no evidence of local recurrence 2 years after IORT (27% if MYCN amplified vs. 68% for nonamplified tumors; p=N.S.). Overall survival was 35% at 2 years (10% if MYCN amplified vs. 46% for nonamplified; $p<0.008$). Based on these outcomes, the authors suggest that re-resection and IORT of locally persistent or recurrent primary tumors results in a high rate of local control with acceptable morbidity, mortality, and OS and should be strongly considered in this very high-risk group of patients [49].

University of Munster/Germany

Ozaki and colleagues performed an HDR-IORT boost after preoperative radiochemotherapy in patients with Ewing sarcoma as part of multimodality therapy for patients treated in a European Intergroup Cooperative Ewing's Sarcoma study [50]. The HDR-IORT boost was administered in 20 patients with close surgical margins. In general, 10 Gy was administered at a distance of 5 mm from the flab surface using a HDR-afterloading device after 45–54 Gy EBRT.

With 24 months median follow-up, only one patient (5%) has experienced local recurrence (this patient also had systemic relapse) and three patients have died of metastatic disease (Table 22.3). The technique was felt to be feasible and there were no intraoperative complications due to the additional radiotherapy, although surgery time was on average 3 h longer. The overall complication did not differ from that in patients treated without brachytherapy.

HDR-IORT Toxicity

In the Memorial HDR-IORT experience [47, 48], the rate of complications potentially related to HDR-IORT (alone or combined with other treatment components) was 12–25%. Eight patients developed peri-operative complications, three of which were grade 3–4. Wound infections requiring reoperation occurred in two patients. One patient developed hepatic veno-occlusive liver disease (VOD) after 24 Gy whole abdominal EBRT and 15 Gy HDR-IORT to the porta hepatis. Grade 2 toxicities included lymphatic leak, delayed wound healing, persistent cytopenia, pneumonia, and persistent fever. Only three patients had documented late events but two of the three were grade 4. One patient died from complications of broncho-esophageal fistula, another underwent resection of infracted bowel 1 year after treatment. A third patient developed bone growth abnormalities and scoliosis after treatment of a large right thoracic field with both EBRT and HDR-IORT [47].

Two young patients with lower extremity rhabdomyosarcoma walked with a limp or experienced delayed ambulation. An additional patient in the rhabdomyosarcoma series died of sepsis 10 weeks after completing postoperative EBRT for para-spinal embryonal rhabdomyosarcoma with extension into the adjacent lumber vertebral body [48].

One potential problem identified for HDR-IORT and the pediatric patient is the threat of cytopenia introduced by the source. As the source dwells in the patient for the lengthy treatment time that often characterizes HDR-IORT, radiosensitive circulating cells are exposed to radiation. This exposure may lead to postoperative leukopenia, a condition which compromises healing and promotes complications. This situation is relevant for the pediatric patient who is likely to be cytopenic at the time of surgery from prior chemotherapy and who may be receiving treatment with granulocyte or granulocyte–macrophage colony-stimulating factors (G-CSF and GM-CSF). Recent studies have demonstrated greater sensitivity for mobilized progenitor cells as compared to bone marrow progenitor cells and that may explain source-induced cytopenia resulting from HDR-IORT [51]. Although this problem has not been previously described, to our knowledge, Memorial authors have reported the possible occurrence of source-induced leukopenia in one patient. She was treated for desmoplastic small cell tumor of the mediastinum. Her HDR-IORT site measured 91 cm^2, covered multiple vertebral bodies, and approximated the great vessels. She also received intensive alkylator-based chemotherapy before and after HDR-IORT and died of pulmonary fungemia presumably due to refractory cytopenia. The cytopenia was seen only after HDR-IORT [46].

In the Ohio State series, 3 of 13 patients developed late toxicity (23%). One patient required reimplantation of her autotransplanted kidney secondary to chronic, urinary tract infections. Another patient required construction of a neobladder secondary to urethral obstruction as well as pinning of her femoral subcapital epiphysis. An additional patient developed mild loss of visual acuity and impaired orbital bone growth 6 months after treatment [28].

Future Possibilities of HDR-IORT

There is a single experience with a HDR-IORT source that might be amenable to the treatment of children with recurrent primary brain tumors. The photon radiosurgery system is a battery-operated high-voltage X-ray generator which is placed stereotactically in a manner analogous to CT-guided biopsy. It has been used to irradiate small intracranial targets because of its rapid gradient in dose. A feasibility study which described the treatment of 14 patients [52], showed the unique ability of this probe to provide HDR-IORT (10–20 Gy) following histologic confirmation of malignancy. Recently, results of a phase I study in children with recurrent brain tumors have been reported [53].

Eight of 14 patients are locally controlled within the surgical bed at a median follow-up of 16 months. Three children developed marginal recurrences in the tumor bed. Eight patients had received prior EBRT. Radionecrosis developed in three patients (21%) who received 10 Gy to a depth of 5 mm. Based on this data, the safe dose level in this population is felt to be 10 Gy to 2 mm. The authors suggest additional lower dose EBRT may improve results and minimize toxicity.

Prognostic Factors

Extent of resection, use of EBRT, and treatment of primary vs. recurrent disease are all treatment factors that have been shown to correlate with local control and treatment outcomes in multiple patient series. In the Denver series by Haase et al. [21] three of five patients who had gross residual disease at the time of IOERT failed with local and disseminated disease suggesting prognostic significance for the amount of residual disease after maximal surgical resection. In the Mayo series, local control was achieved in 15 of 17 patients (88%) who underwent GTR compared to two of three patients (67%) who did not. The estimated Kaplan–Meier overall survival at 15 years in patients who underwent GTR was 57% compared to 33% in those where GTR was not achieved. All the patients in the Mayo series, unlike those in the Haase series, received EBRT in addition to the IOERT [24]. In contrast, a recent report from Oertel and colleagues from Germany revealed excellent local control outcomes in 18 pediatric patients with close or positive surgical margins. This series included a mix of close margins (<0.3 cm) or tumor spillage (five patients) and microscopically positive margins (seven patients). Histologies included neuroblastoma (nine patients) and soft-tissue and bone sarcomas (Ewing, desmoplastic, retroperitoneal). With a median follow-up of 60.5 months, the only patient who experienced local failure was a patient who had subtotal resection for desmoplastic sarcoma of the hip. These excellent results are likely due in part to the large number of favorable histologies (i.e., neuroblastoma) and number of patients with minimal residual disease, as well as the fact that all patients received EBRT as a component of their therapy [45].

The addition of EBRT is consistently associated with improvement in local control in other series as well. In the Ohio State series, local control was 100% (5/5 sites) in patients with soft-tissue sarcomas receiving EBRT compared to 50% (5/10 sites) for IORT alone. The addition of EBRT was also associated with an improvement in OS (40% vs. 0%) highlighting the importance of local control in outcomes for pediatric tumors [29]. Similar results have been observed in neuroblastoma series [34, 38]. Patient selection is critical in these series as properly selected patients have very favorable outcomes with IORT alone. For example, in neuroblastoma, patients without gross residual disease or lymph node involvement at the time of surgery have local control rates as high as 95% with IOERT alone [9].

Treatment for tumor recurrence is sometimes associated with poor outcomes after IORT (see below). Aside from aggressive tumor biology associated with recurrent tumors, radiation doses and surgical options are often limited in patients with recurrent disease, which confounds the outcome data. Especially since the use of adjuvant EBRT is critical for local control, patients who recur after previous radiation would be expected to have poorer outcomes as the further use of EBRT is often very limited.

Presentation with Local/Regional Relapse

The number of pediatric patients who receive IORT as a component of treatment for local or regional relapse has been small in published IORT series. The Ohio pediatric IORT series included five patients treated for recurrent tumors, three of which recurred after EBRT. Local control was

40% in this series (compared to 85% for primary disease) and survival was slightly worse as well (25% vs. 33%). Only two of the 20 patients in the Mayo series were treated for recurrent tumors. Both had STR, IOERT, and adjuvant EBRT. The patient with recurrent desmoid is locally controlled with 19 years of follow-up. The patient with recurrent embryonal rhabdomyosarcoma died of pulmonary metastatic disease and also experienced local progression of disease [24].

As the role of radiation therapy as a part of initial treatment for pediatric solid tumors is being limited or reduced, it would seem that treatment at the time of recurrence, especially in the setting of prior irradiation, would be the ideal way for IORT to find a niche in the treatment of the pediatric patient. Local disease may be an important component of management problems in these patients. Results in adult IORT series for recurrent cervical cancer [54], rectal cancer [55], and retroperitoneal sarcoma [56] show excellent local control and substantial number of long-term survivors in patients previously considered incurable. If recurrent patients had prior EBRT, retreatment with low-dose EBRT (20–30 Gy in 1.8–2.0 Gy fractions) plus concurrent chemotherapy precedes maximal surgical resection and IORT. In view of the limited treatment options for such patients, IOERT or HDR-IORT should be considered as a component of retreatment in patients with locally recurrent disease in whom re-resection is being considered.

Discussion and Future Possibilities

The somatic sequelae of radiation therapy are well documented and are of primary concern when treating pediatric patients. To more accurately irradiate the tumor volume, spare normal tissues from high doses of irradiation, and reduce the possibility of late effects, advanced techniques have been developed to conform the prescription dose to well-defined targets. IJMRT, brachytherapy, IOERT and HDR-IORT can substantially reduce the volume that receives the prescription dose.

IOERT and HDR-IORT are unique in the ability to limit the low-dose irradiated volume and in the administration of treatment with a high-dose per fraction. There is the general lack of understanding of high-dose single-fraction radiation therapy although knowledge is increasing with the explosion of stereotactic body radiotherapy treatments in the adult population. Understanding the mechanisms of action of high-dose single-fraction irradiation, the relationship of high-dose single-fraction irradiation to fractionated radiation therapy, and the role of this treatment when performed in conjunction with fractionated therapy is an area of active research in adult tumors. In the study of late effects, however, the benefit of localized irradiation using IOERT or HDR-IORT might be offset by the increased likelihood of late effects after high-dose per fraction treatment.

Currently, IOERT and HDR-IORT are not identified with the treatment of a particular pediatric tumor. The limited experience of IORT with pediatric patients makes is difficult to suggest IOERT or HDR-IORT as a treatment option to the pediatric oncologist. This situation is perpetuated by the small role that radiation therapy currently plays in the treatment of pediatric patients.

For the present time, single-fraction IOERT or HDR-IORT is more likely to be an adjunct to rather than a substitute for fractionated EBRT. Thus, IOERT or HDR-IORT should be used in an institutional or cooperative group protocol as a local boost treatment in conjunction with fractionated EBRT and maximal resection. Fractionated preoperative EBRT may facilitate resection by causing tumor shrinkage and induce tumor cell damage to decrease the risk of tumor implantation or dissemination at the time of surgery. Limited experience exists to suggest that IORT in combination with maximal debulking surgery in pediatric patients with locally advanced or recurrent abdominal, retroperitoneal or pelvic malignancies results in excellent local tumor control and overall survival [24, 45]. Toxicity appeared acceptable considering the poor prognosis of this group of patients with standard approaches and the high risk of tumor-associated morbidity and mortality.

Future Possibilities

Pediatric cancer management during the past three to four decades has been characterized by substantial gains in overall disease control and survival [1]. These gains have been achieved primarily for leukemia and lymphomas and early-stage bone and soft-tissue sarcomas.

For patients with more advanced solid tumors, the gains in disease control and survival have been less substantial. In fact, for most of these tumors, local control remains an important problem. Unfortunately, the issues of local control are secondary for many high-risk pediatric patients since their overall survival is often influenced by the development of metastases. In addition, investigators are reluctant to rely on EBRT or brachytherapy for local control because of the late effects that are attributable to these modalities. Indeed, with the advent of more effective chemotherapy and aggressive surgical approaches, investigators are attempting to limit the role of EBRT or its use in terms of dose and volume. These efforts continue despite the knowledge that high doses of radiation offer higher rates of local control and new methods are available to deliver the treatment. In general, the use of internal irradiation boost options (IOERT, HDR-IORT) may decrease the dose of the EBRT component required without compromising the efficacy of treatment. In the pediatric population, the toxicity of concern is expected to be most closely linked to the EBRT component if IOERT doses are limited to 10–15 Gy.

Technological advances in radiation therapy delivery systems have changed the patterns of radiotherapy technique in our clinical practice. Many of the patients reported in the series reviewed here were treated using two-dimensional planning and delivery systems. Newer techniques such as image-guided radiation therapy (IGRT) and IMRT are now routinely used for treatment of pediatric patients. Despite the ability to deliver a higher radiation dose to tumor volumes while avoiding normal structures, IMRT often results in an increased volume of normal tissues receiving low-dose radiation. Second malignancy risk after radiation is related to both the total dose as well as the irradiated volume. Especially in infants and young children with a favorable prognosis, the effect of this increase in irradiated volume is unknown but will likely be documented in the next generation of long-term survivor studies [4]. Proton radiotherapy has been suggested as a method to reduce integral dose in pediatric patients. Most reports show 60–70% reduction in integral dose between typical scattered proton plans and three-dimensional or IMRT photon plans [5]; however, proton facilities are not widely available. IOERT as part of multimodality treatment may be a method for institutions without access to a proton facility to reduce the irradiated volume and potentially reduce the tissues at risk for second malignancy.

Because of increased survivorship after childhood malignancies, late effects of cancer therapy are becoming increasingly important. Many end-organs responsible for late toxicity are extremely radiosensitive. Kidney and lung injury as well as bone growth abnormalities are seen after 20 Gy. Even with advances in treatment delivery such as IMRT, it is often difficult to limit the low-dose volume. IORT should be considered as a method to treat tumors adjacent to these organs and reduce the dose to these radiosensitive organs.

IOERT or HDR-IORT should be considered as a component of retreatment in a majority of patients with locally recurrent disease in whom re-resection is being considered. For this to occur, patients may need to be referred to major institutions with IORT capability in HDR-IORT, IOERT, or both. These recommendations are independent of a history of prior EBRT in view of results in adult IORT series for recurrent cervical [54, 55] and rectal cancer [56, 57] and retroperitoneal sarcoma [58, 59]. In those situations, limited dose EBRT (20–30 Gy in 1.8–2.0 Gy fractions) plus concurrent chemotherapy preferably precede the surgical attempt of maximal resection and IORT.

IOERT or HDR-IORT should also be considered as an adjunct to surgical resection and pre- or postoperative EBRT when the preoperative imaging studies or findings at the time of surgery are likely to indicate that high-dose radiation therapy is necessary to prevent local relapse. In this setting, the dose of EBRT can be decreased with substitution of IORT for a part of the EBRT dose thereby decreasing the dose to normal structures and, therefore, minimizing the risk of injury to these tissues.

To clarify the role of IORT in the management of pediatric malignancies it will be important to collect prospective data on disease control, survival, tolerance, and late effects in both single institution and cooperative group settings. High-dose EBRT should be compared to EBRT combined with IORT, in terms of local control and tolerance. It may not be possible to randomly compare results because of limited patient numbers and small number of institutions with IORT capability. However, protocols can be developed which allow for the option of an IORT boost (IOERT or HDR-IORT) vs. EBRT boost (utilizing standard or three-dimensional treatment planning).

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Part V
Conclusions and Future Possibilities

Chapter 23
Conclusions and Future Possibilities: IORT

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Keywords Conclusions • IORT future possibilities • Laparoscopic resection and IOERT • Xoft/AXXENT multi-channel applicator • RADIANCE treatment planning

Long-term experience has shown that the use of IORT as a component of treatment in conjunction with other modalities (EBRT, concurrent and maintenance chemotherapy, maximal surgical resection) is feasible and practical if close multidisciplinary cooperation exists. IORT-containing, multimodality regimens appear to improve local disease control, if not survival, in many disease sites when compared with non-IORT treatment approaches. For patients in whom gross total resection of their cancer is not safely feasible, however, the ability to achieve central or local control is lessened, thus creating the need for prospective clinical trials that address the addition of radiation dose modifiers during both EBRT and IORT. Patients with locally advanced or locally recurrent cancers who are candidates for IORT-containing regimens often have high systemic risks as well. Prospective trials will also be necessary that address the addition of aggressive systemic therapy to the locally aggressive combined treatment.

Improvements in technology have made IORT more feasible in a larger number of institutions and will thus facilitate the conduct of prospective trials in a multi-institution national or international setting. This technology includes mobile electron IORT (IOERT: Mobetron®, Novac-7®, Liac®), HDR-IORT and electronic brachytherapy/low-KV IORT equipment (Zeiss/Intrabeam®, Xoft/Axxent®) that can be used in either an outpatient or OR setting. In addition, specific treatment planning systems for IOERT procedures are under development to help in the treatment decision making process and to document radiosurgical technique, target definition, and dosimetric beam distribution (GMV – RADIANCE®).

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L.L. Gunderson et al. (eds.), *Intraoperative Irradiation: Techniques and Results*, Current Clinical Oncology,
DOI 10.1007/978-1-61779-015-7_23,

Treatment Outcomes

Acute and late morbidity and local disease control are thus far acceptable in patients who can be treated with curative intent utilizing a full component of adjuvant EBRT (±chemo), gross total resection, and IORT. That good local control results are being realized is not unexpected, since a substantially higher radiation dose can be delivered to the target tissue with combined EBRT-IORT approaches while the dose to the adjacent normal tissues is markedly less. Accordingly, there is a large "therapeutic gain." The history of radiation therapy shows that whenever higher radiation doses can be delivered with safety to the target volume, there is an improvement in local control ± survival [1].

Skilled surgeons must attempt to accomplish a gross total resection with negative (R0 resection) or microscopically positive margins (R1) when safely feasible. This both improves the chance of long-term local control and decreases the risk of toxicity such as peripheral neuropathy in previously irradiated and unirradiated patients as lower doses of IORT can be utilized in combination with EBRT for ≤microscopic residual vs. gross residual disease.

Colorectal Cancer

With primary colorectal cancers that are unresectable for cure or for locally recurrent colorectal cancers, both local control and long-term survival appear to be improved with the aggressive local treatment combinations including IORT when compared with results achieved with conventional treatments. These findings are consistent from various institutions and countries (Massachusetts General Hospital [MGH; 2, 3], Mayo Clinic in Rochester [4–8], Europe [9–13], Asia; see Chaps. 15, 16 [2, 8]).

At the ISIORT 2008 meeting in Madrid, large IOERT series were presented for patients with both primary and locally recurrent colorectal cancer. For those who presented with locally advanced primary cancers, single-institution data from Madrid [9] suggested better outcomes in 281 patients with T3-4 rectal cancer who received preop CRT, resection, and IOERT vs. 277 who had resection and postop CRT (pelvic control 91.5% vs. 83.7%, $p=0.03$, DFS 65% vs. 56%, $p=0.05$, OS 68% vs. 58%, $p=0.016$). This is a 15 years institutional experience in a cancer model in which the survival benefit can be explained through significantly improved local control [10]. In the context of neoadjuvant chemoradiation alone or plus IOERT, the IORT boost added a significant improvement in presacral control (95% vs. 84% $p=0.01$) at 10 years [11].

A pooled analysis of 651 IOERT patients from four major European centers found 5-year OS of 67% and 5-year local control of 88% [12]. Preop CRT seemed to improve OS outcomes – 5-year OS of 70% vs. 64%, $p<0.05$. In a recent update of this pooled analysis, risk factors associated with local recurrence (12%) were no downstaging, lymph node metastasis, margin involvement, and no adjuvant chemotherapy [13].

For patients with locally recurrent colorectal cancer, a very large single-institution series of 607 IOERT patients from Mayo Clinic in Rochester was presented by Haddock et al. [7]. Five-year OS was 30% for the entire group of 607 patients and 46% for those with an RO resection.

Upper GI Cancers (Gastric, Pancreas)

Outcomes with IORT as a component of treatment for patients with upper GI cancers can be found for esophagus, gastric, pancreas, and biliary cancer. When residual disease exists after resection of gastric cancers, IOERT with or without external radiation has achieved encouraging survival results (Chap. 12).

With locally unresectable pancreatic cancer, an apparent improvement in local control has been noted with IOERT plus EBRT, but survival has been altered only minimally because of a high incidence of abdominal failure, both liver and peritoneal (Chap. 13) [14–16]. In the most recent update of MGH results, 150 patients with locally unresectable pancreas cancer received IOERT as a component of treatment from 1978 to 2001 in conjunction with EBRT and 5-FU-based chemotherapy [15]. Long-term survival was seen in eight patients and five were alive at or beyond the 5-year interval. Actuarial 1-, 2-, 3-, and 5-year survival for the 150 patients was 54, 15, 7, and 4%, respectively, and median survival was 13 months. For patients with initially unresectable cancers, survival does appear to be improved in a small subset of patients who are able to undergo resection and IOERT after preop chemoradiation, as suggested in a Mayo Clinic Arizona (MCA) series presented at ISIORT 2008 in Madrid [17]. For patients who presented with borderline resectable pancreas cancers in the MCA series, preop CRT followed by resection and IOERT results in survival outcomes similar to patients who present with initially resectable pancreas cancer [17].

A European pooled analysis of 270 IOERT patients with pancreas cancer was presented at ISIORT 2008 by Valentini et al. [18] with median OS of 19 month and 5-year OS of 17.7%. Resection was done in 247 patients (91.5%; R0 resection – 53.4%, R1 – 27.4%, R2 – 19.2%). Preop EBRT or CRT was given in 63 patients and postop EBRT or CRT in 106. Survival and local control appeared better in those with preop EBRT/CRT vs. postop or IORT alone (median OS of 30 vs. 22, 13 month). The definitive report of this pooled analysis emphasizes the sterilizing effect of IORT on the tumor bed in post-resected pancreatic cancer patients (23% 5-year local control) and the positive impact of sequencing external irradiation preoperatively both in local control and survival [19].

Soft Tissue Sarcoma: Retroperitoneal/Abdominal-Pelvic

Excellent local control and long-term survival have been achieved with abdominal and pelvic soft tissue sarcomas with IORT-containing treatment approaches for both primary and recurrent lesions (Chap. 18) [20]. In the randomized National Cancer Institute trial, improved local control was achieved with lower small bowel morbidity with IOERT plus EBRT vs. EBRT alone in patients with marginally resected primary retroperitoneal sarcomas [21]. Mayo Clinic investigators have reported excellent results for locally recurrent as well as locally advanced primary abdominal and pelvic sarcomas [22].

At ISIORT 2008, both single-institution and pooled analysis data were presented [23, 24]. Mayo Clinic in Rochester results were updated by Petersen et al. in a series of 226 IOERT patients with primary (52%) or locally recurrent (48%) retroperitoneal or pelvis soft tissue sarcoma [23]. Both survival and local control outcomes appeared to be better in patients with a gross total resection prior to IOERT (5-year OS: R0 resection – 52%, R1 – 55%, R2 – 28%, $p = 0.08$; 5-year local relapse: R0 – 18%, R1 – 31%, R2 – 61%). A European pooled analysis of 122 IOERT patients with primary ($n = 41$) or locally recurrent ($n = 81$) retroperitoneal sarcoma was presented by Krempien et al. [24]; 40 had been previously irradiated, 75 received postop EBRT. The 5-year OS, DFS, local control, and distant control were 64, 28, 40, and 50%, respectively. Central relapse in the IOERT field was related to degree of resection (R0 – 5%, R1 – 23%, R2 – 75%).

Gynecologic or Genitourinary Cancers

Long-term salvage of ~30% has also been achieved with IORT-containing treatment approaches for locally recurrent gynecologic and renal malignancies (Chaps. 20 and 21, respectively). The IORT results for patients with gynecologic (Gyn) cancer have been presented primarily as

single-institution analyses evaluating IOERT [25–32] (Mayo Clinic in Rochester [25–27], University of Washington [28], University of Navarre[29]), HDR-IORT (MSKCC [30]) or orthovoltage IORT (Stanford University [27, 31, 32]). In the largest Gyn series, 148 patients from Mayo Clinic in Rochester received IOERT for local-regional relapse ($n=125$) or locally advanced primary cancers ($n=23$) with 5-year OS of 27% for the total group (R0/R1 resection – 31% 5-year OS, R2 – 13%, $p=0.01$) [26, 27]. Patients with no prior EBRT had better outcomes in IORT series from Mayo Clinic in Rochester (5-year OS 35% vs. 15%, $p=0.01$) [25–27] and the University of Navarre [29]. Favorable results have been found with IORT as a component of treatment for select patients with recurrent ovarian cancer in separate analyses from Mayo Clinic in Rochester (16 IOERT patients – 5-year OS, 54% [27]) and Stanford (22 evaluable IORT patents – 5-year OS, 22% [32]).

For patients with IORT for genitourinary malignancies (Chap. 21; [33]), the most experience has been in patients with locally recurrent renal cancer with long-term survival of ≥30% in small series from Mayo Clinic in Rochester ($n=28$ [34]), University of Heidelberg ($n=11$ [35]) and University of Navarre ($n=11$ [36]). IORT in the context of multimodal treatment for bladder cancer [33] has proven to be able to sterilize transitional cell carcinoma and should be evaluated more extensively as an addition to chemo-EBRT for bladder preservation.

Breast Cancer

There is increasing interest in the use of IORT as a supplement or alternative to EBRT in selected cases [37–49]. This includes single-institution, multi-institution, and multination series and multi-institution pooled analyses, in addition to phase II and phase III studies.

Investigators from Milan have the most experience in the use of IOERT as the only component of irradiation for early breast cancers [38, 39]. Veronesi et al. reported early results in a series of 237 patients with primary tumors ≤2 cm who had wide excision plus either sentinel lymph node biopsy and/or axillary lymph node dissection [38] plus IOERT doses of 17–21 Gy with 3–9 MeV electrons. Preliminary findings in the phase III Italian trial comparing IOERT alone with standard EBRT for early-stage breast cancers were presented at ISIORT 2008 [45]. Four hundred and fifty-two patients were randomized from January 2003 to December 2007 (227 – IOERT alone, 225 – standard EBRT) with the primary endpoint of local relapse. With median follow-up of 31 month in 314 evaluable patients, no local relapses have occurred to date.

IOERT has been combined with local excision/axillary dissection and EBRT in single and multi-institution series in the USA and Europe [37, 40–42, 44]. The University of Salzburg used IOERT combined with EBRT in 351 consecutive patients from October 1998 to April 2002 and reported their results in the initial 170 patients treated through December 2000 [40]. Local control results were compared to patients treated with EBRT alone; 3-year local control was 100% with an IOERT boost vs. ~97% with EBRT boost.

Sedlmayer reported an ISIORT-Europe pooled analysis at ISIORT 2008 of 1,200 patients who received linac-based IOERT boosts from 10/98 to 12/05, combined with whole breast EBRT doses of 50–54 Gy [44, 46]. As of February 2008, only eight in-breast relapses were observed in 1,121 patients with median follow-up time of 59.6 months (LC 99.3%). Seven-year OS, DFS, and DSS were 91.5, 88.8, and 94.8%, respectively.

Multiple phase II or III trials which evaluate adjuvant IORT are actively accruing patients in the USA (phase II), Europe, United Kingdom, and Australia. Long-term results from these and other trials will be necessary to demonstrate ultimate local recurrence, late effect, and survival data with these approaches [47–49]. Updated results of the Targit and ELIOT phase III trials are seen in Chapter 10.

Miscellaneous (Pediatric, Lung, Extremity/Bone Sarcomas, CNS)

In the treatment of pediatric malignancies with IOERT or HDR-IORT, single-institution reports reveal excellent local control and survival (Chap. 22). In lung cancer, IOERT series have reported promising local control rates when integrated in the multidisciplinary treatment of Pancoast tumors (boosting a tumor bed chest wall region after preoperative CRT plus resection), or in parenchymal lesions with or without mediastinal involvement (Chap. 11). Extremity soft tissue sarcomas are technically simple to treat with IORT (either IOERT or HDR-IORT) with attractive results in terms of cosmesis, function, and limb preservation rates (Chap. 18) [50]. The European pooled analysis based on boosting with IOERT confirmed a 90% extremity preservation rate (320 patients) and 86% with excellent limb function [51] IORT is also being evaluated in other sites including bone sarcomas (Chap. 19), marginally resected or locally recurrent head and neck cancers (Chap. 9), and select CNS cancers (Chap. 8).

New Technology and Dedicated Facilities

Some of the *technical problems* and nuisance aspects of IORT, encountered in the 1980s and early 1990s, can be overcome with dedicated or semidedicated IORT facilities. This can be built as an operating room (OR) in the Radiation Oncology Department as done for IOERT at NCI, Medical College of Ohio, TJUH, Howard University, and others and as done at MSKCC for HDR-IORT. The most ideal situation is to place an IORT facility within or near the OR suite which has been done at Mayo Clinic in Rochester, MGH, MDACC, Ohio State and some European institutions for IOERT and at Beth Israel – NYC and Duke University for HDR-IORT. Either approach simplifies the treatment of patients, necessitates fewer re-operations (refused by some patients and physicians), and avoids transportation and sterility problems. It also prevents the need to shut down the outpatient treatment machine for a "potential" case. However, the dedicated IORT option in an OR setting is quite expensive if an existing OR has to be retrofitted for proper shielding (HDR-IORT, IOERT), and a new linear accelerator is purchased as the electron source (IOERT).

New technologies have improved the availability of IORT from the perspective of cost-effective alternatives. These technologies include mobile HDR-IORT units (see Chap. 4), as being used at MSKCC, Beth Israel (NYC), Duke University, Mayo Clinic in Rochester, and other institutions, mobile IOERT machines (see Chap. 3: Mobetron [52, 53], NOVAC-7 [54, 55], Liac), and mobile low-KV IORT equipment (see Chap. 5: Zeiss/Intrabeam [56, 57], Xoft/Axxent [58, 59]).

For the mobile HDR machine, a shielded facility is necessary in either the OR area or in the radiation oncology department. Instead of shielding an entire OR room, however, technology now exists to create a shielded box (room within a room) into which the patient can be placed for the HDR-IORT component of treatment after surgical resection and placement of the HAM applicator have been accomplished. However, many existing ORs are small and may not be able to accommodate the increasing complexity of such procedures.

The initial Mobetron unit was evaluated at UCSF starting in December 1997 with subsequent units placed in eight other US institutions including Mayo Clinic in Arizona (MCA), University of North Carolina (UNC), and Stanford University as well as 11 European and 6 Asian institutions [52]. The Mobetron IOERT unit is a magnetron-driven x-band accelerator with electron energies of 4–12 MeV and 90% depth doses of 1.0–4.0 cm, has built-in shielding in a C-arm design and could theoretically be moved from one operating room to another, if indicated.

Alternative mobile IOERT options include the Novac-7 [54, 55] and LIAC, which are manufactured in Italy and are quite similar with regard to machine characteristics and function (see Chap. 3). They

are magnetron-driven robotic devices that use similar beam collimation with polymethylmethacrylate applicators and have movable beam stoppers that have to be manually positioned. The electron energy capabilities are more limited than the Mobetron unit with the highest energy in the range of 7–10 MeV, although a special version of the LIAC with 12 MeV capability is available. Both are fully mobile and are currently used primarily in Europe (mainly Italy).

The Zeiss/Intrabeam and Xoft/Axxent devices are interesting low-KV alternatives for IORT in view of favorable machine specifications requiring minimal radiation protection, the transportability of the radiation source and instrumental versatility ([56–59]; Chap. 5). Since 1998, Intrabeam IORT using spherical applicators has been used primarily for the treatment of early breast cancer following breast conserving resection [56, 57]. A phase III trial has recently been completed (TARGIT) and early results were presented at ISIORT 2010 in Scottsdale AZ (see Chap. 10).

The Xoft/Axxent electronic brachytherapy system is being enhanced in an attempt to improve indications for IORT [58, 59], including an increase in the length of the X-ray catheter to increase the working distance from the controller to the treatment location, update of the software to allow dose delivery in multichannel applicators and two applicator developments. The HAM multichannel planar applicator adaption (Fig. 23.1a) is a collaborative effort between Beth Israel Medical Center and Xoft which will allow the treatment of larger areas within the body (pelvic tumors, retroperitoneal sarcomas) or on the body [58]. The design of low-profile applicators which are compatible with robotically assisted minimally invasive surgical procedures (Fig. 23.1b) is a joint effort with Hackensack University Medical Center [59].

Methodological comparison of IOERT, HDR-IORT, low-KV IORT, and perioperative brachytherapy have been discussed in Chap. 6 and will not be reviewed in detail here. The relative advantages or disadvantages of each are based on the amount of residual disease after maximal resection. A comprehensive IORT program would preferably have combinations of IOERT, HDR-IORT, electronic brachytherapy/low-KV IORT, or perioperative brachytherapy available to treat all disease sites and situations. For some institutions, this will mean having or obtaining both IOERT and HDR-IORT, at others it may be having expertise in both HDR-IORT and perioperative brachytherapy or IOERT plus electronic brachytherapy/low-KV IORT, and a few institutions may have expertise in all four options. These modalities are not competitive but rather complement each other.

As noted previously, specific treatment planning systems for IOERT procedures are under development to help in the treatment decision making process and to document radiosurgical technique, target definition, and dosimetric beam distribution (GMV – RADIANCE). Pre-, intra-, and post-planning tools will be of value to improve clinical and technical challenges of IORT complexity. An adequate technological IORT treatment planning system with surgical and anatomical navigator

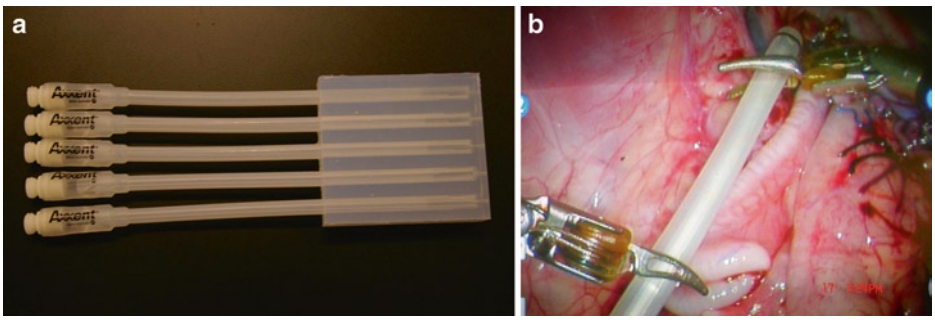

Fig. 23.1 Xoft/Axxent® applicator enhancements: (**a**) Prototype 5-channel HAM applicator adapted for the Axxent low-KV source. (**b**) Axxent low-KV source positioned in a porcine abdomino-pelvic cavity using the Intuitive Surgical Da Vinci S System (photo courtesy of Dr Loren Godfrey, Hackensack University medical Center).

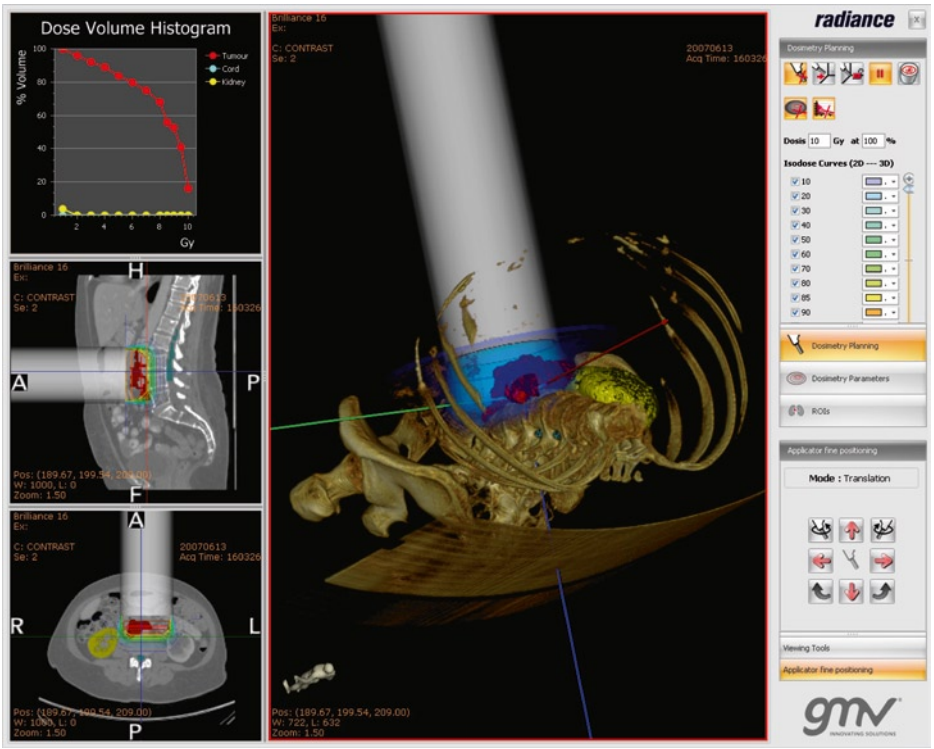

Fig. 23.2 RADIANCE® treatment planning in a patient with unresectable para-aortic nodal recurrence: 2D and 3D dosimetric distribution representation and DVH (tumor, kidney, spinal cord) are available.

features will be instrumental for virtual training for expert groups under new treatment conditions. RADIANCE is a scientific European project initially based on a scientific consortium among the University Hospital Gregorio Marañon and GMV company (Fig. 23.2) [60].

Patient Selection, Multispecialty Treatment Approaches

Optimization of results with IORT treatment approaches will continue to be dependent on proper patient selection as well as appropriate multispecialty treatment (facilities and equipment; aggressive skilled team of multispecialty physicians – surgeon (s), radiation oncologist, and medical oncologist). Progress in cancer surgery can be assumed in IORT programs and the feasibility of performing IORT during laparoscopic cancer surgery has been reported at Gemelli and Gregorio Marañon Hospitals [61, 62] (Fig. 23.3). Previously untreated patients remain the best overall candidates for the aggressive IORT-containing treatment approaches, as optimal combinations of EBRT (± sensitizers), resection, IORT (± dose modifiers), and systemic therapy can be used as planned sequential treatment to optimize both local and distant control of disease.

The best long-term results will be achieved in patients without evidence of distant metastases at time of treatment and in whom good systemic treatment options can be given to high-risk patients in planned sequential fashion. Use of adequate pretreatment staging evaluations is necessary before subjecting patients to the potential risks of the locally aggressive techniques discussed

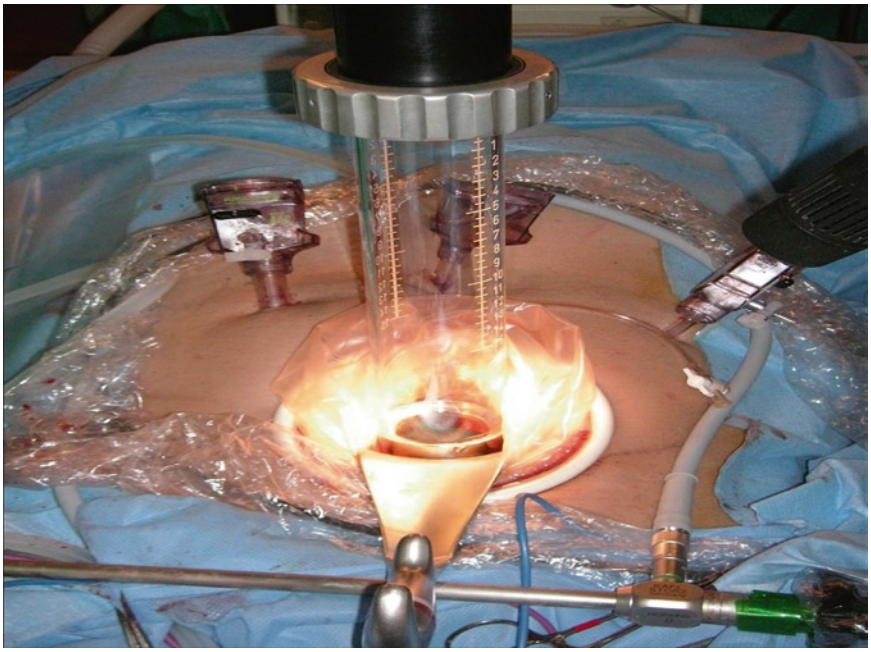

Fig. 23.3 IORT procedure after laparoscopic anterior resection in a rectal cancer treated with neoadjuvant chemoradiation.

in this book. More frequent use of laparoscopy, chest and abdominal CTs, and newer imaging techniques including PET/CT scans and tumor-specific antibody studies would be desirable after preoperative EBRT (± chemo) and prior to exploration, resection, and IORT. Nevertheless, selected patients with oligometastatic disease of indolent nature and/or chemosensitive histologies amenable to surgical rescue have been treated with IORT resulting in long-term NED survivors (9 of 22 patients) [63].

The existence of both dedicated facilities and new technologies increases the likelihood of evaluating IORT in combination with "curative resection" and reduced dose EBRT ± chemotherapy in adjuvant disease settings where adjuvant EBRT doses necessary to achieve local control approach or exceed an acceptable level of normal tissue tolerance. An excellent example of this philosophy was the randomized NCI abdominal sarcoma trial in which adjuvant type doses of EBRT alone resulted in excessive small bowel morbidity in addition to poor local control, but the combination of IOERT with lower-dose EBRT resulted in excellent local control and a low incidence of small bowel morbidity. For lesions of various histologies in which marginal resection with narrow or microscopically positive margins has been accomplished, the use of moderate-dose EBRT (45 Gy in 25 fractions of 1.8 Gy over 5 weeks) plus IORT of 10–12.5 Gy may be preferable to high-dose EBRT of 60–65 Gy with regard to both local control and normal tissue tolerance.

IORT could also potentially be used to replace a component or majority of EBRT in select node-negative patients. European pilot studies have been performed in both breast (T1-2, N0) and rectal cancer patients (T3N0) that demonstrate acceptable tolerance and local tumor control [37–42, 44–46]. Investigators at both MCA and UNC [43] have performed phase II breast cancer studies in which IOERT either replaces 1–1.5 weeks of EBRT boost-dose irradiation (MCA) or serves as the total treatment (UNC).

Future Clinical Trials: Indications, Potential Trial Design

Local Control vs. Peripheral Neuropathy Issues

When a full component of EBRT (45–55 Gy in 1.8–2.0 Gy fractions ± concurrent chemotherapy) can be given to *previously unirradiated patients*, the IORT dose can be limited to 10–12.5 Gy (prescription dose – 90% isodose for IOERT) in patients with a gross total resection but marginally negative or micropositive margins. The chance for local control will be ~90%, and the risk of grade 2 or 3 neuropathy ≤5%.

In *previously irradiated patients*, the retreatment EBRT dose usually has to be limited to 20–30 Gy in 10–15 fractions. If the surgeon can accomplish a gross total resection, an IORT dose of 15–17.5 Gy (prescription dose) has a reasonable chance of achieving local control (≥50%) when combined with preoperative EBRT of 20–30 Gy plus infusion of 5-FU or cisplatin, and the risk of grade 3 neuropathy may be as low as 5% [4–7]. The risk of grade 3 neuropathy is higher (~20%) with IORT doses ≥20 Gy [4–7, 64–68] but may be necessary with gross residual disease after maximal resection or in retreatment situations. When tumor-related risks are higher as in the latter circumstances, the degree of treatment-related risk that both the patient and physician may be willing to undertake will clearly be higher, especially if a reasonable chance of tumor control exists.

Radiation Sensitizers and Dose Modifiers

When gross total resection (R0 or R1) cannot be accomplished, in-field disease control is not optimal, and IORT doses of 15–20 Gy will be indicated. Accordingly, evaluation of dose modifiers during both IORT and EBRT is warranted.

Patients with locally advanced cancers in whom local-regional failure is a common pattern of relapse represent an excellent setting for testing *hypoxic cell sensitizers* [69, 70] in combination with the best currently available modalities (surgery, EBRT plus concurrent chemo, IORT, maintenance systemic therapy). IORT is an ideal model for addressing hypoxic cell radioresistance, as using a large single dose of radiation does not allow reoxygenation to occur. At least part of the local failure rate in large or recurrent tumors at any site may be due to hypoxia. The 2-nitroimidazoles, such as etanidazole, have been studied in conjunction with radiation therapy to sensitize hypoxic cells to irradiation, since up to several logs more cells are killed for the same dose of radiation in the presence of normal oxygen levels as compared to hypoxic conditions. The degree of radiosensitization depends on the concentration of sensitizer in the tumor at the time of IORT [16].

In RTOG 89-06, 42 patients with locally advanced malignancies were entered in an escalating dose scheme for Etanidazole, 5.5–12.0 gm/m^2 [70] given via intravenous infusion over 15 min, followed within 20–30 min by IOERT. Multiple tissue samples from tumor, tumor bed, and/or normal tissue were obtained with simultaneous plasma samples, and etanidazole concentrations in tissue and serum were determined in 33 of the 42 patients. The median time to maximum serum concentration was 25 min and median time to maximum tissue concentration was 40 min. Tissue concentrations began falling approximately 1 h after infusion. Acute drug toxicities were minimal up to the maximum chosen target dose of 12 gm/m^2. Toxicities reported during follow-up appeared to be related to surgery and/or irradiation, not to drug. The concentration of sensitizer in tumor/tumor bed tissues with the 12 gm/m^2 dose level was tenfold greater than in a previous trial at the dose level of 2 gm/m^2 of Etanidazole. A sensitizer enhancement ratio for the hypoxic cells of 2–2.5 was projected. On the basis of tissue biopsy information, IORT should be given ~40 min after the start of a 15 min infusion allowing time for maximum intracellular uptake into tumor cells.

RTOG attempted to test the addition of Etanidazole to standard treatment for locally advanced primary and locally recurrent colorectal cancers in randomized Phase III trials. The number of IORT institutions within RTOG was insufficient at that time to successfully meet accrual objectives and the study was closed. For such trials to be successfully accomplished, international cooperation may be necessary.

Distant Control

With most locally advanced primary or recurrent malignancies, distant metastases continue to be a major issue, especially in patients with high-grade lesions. Incorporation of systemic therapy into locally aggressive treatment regimens will be necessary in order to maximize disease control and survival. Such strategies will differ for chemosensitive vs. chemo-uncertain malignancies (Fig. 23.4). Systemic strategies by disease site were discussed within the chapters on disease site results and future possibilities.

Treatment Tolerance

In situations where IORT doses of 15–20 Gy need to be utilized in proximity to peripheral nerve, randomized studies are indicated to evaluate radioprotectors ± fractionated IORT. In in vivo studies, pretreatment with the radioprotector amifostine (WR 2721) has demonstrated protection of a variety of normal tissues, including bone marrow stem cells, dorsal root ganglion and intestinal cells and renal, lung and liver tissue [71, 72]. In both phase II [73–75] and phase III clinical studies [76], amifostine has also demonstrated the ability to reduce cisplatin-induced neurotoxicity with no evidence of simultaneous tumor protection.

In view of the IOERT dose limitations of peripheral nerve, and an increase in neuropathy as a function of IORT dose, an evaluation of IOERT ± amifostine is indicated when IORT doses of 15–20 Gy are clinically indicated. Although the amifostine daily dose in fractionated EBRT pilot studies has been 300–400 mg/m^2 per day, chemotherapy studies have shown that single doses of 740–900 mg/m^2 can be given. Since a dose of 900 mg/m^2 produces more risk of hypotension, a dose of 740 mg/m^2 has been suggested as an IORT pretreatment dose (on the day of IORT ± also the prior day) to be followed by several doses of 300–400 mg/m^2 in the early postop period. Phase 2 limited institution studies should be conducted before proceeding with a randomized phase III multi-institution study. In the phase II study, tissue and serum levels should be obtained to determine the ideal timing of amifostine prior to IORT.

Other strategies to be tested in clinical situations in which the planned IORT boost dose for gross residual is known to be related with increased severe toxicity include: (1) Design of presurgical treatment components (fractionated EBRT, chemo-irradiation, induction chemotherapy followed by preoperative EBRT, etc.) to induce tumor downstaging and improved resectability. This increases the likelihood of a gross total resection and the ability to use IORT doses of 10–12.5 Gy instead of 15–20 Gy (2). Incorporation of modern EBRT technology in IORT trials that allows safe escalation of total EBRT doses to limited target volumes. Such technology includes more routine use of 3D CRT and IMRT combined with patient immobilization devices, CT-based treatment planning, PET/CT fusion, 4-D treatment planning, image guided irradiation with on-board imaging and gated breating, etc., in an attempt to facilitate dose escalation of the EBRT component of treatment with acceptable tolerance. This may permit a reduction in the IORT boost dose by increasing the dose within reduced EBRT fields beyond the normal adjuvant level of 45–50 Gy.

An exceptional method of IORT dose escalation in recurrent-residual, unresectable or previously treated EBRT patients that may need a single IORT dose of ≥15 Gy for a reasonable chance of local

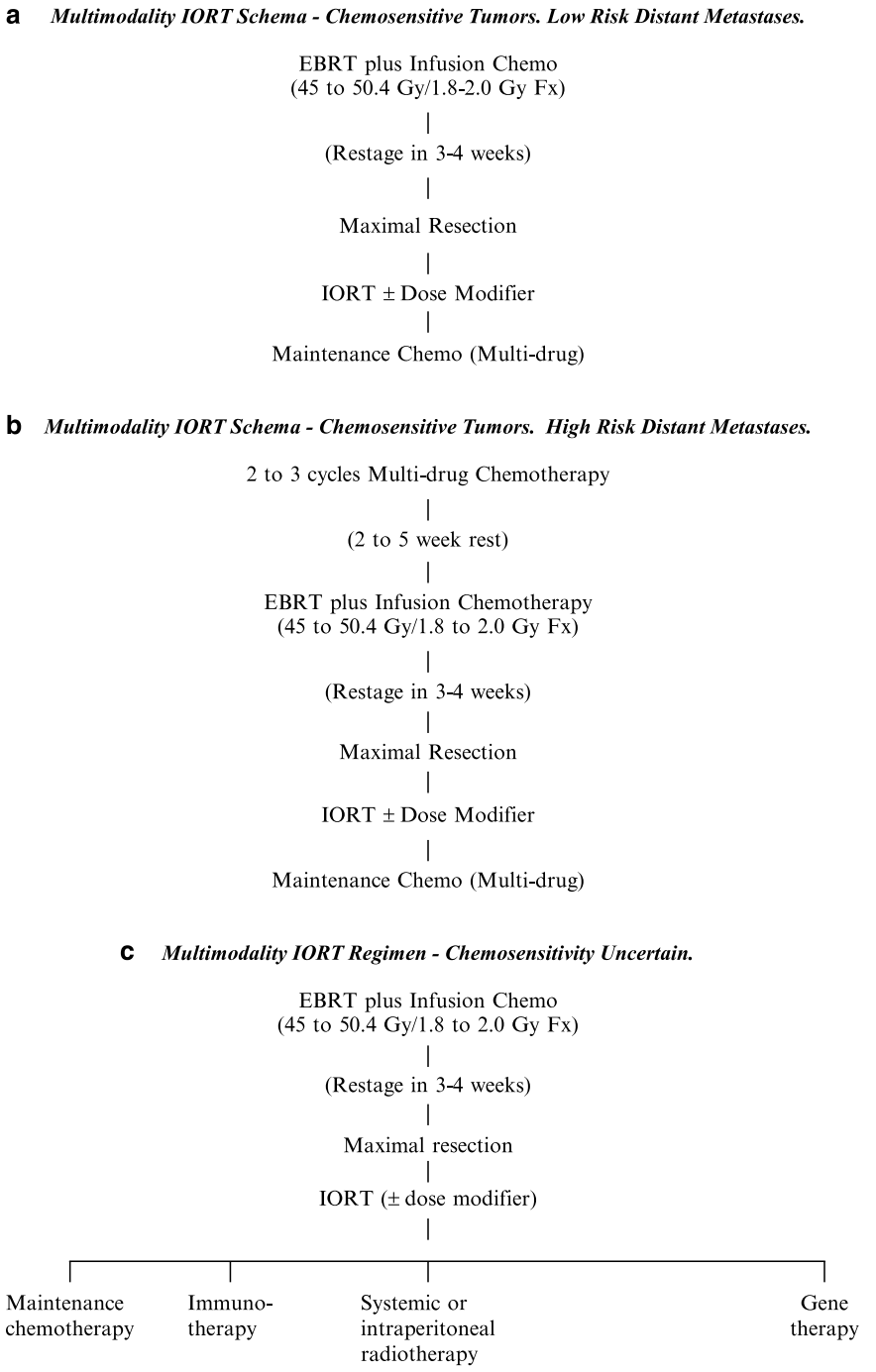

Fig. 23.4 Potential investigational IORT schemas based on chemosensitivity of disease site and risk of distant metastasis (*IORT* intraoperative irradiation; *EBRT* external beam irradiation; *chemo*, chemotherapy). (**a**) Chemosensitive tumor – low-risk distant metastasis (DM). (**b**) Chemosensitive tumor – high-risk DM. (**c**) Chemosensitivity uncertain.

Fig. 23.5 Recurrent pelvic sarcoma surgically resected and incision temporarily closed with a zipper system for delayed IOERT treatment. Notice the final position of the IOERT applicator in the pelvis and the small bowel being removed from the target volume.

tumor control would be fractionated IORT doses of 10–12.5 Gy or the delivery of preop SBRT (stereotactic body EBRT) within 1–2 days of resection and IOERT. Potential methods of accomplishing fractionated IORT would include the following: (1) deliver the first IORT fraction after surgical exploration but before attempted resection and the second fraction after resection but just before surgical reconstruction (4- to 10-h interval); (2) deliver first IORT fraction after resection and the second fraction at time of re-exposure of the target volume 24 h later (surgical use of a zipper system for initial closure of a wound when planned reoperation is indicated may facilitate the integration of fractionated IORT – see Fig. 23.5); (3) deliver SBRT dose of 7.5–10 Gy 1–2 day preop followed by surgical resection and IOERT. Results with fractionated IORT have never been reported, and the clinical feasibility is questionable; however, the described strategies may become acceptable options with progress in the surgical-anesthetic arena.

EBRT Dose De-escalation Models (IORT Alone or Plus EBRT)

As noted in the prior section on patient selection, IORT could potentially be used to replace a component or majority of EBRT in select patients. European pilot studies have been performed in both breast (T1-2, N0) and rectal cancer patients (T3N0) that demonstrate acceptable tolerance and local tumor control [37–42, 44–46]. Investigators at MCA and UNC [43] have performed phase II breast cancer studies in which IOERT replaces 1–1.5 weeks of EBRT boost-dose irradiation (MCA) or serves as the total treatment (UNC).

Screening and early diagnosis generates a wide clinical practice with cancer at initial stages which includes small-sized tumors and/or indolent biological behavior. Disease sites model like very early breast cancer and low-risk prostatic cancer still need radiotherapy for successful treatment. Single-dose IORT can be explored as an efficient alternative to fractionated EBRT in patients requiring surgical resection or surgical exploration for accurate staging. In the breast cancer model feasibility and positive results have been described with 21 Gy IORT only [77] and 12 Gy IORT plus 37 Gy EBRT (13 fractions) in premenopausal women [78]. In the prostate cancer model, IORT with high energy electrons (9–12 MeV) and doses of 10–12 Gy at the completion of radical prostatectomy contributed to a median dose in the anterior rectal wall of 3.9 Gy (range 0.4–8.9 Gy) [79].

An IORT dose of 12 Gy given pre-radical prostatectomy (post-pelvic lymphadenectomy) had equivalent continence and postoperative complications when compared with a matched-pair analysis group of non-IORT prostatectomized patients [80]. In pediatric patients, the strategy of single-dose IORT with no EBRT does not seem to compromise local control [81].

The Future of Clinical Trials

It should be remembered that these areas of investigation will require integrated teams of surgeons, radiation oncologists, medical oncologists, and physicists who are willing to push the therapeutic envelope. The teams will have to be skilled in all aspects of their craft and be willing to accept potentially higher treatment-related risks in the pursuit of improved outcomes. There will only be a handful of institutions in each country that have both the physician expertise and the facilities to explore these horizons. Increasing cooperation among these institutions is an important step in the direction of progress.

Prospective clinical trials with IORT as a component of treatment are needed to evaluate both disease control and treatment tolerance. For patients in whom gross total resection of their cancer is not feasible, the ability to achieve central or local control is decreased, thus the need for phase II/III trials that address the addition of radiation dose modifiers during EBRT and IORT. Nerve tolerance phase II/III trials are also indicated in patients needing IORT doses of 15–20 Gy. Patients with locally advanced or locally recurrent cancers often have both high systemic and local risks; phase II/III trials need to evaluate the addition of aggressive systemic therapy (Fig. 23.2) to the locally aggressive treatment approaches discussed in this textbook.

Attempts to complete phase III IORT clinical trials have been largely unsuccessful when attempted in a single country. The RTOG was able to successfully complete Phase II trials in a variety of disease sites from 1985 to 1993 but was unable to successfully accrue to Phase III trials in pancreas and colorectal cancer. Accordingly, the RTOG IORT protocol committee was disbanded and further trials evaluating IORT as a component of treatment have not been conducted in multi-institution fashion in the USA.

The ISIORT organization attempted to develop a clinical trials program in the early 2000s in which phase II–III studies would be performed in an international multi-institution setting. This did not occur because of the inability to secure funding for centralized statistics and data management.

Improvements in technology and an increase in dedicated IORT facilities have made IORT more feasible in a larger number of institutions in the USA, Europe, and Asia and will thus facilitate the conduct of future prospective phase II/III trials which evaluate IORT in combination with other components of treatment in a multi-institution national or international setting. IORT investigators will have to be innovative in both designing and conducting the trials with appropriate statistics and data management expertise so that the end-results are believable. It is unlikely that central statistics and data management will be feasible for multiple trials unless an existing protocol organization (EORTC, RTOG) is willing to become involved in IORT studies now that a larger number of IORT institutions are in existence in the USA, Europe, and Asia. A more likely scenario is that IORT institutions with in-house statistical and data management expertise (i.e., Mayo Clinic Cancer Center, MSKCC, MDACC, University Hospital Gregorio Maranon – Madrid, Duke University, or a consortium of institutions such as ISIORT-Europe/EORTC) would each serve as the statistical center for 1–2 studies in which other national or international IORT institutions could participate. The need for future phase II/III trials is obvious, but innovation in registration, methodology, and statistical evaluation will be needed to successfully implement and complete them in timely fashion. A successful first step in this direction in managing large databases of multi-institutional origin are the published pooled analysis studies in rectal and resected pancreatic cancer generated in the ISIORT-Europe working party from 2005 to 2009 [12, 13, 18, 19].

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DOI 10.1007/978-1-61779-015-7, © Springer Science+Business Media, LLC 2011

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