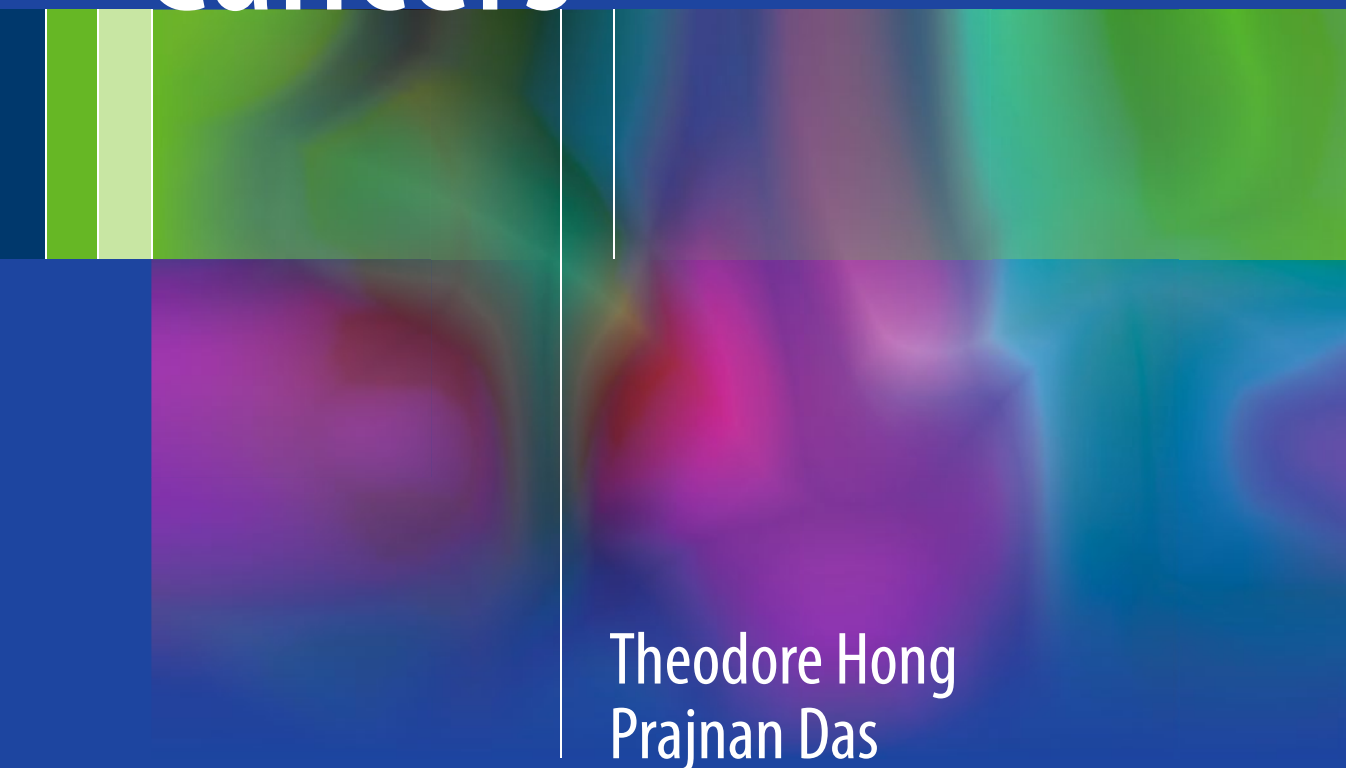
# Radiation Therapy for Gastrointestinal Cancers



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ISBN 978-3-319-43113-0 ISBN 978-3-319-43115-4 (eBook)
DOI 10.1007/978-3-319-43115-4

Library of Congress Control Number: 2017930808

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Printed on acid-free paper

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The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

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# Basics of Chemotherapy

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Ryan D. Nipp and David. P. Ryan

## 1.1 Colon Cancer

1. *Neoadjuvant*
   (a) Data supporting the benefit of neoadjuvant chemotherapy or chemoradiotherapy in colon cancer is limited.
   (b) Patients with resectable colon cancer should undergo surgical resection rather than up-front therapy, if they are surgical candidates.
2. *Adjuvant therapy*
   (a) *Fluorouracil (FU)-based therapy*:
      (i) Mechanism of action: 5-FU is an antimetabolite (pyrimidine analog) that interferes with DNA and RNA synthesis. 5-FU is converted to fluorouridine monophosphate (F-UMP), an active metabolite, and is incorporated into RNA to replace uracil and inhibit cell growth [1]. Another active metabolite of 5-FU, fluorodeoxyuridine monophosphate (F-dUMP), inhibits thymidylate synthetase, which depletes thymidine triphosphate (a necessary component of DNA synthesis).
         (1) Combined with leucovorin (LV), as both drugs together form a stable complex with thymidylate synthetase which permits prolonged inhibition of the enzyme by 5-FU
      (ii) Schedule (Table 1.1).
      (iii) Toxicity: myelotoxicity, diarrhea, mucositis, renal toxicity, palmar-plantar erythrodysesthesia (hand-foot syndrome), angina (coronary vasospasm), fatigue, anorexia, and nausea/vomiting:
         (1) Dihydropyrimidine dehydrogenase (DPD) deficiency: Patients who are partially or totally deficient in DPD cannot adequately degrade fluoropyrimidine therapies, resulting in an increased risk of severe, and even fatal, toxicity. Fluorouracil (FU)-based therapy should be avoided in patients with DPD deficiency, and tests are available to test for the deficiency.
   (b) *Oxaliplatin-containing chemotherapy*:
      (i) Mechanism of action: Oxaliplatin is a platinum-derivative, alkylating agent. The platinum compound binds to DNA forming cross-links and inhibits DNA replication and transcription, which results in cell death.

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© Springer International Publishing AG 2017
T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_1

**Table 1.1** 5-FU treatment schedule

| Short-term infusional fluorouracil and leucovorin for gastrointestinal cancer (modified de Gramont schedule) [2]<br>Each cycle is 14 days | | |
|---|---|---|
| **Drug** | **Dose/route** | **Administration** |
| Leucovorin | 400 mg/m$^2$ IV | Day 1 given over 2 h |
| 5-FU bolus | 400 mg/m$^2$ IV | Day 1 given after leucovorin |
| 5-FU infusional | 2400 mg/m$^2$ IV | Given over 46 h via pump |
| Weekly bolus fluorouracil plus high-dose leucovorin (Roswell Park Memorial Institute regimen) [3]<br>Treatment consists of four cycles (8 weeks per cycle) | | |
| Leucovorin | 500 mg/m$^2$ IV | Weekly for 6 weeks (days 1, 8, 15, 22, 29, 36) |
| 5-FU bolus | 500 mg/m$^2$ IV | Weekly for 6 weeks (days 1, 8, 15, 22, 29, 36) |
| Adjuvant capecitabine [4] | | |
| Capecitabine | 1250 mg/m$^2$ oral | Twice daily on day 1 through 14 every 21 days |

**Table 1.2** Oxaliplatin-containing regimens treatment schedule

| Modified FOLFOX6 chemotherapy [2]<br>Each cycle is 14 days | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Oxaliplatin | 85 mg/m$^2$ IV | Day 1 can give concurrently with leucovorin |
| Leucovorin | 400 mg/m$^2$ IV | Day 1 given over 2 h |
| 5-FU bolus | 400 mg/m$^2$ IV | Day 1 given after leucovorin |
| 5-FU infusional | 2400 mg/m$^2$ IV | Given over 46 h via pump |
| Capecitabine and oxaliplatin (CAPOX) [2]<br>Each cycle is 21 days | | |
| Oxaliplatin | 130 mg/m$^2$ IV | Day 1 given over 2 h |
| Capecitabine | 850 mg/m$^2$ oral | Twice daily from day 1 (pm) to day 15 (am) |

(ii) Schedule (Table 1.2).

(iii) Toxicity: myelotoxicity, peripheral neuropathy (paresthesias and dysesthesias), nausea/vomiting, diarrhea, fatigue, anorexia, hepatotoxicity, and alopecia.

(c) *Adjuvant radiation therapy (RT)*:

(i) Not usually considered a routine component of care for completely resected colon cancer

(ii) May be considered for patients with ascending or descending colon primary with T4 disease or for patients who have a positive resection margin

3. *Metastatic colon cancer*: Eight classes of drugs have been shown to have activity in metastatic colon cancer: (1) 5-FU-based therapies, (2) oxaliplatin-containing, (3) irinotecan-containing, (4) epidermal growth factor receptor (EGFR)-targeting therapies (cetuximab and panitumumab), (5) bevacizumab, (6) intravenous aflibercept, (7) regorafenib, and (8) trifluridine-tipiracil (TAS-102):

(a) *EGFR-targeting therapies (cetuximab and panitumumab)*: appropriate only for patients with KRAS/NRAS wild-type tumors

(i) Mechanism of action: monoclonal antibodies (MoAbs) directed against the epidermal growth factor receptor (EGFR). Inhibits cell growth by blocking phosphorylation and activation of receptor-associated kinases

(ii) Schedule (Table 1.3)

(iii) Toxicity: dermatologic (acneiform rash), stomatitis, keratitis (panitumumab), pulmonary fibrosis/interstitial lung disease (panitumumab), fatigue, neuropathy, diarrhea, and nausea

**Table 1.3** EGFR-targeting therapies' treatment schedule

| *Cetuximab* [6]<br>Each cycle is 1 week | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Cetuximab | 400 mg/m$^2$ IV | Day 1 |
| Cetuximab | 250 mg/m$^2$ IV | Weekly, starting with cycle 2 |
| *Panitumumab* [7]<br>Each cycle is 2 weeks | | |
| Panitumumab | 6 mg/kg IV | Day 1 |

**Table 1.4** Bevacizumab treatment schedule

| Bevacizumab | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Bevacizumab (combined with capecitabine) [8] | 7.5 mg/kg IV | Day 1 of 21 day cycles |
| Bevacizumab (combined with FOLFOX or FOLFIRI) [2, 9] | 5 mg/kg IV | Day 1 of 14 day cycles |

**Table 1.5** Intravenous aflibercept treatment schedule

| Intravenous aflibercept | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Intravenous aflibercept (combined with FOLFIRI) [10] | 4 mg/kg IV | Day 1 of 14 day cycles |

**Table 1.6** Regorafenib treatment schedule

| Regorafenib | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Regorafenib [11] | 160 mg oral | Daily for three of every 4 weeks |

(b) *Bevacizumab*
- (i) Mechanism of action: a monoclonal antibody targeting vascular endothelial growth factor (VEGF)
- (ii) Schedule (Table 1.4)
- (iii) Toxicity: hypertension, venous and arterial thromboembolism, hemorrhage, gastrointestinal perforation, nephrotic syndrome, reversible posterior leukoencephalopathy syndrome, peripheral edema, and fatigue

(c) *Intravenous aflibercept*
- (i) Mechanism of action: a recombinant fusion protein comprised of portions of binding domains for VEGF receptors 1 and 2 acts as a decoy receptor for VEGF-A, VEGF-B, and placental growth factor (PlGF) which works to prevent angiogenesis.
- (ii) Schedule (Table 1.5).
- (iii) Toxicity: hypertension, bleeding, proteinuria, wound infection, thromboembolic events, diarrhea, mucositis, neutropenia, and fatigue.

(d) *Regorafenib*
- (i) Mechanism of action: orally active angiogenic tyrosine kinase inhibitor (including the VEGF receptors 1 to 3), as well as other receptor and intracellular kinases
- (ii) Schedule (Table 1.6)
- (iii) Toxicity: hypertension, fatigue, diarrhea, rash, hematologic, infection, and proteinuria

(e) *Trifluridine-tipiracil (TAS-102)*
- (i) Mechanism of action: an oral cytotoxic agent consisting of the nucleoside analog trifluridine (a cytotoxic antimetabolite that inhibits thymidylate synthetase) and tipiracil, a thymidine phosphorylase inhibitor, which inhibits trifluridine metabolism and also has antiangiogenic properties
- (ii) Schedule (Table 1.7)
- (iii) Toxicity: fatigue, nausea, anorexia, diarrhea, and hematologic

**Table 1.7** TAS-102 treatment schedule

| TAS-102 | | |
|---|---|---|
| Drug | Dose/route | Administration |
| TAS-102 [12] | 35 mg/m$^2$ oral | Twice daily on days 1–5 and 8–12 of 28-day cycles |

**Table 1.8** Irinotecan-containing regimens treatment schedule

| FOLFIRI chemotherapy [5]<br>Each cycle is 14 days | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Irinotecan | 180 mg/m$^2$ IV | Day 1 can give concurrently with leucovorin |
| Leucovorin | 400 mg/m$^2$ IV | Day 1 given over 2 h |
| 5-FU bolus | 400 mg/m$^2$ IV | Day 1 given after leucovorin |
| 5-FU infusional | 2400 mg/m$^2$ IV | Given over 46 h via pump |

(f) *Irinotecan-containing chemotherapy*:
   (i) Mechanism of action: Irinotecan is converted to SN-38 (active metabolite) and binds reversibly to the topoisomerase I-DNA complex which ultimately leads to double-strand DNA breaks and termination of cellular replication.
   (ii) Schedule (Table 1.8).
   (iii) Toxicity: myelotoxicity, diarrhea, nausea/vomiting, dehydration, fatigue, anorexia, hepatotoxicity, and alopecia.

## 1.2 Rectal Cancer

1. *Neoadjuvant therapy*
   (a) Infusional 5-FU during neoadjuvant chemoradiotherapy (225 mg/m$^2$/d Monday–Friday every week or 7 days/week).
   (b) Capecitabine concurrent with neoadjuvant chemoradiotherapy (825 mg/m$^2$/ po bid Monday–Friday every week or 7 days/week).
   (c) Oxaliplatin or irinotecan in addition to 5-FU-based chemotherapy is not considered a standard approach.
2. *Adjuvant therapy*
   (a) Adjuvant fluoropyrimidine-based chemotherapy is recommended for most patients:
      (i) Options include LV-modulated 5-FU, fluoropyrimidine monotherapy, FOLFOX, or capecitabine plus oxaliplatin (XELOX).
3. *Metastatic*
   (a) Potentially resectable metastases: Options include neoadjuvant chemotherapy followed by resection (synchronous or staged) and postoperative fluoropyrimidine-based chemoradiotherapy, neoadjuvant chemotherapy followed by chemoradiotherapy and then resection, or initial surgery followed by chemotherapy alone for pT1-2 N0 disease or chemotherapy plus RT for more advanced T-stage or node-positive disease.
   (b) Unresectable metastatic disease: Treatment depends on the symptomatic nature of the disease.
      (i) Symptomatic: systemic chemotherapy, chemoradiotherapy, surgery of involved rectal segment, or stenting
      (ii) Asymptomatic: follows similar guidelines as outlined above for metastatic colon cancer

## 1.3 Anal Cancer

1. *Neoadjuvant therapy*
   (a) Concurrent use of fluorouracil (FU) plus mitomycin during radiation therapy
      (i) Mitomycin mechanism of action: inhibits DNA and RNA synthesis and produces DNA cross-linking similar to an alkylating agent
      (ii) Schedule (Table 1.9)

**Table 1.9** Concurrent 5-FU plus mitomycin during RT treatment schedule

| 5-FU plus mitomycin with concurrent RT [13] | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Mitomycin | 10 mg/m$^2$ IV | Days 1 and 29 |
| 5-FU | 1000 mg/m$^2$ per day IV | Continuous infusion on days 1–4 and days 29–32 |

**Table 1.10** Concurrent 5-FU plus cisplatin during RT treatment schedule

| 5-FU plus cisplatin with concurrent RT [14] | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Cisplatin | 75 mg/m$^2$ IV | Days 1 and 29 |
| 5-FU | 1000 mg/m$^2$ per day IV | Continuous infusion on days 1–4 and days 29–32 |

**Table 1.11** 5-FU plus cisplatin

| 5-FU plus cisplatin with concurrent RT<br>Each cycle is 28 days | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Cisplatin | 100 mg/m$^2$ IV | Days 1 |
| 5-FU | 1000 mg/m$^2$ per day IV | Continuous infusion on days 1–4 of each cycle |

(iii) Toxicity: myelotoxicity, local skin reaction, diarrhea, stomatitis, thrombotic microangiopathy, pulmonary toxicity, fever, alopecia, nausea, and vomiting

(b) Concurrent use of fluorouracil (FU) plus cisplatin during radiation therapy

(i) Cisplatin mechanism of action: inhibits synthesis of DNA by forming DNA cross-links

(ii) Schedule (Table 1.10)

(iii) Toxicity: myelotoxicity, diarrhea, stomatitis, nephrotoxicity, neuropathy, ototoxicity, alopecia, nausea, and vomiting

2. *Metastatic*

(a) Cisplatin plus 5-FU

(i) Schedule (Table 1.11)

(ii) Toxicity: myelotoxicity, diarrhea, stomatitis, nephrotoxicity, neuropathy, ototoxicity, alopecia, nausea and vomiting, and palmar-plantar erythrodysesthesia

## 1.4 Pancreatic Cancer

1. *Neoadjuvant therapy*

(a) Gemcitabine alone

**Table 1.12** Gemcitabine alone

| Weekly for 7 of 8 weeks for the first cycle and then weekly for 3 of 4 weeks [15] | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Gemcitabine | 1000 mg/m$^2$ IV | Weekly for 7 weeks followed by 1 week of rest in the first cycle<br>Weekly for 3 weeks followed by 1 week of rest in all subsequent cycles |

(i) Gemcitabine mechanism of action: inhibits synthesis of DNA by forming DNA cross-links

(ii) Schedule (Table 1.12)

(iii) Toxicity: myelotoxicity, hepatotoxicity, fever, pulmonary toxicity, thrombotic microangiopathy, edema, rash, alopecia, and nausea

(b) Gemcitabine plus nab-paclitaxel

(i) Nab-paclitaxel mechanism of action: promotes assembly of microtubules by enhancing tubulin dimers and inhibiting disassembly, thereby inhibiting cell replication

(ii) Schedule (Table 1.13)

(iii) Toxicity: myelotoxicity, sepsis, neuropathy, hepatotoxicity, fever, pulmonary toxicity, thrombotic microangiopathy, edema, rash, alopecia, and nausea

(c) FOLFIRINOX

(i) Schedule (Table 1.14)

(ii) Toxicity: myelotoxicity, neutropenia (necessitating growth factor), neuropathy, diarrhea, nausea/vomiting, fatigue, anorexia, hepatotoxicity, and alopecia

2. *Adjuvant therapy*

(a) Gemcitabine for nonmetastatic pancreatic cancer

(i) Schedule (Table 1.15)

(ii) Toxicity: myelotoxicity, hepatotoxicity, fever, pulmonary toxicity, thrombotic microangiopathy, edema, rash, alopecia, and nausea

**Table 1.13** Gemcitabine plus nab-paclitaxel

| Each cycle is 4 weeks [16] | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Gemcitabine | 1000 mg/m$^2$ IV | Days 1, 8, and 15 of 28-day cycles |
| Nab-paclitaxel | 125 mg/m$^2$ IV | Days 1, 8, and 15 of 28-day cycles |

**Table 1.14** FOLFIRINOX

| Each cycle is 14 days [17] | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Oxaliplatin | 85 mg/m$^2$ IV | Day 1, prior to leucovorin |
| Leucovorin | 400 mg/m$^2$ IV | Day 1 |
| Irinotecan | 180 mg/m$^2$ IV | Day 1 |
| 5-FU bolus | 400 mg/m$^2$ IV | Day 1, after leucovorin |
| 5-FU infusional | 2400 mg/m$^2$ IV | Day 1, continuous infusion over 46 h |

**Table 1.15** Adjuvant gemcitabine

| Each cycle is 4 weeks [18] | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Gemcitabine | 1000 mg/m$^2$ IV | Weekly for 3 weeks followed by 1 week without treatment |

3. *Metastatic*
   (a) Gemcitabine monotherapy
   (b) Gemcitabine plus nab-paclitaxel
   (c) FOLFIRINOX
   (d) Modified FOLFOX6

## 1.5 Gastric Cancer

1. *Active regimens*
   (a) Per the UK Medical Research Council MAGIC trial, perioperative chemotherapy (three preoperative and three postoperative cycles of epirubicin, cisplatin, and infusional 5-FU [ECF]):
      (i) Epirubicin mechanism of action: anthracycline that inhibits DNA and RNA synthesis by intercalating between DNA strands
      (ii) Schedule (Table 1.16)

**Table 1.16** ECF

| Each cycle is 21 days [19] | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Epirubicin | 50 mg/m$^2$ IV | Day 1 |
| Cisplatin | 60 mg/m$^2$ IV | Day 1 |
| 5-FU | 200 mg/m$^2$ per day IV | Daily for up to 6 months, continuous infusion with portable infusion device |

      (iii) Toxicity: myelotoxicity, fatigue, renal dysfunction, mucositis, diarrhea, neurotoxicity, and palmar-plantar erythrodysesthesias; epirubicin is associated with dose-dependent cardiomyopathy.
   (b) Per the US Intergroup INT0116, adjuvant combined chemoradiotherapy:
      (i) One cycle of 5-FU (425 mg/m$^2$ per day) and leucovorin (20 mg/m$^2$ per day) daily for 5 days
      (ii) Followed 1 month later by RT (45 Gy in daily 1.8 Gy fractions) given with concurrent 5-FU and leucovorin (400 mg/m$^2$ and 20 mg/m$^2$, respectively) on days 1–4 and on the last 3 days of RT
   (c) Per the CLASSIC trial, adjuvant capecitabine in combination with oxaliplatin:
      (i) Eight cycles (21 days each) of capecitabine (1000 mg/m$^2$ twice daily on days 1–14) plus oxaliplatin (130 mg/m$^2$ on day 1)
   (d) Docetaxel, cisplatin, and fluorouracil (DCF):
      (i) Docetaxel mechanism of action: taxane that promotes microtubule assembly and stabilizes microtubules which then inhibits DNA, RNA, and protein synthesis
      (ii) Schedule (Table 1.17)
      (iii) Toxicity: myelotoxicity, fatigue, renal dysfunction, diarrhea, neurotoxicity, palmar-plantar erythrodysesthesias, hepatotoxicity, alopecia, and stomatitis
   (e) Epirubicin, cisplatin, and capecitabine (ECX):
      (i) Schedule (Table 1.18).

**Table 1.17** DCF

| Each cycle is 21 days [20] | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Docetaxel | 75 mg/m$^2$ IV | Day 1 |
| Cisplatin | 75 mg/m$^2$ IV | Day 1 |
| 5-FU | 750 mg/m$^2$ per day IV | Days 1 through 5, continuous infusion |

**Table 1.18** ECX

| Each cycle is 21 days [19] | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Epirubicin | 50 mg/m$^2$ IV | Day 1 |
| Cisplatin | 60 mg/m$^2$ IV | Day 1 |
| Capecitabine | 625 mg/m$^2$ per dose PO | Days 1–21, twice daily taken within 30 min of a meal |

(ii) Toxicity: myelotoxicity, fatigue, renal dysfunction, mucositis, diarrhea, nausea, neurotoxicity, and palmar-plantar erythrodysesthesias; epirubicin is associated with dose-dependent cardiomyopathy.

(f) Epirubicin, oxaliplatin, and capecitabine (EOX):

(i) Schedule (Table 1.19)

(ii) Toxicity: myelotoxicity, fatigue, mucositis, diarrhea, nausea, neurotoxicity, and palmar-plantar erythrodysesthesias; epirubicin is associated with dose-dependent cardiomyopathy.

(g) FOLFIRI (fluorouracil plus leucovorin and irinotecan)

(h) Modified FOLFOX6

2. *Human epidermal growth factor receptor 2 protein (HER-2)-overexpressing adenocarcinomas*

(a) Trastuzumab-containing regimens

(i) Trastuzumab mechanism of action: monoclonal antibody that binds to the HER-2 extracellular domain

(ii) Schedule (Tables 1.20 and 1.21)

(iii) Toxicity: myelotoxicity, diarrhea, nephrotoxicity, neurotoxicity, palmar-plantar erythrodysesthesias, and pulmonary toxicity; trastuzumab is associated with cardiotoxicity.

**Table 1.19** EOX

| Each cycle is 21 days [19] | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Epirubicin | 50 mg/m$^2$ IV | Day 1 |
| Oxaliplatin | 130 mg/m$^2$ IV | Day 1 |
| Capecitabine | 625 mg/m$^2$ per dose PO | Days 1–21, twice daily taken within 30 min of a meal |

**Table 1.20** Trastuzumab plus 5-FU and cisplatin

| Each cycle is 21 days for total of six cycles [21] | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Cisplatin | 80 mg/m$^2$ IV | Day 1 |
| 5-FU | 800 mg/m$^2$ IV | Days 1–5, continuous infusion |
| Trastuzumab | 8 mg/kg loading dose | Day 1, only with cycle 1 |
| Trastuzumab | 6 mg/kg | Day 1 of subsequent cycles, starts with cycle 2 |

**Table 1.21** Trastuzumab plus capecitabine and cisplatin

| Each cycle is 21 days for total of six cycles [21] | | |
|---|---|---|
| Drug | Dose/route | Administration |
| Cisplatin | 80 mg/m$^2$ IV | Day 1 |
| Capecitabine | 1000 mg/m$^2$ per dose PO | Days 1–14, twice daily within 30 min of a meal |
| Trastuzumab | 8 mg/kg loading dose | Day 1, only with cycle 1 |
| Trastuzumab | 6 mg/kg | Day 1 of subsequent cycles, starts with cycle 2 |

## 1.6 Liver Cancer

1. *Systemic therapy for advanced hepatocellular carcinoma*

Systemic therapy is usually reserved for patients with advanced, unresectable disease or those who are unsuitable for regional therapies such as radiation, ablation, or embolization.

(a) Sorafenib:

(i) Mechanism of action: multikinase inhibitor that inhibits tumor growth and angiogenesis by inhibiting intracellular

Raf kinases and the vascular endothelial growth factor receptor (VEGFR) intracellular kinase pathway
(ii) Schedule per the SHARP trial (included patients with Child-Pugh A cirrhosis), 400 mg twice daily until progression or unacceptable toxicity [22]
(iii) Toxicity: hypertension, fatigue, palmar-plantar erythrodysesthesias, diarrhea, myelotoxicity, and fever

(b) Other agents to consider include gemcitabine-based regimens (e.g. gemcitabine and cisplatin, gemcitabine and oxaliplatin) and 5-FU-based regimens (e.g. FOLFOX, XELOX), and cisplatinbased regimens (e.g. cisplatin and doxorubicin).

## 1.7 Biliary Cancer

1. *Neoadjuvant therapy*
   (a) Preoperative chemoradiotherapy is not considered a standard approach to treatment of cholangiocarcinoma.
2. *Adjuvant therapy*
   (a) Fluoropyrimidine-based chemoradiotherapy is often offered to patients with cholangiocarcinoma following a macroscopically incomplete (R2) resection.
   (b) The European Study Group for Pancreatic Cancer (ESPAC)-3 periampullary trial tested 6 months of leucovorin-modulated 5-FU, 6 months of single-agent gemcitabine, or observation alone and found a survival advantage (although not statistically significant) for adjuvant chemotherapy [23].
3. *Advanced cholangiocarcinoma*
   (a) Gemcitabine-based regimens
      (i) Gemcitabine plus cisplatin has been shown to be superior to gemcitabine alone [24].
      (ii) Gemcitabine plus capecitabine has shown activity as well.
      (iii) Gemcitabine plus oxaliplatin (GEMOX) has shown activity with good tolerability [25].
   (b) Fluoropyrimidine-based regimens
      (i) Leucovorin-modulated 5-FU [26].
      (ii) Infusional 5-FU has been combined with cisplatin [27].
      (iii) Capecitabine monotherapy may also be an option for first-line therapy [28].
   (c) Second-line chemotherapy
      (i) FOLFOX
      (ii) Oxaliplatin plus capecitabine
      (iii) FOLFIRI

## 1.8 Gallbladder Cancer

1. *Adjuvant therapy*
   (a) Chemotherapy alone
      (i) The optimal choice for chemotherapy is not established in gallbladder cancer.
      (ii) Options include fluoropyrimidines, gemcitabine, gemcitabine plus cisplatin, and gemcitabine plus oxaliplatin.
   (b) Chemoradiotherapy
      (i) Guidelines recommend consideration of either adjuvant fluoropyrimidine-based chemoradiotherapy or chemotherapy alone with single-agent fluoropyrimidine or gemcitabine after resection for all tumors with stages higher than T1 N0.
2. *Metastatic*
   (a) Although there is no optimal regimen for advanced gallbladder cancer, guidelines recommend considering a gemcitabine and/or a platinum or fluoropyrimidine-based regimen.
   (b) 5-FU-based therapy:
      (i) Infusional 5-FU plus cisplatin [27]
      (ii) ECF [29]
      (iii) Capecitabine [28]
      (iv) Capecitabine in combination with cisplatin [30] and oxaliplatin [31]
   (c) Gemcitabine-based regimens:
      (i) Gemcitabine is active as a monotherapy [32].
      (ii) Gemcitabine plus 5-FU and leucovorin [33].
      (iii) Gemcitabine plus capecitabine [34].
      (iv) Gemcitabine plus cisplatin [35].
      (v) Gemcitabine plus oxaliplatin [25].
      (vi) Gemcitabine plus oxaliplatin and 5-FU [36].

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# Gastrointestinal Anatomy

# 2

Stuti Ahlawat, Rekha Baby, and Salma K. Jabbour

## 2.1 Esophagus

### 2.1.1 Gross Anatomy

- Figures 2.1 and 2.2
- Fibromuscular tube that allows passage of food from the pharynx to the stomach
- About 25 cm long and has a star-shaped lumen with a 2–3 cm diameter
- Begins at the lower border of the C6 [1]
- Cranially enters the thorax at about T1 and occupies the posterior mediastinum [2]
- Caudally enters the abdomen through esophageal hiatus in the diaphragm through the right crus at about T10 [2]
- Has a slight deviation from right to left with three curves: one on the sagittal and two on the frontal plane [1]
- Divided into cervical, thoracic, diaphragmatic, and abdominal [3]
- No serosal covering [4]
- Esophageal wall consists of four layers: mucosa, submucosa, muscularis propria, and adventitia [4]

### 2.1.2 Physiologic Points of Constriction/Narrowing [2]

- At the origin of the esophagus at the cricopharyngeus muscle (upper esophageal sphincter)
- By the aortic arch, left anterolateral esophageal surface
- By the left main bronchus
- By the diaphragm at the esophageal hiatus

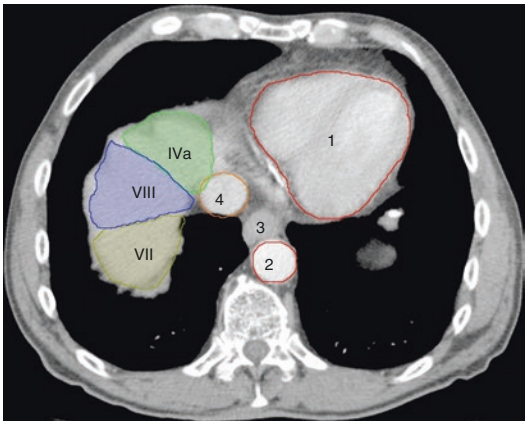


**Fig. 2.1** *1* heart, *2* aorta, *3* esophagus, *4* inferior vena cava

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© Springer International Publishing AG 2017
T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_2

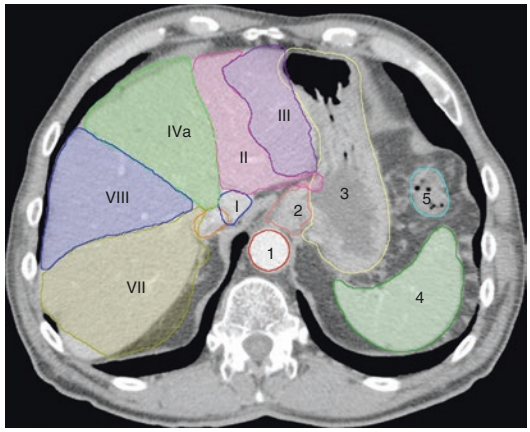


**Fig. 2.2** *1* aorta, *2* GE junction, *3* stomach, *4* spleen, *5* descending colon

### 2.1.3 Esophageal Portions [3]

- Cervical esophagus starts at about 16 cm from the incisors
- Upper thoracic esophagus begins around 20–21 cm from the incisors
- Mid-thoracic esophagus begins at around 24 cm from the incisors, at the level of the carina
- Lower thoracic esophagus begins around 32 cm from the incisors with the lower esophageal sphincter starting at 37–39 cm from the incisors

### 2.1.4 Cervical Portion [1]

- About 4–5 cm long, begins at the lower border of the C6 and extends to the upper border of T2
- Anteriorly, connected to the trachea by soft connective tissues and tracheoesophageal muscular tissues
- Posteriorly, connected to the deep cervical fascia and spinal column through the retroesophageal space
- Laterally, connected to the right and left common carotid arteries and recurrent laryngeal nerve on the right

### 2.1.5 Thoracic Portion [1]

- About 16 cm long, extends from T2 to the diaphragm and is located in the posterior mediastinum
- Upper thoracic esophagus, above the level of the mainstem bronchi
  - Anteriorly connected to the trachea and attached to the initial part of the left main bronchus by the bronchoesophageal muscle
  - Connected posteriorly to the vertebral column, up to T4
  - Laterally on right side, attached to mediastinal pleura forming the azygoesophageal recess. On the left side, connected to the mediastinal pleura, the aortic arch, and the initial part of the descending aorta
- Lower thoracic esophagus, below level of bronchi
  - Connected anteriorly to the posterior part of the pericardium covering the left atrium and the lymph nodes at the tracheobronchial bifurcation
  - Laterally connected to the vagus nerve

### 2.1.6 Diaphragmatic Portion [1]

- About 1–2 cm long, connected to the esophageal hiatus
- Anterior to the aortic orifice, attached by the phrenicoesophageal muscle
- The phrenicoesophageal ligament attaches the esophagus to the diaphragm

### 2.1.7 Abdominal Portion [1]

- About 3 cm in length, begins as it transits the diaphragmatic hiatus and ends into the cardia of the stomach along the lesser curvature forming an acute angle with the gastric wall (the angle of His)
- Anteriorly, related to the posterior surface of the left hepatic lobe

- Posteriorly, the abdominal aorta and the medial diaphragmatic pillars
- Right, hepatic caudate lobe
- Left, bottom of the stomach

### 2.1.8 Lymphatic Drainage [4, 5]

- Cervical and thoracic esophagus – extensive submucosal lymphatic system, continuous longitudinally
- Cervical – efferent vessels drain directly or through the paratracheal nodes into the deep cervical nodes
- Thoracic-posterior mediastinal nodes
- Abdominal – left gastric nodes, celiac nodes, and left and right paracardial nodes. Posterior surface – uppermost aortic nodes
- Direct drainage into the thoracic duct

### 2.1.9 Blood Supply [2, 5]

#### 2.1.9.1 Arterial Supply

- Cervical: inferior thyroid arteries
- Thoracic: bronchial and esophageal branches of the aorta
- Diaphragmatic and abdominal: esophageal branches of the aorta, left gastric, and phrenic arteries

#### 2.1.9.2 Venous Drainage

- Drains into the submucosa and then into the tributary of the paraesophageal plexus
- Thoracic esophagus drains into the azygos vein. Some drainage into hemiazygos and accessory azygos veins into the anterior and posterior intercostal veins
- Cervical: veins merge into the inferior thyroid vein
- Abdominal: veins drain into the left gastric vein and to the portal vein

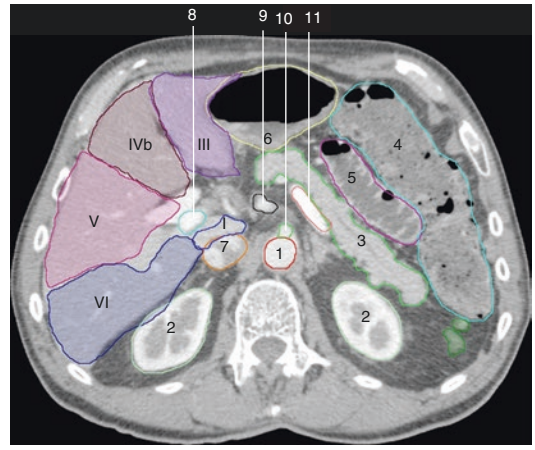


**Fig. 2.3** *1* aorta, *2* kidney, *3* pancreas, *4* colon, *5* small bowel, *6* stomach, *7* inferior vena cava, *8* portal vein, *9* celiac axis, *10* superior mesenteric artery, *11* splenic vein

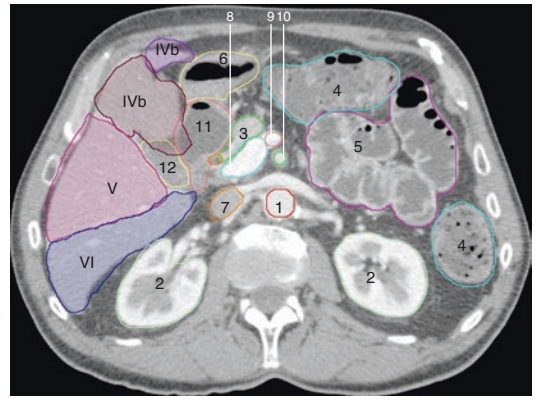


**Fig. 2.4** *1* aorta, *2* kidney, *3* pancreas, *4* colon, *5* small bowel, (jejunum) *6* stomach, *7* inferior vena cava, *8* portal vein/superior mesenteric vein, *9* superior mesenteric artery, *10* splenic vein, *11* duodenum, *12* gallbladder

## 2.2 Stomach

### 2.2.1 Gross Anatomy [1]

- Figs. 2.2, 2.3, 2.4, and 2.12
- Muscular J-shaped, highly vascular organ, in the left upper quadrant of the abdomen

- Gastric wall is made up of four layers: mucosa, submucosa, muscularis propria, and serosa
- Concave right margin: the lesser curvature and a convex left margin, the greater curvature

#### 2.2.1.1 Anterior Surface

- Completely covered with peritoneum and adjacent to the diaphragm
- Related to the left lobe of the liver (segments II, III, and IV) and the distal transverse colon

#### 2.2.1.2 Posterior Surface

- Covered with peritoneum except at the part closer to the cardia where it touches the diaphragm
- Related to the left adrenal gland, the body and tail of the pancreas, aorta, splenic and hepatic arteries, and portal vein

#### 2.2.1.3 Lesser Curvature

- Posterosuperior margin of the stomach
- Starts at the right of the cardia and continues at the right border of the abdominal esophagus and runs a short distance along the right border of the body of the stomach where it turns upward horizontally and descends again to terminate at the level of the pylorus
- The junction of the vertical and horizontal parts of the lesser curvature is called incisura angularis – point of insertion of the hepatogastric ligament connecting the liver and the stomach
- Lesser omentum suspends the stomach from the abdominal wall

#### 2.2.1.4 Greater Curvature

- Starts at the cardiac notch and turns upward to form the dome-shaped margin of the fundus and subsequently goes down and medially up to the intermediate sulcus which separates the antrum and the pyloric canal
- Covered by the peritoneum
- Laterally, the anterior and posterior peritoneal visceral sheets merge to form the gastrosplenic ligament, which connects it to the splenic hilum
- Posteriorly, related to the body and tail of the pancreas and a portion of the left hepatic lobe
- The gastrocolic ligament attaches it to the transverse colon, the right colic flexure, and the duodenum and coincides with the anterior root of the greater omentum
- The greater omentum attaches the stomach to the transverse colon, spleen, and diaphragm
- The omental bursa also known as the lesser sac lies behind the stomach and in front of the pancreas; it communicates with the greater sac (main peritoneal cavity) via the epiploic foramen of Winslow behind the hepatoduodenal ligament (the free edge of the lesser omentum)

### 2.2.2 Portions of the Stomach

- Divided into four parts: the cardia, fundus, body, and pylorus

#### 2.2.2.1 Cardia

- Connects the esophagus to the stomach
- It is the region following the Z-line of the gastroesophageal junction at which the epithelium changes from stratified squamous to columnar epithelium
- The lower esophageal sphincter is located near the cardia

#### 2.2.2.2 Fundus

- Part of the stomach above an imaginary horizontal line drawn from the cardiac notch
- Radiologically, coincides with the gastric bubble (the air-filled part of the stomach which is radiolucent)
- Touches the left hemidiaphragm

#### 2.2.2.3 Body

- The central part of the stomach, main site of acid production

#### 2.2.2.4 Pylorus

- Connects the stomach to the duodenum
- Antrum: prepyloric vestibule, opening into the body of the stomach. May be demarcated from the pyloric canal by a slight groove
- Pylorus: opens into the duodenum through the pyloric orifice which is surrounded by the pyloric sphincter

### 2.2.3 Blood Supply [6, 13]

#### 2.2.3.1 Arterial Supply

- Highly vascular with a rich anastomotic network
- Celiac trunk arises from the abdominal aorta at the level of L1, about 1 cm in length, and divides into the left gastric artery, the common hepatic artery, and the splenic artery
- Left gastric artery runs along the lesser curvature and divides into ascending and descending branches supplying the abdominal esophagus and the lesser curvature, respectively
- Common hepatic artery runs along the superior border of the pancreas to the right and gives rise to the gastroduodenal artery (runs behind the first part of the duodenum) and then continues as the hepatic artery proper
- The left gastric artery anastomoses with the right gastric artery (branch of the common hepatic or hepatic artery proper) along the lesser curvature forming an arcade which gives rise to multiple small arteries supplying the body of the stomach
- The gastroduodenal artery gives rise to posterior superior pancreaticoduodenal artery and then divides into right gastroepiploic artery (runs from right to left along the greater curvature) and anterior superior pancreaticoduodenal artery
- The splenic artery runs to the left along the superior border of the body and tail of the pancreas and gives rise to left gastroepiploic artery (runs from left to right along the greater curvature) which anastomoses with the right gastroepiploic forming an arcade from which multiple small arteries supply the body of the stomach

#### 2.2.3.2 Venous Drainage

- Into the portal vein from the left gastric vein which is formed by the union of superior mesenteric and splenic veins. Also the right gastric and right gastroepiploic drain into the portal vein
- Into splenic vein from the left gastroepiploic and short gastric veins
- The prepyloric vein of Mayo lies on the anterior surface of the pylorus

#### 2.2.3.3 Lymphatic Drainage

- Three different systems:
- Celiac nodes: from the superior part of the anterior and posterior surfaces of the fundus, body, the antrum, and pyloric canal
- Subpyloric and gastroepiploic nodes: from the inferior part of the anterior and posterior surfaces of the body, the antrum, and pyloric canal on the right
- Gastroepiploic nodes: from the left inferior part of the body and left side of the fundus
- Lymph from the stomach flows into the cisterna chyli through the celiac nodes

## 2.3 Pancreas

### 2.3.1 Gross Anatomy [7–10, 11]

- Figs. 2.3, 2.4, 2.5, 2.11, and 2.12
- Does not have a capsule
- About 12–15 cm long and weighs about 80 g in adults
- Lies transversely at the level of the L1 and L2
- Divided into head (50 % of the parenchymal mass), body, and tail (the remaining 50 %)

#### 2.3.1.1 Head

- Attached to the C-loop of the duodenum, lies to the right of superior mesenteric vein (SMV) and superior mesenteric artery (SMA)
- Uncinate process is the extension of the inferior half of the head to the left, wedged posterior to the superior mesenteric vein
- Terminal part of the common bile duct runs posterior to and, at times, through the upper half of the head to join the main pancreatic duct (of Wirsung) forming the ampulla (of Vater)
- Neck (thinnest part) lies anterior to the junction of the superior mesenteric, splenic, and portal vein

#### 2.3.1.2 Body and Tail

- Body is rectangular and is oriented slightly upward to the left above the aorta and left kidney

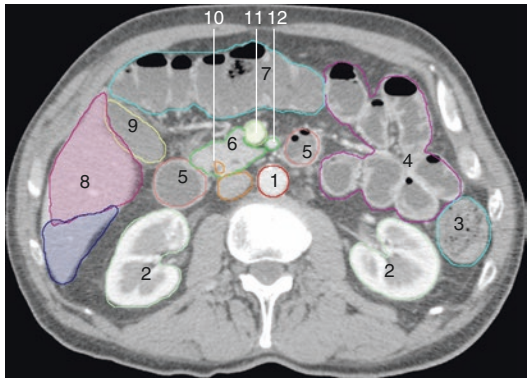


**Fig. 2.5** *1* aorta, *2* kidneys, *3* descending colon, *4* small bowel, *5* duodenum, *6* pancreas, *7* transverse colon, *8* liver, *9* gallbladder, *10* bile duct, *11* superior mesenteric vein, *12* superior mesenteric artery

  - Tail extends to the splenic hilum in the splenorenal ligament
  - The body and tail lie behind the stomach, in the lesser sac
- The transverse mesocolon is attached to the inferior part on the anterior surface of the body and tail

### 2.3.2 Ducts of the Pancreas [12]

Two excretory ducts: the main duct of Wirsung and the accessory duct of Santorini

- The main duct of Wirsung
- Arises from the pancreatic tail traverses horizontally lying between the superior and inferior margins of the gland
- Receives 20–25 secondary ducts entering at right angles to the long axis and turns downward to join the caudal part of the bile duct at the head
- Bile duct and pancreatic duct enter the duodenal wall to terminate on the apex of the major duodenal papilla
- The accessory duct of Santorini
- Connected to the main duct at the junction of the head and the neck
- Lies in the superior part of the head and opens into the duodenum at the apex of the minor papilla

### 2.3.3 Blood Supply [7–10, 11]

#### 2.3.3.1 Arterial Supply

- Highly vascular with supply from the celiac trunk and superior mesenteric artery
- Celiac trunk arises from the anterior abdominal aorta at the level of L1, about 1 cm in length, and divides into the left gastric artery, the common hepatic artery, and the splenic artery
- The superior mesenteric artery arises from the anterior abdominal aorta just below the origin of the celiac trunk at L1 behind the neck
- The common hepatic artery runs along the superior border of the pancreas to the right and gives rise to the gastroduodenal artery (runs behind the first part of the duodenum) and then continues as the hepatic artery proper
- The gastroduodenal artery gives rise to posterior superior pancreaticoduodenal artery and then divides into right gastroepiploic artery and anterior superior pancreaticoduodenal artery
- The inferior pancreaticoduodenal artery arises from the superior mesenteric artery and bifurcates into anterior and posterior branches
- The anterior and posterior branches of the superior and inferior pancreaticoduodenal arteries anastomose to form an arcade – supplies the head, the uncinate process, and the first three parts of the duodenum
- The splenic artery (multiple branches including arteria magna pancreatic) and inferior pancreatic artery (branch of SMA) supply the body and tail

#### 2.3.3.2 Venous Drainage

- Accompany the superior and inferior pancreaticoduodenal arteries
- Superior pancreaticoduodenal vein – drains into the portal vein
- Inferior pancreaticoduodenal vein – drains into the superior mesenteric vein (SMV)
- Uncinate veins – directly into the superior mesenteric vein
- Head – into the gastrocolic trunk
- Body and tail – directly into the splenic vein

#### 2.3.3.3 Lymphatic Drainage [7–10, 11]

- Majority of lymphatics lie in the interlobular septa of connective tissue and are closely related to the blood vessels
- Head – pancreaticoduodenal lymph nodes, lymph nodes in the hepatoduodenal ligament, and prepyloric and postpyloric lymph nodes
- Body and tail – mesocolic lymph nodes and lymph nodes along the hepatic and splenic arteries
- Ultimately drains into the celiac, superior mesenteric, para-aortic, and aortocaval lymph nodes

#### 2.3.3.4 Nerve Supply [7–10, 11]

- Parasympathetic – posterior vagal trunk via celiac branch
- Sympathetic – T6 to T10 via the thoracic splanchnic nerves and the celiac plexus

## 2.4 Liver [13, 14]

- Figs. 2.1, 2.2, 2.3, 2.4, 2.5, 2.10, 2.11, and 2.12
- Largest internal organ and largest gland and processes all nutrients (except fats) absorbed from the GI tract delivered to the liver via the portal vein
- Stores glycogen and secretes bile
- Anterior and superior surfaces are smooth and convex
- Posterior and inferior surfaces are indented by the colon, stomach, right kidney, duodenum, IVC, and gallbladder
- Peritoneal covering except at gallbladder fossa, porta hepatis, and bare area (posterior superior surface where the liver touches the diaphragm)
- Falciform ligament extends from the liver to anterior abdominal wall and marks the plane, which separates the medial and lateral segments of the left hepatic lobe

### 2.4.1 Blood Supply [13]

- Portal vein provides 75–80 % of the blood supply
- Portal vein carries nutrients from the intestines, pancreatic hormones, and oxygen-rich blood to the liver
- Hepatic artery provides 20–25 % of blood to the liver and is usually a branch of the celiac artery (also possible for the hepatic artery to originate from SMA)
- Biliary tree is more dependent on hepatic arterial blood supply than the liver
- Right, middle, and left hepatic veins collect blood from the liver and return it to the IVC at the confluence of the hepatic veins just below the diaphragm and entrance of the IVC into the heart
- Porta hepatic: site of exit of the portal vein, hepatic artery, and bile duct from the liver
- Portal triad: all branches of the portal vein, hepatic artery, and bile duct travel together
- Route of blood/nutrients through the liver: (1) branches of the portal vein and hepatic artery carry blood into the hepatic sinusoids, (2) hepatocytes detoxify blood and product bile, (3) bile collects into ducts, and blood collects in the central veins (4) hepatic veins

### 2.4.2 Segmental Anatomy of Liver [13, 14]

- Figs. 2.1, 2.2, 2.3, and 2.4
- Eight hepatic segments
- Each segment is drained by its own bile duct (intrahepatic) and hepatic vein branch
- Each segment has its own secondary or tertiary branch of the hepatic artery and portal vein
- Segment 1: caudate lobe, which has independent portal triad and hepatic venous drainage to the IVC

### 2.4.3 Left Lobe

- Segment 2: lateral superior
- Segment 3: lateral inferior
- Segment 4A: medial superior
- Segment 4B: medial inferior

### 2.4.4 Right Lobe

- Segment 5: L anterior inferior
- Segment 6: posterior inferior

- Segment 7: posterior superior
- Segment 8: anterior superior
- Right and left lobes are separated by a plane extending vertically through the gallbladder fossa and middle hepatic vein
- Right anterior and posterior segments are divided by a vertical plane through the right hepatic vein
- Left hepatic vein and falciform ligament separate the left lateral and medial segments
- A plane of the main right and left portal vein marks the superior form inferior segments

## 2.5 Biliary Tract [2]

### 2.5.1 Gross Anatomy

- Figs. 2.5 and 2.11
- Biliary tree is divided into intrahepatic and extrahepatic bile ducts [1]
- Bile produced in the liver, concentrated in the gallbladder, and released to duodenum when fat is present in the duodenum
- Hepatocytes produce bile➔bile canaliculi➔interlobar biliary ducts➔ collecting bile ducts➔right and left hepatic ducts➔common hepatic duct joins the cystic duct (draining the gallbladder)➔common bile duct (located at hilum of liver)
- The common bile duct courses along the free edge of the lesser omentum initially, then runs along the posterior part of the duodenum and dorsal head of pancreas to join the main pancreatic duct, and forms the ampulla of Vater (controlled by the sphincter of Boyden)
- Ampulla opens into duodenum through major duodenal (hepatopancreatic) papilla (controlled by the sphincter of Oddi)

### 2.5.2 Blood Supply

#### 2.5.2.1 Arterial Supply

- Hepatic arteries supply intrahepatic ducts
- Cystic artery supplies proximal common bile duct (CBD), right hepatic artery supplies middle CBD, and gastroduodenal and pancreaticoduodenal supply distal CBD
- Cystic artery (from right hepatic artery) supplies gallbladder

#### 2.5.2.2 Venous Drainage

- Intrahepatic ducts drain to hepatic veins
- CBD drains into portal vein
- Gallbladder drains into liver sinusoids and bypass the portal vein

#### 2.5.2.3 Nerve Supply

- Right phrenic nerve provides sensory innervation
- Celiac ganglion and plexus provide parasympathetic and sympathetic stimulation along with cholecystokinin to allow contraction of biliary sphincters
- Preganglionic parasympathetic fibers – branches of the vagus nerve

#### 2.5.2.4 Lymphatic Drainage

- Same course as arterial supply
- Drain to celiac lymph nodes and lymph nodes at omental foramen
- Common drainage to the porta hepatis and pancreatic head from the gallbladder and also between the aorta and the inferior vena cava
- CBD also drains to the left side of the aorta under the left renal vein

#### 2.5.2.5 Gallbladder

- 7–10 cm in length and 3–4 cm in width and has a storage capacity of 30–50 ml
- Saclike organ located in a fossa on the inferior surface of the right lobe of the liver
- Indents the duodenum
- Parts of gallbladder: fundus (tip, projects below liver edge), body (touches the liver, duodenum, transverse colon), neck, and infundibulum (transition between body and neck)
- Cystic duct is 3–4 cm long and mucosa forms spiral folds of Heister to control bile flow
- Innervated by the hepatic branch of the vagus nerve from the anterior vagal trunk and sympathetic nervous system through the celiac plexus

## 2.6 Colon [2]

- The colon is divided into six parts and is mainly responsible for water absorption from material that was not absorbed or digested by the small intestine (chyle) that results in semi-solid stool/feces. Fecal matter is also stored until defecation

### 2.6.1 Cecum

- Encompasses the first portion of the colon, approximately 7 cm in length. Receives contents from the small bowel via the ileocecal valve
- Located in right iliac fossa and attached to the right lateral abdominal wall via cecal folds
- The appendix is a diverticulum arising from the tip of the cecum, varying in length from 6 to 15 cm
- Cecum receives blood supply from ileocolic artery (branch of superior mesenteric artery (SMA)) and vein

### 2.6.2 Ascending Colon

- Figs. 2.5, 2.6, 2.10, 2.11, and 2.12
- Second portion of the colon from the cecum to the transverse colon
- Located in the retroperitoneum, no mesocolon
- 12–15 cm in length
- Vascular supply originates from right colic branch of SMA and superior mesenteric vein (SMV)

### 2.6.3 Transverse Colon

- Fig. 2.5
- Begins at hepatic flexure and extends to splenic flexure
- Completely surrounded by peritoneum
- Vascular supply via middle colic branch of SMA and SMV
- Neurovasculature and lymphatics though transverse mesocolon

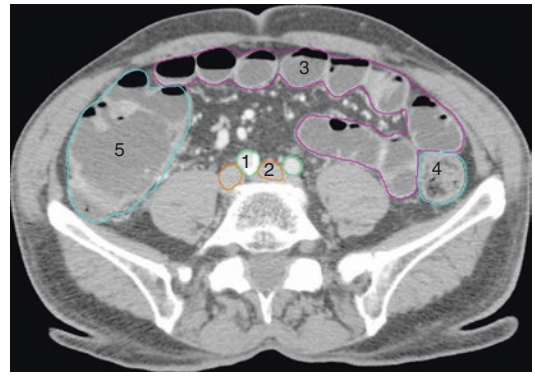


**Fig. 2.6** *1* common iliac artery, *2* common iliac vein, *3* small bowel, *4* descending colon, *5* ascending colon

### 2.6.4 Descending Colon

- Figs. 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.10, 2.11, and 2.12
- Starts at splenic flexure and continues down to left iliac fossa
- Located in retroperitoneum
- Vascular supply via inferior mesenteric artery (IMA) and vein (IMV)

### 2.6.5 Sigmoid Colon

- Fig. 2.7
- Not retroperitoneal, mobile, and covered with peritoneum in the lower part and partially covered in the upper part
- Varies in location and size, but generally located from left iliac fossa to S3 vertebra
- Vascular supply via the IMA and IMV

## 2.7 Rectum [13]

- Figs. 2.8, 2.9, 2.10, and 2.13
- Terminal portion of colon, usually 15–20 cm in length
- Variable location but generally begins around S3 and extends to anal canal
- Superior third of rectum covered with peritoneum on anterior surface and side
- Middle third of rectum covered with peritoneum on anterior surface

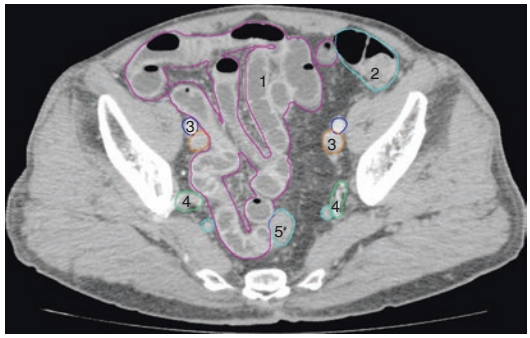


**Fig. 2.7** *1* small bowel, *2* colon, *3* external iliac vessels, *4* internal iliac vessels, *5* sigmoid colon

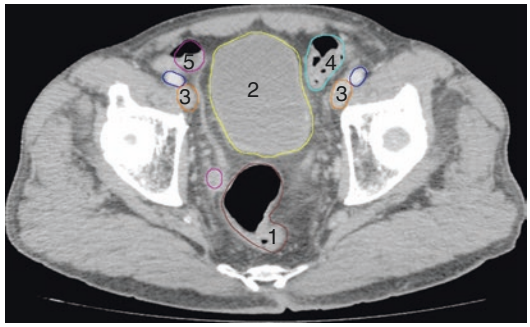


**Fig. 2.8** *1* rectum, *2* bladder, *3* external iliac vessels, *4* colon, *5* small bowel

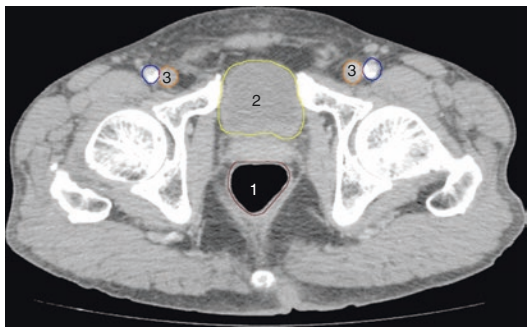


**Fig. 2.9** *1* rectum, *2* bladder, *3* femoral vessels

- Inferior third of rectum below peritoneal reflection
- Mesorectal envelope houses perirectal lymph nodes
- Denonvillier's fascia is the anterior surface of the mesorectum and separates the prostate from the rectum in men or forms the recto-vaginal septum in women

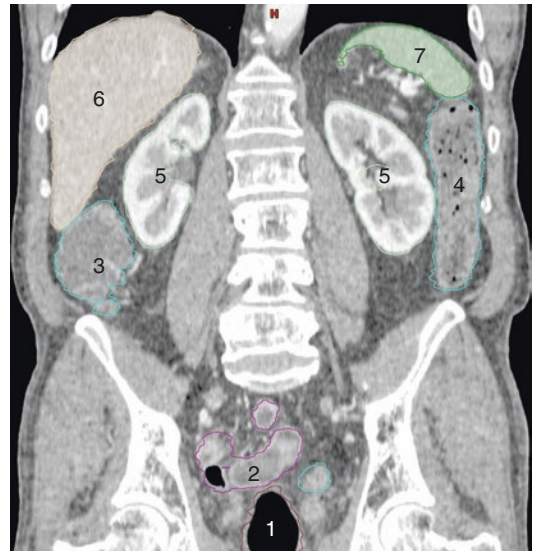


**Fig. 2.10** *1* rectum, *2* small bowel, *3* ascending colon, *4* descending colon, *5* kidney, *6* liver, *7* spleen

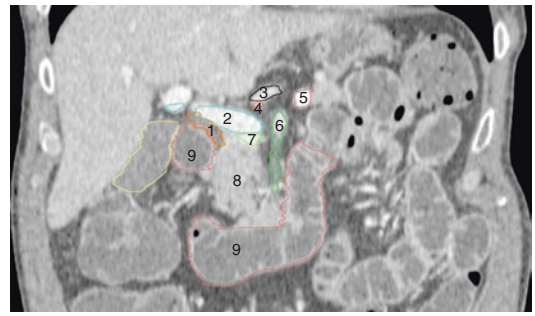


**Fig. 2.11** *1* common bile duct, *2* portal vein, *3* celiac axis, *4* splenic artery, *5* splenic vein, *6* superior mesenteric artery, *7* superior mesenteric vein, *8* pancreas, *9* duodenum

- Presacral fascia covers the rectum posteriorly and is the posterior aspect of the mesorectum

### 2.7.1 Arterial Supply

- Mainly supplied via superior rectal artery from IMA
- Middle rectum supplied via middle rectal artery, a branch of internal iliac artery
- Lower rectum (anorectal junction) supplied via inferior rectal artery (branch of internal iliac artery)

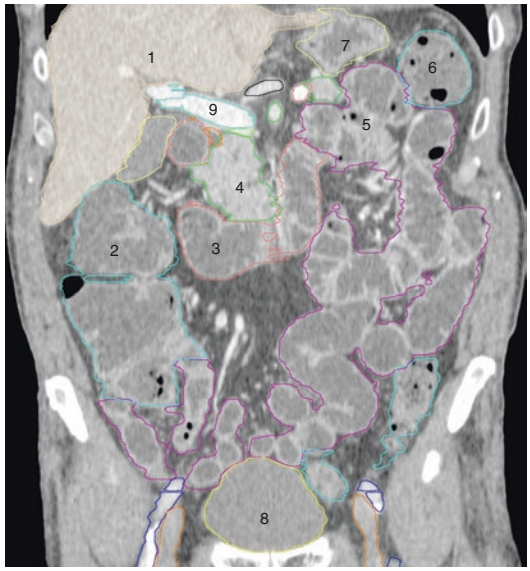


**Fig. 2.12** *1* liver, *2* ascending colon, *3* duodenum, *4* pancreas, *5* small bowel, *6* descending colon, *7* stomach, *8* bladder, *9* portal vein

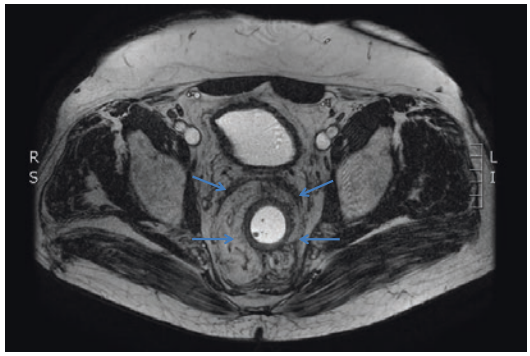


**Fig. 2.13** T2-weighted MRI. *Arrows* designate mesorectum

- Superior, middle, and inferior rectal arteries all anastomose

### 2.7.2 Venous Drainage

- Main drainage via rectal plexus which drains into superior rectal vein which drains into portal system
- Middle and inferior rectal veins also drain the rectum to internal iliac vein thus into inferior vena cava
- Similar to arterial supply, the venous system anastomoses with each other linking portal and caval system

### 2.7.3 Lymph Node Drainage

- Superior half of the rectum drains to perirectal nodes which drain to inferior mesenteric and lumbar nodes
- Inferior half of the rectum drains middle rectal vessels which drain into internal iliac system They also anastomose with anal canal lymphatic plexus

## 2.8 Anal Canal [13]

- The anal canal is the end of the gastrointestinal system
- Approximately 3 cm in length
- Starts at the anorectal junction and ends at the anus
- Pectinate or dentate line demarcates the upper two thirds of anal canal from lower third. Vascular supply differentiated based on this line

### 2.8.1 Arterial Supply

- Superior rectal artery above dentate line
- Inferior rectal artery below dentate line

### 2.8.2 Venous Drainage

- Internal plexus drains to superior rectal vein then to portal system above dentate line
- Below dentate line the plexus drains to inferior rectal veins and caval system

### 2.8.3 Lymphatic Drainage

- Above dentate line drain to internal iliac and common iliac nodes
- Below dentate line drain to superior inguinal lymph nodes

### 2.8.4 Pertinent Normal Structures of the Pelvis [13]

- Posterior to the rectum lies the sacrum
- Lateral to the rectum lie the ureters
- Anterior to the rectum:
  - Base of the urinary bladder
  - Males: prostate, seminal vesicles
  - Females: cervix

**Acknowledgment** The authors would like to thank Drs. Tae Kyoung Kim and Dr. Laura Dawson for the CT images that were used for the figures displayed in this chapter.

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# Esophageal Cancer: Background and Clinical Evidence

3

Matthew J. Boyer, Christopher G. Willett, Manisha Palta, and Brian G. Czito

## 3.1 Epidemiology

(a) In the United States, esophageal cancer constitutes 6 % of all GI malignancies.
(b) Squamous cell carcinoma and adenocarcinoma comprise approximately 95 % of all esophageal cancer types:
  (i) Worldwide, 90 % of patients with esophageal cancers have squamous cell carcinoma.
  (ii) In the United States, the rates of adenocarcinoma now exceed those of squamous cell carcinoma [1].
(c) The rate among white men in the United States is <5/100,000 but is as high as 100/100,000 of the total population in certain regions of Asia [1, 2].
(d) An estimated 17,000 cases will be diagnosed in the United States in 2016 with 15,600 deaths, with males four times as likely to be diagnosed as females [3].

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## 3.2 Risk Factors

(a) In many western countries, the incidence of esophageal adenocarcinoma has been increasing by 5–10 % per year over the last 20 years:
  (i) This may be related to the rising rates of gastroesophageal reflux disease (GERD) and obesity:
    (i) Long-standing GERD can lead to the development of metaplastic columnar esophageal epithelium known as Barrett's esophagus. This finding has been associated with a 10–15 % risk of developing esophageal adenocarcinoma [4]
    (ii) A meta-analysis examining the association of GERD with esophageal adenocarcinoma shows an overall risk factor of 7.4 for patients experiencing daily symptoms of GERD [5]
    (iii) Obesity also raises the risk of esophageal adenocarcinoma by a factor of 2.4–2.8 according to separate meta-analysis [6, 7]
    (iv) A similar risk of esophageal adenocarcinoma has been reported for patients with central adiposity which may lead to decreased lower

© Springer International Publishing AG 2017
T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_3

esophageal sphincter tone and higher rates of hiatal hernia development, as well as increasing rates of low-grade inflammation leading to metabolic and ultimately genetic derangements [8].

(b) In North America and Western Europe, alcohol and/or tobacco use is often associated with the development of esophageal squamous cell carcinoma [9]:
  (i) The combination of these two factors is synergistic with the risk of esophageal cancer increasing by a factor of 155 for patients with the highest rates of consumption of both [10].

(c) Diets high in fiber, fruits, and vegetables lead to a lower risk of esophageal cancer [11, 12], while diets high in nitrosamines portend an increased risk [13, 14].

(d) Patients with long-standing achalasia have an increased risk of squamous cell carcinoma by a factor of 10, resulting in an overall lifetime risk of 5 % [15, 16].

## 3.3 Molecular Biology

(a) Multiple genetic aberrations have been linked to the development of esophageal cancer:
  (i) Patients with heritable tylosis, an autosomal dominant syndrome producing papillomas of the esophagus, are at an increased risk of esophageal cancer [17]. This has been linked to the long arm of chromosome 17 [18] and mutations in the protease RHBDF2 [19].
  (ii) Other investigators have reported mutations in p53 as well as amplification of cyclin D1 and epidermal growth factor receptor (EGFR) underlying squamous cell carcinoma development and overexpression of p53, EGFR, and HER2 associated with development of adenocarcinoma [20].
  (iii) Whole exome sequencing has identified mutations in p53 and the cyclin-dependent kinase inhibitor CDKN2, as well as multiple other known tumor-associated genes, in both adenocarcinoma and squamous cell carcinoma [21, 22].

## 3.4 Staging

(a) In esophageal cancer, tumor (T) staging is based on depth of invasion (Fig. 3.1):
  (i) T1 tumors are further characterized as T1a tumors (limited to the lamina propria or muscularis mucosae) and T1b tumors (invasion of the submucosa).
  (ii) T2 and T3 tumors invade the muscularis propria and the adventitia, respectively.
  (iii) The distinction between T4a and T4b tumors is based on the tumor resectability: tumors extending to the pleura, pericardium, or diaphragm that may be resectable are staged as T4a, while those invading other local structures that are unresectable (aorta, vertebral body, trachea) are deemed T4b.

(b) Involvement of 1–2, 3–6, or ≥ 7 nodes is staged as N1, N2, and N3, respectively.

(c) M1 indicates the presence of distant metastatic disease.

(d) The current AJCC staging system also accounts for the tumor's histologic type (squamous cell carcinoma or adenocarcinoma), histologic grade, and location in early stage, node-negative disease (Fig. 3.1):
  (i) For example, a T1 N0 grade 1 squamous cell carcinoma is staged as IA, while grade 2–3 tumors are stage IB.
  (ii) T2-3 N0 squamous cell carcinomas of the lower esophagus are either stage IB or IIA based on grade of 1 or 2–3, respectively.
  (iii) T2-3 N0 squamous cell carcinomas of the upper and middle esophagus are stage IIA and IIB based on the same grade distinction.
  (iv) For early stage node-negative adenocarcinomas, grades 1 and 2 are grouped such that a grade 3 T1 N0 tumor is stage IB, while similar tumors with a lower grade are stage IA.

## AJCC 2010 TNM Staging

*Tumor*
T1a – tumor invades lamina propria or muscularis mucosae
T1b – tumor invades the submucosa
T2 – tumor invades muscularis propria
T3 – tumor invades adventitia
T4a – resectable tumor invading pleura, pericardium or diaphragm
T4b – unresectable tumor invading adjacent structures

*Regional Lymph Nodes*
N1 – 1-2 regional lymph node metastases
N2 – 3-6 regional lymph node metastases
N3 – 7 or more regional lymph node metastases

*Distant metastases*
M1 – distant metastases

*Grade*
G1 – well differentiated
G2 – moderately differentiated
G3 – poorly differentiated
G4 – undifferentiated, stage grouping as G3 squamous

## Stage Grouping

*Squamous Cell Carcinoma*

| | G1 | G2-3 |
|---|---|---|
| **T1** | IA | IB |
| **T2-3** | IB | IIA |
| **Lower** | | |
| **T2-3** | IIA | IIB |
| **Upper, Middle** | | |

(Location defined by proximal edge)

*Adenocarcinoma*

| | GX, G1-2 | G3 |
|---|---|---|
| **T1** | IA | IB |
| **T2** | IB | IIA |
| **T3** | IIB | IIB |

*Squamous Cell Carcinoma and Adenocarcinoma*

| | N0 | N1 | N2 | N3 |
|---|---|---|---|---|
| **T1** | | IIB | IIIA | IIIC |
| **T2** | | IIB | IIIA | IIIC |
| **T3** | | IIIA | IIIB | IIIC |
| **T4a** | IIIA | IIIC | IIIC | IIIC |
| **T4b** | IIIC | IIIC | IIIC | IIIC |

**Fig. 3.1** American Joint Committee on Cancer 2010 esophageal cancer staging system

(v) T2 N0 tumors are either staged as IB or IIA based on low- (grades 1–2) or high-grade (grade 3) histology.
(vi) T3 N0 adenocarcinomas are stage IIB regardless of grade.
(vii) The remaining stage groupings for more advanced tumors can be seen in Fig. 3.1.

## 3.5 Prognostic Factors

(a) According to SEER Data, the 5-year survival of patients with esophageal cancer is approximately 20 %, and patients with esophageal cancers with lymph node-negative disease, lymph node metastases, and systemic metastases have a 5-year survival rate of 40 %, 21 %, and 4 %, respectively.
(b) Resection status, age, and histologic subtype have been prognostic for patients undergoing surgery alone [23]:
  (i) Survival data from the Intergroup 0113 trial, which randomized esophageal cancer patients to surgery or neoadjuvant cisplatin and 5-FU followed by surgery, reported 5-year survival of patients undergoing an R1 or R2 resection that was significantly inferior to those patients with an R0 resection [24].
  (ii) The CROSS study, which randomized patients to neoadjuvant chemoradiation followed by surgery or surgery only, showed that there was a near doubling of overall survival for patients with squamous cell carcinoma versus adenocarcinoma [25].
(c) Tumor size has also been reported to be prognostic for both adenocarcinoma and squamous cell carcinoma:
  (i) In one series 5-year survival decreased from 77 to 23 % for patients with resected squamous cell carcinomas measuring less than 1 cm compared to those greater than 3 cm [26].
  (ii) Patients with adenocarcinomas greater than 2 cm have also been shown to have significantly worse 5-year survival compared to patients with tumors ≤2 cm [27].

## 3.6 Management

(a) Surgery alone
  (i) Surgery for esophageal cancer often involves a subtotal or total esophagectomy, via a transthoracic or transhiatal approach, with nodal dissection:
    (i) It has been suggested that exposure of the chest cavity with a transthoracic approach can facilitate a more complete resection and therefore improved disease-related outcomes.
    (ii) The question of optimal surgical approach was examined in a Dutch trial which randomized 220 patients to transthoracic or transhiatal resection [28]:
      1. Although the rate of locoregional recurrence was similar between the two surgical approaches (31 % in the transthoracic arm versus 32 % in the transhiatal arm), there appeared to be improved survival at a median follow-up of 4.7 years with the transthoracic approach (40 % vs. 30 %, $p = 0.012$).
      2. Higher rates of perioperative morbidity, pulmonary complications, and lengths of hospital stays were seen in patients undergoing resection by the transthoracic approach.
  (ii) Independent of surgical technique, local recurrence rates range from 32 to 45 % in randomized trials containing a surgery-alone arm (Table 3.1), providing a rationale for multimodality treatment of this malignancy.
(b) *Postoperative therapy*
  (i) One of the advantages of adjuvant therapy is that the pathological stage of the malignancy is known; thus, patients

**Table 3.1** Comparison of surgery alone arms in randomized studies of surgery with or without preoperative chemoradiation

| Trial | Year | Patients, total | Patients, surgical | Median survival (months) | 2-year survival | 3-year survival |
|---|---|---|---|---|---|---|
| Walsh et al. [60] | 1996 | 110 | 55 | 11 | 26 % | 6 % |
| Urba et al. [41] | 2001 | 100 | 50 | 18 | NA | 15 % |
| Bosset et al. [38] | 1997 | 282 | 139 | 19 | 40 % | 35 % |
| Kelsen et al. [36] | 1998 | 440 | 227 | 16 | 37 % | 23 % |
| MRC [61] | 2002 | 802 | 402 | 13 | 34 % | NA |
| Burmeister et al. [62] | 2005 | 256 | 128 | 19 | NA | 31 % |
| Van Hagen et al. [42] | 2010 | 366 | 188 | 24 | NA | 48 % |
| Mariette et al. [39] | 2014 | 195 | 98 | 44 | NA | NA |

with either early stage or metastatic disease, who may not benefit from adjuvant therapy, can be identified.

(ii) Pathologic staging and knowledge of surgical findings are helpful in radiation therapy planning.

(iii) Studies investigating the efficacy of adjuvant radiation therapy following surgery have not consistently demonstrated an improvement in either local control or survival:

(i) French investigators

1. Randomized 221 patients with squamous cell carcinoma of the mid- to distal esophagus to either resection, with or without postoperative radiation therapy alone.
2. Irradiated patients received 45–55 Gy within 3 months of surgery [29].
3. There was no improvement in survival for patients randomized to adjuvant radiation therapy even with a reduction in local recurrence rates from 35 to 10 % [29].

(ii) Hong Kong investigators

1. Evaluated the outcome of 130 patients undergoing surgery and adjuvant radiation therapy alone versus surgery only in patients undergoing curative or palliative resection [30].
2. Similar to the French trial, local recurrence was decreased (31 % vs. 15 %, $p = 0.06$) in the radiation group.
3. Median survival, however, was significantly worse in the adjuvant group (median OS 8.7 vs. 15.2 months, $p = 0.02$), possibly due to morbidity associated with the large dose-per-fraction of 3.5 Gy and high overall dose of 49 Gy in patients treated with curative intent.

(iii) Chinese investigators

1. Study of 549 patients that reported a near doubling of survival at 5 years for lymph node-positive patients receiving adjuvant radiation therapy versus those having surgery alone (17.6–34.1 %) [31].
2. As expected, patients with three or more involved lymph nodes had worse 5-year survival (14.4 %) compared to patients with 1–2 (30.6 %) or no lymph nodes involved (58.1 %).

(iv) Results of the Intergroup 0116 study [32] support an approach of combined chemotherapy and radiation therapy following resection of gastroesophageal junction (GEJ) adenocarcinomas:

(i) This study included patients with gastric or GEJ adenocarcinomas undergoing an R0 resection.
(ii) Five hundred fifty-six patients were randomized to no adjuvant therapy versus adjuvant therapy with 5-FU and leucovorin before, during, and after radiation therapy.
(iii) With a median follow-up greater than 10 years, the HR for survival was 1.32 favoring postoperative chemoradiation [33].
(iv) This benefit was observed across all stages and tumor locations.
(v) Therefore, adjuvant treatment for GEJ adenocarcinomas is advised for resected T2–T4 N0 or any node-positive patients not receiving neoadjuvant therapy.

(c) Preoperative therapy
(i) Preoperative treatment with either radiation or chemotherapy has a number of potential advantages:
(i) For radiation specifically, preoperative treatment often employs smaller radiation fields with less treatment-related morbidity compared to postoperative treatment.
(ii) Resection of the treated esophagus may also limit long-term complications as one of the primary tissues at risk, the esophagus itself, is removed.
(iii) Neoadjuvant chemotherapy may allow for elimination of micrometastatic disease and determination of tumor chemosensitivity.
(iv) Overall, an increased likelihood of resection due to downstaging and avoidance of surgery in patients with progression through treatment underscore the rationale for preoperative therapy.
(v) Preoperative therapy is associted with higher rates of compliance and ability to deliver intended therapy as compared to the adjuvant setting.

(ii) Preoperative chemotherapy
(i) Similar to the conflicting results of adjuvant radiation therapy (described previously), the outcomes of randomized trials of preoperative chemotherapy alone have not consistently shown a survival benefit:
1. Medical Research Council (MRC) OEO2 trial
(a) Largest trial including 802 patients with adenocarcinoma or squamous cell carcinoma of the esophagus randomized to cisplatin and 5-FU for two cycles prior to surgery versus surgery alone [34].
(b) Long-term follow-up at 6 years showed significantly improved 5-year overall survival in the preoperative chemotherapy arm (23 %) versus the surgery-alone (17 %) arm [35].
2. Intergroup 0113 trial
(a) Four hundred forty patients received either cisplatin with 5-FU before and following resection or resection alone.
(b) No difference in 3-year overall survival or local or distant failure was seen [24, 36].
(c) Potential caveats to this study include that only approximately 60 % of patients in either arm underwent an R0 resection, and in patients undergoing R1 resection, the only long-term survivors received adjuvant radiation therapy [24].
3. MAGIC trial
(a) Perioperative combination of epirubicin, cisplatin, and 5-FU (ECF) was evaluated [37].

(b) Although designed for patients with gastric cancer, the study eligibility was later expanded to include patients with distal esophageal and GEJ cancers, and ultimately one-fourth of patients accrued on this study had esophageal or GEJ tumors.
(c) There were no pathologic complete responders to the neoadjuvant chemotherapy component.
(d) The 5-year survival was significantly improved for patients randomized to perioperative chemotherapy (36 %) compared to patients undergoing surgery only (23 %, $p = 0.009$). This survival benefit was seen in all primary sites – esophageal, GEJ, or stomach.

4. Results of the phase III studies of preoperative chemotherapy are summarized in Table 3.2.

(iii) Preoperative chemoradiation:
(i) Preoperative radiation in addition to chemotherapy has been investigated given the limited complete pathological response rate of the primary tumor and discrepancy in survival outcomes with chemotherapy alone:

1. EORTC (European Organisation for Research and Treatment of Cancer) trial:
(a) Randomized 282 patients with squamous cell carcinoma.
(b) Demonstrated a median survival of 18.6 months with or without neoadjuvant chemoradiation, albeit with improvement in disease-free survival and cancer-related deaths with the use of neoadjuvant therapy [38].
(c) In this study, cisplatin alone was administered concurrently with 37 Gy in a split course at 3.7 Gy per fraction.
(d) Postoperative mortality was worse in the patients randomized to preoperative chemoradiation (12 %) versus surgery alone (4 %). This has been hypothesized to be due to the increased fraction size and may

**Table 3.2** Results of preoperative chemotherapy vs. surgery-alone phase III trials

| Study | Median F/U (years) | Path | Arms | Number of patients | pCR | 2-year survival | Survival difference |
|---|---|---|---|---|---|---|---|
| OEO2 [34, 35]<br>MRC | 6.0 | SCC+ adeno | 5-FU-CDDP/ surg<br>surg | 400<br>402 | 4 %<br>– | 43 %<br>34 % | $p = 0.004$ |
| Kelsen et al. [36]<br>Intergroup | 4.6 | SCC+ adeno | 5-FU-CDDP/ surg<br>surg | 213<br>227 | 2.5 %<br>– | 23 % (3 years)<br>26 % (3 years) | NS |
| Cunningham et al. [37]<br>MRC | 4.0 | Adeno | EPI-CDDP-5-FU/surg<br>surg | 250<br>253 | 0 %<br>– | 36 %<br>23 % | $p = 0.009$ |

*SCC* squamous cell carcinoma, *Adeno* adenocarcinoma, *EPI* epirubicin, *5-FU* 5-fluorouracil, *CDDP* cisplatin, *pCR* pathologic complete response, *NS* not significant

potentially account for the lack of overall survival benefit seen [38].

2. FFCD (La Fédération Francophone de Cancérologie Digestive) 9901 trial:
   (a) Randomized 195 patients with clinically staged I–II squamous cell or adenocarcinoma.
   (b) Stopped early due to crossing a prespecified boundary for futility in terms of improved survival [39].
   (c) Although the pathologic complete response rate (33.3 %) was high, there was no difference in R0 resection rate of 93.8 % in the chemoradiation group versus 92.1 % in the surgery group.
   (d) Postoperative mortality was significantly worse with neoadjuvant treatment (11.1 % vs. 3.4 %), with a 3-year overall survival of 47.5 % in the neoadjuvant group compared to 53 % with surgery alone, potentially negating any treatment-related survival benefit.
3. CALGB (Cancer and Leukemia Group B) 9781 trial:
   (a) Randomized 56 patients to 50.4 Gy with concurrent cisplatin/5-FU and surgery or surgery only.
   (b) The 5-year overall survival was 16 % in the surgery-alone arm compared to 39 % with neoadjuvant chemoradiation [40].
4. University of Michigan:
   (a) One hundred patients with either adenocarcinoma or squamous cell carcinoma.
   (b) Three-year survival was improved from 16 to 30 % with the addition of preoperative radiation with 5-FU, cisplatin, and vinblastine to surgery alone, although this did not reach statistical significance [41].
5. CROSS (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study):
   (a) Largest study of combined modality therapy, randomizing 368 patients to 41.4 Gy with weekly paclitaxel (50 mg/m$^2$) and carboplatin (AUC = 2) followed by surgery versus resection alone [42].
   (b) Pathologic complete response was seen in 47/161 patients (29 %) of the chemoradiation group.
   (c) 148/161 of neoadjuvantly treated patients (92 %) underwent R0 resection versus 69 % in the surgery-alone group. Similarly, locoregional failure rates were significantly lower in the chemoradiation group versus the surgery-alone group (22 vs. 38 %, $p < 0.0001$) [25].
   (d) With a median follow-up of 84.1 months in surviving patients, an overall survival benefit to neoadjuvant chemoradiation (median 48.6 vs. 24 months) was reported [25]. This benefit was greater in patients with squamous cell carcinoma (median survival 81.6 months vs. 21.1 months), as compared to adenocarcinoma (median survival 43.2 vs. 27.1 months).

**Table 3.3** Results of preoperative combined chemoradiation vs. surgery-alone phase III trials

| Study | Median F/U (years) | Path | Arms | Number of patients | pCR | 3-year survival | Survival difference |
|---|---|---|---|---|---|---|---|
| Urba et al. [41] Michigan | 8.2 | SCC+ adeno | 5-FU-CDDP-Vinb/45 Gy/surg<br>surg | 50<br>50 | 28 %<br>– | 30 %<br>16 % | $p = 0.15$ |
| Bosset et al. [38] EORTC | 4.6 | SCC | CDDP/37 Gy/surg<br>surg | 143<br>138 | 20 %<br>– | 33 %<br>36 % | NS |
| Walsh et al. [60] Ireland | 1.5 | Adeno | 5-FU-CDDP/40 Gy/surg<br>surg | 58<br>55 | 22 %<br>– | 32 %<br>6 % | $p = 0.01$ |
| Burmeister et al. [62] Australia | 5.4 | SCC+ adeno | 5-FU-CDDP/35 Gy/surg<br>surg | 128<br>128 | 16 %<br>– | 35 %<br>31 % | NS |
| Tepper et al. [40] CALGB | 6.0 | SCC+ adeno | 5-FU-CDDP/50 Gy/surg<br>surg | 30<br>26 | 40 %<br>– | 39 % (5 years)<br>16 % (5 years) | $p = 0.008$ |
| Van Hagen et al. [42] Netherlands | 2.7 | SCC+ adeno | Pac-carbo/41.4 Gy/surg<br>surg | 180<br>188 | 29 %<br>– | 58 % (5 years)<br>44 % (5 years) | $p = 0.001$ |
| Mariette et al. [63] FFCD | 5.7 | SCC+ adeno | 5-FU-CDDP/45 Gy/surg<br>surg | 97<br>98 | 29 %<br>– | 32 mo med OS<br>44 mo med OS | NS |

*SCC* squamous cell carcinoma, *Adeno* adenocarcinoma, *5-FU* 5-fluorouracil, *CDDP* cisplatin, *Vinb* vinblastine, *Pac* paclitaxel, *Carbo* carboplatin, *pCR* pathologic complete response, *NS* not significant

(e) Preoperative chemoradiation did not increase the toxicity of surgery as in hospital mortality was 4 % in each group, and rates of anastomotic leak (30 % vs 22 %) and mediastinitis (6 % vs. 3 %) were worse in the surgery-alone group [42].

6. Table 3.3 summarizes the results of the prospective phase III randomized trials evaluating the role of preoperative chemoradiation.
7. Meta-analyses have been performed to examine the discrepancies in these study results:

(a) In two of these analyses, the 2- and 5-year absolute overall survival rates were higher by 13 % and 6.5 % with preoperative chemoradiation, respectively [43, 44].

(b) A third meta-analysis of over 4000 patients demonstrated an HR of 0.78 for all-cause mortality with preoperative chemoradiation as compared to surgery alone with similar improvement in patients with either adenocarcinoma (HR 0.75) or squamous cell carcinoma (HR 0.80) [45].

(c) In contrast, the survival benefit at 2 years was only 5.1 % with neoadjuvant chemotherapy alone and significant only for patients with esophageal adenocarcinoma and not squamous cell carcinoma [45].

(ii) The addition of cetuximab, a monoclonal antibody directed at EGFR, to preoperative chemoradiation has not been shown to improve outcomes for esophageal cancer patients:

1. SCOPE1 (chemoradiotherapy with or without cetuximab in patients with esophageal cancer) trial
   (a) Multi-institutional trial planned as phase II/III study of the addition of cetuximab to cisplatin and capecitabine concurrently with 50 Gy of radiation [46].
   (b) After recruiting 258 patients, the trial was terminated, and continuation onto the phase III component was not initiated.
   (c) Freedom from treatment failure was worse in the cohort receiving cetuximab (66.4 %) compared to the group that did not (76.9 %) at 24 weeks, although this was not significant.
   (d) Median overall survival was also decreased with the addition of cetuximab (22.1 vs. 25.4 months, $p = 0.035$) correlating with greater rates of grade 3 or 4 toxicity (79 % vs. 63 %, $p = 0.004$).
2. RTOG 0436 trial
   (a) Evaluated the addition of cetuximab for nonoperative esophageal cancer patients.
   (b) Preliminary results of this study showed no difference in 2-year overall survival with (44 %) or without (42 %) EGFR-targeted therapy [47].

(iii) Neoadjuvant chemoradiation compared to neoadjuvant chemotherapy:

1. POET (Preoperative Chemo therapy or Radiochemothe rapy in Esophagogastric Adenocarcinoma Trial):
   (a) Randomized 126 patients with adenocarcinoma of the lower esophagus or gastric cardia [48].
   (b) Although underpowered due to poor accrual, patients in the chemoradiation group showed a pathologic complete response rate of 15.6 % as compared to 2 % in the chemotherapy-alone group despite a low radiation dose of 30 Gy.
   (c) Postoperative mortality was higher in the combined modality group versus chemotherapy-only group (10.2 % vs. 3.8 %, $p = 0.26$), yet there was a trend toward improved 3-year survival with radiation (47.4 % vs. 27.7 %, $p = 0.07$).
2. Australian trial:
   (a) Randomized phase II trial of 75 patients.
   (b) Improvement in histopathologic response rate (8 % vs. 31 %, $p = 0.01$) with 35 Gy in 15 fractions and 5-FU and cisplatin compared to that chemotherapeutic regimen alone [49].
   (c) Although there was an improvement in the noncurative resection rates with

radiation (11 % vs. 0 %, $p = 0.04$), there was no difference in median overall survival (29 % vs. 32 %, $p = 0.83$).

3. Scandinavian trial:
   (a) Randomized phase II study [50].
   (b) While the addition of 40 Gy to chemotherapy with a platinum agent and 5-FU increased the rate of pathologic complete response (9 % vs. 28 %, $p = 0.002$) and R0 resection rate (74 % vs. 87 %, $p = 0.04$), there was no difference in 3-year overall survival between the two arms (49 % in the chemotherapy group vs. 47 % in the chemoradiation group).
   (c) This study was not powered to detect an increase in survival.
4. Given the outcomes of preoperative chemoradiation compared to either preoperative chemotherapy alone or surgery alone for esophageal cancer patients with clinical stage ≥ T2 or node-positive disease, current recommendations call for preoperative chemoradiation therapy in these patients.

(iv) Surgery following preoperative chemoradiation:
   (i) The necessity of immediate surgery following chemoradiation has also been evaluated given the success with chemoradiation and morbidity and mortality associated with esophagogastrectomy.
   (ii) French 9102 study:
      1. Randomized 445 patients, 90 % with squamous cell carcinoma, receiving neoadjuvant chemoradiation (either 46 Gy or a split course of 30 Gy with 5-FU and cisplatin) [51]. Patients achieving at least partial response were then randomized to receive either further chemoradiation or surgery.
      2. Ninety-day mortality rate of 9 % was observed in the surgery group compared to 1 % in the chemoradiation group.
      3. Median overall survival was similar for both randomized arms at 18 versus 19 months.
      4. While clinician reported quality of life was worse in the surgery group, the rates of esophageal stenting and dilatation were worse in the nonsurgical group.
   (iii) German Esophageal Cancer Study Group trial:
      1. One hundred seventy-two patients with locally advanced squamous cell carcinoma received 40 Gy with concurrent 5-FU, leucovorin, cisplatin, and etoposide and were then randomized to receive either further chemoradiation to a dose of at least 65 Gy or proceeding with surgery [52].
      2. Despite only two-thirds of patients in the surgery group actually undergoing surgery, there was an improvement in local progression-free survival at 2 years (64 % in the surgery group vs. 41 % in the chemoradiation group, $p = 0.003$).
      3. This did not translate into a significant improvement in overall survival (31 % vs. 24 %, log rank test for equivalence p = 0.007).
      4. Toxicity in the operative arm was high, with a 70 % postoperative complication rate and 13 % in hospital mortality rate.

(iv) Based on the results of the CROSS trial and others, in operable candidates, a trimodality approach of neoadjuvant chemoradiation and surgery remains standard of care.

(v) Radiation alone:
  (i) Single modality radiation treatment alone is used when long-term survival is predicted to be poor, particularly with more advanced lesions, due to poor overall survival rates:
    1. Five-year overall survival by stage for patients undergoing radiation alone has been reported as 20 %, 10 %, 3 %, and 0 % for stage I, II, III, and IV disease, respectively [53].
    2. In two large reviews, 5-year survival was approximately 6 % when all patients were considered [54, 55].
  (ii) RTOG 85–01:
    1. Patients randomized to radiation only (64 Gy) or radiation (50 Gy) with concurrent 5-FU and cisplatin.
    2. Five-year survival of 26 % in the chemoradiation arm and 0 % in the radiation-alone arm despite an increased radiation dose in the radiation-alone arm [56].
    3. This survival benefit was associated with a decrease in both local (69 % vs. 45 %) and distant (44 % vs. 25 %) recurrences, at the expense of an increase in high-grade toxicity from 3 to 20 % [56].
  (iii) Intergroup 0123 trial:
    1. Follow-up study to RTOG 85–01. Two hundred thirty-six patients randomized to 50.4 Gy with concurrent 5-FU and cisplatin or 64.8 Gy with the same concurrent chemotherapy
    2. Increased radiation dose to the primary tumor from 50.4 to 64.8 Gy, concurrent with chemotherapy, did not improve 2-year survival or locoregional control rates [57].
    3. There was a higher treatment-related mortality rate in the 64.8 Gy arm; however, this did not appear to be related to the higher radiation dose.
    4. Two-year survival rates in this study (31 and 40 %) are comparable to survival rates of patients treated with surgery-alone trials presented in Table 3.1, suggesting possible equivalency of definitive chemoradiation with surgery.
  (iv) For medically fit patients, combined modality therapy is preferred to radiation alone.

## 3.7 Ongoing Studies

(a) Many current trials in esophageal cancer utilize a chemoradiation template with platinum and taxane agents as reported in the CROSS trial.

(b) RTOG 1010:
  (i) Evaluating the addition of trastuzumab (Herceptin), a monoclonal antibody to the Her2 receptor that is overexpressed on approximately 20 % of esophageal adenocarcinomas [58, 59].
  (ii) Patients whose tumors are positive for Her2 overexpression receive 50.4 Gy with carboplatin/paclitaxel, followed by surgery, with a randomization of ± trastuzumab during neoadjuvant radiation therapy/adjuvantly for 13 cycles following surgery.

(c) MAGIC-CROSS:
  (i) ICORG (All-Ireland Cooperative Oncology Research Group) study

(ii) Comparing the CROSS-combined modality regimen with the perioperative chemotherapy-alone regimen in the MAGIC trial

(d) TOPGEAR (Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma):
   (i) Sponsored by the Australasian Gastro-Intestinal Trials Group but enrolling patients in Europe and Canada as well
   (ii) Investigating the addition of preoperative chemoradiation with a fluoropyrimidine to the MAGIC chemotherapy regimen of epirubicin, cisplatin, and 5-FU for gastric and GEJ tumors

(e) ESOPEC (Perioperative Chemotherapy Compared To Neoadjuvant Chemoradiation in Patients With Adenocarcinoma of the Esophagus) trial:
   (i) German trial from the University Medical Center Freiburg
   (ii) Comparing an alternative perioperative chemotherapy regimen FLOT (5-FU, leucovorin, oxaliplatin, and docetaxel) to the CROSS chemoradiation regimen

(f) PET Scan Imaging in Assessing Response in Patients With Esophageal Cancer Receiving Combination Chemotherapy trial:
   (i) Randomized phase II US Alliance group trial
   (ii) Comparing FOLFOX chemotherapy to carboplatin and paclitaxel, followed by further chemotherapy/concurrent chemoradiation regimen dictated by PET response to chemotherapy

(g) Esostrate (Comparison of Systematic Surgery Versus Surveillance and Rescue Surgery in Operable Esophageal Cancer With a Complete Clinical Response to Radiochemotherapy) trial:
   (i) French study from the Centre Hospitalier Universitaire Dijon
   (ii) Evaluating systematic versus salvage surgery in operable esophageal cancer patients achieving clinical complete response to neoadjuvant chemoradiotherapy

**Conclusions**

(a) The rates of esophageal cancer continue to rise in the United States along with an increasing preponderance of adenocarcinomas, likely secondary to rising rates of GERD and obesity.

(b) Trimodality treatment with preoperative chemoradiation is a current standard of care for ≥ T2 lesions and/or those node-positive disease given an improvement in overall survival with this regimen.

(c) Studies are underway in efforts to continue to optimize and refine neoadjuvant approaches in these patients, along with optimizing definitive regimens for non-operative patients.

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# Esophageal Cancer: Radiation Therapy Planning

4

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## 4.1 Anatomy

(a) For purposes of staging and target delineation, the esophagus has been divided into four sections by the American Joint Committee on Cancer (AJCC, Fig. 4.1) [1].
  (i) The most superior portion, the cervical esophagus, includes the region from the upper esophageal sphincter (formed by the cricopharyngeus muscle) to the thoracic inlet and generally extends 15–20 cm from the incisors on esophagogastroduodenoscopy (EGD).
  (ii) The upper thoracic esophagus extends from the thoracic inlet to the lower border of the azygos vein or approximately 20–25 cm from the incisors.
  (iii) The middle thoracic esophagus spans from the lower border of the azygos vein to the inferior pulmonary veins or approximately 25–30 cm from the incisors.
  (iv) The lower thoracic esophagus spans from the inferior pulmonary veins to the stomach, or approximately 30–40 cm from the incisors.
  (v) The gastroesophageal junction (GEJ) is sometimes defined clinically where the first gastric fold is observed but can be more strictly defined as the intersection of the squamous mucosa of the esophagus and glandular epithelium of the stomach (the endoscopically visible Z line).
  (vi) Based on the current AJCC staging system, tumors up to 5 cm distal to the GEJ but involving the GEJ or lower esophagus are considered esophageal carcinomas.
(b) Similar to other gastrointestinal sites, the esophageal wall has well-defined layers.
  (i) The epithelium is separated from the lamina propria by a basement membrane.
  (ii) Sequential layers deep to the lamina propria include the muscularis mucosae, submucosa, and muscularis propria.
(c) With respect to esophageal cancer treatment planning, longitudinal lymphatic channels can extend into the submucosa and lamina propria, potentially allowing for lymphatic spread by even relatively superficial tumors along the entire length of the esophagus.

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© Springer International Publishing AG 2017
T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_4

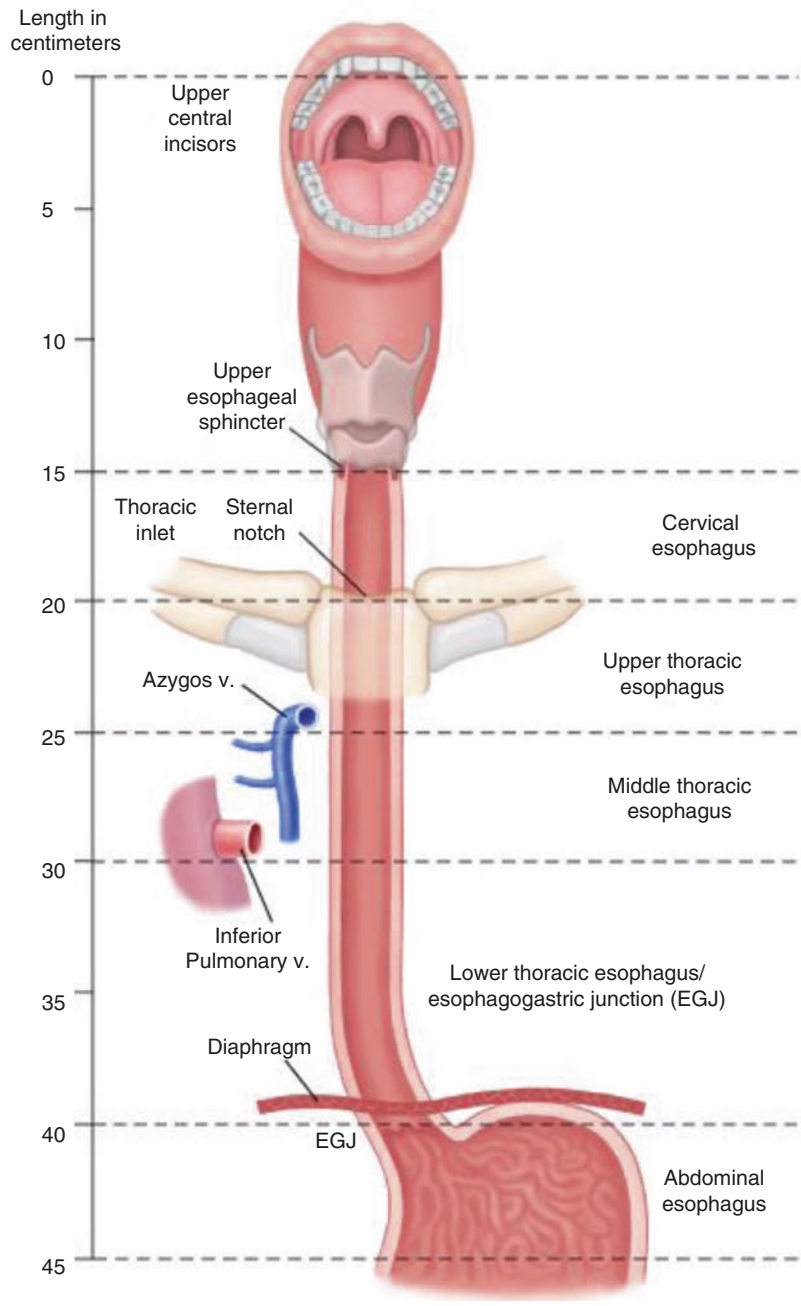


**Fig. 4.1** The esophagus is divided into four regions by the AJCC. The cervical esophagus extends from the upper esophageal sphincter to the thoracic inlet. The upper thoracic esophagus extends from the thoracic inlet to the inferior border of the azygous vein. The middle thoracic esophagus extends from the inferior border of the upper thoracic region to the inferior border of the inferior pulmonary vein. The lower thoracic esophagus extends from the mid-thoracic esophagus to the GEJ. The distance of each from the incisors is indicated on the *left* (Reproduced with permission from: Saltzman and Gibson [44] Copyright © 2016 UpToDate, Inc. For more information visit www.uptodate.com.)

## 4.2 Patterns of Spread

(a) Given the extensive lymphatic channels of the esophagus, nodal spread of disease, both proximally and distally, is common.
   (i) For patients with squamous cell carcinoma of the esophagus, lymph node metastases can be found in 70 % at autopsy [2].
   (ii) In a review of 1,077 patients treated with esophagectomy for squamous cell carcinoma, 6 % had "skip" lymph node metastases [3].
      1. Specifically, in patients with upper thoracic tumors, 55.6 % of patients had involved lymph nodes that were above the level of the carina, and 22.3 % had lymph nodes inferior to

the carina, including 5.6 % with subdiaphragmatic involvement.
2. Similarly 4.5 % of patients with lower thoracic lesions had either upper thoracic and/or cervical lymph node involvement.
3. Finally, 63 % of all involved lymph nodes had microscopic deposits, underscoring the importance of appreciating nodal levels at risk, even in absence of positive imaging findings.

(b) Similar rates of lymph node involvement have been observed for lower thoracic and GEJ adenocarcinomas, where approximately 70 % of patients have nodal metastases at presentation.
   (i) Based on the Siewert classification of GEJ adenocarcinomas [4], type I tumors (defined as arising from 5 to 1 cm proximal to the Z line) spread to both superior and inferior lymphatics, with greater than 50 % involvement of the paraesophageal and left gastric lymph nodes [5].
   (ii) Type II tumors (arising within 1 cm proximal and 2 cm distal to the Z line) have similar rates of left gastric lymph node involvement but less than 10 % involvement of the more superior paraesophageal nodes.
   (iii) Type III tumors (arising 2–5 cm inferior to the Z line) typically spread toward the celiac axis.

(c) Lymph node involvement increases with depth of invasion of the primary tumor with 45 %, 85 %, and 100 % of adenocarcinoma patients with T2, T3, and T4 lesions, respectively, harboring nodal involvement in one series [5].

## 4.3 Imaging

(a) Multiple imaging modalities are used to determine local and distant disease extent and guide the treatment planning process.
   (i) EGD facilitates defining the location of the primary tumor within the esophagus in relation to the distance from the incisors and with respect to the GEJ.
      1. The carina and GEJ are typically located at 25 and 40 cm, respectively, from the incisors.
      2. EGD also facilitates biopsy of sites concerning for satellite lesions or submucosal spread.
   (ii) Depth of tumor invasion as well as paraesophageal and perigastric lymph node involvement is assessed by endoscopic ultrasound (EUS).
      1. As compared to surgical pathology, EUS provides 85–90 % and 75–80 % accuracy rate for depth of invasion and nodal involvement, respectively [6–9]. This is generally better than CT alone which has an approximately 70 % and 50-70 % accuracy for tumor invasion and nodal involvement, respectively.
   (iii) The addition of PET imaging can improve detection of stage III or stage IV disease by approximately 20 % in both scenarios, but is not as accurate as EUS for determining locoregional nodal involvement [10, 11].

## 4.4 Simulation

(a) Patients should undergo CT simulation for treatment planning.
   (i) Patients are typically supine with a customized immobilization device such as a wing board for 3D planning or an alpha cradle, body fix, or Vaclock on indexed wing board for IMRT planning.
   (ii) For more proximal lesions involving the upper thoracic or cervical esophagus, immobilization with a mask may be indicated.
   (iii) Esophageal contrast delivery can aid in delineation of the primary tumor, although it can artificially dilate the proximal esophagus, while small bowel contrast can help identify any bowel in field.
   (iv) IV contrast can aid in distinguishing both involved lymph nodes and arterial structures, including the celiac axis and

its branches, to guide elective nodal coverage.

(v) CT scans are obtained with approximately 2–3 mm slices from the upper neck through the mid-abdomen to provide sufficient visualization of the target tissues and surrounding structures.

(b) Target motion due to respiration, the cardiac cycle, and peristalsis can be evaluated with a 4D CT scan and treatment with respiratory management implemented as necessary. Abdominal compression or breath holding techniques can limit respiratory motion in select cases.

(c) For tumors that involve the lower esophagus and stomach, fasting prior to simulation and treatment each day may allow for greater reproducibility of treatment. In contrast, simulation without fasting and delivery of oral contrast may allow for planning in a "worst-case" scenario when the patient is later instructed to fast prior to treatment delivery.

## 4.5 Target Delineation

(a) Gross tumor volume (GTV) delineation should take into account findings from all pretreatment diagnostic tests including EGD, EUS, barium swallow, CT, and PET imaging.

(i) The primary tumor can often be seen as thickening of the esophageal wall on diagnostic and planning CTs. This should be correlated with findings from EGD which provide useful information as to the tumor location in relation to other anatomical landmarks and length in centimeters.

(ii) The results of EUS can help determine extension of the primary tumor outside of the esophageal wall and into any nearby tissues as well as the extent of nodal involvement.

(iii) Any overt lymphadenopathy should also be included in the GTV.

1. PET imaging can be helpful in identifying nodal disease although the sensitivity of this modality for detecting nodal metastases has been reported to be as low as 67 % [12].
2. The results from PET, however, have been shown to correlate with those from endoscopic ultrasound [8], and the addition of PET reduces variability in GTV contouring.

(b) The clinical target volume (CTV) includes subclinical regions at risk for spread of disease.

(i) As potentially involved sites of subclinical disease are not readily apparent on exam or by imaging, CTV design for esophageal cancer relies on known patterns of spread based on pathologic findings in studies following resection or autopsy specimens.

(ii) In terms of longitudinal spread within the esophagus itself, a pathologic analysis of 66 resections from patients with squamous cell carcinoma of the esophagus demonstrated that a 3 cm margin both proximally and distally on the primary tumor would cover microscopic disease in 94 % of patients [13].

(iii) Similarly, in cancers involving the GEJ, a 3 cm proximal margin and a 5 cm distal margin have been shown to cover subclinical disease in 100 % and 94 % of patients, respectively [13].

(iv) In the CROSS trial comparing preoperative chemoradiation to surgery alone, a 4 cm margin superior and inferior from the GTV to planning target volume (PTV) was employed except with tumor extension into the stomach when a 3 cm distal margin was used [14]. With these margins, locoregional recurrence occurred in 5 % within the target volume, in 2 % in the margins, and in 6 % outside the radiation target volume. Only 1 % had an isolated infield recurrence after CRT plus surgery [15].

(v) The current RTOG 1010 trial investigating the addition of trastuzumab to neoadjuvant chemoradiation recommends a

4 cm margin superiorly and inferiorly and 1–1.5 cm radially from the GTV to CTV expansion, with an additional 0.5–1 cm expansion from the CTV to PTV [16].

(c) Elective nodal coverage incorporated into the CTV varies based on the primary tumor's location in the esophagus.
   (i) A recent consensus contouring guideline panel recommended that the CTV should extend 1 cm superior to the most proximal-involved periesophageal node [17]
   (ii) Lesions of the cervical and upper thoracic esophagus generally require coverage of the supraclavicular and superior mediastinal lymph nodes. Some authors have recommended coverage of the supraclavicular and superior mediastinal lymph nodes with any primary disease at or above the level of the carina [17].
   (iii) Lesions of the middle esophagus should include paraesophageal lymph nodes within the mediastinum but also may consider subdiaphragmatic nodal basins as the involvement of these has been shown to approach 20 % [3]. Coverage of both regions may, however, produce a significantly large treatment volume, and consideration should be given to the potential associated toxicity.
   (iv) For distal esophageal adenocarcinomas, the periesophageal lymph nodes and celiac nodal basins should be included for most, if not all, patients.
      1. A recent consensus contouring guideline panel recommended that CTV should extend to the celiac axis and approximate the lateral border of T12 on the right and extend 0.5–1 cm lateral to the aorta on the left [17].
   (v) In a pathologic analysis by Meier and colleagues, lymphovascular invasion, greater depth of invasion by the primary tumor, and higher grade were all predictive of lymph node involvement, suggesting that the CTV should be extended to include additional at-risk regions in these circumstances [18].
      1. Specifically, for tumors involving the GEJ with lymphovascular invasion, coverage of the left and right gastroepiploic, greater curvature, celiac trunk, and splenic hilum lymph nodes is indicated.
      2. T3 or T4 tumors require treatment of the left and right gastroepiploic, greater curvature, celiac trunk, splenic hilum, splenic artery, and common hepatic artery nodes.
      3. High-grade tumors also correlated with an increased risk of involvement of the left gastroepiploic, greater curvature, and celiac trunk nodes.
      4. In addition, tumors extending greater than 1.5 cm proximal to the Z line have an increased risk of involvement of periesophageal nodes in the middle esophagus, and consideration should be given to covering these areas electively.
   (vi) Elective nodal irradiation for esophageal squamous cell carcinoma patients is an area of controversy.
      1. In a prospective study of 53 patients with T1-4 N0-1 disease treated with 3D-CRT alone to 68.4 Gy in 41 fractions, only 3, or 8 %, had an isolated, out-of-field nodal recurrence [19].
      2. A more recent study of patients with T4 squamous cell carcinoma demonstrated a 1.8 % rate of elective nodal failure out of 56 patients treated with concurrent chemotherapy and radiation [20]. Elective nodal coverage in patients with squamous cell carcinoma remains a topic of study.
   (vii) As before, enlarging target volumes must be balanced with increasing risk of associated toxicity.

(d) Planning target volume (PTV) design takes into consideration both inter- and intrafraction variability including organ motion.

(i) For the esophagus, this can include motion associated with respiration, the cardiac cycle, and peristalsis.
(ii) Reports of esophageal motion range from 0.1 to 0.4 mm in the anterior-posterior direction, 0.3–4.2 mm laterally, and 3.7–10 mm superior to inferior [21]. One study of interfraction motion suggested margins of 12 mm left to right, 10 mm posteriorly, and 9 mm anteriorly to account for this [22].
(iii) In general, margins used to expand from the GTV to PTV include 5 cm proximally and distally and 2–2.5 cm radially [14, 17].

## 4.6 Field Design

(a) *Cervical and upper thoracic tumors*
(i) Treatment of proximal esophageal lesions can require fields spanning from the inferior aspect of the larynx superiorly to the level of the carina inferiorly for the primary tumor and periesophageal/mediastinal lymph nodes as well as the supraclavicular nodal basins.
(ii) Using older methods, this was achieved with lateral parallel opposed or oblique portals to the primary tumor and a single anterior field for the supraclavicular and superior mediastinal nodes.
(iii) Other techniques treated lesions in this region by means of a four-field box approach, using a wax bolus to compensate for the lack of tissue above the shoulders, arc rotations, anterior wedged pairs, and three- or four-field methods using posterior oblique portals combined with a single anterior portal or anteroposterior-posteroanterior (AP/PA) fields.
(iv) Using three-dimensional (3D) approaches, varying techniques have been implemented.
1. Historically, one approach entailed treating the primary tumor and lymph nodes using an AP/PA approach to 39.6–41.4 Gy at 1.8 Gy per fraction, followed by a left or right opposed oblique pair to bring the total dose to 50.4 Gy, thereby limiting the spinal cord dose.
2. This technique will generally exclude the supraclavicular fossa, and a separate electron field is often added, treating to a depth of 2–3 cm, depending upon individual anatomy.

(v) More recently, intensity-modulated radiation therapy (IMRT) has been implemented for cervical lesions, similar to tumors of the anatomically related head and neck.
1. Compared to 3D planning, IMRT has been shown to have improved conformality to the target with decreased dose to normal tissues [23].
2. An IMRT plan, as shown in Fig. 4.2, allows for a single plan that spares normal tissues including the spinal cord and lungs and is our preferred method for treating these tumors.
3. Accurate delivery of treatment via IMRT requires sufficient immobilization of the neck and upper torso as well as strict attention to accurate target delineation and strict normal tissue constraints as described below.

(b) Mid-thoracic tumors
(i) The middle thoracic esophagus extends from 25 to 30 from the incisors, and tumors in this region can arise in close proximity to the bronchi and carina.
(ii) For this reason bronchoscopy should be considered to rule out tumor involvement.
(iii) 3D planning is generally dictated by spinal cord, lung and heart tolerance.
1. A combination of AP-PA and right anterior-left posterior (RAO/LPO) oblique fields is sometimes employed to cover the primary tumor with coverage of the paraesophageal/mediastinal lymph nodes.

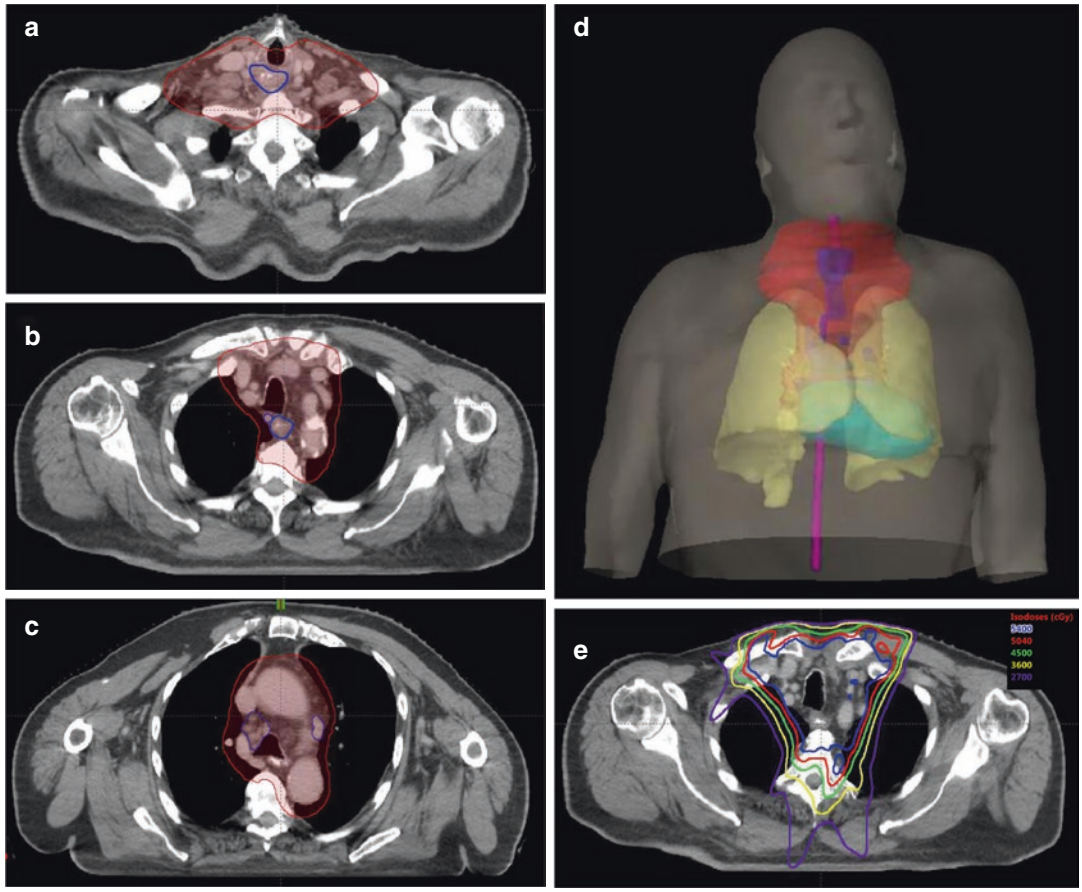


**Fig. 4.2** (**a**–**c**) GTV (*blue*) and PTV (*red*) contours on axial slices of a patient with lymph node positive cervical esophageal cancer treated with IMRT. (**d**) 3D rendering of GTV and PTV volumes in relation to the lungs (*yellow*), heart (*cyan*), and spinal cord (*purple*). (**e**) Representative isodose curves for the same patient

(iv) IMRT has been investigated to improve the dosimetry of these nearby organs.
1. In a study of 15 patients with mid-thoracic esophageal tumors planned with both 3D and IMRT techniques, there was no difference in conformality or homogeneity of the prescribed dose in terms of PTV coverage [24].
2. However, IMRT utilization decreased the average spinal cord dose from 43.6 to 36.1 Gy, the left and right lung V25 from 45.6 to 21.0 % and from 38.4 to 30.2 %, respectively, and the mean heart dose from 29.0 to 22.2 Gy [24].
3. In addition, volumetric modulated arc therapy (VMAT), as compared to IMRT, has been shown to be superior in terms of sparing the lung and heart without compromising PTV coverage for mid-thoracic lesions [25].

(v) Ultimately the choice between 3D and IMRT planning must be made based on individual patient dosimetry.

(c) Lower thoracic and GEJ tumors
(i) Radiation fields for more distal tumors of the esophagus generally cover the periesophageal nodes and extend inferiorly into the abdomen based on the risk of nodal spread.
1. Using CT images obtained at simulation, it is helpful to not only

delineate the known disease but also the uninvolved esophagus with associated lymphatics and arteries along which the nodal stations run, e.g., the celiac axis, to aid in definition of the areas to be treated.

2. A recent consensus contouring guideline panel recommended a 3–4 cm margin from GTV to CTV superiorly and inferiorly except when treating to doses above 45 Gy. At these doses, a 2 cm margin inferiorly was recommended to limit dose to the abdominal organs except for Siewert III lesions or those extending more than 5 cm into the stomach [17].

(ii) Adequate coverage can typically be achieved with 3D planning using a combination of opposed fields.

1. One potential technique is combination of AP-PA and RAO-LPO (or opposed lateral) field arrangement to treat to 45 Gy in 25 fractions and then boost with similar primary or solely opposed lateral fields to an additional 5.4 Gy.
2. The recent RTOG 1010 study guidelines recommend the initial PTV to 45 Gy to include the primary GTV with a 4.5–5 cm expansion superiorly and inferiorly as well as 1.5–2.5 cm radially. The nodal GTV is expanded 1.5–2.5 cm in all directions. A boost to 50.4 Gy can then be delivered to the primary GTV with 0.5–1 cm expansion along the length of the esophagus or the same margin in all directions around the nodal volume [16].
3. An example of a 3D plan for a GEJ tumor is shown in Fig. 4.3.

(iii) Where larger fields are required (e.g., larger tumors with high-risk features in order to cover more at-risk nodal stations), IMRT can be considered to spare normal tissues, in particular the heart, kidneys, and bowel.

1. In a retrospective analysis of ten patients with distal esophageal tumors treated with 3D conformal radiotherapy but replanned with IMRT plans using up to nine fields, IMRT improved the lung V20 by 5 % as well as PTV heterogeneity and conformity [26].
2. Although this study showed no difference in heart doses, another analysis of 19 patients treated with IMRT, compared to a theoretical 3D plan, showed decreased mean heart dose from 28.2 to 22.9 Gy with IMRT [27]. This study did not show a difference in lung dose. Regardless, IMRT should be considered if 3D planning cannot meet acceptable dose constraints.
3. In a single institution retrospective review, use of IMRT decreased all-cause mortality and locoregional recurrence but had no impact on esophageal cancer-specific mortality [28].
4. A five-field beam arrangement with a single AP beam and four oblique beams or a single PA beam, opposed laterals, and two anterior oblique beams has been recommended for IMRT planning [16].
5. An example of an IMRT plan for a GEJ tumor is shown in Fig. 4.4.

## 4.7 Radiation Dose

(a) The NCCN recommended dose for esophageal cancer ranges from 41.4 to 50.4 Gy.

(i) Although the previously described CROSS trial generated excellent results delivering 41.4 Gy in the neoadjuvant setting [14], higher doses to 50.4 Gy allow for a more "definitive" dose, with limited added morbidity, in patients that do not proceed to resection.

(ii) Radiation doses above 50.4 Gy have not been shown to improve outcomes. The Intergroup 0123 trial randomized 236 patients to either 50.4 or 64.8 Gy with 5-FU and cisplatin and 5-FU [29].

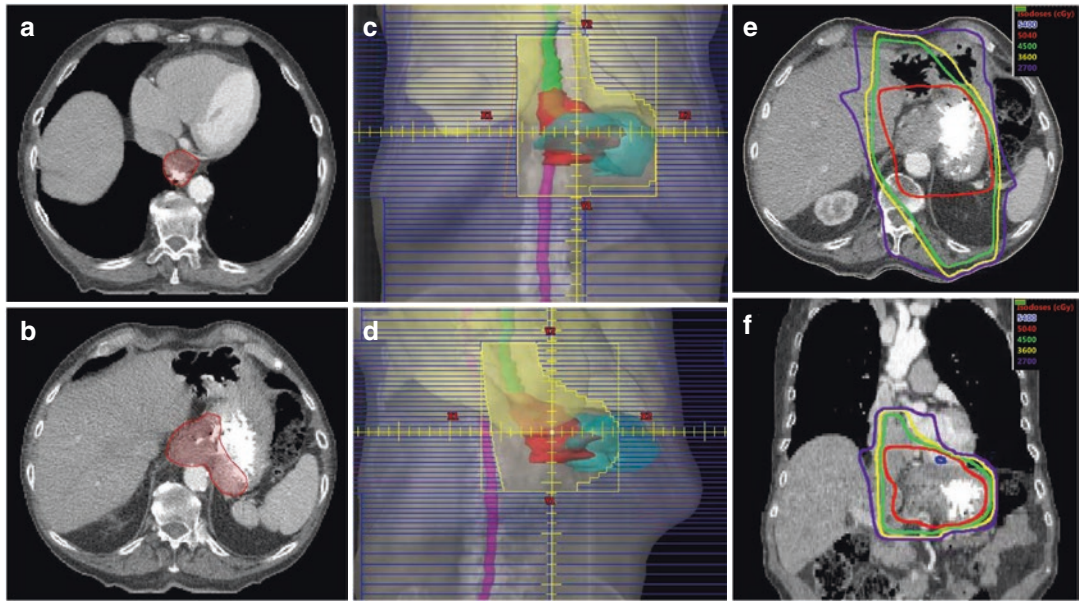


**Fig. 4.3** (**a**, **b**) GTV (*red*) contours on axial slices of a patient with node-negative GEJ adenocarcinoma treated with 3D CRT. AP (**c**) RAO (**d**) beam's eye views showing coverage of GTV as well as rendering of the normal esophagus (*green*), lungs (*yellow*), stomach (*cyan*), and spinal cord (*purple*). (**e**, **f**) Representative isodose curves for the same patient

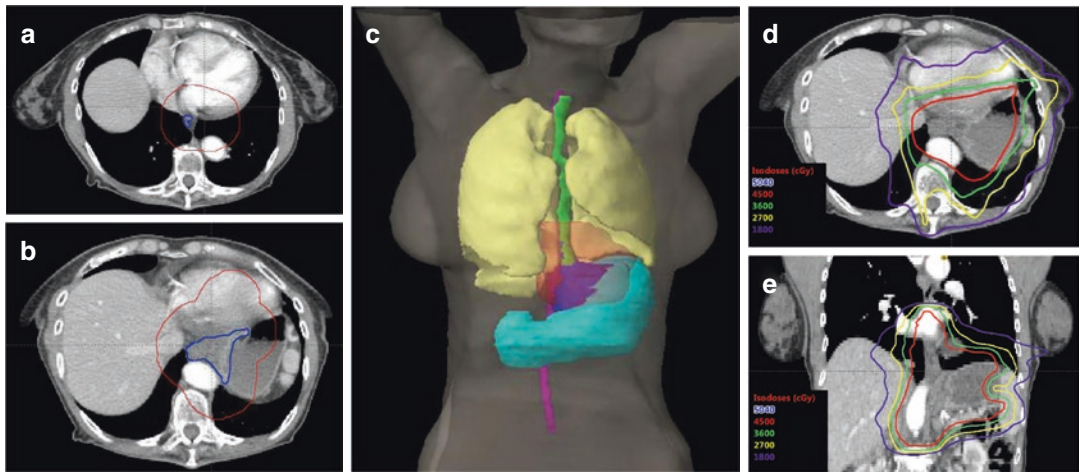


**Fig. 4.4** (**a**, **b**) GTV (*blue*) and PTV (*red*) contours on axial slices of a patient with a T3N1 GEJ adenocarcinoma treated with an eight-field IMRT plan. (**c**) AP projection showing relationship of GTV and PTV as well as rendering of the normal esophagus (*green*), lungs (*yellow*), stomach (*cyan*), and spinal cord (*purple*). (**d**, **e**) Representative isodose curves for the same patient

1. Although 85 % of trial patients had squamous cell carcinoma, trial results showed no difference in 2-year overall survival (40 % in the 50.4 Gy and 31 % in 64.8 Gy group) between groups, although more patients in the dose-escalated arm experienced treatment-related deaths, notably prior to receiving the higher dose.

2. Ongoing trials in Europe (NCT02741856, NCT01348217) and Asia (NCT02556762) are further assessing the role of dose escalation in this disease.

## 4.8 Normal Structures and Constraints

(a) Total radiation dose for esophageal cancer is constrained by surrounding normal tissues including the spinal cord, lungs, heart, kidneys, and liver.
   (i) The maximum spinal cord dose should generally be limited to approximately 45 Gy as the risk of myelopathy increases at higher doses [30]. Higher prescription doses can be successfully achieved by providing an oblique or opposed lateral boost for the final 5.4 Gy of a 50.4 Gy plan using 3D techniques.
   (ii) A number of parameters have been reported to correlate esophageal cancer irradiation with pulmonary toxicity, namely, radiation pneumonitis or pulmonary complications following resection.
      1. Rates of grade 2 and 3 pneumonitis have been reported to be as high as 59 % and 5 %, respectively, in one series from MD Anderson [31].
      2. Postoperative complications at the same institution have been reported as high as 35 % with a V10 $\geq$ 40 % during preoperative radiation as opposed to 8 % at lower doses [32].
      3. The current RTOG 1010 study recommendations include maintaining a V10 $\leq$ 40 % as well as mean lung dose of 20 Gy and V30 $\leq$ 20 %. In addition, for IMRT plans, the integral dose is also important, with 50 % of the lungs limited to 5 Gy or less preferred [16].
      4. However, in a study of dose escalation for inoperable stage III NSCLC (RTOG 0617), only the lung V20 and not the mean lung dose or V5 correlated with radiation pneumonitis [33].
   (iii) The heart, notably the left ventricle when treating distal esophageal lesions, also needs to be considered. Increasing dose to the heart raises the risk of pericarditis, pericardial effusion, myocardial infarction, and heart failure.
      1. A V30 greater than 46 % has been shown to be predictive of pericardial effusion, and rates of this can be as high as 28 % within 15 months after completing treatment [21].
      2. In a more recent retrospective review of 343 esophageal cancer patients, the rate of symptomatic cardiac disease at 5 years was 13.8 %. On multivariate analysis, this risk correlated with increasing heart dose with the lowest significant cutoff values of V45, V50, and V55 of 15 %, 10 %, and 5 %, respectively [34].
      3. A SEER analysis of esophageal cancer patients showed no difference in disease-specific or pulmonary mortality between patients treated with 3D CRT or IMRT but did show an improvement in all cause and cardiac mortality with IMRT use [35].
   (iv) Ultimately, a balance must be struck between lung and heart dose, with the former relatively spared with AP-PA fields at the expense of the latter and vice versa with oblique fields. If appropriate dose constraints are not met, IMRT should be considered.

(b) For treatment fields extending below the diaphragm, inclusion of the celiac and left gastric nodal basins often will lead to additional dose to the liver and kidneys.
   1. Typically, 70 % of the liver is constrained to a dose less than 30 Gy, above which the risk of symptomatic radiation-induced liver disease (RILD) increases.
      (a) A retrospective analysis of 112 distal esophageal cancer patients who

underwent PET scanning during radiation showed 8 % had imaging findings consistent with RILD in either the anatomically-related caudate or left hepatic lobes. However, this did not appear to be clinically significant [36].

(b) Consensus guidelines recommend limiting extension of treatment fields into the liver to 0.5 cm [17].

2. If the kidneys are to receive dose, a nuclear medicine renal scan to assess the contribution of each to urinary output should be considered. Overall, no more than 50 % of the physiologically functional kidney parenchyma should receive more than 20 Gy, if possible [37].
   (a) In one analysis, there was no difference in kidney dose with 3D or IMRT planning for distal esophageal cancers, although the left kidney V18 was approximately twice that of the contralateral kidney [27].
3. If large volumes of these organs are in the treatment field, further attempts at organ sparing through 4D planning with respiratory management can be considered.

## 4.9 Special Considerations

(a) Brachytherapy
   (i) High-dose-rate brachytherapy, typically with Ir-192, can be used in both the definitive treatment, as a boost, and palliative treatment of esophageal cancer.
      1. An afterloading catheter is placed into the esophagus via the nose with fluoroscopic or CT guidance.
         (a) In the curative setting, it has been employed as a boost to EBRT [38].
         (b) In a randomized study of dysphagia palliation in 209 patients with inoperable esophageal cancer, treatment with a single 12 Gy fraction with brachytherapy provided more durable control and better quality of life as compared to stenting alone [39].
         (c) Intra-esophageal brachytherapy can also be combined with EBRT for effective palliation.
            (i) A study from the International Atomic Energy Agency randomized 219 patients to two fractions of 8 Gy prescribed to 1 cm from the source center with or without the addition of 30 Gy in ten fractions using EBRT [40].
            (ii) The addition of EBRT increased relief from dysphagia by 18 % compared to brachytherapy alone, with a nonsignificant increase in fistula formation from 6.4 to 10.9 % of patients.
            (iii) Overall 17.8 % of patients required further dilatation or stenting.

(b) Re-irradiation
   (i) Although the rates of local recurrence were low in the CROSS study with preoperative chemoradiation use [14], local recurrence of disease is still a well-established pattern of failure, and outcomes of re-irradiation may be relevant in clinical practice.
   (ii) In a report of 54 patients, 21 of whom had prior radiation, radiation was associated with improvement in dysphagia in 68 % of patients and median survival of 12 months [41].
      1. The range of doses used was 30–68 Gy with a median of 45 Gy.
      2. There was no grade 5 toxicity, and 1 of 21 patients treated with prior chemoradiation developed late esophageal stenosis [41].
   (iii) However, in another cohort of ten patients receiving prior radiation treatments of 44–50.4 Gy (median of 46.5 Gy), three patients developed a grade 5 tracheoesophageal fistula, and

five experienced progressive disease at 3 months after treatment [42].

(iv) In a nonrandomized study of 69 patients treated with either re-irradiation or stenting for dysphagia, there was a greater improvement in swallowing in the radiation group as compared to the cohort undergoing stenting [43].

(v) Ultimately the potential benefit from re-irradiation to the esophagus must be balanced with increased risk of toxicity to both the treated and surrounding normal tissues.

## Conclusions

(a) Radiation for esophageal cancer involves treatment of the primary tumor and associated nodal basins which may potentially extend above and below the diaphragm.

(b) Given the propensity with which nodal involvement is seen and proximity of the esophagus to other organs with the chest and upper abdomen, accurate target delineation with pretreatment staging and clinical simulation is paramount.

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# Gastric Cancer: Background and Clinical Evidence

5

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## 5.1 Epidemiology and Risk Factors

- The United States in 2016, 26,370 new cases and 10,730 deaths [1]
- Worldwide in 2012, 951,600 new cases and 723,100 deaths [2]
- Large variation in incidence worldwide, highest Asia
- Risk factors: age, male gender, atrophic gastritis, Helicobacter pylori infection, smoking, alcohol use, dietary factors (high salt, nitrates, red and processed meats), obesity, hereditary factors (<5 %; hereditary diffuse gastric cancer, Peutz-Jeghers syndrome, juvenile polyposis syndrome, Lynch syndrome), and prior abdominal radiation

## 5.2 Staging

- EGD with biopsies and EUS
- CT of chest, abdomen, and pelvis
- PET/CT
- Laparoscopy with peritoneal cytology
- AJCC staging [3]

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## 5.3 Prognostic Factors

- Gender/age
- Subtype (intestinal more favorable than diffuse)
- Stage
- Extent of resection (R0 vs. R1 vs. R2)

## 5.4 Molecular Biology

- >90 % adenocarcinoma
- Two distinct morphologic and molecular subtypes: intestinal and diffuse
- Intestinal type:
  - Associated with *H. pylori* infection, dietary factors
  - More commonly well differentiated
  - Progressive accumulation of genetic alterations in oncogenes (K-ras) and tumor suppressor genes (p53, APC, TTF, CDKN1B)
  - More favorable prognosis
- Diffuse type:
  - Clinically can present with "linitis plastica"
  - More commonly poorly differentiated
  - Most cases have loss of E-cadherin (CDH1 gene) expression
  - Worse prognosis
- HER2 overexpression in ~20 %. More common in intestinal subtype and moderately/well-differentiated tumors

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T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_5

- The Cancer Genome Atlas (TCGA) identified four molecular subtypes: [4]
  - Epstein-Barr virus positive (9 %) – PIK3CA mutations, DNA hypermethylation, amplification of JAK2, PD-L1, and PD-L2
  - Microsatellite unstable (22 %) – hypermutation, MLH1 silencing
  - Genomically stable (20 %) – mutations in RHOA, fusions involving RHO-family GTPase, CDH-1. Enriched for diffuse histology
  - Chromosomal instability (50 %) – marked aneuploidy and focal amplification of receptor tyrosine kinases, RAS pathway activation, p53 mutations. Enriched for intestinal histology

## 5.5 Patterns of Failure

- Gunderson reoperation series (US, no adjuvant therapy): Local-regional > peritoneal > distant metastases [5]
- INT-0116 (US, D0-D1 dissection, no adjuvant therapy): Local-regional > distant metastases [6]
- CLASSIC/ARTIST trials (Asia, D2-D3 dissection, adjuvant chemotherapy): Distant metastases > peritoneal > local-regional [7, 8]

## 5.6 Multidisciplinary Treatment

- Early stage (Tis-T1, N0, M0)
  - Endoscopic resection (Tis or T1a and favorable features)
  - Gastrectomy + lymphadenectomy
- Locally advanced (T2-T4 or N+, M0)
  - Neoadjuvant therapy* → gastrectomy + lymphadenectomy → adjuvant therapy*
  - Gastrectomy + lymphadenectomy → adjuvant therapy*
  - Chemotherapy ± chemoradiation (if not a surgical candidate)
    - *Chemotherapy ± radiotherapy
- Metastatic (M1)
  - Palliative systemic therapy ± local therapy

## 5.7 Key Clinical Trials

### 5.7.1 Surgery

- Italian trial of total vs. subtotal gastrectomy for distal tumors [9, 10]
  - Phase 3 RCT, resectable gastric cancer of distal 50 % of stomach ($n = 624$)
  - Total vs. subtotal gastrectomy (proximal clearance ≥ 6 cm) + D2 lymphadenectomy
  - No difference in survival, lower morbidity with subtotal gastrectomy
- Dutch trial of D1 vs. D2 lymphadenectomy [11, 12]
  - Phase 3 RCT, resectable gastric cancer ($n = 711$)
  - Gastrectomy + D1 (perigastric LN) vs. D2 (perigastric + extended regional LN) lymphadenectomy
  - No difference in survival at 15 years median follow-up
  - D2 lymphadenectomy: ↑ perioperative morbidity/mortality, ↓ local-regional recurrence, ↓ cancer-specific mortality
  - Authors recommend spleen-preserving D2 resection at high-volume center
- MRC trial of D1 vs. D2 lymphadenectomy
  - Phase 3 RCT, resectable gastric cancer ($n = 400$)
  - Gastrectomy + D1 lymphadenectomy vs. D2 lymphadenectomy
  - No difference in survival
  - D2 lymphadenectomy: ↑ perioperative morbidity/mortality

### 5.7.2 Postoperative Adjuvant Therapy

- Intergroup 0116 (US) [6, 13]
  - Phase 3 RCT, resected gastric cancer ($n = 556$).

  - Observation vs. 5FU/leucovorin × 1c → RT (45 Gy) + 5FU/leucovorin → 5FU/leucovorin × 2c.
  - Increased risk of death with observation (HR 1.32, $p = 0.005$).
  - No prospective surgical quality control and lymphadenectomy was reported as D2 (10 %), D1 (36 %), or D0 (54 %).
  - Adjuvant therapy reduced local and regional (but not distant) recurrence.
  - Grade 4 adverse events: 32%.
  - Statistically significant benefit in OS in all subgroups, although trend ($p = 0.08$) toward greater benefit in intestinal (vs. diffuse) histology.
  - Establishes postoperative adjuvant chemoradiotherapy as a standard of care for patients with locally advanced, resected gastric cancer who have not received neoadjuvant therapy.
- Intergroup CALGB 80101 (US) [14]
  - Phase 3 RCT, resected gastric cancer ($n = 546$)
  - ECF × 1c → RT (45 Gy) + 5FU → ECF × 2c vs. 5FU/leucovorin × 1c → RT (45 Gy) + 5FU → 5FU/leucovorin × 2c
  - ECF did not improve survival (HR 1.03, $p = 0.8$)
  - ECF associated with lower rate of grade 4 adverse events: 26 % vs. 40 % ($p < 0.001$)
- CLASSIC (Korea) [7, 15]
  - Phase 3 RCT, resected gastric cancer with D2 lymphadenectomy ($n = 1035$)
  - Observation vs. capecitabine/oxaliplatin × 8c
  - Adjuvant chemotherapy reduced risk of death (HR 0.66, $p = 0.0015$)
  - Grade 3/4 adverse events in 56 %
  - Establishes postoperative adjuvant capecitabine/oxaliplatin as a standard of care for patients with locally advanced, resected gastric cancer with D2 lymphadenectomy who have not received neoadjuvant therapy
- ARTIST (Korea) [8, 16]
  - Phase 3 RCT, resected gastric cancer with D2 lymphadenectomy ($n = 458$)
  - Capecitabine/cisplatin × 6c vs. capecitabine/cisplatin × 2c → RT (45 Gy) + capecitabine → capecitabine/cisplatin × 2c
  - Addition of RT + capecitabine did not improve disease-free survival (HR 0.74, $p = 0.09$)
  - In LN+ subset, chemoRT improved disease-free survival (HR 0.70, $p = 0.04$)

### 5.7.3 Neoadjuvant and Perioperative Therapy

- MRC ST02/MAGIC (UK) [17]
  - Phase 3 RCT, resectable gastric, GEJ, or distal esophagus cancer ($n = 503$).
  - Surgery vs. ECF × 3c → surgery → ECF × 3c.
  - Reduced risk of death with perioperative chemotherapy (HR = 0.75, $p = 0.009$).
  - Among patients undergoing gastrectomy, majority (68 %) had a D2 lymphadenectomy.
  - Downstaging with ECF, but pCR: 0 %.
  - 33 % did not receive any doses of planned postoperative ECF.
  - Presence of lymph node metastasis after neoadjuvant chemotherapy and surgery (ypN+, 69 % of patients undergoing surgery) was the only significant independent prognostic factor for survival (HR = 3.36, $p < 0.001$), suggesting that future trials should focus on testing alternative postoperative treatment strategies in this cohort [18].
  - Establishes perioperative ECF as a standard of care for locally advanced resectable gastric cancer.
- CRITICS (Dutch, NCT00407186) [19, 20]
  - Phase 3 RCT, resectable gastric cancer ($n = 788$).
  - ECC/EOC × 3c → gastrectomy → ECC/EOC × 3c vs. ECC/EOC × 3c → gastrectomy → RT (45 Gy) + cisplatin/capecitabine.
  - 87 % had resection of N1 and N2 lymph nodes.

  - 62 % started postoperative adjuvant therapy.
  - Adjuvant chemo (vs. CRT) had higher grade 3/4 neutropenia (34 % vs. 4 %, $p < 0.001$). No difference in other grade 3/4 toxicities.
  - Intent to treat analysis (all patients randomized): no difference in survival (5-year OS 41 % in both arms).
- RTOG 9904 (US) [21]
  - Phase 2 single arm, resectable gastric cancer ($n = 43$)
  - 5FU, leucovorin, cisplatin → RT (45 Gy) + 5FU, paclitaxel → gastrectomy
  - Grade 4 adverse events: 21 %
  - pCR: 26 %, R0 resection: 77 %
  - Median survival: 23.2 months
- MDACC retrospective (US) [22]
  - Single-institution retrospective, 1995–2012 ($n = 192$)
  - Neoadjuvant chemo → chemoRT (45 Gy) → gastrectomy
  - pCR: 20 %, R0 resection: 93 %
  - 5-year OS: 56 %

### 5.7.4 Metastatic Disease

- TOGA [23]
  - Phase 3 RCT, metastatic HER2+ gastric or GEJ carcinoma ($n = 584$)
  - Chemotherapy vs. chemotherapy + trastuzumab
  - Trastuzumab improved survival: median 11.1 → 13.8 months (HR = 0.74, $p = 0.0046$)
  - No difference in grade 3 or 4 adverse events

## 5.8 Outcomes and Toxicities

- 5-year overall survival by stage group (US SEER database, 1991–2000) [3]
  - IA: 71 %
  - IB: 57 %
  - IIA: 46 %
  - IIB: 33 %
  - IIIA: 20 %
  - IIIB: 14 %
  - IIIC: 9 %
  - IV: 4 %
- Toxicities of gastrectomy
  - Postoperative complications: cardiac, pulmonary, bleeding, venous thrombosis/embolism, infection, GI/anastomotic complications
  - Late complications: chronic dysmotility, dumping syndrome, anastomotic stricture, malabsorption
- Toxicities of chemotherapy
  - All cytotoxic agents may cause nausea, vomiting, diarrhea, fatigue, oral mucositis, and bone marrow suppression. Additional toxicities include:
  - Fluoropyrimidines (5FU/capecitabine): stomatitis, cutaneous toxicity
  - Platinum agents (cisplatin/oxaliplatin): peripheral neuropathy, ototoxicity, renal insufficiency, alopecia
  - Anthracyclines (epirubicin): alopecia, injection site reaction, cardiac toxicity
  - Taxanes (paclitaxel, docetaxel): alopecia, peripheral neuropathy, hypersensitivity reaction, cutaneous toxicity, fluid retention, hepatic dysfunction
  - Trastuzumab: hypersensitivity reaction, cardiac toxicity
- Toxicities of radiotherapy
  - Acute: nausea, vomiting, anorexia, fatigue, diarrhea, hematologic toxicity
  - Late: stomach/intestine ulceration/obstruction, malabsorption, renal insufficiency, second malignancy

## 5.9 Future Directions

- Ongoing phase 3 RCTs:
- MRC ST03 (UK, NCT00450203)
  - Resectable gastric, GEJ, or distal esophagus cancer ($n = 1103$), randomized to:
  - Epirubicin, cisplatin, capecitabine (ECC) × 3c → gastrectomy → ECC × 3c
  - ECC + bevacizumab × 3c → gastrectomy → ECC + bevacizumab × 3c → bevacizumab × 6c

  - Subset of HER2+ pts ($n$ = 80) randomized to addition of lapatinib
- TOPGEAR (AGITG, NCT01924819) [24]
  - Resectable gastric/GEJ cancer ($n$ = 752), randomized to:
  - ECF × 3c → gastrectomy → ECF × 3c
  - ECF × 2c → RT (45 Gy) + 5FU → gastrectomy → ECF × 3c
- ARTIST-II (Korea, NCT01761461)
  - Resected, N+ gastric cancer ($n$ = 900), randomized to:
  - S-1 × 8c
  - S-1 + oxaliplatin × 8c
  - S-1 + oxaliplatin × 2c → RT (45 Gy) + S-1 → S-1 + oxaliplatin × 4c

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# Gastric Cancer: Radiation Therapy Planning

6

Christopher L. Hallemeier
and Michael G. Haddock

## 6.1 Relevant Anatomy

- Tumor location and lymph node stations are typically defined by the Japanese Gastric Cancer Association (JGCA) classification [1] (Fig. 6.1, Table 6.1)

## 6.2 Principles of Field Design/ Patterns of Failure

- General principles of field design are based on published series on patterns of nodal involvement at the time of gastrectomy/lymphadenectomy and patterns of disease recurrence after gastrectomy/lymphadenectomy
- Field design is dependent on tumor location, stage, and extent of lymphadenectomy (Table 6.2)

### 6.2.1 Patterns of Disease Recurrence After Curative Intent Gastrectomy

- INT-0116 (US, D0-1 dissection, no adjuvant therapy): [4]
  - Local (anastomosis or gastric bed): 8 %
  - Regional (peritoneal cavity): 39 %
  - Distant metastases: 18 %
  - Unknown: 11 %
- CLASSIC trial (Asia, D2-3 dissection, adjuvant capecitabine/oxaliplatin, no RT): [5]
  - Local-regional: 5 %
  - Peritoneal: 11 %
  - Distant metastases: 12 %
- Yonsei University series [6]

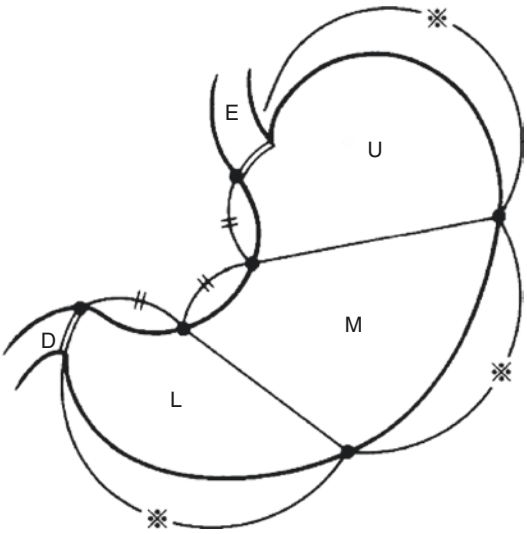


**Fig. 6.1** Japanese Gastric Cancer Association (JGCA) classification of tumor location [1]

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© Springer International Publishing AG 2017
T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_6

**Table 6.1** Japanese Gastric Cancer Association (JGCA) definitions of lymph node stations for gastric cancer [1]

| No. | Definition |
|---|---|
| 1 | Right paracardial LNs, including those along the first branch of the ascending limb of the left gastric artery |
| 2 | Left paracardial LNs including those along the esophagocardiac branch of the left subphrenic artery |
| 3a | Lesser curvature LNs along the branches of the left gastric artery |
| 3b | Lesser curvature LNs along the second branch and distal part of the right gastric artery |
| 4sa | Left greater curvature LNs along the short gastric arteries (perigastric area) |
| 4sb | Left greater curvature LNs along the left gastroepiploic artery (perigastric area) |
| 4d | Right greater curvature LNs along the second branch and distal part of the right gastroepiploic artery |
| 5 | Suprapyloric LNs along the first branch and proximal part of the right gastric artery |
| 6 | Infrapyloric LNs along the first branch and proximal part of the right gastroepiploic artery down to the confluence of the right gastroepiploic vein and the anterior superior pancreatoduodenal vein |
| 7 | LNs along the trunk of left gastric artery between its root and the origin of its ascending branch |
| 8a | Anterosuperior LNs along the common hepatic artery |
| 8p | Posterior LNs along the common hepatic artery |
| 9 | Celiac artery LNs |
| 10 | Splenic hilar LNs including those adjacent to the splenic artery distal to the pancreatic tail, and those on the roots of the short gastric arteries and those along the left gastroepiploic artery proximal to its first gastric branch |
| 11p | Proximal splenic artery LNs from its origin to halfway between its origin and the pancreatic tail end |
| 11d | Distal splenic artery LNs from halfway between its origin and the pancreatic tail end to the end of the pancreatic tail |
| 12a | Hepatoduodenal ligament LNs along the proper hepatic artery, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas |
| 12b | Hepatoduodenal ligament LNs along the bile duct, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas |
| 12p | Hepatoduodenal ligament LNs along the portal vein in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas |
| 13 | LNs on the posterior surface of the pancreatic head cranial to the duodenal papilla |
| 14v | LNs along the superior mesenteric vein |
| 15 | LNs along the middle colic vessels |
| 16a1 | Paraaortic LNs in the diaphragmatic aortic hiatus |
| 16a2 | Paraaortic LNs between the upper margin of the origin of the celiac artery and the lower border of the left renal vein |
| 16b1 | Paraaortic LNs between the lower border of the left renal vein and the upper border of the origin of the inferior mesenteric artery |
| 16b2 | Paraaortic LNs between the upper border of the origin of the inferior mesenteric artery and the aortic bifurcation |
| 17 | LNs on the anterior surface of the pancreatic head beneath the pancreatic sheath |
| 18 | LNs along the inferior border of the pancreatic body |
| 19 | Infradiaphragmatic LNs predominantly along the subphrenic artery |
| 20 | Paraesophageal LNs in the diaphragmatic esophageal hiatus |
| 110 | Paraesophageal LNs in the lower thorax |
| 111 | Supradiaphragmatic LNs separate from the esophagus |
| 112 | Posterior mediastinal LNs separate from the esophagus and the esophageal hiatus |

- 382 patients who underwent curative-intent gastrectomy and D2 lymphadenectomy for stage III (N3) gastric cancer 2004–2008
- 94 % received adjuvant chemotherapy, none received RT
- 63 % developed recurrence
- First site of recurrence (some patients had multiple sites):
  - Local: 7 % (most at anastomosis, few in gastric bed)
  - Regional lymph node: 24 %
  - Peritoneal: 33 %
  - Distant: 20 %
- Highest risk stations: 9, 12, 13, 14, 16a, and 16b (Table 6.3)

**Table 6.2** Patterns of pathologic lymph node metastases by tumor site [2, 3]

| Nodal groups and station numbers | | Upper third (%) $N = 339$ | Middle third (%) $N = 318$ | Lower third (%) $N = 150$ |
|---|---|---|---|---|
| Paracardia | 1/2 | 22 | 9 | 4 |
| Lesser or greater curvature | 3/4 | 25 | 36 | 37 |
| Right gastric artery suprapyloric | 5 | 2 | 3 | 12 |
| Infrapyloric | 6 | 3[a] | 15 | 49 |
| Left gastric artery | 7 | 19 | 22 | 23 |
| Common hepatic artery | 8 | 7 | 11 | 25 |
| Celiac axis | 9 | 13 | 8 | 13 |
| Splenic artery/hilum | 10/11 | 11 | 3 | 2[b] |
| Hepatoduodenal ligament | 12 | 1 | 2 | 8 |
| Others (distant nodes) | 13–16 | 0–5 | 0–5 | 0–5 |

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[a]Risk was 12% in this site in series of Tagliacozzo and Sunderland
[b]These are N3 nodes for lower third tumors and were not routinely dissected. In the series of Tagliacozzo, the risk was 8%

**Table 6.3** Location of regional lymph node recurrence after D2 lymphadenectomy [6]

| Station No. | Node location | Number of patients with positive nodes (% of total) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | At initial surgery | | At first recurrence | | | | | | | | | |
| | | Total ($n = 91$) | | Total ($n = 91$) | | Upper third ($n = 10$) | | Middle third ($n = 23$) | | Lower third ($n = 41$) | | More than two thirds ($n = 17$) | |
| 1 | Right paracardium | 36 | (40) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) |
| 2 | Left paracardium | 7 | (8) | 2 | (2) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (12) |
| 3 | Along the lesser curvature | 52 | (57) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) |
| 4 | Along the greater curvature | 44 | (48) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) |
| 5 | Suprapylorum | 34 | (37) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) |
| 6 | Infrapylorum | 55 | (60) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) |
| 7 | Along the left gastric artery | 37 | (41) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) |
| 8 | Along the common hepatic artery | 31 | (34) | 3 | (3) | 0 | (0) | 1 | (4) | 1 | (2) | 1 | (6) |
| 9 | Around the celiac artery | 34 | (37) | 14 | (15) | 3 | (30) | 1 | (4) | 8 | (20) | 2 | (12) |
| 10 | At the splenic hilum | 2 | (2) | 1 | (1) | 1 | (10) | 0 | (0) | 0 | (0) | 0 | (0) |
| 11 | Along the proximal splenic artery | 18 | (20) | 6 | (7) | 0 | (0) | 0 | (0) | 4 | (10) | 2 | (12) |
| 12 | In the hepatoduodenal ligament | 10 | (11) | 26 | (29) | 0 | (0) | 6 | (26) | 16 | (39) | 4 | (24) |
| 13 | On the posterior surface of the pancreatic head | 3 | (3) | 14 | (15) | 1 | (10) | 2 | (9) | 11 | (27) | 0 | (0) |
| 14 | Along the superior mesenteric vein/artery | 6 | (7) | 18 | (20) | 0 | (0) | 3 | (13) | 8 | (20) | 7 | (41) |

**Table 6.3** (continued)

| Station No. | Node location | Number of patients with positive nodes (% of total) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | At initial surgery | | At first recurrence | | | | | | | | | |
| | | Total ($n = 91$) | | Total ($n = 91$) | | Upper third ($n = 10$) | | Middle third ($n = 23$) | | Lower third ($n = 41$) | | More than two thirds ($n = 17$) | |
| 15 | Along the middle colic vessels | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) |
| 16a | Around the abdominal aorta[a] | 1 | (1) | 53 | (58) | 7 | (70) | 19 | (83) | 19 | (46) | 8 | (47) |
| 16b | Around the abdominal aorta[b] | 0 | (0) | 56 | (62) | 4 | (40) | 19 | (83) | 23 | (56) | 10 | (59) |

Reprinted from Chang et al. [6] with permission from Elsevier
[a]From the upper margin of the celiac trunk to the lower margin of the left renal vein
[b]From the upper margin of the left renal vein to the aortic bifurcation

## 6.3 Simulation

- Fasting for > 2 h before simulation and treatment
- IV contrast is recommended if available and no contraindications
- If IV contrast is not used, oral contrast can be considered, although the impact on reproducibility of stomach position/distension should be considered
- Supine with arms above the head in an immobilization device
- CT-based simulation
- Four-dimensional CT (4DCT) should be considered to evaluate respiratory motion of the target volume, especially for intact disease

## 6.4 Dose, Contours, Fields

### 6.4.1 Dose

- Preoperative: 41.4–50.4 Gy in 1.8–2 Gy/fraction
- Postoperative: 45–50.4 Gy in 1.8–2 Gy/fraction
- Definitive: 45–54 Gy in 1.8–2 Gy/fraction

### 6.4.2 Contours/Fields

- Previous studies (INT 0116) have utilized 2D treatment planning techniques.
- Modern treatment involves CT-based treatment planning.
- Development of target volumes should incorporate information from all pretreatment staging studies, including EGD, CT, and/or PET/CT, operative/pathologic findings, and postoperative imaging.

### 6.4.3 Neoadjuvant/Definitive RT

- European Organization for Research and Treatment of Cancer (EORTC) contouring guidelines for neoadjuvant RT for gastric cancer: [7]
  - $CTV_{stomach}$ includes a minimum 5 cm mucosal margin on the gross tumor within the stomach, although the authors recognize that surgical series show that <5 % of patients have microscopic mucosal extension >3 cm beyond macroscopic disease [8].
  - $CTV_{nodal}$ includes involved lymph node stations as well as elective lymph node volumes (Japanese classification) based on tumor location, as outlined in figures below (Figs. 6.2, 6.3, and 6.4).

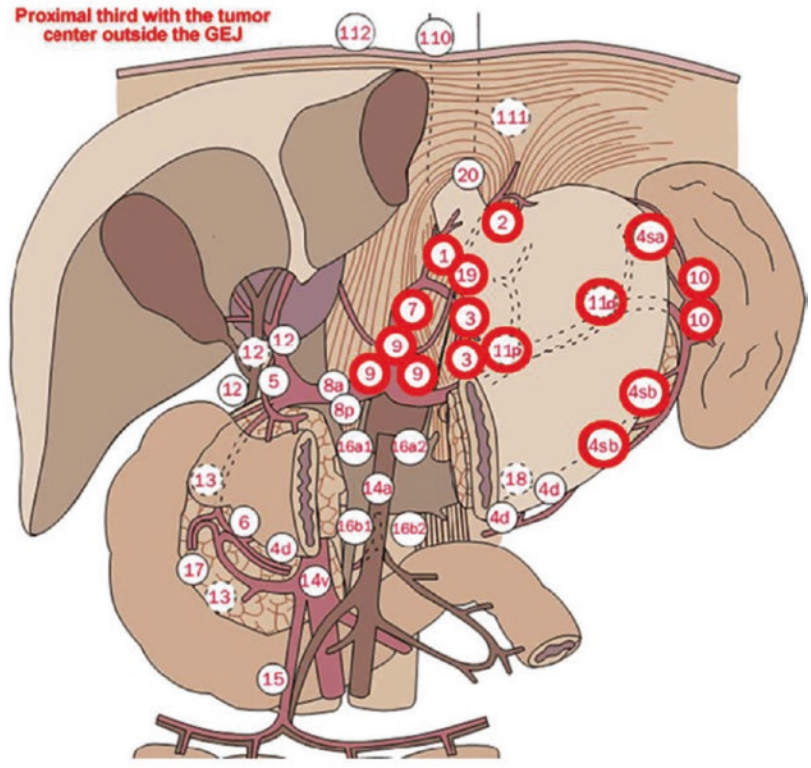


**Fig. 6.2** Elective lymph node stations for neoadjuvant radiotherapy for proximal 1/3 gastric tumors [7] (Reprinted from Matzinger et al. [7] with permission from Elsevier)

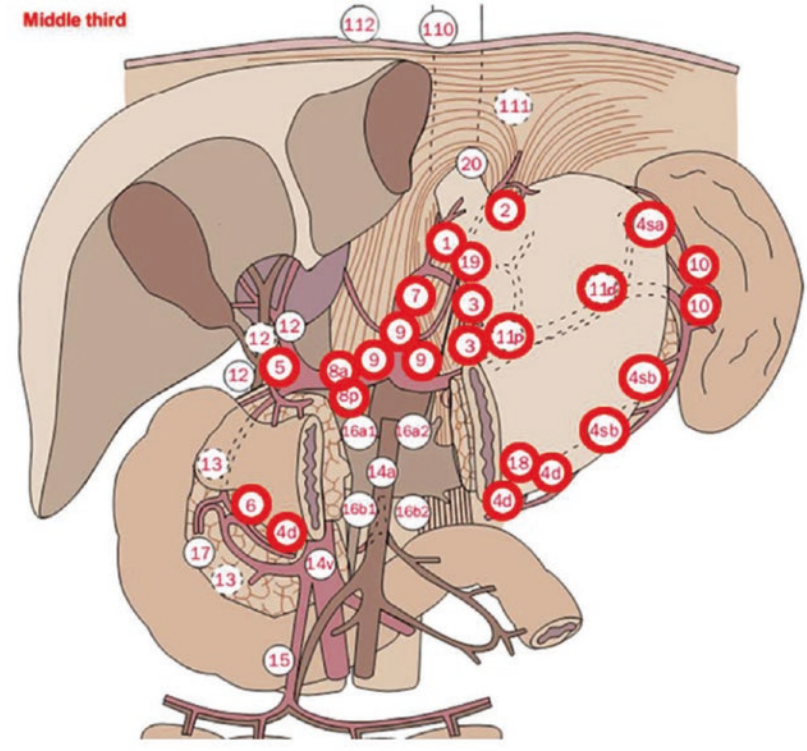


**Fig. 6.3** Elective lymph node stations for neoadjuvant radiotherapy for middle 1/3 gastric tumors [7] (Reprinted from Matzinger et al. [7] with permission from Elsevier)

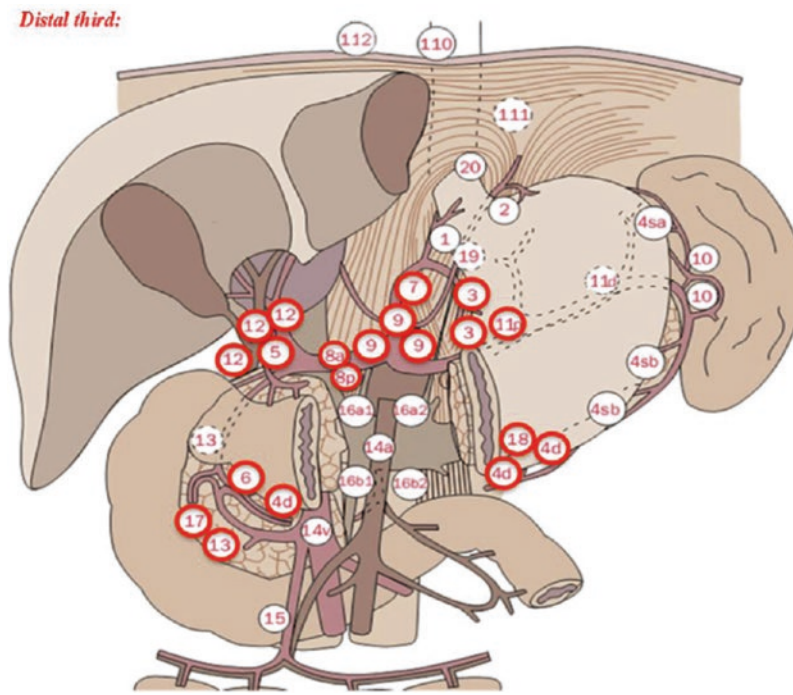


**Fig. 6.4** Elective lymph node stations for neoadjuvant radiotherapy for distal 1/3 gastric tumors [7] (Reprinted from Matzinger et al. [7] with permission from Elsevier)

- Coverage of stations 14 and 16 should also be considered [6].
- An example case of preoperative RT is shown in Fig. 6.5.

## 6.5 Postoperative RT (Tables 6.4, 6.5, 6.6, and 6.7)

- Postoperative RT field design guidelines from previous US intergroup trials have been published and are presented below [3].
- Fields typically included the remnant stomach (if applicable), anastomoses, tumor/gastric bed, and regional lymph node stations. These may be tailored based on T and N stage, tumor location, extent of surgery, and margin status.

### 6.5.1 CTV Construction

- Modern postoperative radiotherapy planning for gastric cancer utilizes CT-based delineation of the CTV.
- The CTV should typically include the anastomoses, tumor bed, and regional lymph nodes.
- An example case of postoperative RT is shown in Fig. 6.6.
- The regional lymph nodes to be covered are dependent on tumor location, as described above for neoadjuvant/definitive RT.
- Additionally, coverage of stations 14 and 16 should also be considered, especially for stage III (N3) [6].
- The CTV may be modified based on postoperative anatomy and risks of toxicity.
- Further descriptions of CTV construction based on tumor location and postoperative anatomy are as follows:

Proximal 1/3/gastric cardia/GEJ tumor after esophagogastrectomy with an intrathoracic esophagogastric anastomosis

- CTVanastomosis includes 3–4 cm mucosa of esophagus and distal stomach
- CTVtumor bed is delineated using the preoperative imaging studies. This typically will also include the medial 2/3 of the left hemidiaphragm.
- CTVLN includes stations 1–4, 7, and 9–13. If the tumor involved the GEJ, stations 20 and

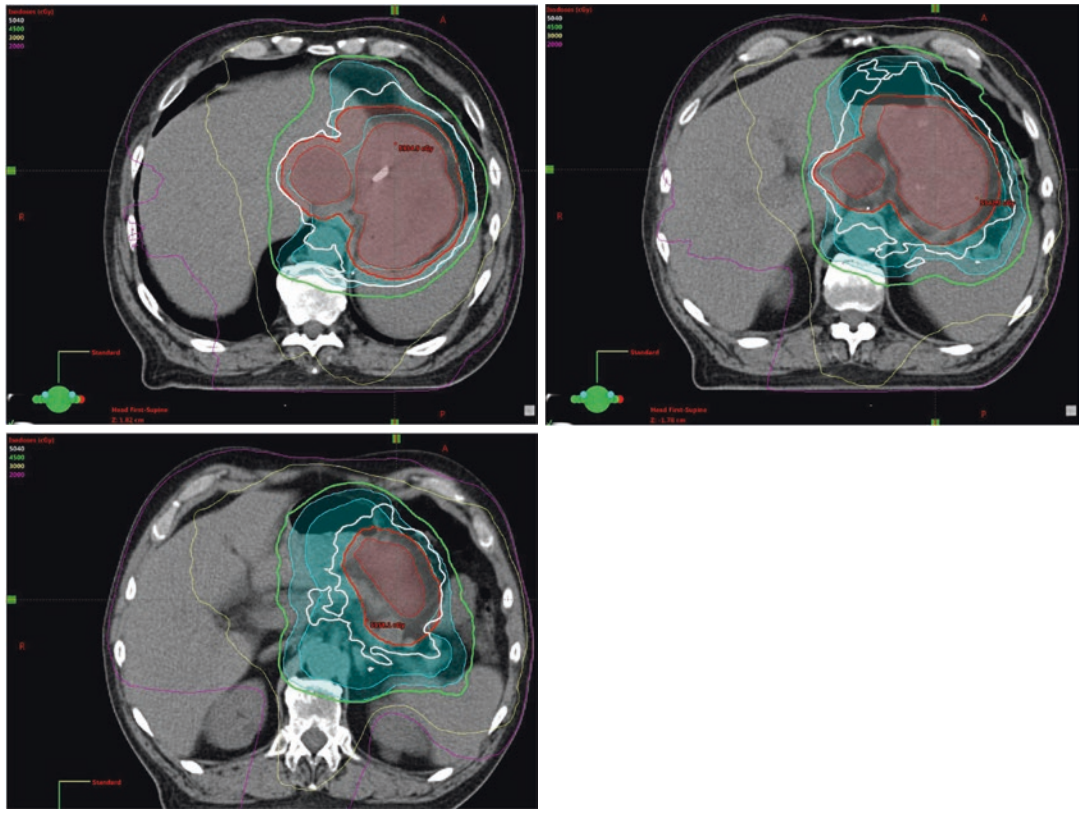

**Fig. 6.5** Preoperative RT for proximal/middle gastric cancer. The patient had a T3N1M0 poorly differentiated adenocarcinoma of the lesser curvature of the gastric fundus measuring 11 cm, with a 5 cm celiac lymph node. The patient received initial chemotherapy (cisplatin, docetaxel, and epirubicin) for three cycles with slight decrease in the size of the primary tumor and lymph node. The patient then received neoadjuvant chemoradiotherapy. A dose of 50.4 Gy (*white isodose curve*) was administered to the red PTV, consisting of the gross tumor and margin. A dose of 45 Gy (*green isodose curve*) was administered to the cyan PTV, consisting of a 3 cm expansion of the primary tumor along the adjacent gastric mucosa and the regional (perigastric, splenic, celiac, and para-aortic) lymph node basins. IMRT was utilized to reduce dose to the kidneys, liver, and large bowel. Subsequently, total gastrectomy and D2 lymphadenectomy was performed with negative margins and a final stage of ypT1aN1 with marked treatment effect (10 % viable cells)

110–111 should also be included. If the tumor involved the middle 1/3 of the stomach, stations 5, 6, and 8 should be included.

- Final CTV is a union of CTVanastomosis + CTVtumor bed + CTVLN, modified based on postoperative anatomy and risks of toxicity.

Middle 1/3 tumor after total gastrectomy with a Roux-en-Y esophago-jejunal anastomosis

- CTVanastomosis includes 3–4 cm mucosa of the esophagus and jejunum.
- CTVtumor bed is delineated using the preoperative imaging studies.
- CTVLN includes stations 3–13. If the tumor involved the proximal 1/3 of the stomach, stations 1–2 should be included.
- Final CTV is a union of CTVanastomosis + CTVtumor bed + CTVLN, modified based on postoperative anatomy and risks of toxicity.

Distal 1/3 tumor after subtotal (distal) gastrectomy with a gastrojejunal anastomosis

**Table 6.4** General guidelines of impact of T and N stage on inclusion of remaining stomach, tumor bed, and nodal sites within irradiation fields [3]

| TN stage | Remaining stomach[a] | Tumor bed | Nodes |
|---|---|---|---|
| T1-2 (not into subserosa) N0 | N | N | N |
| T2N0 (into subserosa)[b] | Variable | Y | N |
| T3N0 | Variable | Y | N |
| T4N0 | Variable | Y | Variable |
| T1-2N+ | Y | N | Y |
| T3-4N+ | Y | Y | Y |

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[a]Inclusion of the remaining stomach is preferable in most patients if two thirds of one kidney can be excluded. This is dependent on the extent of surgical resection and uninvolved margins (in centimeters)

[b]Posterior wall T2N0 lesions, or those that extend beyond muscularis propria, especially tumors located in the proximal or distal stomach, are at risk for local relapse. In addition, patients with low-stage disease with close or positive surgical margins should be considered for treatment to the tumor bed

- CTVanastomosis includes 3–4 cm mucosa of the proximal stomach and jejunum, as well as the proximal 3–4 cm of the duodenal stump.
- CTVtumor bed is delineated using the preoperative imaging studies.
- CTVLN includes stations 3–9 and 11–13. If the tumor involved the middle 1/3 of the stomach, station 10 should be included.
- Final CTV is a union of CTVanastomosis + CTVtumor bed + CTVLN, modified based on postoperative anatomy and risks of toxicity.

### 6.5.2 PTV Margins and IGRT

- An ITV may be utilized to account for respiratory motion, when a 4DCT is performed.
- The PTV should include the CTV/ITV with expansion to account for uncertainties in target volume delineation, inter- and intrafraction motion, and treatment delivery.
- The PTV expansion may range from 5 to 15 mm depending on the type of immobilization, setup, and use of image guidance.
- Daily image guidance should be utilized for setup verification.
- Daily volumetric imaging should be considered.
- Adaptive planning may need to be considered if there is significant change in the anatomy relative to the planning CT.

### 6.5.3 Technique

- 3DCRT or IMRT should be used to best conform the prescription dose to the target volumes and to minimize normal tissue exposure.
- IMRT (vs. 3DCRT) usually reduces kidney V20 and liver V30, but not mean kidney or liver dose [9, 10].
- IMRT (vs. 3DCRT) may reduce risk of clinical nephrotoxicity [10, 11].

## 6.6 Normal Structures and Constraints

- EORTC guidelines: [7]
  - Spinal cord: maximum < 45 Gy
  - Lungs: V20 < 20 %
  - Heart: V40 < 30 %, V25 < 50 %
  - Kidneys: total V20 < 50 %, at least 1 with V20 < 30 %
  - Liver: V30 < 30 %
- National Comprehensive Cancer Network guidelines: [12]
  - Liver: V30 < 40 %, mean < 25 Gy
  - Kidneys: at least 1 with V20 < 33 %
  - Spinal cord: maximum < 45 Gy
  - Heart: V40 < 33 %
- Efforts should be made to reduce dose to bowel outside of the PTV

**Table 6.5** Impact of site of primary gastric lesion and TN stage on irradiation treatment volumes: cardia/proximal one third of stomach (general guidelines) [3]

| Site of primary and TN stage | Remaining stomach | Tumor bed volumes[a] | Nodal volumes | Tolerance organ structures |
|---|---|---|---|---|
| Cardia/proximal 1/3 of stomach | Preferred, but spare 2/3 of one kidney (usually R) | T-stage dependent | N-stage dependent | kidneys, spinal cord, liver, heart, lung |
| T2N0 with invasion of subserosa | Variable dependent on surgical-pathologic findings[b] | Medial L hemidiaphragm, adjacent body of pancreas (± tail) | None or perigastric[c] | |
| T3N0 | Variable dependent on surgical-pathologic findings[b] | Medial L hemidiaphragm, adjacent body of pancreas (+/− tail) | None or perigastric: optional: periesophageal, mediastinal, celiac#[c] | |
| T4N0 | Variable dependent on surgical-pathologic findings[b] | As for T3N0 plus site(s) of adherence with 3-5 cm margin | Nodes related to site of adherence, ± perigastric, periesophageal, mediastinal, celiac | |
| T1-2N+ | Preferable | Not indicated for T1, as above for T2 into subserosa | Perigastric, celiac, splenic, suprapancreatic, ± periesophageal, mediastinal, pancduod, porta hepatis[d] | |
| T3-4 N+ | Preferable | As for T3, T4N0 | As for T1-2N+ and T4N0 | |

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[a]Use preoperative imaging (CT, barium swallow), surgical clips, and postoperative imaging (CT, barium swallow)

[b]For tumors with wide (>5 cm) surgical margins confirmed pathologically, treatment of is residual stomach not necessary, especially if this would result in substantial increase in normal tissue morbidity

[c]Optional node inclusion for T2-3N0 lesions if there has been an adequate surgical node dissection (D2 dissection) and at least 10–15 nodes have been examined pathologically

[d]Pancreaticoduodenal and porta hepatis nodes are at low risk if nodal positivity is minimal (i.e., 1–2 pos nodes with 10–15 nodes examined), and this region does not need to be irradiated. Periesophageal and mediastinal nodes are at risk if there is esophageal extension

**Table 6.6** Impact of site of primary gastric lesion and TN stage on irradiation treatment volumes: body/middle one third of stomach (general guidelines) [3]

| Site of primary and TN stage | Remaining stomach | Tumor bed volumes[a] | Nodal volumes | Tolerance organ structures |
|---|---|---|---|---|
| Body/mid-1/3 of stomach | Yes, but spare 2/3 of one kidney | T-stage dependent | N-stage dependent, spare 2/3 of one kidney | Kidneys, spinal cord, liver |
| T2N0 with invasion of subserosa—especially post wall | Yes | Body of pancreas (± tail) | None or perigastric; optional: celiac, splenic, suprapancreatic, pancreaticoduodenal, porta hepatis[b] | |
| T3N0 | Yes | Body of pancreas (± tail) | None or perigastric; optional: celiac, splenic, suprapancreatic, pancreaticoduodenal, porta hepatis[b] | |
| T4N0 | Yes | As for T3N0 plus site(s) of adherence with 3–5 cm margin | Nodes related to site of adherence ± perigastric, celiac, splenic, suprapancreatic, pancreaticoduodenal, porta hepatis | |
| T1-2 N+ | Yes | Not indicated for T1 | Perigastric, celiac, splenic, suprapancreatic, pancreaticoduodenal, porta hepatis | |
| T3-4N + | Yes | As for T3, T4N0 | As for T1-2N+ and T4N0 | |

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[a]Use preoperative imaging (CT, barium swallow), surgical clips, and postoperative imaging (CT, barium swallow)

[b]Optional node inclusion for T2-3N0 lesions if there has been adequate surgical node dissection (D2 dissection) and at least 10–15 nodes have been examined pathologically

**Table 6.7** Impact of site of primary gastric lesion and TN stage on irradiation treatment volumes: antrum/distal one third of stomach (general guidelines) [3]

| Site of primary and TN stage | Remaining stomach | Tumor bed volumes[a] | Nodal volumes | Tolerance organ structures |
|---|---|---|---|---|
| Pylorus/distal 1/3 stomach | Yes, but spare 2/3 of one kidney (usually L) | T-stage dependent | N-stage dependent | Kidneys, liver, spinal cord |
| T2N0 with invasion of subserosa | Variable dependent on surgical-pathologic findings[b] | Head of pancreas, (± body), 1st and 2nd duodenum | None or perigastric; optional: pancreaticoduodenal, porta hepatis, celiac, suprapancreatic[c] | |
| T3N0 | Variable dependent on surgical-pathologic findings[b] | Head of pancreas, (± body), 1st and 2nd duodenum | None or perigastric; optional: pancreaticoduodenal, porta hepatis, celiac, suprapancreatic[c] | |
| T4N0 | Preferable but dependent on surgical-pathologic findings[b] | As Tor T3N0 plus site(s) of adherence with 3–5 cm margin | Nodes related to site(s) of adherence ± perigastric, pancreaticoduodenal, porta hepatis, celiac, suprapancreatic | |
| T1-2N+ | Preferable | Not indicated for T1 | Perigastric, pancreaticoduodenal, porta hepatis, celiac, suprapancreatic; optional: splenic hilum[c] | |
| T3-4N+ | Preferable | As for T3, T4N0 | As for T1-2N+ and T4N0 | |

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[a]Use preoperative imaging (CT, barium swallow), surreal clips, and postoperative imaging (CT, barium swallow)

[b]For tumors with wide (>5 cm) surgical margins confirmed pathologically, treatment of residual stomach is optional if this would result in substantial increase in normal tissue morbidity

[c]Optional node inclusion for T2-3N0 lesions if there has been an adequate surgical node dissection (D2 dissection) and at least 10–15 nodes have been examined pathologically

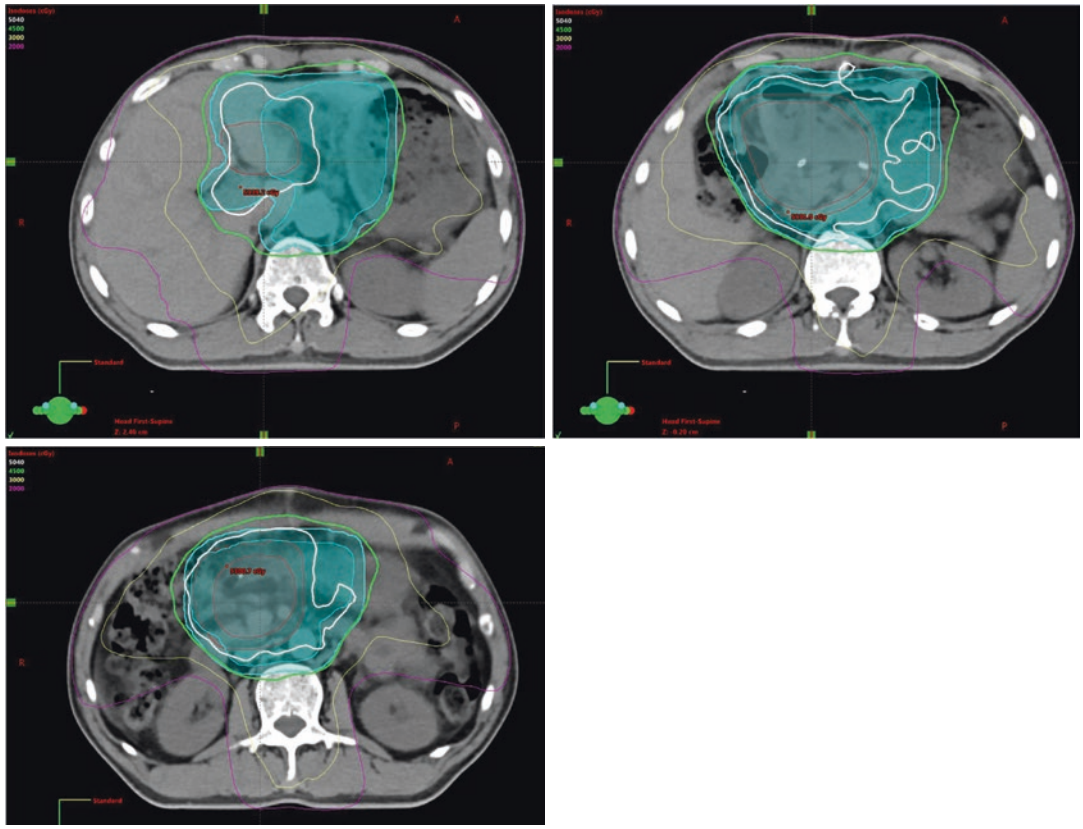

**Fig. 6.6** Postoperative RT for distal gastric cancer. The patient had a pT4aN1M0 adenocarcinoma of the gastric antrum, s/p distal gastrectomy, and D1 lymphadenectomy with a positive radial surgical margin in the pancreas body. The patient received postoperative chemoradiotherapy. A dose of 50.4 Gy (*white isodose curve*) was administered to the red PTV, consisting of the area of suspected microscopic residual disease and margin. A dose of 45 Gy (*green isodose curve*) was administered to the cyan PTV, consisting of the tumor bed and the regional (perigastric, celiac, and para-aortic) lymph node basins. IMRT was utilized to reduce dose to the kidneys, liver, and bowel. The patient received 5-FU, leucovorin, and oxaliplatin before and after chemoradiotherapy

## 6.7 Special Considerations

- Intraoperative RT has been utilized at some centers for primary and recurrent gastric cancer [13].

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# Pancreatic Cancer: Background and Clinical Evidence

7

Richard A. Burkhart, Lauren M. Rosati, and Joseph M. Herman

## 7.1 Epidemiology and Risk Factors

- Despite the improvements in survival seen in many types of gastrointestinal malignancies, pancreatic ductal adenocarcinoma (PDA) remains a highly lethal disease.
- The disease burden in the United States (USA) is increasing with incidence approaching 50,000 cases annually [1].
- With the volume of mortality approaching the incidence of the disease, a diagnosis of PDA is devastating. Only 7 % of patients will be alive at 5 years, most of whom were able to undergo successful surgical resection for locally confined disease [1].
- Despite being only the 12th most frequent cancer encountered in the United States, it is currently the 3rd leading cause of cancer-related death [1–3].
  - Epidemiologic estimates suggest that PDA will surpass breast and prostate cancer to become the second leading cause of cancer-related death in the United States by 2030 [2].
  - Estimates of worldwide disease burden are difficult to quantify, but best evidence suggests that the trend observed in the United States of increasing incidence is occurring in other Western countries [4, 5].
- PDA appears to be a disease of the elderly with the median age at diagnosis near 71 [1].
  - Additional risk factors include tobacco use, chronic diabetes mellitus, chronic pancreatitis, and a personal or family history of oncogenetic mutations such as *BRCA* [6, 7].
- Patients with a strong family history of PDA (i.e., come from a family with ≥2 first-degree relatives—defined as parent, sibling, or child—with PDA and have a first-degree relationship with ≥1 of the relatives with PDA) and/or an established mutation in a gene known to be associated with PDA (i.e., BRCA1, BRCA2, Lynch syndrome, Peutz–Jeghers syndrome to name a few) have an increased risk for developing PDA themselves and are eligible for screening trials such as the Cancer of the Pancreas Screening-5 (CAPS5) study (NCT02000089).

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© Springer International Publishing AG 2017
T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_7

## 7.2 Staging and Work-Up

- The most common staging system used for PDA is derived from a consensus of experts in conjunction with the American Joint Committee on Cancer (AJCC) with a goal of facilitating treatment decisions and prognosis [8].
  - Currently in its seventh edition, staging relies on an evaluation of the primary tumor (T stage), regional lymph nodes (N stage), and presence or absence of metastasis (M stage).
- However, for the purposes of guiding clinical management, we most commonly stage patients as resectable, borderline resectable (BRPC), locally advanced (LAPC), or metastatic.
  - While patients with BRPC are technically resectable, neoadjuvant therapy is typically recommended in an effort to increase the likelihood of margin-negative resection.
  - Although a number of definitions have been published, the widely accepted criteria for BRPC are outlined in Table 7.1.
  - When the extent of local disease exceeds the definition of BRPC above, the term LAPC is used to represent unresectable disease.
- The above staging is evaluated based on diagnostic computed tomography (CT), preferably done with triple-phase contrast enhancement as part of a pancreas protocol with 3D imaging reconstruction (to allow proper visualization of the tumor–vessel interface).
- Magnetic resonance imaging (MRI) and/or fludeoxyglucose positron emission tomography (FDG-PET) may also be utilized.
- In addition to imaging, a pathologic diagnosis is necessary for patients who are not undergoing up-front surgical resection.
  - Ideally, this should be done by endoscopic-guided ultrasound with a fine needle aspiration (FNA).
  - A core biopsy or a cell block through multiple pass FNA is now recommended when possible in order to have adequate tissue for correlative studies when indicated [9].
- If there is a biliary obstruction, placement of metal stents is preferred over plastic stents.
- If patients present with clay-colored stools, flatulence and/or weight loss pancreatic enzyme supplementation should be considered.
- Treatment recommendations are typically offered after baseline evaluation including a history and physical examination, complete blood count, serum chemistries, a carbohydrate antigen 19-9 (CA 19-9), and carcinoembryonic antigen (CEA).
- Multidisciplinary review at a high-volume pancreas center is strongly recommended [10].

## 7.3 Prognostic Factors

- Resectability, as determined by local tumor extension, remains the only chance for cure in the disease.
  - The extent of resection also carries prognostic significance—a patient who undergoes a complete (R0) resection has a better prognosis than a patient who undergoes a resection with microscopically (R1) or grossly (R2) positive margins.

**Table 7.1** Criteria for resectability status

| | Potentially resectable | Borderline resectable | Locally advanced |
|---|---|---|---|
| Portal vein/SMV | TVI <180° | TVI ≥180° and/or *reconstructable* occlusion | Unable to reconstruct |
| Hepatic artery | No TVI | *Reconstructable* short-segment TVI of any degree | Unable to reconstruct |
| Superior mesenteric artery | No TVI | TVI < 180° | TVI ≥ 180° |
| Celiac trunk | No TVI | TVI < 180° | TVI ≥ 180° |

Adapted from Katz et al. [92]
Abbreviation: *TVI* tumor–vessel interface

  - Margin clearance >1.5 mm is necessary for optimal locoregional control, and the extent of clear margins in R0 resections may be used to estimate the risk of locoregional failure [11].
  - When PDA is resected with negative margins, the dominant predictor of prognosis is involvement of the locoregional lymph nodes at the time of resection [12].
  - Tumor size and differentiation appear to be of prognostic significance, with tumors ≥2 cm and poorly differentiated tumors suggesting inferior overall survival [13–15].
- The presence of metastatic disease at the time of diagnosis is the dominant poor prognostic indicator, with metastatic patients estimated to survive a median of 6 months.
- Other prognostic factors that can help discriminate within each stage of the disease include serum and molecular biomarkers.
  - Common serum biomarkers include CA 19-9 and CEA [16].
    - A recent Australian study retrospectively analyzed the role of CEA and CA 19-9 in 393 patients treated for PDA from 2005 to 2012 [17].
      - Both CEA ≤6.9 and CA 19-9 ≤931.4 were positive prognostic factors for survival on univariate analysis ($p < 0.001$).
      - Significance was maintained on multivariate analysis (CEA, hazard ratio [HR] 1.27, 95 % CI 1.00–1.61, $p = 0.054$; CA 19–9, HR 1.38, 95 % CI 1.09–1.74, $p = 0.007$).
      - Furthermore, the linear combination of CEA and CA 19-9 (value ≤845 U/L) was one of the strongest clinicopathologic variables analyzed (HR 2.33, 95 % CI 1.84–2.96, $p < 0.001$).
    - In BRPC patients specifically, normalization of CA 19-9 (<40 U/mL after neoadjuvant therapy) is suggestive of improved survival in both resected (38 vs. 26 months, p < 0.02) and non-resected patients (15 vs. 11 months, $p = 0.02$) [18].
    - Baseline CA 19-9 greater than 90 U/mL was even reported to be a stronger predictor of death than local or distant progression in patients with LAPC treated on a phase I–II study of full-dose gemcitabine and dose-escalated intensity-modulated radiation therapy (IMRT) [19].
    - The number of proposed molecular biomarkers of disease severity is expanding fairly rapidly in the literature as genetic and histologic science becomes more nuanced.
- Finally, the ability of each patient to successfully receive the therapies recommended by the NCCN (directed by clinicopathologic stage assessment) can also serve as a prognostic factor [20].

## 7.4 Molecular Biology

- Advancements in the molecular understanding of PDA have made major strides over the past decade, particularly in the understanding of the genetic basis for disease.
- In 2008, an initial landmark report by Jones and colleagues reported on the comprehensive genetic analysis of 24 pancreatic lesions [21].
  - Genetic deficiencies were identified most commonly in 12 core signaling pathways, including cell cycle control, DNA damage control, and apoptosis. Among other breakthroughs, these data also demonstrated that PDA was a cancer of relatively few mutations (averaging 63 mutations per tumor) with key genes such as *KRAS, TP53*, and *SMAD4* frequently affected.
- Currently, this information is being leveraged in research endeavors in attempts to identify a cure. Unfortunately however, the clinical phenotype of PDA has proven to be more heterogeneous than this initial work suggested.
- Most recently, a genetic study in 456 tumor specimens stratified PDA into four distinct molecular subtypes that correlated with histopathologic findings: squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine/exocrine [22].

- With unique genetic profiles in each tumor subtype, there is a molecular basis to support a personalized therapeutic approach to the disease in the future.
- Drug development, comparative clinical outcomes research, and further molecular studies will continue to shape the treatment of this disease over the next several decades.
- There are several promising preclinical and early-stage clinical studies that have been initiated by an understanding of the genetic underpinnings of PDA.
  - These include efforts to discover novel targeted therapies and those that leverage genetic information to trial combination therapies.
  - One example is an interplay discovered in preclinical studies between AKT activity and radiosensitivity [23].
    - In early-stage translational work, the use of an oral agent enhancing the PI3-kinase/AKT pathway was associated with remarkable clinical response to radiotherapy.

## 7.5 Patterns of Failure

- In patients with locally confined disease who successfully undergo surgical resection, there are two common patterns of failure: locoregional recurrence (in resection bed) and distant recurrence (frequently in the liver and lungs).
  - The most common lesson that can be gleaned from available data is that both locoregional and distant failures of disease control are common (exceeding 50 % each in many reports) [24–26].
- There are important factors that may raise the risk for locoregional disease recurrence following surgical resection, namely, lymph node-positive and margin-positive resection on histopathologic analysis. When these are present, locoregional failure occurs at a rate roughly between 50 and 70 % [24–26].
- The use of radiotherapy following surgical resection, in an attempt to optimize locoregional control, remains controversial in the United States due to historical data demonstrating unclear benefit [27].
  - In a retrospective study of 1,130 patients with resected PDA, the patterns of failure were analyzed.
    - Patients in this study were divided into three groups: those who underwent surgery alone and received no adjuvant therapy ($n$ = 392), those who received adjuvant chemotherapy after surgery ($n$ = 291), and those who received adjuvant CRT after surgery ($n$ = 447).
    - Adjuvant chemotherapy resulted in significantly fewer local and distant recurrences. This afforded an overall survival advantage (HR 0.71, 95 % CI 0.57–0.89).
    - Patients who underwent adjuvant CRT had fewer local recurrences but no change in distant recurrences.
  - This study and others highlight the importance of adjuvant systemic therapy in preventing both local and distant recurrence and of adjuvant radiation therapy in preventing local recurrence [28–31].
- Another contemporary series of 1,051 patients with resected PDA and follow-up data extending to a median of 84 months, locoregional control rates as estimated by the Kaplan–Meier method varied between 68 and 80 % [32].
  - The stratification between high and low rates of locoregional control appeared to be associated with the use of adjuvant CRT with the authors advocating for its routine use.
  - These data are supported by reports from single-institution series documenting improved local control rates versus historical control data, particularly in post-surgical node- or margin-positive cohorts [33, 34].
- Regardless of capacity for surgical resection upon initial patient presentation, the most common cause of death is distant disease progression [33, 35].
  - The multidisciplinary treatment for these patients is often discussed on a case-by-case

basis with options including systemic chemotherapy, palliative surgical or percutaneous interventions, and palliative radiotherapeutic approaches.
- Determining SMAD/DPC4 status of surgically resected samples may predict which patients are more likely to recur locally versus distantly although larger studies are needed to validate these findings [36, 37].

## 7.6 Multidisciplinary Treatment

- Treatment recommendations for PDA are ideally made in a multidisciplinary setting on the basis of clinical stage, performance status, and patient preference.
  - As demonstrated by the Johns Hopkins experience, a multidisciplinary clinic can result in a more accurate diagnosis, and treatment recommendations can be made in a more expeditious manner [10, 38, 39].
  - This is achieved by successful collaboration among the numerous specialties that are dire to delivering care to patients with PDA—medical oncology, radiation oncology, surgery, radiology, pathology, palliative care and pain medicine, and gastroenterology.
  - For the purposes of this chapter, we will focus on trimodality care with chemotherapy, radiation therapy, and surgery.
- Treatment options include:
  - Up-front surgery for resectable PDA
  - Neoadjuvant therapy for resectable PDA
  - Adjuvant therapy for resected PDA
  - Neoadjuvant/definitive therapy for borderline resectable and locally advanced, unresectable PDA
  - Salvage therapy for unresectable locally recurrent PDA
  - Systemic therapy and/or palliative therapy for metastatic disease
- Systemic therapy is typically used in all stages of pancreatic cancer.
  - An exception to this may be patients with comorbidities that prohibit chemotherapy or poor performance status (ECOG > 2).
  - Goals of systemic therapy should be discussed with patients prior to initiation of therapy, and enrollment into clinical trials is strongly encouraged.
  - Close follow-up of patients undergoing therapy is indicated.
- Neoadjuvant/definitive therapy (resectable and borderline resectable PDA):
  - In patients with resectable disease confined to the pancreas, up-front surgery is typically recommended; however, neoadjuvant therapy is standard at some centers [40] and is currently being evaluated in a cooperative group study (NCT01821612).
    - There is limited evidence to recommend specific neoadjuvant regimens for resectable PDA outside of a clinical trial, and practices vary with regard to the use of systemic therapy and radiation therapy.
      - Acceptable regimens include gemcitabine alone, FOLFIRINOX (FFX), or gemcitabine + albumin-bound paclitaxel (Gem/NP). Subsequent radiation (chemoradiation or stereotactic body radiation therapy, SBRT) is often recommended after maximal chemotherapy and if there is no evidence of metastatic disease.
  - Combination chemotherapy, particularly FOLFIRINOX and gemcitabine/nab-paclitaxel, with or without radiotherapy is beginning to repeatedly demonstrate a capacity to downstage patients into a surgical paradigm of management.
    - Importantly, R0 resection can be performed in this group of patients at rates exceeding 85 %.
    - In many of these experiences, chemotherapy is being combined with IMRT prior to resection in an effort to maximize noninvasive therapies [41].
    - For BRPC, a multicenter study established FOLFIRINOX followed by 5-FU-based CRT as a standard approach [42].
      - Induction multi-agent chemotherapy (good PFS) or single-agent chemo-

therapy (poor PFS) followed by RT is typically recommended.
    - Specifically, our institution treats with induction FFX or Gem/NP for 4–6 months followed by hypofractionated SBRT in patients with BRPC and in resectable patients who may not be able to tolerate adjuvant therapy (comorbid disease or poor performance status).
    - If there is direct invasion of the tumor into the bowel or stomach or there are regional lymph nodes, capecitabine-based CRT is recommended.
    - The goal is to select best surgical candidates and sterilize margins to facilitate a margin-negative resection and sterilization of peripancreatic lymph nodes.
  - More recently, SBRT has emerged as a safe and efficacious alternative to achieve local control and/or improve surgical outcomes in patients who are able to be resected.
- Adjuvant therapy (resected PDA):
  - The use of RT after surgical resection to enhance local disease control is controversial; however, patients resected with positive margins and/or nodes should receive 6 months of adjuvant chemotherapy with or without RT.
  - There are both institutional and regional biases that are prevalent in the literature, with many European centers using adjuvant therapy routinely after surgery, while centers in the United States tend to be more selective [27, 43].
    - One area of conflict involves the lack of standardization in treatment protocols.
    - There are two commonly utilized external beam radiotherapy (EBRT) strategies for standard CRT: three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) delivery.
      - Data on the use of 3D-CRT is ultimately conflicting; most historical trials have focused on the use 3D-CRT protocols with mixed results [27, 43].
    - More recently, both multi-institutional analyses and pooled outcomes data suggest that there may, in fact, be a survival benefit afforded by IMRT [44, 45].
    - It should be noted that in these studies, similar to most in the field, selection bias is difficult to avoid, and its effects on the final results are difficult to quantify.
    - Despite a slight increase in the use of neoadjuvant radiotherapy between 2000 and 2010, overall use (adjuvant plus neoadjuvant) has declined over the last decade [46].
  - For resectable PDA, we typically recommend up-front surgery followed by adjuvant chemotherapy with or without CRT.
    - Adjuvant CRT results in improved local control and improved survival in optimally selected patients [47–49].
    - We recommend CRT after 4–6 months of chemotherapy in patients with a good performance status who have margin- and/or node-positive resections.
- Locally advanced, locally recurrent, and metastatic disease:
  - Multidisciplinary treatment is the cornerstone of therapy for patients with PDA who present with unresectable locally advanced or local recurrent disease after resection.
  - Depending on performance status, mono- or combination systemic chemotherapy may be considered as initial therapy prior to radiation (CRT or SBRT) for appropriate patients with locally advanced, unresectable disease.
  - Patients should be evaluated for recovery from hematologic and non-hematologic toxicity prior to initiation of RT (usually 1–2-week break).
  - Patients who progress with metastatic disease are not candidates for RT unless required for palliative purposes.

  - If resected patients with a good performance status relapse (locally or distantly) after receiving adjuvant gemcitabine or 5-FU monotherapy, FFX or Gem/NP are options depending on the length of time since completion of adjuvant therapy.
    - If the recurrence is local only and unresectable, radiation therapy should be considered.
  - For patients with locally advanced/unresectable and locally recurrent PDA, we treat with induction Gem (poor PFS), Gem/NP, or FFX for 2–12 months followed by definitive CRT or SBRT.
    - Select patients with local obstruction or pain may benefit from up-front CRT or SBRT.
    - Select patients in this group may undergo attempted surgical resection after maximal neoadjuvant therapy and if technically resectable.
    - Clinical (radiographic) response is rare and often does not correlate with pathologic response.
    - Integration of MRI and/or PET/CT may assist in determining clinical response to neoadjuvant therapy.
  - In the setting of LAPC, SBRT has become an option in the neoadjuvant, salvage, and palliative setting with dose adjustment based on goals (Table 7.2).
  - Available salvage therapies include the use of systemic chemotherapy, CRT, and palliative endoscopic or surgical therapies.
    - It is important to prospectively identify the goals of therapy in these patients, as toxicity can become a major life-limiting factor.
    - This is particularly true for patients approaching end-of-life care, as interventions can significantly impact quality of life in both positive and negative ways.
- The use of IMRT in PDA has several potential benefits over conventional 3D-CRT, and many centers are greatly increasing their experience with this modality [31, 50].
  - The advantages of IMRT include precise delivery of high-dose therapy and minimization of gastrointestinal and other regional side effects.
  - One concern regarding the routine use of IMRT is "geographic miss," or a decreased radiotherapeutic dose to an unrecognized area at risk, with subsequent increased rates of local recurrence.
  - Recent analysis from a single high-volume institution, however, suggests that IMRT is associated with minimal gastrointestinal toxicity and provides excellent local control rates (less than 20 % of patients developing local failure alone over a median follow-up of 24 months) [31].

## 7.7 Key Clinical Trials

- A major limitation to the interpretation of key comparative effectiveness trials is the relative lack of standardization in therapies used to treat patients with PDA.
  - This is particularly true in patients who present with resectable disease.
- Large series investigating contemporary outcomes in the treatment of PDA support the notion that outcomes are improving. [51].
- Published experience continues to emphasize superior outcomes (particularly in overall survival) with the use of multimodality therapy; disappointingly, however, progress remains incremental and slow.
  - For example, the European Study Group for Pancreatic Cancer (ESPAC)-3 trial evaluated adjuvant chemotherapy after surgical resection. The study showed no significant difference in overall survival between 5-FU/leucovorin and gemcitabine following surgery [52].
  - While a similar study did achieve statistical significance supporting the use of adjuvant gemcitabine after resection, however, the median survival benefit achieved was only 2 months [53].
- The role of *adjuvant chemoradiation* has not been clearly established.

**Table 7.2** Literature supporting SBRT in the historically definitive, neoadjuvant, and salvage settings for localized pancreatic cancer

| Study | Study design | *N* | Regimen | 1-Year FFLP | Median OS (mos) | Acute grade ≥3 toxicity | Late grade ≥2 toxicity | Resection | R0 resection |
|---|---|---|---|---|---|---|---|---|---|
| *Historically definitive setting* (LAPC) | | | | | | | | | |
| Koong et al. (2004) (Stanford) | Prospective | 6 | 25 Gy SBRT, 1 fraction | 100 % | 8.0 | 33 % | – | – | – |
| Hoyer et al. (2005) (Denmark) | Prospective | 22 | 45 Gy SBRT, 3 fractions | 57 % (6 mo) | 5.4 | 79 % | 94 % | – | – |
| Schellenberg et al. (2008) (Stanford) | Prospective | 16 | Gem ➔ 25 Gy SBRT, 1 fraction ➔ Gem | 100 % | 11.4 | 19 % | 47 % | – | – |
| Chang et al. (2009) (Stanford) | Retrospective | 77[a] | 25 Gy SBRT, 1 fraction | 95 % | 11.9 | 5 % | 13 % | – | – |
| Mahadevan et al. (2010) (Beth Israel) | Prospective database | 36 | Median 30 Gy SBRT, 3 fractions ➔ Gem | 78 % | 14.3 | 41 % | 6 % | | |
| Polistina et al. (2010) (Italy) | Prospective | 23 | Gem ➔ 30 Gy SBRT, 3 fractions | 50 % | 10.6 | 0 | 0 | 9 % | 100 % |
| Schellenberg et al. (2011) (Stanford) | Prospective | 20 | Gem ➔ 25 Gy SBRT, 1 fraction ➔ Gem | 94 % | 11.8 | 15 % | 20 % | – | – |
| Mahadevan et al. (2011) (Beth Israel) | Retrospective | 39 | Gem ➔ median 24 Gy SBRT, 3 fractions ➔ Gem | 85 % | 20 | 0 % | 9 % | – | – |
| Rwigema et al. (2011) (UPMC) | Retrospective | 40 | Median 24 Gy SBRT | 38 % | 8.0[b] | 4 % | 0 % | – | – |
| Goyal et al. (2012) (Case Western) | Prospective database | 20 | Median 25 Gy SBRT, 1 fraction | 65 % | 14.4 | 0 % | 16 % | – | – |
| Tozzi et al. (2013) (Italy) | Retrospective | 30 | Gem ➔ 45 Gy SBRT, 6 fractions | 86 % | 11.0 | 20 % | 0 % | – | – |
| Gurka et al. (2013) (Georgetown) | Prospective | 10 | Gem ➔ 25 Gy, 5 fractions | 40 % | 12.2 | 0 % | 0 % | – | – |
| Herman et al. (2015) (Johns Hopkins, Stanford, MSKCC) | Prospective | 49 | Gem ➔ median 33 Gy, 5 fractions ➔ Gem | 78 % | 13.9 | 12 % | 11 % | 8 % | 100 % |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *Neoadjuvant setting* (BRPC/ LAPC) | | | | | | | | | |
| Boone et al. (2013) (Pittsburgh) | Retrospective | 25 (12 BR, 13 LA) | FOLFIRINOX +/− median 36 Gy SBRT (57 %), 3 fractions | – | – | – | 8 %[c] | 43 % (58 % BR, 15 % LA) | 33 % (55 % BR, 10 % LA) |
| Chuong et al. (2013) (Moffitt) | Retrospective | 73 (57 BR, 16 LA) | Gem-based chemo ➔ median 25 Gy SBRT, 5 fractions | 81 %[d] | 16.4 BR, 15.0 LA | 0 % | 5 %[e] | 44 % (56 % BR, 0 % LA) | 97 % (97 % BR, N/A LA) |
| Rajagopalan et al. (2013) (Pittsburgh) | Retrospective | 12 (7 BR, 5 LA) | Chemo ➔ median 36 Gy SBRT, 3 fractions | – | 47.2 | 0 % | – | 11 %[f] | 92 % (86 % BR, 100 % LA) |
| Mellon et al. (2015) (Moffitt) | Retrospective | 159 (110 BR, 49 LA) | Chemo ➔ median 30 Gy SBRT, 5 fractions | 78 %[d] | 18.1 (19.2 BR, 15.0 LA) | 2 % | 6 %[e] | 38 % (51 % BR, 10 % LA) | 97 % (96 % BR, 100 % LA) |
| Moningi et al. (2015) (Johns Hopkins) | Retrospective | 88 (14 BR, 74 LA) | Chemo ➔ median 33 Gy SBRT, 6 fractions | 61 % | 18.4 13.7 (14.4 BR, 18.4 LA) | 3 % | 6 % | 22 % (29 % BR, 20 % LA) | 84 % (84 % BR, 80 % LA) |
| *Salvage setting (re-irradiation and/or locally recurrent)* | | | | | | | | | |
| Koong et al. (2005) (Stanford) | Prospective | 16 | 5-FU + 45 Gy IMRT ➔ 25 Gy SBRT boost | 94 % | 8.3 | 13 % | – | N/A | N/A |
| Lominska et al. (2012) (Georgetown) | Retrospective | 28 | 50.4 Gy IMRT ➔ median 23 Gy SBRT, 3 fractions | 86 % | 5.9 | 4 % | 7 % | N/A | N/A |
| Wild et al. (2013) (Johns Hopkins, Stanford) | Retrospective | 18 | 50.4 Gy IMRT ➔ median 25 Gy, 5 fractions | 62 % | 8.8 | 0 % | 6 % | N/A | N/A |
| Dagoglu et al. (2016) (Beth Israel) | Retrospective | 30 | Median 50.4 Gy CRT ➔ 25 Gy SBRT, fractions | 78 % | 14.0 | 11 % | 7 % | N/A | N/A |

*BR* borderline resectable, *LA* locally advanced, *Gem* gemcitabine, *IMRT* intensity-modulated radiation therapy

[a]Includes 62 % of patients who were treated for medically inoperable, metastatic, and locally recurrent disease

[b]Estimated from survival curve

[c]Unknown time from SBRT

[d]Includes non-resected patients only

[e]Late grade 2 not reported

[f]Percentage calculated based on the total number of patients who were treated with definitive SBRT (n = 105)

- The Gastrointestinal Tumor Study Group (GITSG) conducted the first prospective randomized trial to demonstrate the benefit of adjuvant CRT. Superior survival was observed in the patients treated with adjuvant CRT as opposed to the patients treated with surgery alone (20 vs. 11 months, $p = 0.03$). Two-year OS was 42 % vs. 15 % in the CRT vs. observation group, whereas 5-year OS was 19 % vs. 5 %, respectively [54].
- The European Organization for Research and Treatment of Cancer (EORTC) performed a subsequent study on surgery alone versus adjuvant 5-FU-based CRT and reported similar results [55]. In the 114 patients with PDA, patients in the CRT arm ($n = 60$) had a median OS of 17.1 months versus 12.6 months in the surgery alone arm ($n = 54$). The 2-year OS for the two trial arms were 37 % versus 23 %, whereas 5-year OS was 20 % versus 10 %, respectively ($p = 0.099$). There were no differences in locoregional recurrence rates, which were high among both the CRT (34 of 104, 33 % of patients at risk) and surgery alone (37 of 103, 36 % of patients at risk) arms [55]. Although survival trends favored adjuvant CRT for the 114 patients with PDA, the trial and statistical analysis were poorly designed and executed and warrant caution in interpretation of the results.
- The randomized phase III ESPAC-1 study evaluated adjuvant chemotherapy versus CRT in patients with grossly resected PDA [56]. Patients underwent randomization to four arms: (A) observation, (B) concurrent CRT alone (20 Gy in ten fractions over 2 weeks with 500 mg/m$^2$ 5-FU IV bolus during the first 3 days of RT and then repeated after a planned 2-week break) followed by no additional chemotherapy, (C) 5-FU/leucovorin chemotherapy alone, and (D) CRT followed by six cycles of adjuvant 5-FU/leucovorin. Adjuvant chemotherapy was associated with superior survival, while adjuvant CRT resulted in inferior survival. Initial analysis demonstrated a survival advantage for adjuvant chemotherapy only by merging data from arms B–D; median OS was 19.7 months with adjuvant chemotherapy and 14 months with no adjuvant chemotherapy ($p = 0.005$) [57]. However, the most recent analysis of the ESPAC-1 trial reported that patients who received adjuvant chemotherapy had a survival advantage versus those who did not (2 years 40 % vs. 30 % and 5 years 21 % vs. 8 %, $p = 0.009$), and the rate of local recurrence was 35 % [56]. These results have also stemmed controversy, as there are also concerns regarding the design and execution of this trial [58].
- The CONKO-001 trial demonstrated significant improvements in disease-free survival and overall survival with the use of postoperative gemcitabine as adjuvant chemotherapy versus observation in resectable pancreatic adenocarcinoma [59].
- ESPAC-3 study results showed no significant difference in overall survival between 5-FU/leucovorin and gemcitabine following surgery. When the groups receiving adjuvant 5-FU/leucovorin and adjuvant gemcitabine were compared, median survival was 23.0 months and 23.6 months, respectively [60].
- Data from ESPAC-4 support the use of gemcitabine combined with capecitabine (1660 mg/m$^2$/d d1–21 q 4 weeks) with superiority demonstrated compared to gemcitabine alone (HR 0.82, 95 % CI 0.68, 0.98, $p = 0.032$).
- The use of gemcitabine-based chemotherapy is frequently combined, sequentially, with 5-FU-based CRT.
- No significant differences were observed in the RTOG 9704 study comparing pre- and post-CRT 5-FU with pre- and post-CRT gemcitabine for postoperative adjuvant treatment [61].
- With the hopes of defining the role of adjuvant CRT, the randomized phase III RTOG 0848 trial (NCT01013649) opened to determine the role of erlotinib added to gemcitabine as well as RT (50.4 Gy) added to 5-FU- or capecitabine-based chemotherapy. This study is ongoing.

• *Borderline resectable pancreas cancer (BRPC)* has not been thoroughly studied in the

prospective setting. However, a recent cooperative group pilot study (A021101) revealed that FOLFIRINOX-based multimodality therapy was shown to be well tolerated [42].
  - Of the 23 enrolled patients, most (96 %) initiated neoadjuvant mFOLFIRINOX and CRT. Median age was 64 years and 64 % had an excellent performance status (ECOG of 0).
  - Fourteen patients (64 %, 95 % CI, 41–83 %) had grade ≥3 toxicity during neoadjuvant therapy. Radiographic response consisted of 2 (9 %) complete response, 4 (18 %) partial response, 14 (64 %) stable disease, and 2 (9 %) progressive disease.
  - Seven patients (32 %) did not undergo planned resection due either to progression ($n$ = 6) or refusal ($n$ = 1), while 15 (68 %, 95 % CI, 49–88 %) patients underwent pancreatectomy. Fourteen (93 %) operations had microscopically negative margins, five (33 %) of which consisted of <5 % residual viable tumor cells and two (13 %) pathologic complete responses. Overall survival of all patients at 18 months was 50 %.
  - The follow-up Alliance study (A021501) is expected to open within the next year with the hopes of comparing survival between neoadjuvant mFOLFIRINOX with or without hypofractionated RT (SBRT or hypofractionated image-guided RT).
- *Locally advanced pancreatic cancer (LAPC)*: Historical studies have shown mixed results with definitive CRT in patients with LAPC.
  - ECOG 4201 randomized patients with LAPC ($n$ = 74) to either gemcitabine alone or gemcitabine-based CRT followed by gemcitabine. Although the study was closed early due to poor accrual, median OS was 11.1 months in the CRT arm versus 9.2 months for those who received Gem alone ($p$ = 0.017) [62].
  - The randomized phase II SCALOP trial ($n$ = 70) evaluated gemcitabine- vs. capecitabine-based CRT in LAPC. The addition of capecitabine was associated with improved 1-year OS, PFS, and less toxicity; however, the results of this trial should be interpreted with caution due to variable treatment planning and dosing techniques [63].
  - The (Groupe Coopérateur Multidiscip linaire en Oncologie) GERCOR LAP 07 trial was designed to establish the role of CRT after chemotherapy in patients with LAPC. The data reveal no significant difference in OS between the two arms (15.2 vs. 16.5 months, $p$ = 0.83). Of note, however, the CRT group was associated with decreased local failure rates (32 % vs. 46 %, $p$ = 0.03).
  - In the locally advanced or metastatic setting, the use of multi-agent chemotherapy is gaining favor over single-agent therapies after several well-conducted randomized trials.
  - The two most commonly selected regimens include gemcitabine with nab-paclitaxel or FOLFIRINOX (Table 7.3).
  - Support for the use of chemotherapy combinations is increasingly being reported from trials in the United States and Europe [67–69].
  - The decision to generalize these findings into other settings, such as neoadjuvant or adjuvant protocols around the time of surgical resection, appears to vary by institution.

## 7.8 Outcomes and Toxicities

- Median overall survival by disease stage is as follows:
  - Resectable disease: median ~21 months. Higher with neoadjuvant therapy likely due to patient selection and with the addition of adjuvant therapy.
  - Borderline resectable disease: median ~18–30 months; however, this varies based on the regimen and patient selection (intention to treat). Limited prospective data.
  - LAPC: historically median survival with chemotherapy with or without CRT ranges between 10 and 20 months. With more aggressive treatment including FFX and Gem/NP with or without CRT or SBRT and surgery, median OS has approached that

**Table 7.3** Summary of select reports of patients with locally advanced pancreatic cancer (LAPC) who received neoadjuvant chemotherapy and radiation therapy followed by surgery

| Study | Surgery N | Neoadjuvant chemo | Radiation type | R0 resection | Med OS or path response |
|---|---|---|---|---|---|
| Moffitt *N* = 159 | BR: 51 LAPC: 5 | GTX 81 % BR FFX 43 % LA | SBRT: all 30–50 Gy/5 Fx | BR: 96 % LAPC: 100 % | 34.2 mos |
| Hopkins *N* = 88 | BR: 4 LAPC: 15 | Mixed | SBRT: all 33 Gy/5 Fx | 84 % | 22 mos |
| MSKCC *N* = 101 | LAPC: 31 | FFX 6 mos | CRT: 50 %[a] | Chemo: 79 % CRT: 33 % | PR: >50 % (75 vs. 22)[b] |
| MGH *N* = 188 | BR: 14 LAPC: 26 | FFX | CRT: 14 CRT/IORT: 10 Neoadj proton: 6 | 92 % | ~32 mos |

Mellon; Moningi; Sadot; Ferrone et al.
[a]75 % Gem based
[b]Favor of CRT

of up-front resectable PDA (>21 months, Table 7.3).
  - Metastatic: OS is improved in those patients who can tolerate multi-agent chemotherapy and is now approaching that of LAPC (~6–12 months). However, it can be lower if patients have a poor PFS or are unable to tolerate systemic therapy due to comorbidities or treatment-related toxicity (< 6 months).
- Common toxicities associated with chemotherapy include fatigue, nausea, vomiting, and pancytopenia as well as associated infections. A common toxicity with FFX and Gem/NP is neuropathy that often increases with increased duration of oxaliplatin (FFX) and NP. It can be very debilitating and can lead to an inability to walk and perform basic activities of daily living [61].
- Although FFX has been shown to initially decrease quality of life due to treatment-related toxicity, it resulted in an overall prolonged improvement in QoL presumably due to disease control [61].
- Toxicities with chemoradiation similarly include nausea, vomiting, and fatigue. Utilization of antiemetics is effective at improving nausea. Ulceration or bleeding due to radiation can occur in patients who do not undergo surgical resection (LAPC or BRPC) but is uncommon following surgery or in the adjuvant settings.
- Ulceration and/or bleeding appears to be more common when the tumor is directly invading into adjacent bowel or stomach [71].
- Adjuvant CRT can result in fibrosis of the bowel and result in a bowel obstruction or stricture.
- Use of proton pump inhibitors for 6 months following SBRT may decrease the risk of ulcers and/or bleeding especially following SBRT [71].
- Outcomes do relate to adherence to best-published guidelines.
  - A recent review of large hospitals in the US state of California found that compliance with National Comprehensive Cancer Network guidelines for treatment is associated with reduced risk of mortality [20].
  - Particularly impactful, as surgical resection remains the only chance for disease cure, is a national "failure to operate" on patients originally presenting with locally confined, clinically node-negative disease [70].
- Studies designed to identify dose-limiting toxicity of IMRT have identified a total dose of 55 Gy to be safe with promising efficacy [71].
  - In 12 of 50 patients, surgical resection was safely carried out after radiotherapy with a median duration of survival increased from nearly 15 months (in the non-resected cohort) to 32 months.
- When considering CRT, experience with LAPC would suggest that hypofractionated SBRT reduces gastrointestinal toxicity with equivalent efficacy in PDA [72].
  - A summary of pancreas SBRT trials can be found in Table 7.2 [73–91].

## 7.9 Future Directions

- While the overall survival of patients with PDA remains poor, select patients with all stages of disease appear to live longer with aggressive multi-agent chemotherapy. However, it is unclear why some patients fail to demonstrate any benefit and/or have dose-limiting toxicity that precludes them from receiving chemotherapy.
- The role of radiotherapy remains debated. However, improvements in the delivery of radiation therapy including SBRT and image guidance (use of fiducials and CT and/or MRI) show exciting preliminary results with minimal toxicity and will be officially evaluated in prospective trials.
- Clinical trials are urgently needed to address these current issues in the clinical management of PDA.
- There are several key clinical questions that frame the future of PDA.
  - What is the role of radiotherapy as an adjunct to local disease control?
  - Is there any role for radiotherapy in the treatment of oligometastatic disease?
  - Is there a role for immunotherapy in PDA and can RT enhance the utility of immunotherapy in all stages of disease?
  - Is personalized medicine in PDA a rational and effective strategy?
  - Will a deeper understanding of the molecular biology lead to more refined and effective targeted agents (Figs. 7.1, 7.2, and 7.3)?

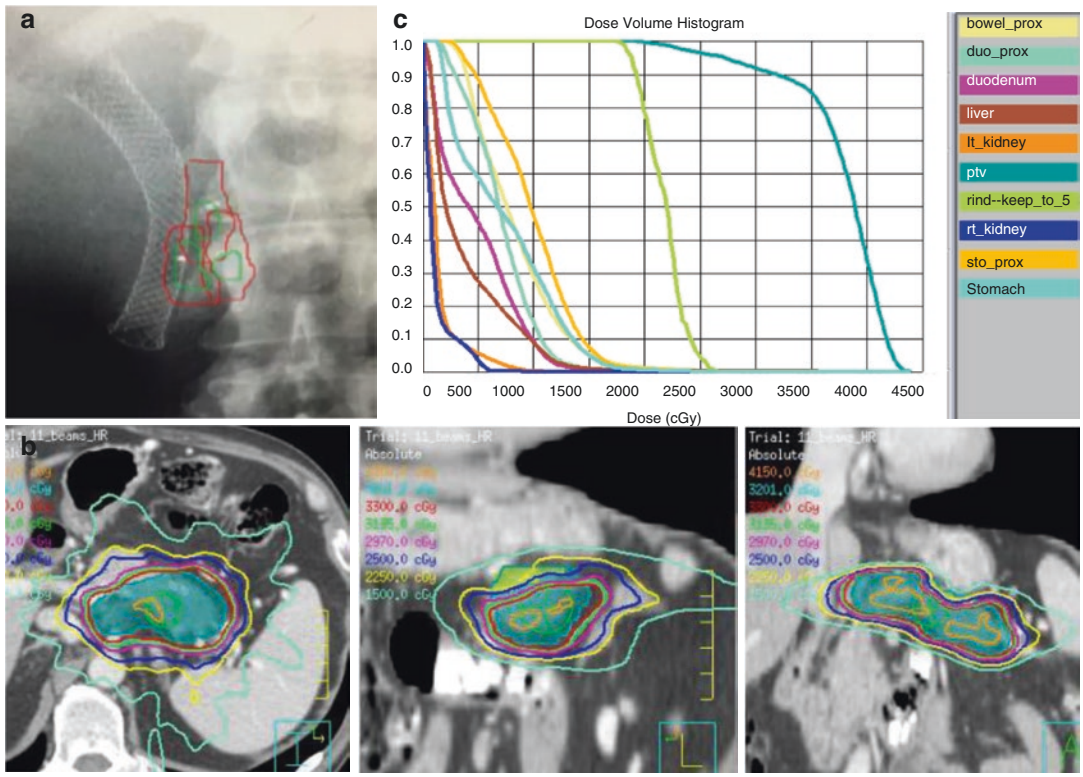


**Fig. 7.1** (**a**) Fluoroscopy demonstrating a biliary stent and gold fiducials in the pancreas tumor with a contour delineating the ITV of the fiducials derived from a four-dimensional computed tomography (4-D CT) scan. (**b**) Stereotactic body radiation plan demonstrating the dose distribution in the axial, sagittal, and coronal planes, respectively. (**c**) Dose–volume histogram (DVH) showing a heterogeneous dose distribution of the pancreatic tumor with the tail approaching 40 Gy in five fractions

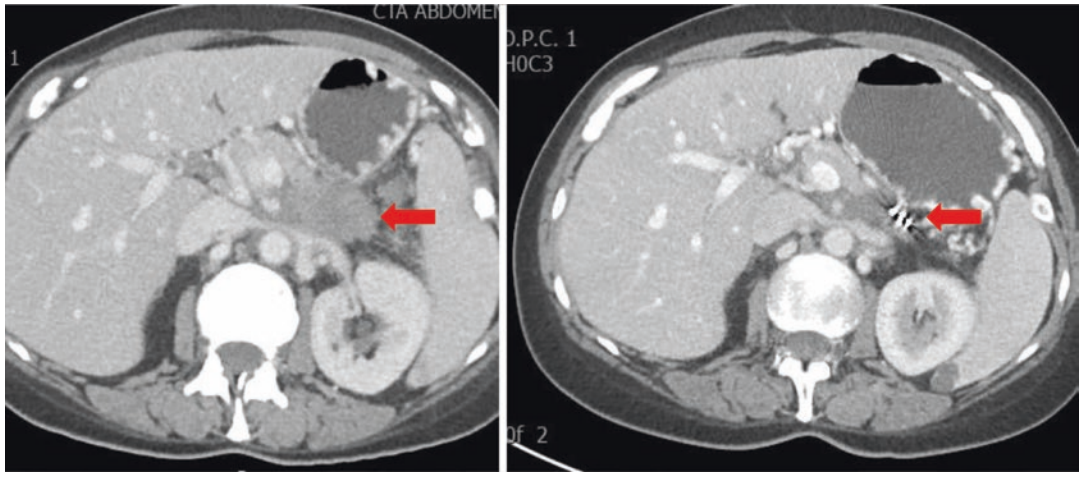


**Fig. 7.2** An example of a locally advanced pancreatic tail tumor following up-front FOLFIRINOX and stereotactic body radiation therapy (SBRT). Patient subsequently underwent a margin-negative resection

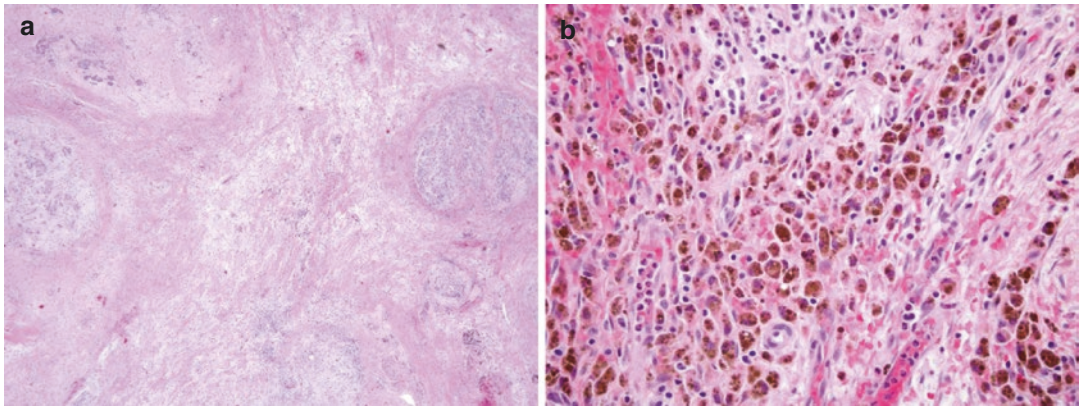


**Fig. 7.3** Pancreatic tumor resection specimen following chemotherapy and stereotactic body radiation therapy (SBRT) showing (**a**) extensive treatment effects and replacement of tumor with fibrosis as well as (**b**) infiltration of hemosiderin-laden macrophages

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# Pancreatic Cancer: Radiation Therapy Planning

8

Ashwin N. Ram, Lauren M. Rosati, and Joseph M. Herman

## 8.1 Principles of Field Design and Patterns of Failure

- Only 10–15 % of patients with pancreatic adenocarcinoma (PDA) are candidates for potentially curative surgical resection. Most present with locally advanced, unresectable (LAPC), or metastatic disease [1, 2].
- Recurrences can occur locoregionally in the resection bed and adjacent lymph nodes or at distant sites most commonly including the liver, peritoneum, lungs, and extra-regional lymph nodes [1, 3, 4].
- In a study performed by Johns Hopkins, patterns of local recurrence in patients with resected pancreatic adenocarcinoma ($n$ = 202) were mapped to inform adjuvant RT planning [5]:
  - Following pancreaticoduodenectomy, patients received no adjuvant therapy ($n$ = 40), adjuvant chemotherapy ($n$ = 34), or adjuvant CRT ($n$ = 128).
  - Local recurrence occurred in 45 % of all patients, in 48 % of those with no adjuvant therapy, 65 % of those who received adjuvant chemotherapy, and 38 % of those who received adjuvant CRT.
  - This study highlights more aggressive therapies are needed to prevent local failure.

## 8.2 Relevant Anatomy

- For the purposes of treatment planning, the pancreas is often categorized into three major parts: the head, body, and tail. The head of pancreas can be further specified into the neck and uncinate process.
- Resectability is based on tumor involvement of adjacent blood vessels.
- Local recurrences typically occur at the uncinate process or superior mesenteric artery (SMA) margin [5].
- The superior mesenteric vein becomes the portal vein (PV) at the bifurcation of the splenic vein.
- The celiac trunk originates at vertebral level T12 and branches into the common hepatic artery, left gastric artery, and splenic artery.

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© Springer International Publishing AG 2017
T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_8

- The superior mesenteric artery originates at vertebral level L1.
- During a pancreaticoduodenectomy (Whipple), the head of the tumor is resected, and anastomoses are made between the jejunum and the pancreas (PJ), stomach (GJ), and liver (HJ) or bile duct (CJ).
- A distal pancreatectomy involves removal of the tail of the pancreas and often the spleen.
- If the tumor involves >180° of the PV or SMV, a venous resection or reconstruction is often necessary [6].
- An Appleby procedure includes resection of the celiac trunk with the tumor. It requires a patent gastroduodenal artery (GDA), which originates at the inferior aspect of the hepatic artery and provides retrograde flow to the liver.

## 8.3 Simulation

- Computed tomography simulation using thin-slice (3 mm) protocol:
  - Patients are simulated supine.
  - An Alpha Cradle (Smithers Medical Products Inc., North Canton, OH, USA) with wing-board (CIVCO Medical Solutions, Coralville, IA, USA) or equivalent immobilization device is used to lift arms out of the field in a reproducible manner.
  - HexaPOD™ Treatment Table robotic localization system or equivalent provides submillimeter 6D conformal positioning accuracy and is used with hypofractionated treatments.
  - IV and oral contrast are used to help to delineate the tumor/tumor bed, lymph nodes, and surrounding organs at risk:
    - Instructing patients to drink 240 cc of oral contrast and to fast 2 h prior to simulation can help to standardize stomach and small bowel volumes in the treatment field.
    - For body/tail lesions adjacent to the stomach, patients are asked to fast without water or contrast to decrease RT dose to the stomach.
  - Surgical clips or endoscopically placed gold markers can assist with motion management of the tumor/tumor bed.
  - Biliary stents can also be used to assist with targeting but have a higher likelihood of shifting and are therefore less reliable.
  - Four-dimensional CT (4D CT) or active-breathing control (ABC) techniques are used to capture tumor excursion:
    - ABC is typically used if there is >3–5 mm of motion in the superior-inferior direction.
  - Motion management during simulation and treatment restricts dose to surrounding organs at risk (OARs)—namely, the duodenum, small and large bowels, stomach, liver, and kidneys:
    - Both inter-fractional (primarily due to setup error) and intra-fractional variation (primarily due to breathing and bowel or stomach distention) are important considerations.
    - Multiple studies demonstrate that the pancreas moves during treatment, especially in the superior-inferior (SI) and anterior-posterior (AP) directions.
    - Reported amplitudes of excursion vary depending on the mode of imaging and the use of voice coaching. Pancreatic excursion in the SI direction has been measured at 0.5–2.4 cm, in the AP direction at 0.16–1.2 cm, and in the LR direction at 0.07–0.6 cm, with 4D CT generally detecting smaller mean motion measurements when compared to other modalities (dynamic or cine magnetic resonance imaging [MRI], fluoroscopy, 3D-CT, cone beam CT) [7–17].
    - For patients with >3 mm breathing motion observed on either fluoroscopy or 4D CT scan, motion management techniques including breath-hold should be used along with target volume tracking.

- For patients with <3 mm of breathing motion, gating may be used, or the patient may be treated free-breathing with an internal target volume (ITV) based on the 0 and 50 % phases of the breathing cycle.

– Image-guided radiation therapy (IGRT) can allow for personalization of nonuniform planning target volumes (PTVs) and can provide a strong framework for motion management in reducing the effects of both inter-fractional and intra-fractional variation:
  - Cone beam CT scans and fluoroscopy can be used for bone and fiducial setup but cannot be used to visualize soft tissue structures including the tumor, bowel, or stomach.
  - Soft tissues can be better visualized with on-board CT on rails or MRI linacs:
    – Respiration-correlated 4D CT images acquired during simulation of 36 LAPC patients with either a biliary stent ($n$ = 16) or implanted fiducials ($n$ = 20) who were treated with real-time position management respiratory-gated IMRT were analyzed [18]:
      - The authors found mean ± SD gross tumor volume (GTV) excursions were 0.3 ± 0.2 cm in the left-right direction, 0.6 ± 0.3 cm in the anterior-posterior direction, and 1.3 ± 0.7 cm in the SI direction.
      - Gating around end exhalation reduced GTV motion by 46–60 %. GTV displacement was best associated with biliary stents and fiducials.
      - These results support the notion that respiratory gating reduces the margin necessary for radiation therapy and validates the use of biliary stents and fiducial seeds as surrogates for daily assessment of GTV position during treatment.
    – Migration of fiducial markers has been reported to be minimal with traditional and Visicoil fiducials [19].

## 8.4 Treatment Techniques

### 8.4.1 Long-Course Fractionation

- Fractionated chemoradiation (CRT) is typically delivered as 30–55 Gy over ~3–6 weeks (1.8–3.0 Gy/fraction) with concurrent oral capecitabine or gemcitabine as a radiosensitizer:
  – In the neoadjuvant setting, RT can be given with 36 Gy in 2.4 Gy fractions with full-dose chemotherapy (usually gemcitabine 1000 mg/m$^2$) or 3 Gy × 10 with concurrent capecitabine.
  – In the definitive or neoadjuvant settings, RT dose generally consists of 45–55 Gy in 1.8–2.2 Gy fractions with concurrent capecitabine or gemcitabine. Doses higher than 55 Gy should be considered on a clinical trial.
  – In the adjuvant setting, RT dose generally consists of 45–46 Gy in 1.8–2.0 Gy fractions to the tumor bed, surgical anastomoses (hepaticojejunostomy and gastrojejunostomy may be omitted if clinically appropriate), and adjacent lymph node basins, followed by an additional 5–9 Gy to the tumor bed and anastomoses, if clinically appropriate [20]. Careful attention to the bowel and stomach is warranted. Escalation above 54 Gy should ideally be avoided or only given when it is possible to limit dose to adjacent small bowel.
  – In the palliative setting, RT dose generally consists of 25–36 Gy in 2.4–5 Gy fractions. Dose and fractionation recommendations should take into account burden of metastatic disease, PFS, comorbidities, and expected survival.
  – An overview of dose constraints is in Table 8.1.

**Table 8.1** Dose constraints for standard chemoradiation

| Structure | Unresectable/neoadjuvant recommendations[a] | Adjuvant/resected recommendations[b] |
|---|---|---|
| Kidney (right and left) | Not more than 30 % of the total volume can receive ≥18 Gy. If only one kidney is functional, not more than 10 % of the volume can receive ≥18 Gy | If two functioning kidneys are present, no more than 50 % of the right and 65 % of the left kidney should receive >18 Gy. For IMRT planning, mean dose to bilateral kidneys should be ≤18 Gy.<br>If only one kidney is present, not more than 15 % should receive ≥18 Gy, and no more than 30 % should receive ≥14 Gy |
| Stomach, duodenum, jejunum | Max dose ≤55 Gy; not more than 30 % of the volume<br>can be between 45 and 55 Gy | Max dose ≤55 Gy; <10 % of each organ volume can receive between 50 and 53.99 Gy. <15 % of each organ volume can receive 45–49.99 Gy |
| Liver | Mean dose cannot exceed 30 Gy | Mean liver dose ≤25 Gy |
| Spinal cord | Max dose to a volume of at least 0.03 cc must be ≤45 Gy | Max dose ≤45 Gy |

Adapted from the National Comprehensive Cancer Network Clinical Practice Guidelines
[a]Adapted from RTOG 0936 (3D conformal, 1.8–50.5) and RTOG 1102 (IMRT, 2.2–55 Gy)
[b]Adapted from RTOG 0848 (3D or IMRT)

- Intensity-modulated radiation therapy (IMRT):
  - IMRT allows for conformal target coverage while minimizing high dose to organs at risk (OARs) [21, 22]:
    - OARs include the stomach, duodenum, bowel, liver, kidneys, and spinal cord.
  - Utilization of intensity-modulated radiation therapy (IMRT) and fiducials should be considered when RT dose is above 55 Gy and when OARs are adjacent or overlapping with the PTV. Placement of fiducials and image-guided radiation therapy with cone beam CT images should also be considered to ensure tumor coverage and avoid OARs.
  - In the adjuvant setting, preoperative diagnostic scans along with the operative note, pathology report, and surgical clips are used to identify areas at risk of residual disease:
    - Tumor bed, peripancreatic elective lymph nodes, and surgical anastomoses (pancreaticojejunostomy, hepaticojejunostomy, gastrojejunostomy) are contoured as the clinical target volume (CTV).
    - If not using breath-hold techniques, an internal target volume (ITV) expansion is placed based on maximum and minimum excursion as defined by 4D CT simulation scans.
    - A planning target volume (PTV) expansion is placed according to physics capabilities and image guidance usage to account for patient setup error and is usually between 0.5 and 1 cm.
    - SBRT in the adjuvant setting has been reported, but data are limited [23, 24].
  - In neoadjuvant, borderline, and locally advanced/unresectable settings, anatomic and functional scans can assist with assessment of gross tumor and involved lymph nodes:
    - GTV is expanded by 5–15 mm to encompass regions at risk for harboring microscopic disease.
    - CTV is expanded to ITV and PTV based on target/breathing motion and image guidance capabilities, respectively.
  - Surgical clips and stents are contoured and expanded by 5 mm to assist with image

guidance during daily setup using cone beam CT.

### 8.4.2 Short-Course Hypofractionation

- Stereotactic body radiation therapy (SBRT):
  - SBRT should be delivered on trial or at experienced centers.
  - SBRT is typically delivered in 3–5 fractions over 1–2 weeks.
  - In the neoadjuvant/definitive/adjuvant settings, SBRT dose generally consists of 25–40 Gy in 5–12 Gy fractions [25].
  - In the palliative setting, SBRT dose generally consists of 25 Gy in 5 Gy fractions.
  - SBRT requires placement of 1–5 (preferably ≥3) fiducial markers for targeting purposes. The fiducial markers are placed directly into the tumor and/or periphery under endoscopic ultrasound (preferred) or CT guidance [26].
  - It is imperative to evaluate the DVH of the PTV and the critical OARs. No clear dose constraints for SBRT exist, but Table 8.2 outlines published dose constraints that have been utilized [27–29].
  - SBRT should be avoided if direct invasion of the bowel or stomach is observed on CT, MRI, or endoscopy as these patients may be at a higher risk of an ulcer or bleeding.
  - GTV is contoured and expanded to ITV, in the absence of breath-hold techniques, or directly to PTV if using ABC.
  - The stomach, duodenum, and bowel are contoured as "proximal organs at risk" and expanded by 2 mm to result in a "proximal OAR + 2 mm" structure.
  - The pancreas PTV expansion is limited by the "proximal OAR + 2 mm" structure to increase the feasibility of delivering high-dose to target volume with rapid dose falloff to adjacent normal tissues (Fig. 8.1).
  - SBRT can be used for re-irradiation of locoregional recurrences, usually with 5 Gy × 5:
    - Three publications have reported on SBRT re-irradiation after an initial median dose of 50.4 Gy CRT.
    - Lominska et al. at the University of Kansas reported on a median of 23 Gy SBRT delivered to 28 previously irradiated patients [30]. Median OS was 5.9 months from SBRT, and local control was 86 %. Late grade 3 GI toxicity was 7 % [30].
    - Wild et al. at Johns Hopkins reported a multi-institutional experience of 18 patients who received re-irradiation [31]. Median OS after SBRT was 8.8 months, and local control was 62 %. Only 1 patient (6 %) experienced a grade 3 GI toxicity.
    - Dagoglu et al. at Beth Israel published on their experience of 30 patients treated with 25 Gy SBRT re-irradiation [32]. Median OS was 14.0 months from SBRT, and local control was 78 %. Late grade 3 toxicity was 7 % and consistent with bowel obstruction.
  - Daily cone beam CT with alignment to bone and shift to fiducials, use of a hexapod, and NPO status with standardized fluid intake 2 h prior to SBRT ensures treatment safety and reproducibility.
- Intraoperative radiation therapy (IORT):
  - The role of IORT is controversial and should only be performed at specialized centers.
  - IORT is delivered with electron beam RT (IOERT) or high-dose-rate brachytherapy (HDR-IORT);
    - An IORT dose of 10–20 Gy is generally delivered in combination with neoadjuvant or adjuvant CRT to 45–50.4 Gy EBRT.
  - It is sometimes used in cases where surgical resection may result in close or involved margins [33].
  - The target volume is determined clinically with feedback from the surgeon(s).

**Table 8.2** Published dose constraints to surrounding organs at risk (OARs) for 3–5 fraction SBRT regimens

| | Mahadevan et al. (2011) | Chuong et al. (2013) | Herman et al. (2015) |
|---|---|---|---|
| SBRT regimen | 8–12 Gy × 3 fractions | *Dose painting technique*: 7–10 Gy × 5 fractions to the region of vessel involvement; 5–6 Gy × 5 fractions to the remainder of the tumor | 6.6 Gy × 5 fractions |
| Disease stage | LAPC | BRPC and LAPC | LAPC |
| kidney (right and left) | 75 % < 12 Gy | Mean < 10 Gy | 75 % < 12 Gy |
| Stomach, duodenum, jejunum | Dmax < 10Gy/fraction | Dmax 35 Gy<br>Mean < 20 Gy<br><5 cc < 30 Gy<br><1 cc < 35 Gy | 9 cc < 15 Gy<br>3 cc < 20 Gy<br>1 cc < 33 Gy |
| Liver | 30 % < 15 Gy | 10 % < 30 Gy | 50 % < 12 Gy |
| Spinal sord | Maximum 12 Gy | Maximum 20 Gy | 1 cc < 8 Gy |
| PTV/GTV coverage | Rx isodose line covers ≥95 % of the PTV<br>A 5 mm or smaller expansion margin (extending up to the outer bowel wall) was included to determine the final planning target volume. Elective nodes not included | GTV to PTV expansion is 3 to 5 mm and treated in 25 to 30 Gy while simultaneously delivering 35 to 50 Gy delivered to the tumor vessel interface. Elective nodes were not included to limit dose to nearby normal structures | No more than 1 cc of the mPTV received >130 % of the prescription dose (49.2 Gy) and >90 % of the modified PTV received 100 % of the prescription dose (33 Gy). If these constraints could not be met, then 100 % of the GTV received ≥25 Gy |

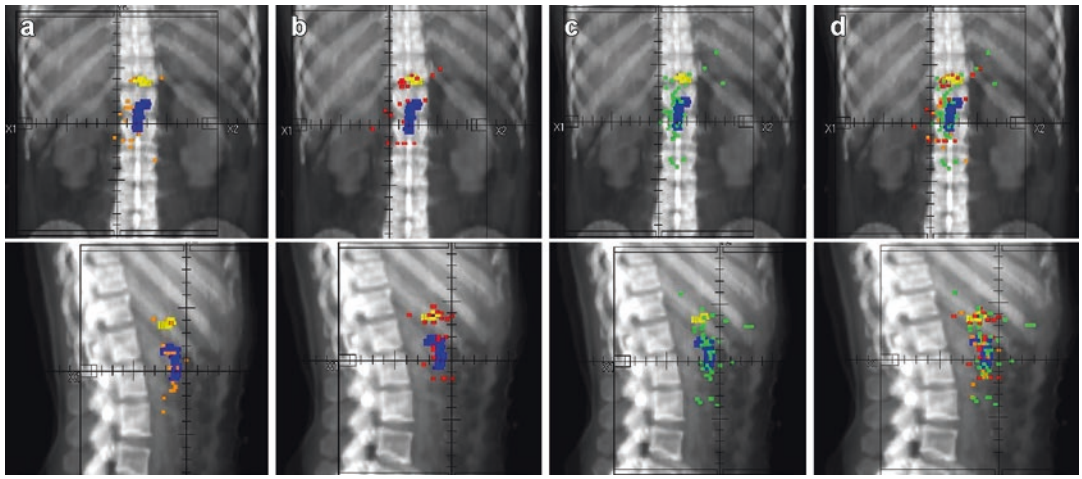


**Fig. 8.1** Anterior-posterior (*top*) and lateral (*bottom*) views of local recurrence plots for (**a**) surgery alone (*orange*), (**b**) chemotherapy (*red*), (**c**) chemoradiation (*green*), and (**d**) all groups. The celiac artery (*yellow*) and superior mesenteric artery (*blue*) are contoured (Adapted from Dholakia et al. IJROBP 2013*)*

  - Areas at high risk for recurrence typically include the uncinate and/or SMA margin. These are determined at the time of surgery:
    - A 1–2 cm margin should be placed around the area at risk.
    - Ideally, the area treated should be photographed and mapped out with surgical clips to determine if the recurrence was within the irradiated field.
  - All normal structures should be displaced and/or shielded with lead from the IORT field.
  - The most critical OARs include the bowel and anastomoses if a bypass is performed.
  - The target volume may include the tumor and peripancreatic lymph nodes with IOERT:
    - Specialized treatment planning tools are needed for IOERT.
- Proton beam therapy (PBT):
  - Proton therapy takes advantage of the Spread Out Bragg Peak to deposit high-dose RT into the at-risk areas while minimizing exit dose, thereby increasing the therapeutic window.
    - Hong et al. performed a phase I/II study of preoperative short-course PBT and capecitabine for resectable pancreatic cancer at the Massachusetts General Hospital [34]:
      - Thirty-five patients were treated in phase II with a dose of 25 GyE in five fractions.
      - Only two (4 %) experienced a grade ≥3 toxicity.
      - Eleven of 48 patients (22 %) did not undergo resection.
    - Median OS and 2-year OS rate were 17.3 months and 42 %, respectively. For the 37 resected patients, median OS was 27.0 months, and locoregional failure and distant metastases occurred in 16.2 % and 73 %, respectively. The effectiveness of PBT for LAPC was reported from two institutions, but no published reports describe long-term outcomes. Further investigations are needed to evaluate long-term impact of PBT on survival because the median follow-up period was limited to 1 year in both these reports [35, 36].
  - Numerous studies have compared dosimetric data among patients receiving PBT:
    - Hsiung-Stripp et al. demonstrated the ability of 130–180 MeV protons to effectively treat LAPC [37]. PBT significantly reduced doses to the spinal cord ($p = 0.003$) and left kidney ($p = 0.025$) when compared to photons.
    - Kozak et al. demonstrated the dosimetric feasibility of hypofractionated PBT for neoadjuvant therapy using anatomical data from nine patients [38]:
      - PBT offered a significant reduction of dose to the liver, kidneys, and small bowel—particularly in the low-dose regions in comparison with IMRT.
    - Lee et al. explored the feasibility of using PBT in the neoadjuvant setting to cover a planning target volume including gross disease and regional lymph nodes [39].
    - Ding et al. compared passively scattered and modulated scanning PBT to a number of photon-based strategies including 3D conformal radiation therapy (3DCRT), 5-field IMRT, and 2-arc volumetric-modulated radiation therapy [40]:
      - PBT was associated with lower doses to the kidneys, stomach, liver, and bowel.

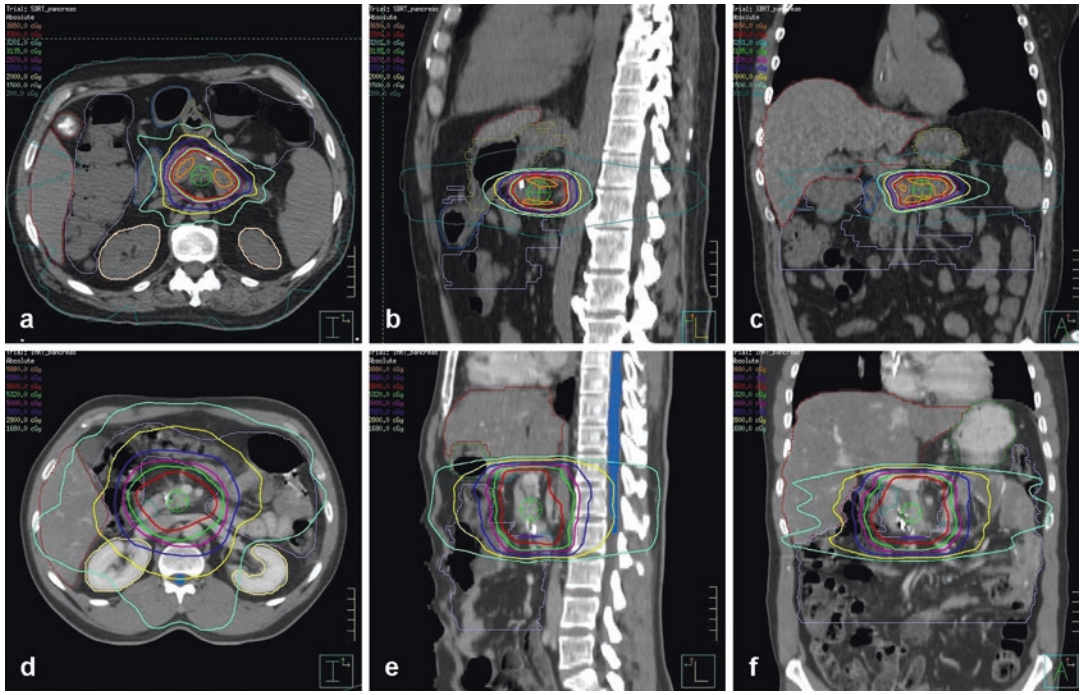


**Fig. 8.2** Treatment volumes and dosimetry comparing stereotactic body radiation therapy (SBRT) and intensity-modulated radiation therapy (IMRT)

  - Thompson et al. compared PBT and IMRT plans in 13 patients with LAPC of the pancreatic head [40]:
    - Both double-scattered and pencil-beam proton plans decreased gastric, duodenal, and small bowel dose in the low-dose regions in comparison to IMRT; however, PBT was associated with increased dose in the mid- to high-dose regions.
- It remains to be seen how PBT for PDA translates clinically; it is unknown whether the reduction of normal tissue exposure leads to differences in acute and late toxicities.
- Limitations and uncertainties of PBT include:
  - Range or depth of a proton beam is dependent on coulombic interactions with electrons in constituent atoms of different tissues:
    - Proton range is significantly greater in air than in tissue; changes in bowel gas may affect the beam range, leading to potential under-coverage of the target or overdose of normal tissue structures (Figs. 8.2 and 8.3).

## Conclusions

- Radiation therapy has become increasingly more conformal with advances in technology that permit high dose to target structures while limiting radiation to surrounding normal tissues.
- IMRT has been established as a standard for radiation treatment.
- SBRT and proton therapy may improve the therapeutic window of radiation therapy, but are still investigational at this time.
- As techniques continue to evolve, improved target coverage and reduced treatment-related toxicities may lead to disease eradication with minimal impact on patient quality of life.

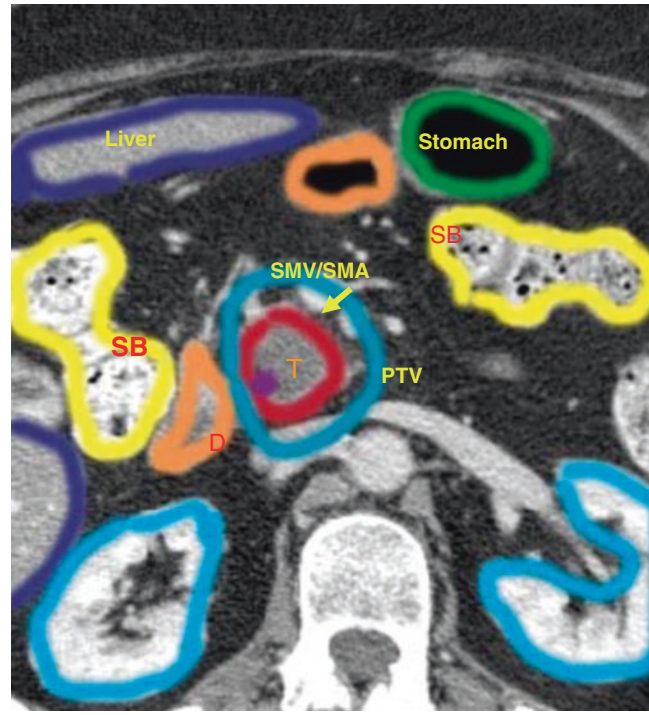


**Fig. 8.3** Axial slice outlining the gross tumor volume (GTV), planning target volume (*PTV*), stomach, duodenum, small bowel, liver, superior mesenteric artery/vein, and fiducials

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# Primary Liver Cancer: Background and Clinical Evidence

9

Florence K. Keane and Theodore Hong

## 9.1 Introduction

- In the year 2016, it is estimated that there will be 39,230 diagnoses and 27,170 deaths from liver and intrahepatic bile duct cancer in the United States [1].
  - Hepatocellular carcinoma (HCC) accounts for the vast majority of these cases.
- Worldwide, HCC is the second leading cause of cancer deaths, with approximately 782,500 new diagnoses and 745,000 deaths from liver cancer each year [2].
  - The majority of cases occur in developing nations [2], but the incidence of HCC in the United States has been steadily increasing over the past 30 years [3].
  - The incidence of intrahepatic cholangiocarcinoma (ICC) has also increased over the past 20 years [4, 5].

## 9.2 Epidemiology and Risk Factors

### 9.2.1 HCC

The risk factors associated with HCC vary by region. Cirrhosis (due to viral, alcoholic, or other etiologies) is associated with the majority of cases (80 %).

- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- Coinfection with HIV in patients with HCV or HBV infection
- Alcoholic cirrhosis
- Additional risk factors include:
  - Nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease
  - Diabetes, in the setting of a metabolic syndrome (which may cause or contribute to NASH)
  - Alpha-1 antitrypsin deficiency, hereditary hemochromatosis, Wilson's disease, autoimmune hepatitis, and exposure to toxins including aflatoxin $B_1$

### 9.2.2 ICC

While there are documented risk factors for ICC, many patients will not have a clear associated risk factor identified.

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© Springer International Publishing AG 2017
T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_9

- Primary sclerosing cholangitis, which may be associated with ulcerative colitis
  - Lifetime risk of developing ICC is 10–15 % [6], with estimated annual risk of 1.5 % [7].
- Liver damage in the setting of hepatitis or cirrhosis
- Fibropolycystic liver disease
- Parasitic infection with *Opisthorchis viverrini* or *Clonorchis sinensis*

## 9.3 Screening

### 9.3.1 HCC

- Surveillance recommendations are based on data from patients with HBV cirrhosis. There are no randomized data in patients with HCV cirrhosis or other etiologies of cirrhosis.
- The American Association for the Study of Liver Disease (AASLD) recommends HCC surveillance in patients with cirrhosis, select HBV carriers, and patients with coinfection with HCV/HBV and HIV.
- Surveillance techniques:
  - AASLD recommends hepatic ultrasound every 6 months (sensitivity 63–94 %) [8].
  - NCCN recommends hepatic ultrasound and serum alpha-fetoprotein (AFP) every 6 months.
- In patients with an abnormal finding identified on surveillance imaging, three-phase CT or MRI is recommended.
  - For single nodules < 1 cm, repeat imaging every 3–6 months is recommended, with further workup and treatment for enlarging lesions.
  - For nodules ≥ 1 cm, the presence of two classic enhancement characteristics (arterial enhancement and rapid venous phase washout) confirms the diagnosis of HCC (OPTN Class V). For lesions which do not exhibit classic enhancement features, repeat imaging is recommended.
    - Biopsy is not recommended for diagnosis in OPTN Class V lesions.
    - Biopsy can be considered in tumors which on repeat imaging again fail to demonstrate both classic enhancement patterns.

### 9.3.2 ICC

- There are no standard screening recommendations for high-risk populations, although some institutions screen patients with primary sclerosing cholangitis with serial imaging and serum CA19-9 levels [7, 9].
- In patients presenting with symptoms concerning for cholangiocarcinoma, including weight loss, jaundice, and right upper quadrant pain, workup should consist of serum chemistries, liver function tests, CA19-9, CEA, and AFP.
- Imaging options include MRI/MRCP, although diagnosis can be challenging in patients with benign biliary strictures in the setting of primary sclerosing cholangitis.
  - ERCP with bile duct brushings may help differentiate between benign and malignant strictures.

## 9.4 Pathology

### 9.4.1 HCC

In patients with underlying cirrhosis, HCC is thought to arise from dysplastic nodules which progress from well-differentiated tumor cells with similar appearance to hepatocytes to poorly differentiated infiltrating lesions characterized by pleomorphism, nuclear atypia, and neovascularization. Tumor cells most often appear in a trabecular pattern, although this can be lost in poorly differentiated lesions [10].

- On immunohistochemical stains, HCC often stains positive for hepatocyte paraffin 1 antigen (Hep Par-1), AFP, polyclonal CEA (pCEA), and CD10 and stains negative for CK7, AE1–3, CK19, EMA, and mucin.

  - Hep Par-1 may be used to differentiate HCC from hepatic metastases.
- Variants of HCC include sarcomatous HCC, scirrhous HCC, clear-cell variant HCC, steatohepatic HCC, and fibrolamellar HCC.

### 9.4.2 ICC

The majority of cholangiocarcinomas are adenocarcinomas.

- The Liver Cancer Study Group of Japan classified ICC based on macroscopic tumor appearance into mass-forming, periductal-infiltrating, and intraductal growth type [11]. Lesions may fall into one or more categories depending on involvement of biliary ducts and hepatic parenchyma.
  - Mass-forming (MF) type: well-defined localized lesions in hepatic parenchyma.
  - Periductal-infiltrating (PI) type: mass extending along biliary ducts which may involve adjacent hepatic parenchyma.
  - Intraductal growth (IG) type: papillary form, involving the lumen of biliary ducts, may present as ductal dilatation or tumor thrombus.
- On immunohistochemical stains, ICC cells will often stain positive for mucin, CEA, CAM5.2, CK 7, and CK 19 and negative for AFP and Hep Par-1.

Mixed hepatocellular cholangiocarcinomas comprise 1–4 % of primary liver neoplasms, with histologic appearances consistent with both HCC and cholangiocarcinoma.

- Unlike patients with HCC, these patients may have minimal elevation in serum AFP.

## 9.5 Staging

### 9.5.1 HCC

Assessment of prognosis in HCC is complicated, as patients face significant mortality risks from not only the tumor but also underlying compromised hepatic function. There are several staging systems for HCC, with variable focus on the extent of the tumor, regional or distant metastases, hepatic function, and performance status. The optimal staging system for a given patient also depends on which, if any, therapies they are candidates for.

- The American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) staging system [12] accounts for tumor size, the presence of solitary vs. multiple tumors, vascular invasion, invasion of adjacent organs, regional lymph node involvement, or metastatic disease. The fibrosis score (none or moderate fibrosis vs. severe fibrosis or cirrhosis) has been incorporated into the AJCC/TNM system but is not used to determine overall stage.
  - The AJCC TNM staging system has been validated in patients undergoing orthotopic liver transplantation [13].
- The Barcelona Clinic Liver Cancer (BCLC) staging classification system [14] stratifies patients by performance status, Child-Pugh cirrhosis score, and size and extent of the primary tumor. The BCLC algorithm also recommends treatment options based on a given patient's stage.
  - Very early stage (0) is defined as a single lesion < 2 cm in a patient with an ECOG PS of 0 and Child-Pugh A cirrhosis.
  - Early stage (A) includes patients with a single lesion or three nodules measuring < 3 cm in patients with an ECOG PS of 0 and Child-Pugh A or B cirrhosis.
  - Intermediate stage (B) is comprised of patients with large multinodular tumors, ECOG PS of 0, and Child-Pugh A or B cirrhosis.
  - Advanced stage (C) includes tumors with portal invasion, extrahepatic spread, and/or patients with ECOG PS 1–2 and Child-Pugh A or B cirrhosis.
  - Terminal stage (D) consists of patients with an ECOG PS of 3–4 and Child-Pugh C cirrhosis.

- Okuda system [15]: The Okuda system divides patients into three stages (I, II, III) based on tumor size (ratio of tumor size to liver area), ascites (clinically detectable vs. absent), serum albumin (<3 mg/dl vs. >3 mg/dl), and serum bilirubin (>3 mg/dl or <3 mg/dl).
  - Does not include vascular invasion or lymph node involvement
  - Validated in patients who did not receive treatment
- CLIP score [16, 17]: The CLIP scoring system divides patients into categories (score 0–6) based on Child-Pugh score, the number of tumor nodules and extension through the liver, serum alpha-fetoprotein (AFP) level (<400 or ≥400 ng/ml), and the presence or absence of portal vein thrombosis.
  - For patients with HCC who were treated with TACE, the CLIP system provided the best estimate of overall survival when compared with other classification systems including the Okuda system, the BCLC system, the Japanese Integrated Staging (JIS) system, the Child-Pugh score, and the model of end-stage liver disease (MELD)-modified CLIP system and JIS system [18].

### 9.5.2 ICC Staging

- AJCC TNM staging for ICC is based on the number and extent of the primary tumors (including the presence of vascular invasion and invasion into extrahepatic structures) and the presence of nodal or distant metastases.
  - Staging system does not include tumor size. Tumor size was not found to be a significant predictor of OS in a SEER analysis of 598 patients who underwent resection for ICC [19].

## 9.6 Prognostic Factors

- Hepatic function (Table 9.1)
  - Child-Turcotte-Pugh classification
    - Assigns scores based on serum albumin, serum bilirubin, serum prothrombin time, the presence of ascites, and the presence of encephalopathy (scores 5–15) to stratify patients into three overall categories (Child-Pugh classes A, B, and C) (Table 9.2)
    - Initially developed as a predictor of perioperative mortality in patients with esophageal varices [20, 21]
  - Model of end-stage liver disease (MELD)
    - Based on serum bilirubin, serum INR, and serum creatinine.
    - Developed as a predictor of survival after elective transjugular intrahepatic portosystemic shunt (TIPS) placement [22].
      - Felt to be more accurate than the Child-Pugh score as a predictor of short-term mortality after transjugular intrahepatic portosystemic shunt [23]. Also more accurate as a predictor of 3-month mortality among patients on the Organ Procurement and Transplantation Network (OPTN) wait list [24]
    - In 2002, the MELD score replaced the Child-Turcotte-Pugh score as the system employed by the United Network for Organ Sharing (UNOS) to assign priority for liver transplantation in the United States.
  - Albumin-bilirubin (ALBI) grade [25] employs only albumin and bilirubin levels to divide patients into three grades (A1, A2, and A3) to predict survival in HCC patients.
    - Developed using data from patients with HCC from Japan and validated using international databases and data from two randomized trials of sorafenib for unresectable HCC
    - Divided patients with Child-Pugh A cirrhosis into two prognostically distinct cohorts, with a 6-month difference in overall survival between ALBI grade 1 and ALBI grade 2 patients

**Table 9.1** Hepatic function classification systems

| | Child-Pugh (CP) score | MELD score | ALBI grade |
|---|---|---|---|
| Prognostic factors included in model | Total bilirubin (mg/dL)<br>INR<br>Albumin (g/dL)<br>Ascites<br>Hepatic encephalopathy | Total bilirubin (mg/dL)<br>INR<br>Creatinine (mg/dL)<br>Hemodialysis twice during prior week<br>Serum sodium (mEq/L) | Total bilirubin (μmol/L)<br>Albumin (g/L) |
| Additional factors contributing to overall score | | Diagnosis of HCC tumor(s) within Milan criteria<br>Time on transplant list | |
| Score calculation | See Table 9.1 B | MELD = 10 × [0.957 × ln(creatinine)] + [0.378 × ln(bilirubin)] + [1.12 × ln(INR)] +6.43.[a] | Linear predictor (ALBI grade) = ($\log_{10}$ bilirubin × 0.66) + (albumin × −0.085) |
| Risk categories | CP A: 5–6 points<br>CP B: 7–9 points<br>CP C: 10–15 points | MELD ≤10<br>MELD 11–18<br>MELD 19–24<br>MELD ≥25 | ALBI grade 1: ≤−2.60<br>ALBI grade 2: >−2.60 - ≤−1.39<br>ALBI grade 3: >−1.39 |

[a] Hyponatremia can be an important marker of the severity of cirrhosis and portal hypertension. As of January 2016, UNOS now uses the MELD-Na score, which is the MELD score adjusted for serum sodium (MELD Na = MELD score – (serum Na) – [0.025 x MELD × (140 – serum Na)] + 140)

**Table 9.2** Child-Turcotte-Pugh classification of cirrhosis

| | 1 point | 2 points | 3 points |
|---|---|---|---|
| Total bilirubin (mg/dl)[a] | <3.4 | 3.4–5.0 | >5.0 |
| INR | <1.7 | 1.7–2.3 | >2.3 |
| Albumin (g/dl) | >3.5 | 2.8–3.5 | <2.8 |
| Ascites | None | Mild | Moderate–severe |
| Hepatic encephalopathy | None | Medically controlled | Refractory |

[a] Bilirubin levels are classified differently for patients with primary biliary cirrhosis or primary sclerosing cholangitis

## 9.7 Molecular Biology

### 9.7.1 HCC

While HCC often develops in the setting of progression from cirrhosis to dysplastic nodules to invasive carcinoma, the mechanisms underlying this process are not yet fully elucidated.

- Altered expression of *mTOR*, inactivation of p53, loss of heterozygosity in IGF2 receptor, and disruption of the Ras/MAPK pathway, the Rb pathway, the PI3-kinase/Akt pathway, and the Wnt/beta-catenin pathway have all been demonstrated in HCC [26].
  - Studies have also attempted to classify mutation expression by cirrhosis etiology. A study of exome sequencing of 243 liver tumors identified mutations associated with alcohol use (*CTNNB1*) or HBV (*TP53*) [27].

### 9.7.2 ICC

- Molecular profiling has demonstrated features distinguishing intrahepatic cholangiocarcinoma from extrahepatic cholangiocarcinoma, including increased rates of *IDH1* and *IDH2* mutations in ICC [28]. Further study is needed to elucidate the specific mutational patterns associated with ICC [29].

## 9.8 Multidisciplinary Treatment

### 9.8.1 HCC

Management of HCC depends not only on the size and extent of the hepatic lesion but also on a patient's hepatic function and performance status.

- Early-stage HCC: Early-stage HCC includes patients with smaller tumors with adequate underlying hepatic function, a sufficient volume of uninvolved liver, and no evidence of vascular invasion or extrahepatic disease. Curative treatment options for early-stage HCC include surgical resection, orthotopic liver transplantation, and radio-frequency ablation for small tumors.
  - Surgical resection: preferred in patients with solitary tumors without vascular invasion without underlying cirrhosis and with a sufficient volume of uninvolved hepatic parenchyma
    - In patients with solitary tumors < 5 cm without vascular invasion, 5-year overall survival (OS) rates range from 60 % to 83 % [30]. Survival declines in patients with larger tumors, multiple tumors, and/ or vascular invasion [31].
    - There is a significant risk of recurrence, with predictors of recurrence after resection that include tumor size, number of tumors, margin status, vascular invasion, histologic grade, and underlying cirrhosis [31].
    - The role of adjuvant treatment after resection is not well defined. The randomized phase III STORM trial did not demonstrate an improvement in outcomes with the use of sorafenib after resection or ablation [32].
      - Randomized 1114 patients with HCC who had undergone surgical resection ($n$=900) or ablation ($n$=214) with a complete radiographic response to adjuvant sorafenib versus placebo.
      - There was no difference in median recurrence-free survival between the two arms (33.3 months with sorafenib vs. 33.7 months with placebo, HR 0.94, 95 % CI 0.78–1.13, one-sided $P$=0.26).
    - There is suggestion that antiviral therapy after resection in patients with HBV-related HCC may improve outcomes [33], but further study is needed.
  - Orthotopic liver transplantation (OLT).
    - Preferred treatment option in patients with unresectable HCC with underlying cirrhosis or compromised hepatic function.
    - Criteria for OLT: UNOS defines eligibility for organ transplantation as patients who fit with the Milan criteria on radiographic assessment, with no evidence of vascular invasion or extrahepatic disease.
      - MELD points are assigned based on underlying hepatic and renal function, with additional points included for the presence of HCC and time spent on the OLT waiting list.
      - Milan criteria: one tumor < 5 cm or three tumors all < 3 cm.
        - Based on a trial of 48 patients with HCC in the setting of HCV/ HBV cirrhosis who underwent OLT between 1991 and 1994
          - In patients whose explanted tumors met the above criteria, 4-year OS was 75 %, and 4-year DFS was 83 %, while in patients whose tumors exceeded this criteria, 4-year OS was 50 %, and 4-year DFS was 59 % [34].
      - Beyond Milan criteria
        - UCSF criteria: one tumor < 6.5 cm or maximum of three tumors all < 4.5 cm with cumulative size < 8 cm
          - Based on UCSF review of 467 patients who underwent OLT for HCC between 1984 and 2006 [35].

  - There was no significant difference in 5-year OS for patients who met Milan criteria versus those patients who exceeded Milan criteria but met UCSF criteria by explant pathology (86 % vs. 81 %, $P$=0.057).
- "Up-to-seven" criteria: sum of the size of the largest tumor (cm) + the number of tumors ≤ 7 [36]
  - Retrospective review of 1556 HCC patients undergoing liver transplantation suggested that microinvasion and accounting for the size and number of tumors could potentially identify patients outside Milan criteria who were candidates for OLT.
  - Included 1112 patients exceeding Milan criteria, with reduced 5-year OS of 53.6 % compared with 77.7 % in patients meeting Milan criteria.
  - However a subgroup of 238 patients who exceeded Milan criteria but did not have microinvasion and were within "up-to-seven" criteria had 5-year OS of 71.2 %.

- Due to long waiting times, 12–38 % of patients will drop off the transplant list within 1 year due to tumor progression or functional decline [37]. Whether patients should proceed with resection instead is a topic of debate and varies based on the patient's overall performance status and underlying hepatic function.
  - Intention-to-treat analysis of resection versus transplantation found that the survival of patients listed for transplantation declined as the wait list times for transplant increased (84 % from 1989 to 1995 versus 54 % from 1996 to 1997), likely due to increased numbers of patients who dropped off the transplant wait list during the latter era [38].
  - There are limited data on transplantation after surgical resection, with some studies suggesting that there was not a significant increase in toxicity [39]. Of note, "salvage transplantation" or transplant in the setting of recurrence after resection may be associated with increased toxicity.
    - Retrospective comparison of patients receiving primary liver transplantation versus transplantation in the setting of recurrence ("secondary" transplantation) after resection demonstrated that secondary OLT was associated with increased operative mortality, increased recurrence, and decreased disease-free and OS [40].
  - Ablative therapies include radio-frequency ablation (RFA), microwave ablation (MWA), and chemical ablation (percutaneous ethanol injection).
    - Effective therapy in the treatment of smaller tumors (< 4 cm) and as a bridge to transplantation.
    - Potential curative therapy in tumors < 2 cm.
    - Local control declines in tumors which are close to large blood vessels and larger lesions.
    - Randomized trials of resection versus RFA conducted in China between 1999 and 2008 randomized patients showed mixed results. One trial of 230 patients with tumors that fit within the Milan criteria demonstrated an improvement in OS and recurrence-free survival (RFS) with resection compared with RFA (OS, 82.6 % vs. 66.1 %; RFS, 60.9 % vs. 46.1 %) [41]. Two additional trials did not demonstrate an improvement in OS or RFS with resection over RFA [42, 43].

  - A meta-analysis of resection versus RFA did not show an improvement in recurrence but did demonstrate an improvement in survival with resection [44].

- Advanced HCC: For patients with unresectable HCC who are not candidates for transplant, treatment options include ablation (described above), arterially directed therapies, radiotherapy, and systemic therapy.
  - There are no randomized data directly comparing these techniques.
  - Selecting an optimal treatment for a given patient depends on multiple factors including:
    - Hepatic function
    - Performance status
    - Tumor characteristics
      - Size and number of tumors
      - Tumor location
      - Vascular invasion
  - Arterially directed therapies include bland embolization, transarterial chemoembolization (TACE), and transarterial radioembolization (TARE).
    - Arterially directed therapies exploit the blood supply of HCC, which is primarily supplied by the hepatic artery as compared to normal hepatic parenchyma which is primarily supplied by the portal vein.
    - Arterially directed therapies, including TACE, have been shown to improve palliation and survival when compared with supportive care [45–47], but there are no randomized trials of arterially directed therapies versus ablative techniques or radiotherapy.
    - Arterially directed therapies are also often not possible in patients with tumor vein thrombosis due to the risk of treatment-related ischemic injury and hepatic failure.
      - Although TARE or selective internal radiotherapy (SIRT) is thought to function via microvascular rather than primarily macrovascular occlusion, outcomes still decline in patients with thrombosis or compromised hepatic function [48].
    - Combination of arterially directed therapies with systemic and other locoregional therapies is an ongoing topic of research.
      - The SPACE (Sorafenib or Placebo plus TACE with doxorubicin-eluting beads for Intermediate Stage HCC) trial [49] showed that the combination of TACE with sorafenib was technically feasible but did not demonstrate an improvement in time to progression with the addition of sorafenib to TACE in patients with intermediate-stage HCC without macrovascular invasion or extrahepatic disease. Phase III trials are ongoing.
      - Multiple series have explored the use of arterially directed therapies in conjunction with RT. RT is discussed in further detail below.
  - Radiotherapy
    - Radiotherapy was historically relegated to the palliative setting; however, the development of modern RT techniques, including intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT), has enabled safe and effective delivery of ablative doses of radiotherapy to tumors while sparing uninvolved hepatic parenchyma.
    - RT has been safely used to treatment numerous patients with HCC, ranging from patients with small tumors who are not operative candidates to patients with large tumors or tumor venous thrombosis. Much of the original data of RT included patients who previously failed arterially directed therapies [50].
      - A series of dose-escalation protocols of hyperfractionated conformal RT with concurrent arterial chemotherapy at the University of Michigan demonstrated the feasibility of liver-directed

RT and provided a framework for assessing the optimal RT dose while minimizing the risk of hepatotoxicity.
    - The series included 128 patients (47 with liver metastases, 35 patients with HCC, and 46 patients with cholangiocarcinoma). Median OS was 15.2 months in patients with HCC and 13.3 months in patients with cholangiocarcinoma.
    - Tumor dose ≥ 75 Gy was predictive of improved overall survival on multivariate analysis (23.9 months vs. 14.9 months, p<0.01) [51].
- Multiple phase I and II prospective single-arm trials and retrospective series have shown impressive local control and survival outcomes, particularly with SBRT and hypofractionated RT, with 1-year OS rates of 48–100 % and 1-year local control rates of 64–100 % [52].
    - Prospective phase I and II trials of 102 HCC patients treated at Princess Margaret Hospital with SBRT reported an overall response rate of 54 %, 1-year local control rate of 87 %, and 1-year OS rate of 55 % [53].
    - Prospective phase II trial of 92 patients with HCC or ICC treated at Massachusetts General Hospital and MD Anderson Cancer Center with hypofractionated proton therapy reported a 2-year local control rate of 94.8 % and 2-year OS rate of 63.2 % for patients with HCC [54].
        - There were low rates of toxicity, with four patients (4.8 %) experiencing grade ≥3 toxicity and only three patients (3.6 %) experiencing a decline in Child-Pugh score from CP A to CP B cirrhosis.
    - The University of Tsukuba reported the largest series of liver-directed proton therapy, consisting of 318 patients with HCC and primarily CP A cirrhosis (73.6 % of patients had CP A cirrhosis, 24.2 % had CP B cirrhosis, and 2.2 % had CP C cirrhosis) [55].
        - For the overall cohort, 1-year OS was 89.5 %, 3-year OS was 64.7 %, and 5-year OS was 44.6 %.
        - Survival was improved in patients with CP A cirrhosis compared with patients with CP B cirrhosis, with 5-year OS of 55.9 % in CP A cirrhosis and 44.5 % in CP B cirrhosis.
        - There were five cases of grade ≥ 3 toxicities.
        - 63 patients in the cohort received more than one course of proton therapy, with 5-year OS of 50.5 %.
    - In patients with smaller tumors (≤ 5 cm) who were not candidates for ablative therapies or resection, outcomes with RT have been particularly impressive, with two series reporting 1-year local control rates of 95–100 % and 1-year OS of 99–100 % [56, 57].
    - Prospective phase II multi-institutional trial demonstrated the safety of 3D-CRT following incomplete TACE, with an overall response rate of 64.5 % [58].
    - RT in conjunction with TACE has also been safely employed in patients with large tumors (> 10 cm), with one series of 72 patients reporting an overall response rate of 76.1 % and a median survival of 12.2 months, without any cases of grade ≥3 toxicity [59].
- Patients with tumor vein thrombosis have particularly poor outcomes, with median survival of 2–4 months. These patients are often not candidates for arterially directed therapies due to the risk of ischemic injury and hepatic failure. Many patients with TVT have been successfully treated with RT with

response rates range from 50 to 79 % and overall survival of 3.8–22 months [52, 53].
  - Prospective phase I and II trials of 102 patients treated with SBRT at Princess Margaret Hospital included 56 patients with TVT, who had a 1-year OS of 44 % [53]. TVT was a strong adverse prognostic factor on multivariate analysis (AHR 2.47, 95 % CI 1.25–4.88, $P$=0.01).

- Systemic therapy: Sorafenib is the first-line therapy for patients with advanced and metastatic HCC, with randomized data demonstrating a small but significant improvement in overall survival.
  - The Sorafenib HCC Assessment Randomized Protocol (SHARP) Trial [60]
    - Randomized 602 patients with advanced HCC and Child-Pugh A cirrhosis to sorafenib versus placebo. 28 % of patients had HCV-related cirrhosis, 26 % had EtOH-related cirrhosis, and 12 % had HBV-related cirrhosis.
    - Trial was stopped after the second planned interim analysis demonstrated improvement in OS with sorafenib (10.7 months vs. 7.9 months, HR 0.59, 95 % CI 0.55 to 0.87, $P$<0.001).
    - There were no complete responses. The partial response rate was 2 % in the sorafenib arm vs. 1 % in the placebo arm ($P$=0.05).
    - Unplanned subgroup analyses [61] by cirrhosis etiology showed increased OS with sorafenib in both HCV-related and HBV-related cirrhosis; however there was no improvement in time to progression in patients with HBV-related cirrhosis. Analysis was limited by small numbers and lack of stratification by viral status.
  - Asia-Pacific Trial [62]
    - Randomized 226 patients with advanced HCC and Child-Pugh A cirrhosis to sorafenib versus placebo. 73 % had HBV-related cirrhosis, and 8.4 % had HCV-related cirrhosis.
    - Median OS was 6.5 months in patients treated with sorafenib vs. 4.2 months in the placebo arm (HR 0.68, 95 % CI 0.5 to 0.93, $P$=0.014).
    - As in the SHARP Trial, there were no complete responses. The partial response rate was 3.3 % in the sorafenib arm versus 1.3 % in the placebo arm.
    - Potential reasons for decreased OS in the Asia-Pacific Trial as compared with the SHARP Trial include the increased number of patients with more advanced disease in the Asia-Pacific Trial (as demonstrated by the higher numbers of patients with extrahepatic disease, increased number of intrahepatic tumors, and poorer performance status in patients in the Asia-Pacific Trial as compared with the SHARP Trial) [62].
    - While there was a difference in cirrhosis etiology between the two studies, neither study was stratified by HCV or HBV status, making comparisons challenging.

### 9.8.2 ICC

- Early stage/resectable: Surgical resection is considered the only curative treatment option for patients with early-stage ICC, including those patients with solitary tumors without vascular invasion, involved lymph nodes, or distant metastases.
  - Outcomes are poor even in patients able to undergo resection, with a median 5-year OS of 25–35 % [63–65]. Margin status and involved lymph nodes are significantly associated with survival [66, 67] with R0 resections associated with 5-year OS as high as 63 % [68].
  - Adjuvant therapy: While there is a significant recurrence risk in ICC, particularly in the setting of R1 resection or involved lymph nodes [66, 67], there are no randomized data

defining the optimal adjuvant treatment regimen.
  - Retrospective series often include patients with both intra- and extrahepatic cholangiocarcinoma, further complicating assessment.
  - A meta-analysis including both gallbladder and biliary tract cancer supported the role of adjuvant therapy (chemotherapy, radiotherapy, or chemoradiotherapy) after resection, particularly in patients with involved lymph nodes or positive margins [69]. Retrospective series also support the role of adjuvant therapy in this population [63, 70].
  - The NCCN guidelines recommend adjuvant therapy, including chemotherapy and/or chemoradiotherapy, for patients with positive margins, involved lymph nodes, and/or gross residual disease after resection [71].
- Locally advanced/metastatic disease: The majority of patients (up to 70 %) have unresectable disease at diagnosis due to vascular invasion, the presence of multiple tumors, and/or nodal or distant metastases [72]. There are limited data, as patients with intrahepatic cholangiocarcinoma are often grouped into studies of patients with extrahepatic cholangiocarcinoma and/or hepatocellular carcinoma.
  - The NCCN guidelines [71] recommend chemotherapy with gemcitabine and cisplatin for patients with unresectable and metastatic intrahepatic cholangiocarcinoma based on the ABC-02 [73] trial.
    - Randomized 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer to cisplatin plus gemcitabine versus gemcitabine monotherapy. 59 % of patients had biliary tract cancer, including both intra- and extrahepatic cholangiocarcinoma.
    - After a median follow-up of 8.2 months, median OS was 11.4 months in patients treated with cisplatin plus gemcitabine versus 8.1 months in patients treated with gemcitabine monotherapy (HR 0.64, 95 % CI 0.52–0.80, $P<0.0001$). There was no significant increase in toxicity with the use of cisplatin in addition to gemcitabine.
  - Meta-analysis of ABC-02 and a Japanese randomized controlled trial (BT-22) continued to demonstrate an improvement in OS with the use of gemcitabine plus cisplatin versus gemcitabine monotherapy [74].
- Radiotherapy has also been employed in patients with unresectable disease [54, 75, 76], with single-arm phase II and retrospective series demonstrating impressive local control and survival rates with increasing doses of RT [77].
  - A retrospective series from Fudan University of 84 patients with unresectable ICC reported improved survival in patients treated with radiotherapy [78].
    - 49 patients did not receive RT, and 35 patients received radiotherapy to the area of gross disease to a total dose of 30–60 Gy in 1.8–2 Gy daily fractions. There was no significant difference in clinicopathologic characteristics (age, stage, tumor size, multifocality) between the two groups.
    - 1-year OS was 38.5 % in the radiation group versus 16.4 % in the non-radiation group. Median OS was 9.5 months in the radiation group versus 5.1 months in the non-radiation group (P=0.003).
  - Prospective phase II trial from Massachusetts General Hospital and MD Anderson Cancer Center of hypofractionated proton therapy for HCC and ICC reported a 2-year local control rate of 94.1 % and 2-year OS rate of 46.5 % for patients with ICC [54].
  - A retrospective series from MD Anderson Cancer Center of 79 patients with ICC reported an overall 3-year survival rate of 44 %, with an impressive

3-year OS rate of 73 % and 3-year local control rate of 78 % in patients treated with increasing doses of RT (BED >80.5Gy) [76].

## 9.9 Future Directions

- Further study is needed to determine the optimal combination of treatment modalities in both hepatocellular carcinoma and intrahepatic cholangiocarcinoma, particularly in those patients with unresectable disease. We strongly recommend protocol enrollment whenever possible. There are numerous ongoing protocols, including the following exploring the role of radiotherapy in conjunction with systemic therapies in HCC and ICC.
  - RTOG 1112 [79], a phase III trial of sorafenib with or without SBRT in patients with unresectable BCLC stage B (intermediate) or C (advanced) HCC who were refractory to TACE or are not candidates for RFA or TACE, will provide prospective data on the role of SBRT in patients with advanced HCC.
    - A study in Singapore of patients with BCLC stage B or C HCC without TVT is randomizing patients to sorafenib versus SIRT with SIR-Spheres (Sirtex Medical, Lake Forest, IL) [80].
  - NRG GI001 [81], a phase III trial of gemcitabine and cisplatin with or without liver-directed radiotherapy for unresectable intrahepatic cholangiocarcinoma, is currently accruing patients.

**Conclusions**

- The incidence of hepatocellular carcinoma and cholangiocarcinoma continues to rise, and treatment remains challenging, particularly in the advanced setting.
- Cooperation across specialties, including hepatobiliary and transplant surgery, medical oncology, radiation oncology, and interventional radiology, is key to maximizing patient outcomes.

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# Primary Liver Cancer: Radiation Therapy Planning

10

Florence K. Keane and Theodore Hong

## 10.1 Radiation Treatment for HCC and ICC

- Advances in radiotherapy treatment planning and delivery allow the safe delivery of tumoricidal doses of radiotherapy with minimal associated toxicity.
- We recommend liver-directed RT in patients who are not candidates for orthotopic liver transplantation, surgical resection, or radiofrequency ablation, including patients with one or multiple lesions measuring 3–6 cm or patients with larger tumors (6–10 cm) with a sufficient volume of normal hepatic parenchyma.
  - Select patients with tumor vein thrombosis with adequate hepatic function can be safely treated with liver-directed RT.
  - Patients with Child-Pugh Class C cirrhosis should not be treated off-protocol.

## 10.2 Treatment Planning

### 10.2.1 Simulation

- Computed tomography (CT) or magnetic resonance (MR)-based simulation.
  - Four-dimensional CT (4D-CT) is needed to assess motion.
- Patients are simulated supine with arms up.
- Immobilization devices are used and may include thermoplastic devices or vacuum bags, with or without a body frame [1].
- Patients receive both oral and multiphasic intravenous (IV) contrast at the time of simulation.

## 10.3 Target Identification

- Both HCC and ICC have variable enhancement patterns on CT and MRI. Multiphasic intravenous (IV) contrast with arterial, portal venous, and delayed phase is needed for accurate tumor identification, as use of only one phase of contrast for target identification increases the risk of undercontouring of the target or inclusion of normal hepatic parenchyma or vasculature in the target volume. Tumor vascular invasion further complicates target identification [2].
  - HCC classically exhibits rapid arterial enhancement with washout on delayed phases [3, 4], but enhancement varies based on tumor size and perfusion [4–7]. Fig. 10.1 and Fig. 10.2
    - Larger nodules may have a fibrous capsule which results in delayed enhancement and washout of contrast [4], while

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© Springer International Publishing AG 2017
T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_10

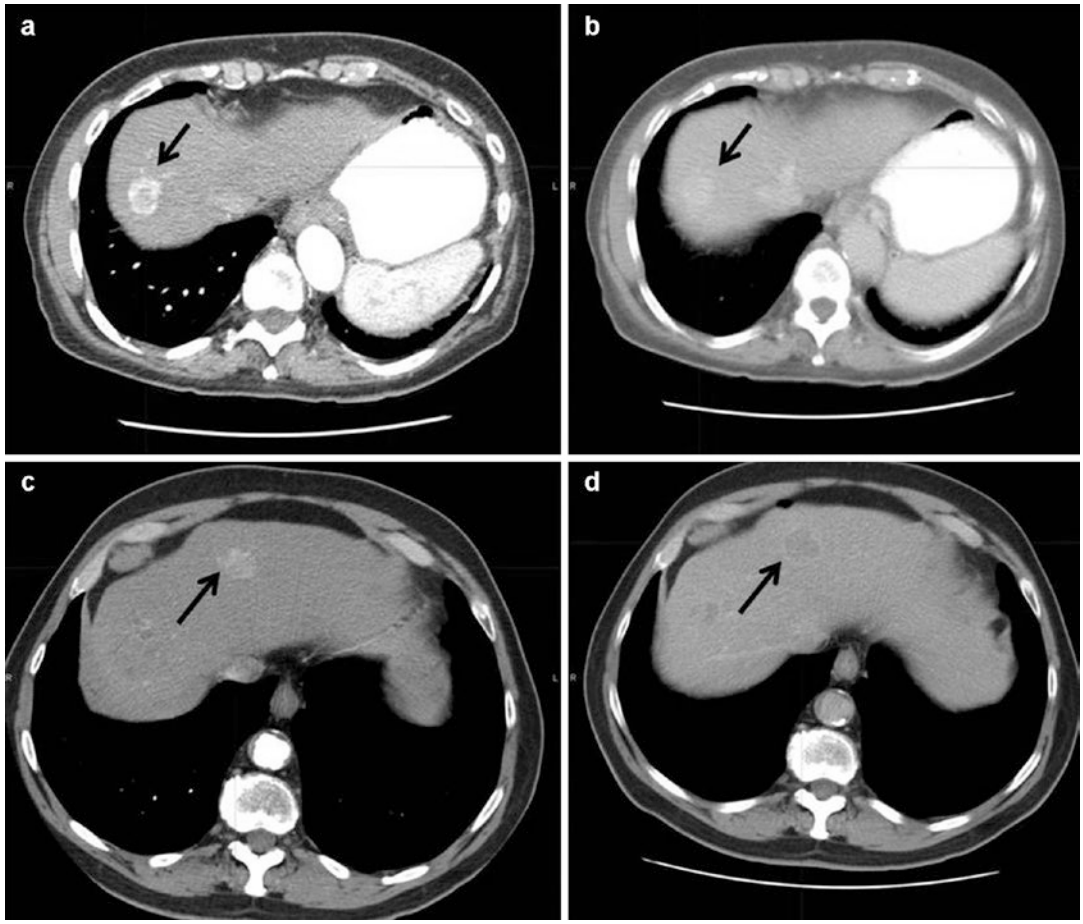


**Fig. 10.1** Hepatocellular carcinoma with best visualization in the arterial phase. Lesion one shows arterial enhancement (**a**) and venous washout (**b**). Lesion two also shows arterial enhancement (**c**) and venous washout (**d**)

diffuse-type HCC often has minimal arterial enhancement [5]. Tumor venous thrombosis and vascular involvement may further alter enhancement patterns.

- On MRI, larger HCC nodules may be hyperintense on T2 series and hypointense on T1 series, while smaller nodules may be T1 isointense before rapid but transient contrast enhancement [8, 9].
- RTOG consensus guidelines recommend contouring the gross tumor volume (GTV) as the union of GTVs across all phases of imaging [2]. This ensures accurate identification of the target while minimizing coverage of normal hepatic parenchyma.
  - This recommendation was supported by a series on IV contrast enhancement and target definition in HCC which demonstrated that there was no one phase which provided optimal tumor identification across tumors. Figs. 10.3 and 10.4 Moreover, a uniform expansion around the GTV from the best visualized phase was inferior when compared with a GTV comprised of the union of GTVs across all available imaging phases [7].

– ICC typically shows delayed enhancement [7, 10–13], but some lesions may appear more similar to HCC, with arterial enhancement and rapid venous washout [14].

- Consensus guidelines are not yet available for ICC, but due to the variable enhancement patterns seen in ICC [7],

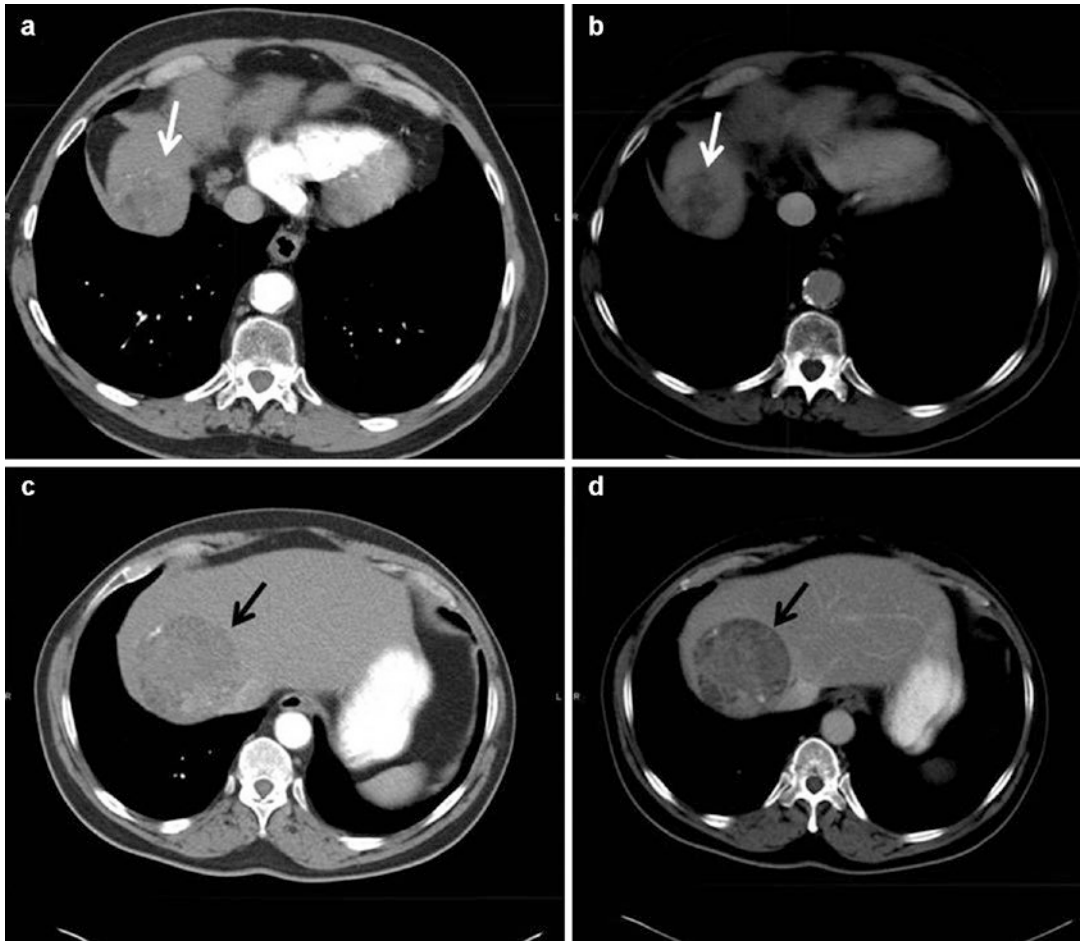


**Fig. 10.2** Hepatocellular carcinoma with best visualization in the portal venous phase. Lesion one shows worst visualization in the arterial phase (**a**) and best visualization in the portal venous phase (**b**). Lesion two also shows worst visualization in the arterial phase (**c**) and best visualization in the portal venous phase (**d**)

all available phases of multiphasic imaging should be evaluated to identify the GTV.

- MRI and MR-based simulation
  - Some lesions may be more visible on MRI than on CT Fig. 10.5.
  - Hepatic MRI with contrast may also help distinguish tumor from perfusion abnormalities in patients with severe cirrhosis [15].
  - MRIs should be carefully reviewed during treatment planning to ensure accurate target identification and coverage.
    - CT-MRI fusions are challenging due to potential organ deformation between series. Suboptimal fusion may lead to target overcontouring [2]. Placement of MR-compatible fiducial markers and obtaining an MRI in the RT treatment may assist with registration.
    - MR-based simulation removes the need for fusion with the planning CT, but is not yet widely available.

## 10.4 Target Motion Assessment and Management

- Patients should have a four-dimensional (4D) CT [16] for treatment planning, as a free-breathing CT may not provide adequate assessment of organ motion.
  - An internal target volume (ITV) may be constructed to account for target motion.

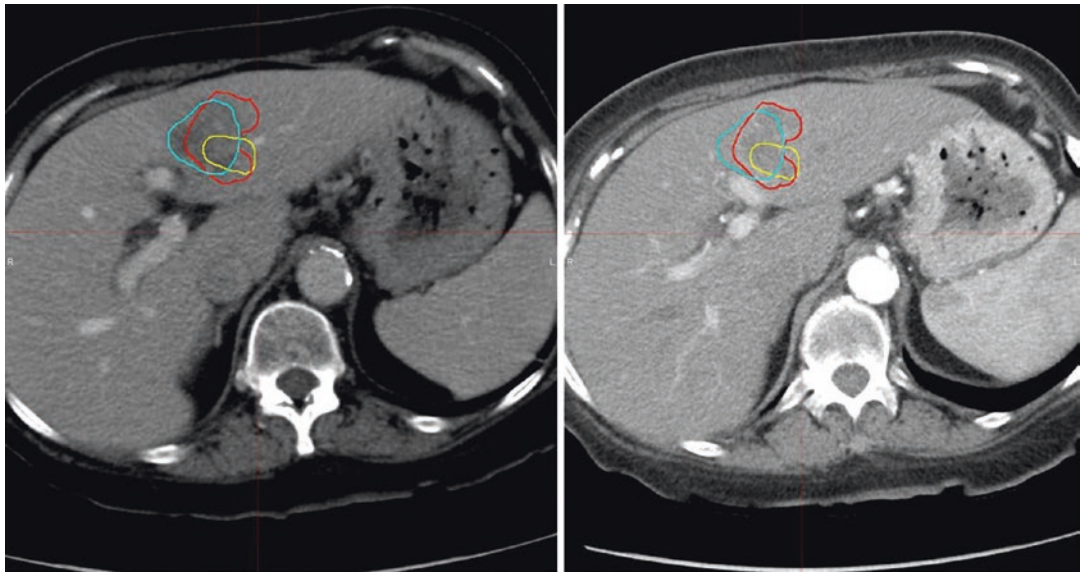

**Fig. 10.3** Lack of overlap between gross tumor volume (GTV) as contoured on the arterial phase (*red*), portal venous phase (*blue*), and delayed phase (*yellow*) for a patient with hepatocellular carcinoma. Images are shown on the portal venous phase (*left panel*) and arterial phase (*right panel*)

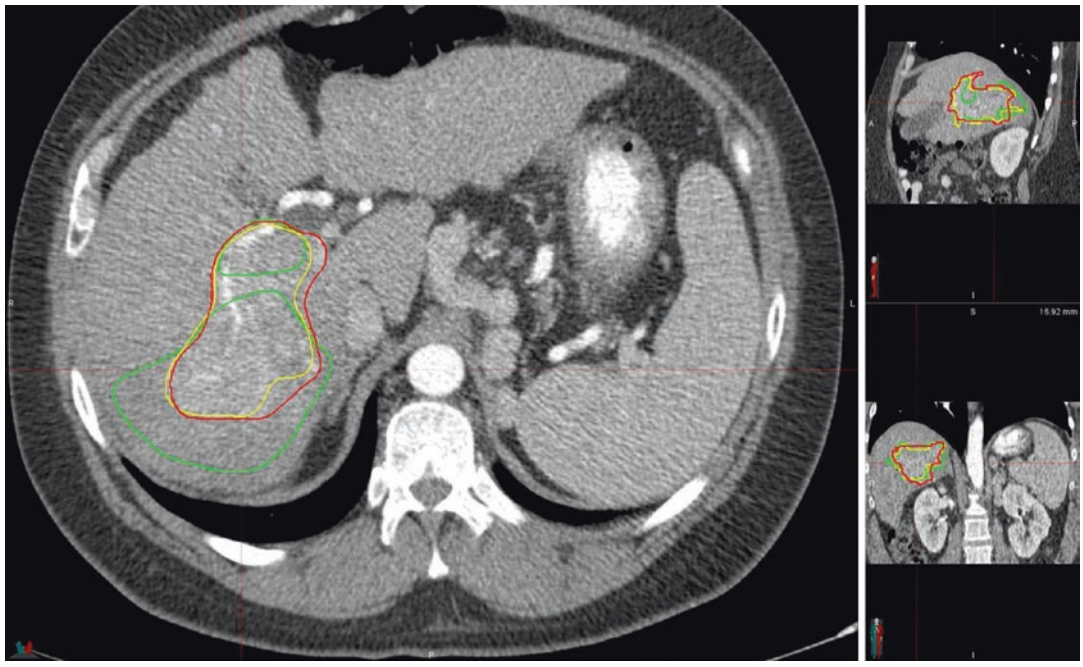

**Fig. 10.4** Lack of overlap between gross tumor volume (GTV) as contoured on the arterial phase (*red*), portal venous phase (*green*), and delayed phase (*yellow*) for a patient with hepatocellular carcinoma. Images are shown on the arterial phase

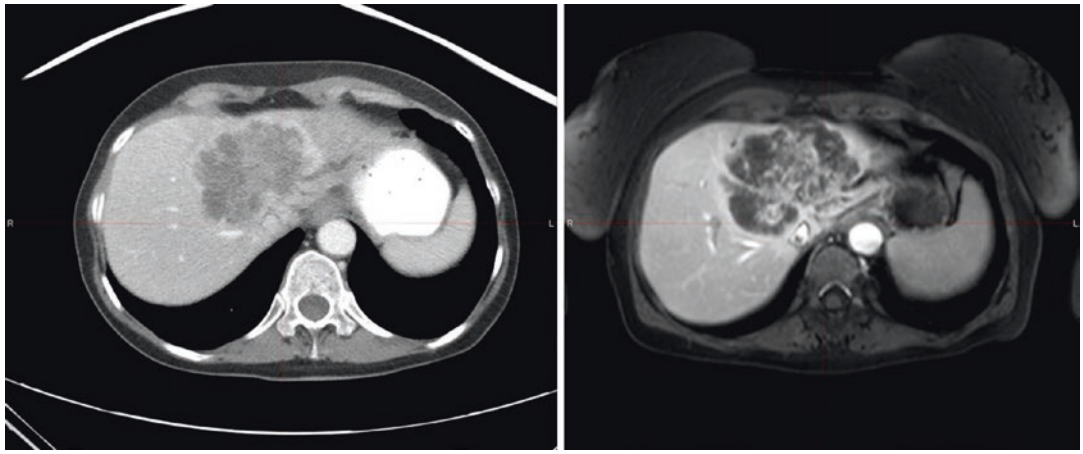

**Fig. 10.5** Intrahepatic cholangiocarcinoma as seen on the arterial phase of a contrast-enhanced CT (*left panel*) and on a contrast-enhanced T1 sequence of an MRI (*right panel*)

- Placement of fiducial markers in the normal hepatic parenchyma prior to simulation facilitates measurement of the liver and target motion. Motion of the target can be compared to the movement of the fiducial markers [16–18]. Fiducial markers are also essential for patient setup and treatment delivery.
- Patients with significant target or organ motion require further intervention to monitor and/or decrease motion.
  - In active breathing control [19–21] or respiratory gating, the patient's respiratory cycle is tracked throughout treatment, with delivery of radiotherapy limited to select phases of the respiratory cycle.
    - Active breathing control reduces intra-fraction variability, but there may be persistent variability between fractions [22].
    - Active breathing control has been employed with both photon [23, 24] and proton [25] RT.
  - Abdominal compression [21, 26–28] causes a small degree of organ deformation [29] and does not reduce organ motion in all patients [27], but in some patients, it significantly reduces organ motion [16, 26, 29].

## 10.5 Treatment Delivery Technique

- Assessment of patient setup and target position will depend on the type of radiotherapy used as well as the delivery system.
  - On-board cone-beam CTs such as on the Elekta Synergy® and on the Varian Trilogy® can be used to assess fiducial and soft tissue position before treatment, in between treatment fields, and after treatment.
  - CyberKnife® tracks the position of implanted fiducial markers using real-time orthogonal X-rays and adjusts treatment delivery accordingly.

## 10.6 Development of Modern Liver: Directed RT

- In the era of two-dimensional (2D) RT, treatment often required radiation of the entire liver, which carried risk of hepatotoxicity and resulting risk of radiation-induced liver disease (RILD). Liver-directed RT was largely relegated to the palliative setting.
  - RILD can develop as early as 2 weeks and as late as 4 months after the completion of RT and is characterized by the triad of

hepatomegaly, ascites, and an increase in alkaline phosphatase with minimal increase in bilirubin.

- The risk of developing RILD varies based on the RT dose, volume of the liver irradiated, and underlying hepatobiliary function [30].
  - Retrospective series of whole liver RT reported rates of RILD of 44 % in patients receiving ≥ 35 Gy [31] and 10 % in patients receiving 33 Gy in 1.5 Gy twice-daily fractions [32].
  - In patients with cirrhosis, the risk of RILD or other treatment-related toxicities increases.
    - Dose-escalation protocols conducted at the University of Michigan of liver-directed RT for patients with hepatocellular carcinoma, cholangiocarcinoma, and liver metastases reported an increased risk of RILD in patients with HCC with underlying cirrhosis as compared to patients with liver metastases [33].
    - A retrospective study of 92 patients with HCC treated with SBRT between 2007 and 2009 included 68 patients with CP A cirrhosis (73.9 %) and 24 patients (26.1 %) with CP B cirrhosis.
      - CP B cirrhosis was associated with a significantly increased risk of grade ≥2 RILD [34].

- Conformal radiotherapy
  - The development of modern RT planning and delivery techniques enabled safe delivery of tumoricidal doses of RT and more refined assessments of hepatotoxicity risk based on the interaction between radiotherapy dose, tumor volume, and the volume of irradiated and unirradiated hepatic parenchyma [35, 36].
  - A series of dose-escalation protocols conducted at the University of Michigan on hyperfractionated conformal RT with concurrent arterial chemotherapy based RT dose on a maximum 10–15 % risk of RILD as calculated by a normal tissue complication probability (NTCP) model [33].
    - The effective liver volume (Veff) parameter was used in the NTCP model to calculate dose and enabled comparison of different RT plans.
    - A total of 128 patients (46 patients with liver metastases, 35 patients with HCC, and 46 patients with cholangiocarcinoma) were treated to a median dose of 60.75 Gy in twice-daily 1.5 Gy fractions.
    - Median overall survival was 15.8 months.

- Stereotactic body radiotherapy (SBRT)
  - SBRT uses multiple conformal beams to deliver high doses of RT with rapid dose falloff. With the development of SBRT and associated stereotactic techniques, the use of liver-directed RT has continued to increase.
  - Prospective Phase I and II trials of liver SBRT conducted at Princess Margaret Hospital treated 102 patients with HCC to a median dose of 36 Gy in six fractions (range 24–54 Gy) [37].
    - The majority of patients had underlying cirrhosis: 38 % had hepatitis C-related cirrhosis, 38 % had hepatitis B-related cirrhosis, and 25 % had alcohol-related cirrhosis. Fifty-five percent of patients had tumor venous thrombosis.
    - CT simulation
      - Patients had a multiphasic CT with or without MRI for treatment planning.
      - Custom immobilization was used, with 51 % requiring abdominal compression and 49 % receiving active breathing control.
    - Targets
      - Gross tumor volume (GTV): the area of arterial enhancement and venous washout as seen on CT and/or MRI
      - Clinical target volume (CTV) 1, CTV1: GTV and contrast-enhancing tumor thrombus

  - CTV2: optional volume, consisted of a 5-mm expansion around the GTV, as well as any areas of nonenhancing venous thrombosis
  - Planning target volumes (PTV): up to 5-mm expansion on CTV1 and CTV2, adjusted based on target motion and patient immobilization
- RT dose to PTV1 was determined based on the maximum allowed Veff (limited to 60 % in Trial 2) and ranged from 30 to 54 Gy in six fractions.
  - Fractions were delivered every other day over 2 weeks.
  - The dose to tumor venous thrombosis plus the PTV margin could be limited to 30 Gy if needed for normal tissue toxicity.
  - The dose to PTV2 (which included nonenhancing tumor thrombus) was recommended to be 27 Gy but was not mandated.
- Results
  - Median OS was 17 months. Local control at 1 year was 87 %.
  - Grade ≥ 3 toxicity was seen in 30 % of patients.
    - There was no classic RILD.
    - Seven patients died within a year after RT. Five patients experienced liver failure, two of whom had massive TVT progression. In one patient, HCC invading the common bile duct likely led to cholangitis. One patient experienced a fatal duodenal bleed after re-irradiation for retroperitoneal nodal disease.

– RTOG 1112 [38]: currently accruing randomized Phase III trial of sorafenib with or without SBRT in patients with unresectable BCLC stage B (intermediate) or C (advanced) HCC who were refractory to TACE or are not candidates for RFA or TACE.
  - Patients may be treated with protons or photons.
- Randomization
  - Randomized to daily sorafenib vs. SBRT followed by daily sorafenib.
  - Patients are stratified prior to randomization by presence/ absence of vascular invasion, cirrhosis etiology (hepatitis B, hepatitis C, or others), region of treatment site, and extent of HCC volume relative to liver volume.
- Simulation: Patients must be immobilized with custom immobilization.
  - Liver-protocol CT with multiphasic IV contrast
  - 4D-CT to assess motion, with exhale breath-hold or average-phase CT used as baseline CT for planning.
- Targets
  - GTV includes parenchymal and vascular disease as seen on arterial, portal venous, and/or delayed phases of CT and/or MR imaging.
    - Note that tumor venous thrombus may be best seen on venous phase imaging.
    - Non-tumor thrombus should not be included in the GTV.
  - CTV: No standard expansion on the GTV.
    - A CTV margin to include areas at high risk for microscopic disease is optional. These include areas of non-tumor thrombus and sites of prior arterially directed or ablative therapies.
  - PTV: The minimum PTV margin is a 4-mm expansion in all directions around the CTV. The maximum PTV margin should ideally be ≤ 10 mm.
    - PTV margin also based on whether the patient is treated with protons or photons.
- Dose
  - The maximum possible dose based on normal tissue tolerances and the mean liver dose should be delivered.
  - Assessment of the effective liver volume (Veff) is optional.

  - There are six possible dose levels based on the mean liver dose (MLD). These doses correspond to the photon doses and the RBE-weighted dose for protons.
    MLD ≤ 13 Gy (Veff<25 %) corresponds to PTV dose of 50 Gy.
    MLD ≤ 15 Gy (Veff 25–29 %) corresponds to PTV dose of 45 Gy.
    MLD ≤ 15 Gy (Veff 30–34 %) corresponds to PTV dose of 40 Gy.
    MLD ≤ 15.5 Gy (Veff 35–44 %) corresponds to PTV dose of 35 Gy.
    MLD ≤ 16 Gy (Veff 45–54 %) corresponds to PTV dose of 30 Gy.
    MLD ≤ 17 Gy (Veff 55–64 %) corresponds to PTV dose of 27.5 Gy.
  - Treatment is delivered in five fractions, with a time interval of 24 to 72 h between fractions.
  - Prescription isodose must cover ≥95 % of the PTV.
- Organs at risk: Constraints include the following items:
  - Liver: As noted above, the PTV prescription dose is determined based on the mean liver dose.
    - As a guideline, the liver volume (liver – GTVs) should consist of a volume > 700 cc, with V10Gy < 70 %.
  - Spinal cord + 5-mm expansion: $D_{0.5\,cc} \leq 25$ Gy
  - Esophagus: $D_{0.5\,cc} \leq 32$ Gy
  - Stomach, duodenum, small bowel: $D_{0.5\,cc} \leq 30$ Gy
  - Large bowel: $D_{0.5\,cc} \leq 32$ Gy
  - Kidney (bilateral mean dose) < 10 Gy
  - It is recommended to avoid hot spots in the common bile duct, keeping $D_{0.5\,cc} \leq 50$ Gy.
  - Adjacent bowel may limit or prevent safe RT delivery, particularly SBRT which relies on delivery of a high dose per fraction. For lesions which are close to bowel, placement of a biologic mesh spacer may sufficiently displace bowel to allow safe administration of RT [39].
    - Treatment delivery requires IGRT with either cone-beam CT or orthogonal kV images with fiducial markers.
- Charged particle therapy
  - Charged particle therapy, including proton therapy and carbon ion therapy, is characterized by sharp dose falloff which in turn minimizes exit dose (Fig. 10.6).
    - There are multiple techniques for the delivery of proton therapy, including passive scattering and pencil beam scanning.
  - There is growing interest in the use of charged particle therapy in the treatment of both ICC and HCC as the properties of charged particle therapy can be exploited to maximize the dose to the tumor while minimizing dose to normal hepatic parenchyma.
    - A retrospective series of 318 patients with HCC treated with proton therapy at the University of Tsukuba reported 5-year OS of 44.6 % with only five cases of grade ≥ 3 toxicity [40].
    - A Phase II multi-institutional trial of hypofractionated proton radiotherapy for 92 patients with HCC or ICC demonstrated impressive overall survival and local control rates at 2 years [41]. Two-year overall survival rates were 63.2 % for HCC and 45.8 % for ICC, while 2-year local control rates were 94.8 % for HCC and 94.1 % for ICC.
      - Dose was adjusted based on mean liver dose as well as proximity to the porta hepatis.
        - Peripheral tumors (located > 2 cm from the porta hepatis) received a planned dose of 67.5 GyE in 15 fractions.
        - Central tumors (located within 2 cm of the porta hepatis) received a planned dose of 58.05 GyE in 15 fractions.
        - RT dose was also adjusted to maintain a mean liver dose ≤ 24 GyE.

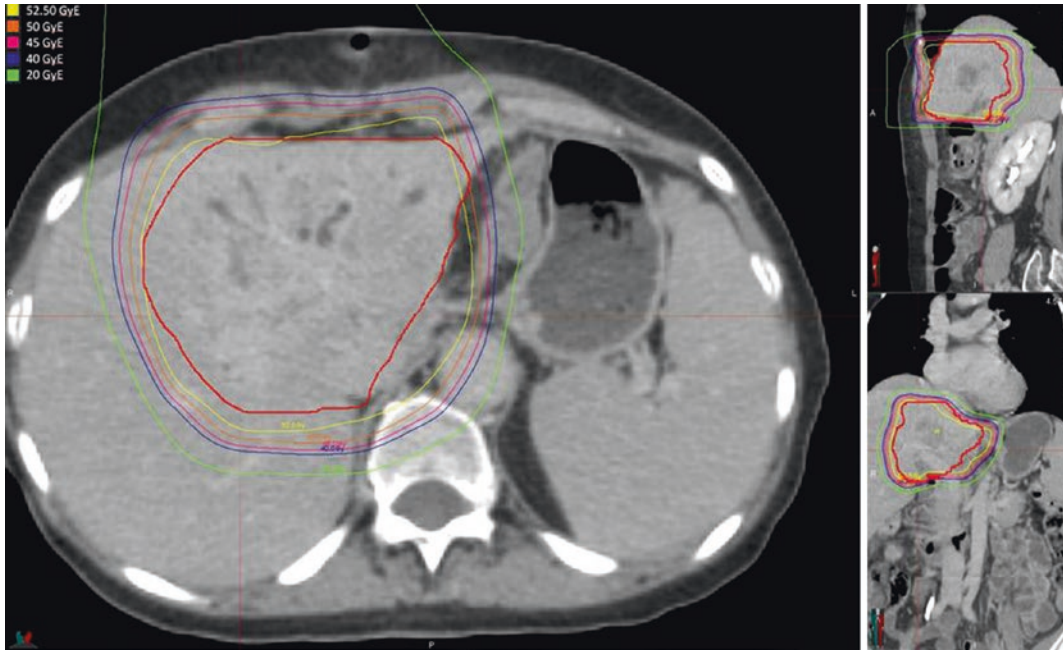


**Fig. 10.6** Proton therapy plan for a patient with intrahepatic cholangiocarcinoma. The CTV is the solid red line

  - There were low rates of toxicity, with four patients (4.8 %) experiencing grade ≥ 3 toxicity and only three patients (3.6 %) experiencing a decline in Child-Pugh score from CP A to CP B.

- Intensity-modulated radiotherapy (IMRT)
  - Similarly to SBRT, IMRT allows for increased conformality of dose around target volumes while sparing uninvolved tissues.
  - NRG GI001 [42]: currently accruing randomized Phase III trial of gemcitabine and cisplatin with or without focal hypofractionated radiation therapy for unresectable intrahepatic cholangiocarcinoma.
    - Patients may be treated with either protons or photons.
    - Randomization
      - Randomized to chemotherapy alone (gemcitabine/cisplatin x 5 cycles) versus sequential chemoradiotherapy (gemcitabine/cisplatin x 1 cycle followed by radiotherapy followed by gemcitabine/cisplatin x 4 cycles). Patients in either arm may receive maintenance gemcitabine.
      - Patients are stratified prior to randomization by tumor size and the presence of satellite lesions.
    - Simulation: Patients must be immobilized with custom immobilization.
      - Liver-protocol CT with multiphasic IV contrast
      - 4D-CT to assess motion, with exhale breath-hold or average-phase CT used as baseline CT for planning
    - Targets
      - GTV includes parenchymal and nodal disease as seen on arterial, portal venous, and/or delayed phases of CT and/ or MR imaging.
      - CTV: CTV expansion on the GTV is optional.
      - PTV: The minimum PTV margin is a 4-mm expansion in all directions around the CTV. The maximum PTV margin is 20 mm.
        - PTV margin also based on whether the patient is treated with protons or photons.

- Dose
  - Prescription dose is based on the proximity of the PTV to the porta hepatis and the mean liver dose.
    - Tumors located within 2 cm of the porta hepatis are restricted to a maximum dose of 58.05 Gy (or 58.05 Gy(E)).
    - The maximum dose for peripheral tumors (located > 2 cm beyond the porta hepatis) is 67.5 Gy (or 67.5 Gy(E)).
  - Dose is then determined based on the mean liver dose, defined as the liver minus GTV. These are four possible dose levels, all of which correspond to the photon dose or the RBE-weighted dose for protons and are delivered in 15 daily fractions.
    MLD ≤ 22 Gy corresponds to PTV dose of 67.5 Gy.
    MLD ≤ 24 Gy corresponds to PTV dose of 58.05 Gy.
    If MLD > 24 Gy, PTV dose decreases to 45 Gy.
    MLD of 27 Gy corresponds to PTV dose of 37.5 Gy.
  - Prescription isodose must cover ≥95 % of the PTV.
- Organs at risk: Constraints include the following items:
  - Liver: As noted above, the PTV prescription dose is determined based on the mean liver dose.
    - The volume of uninvolved liver (liver – GTVs) should be > 700 cc, with V10 Gy < 80 %.
  - Spinal cord + 5-mm expansion: $D_{0.5\,cc} \leq 37.5$ Gy
  - Duodenum, small bowel, esophagus: $D_{0.5\,cc} \leq 45$ Gy
  - Stomach: $D_{0.5\,cc} \leq 40$ Gy
  - Large bowel: $D_{0.5\,cc} \leq 48$ Gy
  - Kidney (bilateral mean dose): ≤ 12 Gy
  - It is recommended to avoid hot spots in the common bile duct, keeping $D_{0.5\,cc} \leq 70$ Gy.
- Treatment delivery requires IGRT with either cone-beam CT or orthogonal kV images with fiducial markers.

## 10.7 Dose and Fractionation

The optimal dose and fractionation pattern for HCC and ICC are not yet known. Responses have been seen with lower doses of radiotherapy, particularly in series of patients with early-stage disease or compromised hepatobiliary function, but there is a suggestion that higher doses of radiotherapy may be associated with improved local control and survival.

- In a series of 82 patients with HCC treated with three-fraction SBRT (median dose 51 Gy, range 33–60 Gy), 2-year local control was 87 %, and 2-year overall survival was 63 %. For patients who were treated with median doses ≥ 54 Gy, local control and overall survival rates were 100 % and 68 % after 4.5 years of follow-up [43].
- In ICC, a retrospective analysis of 79 patients with unresectable disease (median tumor size 7.9 cm) treated with chemotherapy followed by radiotherapy reported a median 3-year OS of 44 %, with a significant improvement in both overall survival and local control in patients who received BED > 80.5 Gy [44].
  - Median RT dose and fractionation were 58.05 Gy in 15 fractions (BED 80.5 Gy).
  - 3-year OS was 73 % with BED > 80.5Gy vs. 38 % with BED < 80.5 Gy ($P$=0.017), while 3-year local control was 78 % with BED > 80.5Gy vs. 48 % with BED < 80.5 Gy ($P$=0.04).

**Conclusions**

- Liver-directed radiation therapy is a safe and effective treatment modality for patients with both hepatocellular carcinoma and intrahepatic cholangiocarcinoma.
- Treatment options for hepatic malignancies include conformal radiotherapy, SBRT, IMRT, and charged particle therapy. These

treatment modalities enable delivery of tumoricidal doses of radiotherapy while sparing maximal volumes of normal hepatic parenchyma.

- Further study is needed to determine the optimal dose and fractionation pattern for both HCC and ICC.
  - Ongoing trials will provide valuable prospective data on the optimal role of RT in the treatment of advanced unresectable HCC and ICC.

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# Biliary Cancer: Background and Clinical Evidence

11

Anusha Kalbasi and Edgar Ben-Josef

## 11.1 Introduction

The management of biliary cancer – specifically, extrahepatic cholangiocarcinoma and gallbladder cancer – is challenging. Surgical resection is the mainstay of therapy, but the complex anatomy of the biliary tree and surrounding structures renders surgery a suboptimal approach as monotherapy. Adjuvant therapies, including chemotherapy and radiation therapy, have been studied retrospectively with mixed results. Emerging prospective data, however, suggests some promise for adjuvant therapy. And for patients with unresectable or metastatic disease, prospective studies have identified systemic therapy combinations with some success. Here we will review the clinical background for extrahepatic cholangiocarcinomas and gallbladder cancers, leading to a summary of the general treatment paradigms while highlighting the rationale for each approach.

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## 11.2 Categorization, Epidemiology, and Risk Factors

### 11.2.1 Categorization

- Biliary cancers are uncommon malignancies that arise from the epithelium of the biliary tract and include gallbladder cancers and cholangiocarcinomas.
- Cholangiocarcinomas are defined as tumors of the bile ducts and are classified as intrahepatic and extrahepatic cholangiocarcinoma. Tumors arriving from the biliary tract within the hepatic parenchyma are categorized as intrahepatic cholangiocarcinoma and account for approximately 5–10 % of cholangiocarcinomas. The remaining 90–95 % of tumors are categorized as extrahepatic cholangiocarcinomas [1].
- Intrahepatic cholangiocarcinomas are discussed in a separate chapter.
- Extrahepatic cholangiocarcinomas centered near the biliary hilum (defined as the confluence of the left and right hepatic ducts) are also referred to as perihilar cholangiocarcinomas, or "Klatskin" tumors. Perihilar cholangiocarcinomas account for approximately

© Springer International Publishing AG 2017
T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_11

two-thirds of extrahepatic cholangio carcinomas.

### 11.2.2 Pathology

- Adenocarcinoma is by far the predominant histology of biliary tract cancers. While cholangiocarcinomas are almost exclusively adenocarcinomas, gallbladder cancers also consist of squamous cell carcinomas and sarcomas in a minority of cases (2 % and 0.2 %, respectively) [2].
- In a minority of cases, gallbladder adenocarcinomas can be subclassified by histology as mucinous adenocarcinoma or papillary adenocarcinoma, the latter of which has a better prognosis [3].
- Macroscopically, adenocarcinoma of the bile ducts and gallbladder can be subclassified as nodular (mass-forming), periductal infiltrating (sclerosing), or intraductal (papillary) tumors based on macroscopic features [4].
- These subtypes, of which infiltrating (sclerosing) is most common, can be associated with imaging findings and in turn can relate to patterns of growth and invasion [5].

### 11.2.3 Epidemiology

- Biliary cancers are the sixth most common gastrointestinal malignancy worldwide, but are notable for wide variation in incidence based on geographic region and ethnicity. These differences are linked to variations in exposures to risk factors, which are discussed below. In general, biliary cancers have a low incidence in the United States.
- Gallbladder cancers, which are more common than cholangiocarcinomas, have a particularly wide variation in incidence. The incidence is highest in parts of South America (Chile, Bolivia, Ecuador), South Asia (India, Pakistan), and East Asia (Japan and Korea) [6].
- The incidence of gallbladder cancer can be five- and twentyfold higher in certain indigenous populations, including Native Americans in the Southwestern United States and Chilean Mapuche Indians, respectively [7].
- Whereas gallbladder cancers can be two- to six-times more common in women than men, there is a slightly higher incidence rate of cholangiocarcinomas among men than women (ratio ~1.5:1) [7].
- Gallbladder cancers and cholangiocarcinomas most commonly present in older age, specifically, in the seventh and eighth decades of life, respectively [2].

### 11.2.4 Risk Factors

- Chronic inflammation (related to a variety of insults) is an important risk factor in the development of the majority of gallbladder cancers and a minority of cholangiocarcinomas. The majority of cholangiocarcinomas are sporadic and lack a clear link to underlying chronic inflammation or other risk factors.
- For gallbladder cancer, the most common insult leading to chronic inflammation is cholelithiasis, which is present in over 70–98 % of patients with gallbladder cancer [8].
- In severe cases, chronic inflammation related to cholelithiasis can cause calcification of the gallbladder, which is termed porcelain gallbladder when the calcification is complete. Porcelain gallbladder has been associated with a particularly high rate of malignancy, but more recent data questions the strength of this association [9, 10].
- There are a variety of risk factors for cholangiocarcinomas, most prominently primary sclerosing cholangitis (PSC), liver fluke infestation, toxin exposure, and congenital choledochal cysts.
- Patients with PSC, an autoimmune disease that often accompanies ulcerative colitis, develop cholangiocarcinoma at a younger age than patients with sporadic forms of cholangiocarcinoma [11, 12]. Eight to 40 % of patients with PSC develop cholangiocarcinoma [13], and it is not associated with the duration or severity of the autoimmune disease.

- Choledochal cysts may predispose to increased inflammation related to biliary stasis and reflux of pancreatic enzymes, which may explain the association with higher rates (10–50-fold increased risk) of cholangiocarcinoma [14]. Like patients with PSC, these patients develop cholangiocarcinomas at younger age than the sporadic forms of cholangiocarcinoma.
- Two liver flukes, *Opisthorchis viverrini* and *Clonorchis sinensis*, are strongly associated with development of cholangiocarcinoma. These flukes can infect humans via ingestion of undercooked or raw fish and dwell in the biliary tract, causing repeated insults to epithelial lining, which is thought to be the carcinogenic mechanism. The risk of cholangiocarcinoma has been reported to be between 2.7 and 27 times higher in patients with liver fluke infestation [15, 16].
- The most well-established toxin associated with cholangiocarcinoma is thorotrast (thorium dioxide), a contrast agent used in imaging during the middle of the twentieth century. Given the discontinuation of the use of thorotrast after 1960, it is highly unlikely that there will be additional cases of thorotrast-related cholangiocarcinoma beyond the publication of this text.
- There are numerous less rigorously established risk factors for cholangiocarcinoma, which include choledocholithiasis, cholangitis, chronic viral hepatitis, cirrhosis, inflammatory bowel disease, obesity, diabetes, and exposure to dioxin, nitrosamines, asbestos, radionuclides, radon, and isoniazid.

## 11.3 Work-Up and Staging

### 11.3.1 Imaging

- Surgical pathology is the key determinant of staging in gallbladder cancer and cholangiocarcinoma. Extent of tissue invasion, involvement of adjacent organs, presence of nodal disease, and histologic grade are included in the American Joint Committee on Cancer TNM staging manual, 7th edition (2010), which provides staging guidelines for both gallbladder cancer and extrahepatic cholangiocarcinoma. However, preoperative imaging is critical in the work-up of gallbladder cancer and cholangiocarcinoma and can aid in staging and determination of resectability.
- Ultrasound is a useful initial intervention, especially for detecting early gallbladder cancers. In patients with visible gallbladder lesions, ultrasound-guided FNA can be diagnostic. Ultrasound can also identify bile duct dilatation, which can be a manifestation of cholangiocarcinoma.
- Cross-sectional imaging by CT or MRI, however, is more useful to complete staging because they provide greater information both on tumor extent, including degree of vascular and biliary involvement, and nodal involvement. And although limited in sensitivity, peritoneal deposits can be identified on both CT and MRI.
- On CT, gallbladder cancer can have indistinct borders and heterogeneous enhancement and may be associated with a thickened gallbladder wall. Cholangiocarcinomas may enhance during arterial and portal venous phases, and the enhancement may be delayed because of the poorly vascular, fibrotic nature of these tumors (unlike early-enhancing lesions in hepatocellular carcinoma). Cholangiocarcinomas tend to spread longitudinally along the biliary tract, which can be visualized on both CT and MRI.
- On MRI, gallbladder cancers and cholangiocarcinomas are hypo- or iso-intense on T1, and hyperintense or variable on T2 imaging. Cholangiocarcinomas can be slowly contrast-enhancing, and there may be delayed enhancement similar to findings on CT.
- There are separate TNM staging systems for gallbladder cancer and extrahepatic cholangiocarcinoma. Perihilar cholangiocarcinoma and distal extrahepatic cholangiocarcinoma also have different TNM staging systems.
- Magnetic resonance cholangiopancreatography (MRCP) can be useful in delineating biliary structures and identifying the location of

biliary obstruction related to cholangiocarcinoma. In combination with MR angiography, these tools can be essential for surgical planning.
- Although 18F–FDG PET/CT does not provide additional clinical information on the primary tumor or nodal disease, it can be important in the identification of distant metastatic disease [17].

### 11.3.2 AJCC TNM Staging, 7th Edition

- TNM staging for distal extrahepatic cholangiocarcinoma more closely mirrors staging for pancreatic adenocarcinoma. For instance, there are four T-stages (T1-T4) without subcategories for T1 or T2, as in gallbladder cancer and perihilar cholangiocarcinoma, respectively. Furthermore, like pancreatic adenocarcinoma (and unlike gallbladder cancer and perihilar cholangiocarcinoma), nodal staging for distal extrahepatic cholangiocarcinoma is limited to N0 and N1 (there is no N2 subcategory).
- Grading of tumors is uniform for all biliary tract cancers; grade 1 is well differentiated, grade 2 is moderately differentiated, grade 3 is poorly differentiated, and grade 4 is undifferentiated.
- For all cases, Tis refers to carcinoma in situ.
- Gallbladder cancer TNM staging:
  - T-stage is determined by depth of invasion, starting with invasion of lamina propria (T1a), followed by muscular layer (T1b), perimuscular connective tissue (T2), serosa/visceral peritoneum (T3), or direct invasion of the liver and/or one other adjacent organ or structure (stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts; T3). Invasion of the main portal vein or hepatic artery or invasion of two or more extrahepatic organs or structures constitutes to T4.
  - Nodal staging for gallbladder cancer reflects echelons of lymphatic drainage. N1 disease refers to involvement of the first and second echelon lymph nodes (cystic duct, common bile duct, hepatic artery, and/or portal vein lymph nodes). N2 disease refers to involvement of third echelon lymph nodes (periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes).
  - Metastasis to distant sites is M1 disease.
  - Stages I (T1), II (T2), and IIIA (T3) refer to disease that does *not* involve lymph nodes (N0).
  - Stage IIIB disease is any N1 disease, unless the disease is T4 N0–1, which is categorized as stage IVA.
  - Involvement of second echelon nodes or metastatic disease (N2 or M1) is categorized as stage IVB.
- Perihilar extrahepatic cholangiocarcinoma TNM staging:
  - T-staging also reflects depth of invasion, starting with tumor confined to the bile duct involving muscle layer or fibrous tissue (T1), followed by extension beyond the bile duct into adipose (T2a) or into hepatic parenchyma (T2b). Invasion of unilateral branches of the portal vein or hepatic artery constitute T3, whereas invasion of the main portal vein or its branches bilaterally constitutes T4. Invasion of the common hepatic artery also qualifies as T4 disease.
  - N-staging and M-staging is identical to gallbladder cancer N-staging.
  - Stage grouping is identical to gallbladder cancer; there is no distinction between T2a and T2b for stage grouping.
- Distal extrahepatic cholangiocarcinoma TNM staging:
  - T-staging also reflects depth of invasion, starting with disease confined to the bile duct (T1), followed by disease beyond the bile duct wall (T2); invasion of the gallbladder, pancreas, duodenum, or other adjacent organs (T3); and celiac axis or SMA involvement (T4).
  - Nodal staging simply reflects presence (N1) or absence (N0) of malignant lymph nodes. M-staging is also binary (M0 versus M1).

  - Patients without nodal disease are grouped as stage IA (T1), stage IB (T2), or stage IIA (T3). Patients with T1–3 N1 disease are grouped as stage IIB. Stage III is synonymous with nonmetastatic T4 disease. Stage IV reflects metastatic disease.
- Perihilar cholangiocarcinomas or "Klatskin" tumors can be subclassified according to Bismuth-Corlette classification, depending on the relationship to the confluence of major hepatic ducts and the extent by which the disease involves one or both major hepatic ducts. Tumors distal to the confluence are stage I; tumors involving the confluence are stage II; tumors involving the confluence and either the right or left hepatic ducts are stage IIIa/b (respectively); multifocal tumors or tumors involving the confluence and both the right and left hepatic ducts are stage IV. Compared to AJCC TNM staging, this system may assist in determining resectability; Bismuth IV tumors are traditionally considered unresectable. However, the Bismuth classification system is most useful when assessed intraoperatively and does not account for vascular involvement (e.g., portal vein, hepatic artery), another key component of resectability.
- In addition to Bismuth classification, other tumor factors negatively influence resectability of gallbladder cancers and cholangiocarcinomas. These include invasion of hepatic artery, portal vein, or more proximal arterial supply (T4 disease), second echelon nodal disease (N2 disease, including (periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes), and liver or other distant metastases (M1).
- Although portal vein invasion impacts resectability, portal vein resection and reconstruction can be considered at highly specialized tertiary centers with experience in this technique.
- Patient factors that influence resectability include presence of underlying liver disease and medical comorbidities.

## 11.4 Prognostic Factors

- The majority of literature on prognosis for patients with gallbladder cancer and cholangiocarcinoma centers on findings at surgical pathology, which include node-positivity, tumor extent (T-stage), margin status, tumor differentiation, and presence of lymphovascular invasion (see Box 2).

### 11.4.1 Extrahepatic Cholangiocarcinoma

- In a set of 173 patients with hilar cholangiocarcinoma treated with curative surgical resection at Memorial Sloan Kettering Cancer Center, three pathologic features were prognostic for survival: node positivity, positive margins, and histologic grade. A nomogram containing these factors was a more accurate prognostic tool than the AJCC staging system, as validated in an external dataset containing 133 patients treated in The Netherlands [18].
- Using the combined dataset of 306 patients with hilar cholangiocarcinoma, Koerkamp et al. found that none of the 76 patients with initially node-positive disease survived beyond 7 years without recurrence (compared to estimated 24 % 8-year recurrence-free survival overall). In the same analysis, margin status, histologic grade, and insufficient nodal evaluation (<4 lymph nodes) were predictive of recurrence-free survival on multivariable analysis [19].
- Similarly, in a retrospective analysis of 121 consecutive hilar cholangiocarcinoma patients who underwent definitive surgical resection alone (17 % received adjuvant therapy), pathologic factors associated with worse prognosis on multiavariable analysis included node positivity, portal vein invasion, and positive margins [20].
- Of 381 patients who underwent curative resection of hilar cholangiocarcinoma in China, node positivity, tumor size > 3 cm, histologic grade, positive margins, and vascular invasion

were associated with worse overall survival on multivariable analysis [21].

- The prognostic impact of an R1 versus R0 resections has been observed in retrospective studies, especially in patients that did not receive adjuvant chemoradiotherapy [22, 23]. Adjuvant chemoradiotherapy may reduce the prognostic significance of R1 resection. SWOG 0809 included 25 patients with extrahepatic cholangiocarcinoma or gallbladder cancer who underwent resection and adjuvant chemoradiotherapy, and survival did not vary according to R0 and R1 resection [24].
- There is inconsistent data on the prognostic significance of preoperative CA 19–9 levels in cholangiocarcinoma. While a few studies have shown that preoperative CA 19–9 level is prognostic of outcome on univariate analysis, this was not consistently the case on multivariable analysis. Singal et al. demonstrated that CA 19–9 >100 U/mL predicts mortality in a dataset consisting of both intrahepatic and extrahepatic cholangiocarcinomas [25].
- However, the kinetics of CA 19–9 decline after two cycles of gemcitabine-based chemotherapy in locally advanced or metastatic cholangiocarcinoma were associated with better survival in a retrospective study of 179 patients [26].
- Other preoperative laboratory testing can also provide prognostic information. In the aforementioned study by Saito et al., laboratory values including CEA > 7.0 ng/mL, albumin < 3.5 g/ dL, C-reactive protein > 0.5 mg/dL, and platelet-lymphocyte ratio > 150 were all predictors for worse disease-specific survival [20]. A higher neutrophil-to-lymphocyte ratio, which has been investigated in several malignancies, was associated with poor survival in a cohort of patients with locally advanced or metastatic cholangiocarcinoma in Korea [27].

### 11.4.2 Gallbladder Cancer

- In gallbladder cancer, jaundice has been associated with poor prognosis. This is likely related to involvement of the gallbladder neck, which along with node-positivity, was an independent predictor of worse outcomes in 192 patients with gallbladder cancer that underwent curative resection in China [28]. Complete surgical resection may be more challenging in patients with bladder neck tumors.
- In patients with T3-T4 disease, inability to achieve an R0 resection can be a poor prognostic sign. From 78 patients with T3-T4 gallbladder cancer who underwent curative resection in Italy, none of those who had R1 resections survived to 5 years (compared to 17 % of patients with R0 resections). Of note, adjuvant radiotherapy was not administered, and data on adjuvant chemotherapy was sparse [29].
- As in extrahepatic cholangiocarcinoma, R1 resections have been associated with worse outcomes with gallbladder cancer, especially in patients that did not receive adjuvant chemoradiotherapy [30]. And likewise, adjuvant chemoradiotherapy may negate the prognostic influence of an R1 resection, as seen in SWOG 0809 [24].
- As expected, AJCC staging is prognostic for gallbladder cancer as well. In particular, stage group, T-stage, and liver involvement were found to be prognostic in a review of 42 patients who had undergone curative resection. Survival of patients with AJCC stage I-II disease was 100 %, compared to 80 % and 39 % in patients with stage III and IV disease, respectively [31].
- A separate analysis, however, indicated that only liver involvement was prognostic for survival in gallbladder cancer after adjusting for differences in rates of PNI, TNM stage, R0 resection rates, and CA 19–9 levels [32].

## 11.5 Molecular Biology

- Understanding of the genetics and molecular biology of cholangiocarcinomas and gallbladder cancers, while still nascent, holds promise for advances in therapy (see Box 1).

- The predominant mutations in cholangiocarcinomas and GB cancers, like in other GI malignancies (especially pancreatic adenocarcinoma), reside within the KRAS and tp53 genes. In a study examining the mutational status of 91 patients with CC (56 with perihilar CC), the most frequently mutated in EH-PCC were KRAS (47.4 %), TP53 (23.7 %), and SMAD4 [33]. Overexpression of mutant p53 was seen in 25 % and 69 % of flat-type or polypoid-type gallbladder carcinomas, respectively [34]. Others have reported up to 92 % of GB carcinomas overexpress p53 [35].
- The mutational profile of biliary tract cancers may be distinct and related to underlying etiology. For example, in addition to TP53, KRAS, and SMAD4 mutations common to pancreaticobiliary cancers, liver fluke-associated cholangiocarcinoma was found to have additional mutations in MLL3, ROBO2, RNF43 and PEG3, and GNAS [36].
- ErbB-2 (Her2/neu) expression is also aberrant in gallbladder cancers and cholangiocarcinomas. As few as 15 % and as many as 69 % of gallbladder cancers harbor ErbB-2 (Her-2/Neu) amplification [37, 38]. A similar rate (18 %) of ErbB-2 (Her-2/neu) overexpression was identified in extrahepatic cholangiocarcinoma by chromogenic in situ hybridization [39]. A role for the ErbB-2 (Her-2/neu) pathway in pathogenesis is supported by transgenic animal models of gallbladder cancer based on overexpression of erbB2 in biliary tract epithelium [40]. Clinical responses to therapies targeting the ErbB-2 (Her-2/neu) pathway in gallbladder cancer and cholangiocarcinoma have been observed, and this approach is under further investigation [37].
- In an immunotherapeutic approach, a subset of CD4+ T cells recognizing a mutation in ErbB-2 adoptively transferred into a patient with refractory and metastatic cholangiocarcinoma led to objective tumor response and prolonged survival. This suggests that cancers of the biliary tract may harbor immunogenic mutations that can be targeted by immunotherapeutic approaches [41].
- EGFR is also overexpressed in a significant proportion (25–94 %) of gallbladder cancers and cholangiocarcinomas [42, 43]. Leone et al. observed EGFR mutations in 15 % of 40 patients with gallbladder cancers and cholangiocarcinomas [44]. These mutations may represent targets for small-molecule EGFR tyrosine kinase inhibitors [45].
- AKT pathway proteins (PTEN, p-AKT, and p-mTOR) were overexpressed in a microarray set of 221 extrahepatic cholangiocarcinomas and were associated with worse outcomes [46]. This highlights a pathway shared by a variety of malignancies and the potential for applying mTOR- or AKT-directed therapies to cholangiocarcinomas.
- Cholangiocarcinomas can also harbor fibroblast growth factor receptor 2 (FGFR2) fusions, which may be more sensitive to targeting by FGFR inhibitors than activating FGFR point mutations [47].
- Many of the proposed epidemiological risk factors for gallbladder cancer and cholangiocarcinoma (liver fluke infestation, cholelithiasis, primary sclerosing cholangitis) point toward an inflammatory component to the pathophysiology. Indeed, malignancy-related inflammatory cytokines and chemokines, including IL-6 and TNF-alpha, as well as the proinflammatory enzyme COX-2, have been implicated in the microenvironment of cholangiocarcinomas and gallbladder cancers [48–50].
- The resulting inflammatory tumor microenvironment contains macrophages which can promote tumor growth through pathways such as WNT signaling [51].

## 11.6 Patterns of Failure

- Surgery is the mainstay of treatment for gallbladder cancer and cholangiocarcinoma. However, despite aggressive surgical intervention, failures are common and can occur in the postoperative bed, regional lymph nodes, and distant metastatic sites, with varying frequency (see Table 11.1).

**Table 11.1** Patterns of initial failure

| | | Isolated locoregional failure rate (%) | Initial distant failure rate (%) |
|---|---|---|---|
| Extrahepatic/hilar cholangiocarcinoma | Surgery alone | 4–34 | 24–40 |
| | +adjuvant chemoradiotherapy (SWOG 0809) | 8 | 29 |
| Gallbladder cancer | Surgery alone[a] | 3–33 | 15–51 |
| | +adjuvant chemoradiotherapy (SWOG 0809) | 0 | 44 |

A limited number of studies reported initial patterns of failure [19, 24, 29, 52, 53, 69]
[a]Most studies of gallbladder cancer reported higher recurrence rates, owing to a lower proportion of patients with stage I/II disease

### 11.6.1 Extrahepatic Cholangiocarcinoma Patterns of Failure

- In a retrospective study of 306 patients with hilar cholangiocarcinoma treated with primary surgery (8 % received adjuvant chemotherapy; 8 % received adjuvant radiotherapy), 58 % recurred. Only 18 % of patients had an isolated initial local recurrence (at the liver hilum, hepaticojejunostomy, liver resection margin, or distal bile duct remnant). Another 8 % of patients had a local recurrence that occurred synchronously with a distant recurrence. The majority of recurrences (69 %) included initial distant recurrences (retroperitoneal lymph nodes, distant intrahepatic site, peritoneum, or lungs) [19].
- Recurrence rates for hilar cholangiocarcinomas after curative intent resection ranged from 49–66 % across 6 studies, while only 4–18 % of patients had an isolated local recurrence [19].
- Another large retrospective study including 76 evaluable patients with hilar cholangiocarcinoma reported a recurrence rate of 68 %. Eighteen of all 76 patients (24 %) recurred initially at a distant site (site of first disease recurrence was not definitively known in 8 patients). In contrast, 26 of 76 patients (34 %) had an isolated locoregional failure (including tumor bed, porta hepatis, and retroperitoneal lymph nodes) [52].
- Results of the prospective SWOG 0809, in which all patients had adjuvant chemoradiotherapy in addition to curative intent surgery, indicated a low rate of isolated local recurrence for patients with hilar cholangiocarcinoma (1 of 13 patients, 8 %). A total of 4 of 13 patients (31 %) with hilar cholangiocarcinoma recurred [24].

### 11.6.2 Gallbladder Cancer Patterns of Failure

- The retrospective analysis by Jarnagin et al. included 80 patients with gallbladder cancer treated with primary surgery (only 14 % received adjuvant therapy). The authors reported a recurrence rate of 66 % [52]. Distant recurrence was the predominant pattern of failure; the initial recurrence was at a distant site in 41 of 80 patients (51 %, first site of recurrence was not definitively known in five patients). Only 7 of 80 patients (9 %) suffered an isolated local failure. Interestingly, recurrences in patients with gallbladder cancer occurred earlier than recurrences in patients with hilar cholangiocarcinoma, a finding also observed in SWOG 0809.
- In a retrospective study of 163 patients with incidental findings of gallbladder cancer (127 of whom underwent re-resection), only 6 patients (4 %) received adjuvant radiotherapy, whereas 31 % received adjuvant chemotherapy. In this context, approximately 20 % of patients recurred at 2 years, 75 % of whom had an isolated distant failure compared to 12.5 % with an isolated local failure. The low recurrence rate may be partly due to inclusion

of a significant number of patients with stage I/II disease (62 %). The presence of lymph node metastasis was the single predictor of disease-free survival on multivariate analysis and 25 % of muscle invasive (T1b) cases presented with lymph node metastases, suggesting that patients with T1b disease may benefit from radical resection including a radical lymphadenectomy [53].

- In a subset of 78 patients with T3-T4 disease, the overall recurrence rate after surgical resection was higher (76 %). Only 33 % of all patients had an isolated hepatic (or local) recurrence, compared to 42 % with either an extrahepatic or combined hepatic and extrahepatic recurrence [29].
- In contrast, of the 25 patients enrolled on SWOG 0809 with gallbladder cancer treated with definitive surgery and adjuvant chemoradiotherapy, 52 % had a recurrence after a median follow-up of 35 months. None of these recurrences were isolated local failures [24].

## 11.7 Rationale for Adjuvant Therapy

- The high rates of locoregional and distant recurrence in gallbladder cancer and extrahepatic cholangiocarcinoma have led to the use of adjuvant chemotherapy, radiotherapy, and chemoradiotherapy to limit failure rates after surgery with the prospect of improving long-term outcomes including survival.
- While there is no high-level evidence to support its use, adjuvant therapy is commonly administered given the propensity for these tumors to recur.
- A randomized phase III study of adjuvant chemotherapy versus observation in pancreaticobiliary malignancies from Japan conducted between 1986–1992 included 139 patients with cholangiocarcinoma and 140 patients with gallbladder cancer. The authors reported improved 5-year survival with adjuvant chemotherapy (mitomycin C and 5-fulorouracil) in patients with gallbladder cancer. Although the survival difference was not observed in the cholangiocarcinoma group, the authors noted a trend toward improved disease-free survival with adjuvant chemotherapy [54].
- SWOG 0809 is a recently published single-arm phase 2 study of adjuvant chemoradiotherapy after resection of gallbladder cancer and extrahepatic cholangiocarcinoma, which demonstrated feasibility of performing a prospective trial in a rare disease population and established baseline outcomes with a commonly used adjuvant approach [24]. See Sect 11.8 for details.
- SWOG 0809 was published after many retrospective analyses of adjuvant radiotherapy and chemoradiotherapy in gallbladder cancer and extrahepatic cholangiocarcinoma, a few summarized below:
  - Kim et al. reported on 168 patients with extrahepatic biliary tract cancer who underwent resection [55]. Postoperative chemoradiation with concurrent 5-fluorouracil-based chemotherapy was administered to 115 of 168 patients. After a median follow-up of 33.8 months, the median survival was 36.4 months in the adjuvant treatment group, versus 27.9 months in the observation group, which was statistically significant on multivariate analysis ($p$=0.005). Likewise, locoregional failure was lower in the adjuvant treatment group on multivariate analysis ($p$=0.001).
  - In 2012, a systemic review and meta-analysis of adjuvant therapy in biliary tract cancer presented data on 20 studies between 1960 and 2010 involving 6712 patients with gallbladder and biliary tract tumors [56]. Adjuvant therapy (including chemotherapy, radiation, and chemoradiation) was associated with a borderline significant improvement in survival ($p = 0.06$). In patients who had undergone R1 resections, adjuvant radiation had a survival benefit ($p$=0.01).
  - In contrast, other series have been more equivocal in regard to benefit of adjuvant radiation therapy. Sagawa et al., reporting on patients with hilar cholangiocarcinoma

who underwent surgical resection, did not reveal an overall survival benefit in a subset that received adjuvant radiation [57].
  - Population studies have not demonstrated a clear benefit with adjuvant radiotherapy. In a Surveillance, Epidemiology, and End Results (SEER) analysis by Shinohara et al., 4758 patients with extrahepatic cholangiocarcinomas treated with surgery or radiation between 1998 and 2003 were assessed for overall survival [58]. Although the median survival was 16 months in the surgery and radiation group compared to 9 months with surgery alone ($p<0.0001$), this did not hold after adjusting for potential confounders.
  - For gallbladder cancer, a study of 73 patients with stage I and II disease who underwent R0 resection reported that overall survival was statistically improved with adjuvant chemoradiation on multivariate analysis, adjusting for T and N stage, as well as pathologic diagnosis [59].
- In summary, the poor outcomes with surgery alone, along with extensive retrospective and limited prospective data, suggest that adjuvant therapies should be strongly considered in patients with gallbladder cancer and extrahepatic cholangiocarcinoma.

## 11.8 Multidisciplinary Treatment by Presentation

- Gallbladder cancer: incidental finding at time of cholecystectomy
  - If T1a: observe.
  - If ≥T1b or positive margin, needs further staging and treatment:
    - Obtain CT or MRI of the abdomen for local staging; consider MRCP.
    - CT chest to rule out distant metastasis.
    - If resectable, proceed with radical cholecystectomy, which includes hepatic resection, lymphadenectomy, and may require bile duct excision.
- Imaging finding of a *resectable* gallbladder mass or extrahepatic cholangiocarcinoma
  - Evaluation and work-up:
    - Assess medical comorbidities and tolerance of hepatic resection.
    - Obtain CT or MRI of the abdomen for local staging; consider MRCP.
    - CT chest to assess for distant metastatic disease.
    - Obtain baseline CA 19–9, CEA.
    - If elevated bilirubin or jaundiced, evaluate for biliary drainage preoperatively.
  - Standard Approach:
    - Gallbladder Cancer
      - If resectable, proceed with diagnostic laparoscopy [60]. If negative, proceed with radical cholecystectomy, which includes resection of at least a rind of hepatic parenchyma (and often hepatic segmentectomy), lymphadenectomy, and may require bile duct excision.
    - Extrahepatic cholangiocarcinoma
      - For resectable disease, diagnostic laparoscopy can be considered in select patients at higher risk for distant metastasis [61].
      - For hilar cholangiocarcinoma, surgery requires resection of the involved extrahepatic biliary structures and hepatectomy (commonly, extended right hepatectomy or left hepatectomy), as well as a biliary-enteric anastomosis (choledocho- or hepaticojejunostomy).
      - Preoperative biliary drainage and/or portal vein embolization can be considered in select patients with hilar cholangiocarcinoma to decrease the likelihood of liver failure [62].
      - For distal extrahepatic cholangiocarcinoma, resection involves removal of the involved extrahepatic biliary ducts, usually with a pancreaticoduodenectomy and biliary-enteric anastomosis.

  - Alternative approach for select patients at select centers:
    - For extrahepatic (hilar) cholangiocarcinoma with disease confined to the primary site without nodal metastasis (includes patients with primary sclerosing cholangitis), consider neoadjuvant chemoradiotherapy (including brachytherapy) followed by orthotopic liver transplantation [63].
      - Selection criteria include patients with pathologically confirmed diagnosis of hilar cholangiocarcinoma or a lesion (< 3 cm diameter) on imaging causing biliary obstruction on cholangiography with malignant endoluminal brushings.
      - Neoadjuvant therapy involves external beam radiation with concurrent chemotherapy (bolus intravenous 5-fluorouracil) followed by transluminal brachytherapy with Iridium-192 delivered through biliary catheters. Patients are then treated with 5-fluorouracil or capecitabine until transplantation.
      - Patients then undergo a staging surgical procedure to rule out presence of pathologic lymphadenopathy.
      - Of 71 patients with unresectable cholangiocarcinoma on a transplant treatment protocol at the Mayo Clinic, 38 underwent transplantation, among whom 5-year survival was 82 % (or 58 % if calculated on an intent-to-transplant basis) [63]. Twelve transplant centers combined data and reported a 5-year survival rate of 53 % (intent-to-treat analysis) [64]. Of transplanted patients, 65 % remained disease-free. Drop-out rate from transplant was 25 %.
- Adjuvant therapy after surgical resection of gallbladder cancer or extrahepatic cholangiocarcinoma:
  - Strongly consider adjuvant therapy in all patients with gallbladder cancer except T1aN0M0 gallbladder cancer (see Sect 11.6). Strongly consider adjuvant therapy in all patients with extrahepatic cholangiocarcinoma.
  - Adjuvant therapy can include one of several approaches involving chemotherapy and radiation. In general, these approaches include:
    - (1) Concurrent chemoradiotherapy
    - (2) Chemotherapy, followed by concurrent chemoradiotherapy
    - (3) Chemotherapy, followed by concurrent chemoradiotherapy, followed by additional chemotherapy
    - (4) Chemotherapy alone
    - (5) Radiotherapy alone (when patient unable to tolerate systemic therapy)
  - To determine the appropriate adjuvant approach, weigh the risks of locoregional versus distant disease recurrence.
    - Patients with a high likelihood of distant recurrence: extensive or second echelon nodal disease, baseline CA 19–9 > 100 U/mL, imaging findings suspicious but not conclusive for distant metastases
    - Patients with a high likelihood of locoregional recurrence: T3/T4 tumors, biliary obstruction or other local disease symptoms at presentation, incomplete or margin-positive resection, lymphovascular invasion/perineural invasion
  - For most patients, consider initial course of systemic therapy, followed by chemoradiotherapy if patient does not develop distant metastasis.
  - For patients at high-risk for locoregional recurrence, consider upfront chemoradiotherapy.
- Imaging finding of an *unresectable*, nonmetastatic gallbladder cancer or extrahepatic cholangiocarcinoma; unresectable due to second echelon nodal involvement or extensive primary tumor invasion (e.g., vascular invasion)

  - Obtain CT or MRI of the abdomen for local staging.
  - CT chest to assess for distant metastatic disease.
  - Baseline CA 19–9, CEA.
  - If elevated bilirubin or jaundiced, evaluate for biliary drainage prior to therapy.
  - Assess tolerance for systemic therapy.
  - Proceed with systemic therapy with or without radiotherapy.
    - Consider upfront chemoradiotherapy in patients with locally symptomatic or T3/T4 disease.
    - In patients with greater concern for metastatic dissemination, consider upfront chemotherapy followed by chemoradiotherapy if there is no evidence of distant metastasis.
- Metastatic disease
  - Clinical trial enrollment where possible.
  - Proceed with systemic therapy.
  - Consider local therapies, including radiation, biliary stenting, and biliary drainage for palliation.
  - Multidisciplinary supportive and palliative care.
- Systemic therapy choices
  - Chemotherapy alone for metastatic or unresectable disease:
    - Gemcitabine and cisplatin
    - Alternative chemotherapy alone options:
      - Gemcitabine and oxaliplatin (patients unable to tolerate cisplatin)
      - Gemcitabine alone (elderly patients or patients with comorbidities)
      - Clinical trial
  - Chemotherapy alone in the adjuvant setting:
    - Gemcitabine and capecitabine
    - Gemcitabine and cisplatin (investigational)
  - Chemotherapy concurrent with radiotherapy:
    - Capecitabine
    - 5-fluorouracil
    - Gemcitabine (with caution)
- Radiation therapy details: see the next chapter

## 11.9 Key Clinical Trials, Outcomes

- Systemic therapy versus Best Supportive Cancer for Unresectable Gallbladder Cancer
  - Randomized study of 81 patients [65].
    - (1) Best supportive care versus (2) fluorouracil and folinic acid versus (3) modified gemcitabine and oxaliplatin.
  - Response rates were 0 %, 14.3 % and 30.8 % in arms (1), (2), and (3), respectively.
  - Median overall survival: 4.5, 4.6, and 9.6 months, respectively.
- ABC-02: Gemcitabine plus cisplatin versus gemcitabine alone for advanced biliary cancers
  - This was a phase 3 randomized study and a continuation of ABC-01, a phase 2 study demonstrating improved progression-free survival with gemcitabine plus cisplatin compared to gemcitabine alone [66].
  - The study included 410 patients with locally advanced (25 %) and metastatic (75 %) cancer of the gallbladder (36 %), biliary tract (59 %) and ampulla (5 %).
  - Gemcitabine plus cisplatin improved progression-free and overall survival compared to gemcitabine alone:
    - Median survival: 11.7 months versus 8.1 months
    - Progression-free survival: 8 months versus 5 months
  - Gemcitabine plus cisplatin was associated with higher rates of neutropenia. Gemcitabine alone was associated with higher rates of worsening liver function, likely related to disease progression.
- SWOG 0809: adjuvant chemoradiotherapy for gallbladder cancer and extrahepatic cholangiocarcinoma
  - This was the first prospective study of adjuvant therapy in biliary tract cancers; single-arm phase 2 study of 79 patients, including hilar cholangiocarcinoma ($n$=38), distal extrahepatic cholangiocarcinoma ($n$=13), and gallbladder cancer ($n$=25); 83 % of patients had pathologic stage IIB disease or higher [24].

- Median survival was 35 months.
- Isolated local failures were observed in 14 %, isolated distant failures in 24 %.
- The authors observed a high rate of R0 resection (68 %); there was no difference in outcomes between R0 and R1 patients.
- Only three patients discontinued therapy due to adverse effects.

## 11.10 Future Directions

- NCT00363584 is a randomized phase 3 study from the United Kingdom of capecitabine versus observation after surgery in patients with extrahepatic cholangiocarcinoma or gallbladder cancer, which has completed accrual (360 patients). Results are pending.
- ACTICCA-1 is an ongoing European study investigating adjuvant gemcitabine and cisplatin versus observation after curative intent resection of cholangiocarcinoma and muscle invasive gallbladder carcinoma [67]. This trial is based on positive results with the use of gemcitabine and cisplatin from the ABC-02 study.
- Targeted therapeutic approaches aimed at EGFR, MEK, FGFR2, and VEGFR pathways, as well as mTOR inhibitors and multi-targeted tyrosine kinase inhibitors are under investigation in advanced extrahepatic cholangiocarcinoma and gallbladder cancer.
- Early clinical data suggest that immunotherapy, already with measurable impact in solid tumors including melanoma, non-small cell lung cancer and renal cell carcinoma, may have a role in gastrointestinal malignancies. The potential for adoptive T cell therapy in metastatic cholangiocarcinoma has been demonstrated [41], and the activity of immune checkpoint blockade in advanced biliary cancers is under investigation. Vaccine approaches, which have demonstrated benefit in pancreatic adenocarcinoma, may hold promise for biliary tract malignancies given their shared features [68].

**Box 11.1 Common Genetic Alterations and Potential Molecular Targets in Extrahepatic Cholangiocarcinoma and Gallbladder Cancer**

| |
|---|
| P53 |
| KRAS |
| ErbB-2 (Her-2) |
| EGFR |
| AKT pathway (including AKT, mTOR, PTEN) |
| FGFR2 |

**Box 11.2. Key Predictors of Poor Prognosis**

| |
|---|
| Node-positive disease |
| Extent of resection |
| Vascular invasion and/or adjacent organ involvement (T4 disease) |
| Elevated baseline CA 19–9 |
| Histologic grade |
| Extent of nodal evaluation |

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# Biliary Cancer: Radiation Therapy Planning

12

Anusha Kalbasi and Edgar Ben-Josef

## 12.1 Introduction

Radiation therapy, as discussed in the previous chapter, is a critical part of the multidisciplinary care of patients with gallbladder cancers and extrahepatic cholangiocarcinomas. Radiation can help augment locoregional control in the adjuvant setting, limit disease progression in the unresectable setting, and provide palliation for metastatic disease. However, there is no high-level evidence for the benefit of radiotherapy in biliary cancers. Thus, the approach to targets and dose must be personalized, with respect to the goals of therapy and limiting treatment toxicities. Here, we will review radiation treatment planning, including simulation, target definition, tolerance of organs at risk, and dose and technique selection.

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## 12.2 Principles of Field Design/ Patterns of Failure and Relevant Anatomy

- The retrospective studies in which radiotherapy was examined for gallbladder cancer and extrahepatic cholangiocarcinoma predominantly utilized 3D-conformal technique. SWOG 0809, a study of adjuvant chemoradiotherapy for these malignancies, allowed the use of both 3D-conformal and intensity-modulated radiotherapy. In both cases, target structures and organs at risk should be contoured.
- In the adjuvant setting, the clinical target volume (CTV) is defined by the surgical bed and the lymphatic drainage basin, based on patterns of failure as described in the previous chapter. This is generally true in the definitive setting, although coverage of at-risk nodal regions is more controversial (see Figs. 12.1a–f and 12.2a–f).
- The surgical bed is best defined by careful examination of the operative report and may be highlighted on imaging by radiopaque clips or staples left by the surgeon. Normal anatomic relationships may be disrupted postoperatively. Careful study of the preoperative scans and detailed discussion with the surgeon are critical.
- For hilar cholangiocarcinoma, surgery requires resection of the involved extrahepatic

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T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_12

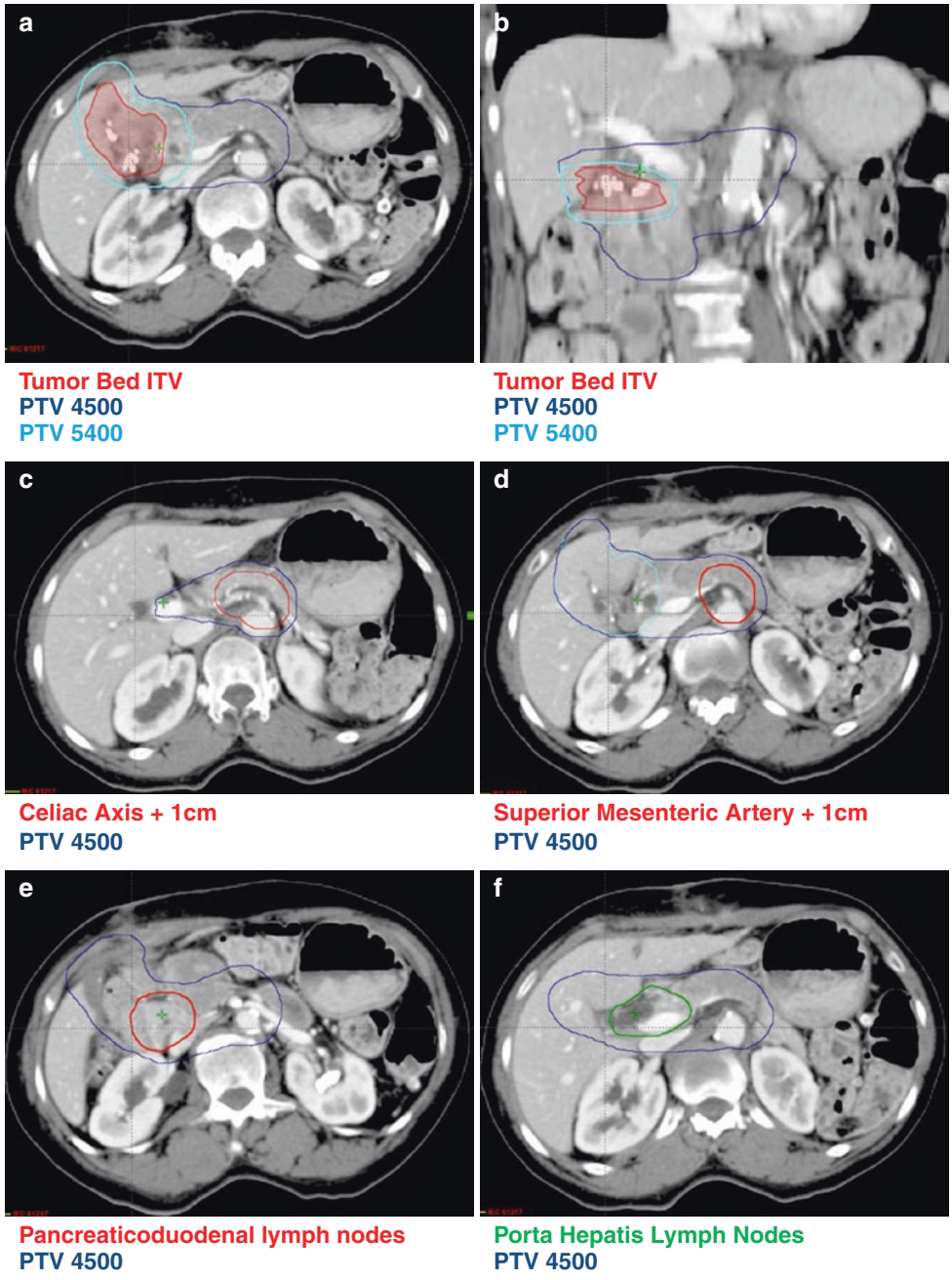


**Fig. 12.1** Representative contours for postoperative external beam radiotherapy of a pT2N1M0 stage IIIB adenocarcinoma of the gallbladder. Representative axial (**a**) and coronal (**b**) sections of the tumor bed ITV as well as the PTV volumes receiving 4500 and 5400 cGy. Tumor bed ITV was generated based on 4D-CT images. Representative contours of the celiac axis (**c**) and superior mesenteric artery (**d**) expansions that comprise the PTV receiving 4500 cGy. Representative contours of the pancreaticoduodenal (**e**) and porta hepatis (**f**) lymph node regions that also comprise the PTV receiving 4500 cGy

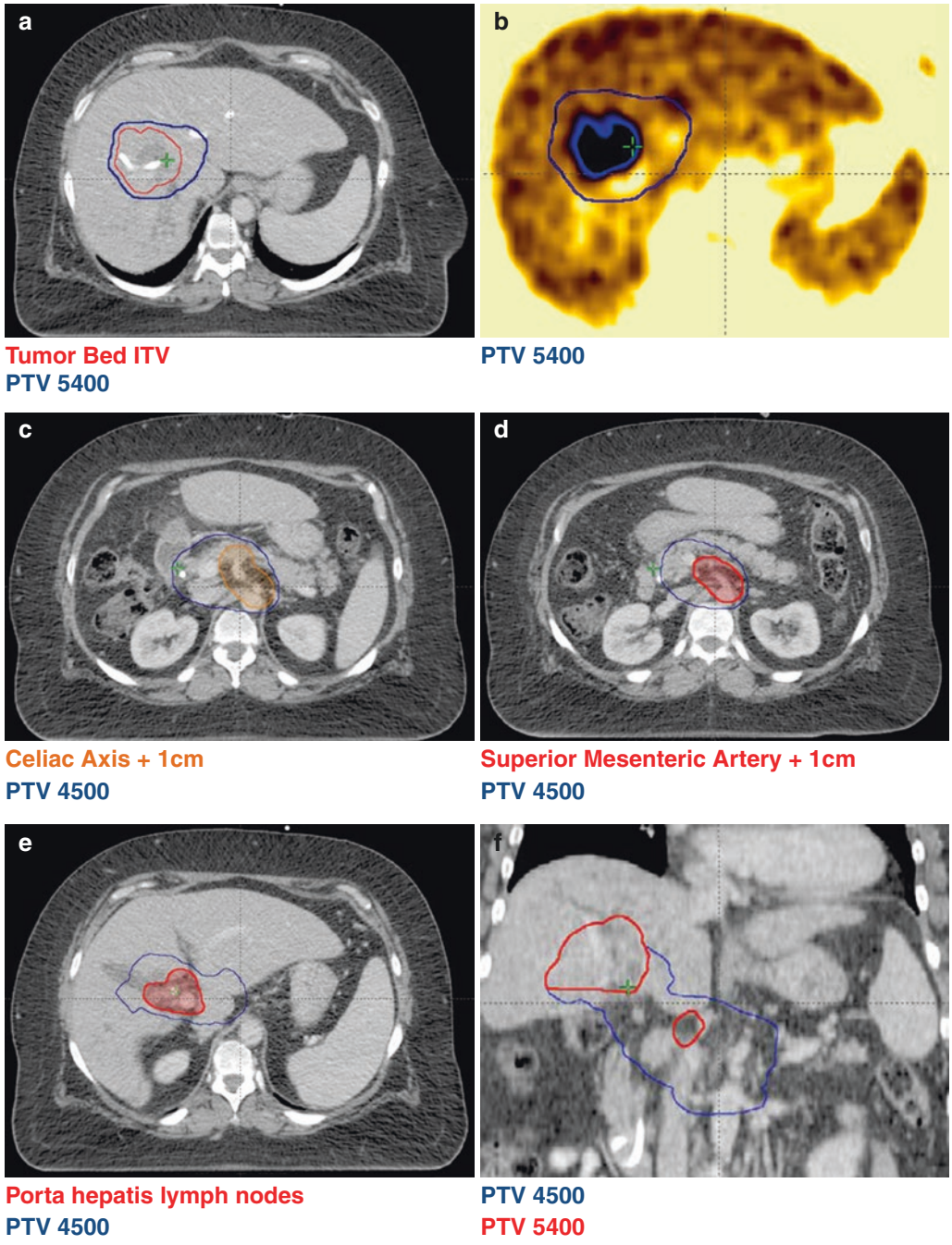


**Fig. 12.2** Representative contours for definitive external beam radiotherapy of a cT2bN1M0 stage IIIB hilar cholangiocarcinoma with positive surgical margins. Representative axial (**a**) section of the primary tumor ITV as well as the PTV for the 4500 cGy dose level. Tumor ITV was generated based on 4D-CT images. (**b**) Axial section of PET scan with overlay of PTV for the 4500 cGy dose level. (**c**) Representative contours of the celiac axis (**c**) and superior mesenteric artery (**d**) expansions that comprise the PTV for the 4500 cGy dose level. (**e**) Representative contours of the porta hepatis lymph node region that comprises the PTV receiving 4500 cGy. (**f**) Coronal section with overlays of the PTV for 4500 and 5400 cGy dose levels

biliary structures and adjacent hepatic parenchyma, as well as a biliary-enteric anastomosis (choledocho- or hepatico-jejunostomy). Thus, the surgical bed tracks along the medial aspect of the remaining liver, within a reasonable radius around surgical clips, and includes the surgical anastomosis.

- For distal extrahepatic cholangiocarcinoma, resection involves the involved extrahepatic biliary ducts, with or without a pancreaticoduodenectomy and biliary-enteric anastomosis. The postoperative bed is centered on the new anastomosis between the biliary tree and small bowel and guided by surgical clips.
- For gallbladder cancer, surgery requires radical or extended cholecystectomy, which involves resection of a margin of hepatic tissue around the gallbladder. This relates to the tendency of gallbladder cancers to infiltrate through Rokitansky-Aschoff sinuses and the gallbladder wall into adjacent hepatic tissue. Thus, the tumor bed includes a rim of hepatic tissue in the space previously occupied by the gallbladder (as indicated by surgical clips, see Fig. 12.1a, b).
- The pattern of lymphatic drainage for extrahepatic and hilar cholangiocarcinomas has been described in a study using blue dye technique [1].
- The first site of drainage is the pericholedochal lymph node station. The lymphatic drainage then descends either along the portal vein into the surrounding nodes, along the common hepatic artery into the surrounding nodes, or along the biliary tree to the pancreaticoduodenal node station.
- Notably, lymph flow does not ascend toward the hepatic hilum. The tertiary nodal stations include the nodes surrounding the celiac axis and superior mesenteric artery as well as the aortocaval nodes.
- This lymphatic flow pattern is supported by clinical studies. In a study by Kitagawa et al., 110 patients underwent lymph node dissection in addition to surgical resection, of which 52 % of patients had nodal disease [2]. The pericholedochal lymph node group was the most frequent site of lymph node metastasis (42 %), followed by the nodes along the portal vein (31 %), nodes along the common hepatic artery (27 %), and the pancreaticoduodenal nodes (15 %).

## 12.3 Simulation (Including Motion Management, IGRT)

- CT simulation with intravenous and oral contrast.
- Arms up in shuttle board, partial body vacuum-lock bag for immobilization.
- 4D-CT to evaluate target motion and creation of internal target volume (ITV).
- If gross disease is suspected, consider MRI simulation or fusion with MRI images for target delineation.
- For treatment, use daily orthogonal kV images for IGRT, with weekly cone beam CT to evaluate target coverage and bowel/target interface changes.

## 12.4 Dose

- General external beam radiation therapy dose guidelines:
  - Gross disease with margin for microscopic extension and daily setup variation treated with 54 Gy to 64.8 Gy in 1.8 Gy per fraction respecting tolerance of organs at risk.
  - Postoperative bed treated with 50.4 to 59.4 Gy in 1.8 Gy per fraction, with consideration to margin status and organs at risk.
  - At-risk nodal stations treated to 45 Gy in 1.8 Gy per fraction.
  - Intensity-modulated radiotherapy (IMRT) technique can be considered to spare organs at risk (see Fig. 12.3a–c).
- There is limited data to guide dose selection in radiation therapy of cancers of the gallbladder and bile ducts. Most series support radiation doses consistent with other tumors of the gastrointestinal tract because of shared OARs. The use of concurrent chemotherapy should also be considered in dose determination.

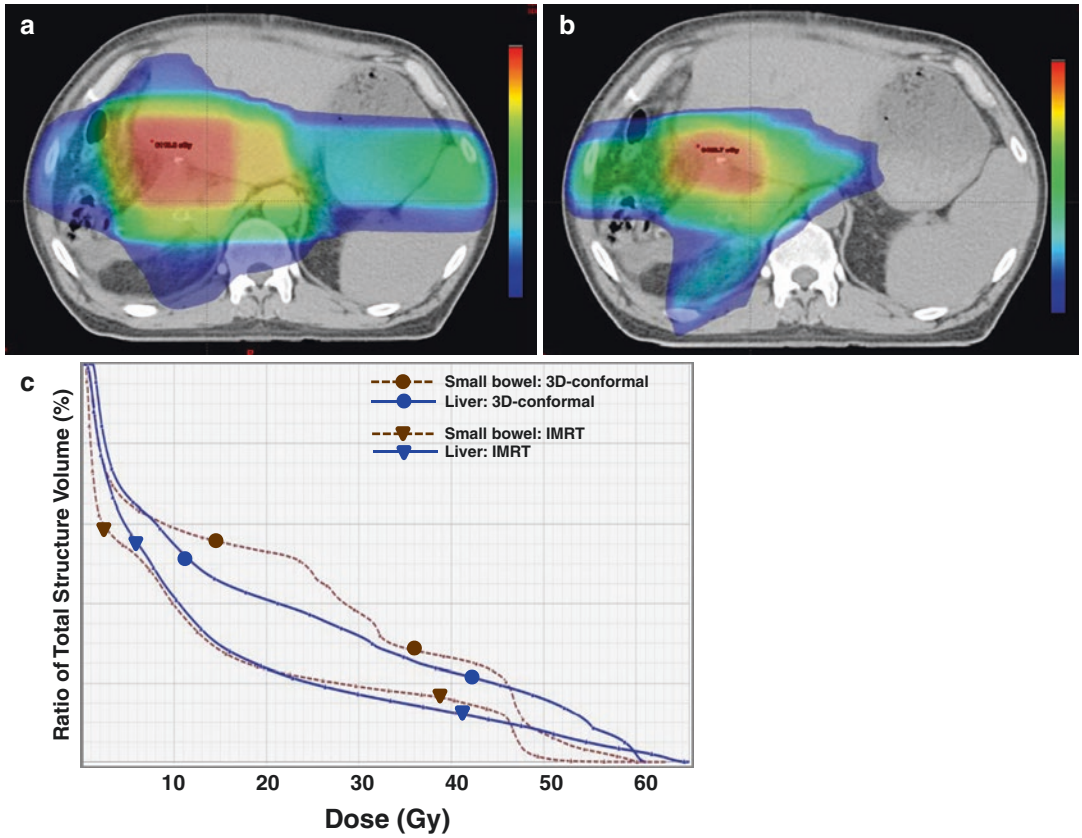


**Fig. 12.3** Dose distribution of external beam radiation for postoperative treatment of extrahepatic cholangiocarcinoma, using 3D-conformal technique with four fields (**a**) and intensity-modulated radiotherapy (IMRT) (**b**). Dose range shown is 25 Gy (*blue*) to 64 Gy (*red*). In (**c**), dose volume histogram shows sparing of the liver and small bowel with IMRT (Previously published in: Kalbasi and Ben-Josef [26])

- For extrahepatic and hilar cholangiocarcinoma, in the adjuvant setting, most studies using external beam radiotherapy alone report median doses ranging from 45 to 54 Gy in 1.8–2.0 Gy per fraction [3–7]. Similar doses were utilized in studies of adjuvant radiation in gallbladder cancers [8–10].
- In the unresectable or definitive setting, for typical fractionated radiotherapy, most recent studies have reported similar doses – 45–60 Gy in standard 1.8–2.0 Gy per fraction [4, 10–12]. Given the pattern of failure and the stated goal of delaying progression for as long as possible, a reasonable approach would be to deliver as high a dose as safely possible given the OAR constraints.

## 12.5 Contours

Please refer to Figs. 12.1a–f and 12.2a–f for this section.

- GTV
  - Any gross residual disease on imaging is the gross tumor volume (GTV) and should be delineated separately.
- CTV
  - Include the GTV with a margin for microscopic extension (~1.0–1.5 cm).
  - In the adjuvant setting, the postoperative bed and related anastomoses are included in the CTV, which are described in detail in Figure 12.1a and 12.1b.

  - In the adjuvant setting, the regional lymph nodes are included in the CTV.
    - Regional lymph nodes for extrahepatic and hilar cholangiocarcinoma thus include the pericholedochal lymph nodes. For hilar cholangiocarcinomas, these nodes are within the hepatic hilum and porta hepatis.
    - The CTV also extends to a 1 cm margin around the portal vein from the hepatic hilum to its junction with superior mesenteric and splenic veins to include the surrounding nodes.
    - To encompass the pancreaticoduodenal nodes, the CTV will also include the area surrounding the groove between the pancreatic head and duodenum, and in particular its posterior aspect, with a 0.5–1.0 cm margin.
    - The celiac trunk and the proximal superior mesenteric artery, also typically with a 1 cm margin, are also within the CTV to include corresponding lymph nodes (similar to RTOG guidelines for postoperative treatment of pancreatic cancer).
    - For distal extrahepatic cholangiocarcinoma, para-aortic lymph nodes can be included.
  - For intact extrahepatic cholangiocarcinoma and gallbladder cancer, the regional nodes have typically also been included in the CTV. However, given the patterns of failure (primarily at the site of gross disease or at distant sites), the rationale for this practice is debatable.
- ITV
  - Using 4D-CT, adjust volumes to encompass all targets on all phases of breathing cycle. This is most straightforward when gross disease is present. For 4D adjustments to the postoperative bed and lymph node regions, surgical clips and anatomical boundaries (e.g., vessels) to lymph node groups can be helpful.
- PTV
  - Add 0.5 cm to CTV in all directions for daily setup variation, but this will depend on immobilization and the type and frequency of IGRT.

## 12.6 Normal Structures and Constraints

- Left or right kidney: V20 Gy <33 %; combined kidney mean <18 Gy.
- Liver: mean dose <30 Gy if no underlying liver dysfunction; 700 cc ≤15 Gy (for SBRT).
- Stomach and small bowel: maximum dose ≤54 Gy, 2 % of volume between 50 and 54 Gy, 25 % between 45 and 54 Gy. If the small bowel contoured as a bag, use V45 Gy <150 cc. If the small bowel contoured as loops of bowel, use V15 Gy <120 cc.
- Duodenum: maximum dose ≤56 Gy; no more than 1 cc >55 Gy; <33 % of volume between 45 and 54 Gy.
- Spinal cord: maximum dose ≤45 Gy.
- Gallbladder: maximum dose ≤60 Gy; 75 % of volume less than 55 Gy.

## 12.7 Special Considerations

### 12.7.1 Brachytherapy

- Brachytherapy is an option for patients with extrahepatic cholangiocarcinoma and gallbladder cancer when the target extends radially no more than 1 cm from the biliary duct. It can be used in three scenarios: (1) as a boost after external beam radiotherapy, (2) adjuvant therapy after surgery (e.g., intraoperative), and (3) palliation [13].
  - For biliary tumors, high-dose brachytherapy is preferred and is administered through intraluminal catheters that are often placed by interventional radiologists to relieve biliary obstruction.
    - If the biliary drain traverses the tumor obstruction, it is well positioned for placement of a brachytherapy catheter using fluoroscopy.
    - The brachytherapy catheter, once in place, is connected to an afterloader for

delivery of the high-dose rate brachytherapy source.
- The dose is prescribed 1 cm from the source.
- For a boost after external beam radiotherapy, 15–20 Gy is delivered in 3–4 fractions.
- For definitive treatment of gross disease, 30–40 Gy is delivered in 5–8 fractions BID.
- For patients with hilar cholangiocarcinoma enrolled on a liver transplantation protocol, brachytherapy is used in combination with external beam radiotherapy (45 Gy) as part of the neoadjuvant treatment approach. Various high-dose rate brachytherapy prescriptions have been reported, typically with iridium-192, ranging from 1025 to 3000 cGy [14, 15].

– Intraoperative radiation therapy using interstitial brachytherapy can be utilized for unresectable tumors or tumors with great concern for positive margins, but these are often hepatic tumors rather than extrahepatic cholangiocarcinomas or gallbladder cancers.

### 12.7.2 Stereotactic Body Radiotherapy

- A few groups have investigated the use of stereotactic body radiotherapy (SBRT) [16–18].
- This approach is not standard for extrahepatic cholangiocarcinomas and gallbladder cancers given the proximity to central biliary structures and viscous organs including the bowel and gallbladder.
- However, SBRT at conservative doses may be an alternative in cases where only gross disease is targeted.
  – In a retrospective review of patients treated with SBRT for hepatocellular carcinoma (mostly 40 Gy in 5 fractions), the gallbladder or biliary tract received > 20 Gy in 55 cases. After a limited median follow-up of 18 months, there were only two cases of asymptomatic biliary stenosis [19].
- For patients with hilar cholangiocarcinoma enrolled on a liver transplantation protocol, SBRT has been used alone or in combination with external beam radiotherapy as part of the neoadjuvant treatment approach [15, 20]. Doses range from 40 to 60 Gy in 3–5 fractions.

### 12.7.3 Proton Radiotherapy

- Proton radiotherapy can be considered as a modality when treating patients with gallbladder and extrahepatic cholangiocarcinoma with external beam radiotherapy.
- Because of the finite penetration of protons within tissue, most of the therapeutic dose can be delivered within a narrow window near the target. In particular, tissues beyond the target can be spared more effectively than with photon radiotherapy.
- In hepatic and biliary tumors, this approach can be advantageous to reduce mean liver dose, a critical determinant of liver toxicity [21–24].
- For hilar cholangiocarcinoma and distal extrahepatic cholangiocarcinoma, proton therapy can reduce the volume of tissue receiving low-to-medium doses of radiation. However, limiting maximum doses to immediately adjacent organs at risk (e.g., duodenum) continues to be a challenge [25].

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# Rectal and Colon Cancer: Background and Clinical Evidence

13

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## 13.1 Epidemiology and Risk Factors

### 13.1.1 Epidemiology

- Colorectal cancer (CRC) is the third most commonly diagnosed cancer and third leading cause of death among men and women in the United States [1].
- Estimated 134,490 new cases of large bowel cancer diagnosed annually in the United States, including about 95,270 colon and 39,220 rectal cancers [2].
- The lifetime risk of developing CRC is about 1 in 20 (5 %).
- Death rate from CRC has been dropping in both men and women for more than 20 years, secondary to screening and improvements in treatment. There are currently more than one million survivors of CRC in the United States [1].
- Approximately 2/3 of CRCs occur in the colon and 1/3 occur in the rectum.

### 13.1.2 Risk Factors

- Approximately 75 % of CRCs are sporadic, whereas 15–20 % occur in those with a positive family history or a personal history of polyps.
- The etiology of CRC appears to be multifactorial (Table 13.1).
  - Age
    - Incidence increases after age 40.
    - 90 % of cases occur after age 50.
      - However, studies suggest that incidence is increasing in younger patients [3, 4].
  - Diet
    - Migrants from low-incidence regions in Africa and Asia who migrate to high-incidence regions of North America or Australia assume the incidence of host country within one generation [5].
    - Red, processed meats [6].
  - Low socioeconomic status
    - Likely confounded by unhealthy behaviors.
  - Cigarette smoking
  - Sedentary lifestyle
  - Alcohol consumption

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© Springer International Publishing AG 2017
T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_13

**Table 13.1** Risk factors of colorectal cancer

| Inherited colon cancer syndromes (5 %) | Family history of polyps or colorectal cancer (15 %) | Inflammatory bowel disease | Sporadic (75 %) |
|---|---|---|---|
| Hereditary nonpolyposis colorectal cancer (HNPCC), Lynch syndrome: defect in mismatch repair (*MMR*) genes | Personal history: large (>1 cm) adenomatous polyps or polyps with villous or tubulovillous histology (3.5–6.5 RR) [52] | Ulcerative colitis: increased risk begins 8–10 years after diagnosis of pancolitis; 15–20 years for colitis limited to left colon [53] | Low socioeconomic status, confounded by associated unhealthy behaviors (e.g., high-fat diet) |
| Familial adenomatous polyposis (FAP): *APC* gene | Twofold risk if first-degree relative with colorectal cancer [8] | Crohn's disease: less data | Age, incidence increases after age 40 (90 % cases after age 50) |
| | | | African Americans: younger age, higher mortality |

- African-Americans often diagnosed at a younger age, associated with a higher mortality [7].
- Personal or family history
  - Having a single first-degree relative with CRC increases the risk about twofold over that of the general population [8].
- Inflammatory bowel disease (IBD)
- Prior abdominal radiation (RT) (typically from childhood cancer)
- Protective factors
  - Physical activity
  - Diet high in fiber
  - Vitamin B6
  - Calcium/vitamin D
  - Fish consumption
  - Aspirin and NSAIDS [9]
- Inherited cancer syndromes and genetics
  - Hereditary nonpolyposis CRC (HNPCC) or Lynch syndrome
    - Autosomal dominant disorder; defects in mismatch repair genes.
    - Increased risk of CRC as well as endometrial, ovarian, stomach, small bowel, hepatobiliary, brain, and renal pelvis cancers.
  - Familial adenomatous polyposis (FAP)
    - Symptoms appear around age 16; CRC occurs in 90 % of untreated individuals by age 45.
    - Autosomal dominant inheritance.
    - Mutations in the *APC* gene lead to multiple polyp formation.
    - *MYH* is involved in oxidative DNA damage repair; mutation causes an autosomal recessive form of FAP.

### 13.1.3 Screening

- Screening recommendations (per US Preventive Services Task Force 2008 [10]).
  - For those age ≥50, no family history of CRC, no personal history of prior polyps, asymptomatic:
    - Colonoscopy every 10 years OR
    - Flexible sigmoidoscopy every 5 years with fecal occult blood test every 3 years OR
    - Annual fecal occult blood testing
  - High-risk individuals
    - Diagnosis in first-degree relative: colonoscopy at age 40 or 10 years before earliest familial diagnosis.
    - IBD: colonoscopy every 1–2 years, initiate 8 years after symptom onset.
    - FAP: *APC* gene testing, early screening (age 10–12), annual colonoscopy, colectomy near time of initial diagnosis.
    - HNPCC: colonoscopy every 1–2 years, initiate at age 20 or 2–5 years prior to the earliest age of CRC diagnosis in the family.

## 13.2 Anatomy

- Rectum is ~ 15 cm long; subdivided into three parts based on distance from the anal verge.
  - Upper 1/3 (12–16 cm)
  - Middle 1/3 (6–12 cm)
  - Lower 1/3 (<6 cm)
- Anterior peritoneal reflection represents the point below which the rectum exits the peritoneal cavity and becomes a retroperitoneal structure.
  - Below this, there is a mesorectal resection margin encompassing the rectum, with a layer of visceral fascia enclosing both the rectum and mesorectum.
- Lymphatics
  - Lymphatic drainage passes along the superior hemorrhoidal arterial trunk toward inferior mesenteric artery.
- Venous drainage
  - Upper rectum ➔ to inferior mesenteric vein via superior hemorrhoidal vein ➔ portal system
  - Lower rectum ➔ to internal iliac veins and inferior vena cava

## 13.3 Clinical Presentation

- Asymptomatic individuals
  - found on routine screening
- Symptomatic individuals
  - Common symptoms include gross red blood in stools and change in bowel habits such as constipation, diarrhea, or reduction of stool caliber. Iron deficiency anemia may also be found on laboratory evaluation.
  - Hemorrhoidal bleeding is a diagnosis of exclusion.

### 13.3.1 Workup

- History ➔ include family history of CRC or polyps.
- Physical examination ➔ focus on digital rectal examination, which can assess tumor size, ulceration, and fixation to surrounding structures. Can also determine distance from anal verge and evaluate sphincter function.
- Labs: CBC to assess for anemia, carcinoembryonic antigen (CEA) level.
- Full colonoscopy + biopsy.
- Local staging
  - Endorectal ultrasound can be used to assess tumor extension and T stage or pelvic MRI for extent of primary tumor, distance to the mesorectal fascia, and lymph node involvement.
- Distant staging
  - Computed tomography of chest/abdomen/pelvis.

## 13.4 Staging

- AJCC staging (7th edition) [11] (Table 13.2)
  - Primary tumor (T)
  - Lymph nodes (N)
  - Metastases (M): CRC most frequently metastasizes to the liver, lung, or peritoneum.
    - Liver metastases are most frequently associated with upper rectal tumors which have venous drainage directly to portal system.
    - Lung metastases are associated with lower rectal tumors which have venous drainage directly to IVC.
- Stage I
  - T1-T2 N0
- Stage II
  - Stage IIA: T3 N0
  - Stage IIB: T4aN0
  - Stage IIC: T4bN0
- Stage III
  - Stage IIIA: T1-T2N1 or N1c, T1N2a
  - Stage IIIB: T3-T4aN1 or N1c, T2-T3N2a, T1-T2N2b
  - Stage IIIC: T4aN2a, T3-T4aN2b, T4bN1-T2

**Table 13.2** AJCC 7th edition TMN staging system for colorectal cancer [11]

| | |
|---|---|
| *Primary tumor (T)* | |
| Tx | Primary tumor cannot be assessed |
| Tis | Carcinoma in situ: intraepithelial or invasion of the lamina propria |
| T1 | Tumor invades submucosa |
| T2 | Tumor invades muscularis propria |
| T3 | Tumor invades through the muscularis propria into pericolorectal tissues |
| T4a | Tumor penetrates to the surface of the visceral peritoneum |
| T4b | Tumor directly invades or is adherent to other organs or structures |
| *Regional lymph nodes (N)* | |
| N1 | Metastasis in 1–3 regional lymph nodes<br>N1a: 1 regional node<br>N1b: 2–3 regional nodes<br>N1c: tumor deposit(s) in subserosa, mesentery, or perirectal tissue without lymph node involvement |
| N2 | Metastasis in ≥4 regional lymph nodes<br>N2a: 4–6 regional nodes<br>N2b: 7 or more regional nodes |
| *Metastasis (M)* | |
| M1 | Distant metastasis<br>M1a: Metastasis confined to one organ or site<br>M2a: Metastasis in more than one organ/site or the peritoneum |

- Stage IV: metastatic disease
  - Stage IVA: Any T, Any N, M1a
  - Stage IVB: Any T, Any N, M1b

## 13.5 Prognostic Factors

- T stage
  - The local extent of disease (depth of penetration) independently predicts for survival.
- N stage
  - The number of involved lymph nodes is a strong predictor for outcome.
  - Degree of lymph node (LN) dissection.
    - Total number of lymph nodes resected during surgery has been suggested to influence prognosis [12].
  - LN ratio
    - This has been suggested as a means to incorporate involved nodes and total number resected for prognostication.
- Lymphovascular invasion
  - Both venous and lymphatic invasion represent independent adverse factors.
- Perineural invasion
- Obstruction/perforation
  - Several studies suggest that clinical obstruction or gross perforation at the time of diagnosis portends worse outcomes; this may be due to aggressive histology necessitating the need for emergency surgery.
- Oncologic resection
  - Relates to outcomes
    - R0: complete tumor resection with all margins histologically negative
    - R1: incomplete tumor resection with microscopic surgical resection margin involvement
    - R2: incomplete tumor resection with gross residual tumor that was not resected
- Circumferential margin status
  - Refers to the surgically dissected nonperitonealized surface of the specimen, any aspect of the colorectum that is not covered by a serosal layer of mesothelial cells and that must be dissected from the retroperitoneum.
    - For mid- and distal rectal cancers that are entirely subperitoneal in location, the entire external surface of the specimen is considered a CRM.
    - The CRM status is an important prognostic factor for local and distant recurrence.
- Preoperative CEA
  - CEA levels ≥5 ng/mL may have an adverse impact on survival.
- Response to neoadjuvant therapy
  - Tumor downstaging as detected by pathologic examination of the resected specimen is associated with better prognosis as compared to patients with residual tumor, especially nodal disease.
- Molecular biology (as below)

## 13.6 Molecular Biology

- KRAS
  - KRAS mutations in codon 12 or 13 are identified in 12–75 % of tumors. They are associated with poor prognosis in some studies, but not all [13, 14]. This may be due to different mutations within the gene that may exert different influences.
  - Activating mutations in KRAS results in constitutive activation of the Ras-Raf-ERK pathway, resulting in resistance to anti-EGFR therapy.
- BRAF
  - RAF-activating mutations, specifically V600E, occur in less than 10 % of sporadic colorectal cancers and are a negative prognostic factor. Data are mixed as to whether BRAF mutations also confer resistance to anti-EGFR therapy [15].
- MSI
  - Mutations in mismatch repair (MMR) genes are found in Lynch syndrome and 15–20 % of sporadic colon cancer.
  - Tumors with deficient MMR result in a high number of DNA replication errors and high levels of DNA MSI (microsatellite instability). Tumors that are MSI high are associated with longer survival than MSI-low or microsatellite-stable tumors.
- 18q deletions
  - Allelic loss of a region on the long arm of chromosome 18 commonly occurs in CRC.
    - Evidence suggests an association between 18q loss and an inferior prognosis in patients with node-negative and node-positive disease [16].

## 13.7 Genetics

- The Cancer Genome Atlas (TCGA) published its genomic profile of colorectal cancer after sequencing 224 samples [17].
  - 16 % of colorectal cancers were found to be hypermutated.
  - Three-quarters had expected high microsatellite instability.
  - Colon and rectal cancers were found to have similar patterns of genomic mutations.
  - Frequent mutations were found in the expected *APC*, *TP53*, *SMAD4*, *PIK3CA*, and *KRAS*. Mutations were also found in *ARID1A*, *SOX9*, and *FAM123B*.
  - Copy number alterations include amplifications of *ERBB2* and *IGF2*.
  - Chromosomal translocations included the fusion of *NAV2* and *TCF7L1*.
  - Tumors from the right (ascending) colon were more likely to be hypermethylated and to have higher rates of mutation compared to other CRCs.
  - Mutations frequently target MAPK and PI3K pathways but less frequently receptor tyrosine kinases.

## 13.8 Treatment Paradigms

- For treatment recommendations, it important to distinguish between colon and rectal cancer.
  - Colon cancer ➔ role for RT is poorly defined.
    - Risk of local recurrence in colon cancer is <5 %; the issue is distant metastatic disease.
      - Retrospective studies suggest the use of adjuvant radiation in select high-risk patients:
        - Massachusetts General Hospital (MGH) series found that RT for T4 tumors with extension into adjacent structures led to favorable local control and recurrence-free survival rates [18].
        - Mayo Clinic series utilizing adjuvant RT in 27 patients with locally advanced tumors demonstrated improved local control [19].
        - Follow-up series from MGH found favorable long-term outcomes in

152 patients with T4 or residual disease with the use of adjuvant RT.
  - 79 patients with T4 node-negative disease and 44 patients with node-positive disease demonstrated a 10-year local control rate of 88 % and a recurrence-free survival of 58 % [20].
- Intergroup 0130: Prospective, randomized trial evaluating the utility of adjuvant chemoradiation (chemoRT) compared to adjuvant chemotherapy alone in T3N1 or T3N2 colon cancers [21].
  - Overall 5-year survival was 62 % for the chemotherapy patients compared to 58 % for chemoRT patients ($p$>0.50). 5-year disease-free survival (DFS) was 51 % for both groups, and toxicity (grade ≥3) occurred in 42 % of chemotherapy alone patients vs 54 % of chemoRT patients ($p$ = 0.04).
  - Limitations included the absence of radiation quality control and central pathologic review, as well as the inclusion of patients with T3 tumors in whom the benefit may be less than with T4 tumors.
    - This remains the only prospective phase III trial to utilize radiation in colon cancer.
- At this time, adjuvant radiation is typically reserved for patients with markedly increased risk of local recurrence, i.e., those with positive margins and/or gross residual disease.

- What makes rectal cancer different?
  - Local recurrence for rectal cancer is typically 25–50 %. Surgery for rectal cancer is much more difficult than for colon cancer, as the pelvis is narrow.
    - How to decrease local recurrence rates in rectal cancer?
      - Better surgery (see "TME" below), nodal dissection
      - Addition of adjuvant treatment, including chemotherapy and RT

## 13.9 Multidisciplinary Treatment

### 13.9.1 Stage I (T1N0, T2N0): Surgery

- Optimal surgical approach depends on size, stage, and location of the primary tumor.
- Local excisions for early stage and superficial tumors without clinical lymph node involvement are primarily performed by conventional transanal excision (TAE) and transanal endoscopic microsurgery (TEM).
- The concern regarding perirectal lymph node involvement in rectal cancer is not insignificant.
  - As tumor stage increases, the incidence of perirectal nodal involvement increases.
    - Lymph node involvement seen in:
      - 5–12 % of T1 tumors
      - 10–35 % of T2 tumors
      - Up to 70 % of T3 lesions [22–25]
    - Histologic grade and vascular involvement are also independent predictors of nodal involvement with one study revealing a 29–50 % risk of perirectal nodal disease for patients with T1 and T2 tumors showing poorly differentiated histology or lymphatic/blood vessel invasion [24].
- Complete mesocolic resection is recommended to obtain adequate lymph nodes for staging.
  - Procedure dependent on location of the primary colorectal tumor.
- For rectal cancer, total mesorectal excision (TME) is recommended.
  - Involves sharp dissection of the avascular plane between the mesorectal visceral lining and the pelvic parietal fascia. Hence, a TME not only removes the primary tumor but also the draining lymph nodes, providing optimal clearance of proximal, distal, and radial margins.
  - At least 12 nodes should be removed.

### 13.9.2 Stage II and Beyond: T3/T4 Tumors or Node-Positive Disease: Trimodality Therapy for Rectal Cancers

- *Current standard of care within the United States: Neoadjuvant standard fractionated chemoradiation--> TME--> Adjuvant 5-fluorouracil (5-FU)-based chemotherapy × 4–6 months*
- The observation of high local recurrence rates following resection alone led to studies exploring the possible benefit of postoperative therapies [26, 27].
  - Pre-TME era
    - United States Trials
      - GITSG 7175 (1985/6) [27, 28]
        - 227 patients who had undergone "curative" surgical resection for locally advanced rectal adenocarcinoma were assigned to one of four treatment arms:
          - No adjuvant treatment
          - RT alone (40 or 48 Gy)
          - Chemotherapy alone (semustine and 5-FU)
          - ChemoRT (5-FU during RT followed by semustine)
        - Compared with surgery alone, chemoRT improved 5-year overall survival ($OS_5$) and local failure (LF) rate:
          - $OS_5$: 36 % surgery alone vs 56 % combined therapy ($p = 0.005$) [27]
          - LF: 24 % surgery alone vs 11 % combined therapy ($p$ = not significant [NS])
      - NSABP R01 [29]
        - 555 patients with T3-T4N0 or N+ randomized to one of three arms after surgery:
          - Observation
          - RT alone (AP:PA to pelvis with boost, total 46–47 Gy)
          - Chemotherapy (5-FU/semustine/vincristine=MOF) × 8 cycles
        - Overall survival benefit seen in *males* for chemotherapy, improving $OS_5$ to 60 % as compared to 37 % in surgery alone ($p = 0.001$).
        - RT alone improved locoregional recurrence (LRR) from 25 to 16 % ($p = 0.06$) but no OS benefit.
      - NSABP R02 [30]
        - 694 patients with T3-T4N0 or N+ randomized after surgery to:
          - Chemotherapy alone (females received 5-FU/leucovorin, males received 5-FU/leucovorin or MOF)
          - ChemoRT (RT to 45 Gy)
        - ChemoRT improved local recurrence (LR) (13 % vs 8 %) but had no impact on DFS or OS.
      - Conclusions: chemotherapy improves risk reduction for distant metastases which impacts overall survival; RT decreases local recurrence but has no impact on overall survival.
    - European studies
      - Swedish rectal trial [31]
        - 1,168 patients with stage I–III disease randomized to:
          - Surgery alone
          - RT 5 Gy × 5 followed by surgery within 1 week
        - $OS_{13}$ 38 % RT vs 30 % no RT ($p = 0.008$)
        - $LF_{13}$ 9 % RT vs no RT 26 % ($p<0.001$)
          - No difference with regards to distant metastases
  - Post-TME era: is there a role for radiotherapy with improved local (surgical) therapy?
    - Dutch rectal trial [32]
      - 1,805 patients with resectable rectal cancer randomized to:
        - TME alone
        - RT 5 Gy × 5 followed by surgery (TME)

  - 10-year LRR improved with radiation (5 % vs 11 % in surgery alone, $p<0.001$).
  - OS did not differ between two groups.
    - Conclusion: RT still improves local control (LC) even with better surgery.
- German rectal trial [33]
  - 823 patients with T3-T4N0 or N+ randomized to:
    - Surgery ➔ chemoRT (5-FU and RT to 55.8 Gy) ➔ 5-FU × 4 cycles
    - chemoRT (5-FU and RT to 50.4 Gy) ➔ surgery ➔ 5-FU × 4 cycles
  - 9 % of the preoperative chemoRT group achieved a pathological complete response (pathCR) at the time of surgery.
  - $OS_{10}$ was 59.6 % for preoperative chemoRT vs 59.9 % for postoperative chemoRT ($p$ = NS).
  - $LR_{10}$ was 7.1 % for preoperative chemoRT vs 10.1 % for postoperative chemoRT ($p = 0.048$) [34].
  - Grade 3 or 4 toxicities were observed in 27 % of patients in the preoperative chemoRT arm as compared to 40 % in the postoperative chemoRT arm.
    - Preoperative therapy improved local control, was better tolerated, and improved rates of sphincter preservation, no difference in survival between preoperative and postoperative therapy.

➔ Due to the results of this trial, preoperative therapy has become standard of care for T3/T4 or node + rectal cancer.

*Do we need concurrent chemotherapy with preoperative RT?*

- Federation Francophone de Cancerologie Digestive (FFCD) 9203 [35]
  - Randomized patients with resectable T3-T4 tumors to receive preoperative RT alone (45 Gy) or preoperative chemoRT (with 5-FU) followed by surgery.
    - Preoperative chemoRT led to a pathCR of 11.4 % compared to 3.6 % in the preoperative RT alone arm ($p<0.05$).
    - LC rates at 5 years was also improved (8.1 % vs 16.5 %, chemoRT vs RT alone, $p<0.05$).
      - Had no impact on OS
- European Organization for Research and Treatment of Cancer (EORTC) 22,922 [36].
  - Randomized 1,011 patients with resectable T3-T4 rectal cancer in a 2 × 2 design to four arms:
    - Preoperative RT to 45 Gy
    - Preoperative chemoRT with 5-FU
    - Preoperative RT and four cycles of postoperative chemotherapy with 5-FU
    - Preoperative chemoRT and postoperative chemotherapy
  - No difference in OS seen between groups receiving chemotherapy preoperatively or postoperatively.
  - Significant reduction in rates of 5-year local recurrence among patients who received chemotherapy vs those who did not ($p = 0.002$).
- Conclusion from EORTC and FFCD ➔ preoperative concurrent chemoRT improves tumor downstaging and local control.

*What kind of chemotherapy to use?*

- MOSAIC trial ➔ experience in colon cancer [37]
  - Randomized 2,246 patients who had undergone resection with curative intent for stage II or III colon cancer to:
    - Postoperative 5-FU
    - Postoperative 5-FU + oxaliplatin (FOLFOX)
      - The addition of oxaliplatin improved 5-year disease-free survival (DFS) from 67.4 to 73.3 % ($p = 0.003$).
- NSABP R04 evaluated whether the benefit seen in adjuvant treatment of colon cancer

with oxaliplatin could be applied to neoadjuvant treatment of rectal cancer [38].
- 1608 patients with resectable stage II/III rectal cancer randomized to preoperative 5-FU or capecitabine +/− oxaliplatin with concurrent RT to 50.4–55.8 Gy
  - PathCR rate between patients who received 5-FU or capecitabine: 18.8 % vs 22.2 % ($p = 0.12$).
  - PathCR rate between patients who received oxaliplatin or no oxaliplatin: 20.9 % vs 19.1 % ($p = 0.46$).
  - Grade 3 or 4 toxicities were significantly higher in the oxaliplatin group (15.4 % vs 6.8 %, $p = 0.0001$).

➔ The result of this study favors the use of preoperative chemoradiation with 5-FU or capecitabine without oxaliplatin.

### 13.9.3 Additional Treatment Considerations

- Postoperative chemotherapy
  - CHRONICLE trial [39]
    - Examined benefit of postoperative capecitabine and oxaliplatin after neoadjuvant chemoradiation.
      - Patients all received preoperative fluoropyrimidine-based chemoRT followed by resection, assigned to either observation alone or postoperative chemotherapy with capecitabine and oxaliplatin (6 cycles).
        - Closed early due to poor accrual, but no difference seen in DFS or OS between two arms.
          - Poor accrual and small numbers hamper ability to interpret results.
  - PROCTOR/SCRIPT 2015 [40]
    - Compared adjuvant chemotherapy (5-FU/leucovorin or capecitabine) to observation alone.
      - Patients all received preoperative 5-FU-based chemoRT, followed by surgery.
        - 470 patients enrolled
          - 221 assigned observation
          - 216 assigned chemotherapy
        - No difference in 5-year OS or DFS.
  - ADORE [41]
    - Randomized phase II trial looking at oxaliplatin, fluorouracil, and leucovorin (FOLFOX) vs fluorouracil/leucovorin (5-FU/LV) as adjuvant chemotherapy after preoperative chemoRT followed by surgery.
      - Patients enrolled were ypT3-T4 or N + after surgery.
        - 3-year DFS 71.6 % FOLFOX group vs 62.9 % in the 5-FU/LV group, $p = 0.047$.
          - By stage, 3-year DFS was 81.6 % vs 71.3 %, respectively, in yp stage II ($p = 0.47$).
          - 3-year DFS was 66.6 % vs 57.3 %, respectively, in yp stage III ($p = 0.04$).
        - 3-year OS 95 % vs 85.7 %, respectively, $p = 0.036$.
      - Benefit of FOLFOX appears to be restricted to yp stage III patients.
- Can radiation be omitted from treatment?
  - MSKCC pilot study of 32 patients [42].
    - All patients underwent baseline staging and received FOLFOX-bevacizumab x4, followed by FOLFOX x2. All patients were restaged at that time.
      - If stable disease or evidence of clinical response, patients went on to surgery.
        - Adjuvant chemotherapy warranted if R1/R2 resection.
      - If progressive disease, patients received chemoradiation, followed by surgery, followed by adjuvant chemotherapy.
      - *Results*: All 32 patients had an R0 resection.
        - 30 patients completed chemotherapy and went on to surgery; two patients underwent preoperative chemoradiation because they

could not complete preoperative chemotherapy (due to cardiac toxicity).
    - PathCR rate of chemotherapy alone was 8 (25 %).
    - 4-year DFS and OS are 84 and 91 %, respectively.
- Building on the results of this study, the prospective PROSPECT trial is underway.
  - Arm 1: FOLFOX chemotherapy for six cycles➔ evaluation with imaging.
    - If tumor decreased in size by at least 20 %, the patient proceeds to surgery.
    - If the tumor has not decreased in size by at least 20 %, the patient receives 5-FU or capecitabine with radiation, then proceeds to surgery.
    - Post-surgery, patients receive six cycles of FOLFOX if all borders are normal. If borders of the tumor are not normal, the patient receives chemoradiation therapy, along with four cycles of FOLFOX.
  - Arm 2: Patients receive 5-FU or capecitabine with concurrent radiation ➔ surgery ➔ eight cycles of FOLFOX.
- MERCURY trial [43].
  - Utilized high-resolution MRI to accurately stage rectal cancer and predict good prognosis tumors suitable for treatment with surgery alone.
    - Prospective trial using high-resolution MRI to stage rectal cancer patients, finding "good" prognosis tumors adequate for surgery alone.
      - "Good" prognosis defined as MRI-predicted safe circumferential resection margins, with MRI-predicted T2/T3a/T3b, regardless of MRI N stage.
    - Of 324 patients, 122 were defined as "good prognosis" stage III or less. Patients with node-positive disease were able to receive adjuvant single-agent fluoropyrimidine-based systemic chemotherapy. None of the patients received radiation.
      - Overall and disease-free survival at 5 years for this cohort was 68 and 85 %, respectively.
    - This approach has become the standard of care in the UK.

- Can surgery be omitted from treatment?
  - Retrospective study with 183 patients, clinical stage T2-T4, N0-N2, M0 [44]
    - ChemoRT to 50.4–54 Gy ➔ if clinical complete response, follow with 1–2 month-digital rectal exam and rigid proctoscopy, CEA every 2–3 months, imaging at 6 months to assess mesorectum, followed by yearly imaging
      - 90/183 pts (49 %) had a clinical complete response.
        - 28 patients of the 90 had local recurrence (31 %).
          - More than half developed within 12 months of follow-up.
          - Salvage therapy possible in >90 %, leading to 94 % LC and 78 % organ preservation at 5 years.
      - This study is controversial, as patients included could have early stage disease.
  - Wait-and-see policy
    - Small study of 21 patients out of the Netherlands [45].
      - Patients with a complete clinical response after chemoradiation were selected for the wait-and-see policy using MRI and endoscopy plus biopsies. Follow-up was performed every 3–6 months and consisted of MRI, endoscopy, and CT scans.
        - After a mean FU of 25 months, one patient developed a local recurrence and had salvage surgery; all 20 others are alive without disease.
      - These data suggest that a wait-and-see policy with strict selection criteria, up-to-date imaging techniques, and follow-up is feasible and has promising outcome.

- OnCoRe project: watch-and-wait approach vs surgical resection after chemoradiation [46]
  - Propensity-score matched cohort analysis study, including patients diagnosed with rectal adenocarcinoma without metastases who had received preoperative chemoradiation at a tertiary cancer center in the UK.
    - Patients with clinical CR offered management of watch-and-wait; patients without a clinical CR were offered surgical resection. For comparative analysis, one-to-one paired cohorts were derived using propensity-score matching (including T stage, age, and performance status).
      - 129 patients managed by watch and wait. 44 had local regrowths, but 36/41 (88 %) were salvaged.
      - In the matched analysis, there was no different in 3-year disease-free survival between watch-and-wait group vs surgical resection (88 % vs 78 %, time-varying $p = 0.043$). There was no difference in 3-year overall survival (96 % vs 87 %, time-varying $p = 0.024$). Patients managed with watch and wait had better 3-year colostomy-free survival compared to the surgical resection cohort (74 % [95 % CI 64–82] vs 47 % [95 % CI 37–57], $p<0.0001$).
    - This study suggests that patients managed by the watch-and-wait approach can avoid major surgery and permanent colostomy at 3 years.
      - Longer follow-up is needed.
- Short-course radiation
  - Swedish rectal [31]: utilized 5 Gy × 5 prior to surgery.
    - $OS_{13}$ 38 % RT vs 30 % no RT ($p = 0.008$).
    - $LF_{13}$ 9 % vs 26 % ($p<0.001$).
  - Dutch rectal [32]: utilized 5 Gy × 5 prior to surgery.
    - 10-year LRR improved with radiation (5 % vs 11 % in surgery alone, $p<0.00001$).
    - OS did not differ between two groups.
  - MRC CR07 and NCIC-CTG C016 [47].
    - 1350 patients randomized to either short-course RT (5 Gy × 5) or no preoperative RT, followed by surgery.
      - Postoperative chemotherapy if positive margins or nodes, patients who had not received any radiation were offered RT if had positive margins at time of surgery.
        - Median follow-up of 4 years, LR decreased for preoperative RT group (4.4 % vs 10.6 %, $p<0.001$).
        - In patients who had a TME, LR was 1 % in the preoperative RT group vs 6 % no RT group.
        - 3-year DFS improved with preoperative RT (78 % vs 72 %, $p = 0.013$).
        - No difference in OS.
      - This trial was criticized as TME was not mandated as part of surgery; the trial also had a large number of stage I patients.
  - Short-course radiotherapy appears to improve OS in pre-TME era (Swedish trial) but appears to only improve LC in the post-TME era (Dutch).
- Short-course vs long-course preoperative RT
  - Polish study [48]
    - 312 patients with clinical T3-T4 resectable rectal cancers.
    - Two-arm trial, randomized to:
      - Preop RT (25 Gy/5 fractions [fx]) ➔ TME within 7 days
      - Preop RT (50.4 Gy/28 fx) + bolus 5-FU during weeks 1 and 5 ➔ TME after 4–6 weeks
      - TME recommended for low-lying tumors, subtotal mesorectal excision recommended for mid-rectal tumors
        - Short-course vs long-course (median follow-up 4 years):
          - Sphincter preservation: 61 % vs 58 %, $p = 0.57$
          - Circumferential margin positive: 13 % vs 4 %, $p = 0.017$

  - pathCR: 1 % vs 16 %, no p value
  - Acute toxicity: 3 % vs 18 %, $p<0.001$
  - Late toxicity: 10 % vs 7 %, $p = 0.36$
  - 4-year LR: 11 % vs 16 %, $p = 0.21$
- TROG 0104 [49]
  - 326 patients with T3N0-2M0, two-arm trial, randomized to:
    - RT (25 Gy/5 fx) ➔ TME surgery ➔ 5-FU x 6 cycles
    - RT (50.4 Gy/28 fx) + continuous infusion 5-FU ➔ TME surgery ➔ 5-FU x 4 cycles
      - Short-course vs long-course (median follow-up 5.9 years):
        - 5-year LR: 7.5 % vs 5.7 %, NS
        - 5-year OS: 74 % vs 70 %, NS
        - pathCR: 1 % vs 15 %, no p value
        - No significant differences in acute or late toxicity
- Stockholm III trial interim analysis [50]
  - Randomized prospective trial randomizing patients to either short-course RT with immediate surgery, short-course RT with surgery delayed 4–8 weeks or long-course RT with surgery delayed 4–8 weeks. Preplanned interim analysis examined the pathological outcome of delaying surgery.
    - 462 of 545 randomized short-course patients had tumor specimens available for assessment. Long-course patients were not analyzed in this study.
      - Patients randomized to the short-course RT with delayed surgery had a higher rate of pathological complete response compared to short-course RT with immediate surgery (11.8 % vs 1.7 %, $p<0.001$).
    - Short-course RT induces improved tumor downstaging if surgery is delayed 4–8 weeks.
- Polish trial examined short-course RT, followed by consolidation chemotherapy, followed by surgery, compared to long-course chemoradiation [51].
  - Consolidation chemotherapy consisted of three cycles of FOLFOX.
    - 515 patients eligible for analysis: 261 in the short-course RT followed by chemotherapy and surgery group (group A) and 254 in the long-course chemoradiation group (group B).
    - Results for group A vs group B were (median FU 35 months):
      - Any toxicity 75 % vs 83 %, grade III–IV toxicity 23 % vs 21 %
      - R0 resection 77 % vs 71 %, $p = 0.07$
      - PathCR 16 % vs 12 %, $p = 0.17$
      - 3-year OS 73 % vs 65 %, $p = 0.0046$
      - 3-year DFS 53 % vs 52 %, $p = 0.85$
      - Local failure cumulative incidence 22 % vs 21 %, $p = 0.82$
      - Postoperative complications 29 % vs 25 %, $p = 0.18$
      - Late complications 20 % vs 22 %, $p = 0.54$
    - Concluded that there were no differences observed in local efficacy between the two groups but that there was an improved OS and lower acute toxicity favoring the short-course RT followed by consolidation chemotherapy schedule.
- Conclusions
  - Advantages to short-course radiotherapy:
    - Similar LC and OS compared to standard fractionation with chemotherapy
    - Shorter treatment time, lower costs
  - Disadvantages to short-course radiotherapy:
    - Minimal downstaging, however, interim analysis of the Stockholm III trial shows improved downstaging with delayed surgery [50]. Will need

to wait for final results for comparison to long-course RT.
- Concern about late effects (follow-up time relatively short in above studies)

## 13.10 Conclusions and Future Directions

- The treatment of locally advanced rectal cancer has evolved due to the significant failure rate of surgery alone, particularly in the pre-TME era.
- Preoperative and postoperative therapy options have been explored, with most centers in the United States utilizing preoperative chemoradiation, followed by TME, followed by adjuvant FOLFOX chemotherapy × 4 months.
- There have been studies focusing on omitting surgery or omitting radiation in subsets of patients, although these are reserved for highly selected individuals, and more data are needed.
- Research is ongoing with regard to targeted therapy, focusing on specific mutations (*KRAS*, *BRAF*, etc.) to determine how to further personalize therapy and treatments.

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# 14 Rectal and Colon Cancer: Radiation Therapy Planning

Sophia C. Kamran, Harvey J. Mamon, and Jennifer Y. Wo

## 14.1 Radiation Treatment for Locally Advanced Colorectal Cancer

- Indicated for clinical T3–4, or node-positive rectal cancer.
- Preoperative chemoradiation therapy (CRT) followed by surgery and adjuvant chemotherapy remains the standard of care in the United States.
  - Preoperative CRT results in improved local control and toxicity profile compared to postoperative therapy.
  - May allow for downstaging to facilitate a sphincter-sparing low anterior resection for selected tumors that may have initially required an abdominoperineal resection.
- Postoperative chemoradiation can be used if patients have up-front abdominoperineal resection (APR) or low anterior resection (LAR).
  - Postoperative complication rates and overall treatment-related toxicities were slightly higher with postoperative compared to preoperative chemoradiation in an important study carried out in Germany in 2001 [1, 2].

## 14.2 Simulation

- Computed tomography simulation
  - Patients simulated prone, arms up.
    - A belly board is commonly used to help get the small bowel out of the treatment field.
    - Instructing patients to have a comfortably full bladder can also help displace small bowel from the pelvis.
  - Rectal tube, anal verge marker, and IV and oral contrast may be helpful to delineate nodal and other tissues.

## 14.3 Fractionation

### 14.3.1 Short Course Versus Long Course

- Two trials compared these different fractionation schedules [3, 4].
  - Short-course preoperative 5 Gy × 5 versus long-course preoperative standard fractionation with concurrent chemotherapy.

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© Springer International Publishing AG 2017
T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_14

    - Found similar local control and overall survival rates between the two fractionation schedules.
    - Minimal downstaging at time of surgery with short-course radiation.
- Most common radiation schedule in the United States for rectal cancer is long-course radiotherapy, or 50.4 Gy in 28 fractions.
- Short-course radiation therapy is commonly used in Europe.
  - Concern regarding late toxicity due to hypofractionated schedule is a significant deterrent for US physicians.

## 14.4 Technique/Treatment Modalities

### 14.4.1 Three-Dimensional Conformal Radiation Therapy (3DCRT)

- 3D planning allows for target localization and normal tissue dose analysis via dose-volume histograms (DVHs).
- Highly conformal radiation planning allows for potential reduction in radiation therapy (RT) toxicities, by reducing dose to the bowel and bladder.
- Conformal RT might allow for dose escalation to target areas, leading to improved tumor control.
- In 3DCRT era, 45 Gy is delivered to the rectum, mesorectum, and internal iliacs, with 5.4 Gy boost to the rectum, often including the presacral space.
  - The rectum, mesorectum, internal iliacs, external iliacs, and presacral nodal chains are contoured. Normal tissue structures include the small bowel, large bowel, bladder, and femoral heads.
    - External iliacs are included for T4 tumors invading anterior structures such as the prostate, vagina, or bladder.
  - Blocks are then drawn on PA and lateral films.
    - Typical block borders:
      - PA: superior, L5/S1; inferior, 2.5–3 cm below tumor; lateral, 1.5–2 cm outside the pelvic brim (Fig. 14.1)
        - Corner blocks outside sacroiliac joints; block the femoral heads. Do not block the obturator foramen.
      - Lateral: superior, L5/S1; inferior, 2.5–3 cm below tumor; 1 cm posterior to the sacrum, 2 cm anterior to the rectum
        - Adjust blocks to be a few cm anterior to the tumor with sparing of some bowel/bladder.
- For postoperative low anterior resection (LAR) patients, fields are the same, and the dose is typically 50.4 Gy.
- For postoperative abdominoperineal resection (APR) patients, fields are the same. The perineal scar is wired at the time of simulation and included in the field (perineal scar inferior to the sacrum). At treatment, bolus may be used on the scar every other day, typically with a 0.5 cm bolus. The dose is 50.4 Gy or 55.8 Gy for gross disease.
- In the Dutch Rectal Trial [5], the superior border was at the level of L5/S1 (sacral promontory). In a follow-up study evaluating the local recurrences in those enrolled on the Dutch Rectal Trial, most cranial recurrences were located a few centimeters caudal of the promontory regardless of RT treatment or not. For patients without primary nodal involvement, the most cranial recurrences were located at the level of S2–S3. These results suggest that the cranial border of the pelvic field may be able to be lowered in early rectal cancers [6].
- In the Swedish Rectal Trial [7], the superior border was at the mid-L4. In a follow-up study examining the local recurrences among patients enrolled on the Swedish Rectal Trial treated both with and without radiation, all recurrences were located below the S1–S2 interspace [8].

### 14.4.2 Intensity-Modulated Radiation Therapy (IMRT)

- IMRT allows for increased conformality around target and at-risk structures.

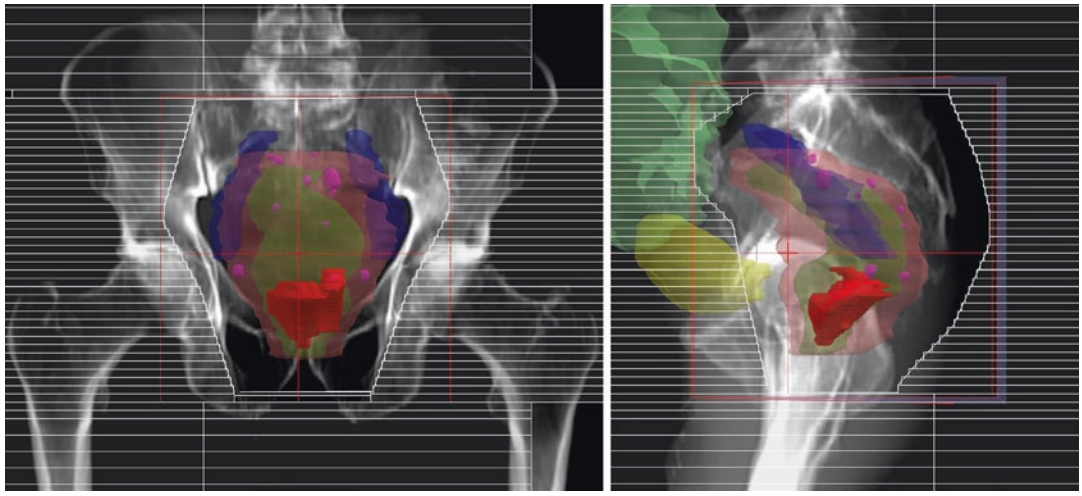

**Fig. 14.1** AP and lateral films for 3D conformal radiation planning. AP and lateral films demonstrating appropriate borders based on bony landmarks for radiation therapy. Colors: *red* gross tumor volume, *pink* mesorectum, *magenta* lymph nodes, *dark blue* vessels, *green* rectum, *light green* small bowel, *yellow* bladder

  - IMRT "conforms" radiation delivery to the shape of the tumor using concave/convex isodose lines (Fig. 14.2).
- This modality allows for a reduction of high doses to organs at risk, without compromising target coverage.
  - The small bowel is radiosensitive, as acute radiation enteritis occurs in many patients undergoing RT for rectal cancer (Fig. 14.3).
    - RTOG grade 3–4 acute toxicity is reported in up to 23 % of patients treated with preoperative chemoRT, escalating to 37 % with doses >50 Gy [9, 10].
      - Data suggest that the small bowel volume receiving 15 Gy ($V_{15Gy}$) is strongly associated with the degree of toxicity [9].
  - IMRT has been previously demonstrated to reduce bowel irradiation in prostate, cervical, and endometrial cancers.
- Dosimetric analysis in rectal cancer patients, simulated prone with a full bladder, found that the use of inverse planning IMRT was associated with a 64 % reduction in the percentage of bowel volume irradiated to 45–50 Gy compared with 3DCRT [11].
  - Unclear how this translates clinically
- NRG Oncology RTOG 0822 [12] sought to determine whether IMRT could decrease the rate of GI toxicity in combination with multiagent neoadjuvant chemoradiation in locally advanced rectal cancer. Neoadjuvant chemotherapy consisted of capecitabine and oxaliplatin.
  - RTOG 0822 was based on RTOG 0247 [13], a phase II randomized trial comparing capecitabine and oxaliplatin with 3DCRT versus capecitabine and irinotecan with 3DCRT.
    - There was an unexpectedly high rate of grade 3–4 GI toxicity in both arms.
  - RTOG 0822 included radiation delivery using inverse-planned IMRT to the rectum and lymphatics at risk to 45 Gy (1.8 Gy fractions) followed by a 3D chemoradiation boost to the gross disease with a 2-cm margin including all of the presacral space to 5.4 Gy (1.8 Gy fractions). Patients were simulated either supine or prone.
    - T3 tumors: Clinical target volume (CTV) included all gross diseases as well as internal iliac lymph nodes and the mesorectum (i.e., perirectal fat and presacral space).
    - T4 tumors: CTV included same structures as well as the external iliac lymph nodes.

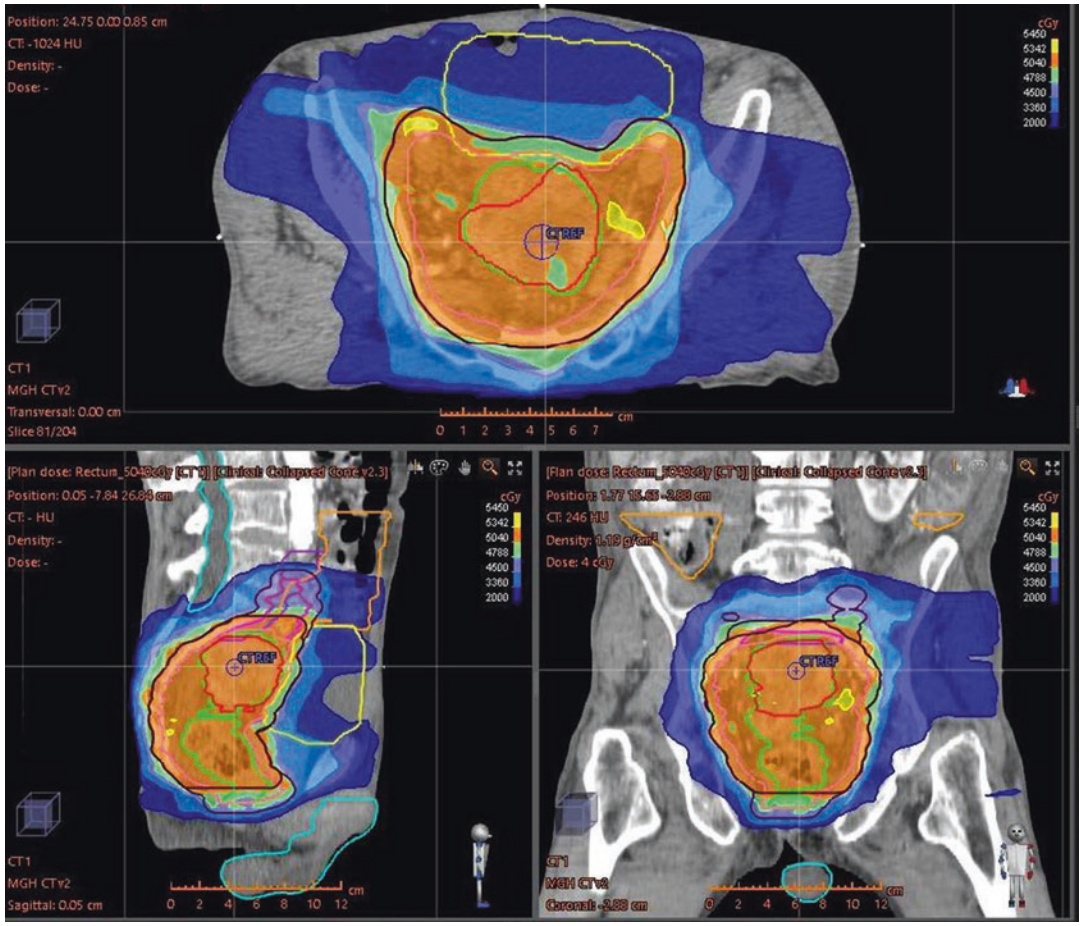


**Fig. 14.2** IMRT plan for rectal cancer. IMRT allows for highly conformal dose distributions, as demonstrated on the axial, coronal, and sagittal slices. The GTV is outlined in red

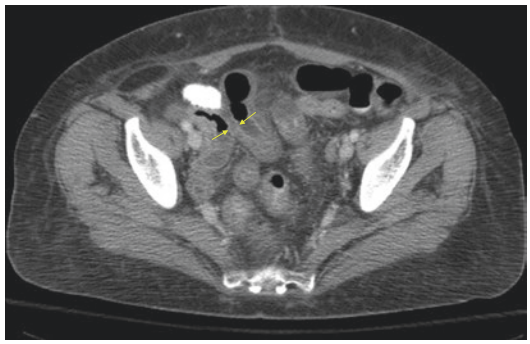

**Fig. 14.3** Acute radiation enteritis. CT scan of a patient with acute radiation enteritis after undergoing chemoradiation for rectal cancer. Enteritis is identified by the diffusely thickened small bowel present on the scan

- Unified CTV included: rectal gross tumor volume (GTV) expanded 1.5 cm radially and 2.5 cm craniocaudally, nodal GTV expanded 1.5 cm symmetrically, uninvolved internal (and external if T4 disease) iliac vessels expanded 1 cm symmetrically, presacral space defined as the 8 mm of soft tissue anterior to the sacrum from mid-S1 to S5, and the mesorectum/perirectal lymphatics.
- Planning tumor volume (PTV): 0.5 symmetric expansion of the unified CTV.
  - Treatment plan had to cover ≥98 % of the PTV with ≥93 % of the prescription (≤10 % of the PTV could

receive ≥105 % of the prescribed dose, and ≤5 % of the PTV could receive ≥110 % of the prescribed dose).
  - Organs at risk included the small bowel, i.e., peritoneal space containing the small bowel ($V_{35Gy}$<180 cc, $V_{40Gy}$<100 cc, $V_{45Gy}$<65 cc, max point <50 Gy), femoral heads, and bladder.
- Primary endpoint was to determine the rate of grade ≥2 GI toxicity with the goal of identifying 12 % reduction in adverse effects compared to what was seen in RTOG 0247.
- The study showed a 51.5 % rate of grade ≥2 GI toxicity, which exceeded the observed rate of 40 % in RTOG 0247.
  - Both trials assessed toxicity in setting of multiagent chemotherapy; however, it is unlikely that oxaliplatin will be employed with neoadjuvant chemoRT in rectal cancer given its lack of benefit in phase III studies [14, 15].
  - Volume of the bowel receiving low-dose RT (e.g., 15 Gy) may be more important when using multiagent chemotherapy, suggesting that low-dose constraints may need to be more stringent.
- RTOG contouring guidelines have been published to define targets and elective tissue coverage with IMRT planning. Target volumes for rectal cancer differ substantially from genitourinary or gynecological cancers, as the rectum and its associated mesentery represent first-echelon drainage from the rectum and are thus part of target coverage, as opposed to avoidance structures [16].
- The role of IMRT in rectal cancer remains to be determined. It may be more beneficial in situations where there is more volume of the bowel within a 3DCRT field, in patients with T4 tumors requiring external iliac coverage, or in the postoperative setting.

### 14.4.3 Proton Beam Therapy

- Proton therapy uses charged particles and takes advantage of the Bragg peak to deposit dose in the tumor with sharp falloff to avoid most normal structures (Fig. 14.4).
- A dosimetric analysis from the University of Florida [17] comparing 3DCRT, IMRT, and conformal proton therapy with eight patients showed that all three modalities covered the target volume and met normal tissue metrics.
  - Bladder $V_{40Gy}$ was significantly lower with IMRT and proton beam therapy compared to 3DCRT, though no difference was seen between IMRT and protons (29 % IMRT, 31 % proton, 41 % 3DCRT, $p$ = 0.016). Small bowel $V_{40Gy}$ was also significantly lower in the IMRT and proton therapy plans compared to 3DCRT, but this metric was again comparable between IMRT and protons (19 % IMRT, 22 % proton, 27 % IMRT). The only small bowel metric that was improved with protons compared to IMRT was $V_{10Gy}$ (45 % from 90 %, $p$ = 0.015) and $V_{20Gy}$ (39 % from 56 %, $p$ = 0.015).
  - At all dose levels evaluated, proton plans offered significantly reduced pelvic bone marrow exposure over 3DCRT and IMRT.
    - This could be of substantial benefit in 30 % of patients who may recur distantly at 10 years (per German Rectal Trial updated report [18]) and will require myelosuppressive systemic therapy.
- It remains to be seen how proton beam therapy for rectal cancer translates clinically; it is unknown whether the reduction of normal tissue exposure leads to differences in acute and late toxicities.
  - Proton beam limitations/uncertainties:
    - Range or depth of a proton beam is dependent on coulombic interactions with electrons in constituent atoms of different tissue.
      - Proton range is significantly greater in air than in tissue; changes in rectal

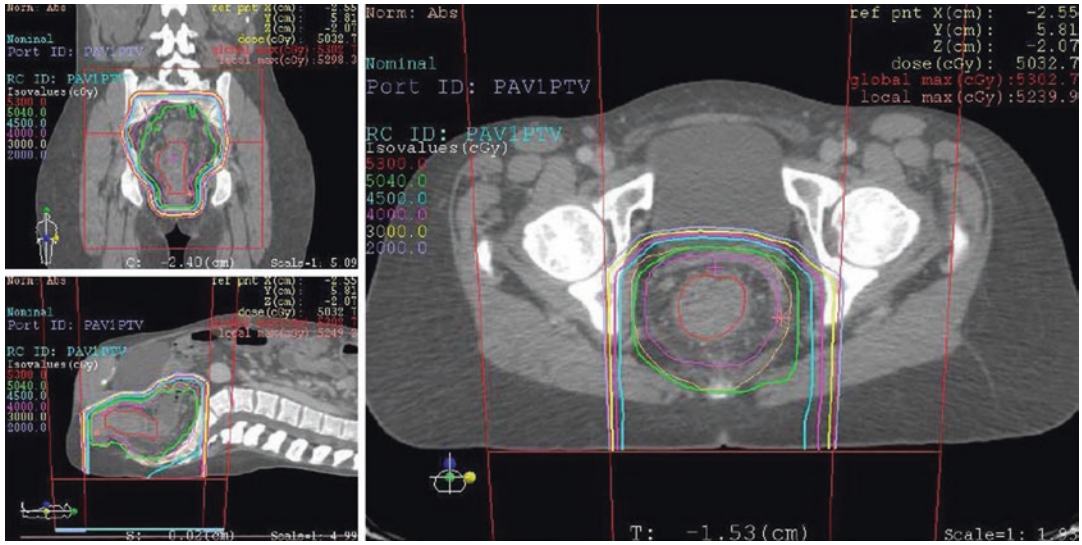


**Fig. 14.4** Proton radiation plan for rectal cancer. Proton radiotherapy takes advantage of the Bragg peak to deliver dose to the target (outlined in *red*) and avoid normal structures

gas may affect the beam range, leading to potential undercoverage of the target or overdose of normal tissue structures.

### 14.4.4 Stereotactic Body Radiation Therapy (SBRT)

- SBRT has recently emerged as a potentially effective therapy for pelvic cancers, particularly pelvic recurrences of rectal cancer, in the reirradiation setting.
  - The technique allows for smaller expansion margins and greater conformality, maximally avoiding normal structures.
- A study from the Beth Israel Deaconess Medical Center in Boston, MA, using CyberKnife-based SBRT reported on outcomes of 18 patients with 22 pelvic recurrences [19]. Fiducial markers were placed percutaneously within or near the tumor. Patients underwent CT simulation with body immobilization.
  - Five fractions were used when the tumor was adjacent to dose-limiting structures; three fractions were used for all others.
  - Total dose ranged from 24 to 40 Gy (median, 25 Gy).
  - 1-year, 2-year, and 3-year local control rates were 100, 94, and 86 %, respectively. Median local progression-free survival was 39 months.
  - Toxicities included fatigue for most patients. One patient developed a small bowel perforation requiring surgery; two patients treated for pelvic sidewall recurrence had symptomatic neuropathy; one patient developed ureteral fibrosis and resulting hydronephrosis requiring a stent.
- Abusaris et al. reported on 21 patients who received reirradiation with SBRT for abdominal and pelvic recurrences [20]. Thirteen patients had primary rectal cancer.
  - Median maximum cumulative biologically equivalent dose of the first and second treatment combined was 152 Gy (range, 93–468 Gy) for normal tissue ($\alpha/\beta$ of 3).
    - There were no acute or late grade 3 or 4 toxicities.
  - Two-year local control was reported to be 53 %.

- A similar study reported a 4-year local control of 74 % with no grade 4 toxicity in patients who underwent reirradiation with SBRT [21].
- SBRT may be a feasible treatment modality in patients with lower abdominal or pelvic recurrences within the field of prior adjuvant radiotherapy.

### 14.4.5 Hyperfractionation

- Hyperfractionated regimens have been explored as an alternative approach to SBRT for reirradiation.
  - A prospective phase II trial of 59 patients used twice-daily fractionation (1.2 Gy delivered twice a day with a minimum of 6-h interval) [22]. Concurrent chemotherapy was also delivered (5-fluorouracil). Patients were evaluated for potential surgical resection 4–6 weeks after completion of chemoradiation.
    - The response rate after chemoradiation was 44.1 %. The incidence of grade 3 lower gastrointestinal acute toxicity was 5.1 % and no development of grade 4 toxicity. Overall median survival was 42 months. One-third of patients were able to achieve an R0 resection, and 2/3 of patients were alive at 5 years.
  - A retrospective study of 50 patients treated with hyperfractionated accelerated radiation therapy with a history of prior pelvic radiotherapy showed that 150 cGy fractions twice a day to a total dose of 39 Gy if the retreatment interval was ≥1 year or 30 Gy if the treatment interval was <1 year led to a 3-year rate of freedom from local progression of 33 % [23].
    - Three-year freedom from progression was 47 % in patients who had surgery and 27 % in patients who did not have surgery.
    - Two patients had grade 3 acute toxicity and late toxicity occurred in 13 patients (grade 3 and 4). The 3-year overall survival rate was 39 %.

### 14.4.6 Intraoperative Radiation Therapy (IORT)

- IORT is a good option for tumors that cannot be fully resected, or with a positive or close resection margin (<5 mm), at time of surgery (Fig. 14.5).
  - IORT commonly delivers a single, directed dose of radiation via the open surgical cavity to the specific site of concern at the time of surgery with electrons.
    - This allows for direct targeting of radiation to the tumor bed while sparing normal surrounding tissues.
    - Most IORT treatments can be delivered through the abdomen, although occasionally a perineal port is used to treat low-lying tumors of the coccyx or distal pelvic sidewall.
    - IORT can be used in conjunction with preoperative chemoradiation and surgery if there is gross residual disease at time of operation or tumor adherence to the pelvic sidewall.
  - Areas of highest risk for local tumor recurrence are defined by surgeon and radiation oncologist.
  - Cones are used with internal diameters ranging from 4 to 8 cm. Most have beveled ends to enable good apposition of the cone to sloping surfaces in the pelvis.
    - Cone size is selected to fully cover the high-risk area.
    - The cone must abut the site being treated, and the angle of the edge of the cone should optimally be placed flat against the body surface to maximize dose homogeneity.
  - If necessary, lead sheets can be cut to block sensitive normal tissues that cannot be removed from the path of the beam.
  - Typical doses delivered intraoperatively range between 10 and 20 Gy, with lower doses given for minimal residual disease and higher doses for gross residual disease at time of resection.

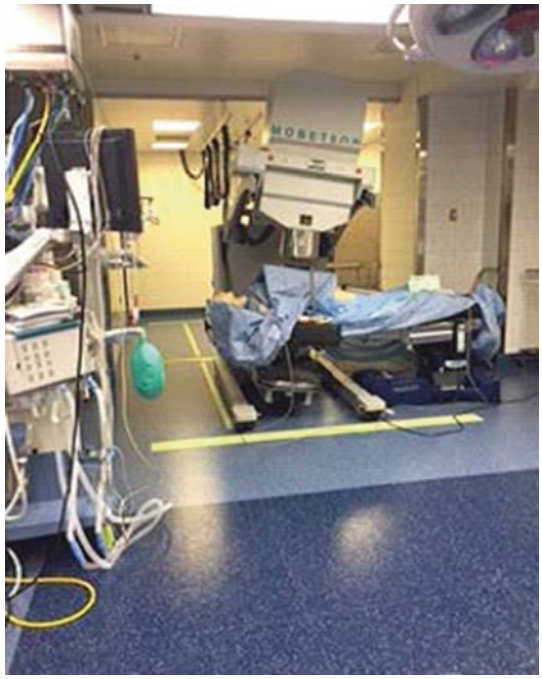

**Fig. 14.5** Intraoperative radiation therapy. IORT is a good option for patients with rectal cancer with a positive margin or pelvic sidewall disease at the time of surgery. This figure demonstrates an IORT suite (*left*), as well as the positioning of a cone to aim the electron radiotherapy at the site of gross disease or positive margin (*right*)

  - Typical electron energies used are between 9 and 15 MeV, depending on the thickness of the residual tumor.
- Single-institution studies have reported good local control and survival rates with IORT.
  - Nakfoor et al. reported on 73 patients with locally advanced rectal cancer treated with preoperative CRT followed by surgical resection and IORT [24]. Five-year actuarial rates of local control and disease-specific survival were 89 and 63 % for patients with an R0 resection and 57 and 14 % for patients with an R2 resection.
  - The Mayo Clinic reported on 146 patients receiving a combination of preoperative radiation followed by surgery and IORT [25]. Five-year local recurrence-free and disease-free survival was reported as 85 and 43 %, respectively.
  - Kreimpien et al. reported on the experience at the University of Heidelberg with 210 patients with locally advanced rectal cancer treated with TME, IORT, and preoperative or postoperative chemotherapy [26]. With a median follow-up of 61 months, 5-year actuarial overall survival was reported as 69 %, disease-free survival was 66 %, and local control rate was 93 %.

### 14.4.7 IORT with High-Dose Rate Brachytherapy

- An alternative approach to IORT is to use high-dose rate (HDR) brachytherapy instead of electrons.
  - One group evaluated 100 patients who received HDR brachytherapy intraoperatively to a median dose of 12.5 Gy patients between 2001 and 2010 [27].
    - Eighty-two patients underwent external beam irradiation prior to surgery and IORT. R0 resection rates were 58 %, and postoperative grade ≥3 complications were 33 %. Five-year local control was 94 %.

- Another group out of Australia prospectively evaluated the outcomes of using HDR IORT in patients with T4 rectal cancer or pelvic recurrence, deemed suitable for surgery but at high risk for positive resection margins [28].
  - Thirty patients were enrolled, and IORT was delivered in 90 %. IORT was 10 Gy.
    - Ten patients experienced grade 3 or 4 toxicities. At 2.5 years, local recurrence-free, failure-free, and overall survival rates were 68, 37, and 82 %, respectively.

**Conclusions**

- Radiation therapy has become increasingly more conformal with advancing technologies that permit dose to target structures while limiting radiation to surrounding normal tissues.
- 3DCRT has been established as a standard for radiation treatment.
- IMRT and proton therapy are two modalities that may provide more conformality and reduce radiation to organs at risk; however, the role of these modern techniques for rectal cancer remains to be elucidated.
- SBRT may be a reasonable treatment option for those with pelvic recurrences in previously irradiated fields. Hyperfractionated, accelerated irradiation is also a reasonable alternative.
- IORT is a good option for cancers that cannot be fully resected at the time of surgery.
- As techniques continue to improve, the application of these technologies to reduce treatment-related toxicities and improve target coverage is attractive in order to eradicate disease without significantly impacting patient quality of life.

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# Anal Cancer: Background and Clinical Evidence

15

Eleanor Osborne, Christopher Crane, and Prajnan Das

## 15.1 Epidemiology/Risk Factors

(a) In 2015, there will be an estimated 7000 new cases of anal cancer, resulting in 1000 deaths [1]. While the incidence of anal cancer has been on the rise over the past several decades [2], it still only comprises ~1 % of all GI malignancies.
(b) Anal cancer is more prevalent in women than men (2:1, female to male) [1].
(c) The median age at diagnosis is 60 years [3].
(d) Pathology:
    (i) Squamous cell carcinoma (SCC) is the most common histology and accounts for 85 % of anal cancer tumors. The second most prevalent histology is adenocarcinoma (10 % of cases), which carries a poorer prognosis than SCC and is treated according to the rectal adenocarcinoma paradigm (neoadjuvant chemoradiation followed by surgical resection). Rarer histologies of the anal canal include neuroendocrine tumors and melanoma [4].
(e) Risk factors: [5–7]
    (i) Human papillomavirus (HPV) infection
    (ii) Receptive anal intercourse
    (iii) Multiple sexual partners or a personal history of a sexually transmitted disease
    (iv) Immunosuppression (HIV, chronic steroid use)
        1. A CD4 count of less than 200/μl is associated with an increased risk of anal cancer [8, 9].
    (v) Personal history of cervical/vaginal/vulvar dysplasia or cancer
    (vi) Smoking
(f) Currently, there is no clear evidence to recommend routine anal cancer screening [10, 11]. Some investigators have evaluated screening with anal cytology and high-resolution anoscopy in high-risk populations, but there is no consensus yet about the role of these studies [12].
(g) HPV vaccination has been shown to reduce the risk of anal intraepithelial neoplasia in men who have sex with men [13]. In the future, HPV vaccination could potentially reduce the risk of developing anal cancer in both men and women.

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© Springer International Publishing AG 2017
T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_15

## 15.2 Staging

(a) Table 15.1 [14]

## 15.3 Prognostic Factors

(a) Poor prognostic factors
  (i) Male gender: Male gender has been shown to be associated with poorer locoregional failure and OS at 5 years in multiple large randomized controlled trials (EORTC 22861, RTOG 98-11, ACT II) [11, 15–17].
  (ii) TN category: A retrospective analysis of RTOG 98-11 database showed poorer OS, DFS, local failure, and distant metastasis rate in patients with T3/T4 and node-positive disease [18]. Other retrospective studies using multivariate analyses have also shown poorer DFS, OS, and locoregional recurrence in patients with tumors greater than 5 cm (T3) and increased rates of distant metastasis in patients with more advanced N stages [15, 19].
  (iii) HPV negative: HPV-negative tumors are associated with poorer local control and overall survival than HPV-positive tumors [20, 21]. This may be, in part, due to high rates (80 %) of deleterious p53 mutations in HPV-negative tumors [22].
  (iv) Cigarette smoking: Current or former smokers have poorer OS compared to never smokers [23]. One hypothesis is that cigarette smoking affects the ability of the immune system to clear the HPV infection [11].
  (v) Anemia: Low baseline hemoglobin levels predict for poorer colostomy-free survival and DFS [16].
  (vi) HIV positive: In the era of highly active antiretroviral therapy (HAART), HIV-positive patients treated with chemoradiation appear to have similar rates of response and survival compared to HIV-negative patients [24, 25].

## 15.4 Molecular Biology

(a) *Human papillomavirus (HPV)*
  (i) HPV is a DNA virus that is found in 80–90 % of anal tumors [5, 22, 26] and is associated with better survival outcomes [20, 21].
  (ii) ~100 different genotypes of this virus exist, but HPV-16 is the most high-risk subtype and is present in 70 % of anal tumors [5, 6, 26].

**Table 15.1** TNM classification and stage grouping for anal cancer

| | | | | | |
|---|---|---|---|---|---|
| T1 | ≤ 2 cm | N1 | Perirectal node(s) | M0 | No distant metastasis |
| T2 | 2–5 cm | N2 | Unilateral internal iliac and/or inguinal node(s) | M1 | Distant metastasis |
| T3 | > 5 cm | N3 | Perirectal and inguinal nodes and/or bilateral internal iliac and inguinal nodes | | |
| T4 | Invasion of nearby organs (vagina, urethra, bladder) | | | | |

| | |
|---|---|
| Stage I | T1 N0 M0 |
| Stage II | T2–T4 N0 or T1–T3 N1 |
| Stage III | T4 N1 or any N2 or N3 |
| Stage IV | Any M1 |

1. Other subtypes include HPV-18 (second most common high-risk subtype), HPV-6, HPV-11, and HPV-31 [3].

(iii) HPV encodes two viral oncoproteins – E6 and E7 – which augment progression through the cell cycle. E6 binds p53, a critical tumor suppressor protein, and triggers its degradation via the ubiquitination pathway. E7 binds retinoblastoma-associated tumor suppressor proteins and facilitates transition from the G1 to S phase. Both of these actions result in abnormal cellular proliferation.

(iv) Typically HPV is rapidly cleared by an individual's immune system, but ~1 % of the general population is chronically infected. These chronic carriers present with anogenital warts [27].

1. Immunosuppression increases the risk of anal cancer by allowing reactivation of the virus in those with latent, persistent HPV infections [3, 5].

(v) Premalignant lesions.

1. Similar to cervical cancer, anal cancer results from the progression of early premalignant lesions (SILs) to invasive carcinoma.
   (a) Low-grade squamous intraepithelial lesions (LSILs) [28] are typically self-limited in nature. These lesions are characterized by nuclear atypia or atypical mitoses that are limited to the basal layers of the epithelium. Anal intraepithelial neoplasia type 1 (AIN1) is a type of LSIL.
   (b) High-grade squamous intraepithelial lesion (HSIL) [28, 29] harbors the potential to progress to invasive carcinoma. Pathologic examination typically shows marked nuclear atypia or atypical mitoses throughout all epithelial layers, and tissue will stain positive for p16. AIN2 and AIN3 are types of HSIL.
   (i) The progression of HSIL to an invasive cancer is influenced by various factors including infection with a high-risk HPV subtype and immunosuppression [29].

## 15.5 Patterns of Failure

(a) *Anal canal*

(i) *Anatomy*: The anal canal is the terminal portion of the large intestine. It measures roughly 4 cm and extends from the anorectal ring to the anal verge. The dentate line is located approximately 2 cm cranial from the anal verge and separates the anal canal into two segments – proximal (columnar/glandular epithelium) and distal (squamous epithelium). A zone of transitional epithelia (transitional zone) exists proximal to the dentate line.

(ii) *Patterns of spread*.

1. Most patients (~50 %) present with disease localized to the anus [30].
2. Regional lymph node spread is seen in ~30 % of patients [11, 30]. The risk of lymphatic spread is correlated to primary tumor size [3]. The lymph nodes at risk depend on the location of the primary tumor. Tumors proximal to the dentate line drain to the perirectal nodes and along inferior/middle hemorrhoidal vessels to the internal iliac, obturator, and presacral nodes. Tumors distal to the dentate line drain to the superficial inguinal nodes.
3. Around 10 % of anal cancer patients have metastatic disease at the time of diagnosis [30]. The liver and lungs are the most common sites of metastatic spread.

(iii) *Patterns of failure*.

1. Locoregional failure

(a) Locoregional recurrence is the most common cause of failure following chemoradiation, occurring in approximately 10–30 % of patients [3]. Factors associated with increased risk of locoregional failure include higher T stage and N stage [19].
(b) The vast majority (~90 %) of recurrences will develop within the first 2 years after treatment [31].

2. Distant failure
(a) 10–20 % of patients will develop metastatic disease after their primary treatment [32, 33]. The most common site of distant failure is the liver.
(b) Retrospective studies have shown that higher N stage is correlated with increased risk of distant failure [19].

(b) *Anal margin*
(i) *Anatomy*: The anal margin is the region of perianal skin spanning 5 cm radially from the anal verge. The superficial inguinal lymph nodes are the first echelon of lymph node drainage.
(ii) *Patterns of spread*: SCCs of the anal margin are typically well-differentiated tumors harboring a low potential for distant spread. Like anal canal tumors, the risk of lymphatic spread is directly correlated to the size of the primary tumor. Up to 67 % of patients with primary lesions greater than 5 cm have evidence of nodal involvement at diagnosis [34].
(iii) *Patterns of failure*: Locoregional failure is most common in anal margin tumors.

## 15.6 Multidisciplinary Treatment of Anal Canal Tumors

(a) *History and physical*
(i) *History*: A detailed history focusing on presenting symptoms and risk factors should be obtained.
1. Presenting symptoms
(a) Rectal bleeding – the most common presenting symptom
(b) Pain
(c) Pruritus
(d) Tenesmus
(e) Fecal incontinence or change in bowel habits
(f) Anal mass
2. Risk factors
(a) Sexual history (history of STDs or HIV, receptive anal intercourse)
(b) History of immunosuppression, such as corticosteroid use or organ transplant
(c) History of abnormal Pap smear

(ii) *Physical*: A focused physical examination revolving around a thorough rectal and lymph node examination.
1. External examination and inspection of the anal margin.
2. Digital rectal examination (DRE) to assess location, size, and mobility of the tumor as well as functionality of the anal sphincter. During palpation, it is important to assess for involvement of other nearby structures including the vagina and prostate.
3. Anoscopy to visualize and assess the anal mucosa including the location of the mass relative to the anal verge. During anoscopy, the anal mass should be biopsied.
4. Inguinal lymph node examination.
5. Gynecologic exam including Pap smear for women to assess for vaginal involvement as well as screen for synchronous cervical cancer.

(b) *Laboratory work-up*
(i) Complete blood count with blood transfusion, if indicated
(ii) Liver function tests
(iii) Complete metabolic panel
(iv) HIV serology and if positive CD4 count and viral load

(c) *Imaging*
   (i) CT or MRI of the pelvis to assess local disease and pelvic or inguinal adenopathy.
   (ii) CT of the chest and abdomen to detect distant metastases.
   (iii) PET/CT is used in many centers for staging of anal cancer. PET/CT is more sensitive than CT scan in detecting the primary anal tumor, but more importantly has greater sensitivity in detecting occult nodes which can result in nodal upstaging and modifications to the radiation treatment plan [11, 35].

(d) *Treatment*
   (i) *Anal canal*
      1. M0: Patients with locoregionally confined disease should be treated with chemoradiation with concurrent mitomycin C (MMC) and 5-FU.
         (a) Chemotherapy: MMC is commonly delivered as a 10 mg/m$^2$ IV bolus on days 1 and 29. 5-FU is given as a continuous infusion (100 mg/m$^2$/day) in days 1–4 and days 29–32. Several studies suggest that capecitabine (825 mg/m$^2$ oral bid, Monday through Friday) can be used in the place of 5-FU [36–38], but this has not been tested in a randomized phase III trial.
         (b) Radiation: The primary tumor and at-risk lymph nodes (perirectal, presacral, internal iliac, external iliac, and inguinal) should be covered [39]. At-risk nodal regions should receive at least 36 Gy (if conventional fractions are used), while the primary tumor and involved nodes should be treated to at least 45 Gy. An additional 9–14 Gy boost should be delivered to large primaries (T3-4) and bulky lymph nodes [40]. Radiation should be delivered using intensity-modulated radiation therapy (IMRT) to minimize treatment-associated toxicities [41]. There is no role for dose escalation in excess of 59 Gy [42, 43], and extended treatment breaks should be avoided [44].
            (i) Radiotherapy alone: Some institutions have reported excellent outcomes with radiation therapy alone, without concurrent chemotherapy, especially for T1 and N0 patients [45, 46]. Radiation therapy alone could therefore be considered as an acceptable treatment option for T1 N0 patients.
            (ii) Brachytherapy: Interstitial brachytherapy can be used to provide a boost (10–20 Gy) following EBRT, with acceptable toxicity and excellent local control [47, 48]. However, the use of brachytherapy remains limited to selected centers.
      2. M1: Patients with metastatic disease should be treated with cisplatin-based chemotherapy [40]. An international trial is currently comparing 5-FU and cisplatin versus carboplatin and paclitaxel [49, 50]. Palliative radiation can be considered for bulky primary disease [40]. Definitive chemoradiation and surgical resection may be considered in patients with oligometastatic disease [49, 51].
      3. Recurrent disease:
         (a) Local: Salvage APR is the standard of care [11]. If patients with local failure are eligible for salvage surgery, 5-year cancer-specific survival from the time of recurrence is 40–64 % [52, 53].
         (b) Inguinal nodes: Inguinal lymph node dissection [11].

(c) Metastatic: Cisplatin-based chemotherapy.

4. HIV/AIDS patients: HIV-positive patients with CD4 counts greater than 200/mm$^3$ should be treated according to the same approach as HIV-negative patients. Retrospective studies have shown equivalent survival outcomes for HIV-positive and HIV-negative individuals [24, 25]. However, toxicities including moist desquamation and severe diarrhea are significantly higher in patients with CD4 counts less than 200/mm$^3$ [54]. Therefore, dose reduction or omission of MMC and smaller radiation fields should be considered in this population.

(ii) *Anal margin*

1. Squamous cell carcinomas.
   (a) For small (T1 N0), well-differentiated tumors that do not involve the anal sphincter, the standard treatment is wide local excision with a goal of 1-cm radial margins [55, 56]. If the margin is positive, a re-excision should be attempted. Alternatively, the patient with a positive or close margin can be treated with adjuvant radiation (with or without 5-FU chemotherapy) to a dose of 60–66 Gy [3].
   (b) For T1 N0 tumors or small T2 N0 tumors involving the anal sphincter, the primary tumor and inguinal lymph nodes can be treated with radiation alone [55].
   (c) For T3/T4 or N+ disease, the treatment paradigm is the same as that for anal canal tumors. Patients should receive definitive radiation including inguinal and pelvic radiation with concurrent 5-FU and mitomycin C-based chemotherapy.
2. Melanomas and basal cell carcinomas should be treated as skin cancers – surgery with wide local excision [31].

## 15.7 Key Clinical Studies

Historically, tumors of the anal canal were treated surgically. Seminal work by Dr. Nigro at Wayne State University in the 1970s suggested that neoadjuvant, concurrent chemoradiation therapy (CRT) to a low dose of 30 Gy with continuous-infusion 5-FU and MMC was sufficient to cure patients of their cancer, thereby enabling organ preservation and avoiding the need for up-front, radical surgical resection [57]. Since this early work, six randomized controlled trials (RCTs) have assessed the role and timing of chemotherapy and radiation in the treatment of anal carcinoma (Table 15.2). More recent studies have evaluated the role of IMRT.

(a) *Chemoradiation* versus *radiation alone*: The first two, large anal cancer RCTs were both initiated in the late 1980s in Europe and compared local control following chemoradiation with 5-FU and mitomycin C versus radiation alone. Both trials showed improved local control, colostomy-free survival (CFS), and disease-free survival (DFS) in the chemoradiation arm. The radiation was delivered using split-course fractionation, which is no longer used.

(i) *United Kingdom Coordinating Committee on Cancer Research (UKCCCR) Anal Cancer Trial (ACT) I*: ACT I is one of the larger anal cancer RCTs to date and has the longest median follow-up (13.1 years) [58]. 577 patients were randomized to either radiation alone or radiation with 5-FU/mitomycin C. The primary endpoint was local control. The trial involved a split course of radiation with the initial 45 Gy being delivered in 20–25 fractions, followed by a 6-week break and

**Table 15.2** Key randomized controlled trials in anal cancer

| Trial | Years open | Patient population | # of pts. eligible | Median follow-up (years) | Time point (years) | Arms | RT schedule | Primary Endpoint | LC | CFS | DFS | OS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ACT I [33, 58] | 1987–1994 | T2–T4 M0 | 577 | 13.1 | 12 | A. RT alone<br>B. CRT with 5-FU+MMC | 1. 45 Gy in 20–25 fractions<br>2. Reassess at 6 wks<br>(a) If >50 % response ➔ boost 15 Gy with EBRT or 25 Gy with Ir-192 brachytherapy<br>(b) If <50 % response ➔ surgery | Local control | A. 41 %[a]<br>B. 66 % | A. 20 %[a]<br>B. 30 % | A. 18%[a]<br>B. 30 % | A. 28%[b]<br>B. 33 % |
| EORTC 22861 [32] | 1987–1994 | Locally advanced (T3–T4 or N1–N3 M0) | 103 | 3.5 | 5 | A. RT alone<br>B. CRT with 5-FU+MMC | 1. 45 Gy in 25 fractions<br>2. Reassess at 6 wks<br>(a) If partial response ➔ boost 20 Gy<br>(b) If complete response ➔ boost 15 Gy<br>(c) If no response ➔ surgery | Local control | A. 50%[a]<br>B. 68 % | A. 40%[a]<br>B. 72 % | A. 42 %[bc]<br>B. 58 % | A. 54%[bc]<br>B. 58 % |

(continued)

**Table 15.2** (continued)

| Trial | Years open | Patient population | # of pts. eligible | Median follow-up (years) | Time point (years) | Arms | RT schedule | Primary Endpoint | LC | CFS | DFS | OS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RTOG 87-04 [59] | 1988–1991 | Any stage, M0 | 291 | 3 | 4 | A. CRT with 5-FU+MMC<br>B. CRT with 5-FU alone | 1. 45–50.4 Gy in 25 fractions<br>2. Biopsy 4–6 wks post-RT<br>(a) If positive ➔ boost additional 9 Gy (5fxns) with 5-FU+Cis<br>(b) If negative ➔ no additional RT | Local control, including 6 wk. biopsy | Negative 6 wks biopsy:<br>A. 92 %[b]<br>B. 86 % | A. 71 %[a]<br>B. 59 % | A. 73 %[a]<br>B. 51 % | A. 75 %[bc]<br>B. 70 % |
| RTOG 98-11 [15, 17] | 1998–2005 | T2–T4, M0 | 649 | Unknown | 5 | A. CRT with 5-FU+MMC<br>B. NACT 5-FU+CDDP × 2c ➔ CRT with 5-FU+CDDP | 1. 45 Gy in 25 fractions<br>2. If T3/T4, node positive, or residual T2 disease after 45 Gy ➔ 10–14 Gy boost | DFS | A. 80 %[b]<br>B. 74 % | A. 72 %[b]<br>B. 65 % | A. 68 %[a]<br>B. 58 % | A. 78 %[a]<br>B. 71 % |
| ACT II [79] | 2001–2008 | Any stage, M0 | 940 | 5.1 | 3 | A. CRT with 5-FU+MMC<br>B. CRT with 5-FU+CDDP<br>C. CRT with 5-FU+MMC ➔ maintenance 5-FU/CDDP<br>D. CRT with 5-FU+CDDP ➔ maintenance 5-FU/CDDP | 1. 50.4 Gy in 28 fractions | 1. CR at 26 wks<br>2. DFS | CR at 26 weeks<br>1. MMC: 91 %[b]<br>2. CDDP: 90 % | A. 75 %[b]<br>B. 72 %<br>C. 73 %<br>D. 75 % | A. 73 %[b]<br>B. 72 %<br>C. 73 %<br>D. 74 % | A. 86 %[b]<br>B. 84 %<br>C. 82 %<br>D. 83 % |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ACCORD 03 [42] | 1999–2005 | Primary >4 cm or N1–N3, M0 | 307 | 5 | 5 | A. CRT with 5-FU/CDDP w/ standard boost<br>B. CRT with 5-FU/CDDP w/ high-dose boost<br>C. NACT 5-FU/CDDP ➔ CRT with 5-FU/CDDP w/ standard boost<br>D. NACT 5-FU/CDDP ➔ CRT with 5-FU/CDDP w/ high-dose boost | 1. 45 Gy in 25 fractions<br>2. Reassess at 3 wks:<br>(a) If any response ➔ receive standard (15 Gy) or high-dose (20–25 Gy) boost.<br>(b) If no response ➔ surgery | CFS | A. 84 %[b]<br>B. 78 %<br>C. 72 %<br>D. 88 % | A. 77 %[b]<br>B. 73 %<br>C. 70 %<br>D. 82 % | A. 67 %[b]<br>B. 62 %<br>C. 64 %<br>D. 78 % | 1. No NACT: 71 %[b]<br>2. NACT: 75 % |

*LC* local control, *CFS* colostomy-free survival, *DFS* disease-free survival, *OS* overall survival, *RT* radiation therapy, *CRT* chemoradiation therapy, *wks* weeks, *5-FU* 5-fluorouracil, *MMC* mitomycin C, *CDDP* cisplatin, *NACT* neoadjuvant chemotherapy, *CR* complete response

[a]Statistically significant ($p<0.05$)

[b]Not statistically significant ($p\geq0.05$)

[c]Estimated from published figs

clinical reassessment. Depending on the degree of response (≥50 %, <50 %), the patient would receive either a boost or proceed to surgery. For those treated with CRT, there was a statistically significant improvement in 12-year local control (66 % vs 41 %), CFS (30 % vs 20 %), and DFS (30 % vs 18 %), resulting in a relative improvement of ~33 % in all of these endpoints. In addition, there was a trend toward improved overall survival in the CRT arm (median OS 7.6 years vs 5.4 years). While this did not reach statistical significance, there was a statistically significant reduction in the number of deaths from anal cancer (p=0.004) [58].

(ii) *European Organization for Research and Treatment of Cancer (EORTC)*: The EORTC trial is similar to ACT I in purpose and design, with only a few small differences. The EORTC study was considerably smaller (103 vs 577 patients) with a shorter median follow-up (3.5 years vs 13.1 years). A split course of radiation was also used in this trial with reassessment at 6 weeks following an initial dose of 45 Gy. Complete responders received an extra 15 Gy boost to the original tumor and involved nodes, partial responders received a 20 Gy boost, and nonresponders proceeded to surgery. The rate of side effects was comparable in the CRT and radiation arms. Despite the relatively small cohort and short follow-up, there was a significant improvement in 5-year local control (68 % vs 50 %) and CFS (72 % vs 40 %). No overall survival benefit was seen (5-year OS approximately 55 % in both arms) [32].

(b) *Alternate chemotherapy regimens*: After ACT I and EORTC showed a clear benefit of CRT, subsequent studies have looked at whether less toxic chemotherapy regimens or the use of neoadjuvant or adjuvant chemotherapy could be used in the place of 5-FU/MMC. In summary, none of these trials have shown a benefit to alternative chemotherapy regimens, and concurrent CRT with 5-FU/MMC remains the standard of care.

(i) *Radiation Therapy Oncology Group (RTOG) 87-04/Eastern Cooperative Oncology Group (ECOG) 1289*: In an attempt to drop the more toxic MMC from the chemotherapy regimen, this trial compared concurrent CRT with 5-FU/MMC versus 5-FU alone. A split-course radiation regimen was used to treat all patients, this time with a "post-induction" biopsy obtained 4–6 weeks after delivery of the initial 45–50.4 Gy. If the post-induction biopsy was positive, an additional 9 Gy boost was delivered, and the patient was considered to have a local failure. The primary endpoint was local control. The rate of negative post-induction biopsies (i.e., immediate local control) was 92 % in the 5-FU/MMC arm and 86 % in the 5-FU arm ($p$ = 0.135), and the 4-year CFS was significantly lower in the 5-FU/MMC arm (71 % vs 59 %). The prevention of colostomies with MMC was driven primarily by patients with bulky (T3/T4) disease ($p$ = 0.019). The 4-year DFS was also significantly improved (73 % vs 51 %, $p$ = 0.0003). While the 5-FU/MMC regimen was superior, it did lead to greater acute hematologic complications (18 % vs 3 %, $p$ < 0.001). Chronic side effects were similar [59].

(ii) *RTOG 98-11*: Since RTOG 87-04 showed that MMC could not simply be excluded from the chemotherapy regimen, RTOG 98-11 investigated whether the addition of neoadjuvant chemotherapy and replacement of MMC with a less toxic drug (cisplatin) could improve outcomes compared to the standard 5-FU/MMC. Cisplatin was an appealing alternative drug as it had been shown to be successful for anal cancer in phase II studies and was also effective in other HPV tumors including cervical cancer

and oropharyngeal cancer [44, 60]. RTOG 98-11 accrued from 1998 to 2005 and randomized 649 patients to the standard arm (CRT with 5-FU/MMC) or the experimental arm (neoadjuvant chemotherapy with 5-FU/cisplatin for two cycles, followed by concurrent CRT with 5-FU/cisplatin). This trial was, therefore, not a direct comparison of 5-FU/MMC versus 5-FU/cisplatin. All patients received an initial 45 Gy in 25 fractions followed by a 10–14 Gy boost for patients with T3/T4 disease, positive nodes, or T2 tumors with residual disease after 45 Gy. Radiation was not delivered with a split course as in earlier trials. The 5-year DFS (primary endpoint) (68 % vs 58 %, $p = 0.006$) and OS (78 % vs 71 %, $p = 0.026$) were significantly improved in the 5-FU/MMC arm. The 5-year CFS was also better for patients receiving 5-FU/MMC (72 % vs 65 %, $p = 0.05$). It is difficult to conclude from this trial whether the inferior outcomes in the cisplatin arm were due to the use of induction chemotherapy or due to the difference in the concurrent chemotherapy regimens. Delaying the initiation of definitive CRT with neoadjuvant chemotherapy may have resulted in poorer outcomes in the cisplatin arm, or resulted in platinum-based radio resistance [17, 61]. Nevertheless, based on this trial, concurrent CRT with 5-FU and mitomycin remains the standard of care.

(iii) *UKCCCR ACT II*: ACT II was a 2 × 2 study that compared CRT with 5-FU/MMC versus 5-FU/cisplatin and also examined the impact of maintenance chemotherapy with 5-FU/cisplatin. A total of 940 patients were randomized to one of four arms: (1) CRT with 5-FU/MMC, (2) CRT with 5-FU/cisplatin, (3) CRT with 5-FU/MMC followed by maintenance 5-FU/cisplatin, and (4) CRT with 5-FU/cisplatin followed by maintenance 5-FU/cisplatin. For radiation, all patients were treated to 50.4 Gy in 28 fractions. The primary endpoints of the study were complete response at 6 months and progression-free survival. Neither of these were significantly different in any of the four arms. Additionally, none of the other survival endpoints (OS, CFS) were different. Hence, this trial indicates that concurrent 5-FU/cisplatin leads to equivalent outcomes as concurrent 5-FU/MMC. Further, the cisplatin arms had significantly lower grade 3+ hematologic side effects (16 % vs 26 %, $p < 0.001$); however, the authors cited increased resources needed for the administration of cisplatin infusions compared to mitomycin. This study also indicates that there was no benefit to maintenance chemotherapy, though only 44 % of patients randomized to the maintenance arms completed both cycles of maintenance chemotherapy.

(c) *Dose escalation*:

(i) *Intergroup ACCORD 03*: ACCORD 03 was another 2x2 study that investigated the potential role of dose escalation as well as neoadjuvant chemotherapy. ACCORD 03 was a smaller study than ACT II (only 307 patients) and randomized patients to four arms: (1) CRT with 5-FU/cisplatin + standard boost, (2) CRT with 5-FU/cisplatin + high-dose boost, (3) induction 5-FU/cisplatin × two cycles followed by CRT + standard boost, and (4) induction 5-FU/cisplatin × two cycles followed by CRT + high-dose boost. Unlike RTOG 98-11 and ACT II, radiation was again delivered in a split-course fashion with a 3-week break after the initial 45 Gy, at which time patients were reassessed for clinical response. If patients had some degree of response, they proceeded on to receive either a standard boost (15 Gy) or high-dose boost (20–25 Gy). There was no significant difference across the four arms in

terms of CFS (primary endpoint) or other survival endpoints. In addition, even when combining the two induction chemotherapy arms or the two high-dose boost arms, there was no significant difference in colostomy-free survival (3-year CFS 79 % vs 76 %, $p = 0.37$ and 3-year CFS 79 % vs 76 %, $p = 0.067$, respectively). In summary, this trial suggests that there is no clear role for induction chemotherapy or boosting gross disease to doses in excess of 60 Gy.

(d) *Induction chemotherapy*: The RTOG 98-11 and ACCORD 03 trials discussed above both failed to show any benefit from induction chemotherapy.

(e) *Maintenance chemotherapy*: As discussed above, the ACT II trial showed no benefit from maintenance chemotherapy.

(f) *IMRT*: In order to decrease the acute and long-term toxicities associated with high-dose radiation to the anal canal, recent retrospective and prospective studies have investigated the role of intensity-modulated radiation therapy (IMRT) in reducing dose to normal tissues during radiation treatment. Overall these studies show excellent survival outcomes and lower rates of severe side effects compared to the historic RCTs (Table 15.3) [62–70]. A few of the larger retrospective studies and RTOG 05-29 are highlighted below.

(i) *Retrospective*:

1. *Salama, 2007* [62]: This multicenter retrospective study was the largest early study assessing outcomes with IMRT-based chemoradiotherapy in anal cancer. It looked at the outcomes of 53 patients treated from 2000 to 2006, but had relatively short median follow-up (14.5 months) and only reported 18-month survival outcomes. While the rate of acute toxicities was high compared to some of the more recent retrospective studies (59 % of patients suffering acute grade 3+ hematologic toxicities, 38 % of patients with grade 3 dermatitis), they were considerably lower than the earlier randomized controlled trials, including RTOG 98-11.
2. *Kachnic, 2012* [63]: This retrospective series of 43 patients was the first to analyze the results from "dose-painting IMRT" (DP-IMRT). Prior studies had utilized the technology of IMRT and multiple beams to precisely shape the radiation and avoid critical structures; however, dose was ultimately delivered with sequential boosts as opposed to utilizing a simultaneous integrated boost, or DP-IMRT. DP-IMRT allows radiation to be delivered using a single plan. In this study, patients with T2 N0 disease had the primary tumor treated to 50.4 Gy and the elective nodal CTV treated to 42 Gy in 28 fractions, while patients with more advanced disease received two extra fractions with the primary tumor treated to 54 Gy and the nodal CTV treated to 45 Gy in 30 fractions. This study showed comparable survival outcomes compared to earlier studies and very low non-hematologic acute toxicities (grade 3+ skin 10 % and grade 3+ GI 7 %).
3. *Mitchell, 2014* [64]: A more recent study from MD Anderson Cancer Center incorporated a simultaneous integrated boost technique that treated the GTV in 2 Gy fractions (as opposed to 1.8 Gy fractions in RTOG 05-29 and Kachnic, et al.). A total of 65 patients were analyzed, and outcomes from this study were excellent with a 2-year local control rate of 91 % and 2-year overall survival of 96 %. Acute complication rates were very low (3 % hematologic, 17 % skin, 9 % gastrointestinal). The low rate of hematologic side effects compared to other series was due, in part, to the use of concurrent 5-FU and cisplatin in the majority of patients, as

**Table 15.3** Representative selection of retrospective and prospective series investigating the use of IMRT in anal cancer

| Studies | # pts | Median dose to GTV (range) (Gy) | Concurrent chemo, % | Median f/u (month) | Time point (year) | LRC, % | DMFS, % | PFS, % | CFS, % | OS, % | Acute G3+ hemetox, % | Acute G3+ skin tox, % | Acute G3+ GI tox, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RTOG 05-29, 2013 [41] | 52 | 50.4 (T2 N0); 54 (rest) | 100 % | 26.7 | 2 | 80 % | [a] | 77 % | 86 % | 88 % | 58 % | 23 % | 21 % |
| Milano, 2005 [65] | 17 | 54 | 82 % | 20.3 | 2 | 82 % | 74 % | 65 % | 82 % | 91 % | 76 % | 0 | 0 |
| Salama, 2007 [62] | 53 | 51.5 | 100 % | 14.5 | 1.5 | 84 % | 93 % | [a] | 84 % | 93 % | 59 % | 38 % | 15 % |
| Pepek, 2010 [66] | 45 | 54 | 89 % | 14 | 2 | 90 % | 78 % | [a] | 82 % | 85 % | 24 % | 0 | 15 % |
| Bazan, 2011 [67] | 29 | 54 | 100 % | 32 | 3 | 92 % | [a] | 84 % | 91 % | 88 % | 21 % | 21 % | 7 % |
| Vieillot, 2012 [68] | 39 | 63 | 85 % | 24 | 2 | 77 % | [a] | 70 % | 85 % | 89 % | 25 % | 42 % | 10 % |
| Kachnic, 2012 [63] | 43 | 50.4 (T2 N0); 54 (rest) | 100 % | 24 | 2 | 95 % | 92 % | [a] | 90 % | 94 % | 51 % | 10 % | 7 % |
| Chuong, 2013 [69] | 52 | 56 | 100 % | 19 | 3 | 92 % | [a] | 73 % | 94 % | 86 % | 63 % | 12 % | 10 % |
| Mitchell, 2014 [64] | 65 | 54 | 100 % | 19 | 2 | 93 % | 93 % | 86 % | [a] | 96 % | 3 % | 17 % | 9 % |
| Call, 2016 [70] | 148 | 51.25 | 99 % | 26.8 | 3 | 97 % | 91 % | [a] | [a] | 87 % | 41 % | 20 % | 11 % |

*LRC* locoregional control, *DMFS* distant metastasis-free survival, *PFS* progression-free survival, *CFS* colostomy-free survival, *OS* overall survival, *G3+* grade 3 or higher
[a]Not reported

opposed to 5-FU and mitomycin C. Additionally, the utilization of vaginal dilators for female patients may have decreased the rate of acute vulvar and skin toxicities.

(ii) *Prospective*:

1. *RTOG 05-29* [41]: This multi-institutional, phase II study assessed toxicities following IMRT-based chemoradiation for anal cancer. The radiation technique utilized in this study was the same as in the Kachnic, et al. retrospective series. Patients with T2 N0 disease had the primary tumor treated to 50.4 Gy and the elective nodal CTV treated to 42 Gy in 28 fractions, while patients with more advanced disease had the primary tumor treated to 54 Gy and the CTV treated to 45 Gy in 30 fractions. While the primary outcome of the study (grade 2 or higher gastrointestinal/genitourinary toxicity) was not met, grade 3 or higher GI toxicities and grade 3 or higher dermatologic toxicities were significantly reduced compared to RTOG 98-11 (21 % vs 36 % and 23 % vs 49 %, respectively). Survival outcomes were similar to prior studies – 2-year locoregional control 80 %, 2-year DFS 77 %, and 2-year OS 88 % (Table 15.3). One critical finding from this trial was that 81 % of IMRT plans submitted for central review required planning revision, with 55 % of plans under-contouring the mesorectum. Nearly half of these plans (46 %) required multiple revisions before treatment delivery. This high rate of inter-practitioner discrepancy emphasizes the need to educate physicians on appropriate anal contouring prior to their using IMRT to treat patients.

(g) *Brachytherapy*: An alternative method for treating the primary tumor to a higher dose is to provide a brachytherapy boost following the initial external beam pelvic radiation treatment. Typically, boosts provide an additional 10–20 Gy to the primary tumor and are offered to patients without evidence of pelvic or inguinal gross nodal disease and who have non-circumferential, relatively superficial primary tumors.

(i) Several small, retrospective series have examined the role of a brachytherapy boost following external beam radiation [71–76]. Brachytherapy boosts have been delivered using low-dose rate (LDR) [74, 75], pulsed dose rate (PDR) [71, 72], and high-dose rate (HDR) techniques [73, 76]. While these retrospectives are small, the limited data suggests good rates of local control (2 years 80–90 %) [72, 73, 76] and overall survival (2 years 85–90 %) [72, 73] with minimal additional toxicity.

(ii) In addition, there have been retrospective studies comparing results from external beam boosts versus brachytherapy boosts [48, 77, 78]. These studies showed relatively similar outcomes between brachytherapy and external beam boosts, with slightly reduced acute bone marrow suppression, dermatitis, and proctitis in the brachytherapy arms [77, 78]. Currently, the use of brachytherapy remains limited to certain clinical centers.

## 15.8 Follow-Up, Outcomes, and Toxicities

(a) *Follow-up*:

(i) *Short-term follow-up*: Patients should be assessed with a DRE and inguinal lymph node exam approximately 8 weeks after completing definitive chemoradiation. If there is persistent palpable disease, a biopsy should *not* be immediately performed as anal tumors can take up to 26 weeks to completely regress [79] and premature biopsy may lead to fistula formation and wound healing issues.

Instead, these patients should be closely observed and seen for reevaluation in 4–6 weeks. If there are continued signs of regression, patients can continue to be closely observed up to 6 months before a biopsy is pursued [11, 40]. At any time, if there is evidence of disease progression or ulceration, a biopsy should be performed.

(ii) *Long-term follow-up*: The risk of recurrence is highest in the first 2 years after treatment, justifying the need for more frequent follow-up during that time. Follow-up can help in the management of long-term toxicities, in addition to oncologic surveillance [40].

1. At our institution, patients undergo follow-up with history, inguinal lymph node exam, and DRE every 3 months for 2 years and every 6 months for years 3–5. Anoscopy is performed every 2–3 months until there is a complete response and then annually until years 4–5. Patients also undergo annual CT scan of the chest and abdomen for the first 4–5 years.
2. The NCCN guidelines recommend DRE and inguinal node exam every 3–6 months for 5 years and anoscopy every 6–12 months for 3 years. Additionally, patients with initial T3/T4 disease are recommended for annual imaging of the chest, abdomen, and pelvis for 3 years [40].
3. The ESTRO guidelines consider both routine anoscopy and CT imaging optional [11].

(b) *Outcomes*: Overall, the survival rates for patients with nonmetastatic disease are very good with 5-year OS of 60–80 % in the era of chemoradiation [17, 32, 33]. These favorable outcomes are driven by the high success rate of APR as a salvage local therapy. However, patients with metastatic disease have very poor outcomes with a 5-year OS of 10–20 % [2].

(i) *Quality of Life* (QOL): A patient's QOL can be significantly affected following definitive chemoradiation for anal cancer. While gastrointestinal issues including fecal incontinence and diarrhea are bothersome for patients, most studies have shown acceptable overall QOL metrics following treatment [80–84]. However, sexual dissatisfaction is frequently cited as a major contributor to impaired QOL following chemoradiation, with approximately 70 % of long-term anal cancer survivors reporting sexual dissatisfaction following treatment [80, 82, 83]. Sexual functioning scores remained suboptimal even if radiation was delivered with IMRT [82]. However, female patients who use vaginal dilators during treatment appear to have improved sexual function scores [82].

(c) *Toxicities*: Definitive chemoradiation can lead to severe acute and long-term toxicities. These side effects can be reduced with careful radiation planning with IMRT and aggressive symptom management during on-treatment visits.

(i) *Acute side effects*:

1. Dermatitis – Assessment of perianal skin integrity should be performed routinely during a patient's radiation course. Commonly used treatments include moisturizing ointments, barrier creams (with lanolin), sitz baths, and gel sheets.
2. Diarrhea – Loperamide (Imodium) and/or diphenoxylate/atropine (Lomotil) can be used for diarrhea. These can be titrated up to maximum daily allowance based on stool frequency.
3. Pain – Moisturizing ointments, barrier creams, sitz baths, and gel sheets can provide symptomatic relief. Hydrocortisone (Anusol) cream and suppositories can be used for hemorrhoidal pain. Narcotic pain medications may be necessary for moderate to severe pain.
4. Neutropenia – Blood counts should be monitored closely when giving

MMC, with appropriate supportive medications.

5. Nausea – Antiemetics such as ondansetron and prochlorperazine can be used for chemotherapy-induced nausea.
6. Urinary – Pyridium can be used for radiation cystitis, after urinary tract infections have been ruled out. Tamsulosin (Flomax) can be used for urinary obstructive symptoms in men.

(ii) *Long-term side effects*:

1. Fecal incontinence (including increased frequency and urgency): Severe fecal incontinence is relatively rare, but chronic fecal urgency or diarrhea is reported in 20–30 % of patients [80, 82, 83].
2. Chronic dermatitis: Skin darkening or telangiectasias can occur following radiation, especially in those patients who experienced severe acute dermatitis. Chronic skin toxicity was reported in 20 % of patients in ACT I [58].
3. Sexual dysfunction: Dyspareunia occurs in a large proportion (ranging from 25 to 60 %) of female patients following irradiation [64, 83]. A prospective study has shown that the severity of vaginal stenosis can be reduced with the routine use of a vaginal dilator after radiation treatment [85]. To prevent severe stenosis, the mean vaginal dose should be limited to less than 43 Gy [86]. Decreased sexual arousal is reported in 65–70 % of patients (both women and men) following irradiation. Roughly two-thirds of men have difficulty obtaining, or maintaining, an erection [80, 83].
4. Infertility: Young patients should be counseled regarding fertility preservation (oopexy, sperm banking) prior to initiating chemoradiation.
5. Anal fistulae or ulcers: Chronic ulceration and radionecrosis were reported in 8 % of patients in ACT I [58]. In ACT II, only 2 % of patients required a colostomy for treatment-associated morbidity [16].
6. Pelvic fracture: Pelvic irradiation for anal cancer in women over 65 has been associated with increased pelvic fracture risk (HR 3.16), more so than pelvic irradiation for cervical or rectal cancer, likely because of inclusion of the inguinal lymph nodes. The overall 5-year rate of fracture following irradiation is 14 % [87]. However, these rates are likely to be lower with the use of IMRT.

## 15.9 Future Directions

(a) While chemoradiation leads to excellent outcomes in the majority of patients, patients with locally advanced disease have relatively low rates of disease-free and overall survival. Trials are warranted to improve outcomes in these patients. Potential areas of investigation could include selective radiation dose escalation, more effective concurrent and systemic therapies, and vaccines targeting HPV.

(b) Given good survival outcomes with chemoradiation, the focus should also turn to improving quality of life. Potential strategies could include dose de-escalation or the use of smaller radiation fields in selected patients.

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# Anal Cancer: Radiation Therapy Planning

16

Eleanor Osborne, Christopher Crane, and Prajnan Das

1. *Principles of Field Design/Patterns of Failure*: The goal of radiation field design is to cover the primary tumor, grossly involved lymph nodes, and at-risk regional lymph nodes. Around 30 % of patients with anal cancer have regional nodal involvement at presentation [1, 2]. However, even those without evidence of nodal involvement at presentation have significant risk of developing nodal recurrences. The risk of lymphatic spread is associated with the size and location of the primary tumor [3]. Tumors proximal to the dentate line can spread to perirectal nodes and along inferior/middle hemorrhoidal vessels to internal iliac, obturator, and presacral nodes. Tumors distal to the dentate line can spread to superficial inguinal nodes. Hence, the standard of care is to comprehensively treat the pelvic and inguinal nodes. IMRT and dose-painting can be utilized to give higher doses to the primary anal tumor and involved lymph nodes, while giving lower doses to prophylactically cover the regional pelvic and inguinal nodes.
2. *Simulation*: Prior to simulation, practitioners should carefully review all pertinent aspects of the patient's case including digital rectal exam, gynecologic exam, endoscopy, and radiographic imaging. These findings will influence how the patient is positioned for simulation and whether additional measures (i.e., bolus, prone positioning, etc.) need to be taken.
   (a) *Positioning*: Patients are typically positioned supine or prone on the simulator table, with arms placed overhead. The lower extremities should be immobilized using a customized lower body cradle, or other immobilization device. A radiopaque marker and radiopaque wires can be used to demarcate the anal verge, perianal/dermal involvement, urethra, and surgical scars.
      (i) Supine: Treating a patient in the supine position offers better setup reproducibility. If treating supine, the patient can be positioned in a "frog leg" position to decrease skin folds in the groins and reduce the risk of dermatitis.
      (ii) Prone: Prone positioning with a belly board can help displace small bowel away from the radiation field and should be especially considered in

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© Springer International Publishing AG 2017
T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_16

patients with a large volume of small bowel in the pelvis. However, there may be increased interfraction setup variability with prone positioning compared to treating supine.

(b) *Isocenter*: The isocenter should be placed at mid-depth above the femoral heads.

(c) *Additional measures:*

(i) *Full bladder*: Patients can be simulated with a full bladder to displace and reduce dose to the small bowel, akin to patients being treated for prostate or gynecologic malignancies [4]. If bladder distention is utilized, it is important that the degree of bladder filling is consistent between fractions in order to prevent small bowel from falling into the high-dose field.

(ii) *Vaginal dilator*: Insertion of a silicone vaginal dilator at simulation and during treatments can reduce the mean dose delivered to the vagina by 5.5 Gy [5]. This decreased dose appears to be significant, as the use of a vaginal dilator has been shown to decrease the rates of acute skin toxicity as well as the risk of long-term sexual dysfunction [6].

(iii) *Scrotal shield or shelf*: The use of a scrotal shield to reduce the risk of male infertility in men with anal cancer has been investigated [7]. At our institution, male patients are simulated with their scrotum elevated on a plastic shelf to keep the genitalia from falling into the high-dose fields.

(iv) *Bolus*: Bolus may be needed if the primary tumor involves the anal margin or protrudes through the anal canal. In the perianal region, wet gauze can be used as bolus. Additionally, if there are superficial, grossly involved inguinal lymph nodes, bolus may be needed over the groins to ensure adequate dose buildup.

3. *Techniques, Doses, and Contours*

(a) *Techniques, Fields, and Doses*: Traditionally, AP/PA and 3D conformal techniques were used to treat anal cancer. In recent years, IMRT has been widely adopted, with either a sequential field technique or simultaneous integrated boost technique.

(i) AP/PA [8]: Patients are treated with a wide AP field (including medial inguinal nodes) and a narrow PA field (1.5–2 cm margin on pelvic rim) to 30.6–36 Gy in 1.8 Gy fractions, with the superior border at the L5-S1 interspace and the inferior border 3 cm below the inferior extent of the tumor. Subsequently, patients are treated with an AP/PA cone down to 45 Gy in 1.8 Gy fractions, with the superior border lowered to the bottom of the sacroiliac joints. Finally, a boost is administered to the primary anal tumor and involved nodes to 50.4–59 Gy, in 1.8–2 Gy fractions. The final dose is typically based on tumor size, with higher doses for T3–T4 tumors. Supplemental electron fields are used to treat uninvolved inguinal regions to 30.6–36 Gy and involved inguinal nodes to 50.4–59 Gy.

(ii) 3D conformal: Our institution used a modification of the above technique that resulted in lower bowel and genitalia doses [9]. Patients are treated with AP/PA fields to 30.6 Gy in 1.8 Gy fractions, with the superior border at the L5-S1 interspace, the inferior border 3 cm below the inferior extent of the tumor, and the lateral borders encompassing the medial inguinal nodes. Subsequently, patients are treated with a three-field technique (PA and laterals) to 45 Gy in 1.8 Gy fractions, with the superior border lowered to the bottom of the sacroiliac joints and the lateral borders with 1.5–2 cm margin on pelvic rim. Similar to the above technique, a conformal boost to 50.4–59 Gy is administered to the primary anal

tumor and involved nodes, and supplemental electron fields are used to treat uninvolved inguinal regions to 30.6–36 Gy and involved inguinal nodes to 50.4–59 Gy. Other multifield 3D conformal techniques can also be used for treating anal cancer.

(iii) IMRT with simultaneous integrated boost (SIB): IMRT offers the advantage of dose-painting which allows boosting areas of gross disease using a single radiation plan. This eliminates the need for multiple, sequential plans. Higher doses are used to treat the primary tumor and involved nodes, while simultaneously delivering a lower dose to elective nodal regions. Different approaches have been reported with differences in total doses and fraction sizes [10].

1. RTOG 0529 [11]: The most widely used approach for IMRT is based on the RTOG 0529 trial. In this technique, gross disease is treated using 1.8 Gy fractions, and at-risk lymph nodes are electively covered using 1.5 Gy fractions. The total dose and number of fractions are based on the stage.
   (a) T2 N0: 28 fractions. The primary tumor is treated to 50.4 Gy, and at-risk nodal basins are treated to 42 Gy.
   (b) T3/T4 or node positive disease: 30 fractions. The primary tumor is treated to 54 Gy and the elective nodal volume is treated to 45 Gy. Involved lymph nodes <3 cm in size are treated to 50.4 Gy, while those > 3 cm are treated to 54 Gy.
2. MD Anderson [6]: This technique uses higher total doses and larger fraction sizes, compared to the RTOG 0529 technique. All areas of gross disease are treated in 2 Gy fractions, and elective nodal basins are treated in ~1.6–1.7 Gy fractions.
   (a) T1: 25 fractions. 50 Gy to primary tumor and 43 Gy to elective nodal volume (Fig. 16.1)
   (b) T2: 27 fractions. 54 Gy to primary tumor and 45 Gy to elective nodal volume (Fig. 16.2)
   (c) T3–T4: 29 fractions. 58 Gy to primary tumor and 47 Gy to elective nodal volume (Fig. 16.3)
   (d) Involved nodes are treated based on the size of the node, with 50 Gy for size <2 cm, 54 Gy for size 2–5 cm, and 58 Gy for size >5 cm

(iv) IMRT with sequential courses: An alternative IMRT technique is to use sequential courses with field reductions, more closely replicating the doses and fractionation schemes from the AP/PA and 3D conformal techniques discussed above [12]. Patients are initially treated with 30.6 Gy in 1.8 Gy fractions to the pelvic and inguinal regions, followed by an additional 14.4 Gy (total 45 Gy) in 1.8 fractions to the low pelvic region, followed by a total dose of at least 54 Gy to gross disease. Developing multiple sequential IMRT plans can make treatment planning more challenging. However, an advantage of this technique is that dose is limited to 30.6 Gy in part of the treatment volume.

(b) *Contours*: Consensus contouring guidelines for IMRT-based treatment planning of anal tumors have been compiled by two international organizations – the Radiation Therapy Oncology Group (RTOG) and Australasian Gastrointestinal Trials Group (AGITG).

(i) *RTOG* [13]

1. Boost CTV: Includes the primary anal tumor and any enlarged pelvic or inguinal lymph nodes.

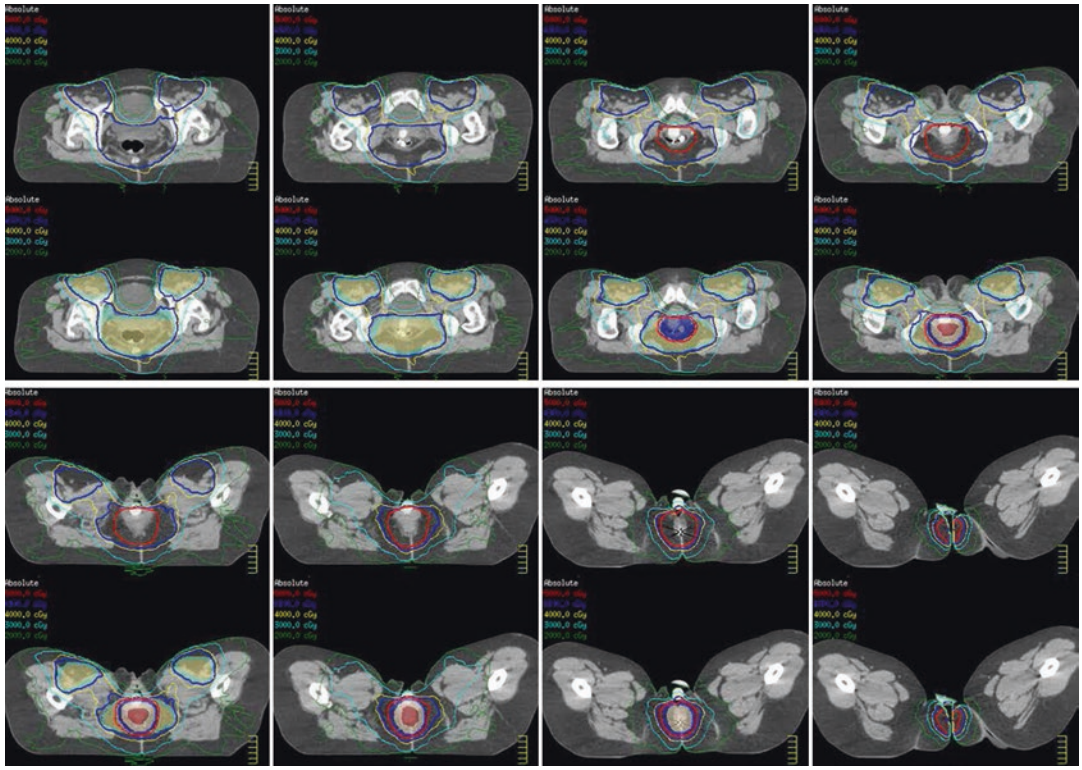


**Fig. 16.1** Representative plan with and without contours (color wash) of the low pelvis of a woman with T1 N0 anal cancer treated with the MD Anderson SIB technique. This case highlights the benefit of a vaginal dilator as the external genitalia and anterior vaginal wall receive less than 30 Gy. Elective nodal CTV = *yellow*, elective nodal PTV = *turquoise*. Anal tumor = *maroon*, anal tumor CTV = *khaki*, anal tumor PTV = *blue*

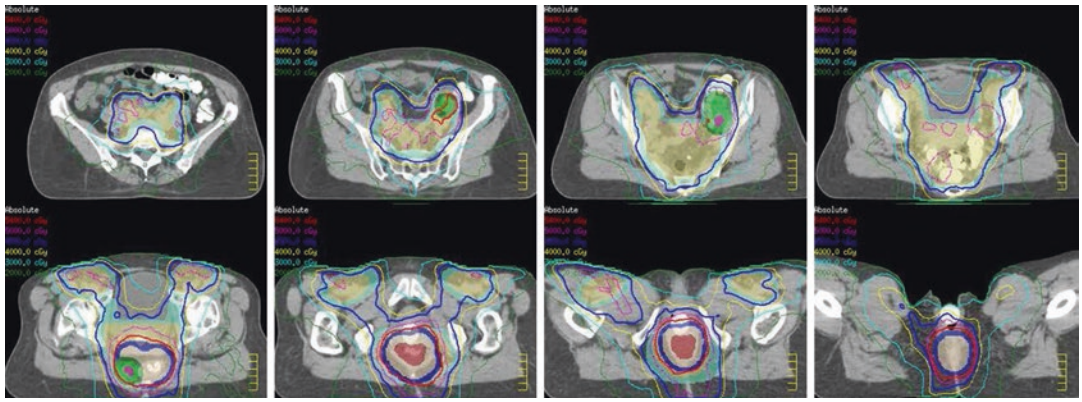


**Fig. 16.2** Representative plan of a woman with locoregionally advanced, T2 N3 anal cancer treated with the MD Anderson SIB technique. She had small left external iliac and perirectal lymph nodes that were treated to 50 Gy. She was treated with a vaginal dilator. Elective nodal CTV = *yellow*, elective nodal PTV = *turquoise*. Gross nodal GTV = *purple*, gross nodal CTV = *light green*, gross nodal PTV = *dark green*. Anal tumor = *maroon*, anal tumor CTV = *khaki*, anal tumor PTV = *blue*

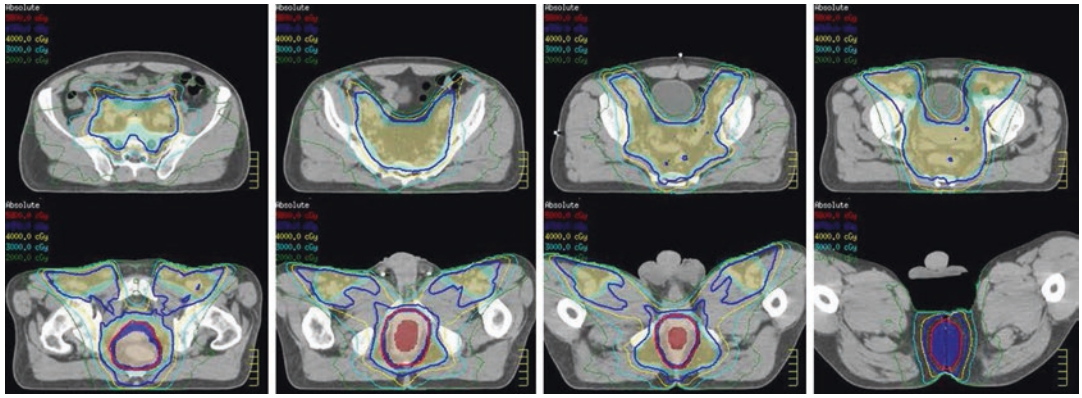


**Fig. 16.3** Representative plan of a man with T3 N0 anal cancer treated with the MD Anderson SIB technique and a scrotal shelf. This case highlights how the scrotal shelf elevates the external genitalia out of the high-dose region. Elective nodal CTV = *yellow*, elective nodal PTV = *turquoise*. Anal tumor = *maroon*, anal tumor CTV = *khaki*, anal tumor PTV = *blue*

For the boost CTV, RTOG recommended a 2.5 cm expansion on the primary GTV and 1 cm expansion on the nodal GTV.

2. Elective nodal volumes: The RTOG consensus guidelines (Fig. 16.4) describe three separate elective nodal CTV, named CTVA, CTVB, and CTVC, all of which should be covered for anal cancer. In general, all CTV volumes should include at least a 7 mm margin on the target vessels [14].
   (a) CTVA: presacral, perirectal, and bilateral internal iliac lymph nodes.
      (i) Cranial border: The sacral promontory/bifurcation of the common iliacs branching into the internal and external iliacs.
      (ii) Caudal border: 2 cm beyond the anal verge or most distal aspect of gross disease.
      (iii) Anterior border:
         1. High pelvis: at least 1 cm anterior to the sacrum
         2. Mid/Low pelvis: 1 cm into the posterior bladder
      (iv) Posterior and lateral borders: Extend contours to the pelvic sidewall muscles and sacrum, carving out of bone and muscles. Levators should be included.
      (v) For T4 disease, CTVA should include a 1–2 cm margin around the area of invasion.
      (vi) Although the RTOG consensus guidelines do not recommend inclusion of the ischiorectal fossa, many radiation oncologists recommend including this region in patients with anal cancer.
   (b) CTVB: external iliac lymph nodes
      (i) Cranial border: Branching of the external iliac vessels from common iliac vessels

(ii) Caudal border: Distal extent of the internal obturator vessels, with the superior pubic rami serving as a bony landmark
(iii) Anterior/posterior and lateral borders: 7–8 mm margin on external iliac vessels, usually with ~10 mm anterolateral margin

(c) CTVC: Inguinal lymph nodes
(i) Cranial border: Distal extent of the internal obturator vessels, with the superior pubic rami serving as an approximate bony landmark.
(ii) Caudal border: 2 cm distal to the saphenous/femoral junction which is approximately at the level of the lesser trochanter.
(iii) Anterior/posterior and lateral borders: The inguinal region should be contoured as a compartment, including any visible nodes, while carving out of bone and muscles.

3. PTV: A 0.7–1 cm margin was recommended.

(ii) *AGITG* [15]

1. Boost CTV: Includes the primary tumor, the entire anal canal, and the internal and external anal sphincters with a 2 cm margin, while following anatomical boundaries. Involved nodes or nodal regions should be included with a 1–2 cm margin, also while following anatomical boundaries.
2. Elective nodal CTV: The AGITG guidelines (Fig. 16.5) describe specific nodal regions including the mesorectum, presacral space, internal iliac nodes, ischiorectal fossa, obturator nodes, external iliac nodes, and inguinal nodes.

(a) Mesorectum: Extends from the rectosigmoid junction cranially to the anorectal junction caudally (where the mesorectal fat space ends). Anteriorly, extends to the penile bulb, prostate, seminal vesicles, and bladder in men and to the vagina, cervix, uterus, and bladder in women. An additional 1 cm anterior margin is recommended to account for changes in bladder filling. The mesorectum extends posteriorly to the presacral space and laterally to the levator ani in the lower pelvis and to the internal iliac region in the upper pelvis.
(b) Presacral space: The anterior extent should cover at least 1 cm anterior to the sacrum and include presacral vessels and lymph nodes. Extends from the L5-S1 interspace cranially to the tip of the coccyx caudally and laterally out to the sacroiliac joints.
(c) Internal iliac nodes: Extends from the bifurcation of the common iliacs around the L5-S1 interspace down to the level of the obturator canal. Extends 7 mm medially or to the mesorectum/presacral space. Extends laterally to bone or muscle.
(d) Ischiorectal fossa: Covered in the AGITG guidelines, unlike in the RTOG guidelines. Includes the fatty space formed by the pelvic wall muscles and ischial tuberosi-

ties from the levator ani down to the anal verge.

(e) Obturator nodes: Extends from 3 to 5 mm cranial to the obturator canal down to the obturator canal. This region is surrounded by the internal iliac lymph nodes posteriorly, the obturator internus muscle anteriorly, and the bladder medially.

(f) External iliac nodes: Extends in the craniocaudal dimension from the bifurcation of the common iliacs to the point where the external iliac vessels exit the bony pelvis. This region includes a 7 mm

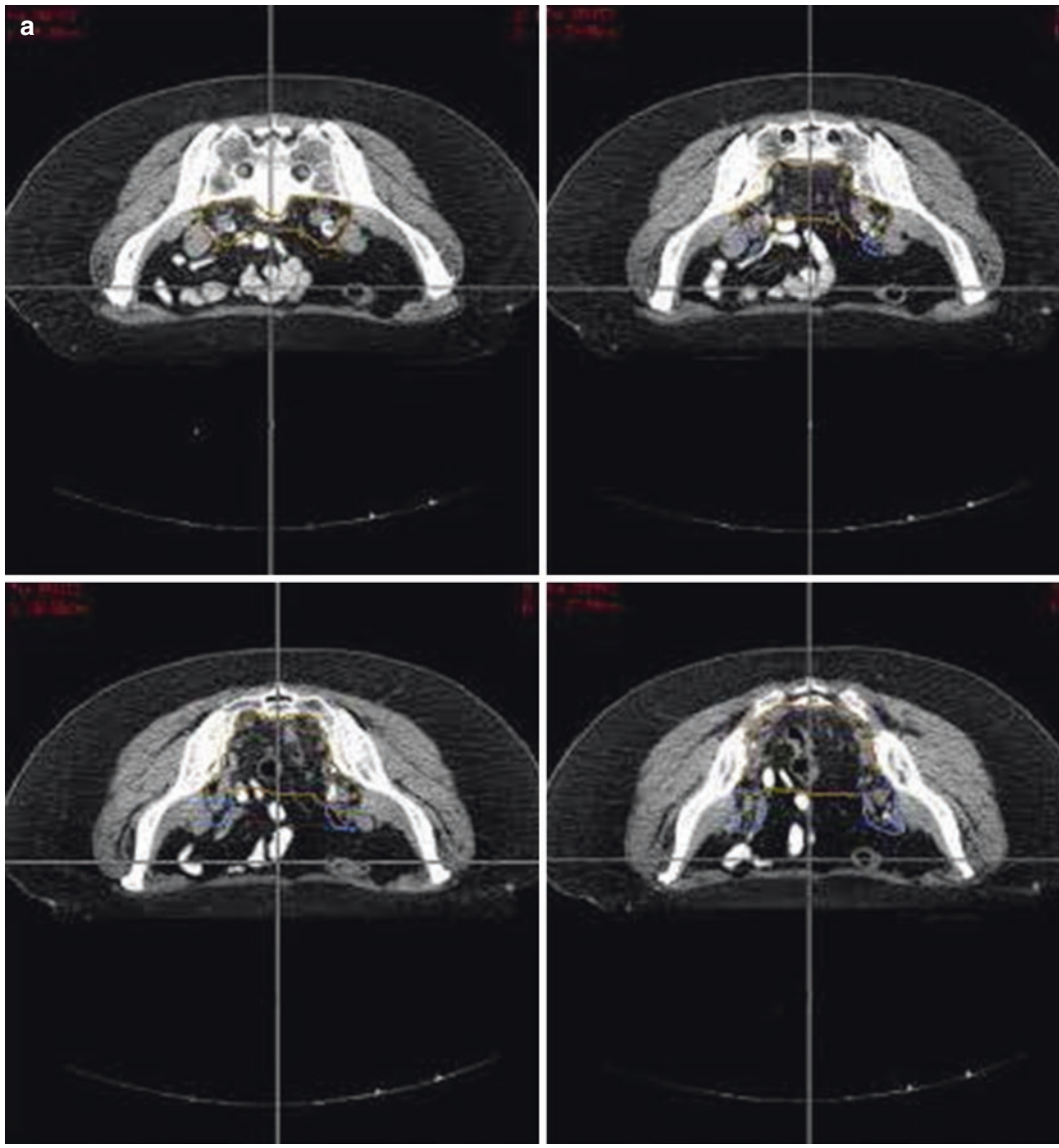



**Fig. 16.4** RTOG anorectal consensus contours for elective nodal coverage in the (**a**) upper pelvis, (**b**) mid-pelvis, and (**c**) low pelvis. *Brown* = CTVA. *Blue* = CTVB. *Red* = CTVC (Adapted from Myerson et al. [13])

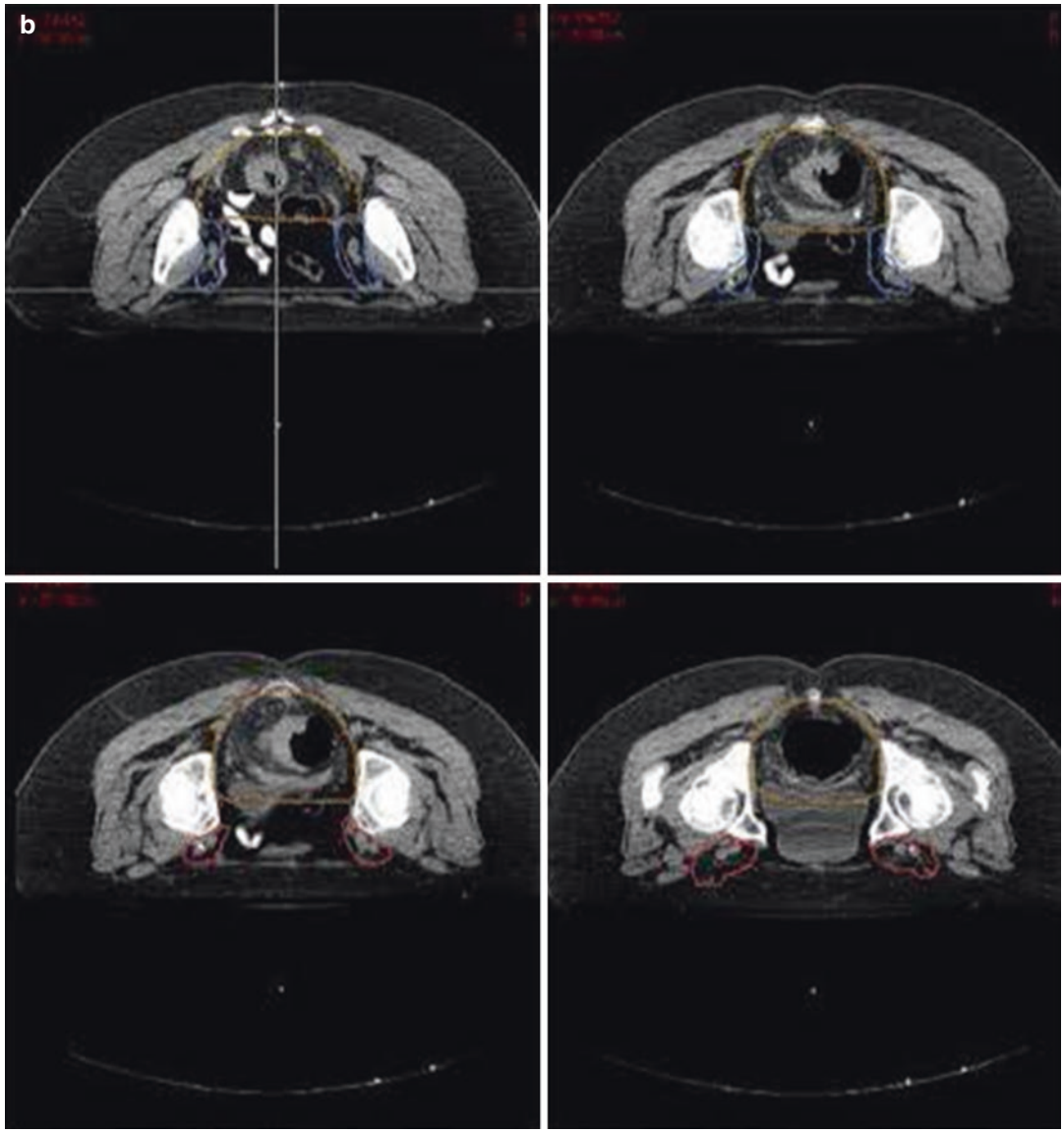



**Fig. 16.4** (continued)

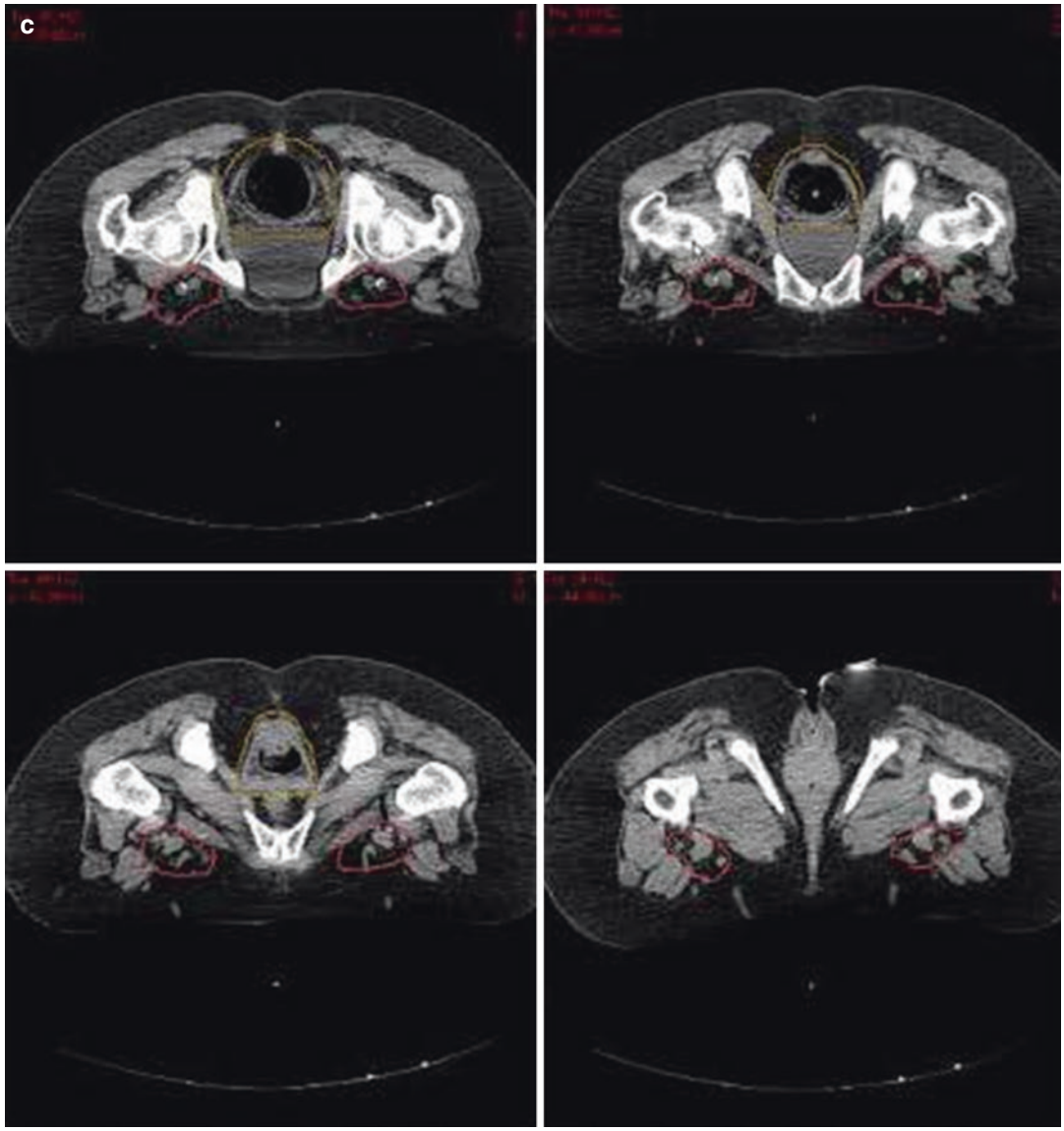



**Fig. 16.4** (continued)

margin around the vessels, carving out of the pelvic musculature, bone, and bladder.

(g) Inguinal nodes: This region includes superficial and deep inguinal lymph nodes of the femoral triangle. The cranial extent lies at the level where the external iliac artery exits the pelvis, while the caudal extent lies at the inferior edge of the ischial tuberosity. Extends posteriorly to the iliopsoas, pectineus, and adductor longus muscles (i.e., femoral triangle). Includes at least a 2 cm margin on the inguinal vessels and a 1–2 cm margin around

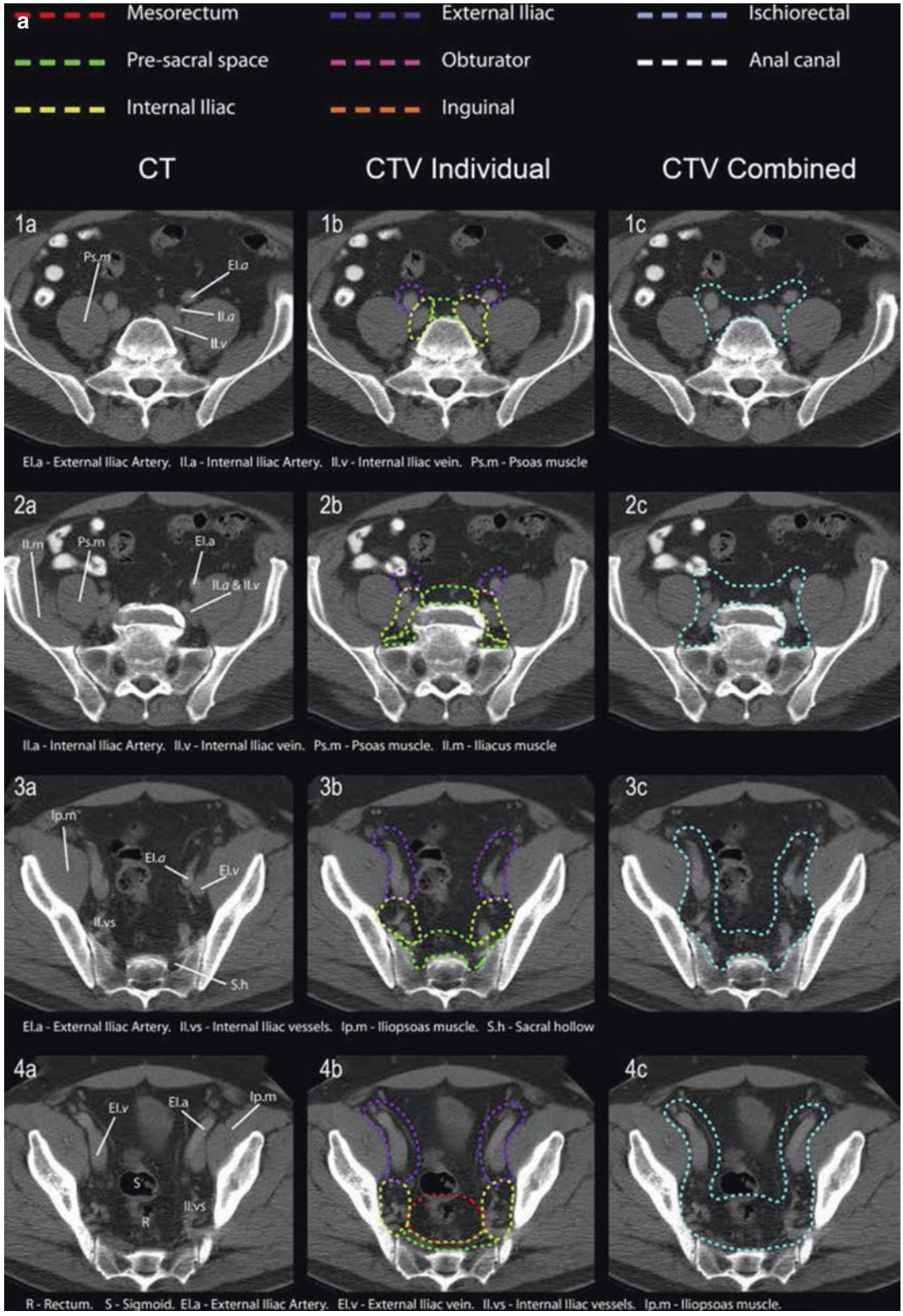
the femoral vessels. The lateral border extends to the sartorius/iliopsoas muscle.

3. PTV: A 5–7 mm margin is recommended if daily image guidance is used.

(iii) *Additional Considerations*

1. Inguinal region: Based on an analysis of 22 patients with involved inguinal nodes, Kim et al. have provided additional guidelines on contouring the inguinal region [16]. These authors recommend contouring the inguinal region as a compartment defined by the following boundaries: medial border of the iliopsoas laterally, lateral border of adductor longus or medial end of pectineus medially, iliopsoas and pectineus posteriorly, and anterior edge of sartorius anteriorly.
2. Use of limited fields: In an effort to reduce treatment-related toxicity, some clinicians have questioned whether uninvolved inguinal regions and high pelvic nodes may be left out of the treatment field in selected patients. In a prospective trial by the Trans Tasman Radiation Oncology Group (TROG), 40 patients with T1–T2 N0 anal cancer were treated with limited pelvic fields, without treatment of the inguinal regions. The rates of isolated inguinal failure and overall inguinal failure were 12.5 % and 22.5 %, respectively [17]. Ortholan et al. conducted a retrospective study on 181 node-negative patients, of whom 106 did not receive inguinal radiation and 75 received 45–50 Gy to the inguinal region [18]. The 5-year risk of inguinal recurrence was 16 % with no inguinal radiation and 2 % with inguinal radiation. In contrast to the high locoregional recurrence rates in these studies, other investigators have reported excellent outcomes with the use of limited fields. Hatfield et al. reported treatment with a dose of 30 Gy in 21 patients with low volume disease (17 post-excision with close/positive margins, 4 T1 N0) [19]. Of these patients, 18 were treated with an involved field approach. Only one patient developed a local recurrence. Crowley et al. evaluated a three-field technique without treatment of the inguinal or high pelvic regions in 30 patients with T1–T3 N0 anal cancer. Only one patient developed a nodal relapse and was salvaged with an inguinal dissection [20]. Zilli et al. have reported an isolated inguinal recurrence rate of <5 % in 42 patients with T2 N0 anal cancer treated without inguinal radiation [21]. Since studies on limited fields have yielded mixed results, the current standard of care is to comprehensively include the full pelvic and inguinal nodal regions in the treatment field for all patients. However, prospective studies are warranted to evaluate the role of limited radiotherapy fields in selected, early-stage patients.

**Fig. 16.5** AGITG anal cancer consensus contours for elective nodal coverage in the (**a**) upper pelvis, (**b**) mid-pelvis, and (**c**) low pelvis (Adapted from Ng et al. [15])


a
Mesorectum
Pre-sacral space
Internal Iliac
External Iliac
Obturator
Inguinal
Ischiorectal
Anal canal
CT
CTV Individual
CTV Combined
1a
Ps.m
El.a
Il.a
Il.v
1b
1c
El.a - External Iliac Artery. Il.a - Internal Iliac Artery. Il.v - Internal Iliac vein. Ps.m - Psoas muscle
2a
Il.m
Ps.m
El.a
Il.a & Il.v
2b
2c
Il.a - Internal Iliac Artery. Il.v - Internal Iliac vein. Ps.m - Psoas muscle. Il.m - Iliacus muscle
3a
Ip.m
El.a
El.v
Il.vs
S.h
3b
3c
El.a - External Iliac Artery. Il.vs - Internal Iliac vessels. Ip.m - Iliopsoas muscle. S.h - Sacral hollow
4a
El.v
El.a
Ip.m
S
R
Il.vs
4b
4c
R - Rectum. S - Sigmoid. El.a - External Iliac Artery. El.v - External Iliac vein. Il.vs - Internal Iliac vessels. Ip.m - Iliopsoas muscle.

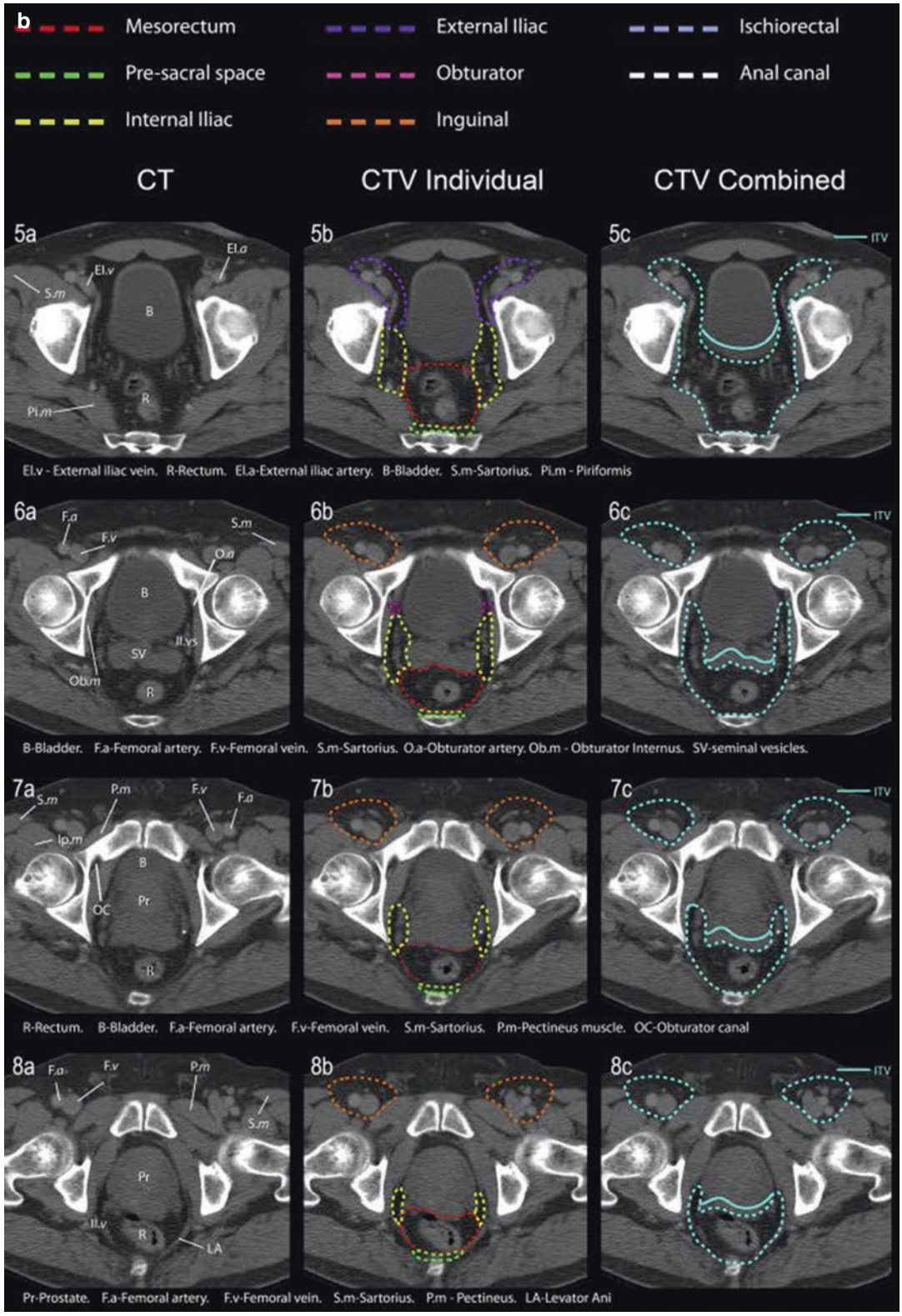



**Fig. 16.5** (continued)

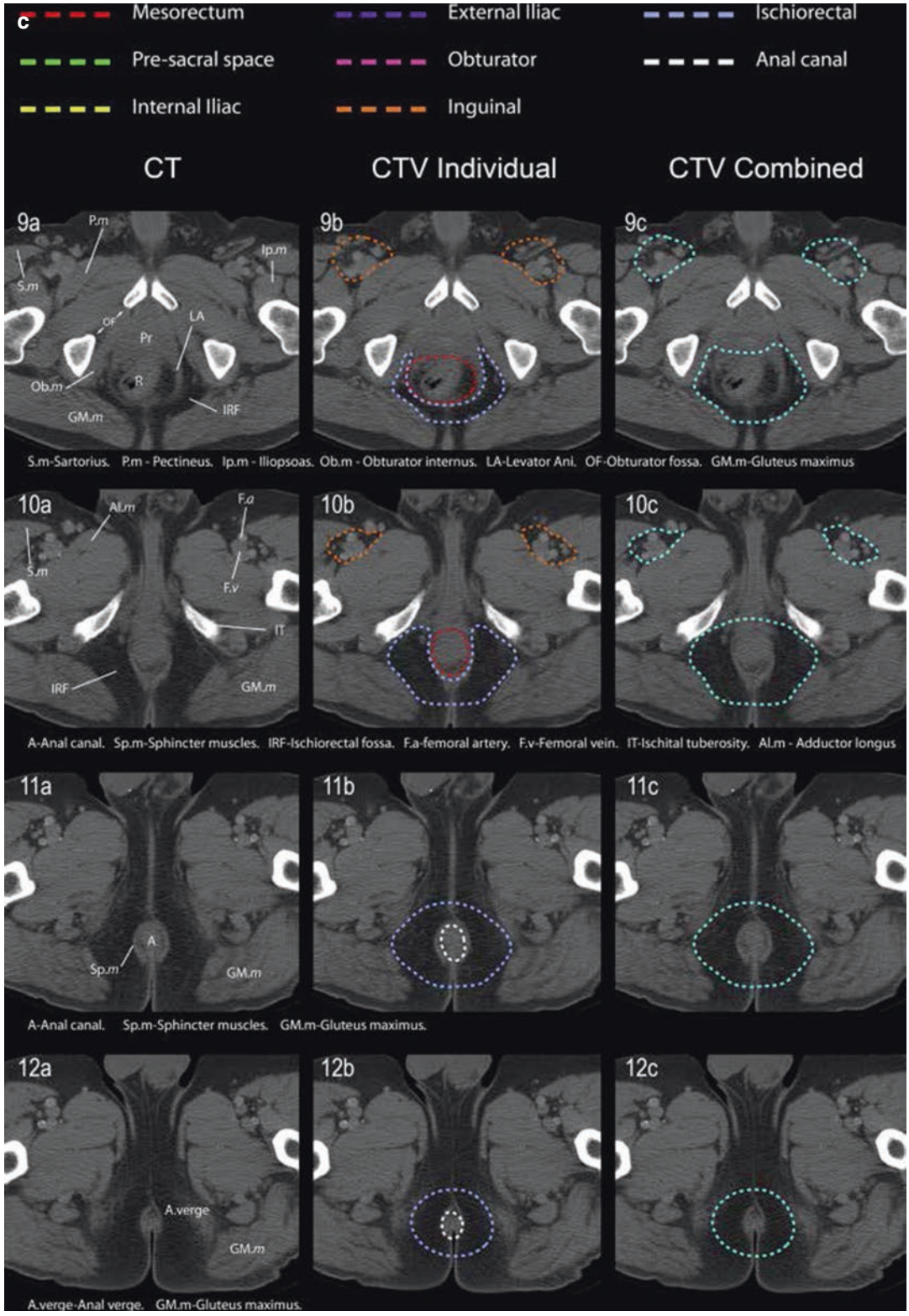



**Fig. 16.5** (continued)

4. *Normal Structures and Dose Constraints:* Given the relatively recent utilization of IMRT for the treatment of anal cancer, the precise DVH recommendations for critical structures remain under investigation. Dose constraints from RTOG 05–29 serve as a useful benchmark for DVH goals [11]. In many cases, adequate coverage of the treatment volume has to be prioritized over strict adherence to these avoidance criteria.
   (a) *Femoral heads*: Femoral head contours should include greater and lesser trochanters. V30 <50 %, V40 <35 %.
   (b) *Bladder*: V35 <50 %, V40 <35 %.
   (c) *Bowel*: Bowel should be contoured from 1 to 1.5 cm cranial to the most superior edge of the PTV down to the rectosigmoid junction. The maximum dose should be less than 50 Gy. V30 <200 cc, V35 <150 cc, V45 <20 cc.
   (d) *External genitalia/perineum*: Include the penile bulb, scrotum, penis, and overlying skin in men. For women, include the labia, clitoris, and skin/fat anterior to the pubic symphysis [22]. V30 <35 %.

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# 17 Stereotactic Body Radiation Therapy for Liver Metastases: Background and Clinical Evidence

Karyn A. Goodman and Arya Amini

## 17.1 Background and Epidemiology

- Metastatic liver disease arises most commonly in colorectal, lung, and breast cancers [1].
- In colorectal cancer patients up to 15–25 % present with synchronous metastases at diagnosis, and 50–70 % will develop metastases to the liver at some point during their clinical course [2].
- Cancers of the gastrointestinal tract commonly metastasize to the liver due to draining blood supply into the portal circulation.
- Historically, metastatic disease to the liver was often treated with systemic therapy alone.
- The term "oligometastases" [3, 4], referring to an intermediate stage of metastases where the number and site of metastatic disease is limited and potential local forms of treatment including surgery, radiation, and thermal ablation could be used for curative intent, has changed our approach to liver metastases and now includes local and systemic treatment options.
- The rationale for adding local ablative therapies in certain metastatic patient who otherwise have well-controlled systemic disease is that many can progress at sites of increasing tumor burden including the liver.
- With better combination chemotherapy and targeted agents today, overall response rates have improved by 50 % and have doubled median survival from 10 to 20 months in patients with metastatic colorectal cancer [5].
- For patients with well-controlled systemic disease, but liver-dominant metastases, death may result from local progression causing normal liver parenchymal loss and liver failure [6]. Up to 40 % of patients with metastatic colorectal cancer patients have been found to have disease confined to the liver, and 5-year survival for these patients with untreated liver metastases can be less than 3 % [7, 8].
- Early surgical series demonstrated a benefit for local therapy in the management of metastatic colorectal cancer to the liver.
- Prior to the introduction of intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT), radiation oncologists were limited by the tolerance of the liver to radiation.
- Older techniques involving portal imaging and radiation to the entire liver have now been replaced with dose conformal IMRT,

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© Springer International Publishing AG 2017
T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_17

image-guided radiation therapy (IGRT), and improved motion management to enable clinicians to deliver ablative SBRT.
- SBRT local control rates are now exceeding 90 % in modern series.

## 17.2 Local Therapy Options

### 17.2.1 Surgical Resection

- Initial reports in the 1980s and 1990s of surgically resected liver metastases demonstrated encouraging outcomes with 5-year overall survival rates ranging from 30–60 % [9–11].
- Unfortunately, in metastatic colorectal cancer, for example, 80–90 % of patients have unresectable disease at presentation, and only a minority of them (10–30 %) may be downstaged and operable following systemic treatment [12, 13].

### 17.2.2 Nonoperative Ablative Therapies

- For patients with unresectable liver disease, there are a number of minimally or noninvasive procedures to deliver local therapy to liver metastases.
- These nonsurgical ablation treatments include:
  - External beam radiation
  - Thermal ablation
  - Transarterial chemoembolization (TACE)
  - Irreversible electroporation
  - Selective internal radiation therapy (SIRT)
  - High-dose SBRT
- Percutaneous and intraoperative thermal ablation with radio-frequency ablation (RFA) and microwave ablation (MWA) are commonly utilized.
- RFA works by alternating electrical current in the radio-frequency range, causing charge agitation and subsequent heating in tissues [14]. This leads to rapid coagulative necrosis when temperatures exceed 60 °C. RFA is typically limited by tumor size ≤3 cm where inferior local control is observed.
- MWA functions through a similar process and in general has more rapid heating and can potentially ablate larger lesions [15]. Irreversible electroporation (IRE) works through electrical field-induced disruptions causing irreversible membrane damage and cell death [16].
- Other minimally invasive options include arterial embolization with Yttrium-90 ($^{90}$Y) and transarterial chemoembolization (TACE). $^{90}$Y microspheres confer several advantages including selective delivery via the hepatic artery and its short depth dose as a beta emitter.
- Recent data also supports combination radiation and chemoembolization. Seong and colleagues evaluated 30 patients treated with TACE followed by radiation and found a 63 % objective response rate and a median survival of 17 months [17].

## 17.3 Unique Morphologic and Clinical Features of the Liver

- The liver has a dual blood supply, receiving 20 % of its supply for the hepatic artery and 80 % from the portal vein. In general hepatic metastases derive their blood supply from the hepatic artery, whereas the majority of normal liver cells derive their blood supply from the portal vein. One technique that takes advantage of the dual blood supply of the liver is hepatic arterial infusion (HAI) where chemotherapy is directly infused into the hepatic artery, providing a maximal dose of chemotherapy to both resected and unresected metastases. Prospective trials have demonstrated local response rates ranging from 42 to 62 % in liver metastases [18–20].
- The liver is arranged in a parallel arrangement of functional subunits, similar to the lung, making it more sensitive to the volume effect. Thus, historically, liver irradiation was limited due to toxicity concerns since liver radiotherapy was delivered using two-dimensional (2D)

planning with very large fields, often encompassing the entire organ.
- The primary dose-limiting toxicity from whole-liver radiation was radiation-induced liver disease (RILD).
- RILD is a clinical syndrome first described nearly 50 years ago in patients undergoing whole-liver radiation [21].
- RILD is defined as a triad of anicteric hepatomegaly, ascites, and elevated liver enzymes, typically occurring 3 months after completing radiation [22, 23].
- Histologically, RILD includes veno-occlusive injury with fibrin deposition in central veins [24]. Modern studies have demonstrated that transforming growth factor-β (TGF-β) leads to the stimulation of fibroblast migration and development of liver fibrosis in RILD [25]. This complication thus far has rarely been observed with SBRT.
- Early reports demonstrated that patients treated to doses exceeding 30 Gy had higher rates of RILD [26, 27].
- The Radiation Therapy Oncology Group (RTOG) conducted a dose-escalation whole-liver radiation study (RTOG 8405) and reported rates of RILD for doses of 27–30 Gy and 33 Gy of 0 % and 10 %, respectively. These low doses were ineffective in controlling gross disease; thus, palliative whole-liver RT was used infrequently in the management of liver metastases.
- With the introduction of three-dimensional (3D) radiation planning, investigators began exploring partial liver radiation and found that higher doses could be achieved, while sparing normal liver parenchyma. This leads to a series of trials evaluating higher-dose conformal 3D radiation to the liver [28, 29].
  - Dawson and colleagues [28] reported that partial liver irradiation to doses as high as 70–90 Gy in 1.5 Gy twice daily fractions could be tolerated. In a subsequent report of 203 patients [30], they found no cases of RILD when the mean liver doses were maintained below 31 Gy.
  - While these studies demonstrated improvement in tumor control, sustained local response continued to be suboptimal [31].
- The introduction of stereotactic body radiation (SBRT) allows for more intensive tumor dose escalation delivered over fewer treatments with high conformality and steep dose gradients outside the target to therefore limit the amount of normal liver parenchyma receiving radiation and decrease complication rates.
- In addition, SBRT has been shown to have a direct effect on tumor vasculature in preclinical models. For example, high-dose radiation with 10 Gy or higher in a single fraction has been shown to cause severe vascular damage in human tumor xenografts or animal tumors [32, 33].
- Additionally, the vascular injury and ensuing chaotic intratumor environment, such as hypoxic, acidic, and nutritionally deprived environment caused by high-dose fraction SBRT, may significantly hinder the repair of radiation damage [34]. As the survival and proliferation of tumor cells are directly dependent on the blood supply, the vascular effects of SBRT may lead to the ablative effects seen clinically.

## 17.4 Clinical Studies for Stereotactic Body Radiation Therapy for Liver Metastases

- One of the first reports of the use of SBRT in extracranial tumors including liver was published by Blomgren and colleagues in 1998 [35, 36]. The study included 17 primary tumors and 21 liver metastases. Total radiation dose delivered was 20–45 Gy (mean 34.1 Gy) in two to four fractions. Actuarial local control of liver metastasis at 1-year and 2-year intervals was 76 % and 61 %, respectively. There were no reported grade 3 or higher toxicities.

- A subsequent study of 34 patients with 42 lesions (13 lung, six hepatocellular, 23 lung or liver metastases), treated to 45 Gy in three fractions, demonstrated a 2-year tumor control probability of 83.6 % [37]. Tumor size appeared to be the greatest predictor of response with 95 % local control in tumors <3 cm and only 58.3 % in tumors ≥ 3 cm.
- A summary of select prospective trials using SBRT for liver metastases is presented in Table 17.1.
  - The majority of these trials treated one to five liver metastases, with tumors measuring no greater than 6 cm in largest diameter.
  - The trials included patients with both favorable and unfavorable prognoses [47].
  - The majority of metastatic liver lesions were from colorectal cancer. Overall, 1- and 2-year local control rates ranged from 70 to 100 % and 60 to 90 %, respectively.
  - Median survival ranged from 10 to 34 months, with 2-year overall survival rates of 30–83 %.
  - The majority of these patients on long-term follow-up would later develop out-of-field metastases.
  - The studies vary in dose heterogeneity, primary histology included, tumor volumes, total radiation dose, dose per fraction, and dosimetric planning criteria. Total radiation doses typically ranged from 30 to 60 Gy in one to six fractions. The following are all phase I or II trials.
  - To date, there are no published phase III data.

### 17.4.1 Single-Fraction Stereotactic Body Radiation Therapy

- There was early interest in single-fraction treatment for liver SBRT, similar to the single-fraction approach used in stereotactic radiosurgery for the brain.
- Herfarth and colleagues [38] from the University of Heidelberg were the first to report prospective outcomes of SBRT for liver metastases.
  - The study enrolled 37 patients, with 55 liver metastases treated with single-fraction SBRT at a dose of 14–26 Gy.
  - Local control at 18 months was reported to be 67 %. No significant toxicity was reported.
  - There was a statistically significant difference in local tumor control between tumors treated with 14–20 Gy vs. 22–26 Gy, though this may have been due to a learning phase as investigators had noted local control also improved in patients who were enrolled later in the study, as more proper margin expansions were performed; patients enrolled in later years had an actuarial local control rate of 81 % at 18 months [38, 48].
- Goodman and colleagues [44] at Stanford University performed a phase I single-fraction dose-escalation study for primary and metastatic liver tumors.
  - Of the 26 patients included, 19 patients had hepatic metastases.
  - Total radiation dose was escalated from 18 to 30 Gy at 4-Gy increments.
  - At a median follow-up of 17 months, there were no dose-limiting toxicities reported. There were nine acute grade 1, one acute grade 2, and two late grade 2 gastrointestinal toxicities observed.
  - Local control at 1 year was 77 %. For liver metastases patients, the 1-year and 2-year overall survival rates were 62 % and 49 %, respectively.
  - Investigators concluded that single-fraction SBRT is feasible with promising local control rates and tolerable side effects from treatment.

### 17.4.2 Hypofractionated Stereotactic Body Radiation Therapy

- While the results of single-fraction liver SBRT appeared promising, the potential toxicity of the ultrahigh dose radiotherapy in the

**Table 17.1** Select prospective studies of SBRT for liver metastases

| Study | Inclusion | Number of patients | Type of metastasis | Total dose per fraction | Toxicity | Median follow-up (months) | Local control rate | Survival |
|---|---|---|---|---|---|---|---|---|
| Herfarth et al. (2001) [38] | 1–3 lesions | 37 | Not reported | 14–26 Gy/1 | No significant toxicity reported | 14.9 (mean) | 18 mo: 67 % | 1 yr.: 76 %<br>2 yr.: 55 % |
| Hoyer et al. (2006) [39] | 1–6 lesions, largest ≤6 cm | 44 | CRC (44) | 45 Gy/3 | 1 liver failure2 severe late GI | 52 | 2 yr.: 86 % | 1 yr.: 67 %<br>2 yr.: 38 % |
| Mendez-Romero et al. (2006) [40] | 1–3 lesions, largest <7 cm | 25 | CRC (14), Lung (1), Breast (1), Carcinoid (1) | 37.5 Gy/3 | Acute grade ≥ 3: 4 casesLate grade 3: 1 case | 12.9 | 2 yr.: 86 % | 1 yr.: 85 %<br>2 yr.: 62 % |
| Rusthoven et al. (2009) [41] | 1–3 lesions, largest <6 cm | 47 | CRC (15), lung (10), breast (4), ovarian (3), Esophageal (3), HCC (2), Other (10) | 60 Gy/3 | Late grade 3/4: <2 % | 16 | 2 yr.: 92 %<br><3 cm: 100 % | Median: 17.6 mo |
| Lee et al. (2009) [42] | No maximum number or size | 68 | CRC (40), breast (12), gallbladder (4), lung (2), anal (2), melanoma (2) | 28–60 Gy/6 median 42 Gy | Acute grade 3: 8 casesGrade 4: 1 case (thrombocytopenia) | 10.8 | 1 yr.: 71 % | 18 mo: 47 % |
| Ambrosino et al. (2009) [43] | 1–3 lesions, largest <6 cm | 27 | CRC (11), other (16) | 25–60 Gy/3 median 36 Gy | No significant toxicity reported | 13 | 74 % | Not reported |
| Goodman et al. (2010) [44] | 1–5 lesions, largest <5 cm | 26 | CRC (6), pancreatic (3), gastric (2), ovarian (2), other (6) | 18–30 Gy/1 | Late grade 2: 4 cases (2 GI, 2 soft tissue/rib) | 17.3 | 1 yr.: 77 % | 1 yr.: 62 %<br>2 yr.: 49 % |
| Rule et al. (2011) [45] | 1–5 lesions | 27 | CRC (12), carcinoid (3), melanoma (2), other (10) | 30 Gy/3,<br>50 Gy/5,<br>60 Gy/5 | No grade 2 or higher reported | 20 | 30 Gy: 56 %<br>50 Gy: 89 %<br>60 Gy: 100 % | 30 Gy: 56 % (2 yr)<br>50 Gy: 67 % (2 yr)<br>60 Gy: 50 % (2 yr) |
| Scorsetti et al. (2013) [46] | 1–3 lesions largest <6 cm | 61 | CRC (29), breast (11), gynecologic (7), other (14) | 52.5–75 Gy/3 | No grade 3 or higher reported | 24 | 91 % | 1 yr.: 80 %<br>2 yr.: 70 % |

Abbreviations: *SBRT* stereotactic body radiotherapy, *yr.* year, *mo* months, *CRC* colorectal cancer, *HCC* hepatocellular carcinoma

abdomen lead many groups to evaluate the use of hypofractionated SBRT [39, 40].

- Hoyer and colleagues [39] reported outcomes of 44 hepatic lesions treated with SBRT 45 Gy in three fractions, with a 2-year actuarial local control of 79 %.
  - One and 2-year overall survival was 67 % and 38 %, respectively.
  - Treatment-related toxicity included one patient who died of hepatic failure, one patient with colonic perforation requiring surgical management, and two patients with duodenal ulceration treated conservatively.
- Méndez-Romero and colleagues [40], evaluated 34 liver metastases treated to 37.5 Gy in three fractions.
  - Two-year local control rate of 86 %.
  - One and 2-year overall survival was 85 % and 62 %, respectively.
  - Three grade 3 toxicities were documented among the patients with liver metastases.
- Schefter (phase I) and Rusthoven (phase II) and colleagues at the University of Colorado prospectively evaluated patients with three of fewer liver metastases, measuring less than 6 cm [41, 49].
  - In the phase I portion of the trial which included 18 patients, the dose of SBRT was escalated from 36 Gy to 60 Gy in three fractions, and no dose-limiting toxicity was observed.
  - In the subsequent combined phase I/II multi-institutional trial, 47 patients with 63 liver metastases were enrolled and treated at seven participating institutions to 60 Gy in three fractions, 13 patients received <60 Gy, and 36 patients received 60 Gy [41]. Of patients with at least 6 months of radiographic follow-up after SBRT, only three in-field local failures among 47 lesions occurred. At 2 years, the actuarial local control of all SBRT-treated lesions was 92 %; among lesions <3 cm, the 2-year actuarial local control was 100 %. Two-year overall survival was 30 %. One patient experienced late grade 3 soft tissue breakdown. There were no reported grade 4–5 toxicities or RILD.
- Lee and colleagues [42] from Princess Margaret Hospital also published their phase I trial of SBRT delivered in six fractions (median prescription dose of 41.8 Gy) in 68 patients with metastatic liver disease.
  - Individualized radiation doses were chosen based on normal tissue complication probability (NTCP)-calculated risk of RILD at three risk levels (5 %, 10 %, and 20 %).
  - Observed 1-year local control was 71 % and no dose-limiting toxicity was observed.
  - Two patients experience acute grade 3 liver enzyme changes, and six patients had additional acute grade 3 toxicities including gastritis (2), nausea (2), lethargy (1), and thrombocytopenia (1). There was one grade 4 thrombocytopenia reported.
- Ambrosino and colleagues [43] prospectively evaluated 27 patients with liver metastases treated with 25–60 Gy (median 36 Gy) delivered in three fractions.
  - Mean tumor volume was 81.6 ± 35.9 ml.
  - At a median follow-up of 13 months, crude local control was 74 %.
  - Mild to moderate transient hepatic dysfunction was observed in nine patients, pleural effusions in two, and partial portal vein thrombosis, pulmonary embolism, and upper gastrointestinal tract bleed in one patient each.
- Rule and colleagues [45] from the University of Texas Southwestern reported results from their phase I SBRT dose-escalation trial, with three dose groups, 30 Gy/3 fractions, 50 Gy/5 fractions, and 60 Gy /5 fractions.
  - At 2 years, local control was 56 %, 89 %, and 100 %, respectively. Two-year overall survival was 56 %, 67 %, and 50 %, accordingly.
  - Further, there appeared to be a significant dose-response relationship between 30 Gy and 60 Gy ($p = 0.009$).
  - There were no grade 4–5 toxicities and one grade 3 asymptomatic transaminitis occurring in the 50 Gy cohort.

- Scorsetti and colleagues [46] reported findings from a phase II trial including 61 patients with 76 liver metastases treated to 25 Gy in three fractions.
  - At a median follow-up of 12 months, the overall local control rate was 95 %.
  - One and 2-year overall survival was 80 % and 70 %, respectively.
  - No reported events of RILD; one patient experienced late grade 3 chest wall pain.

### 17.4.3 Additional Studies

- Chang and colleagues [50] performed a multi-institutional analysis reporting on prognostic factors following SBRT for colorectal liver metastases.
  - The study included 65 patients treated at three institutions. All patients had one to four lesions and received one to six fractions of SBRT to a median total dose of 42 Gy (range 22–60 Gy).
  - The median follow-up was 1.2 years. On multivariate analysis, total dose of radiation, dose per fraction, and the BED were significantly associated with local control.
  - Local disease control also appeared to be a borderline significant factor associated with improved overall survival under multivariate analysis ($p$=0.06), demonstrating the impact local ablative therapy can have on overall survival.
  - The study further examined the correlation between total radiation dose and local control in a tumor control probability (TCP) model. Results from the TCP curves demonstrated that a 1-year local control rate exceeding 90 % could be achieved when doses of 46–52 Gy in three fractions were delivered and concluding doses of 48 Gy or higher in three fractions should be offered if feasible.
- Several studies have also evaluated the role of hypofractionation using more than five fractions.
  - Sato and colleagues [51] evaluated 18 patients with 23 primary or metastatic liver lesions treated to a total dose of 50–60 Gy in five to ten fractions. At 10-month follow-up, the crude local control rate was reported at 100 %. Toxicity included 5 % with grade 1–2 and 5 % with grade 3–4.
  - Wurm and colleagues [52] included three patients. Patients were treated to a total dose of 74.8–79.2 Gy in 8–11 fractions to three patients with four liver metastases; they also noted a local control rate of 100 % (unspecified follow-up time).
  - Katz and colleagues [53] published results of 174 metastatic liver lesions treated to a median total dose of 48 Gy (range, 30–55 Gy), delivered in 2–6-Gy fractions. At a median follow-up of 14.5 months, actuarial local control rates were 76 % and 57 % at 10 and 20 months, accordingly. For liver metastases, the median overall survival was 14.5 months and progression-free survival at 6 and 12 months was 46 % and 24 %, respectively. There were no grade 3 or higher toxicity reported.
- RTOG 0438 is a phase I trial evaluating dose-escalated hypofractionation for hepatic metastases and is currently presented in abstract form only [54].
  - Enrolled 26 patients and four dose levels were achieved: 35 to 50 Gy in 5-Gy increments delivered in ten fractions.
  - No dose-limiting toxicities reported. Four patients (two patients at 45 Gy, two patients at 50 Gy) developed grade 3 toxicity.
  - Concluded that a hypofractionated regimen of 50 Gy in ten fractions is a reasonable and safe approach to treat metastatic liver lesions.
  - Local control and survival outcomes have not been reported to date.

## 17.5 Long-Term Sequelae

- Most published series of liver SBRT have relatively short follow-up due to the nature of treating metastatic disease.

- Thus, the question remains as to what the long-term effects of SBRT may be on the biliary tree and overall liver function. The late effects of SBRT may become more significant as patients live longer with better systemic therapies.
- Fortunately, several small retrospective studies have reported data on long-term follow-up and toxicity from SBRT to the liver.
  - Gunvén and colleagues [55] reported long-term radiation sequelae in 11 patients with up to 13-year follow-up.
    - Follow-up tests included regular blood chemistry panels in addition to clearance of indocyanine green and a segmental function study by single-photon emission-computed tomography (SPECT) using hepatic iminodiacetic acid (HIDA) derivatives including mebrofenin to evaluate uptake by normal functioning hepatocytes.
    - Their findings which demonstrated overall elevations in liver lab values including alanine aminotransferase were uncommon, typically occurred within 2 years after SBRT, and were transient; these findings were more common in patients with preexisting liver damage.
    - Late liver function did not appear to be affected by treatment, even in the presence of cirrhosis.
    - Two patients received equivalent 2 Gy ($EQD_2$) doses of 40 and 161 Gy to hilar structures, and no long-term bile duct damage was found. In two cases, moderate late liver dysfunction occurred in one patient after three courses of radiation and in a cirrhotic patients after two liver resections and radiation.
  - Fode and colleagues [56] included 321 patients (68 % with liver metastases) treated to 587 lesions with SBRT over a 13-year period.
    - The median follow-up was 5 years. Reported overall survival at 1, 3, 5, and 7.5 years was 80 %, 39 %, 23 %, and 12 %, respectively.
    - The study identified positive prognostic factors for overall survival which included performance status, solitary metastasis, metastasis measuring 30 mm or less, metachronous metastases, and pre-SBRT chemotherapy.
    - Severe acute grade 3–4 toxicities occurred in 11 patients (3 %), and late grade 3–4 toxicities occurred in three patients (1 %); specific to liver SBRT, one patient developed grade 3 gastritis and chronic skin reactions, and a second patient developed grade 3 chronic skin reaction after SBRT for liver metastases.
    - An additional ten patients receiving SBRT to the lung or liver experienced rib fractures 6–18 months after SBRT and were managed with pain medications.
    - There were three possible treatment-related deaths: one deteriorated and died 6 weeks after SBRT; the second died of hepatic failure 7 weeks after SBRT; and the third patient developed a fistula from the stomach to the skin and died 15 months after SBRT. All three patients received 45 Gy in three fractions.
  - Klein and colleagues [57] evaluated 222 patients treated with SBRT for hepatocellular carcinoma, liver metastases, or intrahepatic cholangiocarcinoma.
    - SBRT total dose ranged from 24 to 60 Gy in six fractions. Prospective quality-of-life forms based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (QLQ-30) and/or Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep, version 4) questionnaires were provided at baseline and up to 12 months after treatment.
    - Appetite and fatigue were clinically and statistically worse by 1 month but appeared to recover by 3 months after treatment. At 12 months, quality of life

had improved in 23 %, worsened in 39 %, and was stable in 38 %.

## 17.6 Future Directions

- There are currently no randomized studies comparing SBRT and surgery for metastatic liver lesions and there will likely not be one for some time, due to limited patient numbers and difficulty in accruing.
- Extrapolating from recent data published in non-small cell lung cancer (NSCLC), there appears to be promising results with SBRT when compared to surgery [58]. These results in lung cancer which demonstrate the need for prospective trials evaluating outcomes comparing surgery to SBRT for metastatic liver lesions are very much needed to assess local control rates, overall survival, and quality-of-life metrics.
- Further, given the heterogeneity in the currently published trials evaluating SBRT for liver metastases, multi-institutional prospective studies to evaluate the appropriate dose, fractionation scheme, and appropriate margins are urgently needed.
- Future studies comparing surgery to SBRT for metastatic liver lesions are very much needed to assess local control rates, overall survival, and quality-of-life metrics.
- Further data will also be needed to assess which noninvasive or minimally invasive modality to perform in select patients with liver metastases.
- There is currently at least one ongoing phase III randomized trial (NCT01233544) comparing RFA to SBRT in colorectal carcinoma liver metastases [59]. The primary endpoint of the study is local progression-free survival.
- Novel radiation delivery techniques including charged particle-based therapy may also provide an avenue for highly conformal dose-escalated treatment in liver tumors.
- Currently, most studies evaluating proton beam and carbon ion beam therapy have been in primary hepatocellular carcinoma.
  - In several small, nonrandomized studies, for example, high-dose radiation with protons has demonstrated similar local control and survival rates to photon-based treatment in hepatocellular carcinoma [60–62].
  - Hong and colleagues evaluated respiratory-gated proton beam therapy for liver tumors, including primary hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and liver metastasis, and found comparable local control rates and toxicity outcomes [63].
- Delivery of SBRT with systemic therapies is also an integral part in management for patients with metastatic liver disease. In patients with oligometastatic disease, the goal of SBRT is to minimize macrometastases, while systemic treatment is used to control micrometastases. Future studies evaluating combined modality treatment with SBRT and systemic therapies are needed.

**Conflicts of Interest** The authors have no conflicts of interest to report.

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# 18 Stereotactic Body Radiation Therapy for Liver Metastases: Radiation Therapy Planning

Karyn A. Goodman and Arya Amini

## 18.1 Introduction

- Stereotactic body radiation therapy (SBRT) offers a novel, noninvasive definitive local therapy for metastatic liver disease.
- With advances in target localization, tumor motion control, and radiation planning systems, SBRT has become a highly conformal, ablative, and relatively safe treatment modality for these tumors.
- The parallel arrangement of functional subunits in the liver provides some protection against ablative doses of radiation, as long as an adequate proportion of the normally functioning liver is preserved.
- Early clinical data has been promising, with local control rates exceeding 90 %.
- This chapter will discuss SBRT contouring and treatment planning for metastatic liver lesions.

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## 18.2 Overview of Stereotactic Body Radiation Therapy

- SBRT relies on three fundamental principles [1]:
  1. Precise, reproducible stereotactic localization of the tumor (either using internal or external references)
  2. Daily image guidance for tumor relocalization as well as visualization of critical normal organs
  3. Treatment delivery in one to five fractions
- Integration of SBRT into the management of liver metastases can only be accomplished with sophisticated treatment planning systems, tumor motion control, and localization techniques to allow for accurate and consistent targeting of the tumor.
- These allow for ablative tumor doses while minimizing toxicity to critical organs at risk including the uninvolved liver parenchyma, the chest wall, and the gastrointestinal tract.
- Now several prospective trials use single-fraction versus multifraction SBRT for liver metastasis.
  - The majority of these trials treated 1–5 liver metastases, with tumors measuring no greater than 6 cm in largest diameter. The trials included patients with both favorable and unfavorable prognoses [2].

© Springer International Publishing AG 2017
T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_18

  - Most metastatic liver lesions were from colorectal cancer.
  - Overall, 1- and 2-year local control rates ranged from 70 to 100 % and 60 to 90 %, respectively.
- Fractionated SBRT allows for delivery of highly conformal treatment of targets that are in close proximity to critical structures.
- Fractionation has been hypothesized to improve the therapeutic ratio, thereby reducing the risk of late complications potentially associated with a large single dose [3].
- Radiobiologically, the higher dose per fraction with SBRT-based treatments has been shown to provide improved local control over standard fractionation [4].

### 18.2.1 Patient Selection

- Patients eligible for SBRT treatment to the liver should be discussed in a multidisciplinary fashion.
- Cases that may be resectable and who have adequate hepatic function should be reviewed with the surgeon.
- Based on data from current prospective trials treating liver lesions with SBRT, patients considered for SBRT should typically have five or fewer lesions with a size of no more than 6 cm in maximum diameter [5].
- Adequate baseline liver function and sufficient uninvolved liver volume which can be spared should be established prior to treatment.
- Tumors which are in close proximity to adjacent radiosensitive structures, such as those close to the hilum, can potentially be treated with SBRT, but the total dose and fractionation scheme may need to be adjusted to meet the dose constraints of the adjacent organs.
- Outside of current published studies, SBRT to lesions that are large (>6 cm) or patients who present with multiple lesions need to be considered on a case by case basis.

## 18.3 Image-Guided Radiation Therapy (IGRT)

- Lars Leksell [6] developed the first frame-based radiosurgery technique called Gamma Knife® (Eklekta AB, Stockholm, Sweden), which was utilized to treat intracranial disease.
- Subsequently, Blomgren and colleagues [7] utilized a frame-based technique encompassing the head down to the thigh, enabling stereotactic delivery of high-dose radiotherapy to liver and lung lesions.
- Early experience with SBRT for liver lesions was based on the use of a stereotactic body frame to coordinate points in a patient with points in stereotactic space.
- With improvements in onboard imaging, the use of image-guided radiotherapy has superseded the need for the stereotactic frame.
- The patient setup process has changed significantly over the last 10 years, and most institutions are using more standard molds for patient immobilization.
- With the reliance on image guidance during delivery of radiotherapy, there is a greater need for accurate target localization.
- As opposed to lung lesions, visualization of tumors in the liver is limited based on non-contrast cone beam CT scan.
- Fiducial markers should be placed prior to the simulation process to allow for accurate identification of the target and to assess the motion of the target to account for respiratory motion using techniques that will be described later.
  - Gold fiducials are often placed percutaneously into or around the liver lesion to assist in target identification [8].
  - At least two to three fiducial markers are necessary to triangulate where the tumor is located and for tumor tracking during treatment.
  - Postoperative clips can also sometimes be used to localize the treatment target.

- Most new linear accelerators can obtain higher-quality diagnostic x-rays and have onboard three-dimensional (3D) CT imaging, known as cone beam CT (CBCT).
- This provides real-time assessment of tumor positioning while the patient is lying on the treatment table.
- Image-guided radiation therapy (IGRT) has significantly advanced the radiation oncology field, allowing for better target alignment which is critical when treating with SBRT to organs such as the liver, as there is substantial degree of inter- and intra-fraction variability.

## 18.4 Motion Management

- Smaller fields required for SBRT may miss the liver target if tumor motion with respiration is unaccounted for.
- Studies have shown that the liver can move as much as 1–8 cm in the superior-inferior direction and to a much lesser degree from anterior-posterior with respiration [9].
- Variation in hollow organ filling due to gastric contents may also contribute to both inter- and intra-fraction motion.
- Due to significant liver motion, alignment to bony landmarks is not optimal.
- IGRT, combined with motion management, is therefore frequently utilized for liver SBRT.
- Motion management incorporated in the radiation oncology clinic today can broadly be categorized as motion compensating or motion restricting [8].

### 18.4.1 Motion-Compensating Techniques

- Respiratory gating relies on delivery of radiation at specific phases of the breathing cycle, usually during the expiratory phase where motion is the smallest.
  - To allow for the linear accelerator to trigger the beam on time, there are several systems available which use external body markers to track the patient's respiratory cycle.
  - RPM system (Varian Medical Systems, Palo Alto, CA) uses external infrared-emitting markers placed on the patients' chest or abdominal wall and can be tracked by an infrared camera.
  - Chest wall motion throughout the respiratory cycle can be recorded, and at a particular height of the fiducial (amplitude-based gating), the system will activate radiation beam on time during the appropriate cycles of respiration.
  - External fiducial movement can be approximated to the breathing cycle, triggering beam on during particular phases of respiration, known as phase-based gating.
  - These forms of respiratory gating correlate with chest wall motion, which does not necessarily correlate with the motion of internal organs including the liver.
  - One option is to take intra-fraction kilovoltage imaging of the target and use the gold fiducials that were placed in or around the liver tumor to confirm in real time that the fiducial markers are moving into the appropriate position when the beam is on.
  - Fluoroscopy can be used prior to treatment to evaluate the excursion of the fiducial markers.
- Tumor tracking using the CyberKnife® system utilizes fiducial markers to localize the tumor [10, 11] and can track tumors in real time.

### 18.4.2 Motion-Restricting Techniques

- Abdominal compression
  - Abdominal compression uses a belt that compresses the abdominal cavity, increasing intra-abdominal pressure and limiting diaphragmatic respiratory motion, which

translates to decreased liver motion during respiration.
  - Abdominal compression can reduce superior-inferior tumor motion by as much as 50 % [12].
- Active breathing control (ABC)
  - Deliver treatment while a patient holds his or her breath during a specific phase of the breathing cycle.
  - This requires patient instruction on proper respiration patterns in addition to video tracking to deliver radiation at indicated points of the breathing cycle.
  - Dawson and colleagues [13] reviewed patients undergoing SBRT for unresectable liver cancers immobilized with ABC. They found that absolute systemic errors were reduced from 4.1 to 1.1 mm superior-inferior, from 2.4 mm to 1.3 mm anterior-posterior, and from 3.1 to 1.6 mm medial-lateral.

## 18.5 Patient Setup and Simulation

- The simulation process for SBRT should be done at least 3–5 days after placement of the fiducial markers to minimize any potential changes due to local inflammation or migration of the fiducial marker after the planning process.
- Simulation typically includes a computerized tomography (CT) simulation with intravenous (IV) contrast.
- Many institutions now employ four-dimensional (4D) CT to better delineate the motion of the liver lesion.
  - 4DCT is acquired using a modified CT scanning technique that is synchronized with the respiratory pattern of the patient.
  - The respiratory cycle of a patient is divided into numerous breathing phases, with end inspiration, end expiration, and interval phases between inspiration and expiration.
  - For each breathing phase, a three-dimensional construction is created, and these imaging sets at different breathing phases are constructed and analyzed to determine organ positions at all phases of respiration.
- Most patients will also have a diagnostic multiphasic contrast-enhanced helical CT scan to assist in target localization.
- For liver tumors in particular, CT scans alone may not clearly delineate disease.
- Therefore, incorporation of a fluorodeoxyglucose positron emission tomography (FDG-PET) scan and magnetic resonance imaging (MRI) during planning can be helpful in better identifying the target.

## 18.6 Target Definition and Dose Prescription

- Gross tumor volume (GTV) encompasses disease delineated by the simulation CT acquired and additional imaging including MRI and PET/CT.
- Internal tumor volume (ITV): If there is 4DCT capability, an ITV, which encompasses the entire motion of the tumor during respiration, can be contoured to create patient-specific margin expansions.
- Planning tumor volume (PTV) depends on the type of motion management approach and can range from 3 to 5 mm in cases where devices are available for real-time tracking of respiratory motion to larger margins of 5–10 mm in the presence of motion compensation techniques.
- Total dose of radiation is typically prescribed to the isodose lines that encompass the PTV.
- From the current prospective SBRT liver trials, there is substantial variability with the prescription dose covering anywhere from the 65 to 90 % isodose line [14–17].
- General dose recommendations range from 18 to 30 Gy in one fraction and 30 to 60 Gy in two to five fractions.

- Fairly standard fractionation schemes based on current literature include 20 Gy × 3 and 15 Gy × 5 for tumors adjacent structures such as bowel or central bile ducts.
- Central tumors near the liver hilum may need to be treated to lower doses or a higher number of fractions due to the proximity to critical structures [16].

## 18.7 Treatment Planning and Delivery

### 18.7.1 Intensity-Modulated Radiation Therapy (IMRT)

- Treatment plans undergo automated optimization using intensity-modulated radiation therapy (IMRT) planning (Fig. 18.1).
- IMRT planning takes into account the prescribed target volume and dose constraints on normal tissue and utilizes a computer-optimized algorithm to deliver radiation to achieve proper dose coverage while maintaining dose-constraint goals.
- The computer software is able to define the high-dose regions covering the tumor and subclinical disease while limiting dose to normal organs based on inputted constraints.
- Volumetric modulated arc therapy (VMAT), a form of IMRT, allows for rapid conformal delivery of radiation with multiple gantry rotations, gantry speeds, and dose rates, with dynamic multileaf collimators (MLC).
- VMAT employs multiple coplanar and noncoplanar beams of variable intensity, delivered from many different angles.

### 18.7.2 Dose Constraints for SBRT Liver Metastases

- Surgical series have demonstrated as much as 80 % of normal liver can be resected without causing liver failure [18, 19].
- Prior to SBRT, radiation had a limited role in ablative treatment of liver metastases due to low whole-liver tolerance with a 5 % risk of radiation-induced liver disease (RILD) with whole-liver doses of 30–35 Gy in 2 Gy per fraction [20, 21].
  - RILD syndrome is characterized by anicteric ascites with elevated alkaline phosphatase and liver transaminases, which typically occurs several weeks to months after radiation therapy.
  - RILD can lead to liver failure and death.

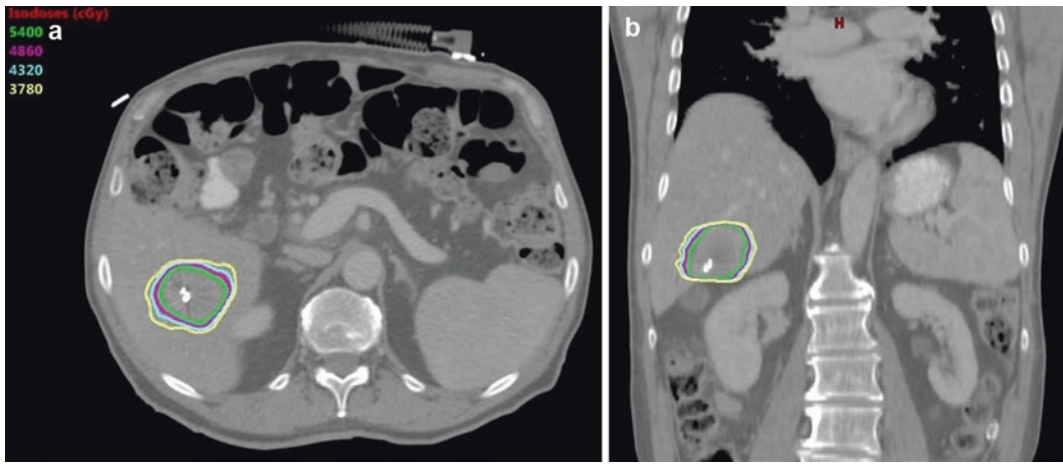


**Fig. 18.1** Patient with oligometastatic pancreatic cancer with an enlarging right hepatic lobe segment 6 lesion measuring 1.8 cm, treated with stereotactic body radiation, 54 Gy in three fractions. Axial (**a**) and coronal (**b**) computerized tomography imaging illustrating the final treatment plan

## 18.8 Potential Toxicities from Treatment

### 18.8.1 Hepatotoxicity

- Most commonly utilized dose-tolerance model used in SBRT for normal parenchyma is that at least 700 mL of normal liver receive <15 Gy of total dose.
  - Model was first introduced by Schefter and colleagues [15] in a phase I dose-escalation trial for hepatic metastases.
  - In this study, dose was escalated from 36 Gy to 60 Gy in three fractions, and a "critical volume" model requiring at least 700 ml of normal receive <15 Gy of total dose was implemented.
  - There was no grade 3 or higher hepatotoxicity reported.
  - Currently, there are no reported prospective dose-escalation trials that have reached a maximum-tolerated dose (MTD) for hepatotoxicity [14–17, 22, 23].
- The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) therefore suggest ≥700 mL of normal liver receives ≤15 Gy in three to five fractions [24].
- Additional QUANTEC recommendations of mean normal liver dose for SBRT liver metastases include <15 Gy for liver metastases, in three fractions, and <20 Gy for liver metastases, in six fractions.
- Other available liver constraints include limiting the $V_{15}$ and $V_{21}$ to 50 % and 30 %, respectively, for three fractions [25].
- A number of models estimating volume dependence of normal tissue toxicity in liver have been used.
  - The Lyman model was one of the first which assumes a sigmoid relationship between a dose of uniform radiation given to a volume on an organ and the chance of a complication occurring.
  - However, as dose distributions are not uniform, additional calculations needed to be made.
  - Effective liver volume (Veff) irradiated is defined as the normal liver volume minus all GTVs, which if irradiated uniformly to the treatment dose would be associated with the same risk of toxicity or normal tissue complication probability (NTCP) as the nonuniform dose distribution [26].
    - Dawson and colleagues [27] analyzed the risk of RILD in 203 patients followed prospectively after being treated with conformal liver RT, using the Lyman-Kutcher-Burman (LKB) NTCP model.
    - Mean liver dose was 32 Gy, and the majority was treated with partial liver radiation.
    - The lower Veff correlated with significantly lower risks of RILD, demonstrating that in the setting of dose escalation, high doses can be delivered as long as the mean dose to the liver is taken into account.
    - In their analysis, a threshold volume effect was demonstrated with nearly zero incidence of RILD at an effective liver volume of less than one-third.
- Cirrhotic livers are known to have lower tolerances to SBRT [24, 28], and therefore most prospective trials excluded patients with Child-Pugh B classification or higher [15–17, 22].
- Overall, RILD occurs in less than 5 % of all reported SBRT cases.
  - In the phase II SBRT liver metastases study conducted by Méndez-Romero and colleagues [28], there were two cases of RILD, one classic and one nonclassic; an additional patient with hepatocellular carcinoma and baseline Child-Pugh B experienced portal hypertension and nonhepatic infection and died within 2 weeks of treatment.
  - Hoyer and colleagues [29] prospectively evaluated 61 patients treated with SBRT for colorectal metastases to 45 Gy in three fractions and observed severe liver

toxicity in one patient who died of hepatic failure 7 weeks after completing radiation; 60 % of the liver received ≥10 Gy.

– Princess Margaret Hospital performed two phase I trials of SBRT for primary liver tumors [30] and liver metastases [31] deriving total SBRT dose from a normal tissue complication probability (NTCP) modeling.
  - The study included patients with primary hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and hepatic metastases.
  - Approximately 17 % of patients with hepatocellular carcinoma or intrahepatic cholangiocarcinoma were found to progress from Child-Pugh A to B within 3 months after radiation.
  - In contrast, there were only two grade 3 liver enzyme changes in the liver metastases cohort, likely demonstrating that those with liver metastases present with healthier baseline liver parenchyma.

- To minimize the risk of RILD, the current QUANTEC recommendations suggest that mean normal liver dose should be less than 6 Gy for primary liver cancer and Child-Pugh B undergoing 3–6 Gy per fraction [24].
- However, in contrast to patients presenting with hepatocellular carcinoma, the majority of patients with hepatic metastases do not present with underlying cirrhosis and are therefore less susceptible to RILD.

### 18.8.2 Chest Wall Toxicity

- Chest wall pain and rib fracture, while rare, can be very painful. The most commonly used metric is the volume of chest wall receiving ≥30 Gy ($V_{30}$) [32–34].
- Dunlap and colleagues [34] combined SBRT data in lung cancer from multiple institutions, including 60 patients treated with three to five fractions of SBRT to peripheral lung lesions.
  – Reported no incidences of pain or fracture when the $V_{30}$ was maintained below 30 cc, whereas 30 % of patients experienced chest wall toxicity when the $V_{30}$ exceeded 35 cc.
- Cleveland Clinic group validated the findings of $V_{30}$ and went further by developing a modified equivalent uniform dose (mEUD) model, accounting for variability in dose-fraction regimens and inhomogeneity [35].
- Memorial Sloan-Kettering Cancer Center prospectively followed 126 patients treated with SBRT with doses ranging between 40 and 60 Gy in 3–5 fractions for non-small cell lung cancer and found chest wall $V_{30}$ ≥70 cc significantly correlated with grade 2 or higher chest wall pain [36].

### 18.8.3 Gastrointestinal Toxicity

- Peripheral and hilar liver lesions may place patients at risk for gastrointestinal toxicities including ulcerations and perforations.
- Blomgren and colleagues [7]: one patient experienced hemorrhagic gastritis when less than one-third of the stomach received more than 7 Gy, another patient had a duodenal ulcer after the distal stomach, and proximal duodenum received 5 Gy in four treatments.
- Hoyer and colleagues [29]: one patient experienced a colonic perforation, which required surgical intervention, and two additional patients had duodenal ulcers, which were treated conservatively.
- Additional SBRT studies suggest that the point dose to the duodenum should not exceed 10 Gy per fraction for three fraction regimens [15]. In all three settings, intestinal doses exceeded 30 Gy [15, 37].
- More recent trials using conservative dose constraints have reported minimal gastrointestinal toxicity, and normal tissue tolerance estimates for single and multiple fraction SBRT have been published [38].

| Organ at risk | Dose constraints (QUANTEC) | Dose constraints RTOG 0438 (hypofractionation) |
|---|---|---|
| Liver | ≥700 cc of normal liver receives ≤15 Gy in 3–5 fractions<br>Mean normal liver dose:<br><15 Gy in 3 fractions or<br><20 Gy in 6 fractions | $V_{27}$ less than or equal to 30 %<br>$V_{24}$ less than or equal to 50 % |
| Spinal cord | Max dose <50 Gy (0.2 % risk myelopathy) | Max dose ≤ 34 |
| Stomach | $D_{100}$ <45 Gy (<7 % risk ulceration) | Max dose 37 Gy to 1 cc |
| Small bowel | $V_{45}$ <195 cc (<10 % risk grade 3 + toxicity) (peritoneal cavity) | Max dose 37 Gy to 1 cc |
| Bilateral kidneys | Mean <15–18 Gy (<5 % risk clinical dysfunction) | No more than 33 % of combined volume ≥18 Gy |

## 18.9 Future Directions

- Delivering SBRT to large tumors (>7 cm) continues to be a challenge and in general was an exclusion criteria in the currently published prospective studies discussed.
  - Novel planning and delivery techniques are necessary to approach these larger tumors with similar ablative doses, while minimizing toxicity.
  - Further, tumors adjacent to critical structures including bowel also pose a challenge.
  - A recent strategy to treat these larger tumors discussed by Crane and Koay [39] is called simultaneous integrated boost (SIB) with simultaneous integrated protection (SIP).
    - The technique involves hypofractionation to achieve a biologically equivalent dose (BED) of 100 Gy in 15–25 fractions, followed by decreasing the CTV and PTV margins within normal liver tolerance, creating margins around organs at risk (OARs), and then treating the hypoxic center of the tumor to a BED >140 Gy if possible.
- Improvements in imaging to delineate normal liver parenchyma will also be important, and there are currently several imaging modalities being investigated [39].
  - Indocyanine green (ICG) is a water-soluble compound that binds to albumin and is selectively taken up by hepatocytes.
    - Its uptake correlates with hepatic function and can be used during planning to attempt sparing of normal liver tissue.
  - Sulfur colloid technetium 99 single-positron emission CT/CT is another imaging modality that can localize functional from nonfunctional liver tissue.
  - Eovist (gadolinium-ethoxybenzyl-diethylenetriamine) is another molecule which can be taken up by hepatocytes and correlates with normal liver tissue [39].
- Additionally, better management of respiratory motion is needed to achieve higher ablative doses.
  - Newer technologies are constantly being introduced.
  - Poulsen and colleagues [40] recently published feasibility results in their study using respiratory gating based on internal electromagnetic monitoring during liver SBRT.
    - Two patients with solitary liver metastases undergoing SBRT were implanted with electromagnetic transponders, using the Calypso® system (Varian Medical Systems, Palo Alto, CA).
    - Electromagnetic transponders are implanted percutaneously in or around the lesion. A 4DCT scan and breath hold end-exhale CT scan are obtained for planning.
    - During treatment, the treatment beam is gated based on positioning of the three transponders; when the transponders deviate more than 3 mm in the left-right

or anterior-posterior direction or more than 4 mm in the cranio-caudal direction, the treatment beam turns off.
    - With gating, they found the mean geometric error in any direction to be 1.2 mm.
- Lastly, to reach higher ablative doses, newer approaches are needed to reduce toxicity to surrounding organs at risk.
  - Biologic mesh spacers (BMS)
    - Yoon and colleagues [41]: the use of BMS to displace nearby organs from the liver, including the stomach, duodenum, small bowel, and colon.
    - BMS typically is placed laparoscopically and secured to adjacent soft tissue or liver using 10 mm clips or intracorporeal sutures.
    - In their study, Yoon and colleagues [41] performed this technique in 14 patients who were then treated with radiation (median dose 54 Gy in 5–15 fractions).
    - At 1 year, only one patient experienced grade 3 abdominal pain, and there were no additional grade 3–4 gastrointestinal toxicities.
    - Of the 12 patients treated, 11 had local disease control.
- Future techniques to enable higher doses to tumors in sensitive areas including the liver are highly needed.

**Conflicts of Interest** The authors have no conflicts of interest to report.

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T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4