Frontiers of
Radiation Therapy and Oncology
Editors: J.L. Meyer, W. Hinkelbein
Vol. 36

Controversies in Uro-Oncology

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Frontiers of Radiation Therapy and Oncology

Vol. 36

Series Editors

John L. Meyer *San Francisco, Calif.*
W. Hinkelbein *Berlin*

KARGER

5th International Symposium on Special Aspects of Radiotherapy,
Berlin, Germany, May 11–13, 2000

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32 figures, 1 in color, and 37 tables, 2002

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Frontiers of Radiation Therapy and Oncology
Founded 1968 by J.M. Vaeth, San Francisco, Calif.

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Library of Congress Cataloging-in-Publication Data

International Symposium on Special Aspects of Radiotherapy (5th : 2000 : Berlin, Germany)
Controversies in uro-oncology / volume editors T. Wiegel ... [et al.] ; 5th International Symposium on Special Aspects of Radiotherapy, Berlin, Germany, May 11–13, 2000.
p.; cm. -- (Frontiers of radiation therapy and oncology ; vol. 36)
Includes bibliographical references and indexes.
ISBN 3805572174 (alk. paper)
1. Prostate--Cancer--Radiotherapy. 2. Bladder--Cancer--Radiotherapy. 3. Radioisotope brachytherapy. I. Wiegel, T. II. Title. III. Series.
[DNLM: 1. Prostatic Neoplasms--radiotherapy--Congresses. 2. Bladder Neoplasms--radiotherapy--Congresses. 3. Brachytherapy--Congresses. 4. Prostatectomy--Congresses. WJ 752 I6125c 2001]
RC280.P7 I565 2001
616.99′463--dc21

2001038673

Bibliographic Indices. This publication is listed in bibliographic services, including Current Contents® and Index Medicus

www.karger.com
Printed in Switzerland on acid-free paper by Reinhardt Druck, Basel
ISBN 3–8055–7217–4

Contents

Preface

This monograph represents contributions presented at the 'Fourth Meeting on Special Aspects of Radiotherapy' which was held jointly by the Departments of Radiotherapy and Urology of the University Hospital Benjamin Franklin of the Freie Universität Berlin in Berlin in June 2000. In particular, the meeting was aimed at identifying 'Controversies in Uro-Oncology'.

By definition, a controversy is a prolonged argument especially over social, moral or political matters. Now, what is the prolonged argument in uro-oncology about? Therapy of prostate cancer and bladder cancer are fields in which tremendous progress has been made in the past few years. Much improved surgical techniques as well as new forms of radiotherapy, chemotherapy and hormonal therapy are now available. Thus, the therapeutic armentarium has drastically increased and is under intense evaluation to provide the best possible care for patients with urologic cancer. In this situation – which was made clear to all participants of the meeting – an interdisciplinary approach to patient care may be the best choice.

The aim of this book is to provide an overview on therapeutic options in urologic cancer. To achieve this goal, the editors have assembled an outstanding group of contributors who describe the most recent progress in their fields of expertise.

Thus, convergence and an interdisciplinary approach to urologic cancer rather than controversy turned out to be the major trend in uro-oncology. This is reflected by the many excellent contributions that are shared herein. We expect that the broad scope of the book will allow its use across the disciplines involved in the care of patients with urologic cancer.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 1–9

Planning Target Volume and Dose Prescription in Definitive Radiotherapy for Prostate Cancer with Favourable Prognostic Factors

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Introduction

Technological developments during the last 10 years have led to a successful implementation of conformal three-dimensional radiotherapy (3DCRT) into curative treatment of localized prostate cancer. The unquestionable background is formed by an accurate targeting of the prostate which allows the delivery of higher amounts of radiation in combination with selective sparing of normal tissues. Published data of thousands of patients demonstrate very clearly remarkable improvements in terms of higher cure rates and decreased rates of acute and late GI and GU morbidity. Long-time cure is not only related to an appropriate radiation dose, an adequate treatment planning and delivery procedure, but also depends on favourable or unfavourable risk factors.

As described in many previous studies, pretreatment variables such as the serum prostate-specific antigen (PSA) value, clinical stage and the grade of differentiation could be identified as independent prognostic factors affecting the outcome in terms of biochemically no evidence of disease (bNED). A pretreatment serum PSA level ≤ 10 ng/ml, a Gleason score ≤ 6 and a clinical stage T1–T2 are well-accepted favourable prognostic parameters [16, 17, 36, 37]. It should be noted that the clinical staging only by digital rectal examination misses up to 40% of pathological extraprostatic diseases as shown in prostatectomy series [25]. Prognostic factors currently under investigation are numbers of positive biopsies (given as percentage) and calculated prostate cancer volume [4]. However, there are still many unresolved questions in regard to target volume definition and dose prescription.

Important aspects will be addressed, particularly in the following paper, by an overview of the literature supplemented by personal experiences at the University Hospital of Vienna during the last 6 years.

Target Definition

Following the ICRU recommendations, as described in the ICRU Report 50 [12], each treatment prescription for any individual patient demands a clear volume decision in regard to the definition of gross tumour volume (GTV), clinical target volume (CTV) and planning target volume (PTV). In 3DCRT of prostate cancer the GTV can hardly be defined. Therefore, for treatment planning, one mostly has to rely on the information of the computed tomography in approximately 5 mm transversal section, which allows a reasonably valid delineation of the prostatic gland and the seminal vesicles.

Clinical Target Volume

When defining the appropriate CTV for curative radiation therapy of prostate cancer, three main questions arise: (1) Is there any benefit from pelvic lymph node irradiation? (2) Is there any necessity for seminal vesicle inclusion? (3) Are there any improvements in the delineation of the prostatic gland by additional imaging modalities?

Overall, no additional benefit has been demonstrated for pelvic lymph node irradiation, in particular for patients with favourable prognostic factors. Therefore, the usual CTV includes the prostatic gland $\pm$ (parts of) seminal vesicles. Serum PSA values, histological differentiation and clinical tumour extent as determined by digital rectal examination are the most significant factors for the probability of seminal vesicle involvement [7]. Taking into account the formula reported by Roach, [probability of SV involvement = initial PSA value + (Gleason score – 6) $\times$ 10], the probability of seminal vesicle involvement is $\leq 10\%$ for favourable subgroups as defined above. The sensitivity of TRUS in detecting seminal vesicle invasion is $<50\%$ [3, 23]. In a review by Oyen et al. [27], tumour spread to the seminal vesicles was directly correlated with a tumour volume >4 cm^3. D'Amico and Roach [4] have shown an improvement for the prediction of extraprostatic disease of 15% by use of an endorectal coil MRI in 36 intermediate risk patients (PSA 10–20 and Gleason score 7 or PSA 4–10 and Gleason 5–7, all with at least 50% positive biopsies) for an intermediate risk prostatectomy patient group.

However, an inclusion of seminal vesicles within the CTV leads to a significant increase of irradiated rectum volume and rectal morbidity and should there-

fore not be recommended in patients with favourable prognostic parameters routinely.

One important issue of integration of MRI in treatment planning is the definition of the apex, which is difficult on axial CT slices. An underestimation of the apex would lead to a potential geographical miss of the apical posterior region, whereas an overestimation could increase the dose to organs at risk, such as the rectum and the urethra and penile structures unnecessarily [5, 34]. Also the additional use of retrograde urethrogram is of limited value since the distance of the apex above the tip of the urethrogram varies. However, Algan et al. [1] have found a better correlation when using CT and urethrogram with the position of the apex at the MRI than using the urethrogram alone. The localization of the apex with the urethrogram alone was 5 mm caudal to the apex at the MRI, with the combination of CT and urethrogram it was 3 mm caudal to the MRI apex. Milosevic et al. [20] have also found MRI superior to CT and urethrography for localization of the prostatic apex, and recommend the use of MRI or a technique of equal precision to assure adequate dose delivery to the entire prostate and to minimize the unnecessary irradiation of normal tissues. In agreement with these data, our analysis of 14 patients has shown the MRI to be superior to CT for the localization of the prostatic apex with a mean distance between the intertrochanteric line and the apex of 21 mm for the CT, 27 mm for the axial MRI and 26 mm for the sagittal MRI [35]. Due to the better soft tissue contrast, MRI enables to distinguish better between prostate and periprostatic tissue (periprostatic vessels, neurovascular bundle) which is the main reason that prostate volumes observed from MRI are smaller than on CT. The average prostate volume reported by Kagawa et al. [14] was 63.0 ($\pm$ 25.8) cm^3 and 50.9 ($\pm$ 22.9) cm^3 determined by CT and MRI, respectively. In our own interobserver analysis [35], CT volumes of the prostatic gland were on average 21% larger than MRI volumes (fig. 1). To take full advantage of the additional improvements by integration of MRI into the target definition process, the use of computerized systems which allow an adequate image registration procedure and the accurate transfer of MR information to the CT is highly recommended. One can expect that these particular features, either within commercially available treatment-planning systems or within dedicated image fusion systems, will gain significance.

Planning Target Volume

The background of the definition of PTV refers to a geometrical concept. The PTV considers patient- and treatment-related uncertainties (e.g. accuracy of mechanical components like linear accelerators, systematic uncertainties of daily setup) as well as patient-related factors (e.g. organ motion). Both components

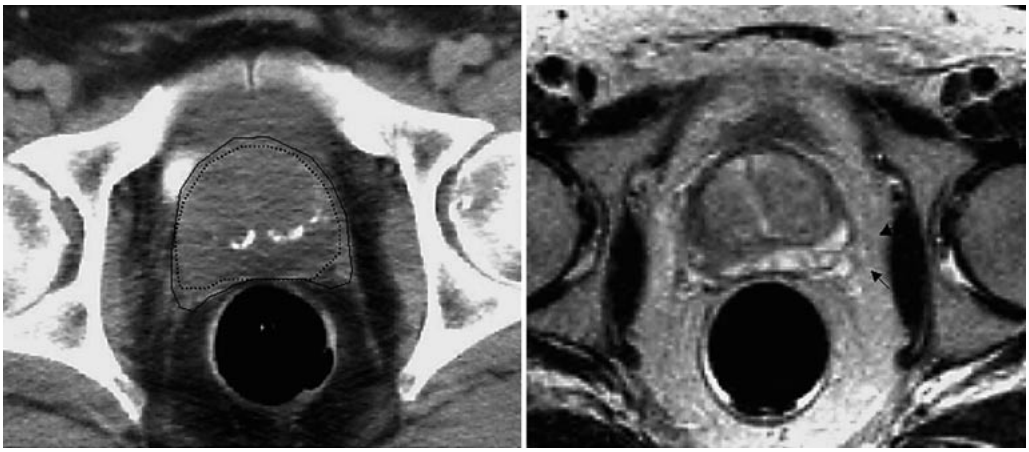

Fig. 1. Axial CT image (left) and axial T2-weighted MRI image (right). As indicated (→) the periprostatic tissue and the prostatic capsule can only be identified on the MRI image, leading to an overestimation of prostate volume on CT. Transfer of MR contour (dotted line) to corresponding CT contour.

have to be taken into account to ensure that the prescribed dose is delivered to the CTV. According to the ICRU Report 62 [13], two margins can be separated to define the PTV: the Internal Margin (IM) that accounts for the movement of the prostate and the setup margin (SM) that accounts for uncertainties in the positioning of the patients.

Motion of the prostate in dependence of different bladder and rectum fillings that are reported vary between 2 and 4 mm standard deviation in the anterior-posterior and superior-inferior direction with less motion in the left-right direction [19, 31, 33]. Portal deviations from simulation reported by the literature are between 2 and 4 mm and comparable to the data from our institute (table 1) [6, 9, 11, 28–30].

Immobilization devices are used to reduce both organ motion and setup deviation. Our study group has demonstrated on average a 2-mm reduction of anterior-posterior prostate motion by daily use of a rectum balloon catheter (table 2) [8].

In the literature the benefit of the use of external immobilization devices is discussed controversially. Rosenthal et al. [29] reported a reduction of the mean and median simulation-to-treatment variability from 0.6 to 0.4 cm for those patients treated with immobilization. A randomized study of the use of a customized immobilization system in the treatment of prostate cancer with conformal radiotherapy recently published by Nutting et al. [22] had shown no improvement

Table 1. Reported setup deviations from the literature and personal data [6, 9, 11]

Group (first author)	Patients	Deviations	x-Axis mm	y-Axis mm	z-Axis mm
Gildersleve [9]	15	Mean deviation	1.96	1.76	0.47
		Standard deviation	2.22	3.26	3.62
El-Gayed [6]	10	Mean deviation	0.4	1.1	0.7
		Standard deviation	2.8	1.6	2.5
Hanley [11]	50	Mean deviation	–0.1	0.4	–0.3
		Standard deviation	2.7	2.2	2.3
Univ. Vienna [pers. data]	83	Mean deviation	1.97	–0.15	–0.43
		Standard deviation	4.05	3.68	2.05

Table 2. Influence of a rectal balloon catheter on motion of the prostatic gland during the radiotherapy treatment course [data modified from 8]

	Standard deviation, mm	
	with balloon	without balloon
Anterior edge of prostate	1.9 (0.6–3.6)	2.9 (0.6–6.4)
Posterior edge of prostate	2.2 (0.6–5)	4.4 (1.5–6.8)

in treatment accuracy. A different recently reported approach to reduce setup uncertainties and uncertainties of prostate motion is the daily use of an ultrasound probe to verify the position of the prostate and correct for both uncertainties at daily treatment [21].

Only few data are available for combined uncertainties of daily setup variabilities and organ motion. According to the study of Tinger et al. [32] considering both uncertainties, setup variations and organ motion, PTV margins of 9.6, 12 and 13.2 mm in the LR, AP and SI directions would be required to encompass 99% of the uncertainty in the position of the prostate, 95% coverage of the prostate would require PTV margins of 6.4 mm in the LR direction, 8 mm in the AP direction, and 8.8 mm in the SI direction. It was not known at the time if less tumour control would be observed if the margins that were used encompassed <95% of the prostate.

Since dose-escalation studies have demonstrated a dose-volume relationship for rectum morbidity, small margins of 5 mm or less have been used to limit the risk for normal tissue complications for dose-escalation protocols. Lee et al. report

a reduction of the distance between the prostate and the posterior block edge from 15 to 5 mm for the last 10 Gy, prescribing a total dose of 75 Gy to the prostate, which leads to a reduction from 22 to 7% grade 2–3 late rectal morbidity. However, PTV margins as small as 5 mm or smaller may not adequately cover the target volume. In our department, by reduction of the posterior margin between CTV and PTV from 15–20 to 5–10 mm, a decrease of acute rectal morbidity grade 1 or 2 from 58 to 48% at the end of radiotherapy was observed.

The definition of PTV is getting more sophisticated when thinking about intensity modulated radiotherapy (IMRT). Several subregions of the PTV could be defined such as the overlap region between PTV and the rectum, where the dose is kept within a tolerance limit, as reported by Burman et al. [2]. On the other hand, IMRT can be used to treat subregions of the prostate supposed to have a higher tumour concentration to a higher dose while treating the entire prostate to a lower dose and not exceeding normal tissue tolerances. Such a concept was reported by Picket et al. [24] using MRI spectroscopy to determine the so-called 'dominant intraprostatic lesion'.

Radiation Dose and Dose Prescription

In many (European) institutions the recommended radiation dose for curative external beam therapy does not exceed 70 Gy for the favourable group of patients with pretreatment PSA <10 ng/ml. These recommendations have been supported by the data from Fox Chase Cancer Centre (FCCC) [10] reported in 1996, where an increase of dose >71 or 73 Gy did not result in improved bNED survival for patients with pretreatment PSA <10 ng/ml at 2 or 3 years.

A study from Cleveland Clinic [15a] described an equivalent 5-year biochemical relapse-free survival in 607 patients with clinical stage T1–2 and a pretreatment PSA level ≤ 10 ng/ml, treated between 1987 and 1996, either with radiotherapy or radical prostatectomy and observed no difference in biochemical control between irradiated or surgically treated patients (75% RT, 76% RPE at 5 years).

Also with a slightly lower radiation dose of 66 Gy, which was the clinical practice in our department before 1999, a comparable 3-year bNED rate of 78% for the favourable subgroup was achieved. However, with a longer follow-up a dose response was reported by FCCC in a poor prognosis subset (T2b/T3, Gleason score ≥ 7) of patients with PSA ≤ 10 ng/ml [26]. Recent studies have also demonstrated a statistically significant improvement of biochemical disease-free survival for favourable subgroups including PSA ≤ 10 ng/ml, Gleason score ≤ 6 and $T_{1/2}$. Lyons et al. [18] reported for these favourable tumours a 5-year bRFS rate of 98% for patients who received radiation doses ≥ 72 Gy versus 81% for

those who received <72 Gy (p = 0.023). For unfavourable tumours, the 5-year bRFS rate for patients who received radiation doses of ≥72 Gy versus <72 Gy was 75 and 41%, respectively (p = 0.001).

It is important to note that the reported dose does not always represent the ICRU dose at the ICRU reference point [12]. At the FCCC, the reported dose is prescribed to the 95% isodose line encompassing the PTV, which means that the corresponding dose at the ICRU reference point is 5% higher than the reported dose [26]. The minimum dose to the PTV is reported at many institutions in the United States, whereas in most European institutions the dose at the ICRU reference point is reported. These differences have to be taken into account when comparing different reports from dose-escalation studies (e.g. FCCC: 95% isodose line; Cleveland Clinic: ICRU reference point or isodose line covering the prostate; Memorial Sloan Kettering: minimum dose to the PTV [18, 26, 37]).

Conclusion

Although improvement of outcome has been observed for patients with low-risk characteristics, the need to increase the radiation dose for favourable subgroups of patients is still discussed controversially. On the one hand, it is often obviously assumed by radiooncologists that by irradiation and surgery similar results can be obtained, particularly for patients with a favourable tumour situation at the time of diagnosis, and published data seem to acknowledge for that. On the other hand, some ambiguity emerges if one wants to compare results between different radiotherapy departments. Therefore, it is important that within the radiotherapy community a proper use and an unmistakable interpretation of technical terms concerning target volume definition and dose prescription is guaranteed to take full advantage of the developments in 3DCRT.

At present it still remains unclear how and to what extent the recommendations of the ICRU Report 62 can be transferred into clinical practice. However, in order to guarantee a comparability of data between different institutions, recording and reporting of target volume definitions (CTV, PTV) and radiation dose as proposed in the ICRU report is highly recommended.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 10–15

Dose Escalation for Prostate Cancer: Which Dose for Which Person?

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Data supporting the use of higher doses of external beam radiation therapy for the treatment of adenocarcinoma of the prostate has been accumulating over several years. The peer-reviewed reports of several large institutional experiences as well as secondary analysis of data from the Radiation Therapy Oncology Group (RTOG) are strongly supportive of dose escalation strategies [1–4]. There is a clear implication that higher doses of radiation therapy to the prostate results in longer intervals free from biochemical relapse. However, the ultimate effect of this improvement in tumor control on disease-specific survival remains to be seen.

It is clear that, fundamentally, intensification of local therapy will only result in improved survival among patients who have no clinically significant metastatic disease at the time they undergo external beam radiation therapy. In addition, it may be difficult to detect a benefit for patients with extremely favorable disease since it may take more than 10 years for any benefit to be observable. Thus, data that evaluates the benefit of treatment for different subsets of patients is particularly relevant for this discussion.

As an illustration of the results from single institutional experiences using a serial dose escalation strategy, investigators at Fox Chase Cancer Center treated a large cohort of patients to higher and higher doses over time as tolerance permitted and have grouped their patients by their pretreatment PSA level [1]. Patients are grouped into presentation PSAs of 0–10, 10–20 and >20 ng/ml. In addition, within each PSA subset, they are further subgrouped into favorable and unfavorable subsets. Patients are noted to be unfavorable if they have clinical T2b–3 disease, Gleason score 7–10, or have perineural invasion present on the biopsy specimens. Since the Fox Chase Cancer Center has a relatively long history of performing high-dose conformal external beam radiotherapy, they have reported 5-year biochemical freedom from relapse (bNED) data using the American Soci-

ety of Therapeutic Radiology and Oncology (ASTRO) consensus definition [5]. These 5-year data were used to create a dose-response curve for the PSA subsets, which were subdivided by the favorable and unfavorable criteria. Using this 5-year data, there is a dramatic dose response for patients between the doses of 70 and 80 Gy for the intermediate subset with a pretreatment PSA of 10–20 ng/ml regardless of whether the patients had the favorable or unfavorable criteria. The improvement in freedom from relapse is approximately from 50% bNED to 80% bNED for the unfavorable patients at 5 years and from 70% bNED to 85% bNED for the favorable patients. Those patients with PSA >20 ng/ml had an equally dramatic dose response for patients in the favorable subset. However, patients with unfavorable disease had no observable dose response. For the most favorable patients with the PSA of up 10 ng/ml, it is difficult to appreciate any dose response within the range of 70–80 Gy. This response seems to indicate a significant advantage to dose escalation for patients with disease (1) that is aggressive enough to be clinically significant over a 5-year period and (2) that has a relatively low risk of subclinical metastatic disease.

Although this data is encouraging, it suffers from the obvious flaw that patients treated in the most recent times were treated to higher doses and have shorter follow-up, which may influence results, especially when using the ASTRO consensus definition of PSA failure [6]. In addition, due to more aggressive screening strategies for prostate cancer, patients treated most recently may have somewhat more favorable disease, even when attempting to match for known prognostic factors.

One study that attempted to address this methodologic problem was a secondary analysis of older RTOG clinical trials for localized prostate cancer [4]. This report combined patients treated on 4 older, randomized RTOG studies (RTOG 75-06, 77-06, 85-31 and 86-10) that employed external, nonconformal radiotherapy for prostate cancer. These studies allowed for some variation in the total radiotherapy dose used for treatment and yet were still within the protocol guidelines. Although very high doses were not used and the variation of dose was not large, a difference in outcome favoring higher doses was observed. Importantly, because the follow-up was so long on these older studies, patients were followed up long enough to observe – above and beyond mere biochemical freedom from relapse – a benefit in disease-specific survival and in overall survival for patients with high-grade disease.

Naturally, retrospective studies and secondary analyses ultimately can only be used for hypothesis generation. Progress in oncology is traditionally and appropriately based upon the results of well-designed, randomized clinical trials and one has recently been reported which explored the role of external beam dose in the treatment of prostate cancer. Pollack et al. [7] at MD Anderson Hospital have reported the results of a randomized trial performed at their institution. This trial

followed up their single-arm dose escalation experience, which was supportive of the use of higher doses. The randomized trial was designed with enough patient accrual to detect an improvement in biochemical freedom from relapse and thus will be unlikely to contain enough power to detect a small disease-specific survival advantage, if one exists. Approximately 300 patients were entered into the randomized trial. One group of patients received 70 Gy using conventional treatment, that is without explicit conformal therapy techniques. The experimental arm received 78 Gy using a three-dimensional conformal radiation therapy boost after 46 Gy. This ambitious study completed its accrual of patients over a 5-year period. Preliminary results have recently been reported and would suggest an overall benefit in freedom from biochemical failure of approximately 10% from 69 to 79% at 5 years ($p = 0.058$). The authors identified patients who benefited most from the 8-Gy escalation and they observed improvement and freedom from relapse from 48 to 75% at 5 years for patients who had a PSA pretreatment >10 ng/ml. There was no benefit observed when the pretreatment PSA was >10 ng/ml. Given the nature of prostate cancer – with typically a long interval between diagnosis and death from disease – no survival benefit has been observed from these preliminary data. However, one intriguing finding of this data is a suggestion of an improvement in freedom from distant metastasis for patients with a PSA of >10 ng/ml: 98 vs. 87% ($p = 0.054$). This finding has been observed previously by Hanks et al. [8] in a retrospective analysis.

The results of this MD Anderson randomized trial are strikingly different from the results of a randomized dose escalation trial performed using a proton boost [9, 10]. This study was performed before PSA was available and was confined to patients with locally advanced disease. Clearly, that study was performed in a different era and would have been made up primarily of patients considered highly unfavorable by today's standards; most of the patients would have been expected to have had subclinical metastatic disease and this would have diluted the pool of patients who might potentially benefit from dose intensification. Thus, the proton dose escalation study, which was attempting to observe a difference in overall cure rates, may have been assigned an impossible task. Yet, the proton study did show a difference in local freedom from relapse in the patients treated to high dose with the proton boost, which can be argued is adequate evidence for a beneficial biological effect with more intensive therapy.

A phase III study has been proposed in RTOG to expand upon the results of single institutional trials and to be large enough to detect a survival benefit if one exists. This study will be based upon the large phase I dose escalation study, RTOG 9406. This phase I study has accrued more than 1,000 patients to several dose levels and may be the largest phase I study ever performed in oncology. Patients were divided into three different prognostic groups based upon the clinical T-stage and the risk of seminal vesical invasion using the Roach formula [11].

Once the prognostic group was assigned, sequential dose escalation was performed within each prognostic group. The first dose level was 68.4 Gy given at 1.8 Gy/day. Subsequent dose levels, also using 1.8-Gy fractions, were sequentially increased to 73.8 Gy, then 79.2 Gy. At that point, a decision was made to increase the dose per fraction to 2 Gy/day and the dose was reduced to 74 Gy. More recently the highest dose level of 78 Gy using 2 Gy/day and minimum PTV dose met its accrual goals. The maximum tolerated dose from this arm will be randomized to a dose of approximately 70 Gy. It is expected that approximately 2,000 patients will participate in this large randomized trial. It is hoped that this trial will be definitive in determining both a biochemical benefit and a survival benefit for patients with localized prostate cancer. Who will be eligible for this study? Based on the data discussed above, patients at intermediate risk are expected to be the patients most likely to benefit from dose escalation, and these will be the patients enrolled in this trial.

Obviously, there is great enthusiasm for dose intensification using external beam radiotherapy techniques for patients with prostate cancer, but is there reason to suspect that quality of life will be adversely affected by more intensive therapy? Unfortunately, there has been little in the way of well-designed studies assessing the toxicity of all the treatment modalities used for localized prostate cancer. Recently, a group at the University of Michigan created a modification of the UCLA Prostate Cancer Index and validated its use in the treatment of localized prostate cancer for patients treated with radical prostatectomy, external beam radiotherapy and prostate brachytherapy [12]. This expanded and revalidated instrument is currently known as the Expanded Prostate Cancer Index Composite (EPIC). The EPIC instrument has been factored into four prostate cancer-related domains (urinary, sexual, bowel and hormonal). Within each domain, items are grouped to derive complementary function and bother subscales (table 1).

This study provided a method to examine what the role of dose escalation would be in influencing the patient-reported quality of life after prostate cancer therapy [13]. Health-related quality of life (HRQOL) was assessed with respect to tumor and treatment variables including: Pre-RT PSA, Gleason score, patient age, T-stage, duration of androgen ablation, interval between 3DCRT and survey, total dose of 3DCRT, and whether the radiotherapy was given definitively or post-prostatectomy. 181 patients (72% response rate) who had undergone 3DCRT provided written informed consent and returned a completed HRQOL survey instrument as part of this IRB-approved study. Median radiotherapy dose was 75 Gy (interquartile range (IQR) 71.8–78.2) and increased gradually over the study period, which allowed a comparison HRQOL as a function of radiotherapy dose. Thirty patients were treated after radical prostatectomy. Overall scores vs. age-matched controls are shown in table 1. Multivariate analysis revealed that

Table 1. Overall HRQOL scores for external beam patients and aged-matched controls

HRQOL domain	External beam radiotherapy	Controls
Urinay HRQOL		
EPIC urinary function	91	95
EPIC urinary bother	80	85
Bowel HRQOL		
EPIC bowel function	87[1]	92
EPIC bowel bother	83	93
Sexual HRQOL		
EPIC sexual function	30[1]	56
EPIC sexual bother	46	74
Hormonal HRQOL		
EPIC hormonal function	84[1]	90
EPIC hormonal bother	89	93

[1] Mean scale score is significantly different from the control group, when adjusted for age.

longer duration of androgen ablation was significantly associated with poorer hormonal function and bother scores and poorer sexual function scores. Older patients had significantly worse sexual bother and function. As expected, urinary function was significantly worse among patients who received radiotherapy after prostatectomy. Importantly, increased dose of 3DCRT *was not* associated with function or bother in any domain. The authors concluded that 3DCRT is capable of delivering high doses of radiotherapy and these higher doses are not associated with worse HRQOL outcomes.

In summary, evidence supports the benefit of higher doses of radiotherapy for prostate cancer, although strong evidence for a survival benefit still awaits longer follow-up. Given that PSA testing revolutionized the presentation of prostate cancer, survival data from the PSA era is still immature, since PSA only became widely used for prostate cancer screening in the late 1980s. In addition, there is evidence that modern dose delivery techniques, such as those used at the University of Michigan [14], can provide substantial doses of radiotherapy without adversely affecting patient-reported quality of life. The use of randomized trials, such as the planned, large RTOG randomized dose study will be pivotal in securing the role of high-dose, external beam therapy for prostate cancer and should be supported.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 16–24

Planning Target Volume Definition in Dose-Escalation Studies

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Introduction

Doses beyond 70 Gy have been demonstrated to be beneficial, at least for certain subgroups, in radical radiotherapy of carcinoma of the prostate [1, 2]. The ideal dose and the selection of patients for various treatment protocols according to prognostic factors (PSA, grading, T stage) is the subject of recently published and ongoing clinical trials. The introduction of conformal radiotherapy and, in particular, dose escalation has led to a critical evaluation of target volume concepts in radiotherapy of carcinoma of the prostate. Issues such as organ motion, setup accuracy, organ delineation in different imaging modalities and interobserver variability in target volume contouring have been at the center of debate [3–5]. The present paper aims to review these results and their integration into the actual planning target volume (PTV) definition in clinical trials of dose escalation.

Setup Accuracy, Organ Motion and PTV Margins

The goal of radical radiotherapy of the prostate – high local control probability and acceptable rates of gastrointestinal and genitourinary toxicity – is compromised by uncertainties in actually treating the volume defined on initial planning. Setup deviations and motion of the prostate mainly contribute to these unwanted

effects. Several investigators have described the amount of uncertainty introduced by these mechanisms under different patient fixation conditions and proposed safety margins of various extent around the clinical target volume (CTV) of prostate ± seminal vesicles. In an early study without fixation (supine positition), Rudat et al. [3] found the prostate motion to be normally distributed in the anterior-posterior (AP) and mediolateral (ML) direction. One standard deviation (SD) of movement in the AP direction was 3.7 mm and in the ML direction 1.9 mm. In the same study, patient positioning variability was 4.9 mm (AP), 3.1 mm (ML) and 5.4 mm in the craniocaudal (CC) direction, leading to an estimated combined error of 6.1 mm (AP) and 3.6 mm (ML). In a study from the M.D. Anderson Cancer Center, setup errors (1 SD) were measured to be 5.1 mm (AP), 4.0 mm (ML) and 2.3 mm (CC), in addition to prostate motion of 3.6 mm (AP), 0.7 mm (ML) and 3.4 mm (CC) [6]. The authors found a significant effect of rectal volume, but not of bladder volume, on prostate mobility. Finally, Tinger et al. [4] reported data on patients immobilized in an alpha cradle. Setup variability (1 SD) was 3.0 mm (AP), 3.1 mm (ML) and 2.1 mm (CC), whereas organ motion was found to be 2.6 mm (AP), 0.9 mm (ML) and 3.9 mm (CC). Total setup uncertainty derived from this data was 4.0 mm (AP), 3.2 mm (ML) and 4.4 mm (CC), with separate analysis of the seminal vesicles leading to very similar values.

A variety of other investigations on this issue have demonstrated setup variability (1 SD) to be in a range of 2.4–7.3 mm (AP), 2.5–5.5 mm (ML) and 2.2–12.5 mm (CC) [7–12]. The respective values for organ motion ranged between 1.5 and 5.2 mm (AP), 0.7 and 2.7 mm (ML) and 1.7 and 5.1 mm (CC).

The above data permits conclusions concerning PTV definition. According to the International Commission on Radiation Units and Measurements (ICRU) [13], the PTV is defined as the CTV (in the treatment of carcinoma of the prostate usually equivalent to the gross tumor volume (GTV), i.e. prostate ± seminal vesicles) plus a margin to allow for geometrical uncertainty in its shape and variations in its location relative to the beams due to organ mobility, organ deformation and patient setup variations [13]. Selected recommendations on margins to be used in radical radiotherapy of the prostate are given in table 1. In general, these conclusions are based on margins with a magnitude of 2 SD of the total CTV variability in each direction. In an evaluation of mathematical models to derive PTVs from CTVs in carcinoma of the prostate, however, Antolak and Rosen [14] calculated complete coverage of the CTV by the PTV 95% of the time would require an expansion by 2.8 SD in each direction. They recommend using a margin of 1.65 SD in each direction, reflecting a CTV dose of >95% of the minimum PTV dose (i.e. over >90% of the prescribed dose if dosage is according to ICRU 50).

Table 1. Recommendations for PTV margins in radical radiotherapy of the prostate, as derived from setup variability and organ motion studies

Group (first author)	AP, mm	ML, mm	CC, mm
Rudat, 1996 [3]	12.2	7.2	13.0
Antolak, 1998 [6]	11.0	7.0	7.0
Tinger, 1998 [4]	8.0	6.4	8.8
Dawson, 1998 [33]	12.4	5.6	10.3

Imaging Modalities and Inter-Observer Variability in Target Volume Definition

The above data is based on repeated computed tomography (CT) scans and portal film or portal imaging verification during a course of radiotherapy. The recommendations concerning margins do not consider the reliability of CT in outlining the GTV of prostate or seminal vesicles nor a possible variability between radiation oncologists in contouring these organs. Most importantly, the application of magnetic resonance imaging (MRI) has produced prostate volumes smaller than on CT by a mean factor of 1.3 [15]. In 10 patients, the main distinct areas between both modalities were the posterior part and the apex, with mean maximum differences of 7 and 4.5 mm, respectively.

Other investigators found the CT-defined apex to be on average 3 and 5 mm, respectively, more caudal than the MRI-defined one [16, 17]. Rasch et al. [5] reported an average volume ratio of 1.4 between axial CT and axial MRI. Average distances between the volumes were 6 mm at the apex and 7 mm at the seminal vesicles. The precise delineation of prostate and seminal vesicles by MRI and the development of magnetic resonance spectroscopy (MRS) have prompted the development of protocols treating a dominant intraprostatic lesion to an escalated dose [18]. Transrectal ultrasound (TRUS) has demonstrated a high correlation with CT concerning the measurement of prostate volumes [19]. However, the use of ultrasound in radiotherapy of the prostate has so far been limited to brachytherapy [20] and to daily verification of prostate position in conformal external-beam therapy, a method proposed to partially overcome setup and organ motion problems [21, 22].

The variability between different radiation oncologists in contouring the prostate and the seminal vesicles on CT images was investigated by Fiorino et al. [23]. The variability of total CTV (1 SD) ranged from 10 to 18%, the most critical

areas being the anterior border of the cranial portion of the prostate (SD of contour distances 7 mm) and the posterior and lateral border of the cranial portion as well as the inferior border of the prostate (SD 3 mm). Another study found a good agreement between seven observers concerning prostate contour, but low correlation of seminal vesicle outlines [24]. The use of urethral and bladder contrast improved the reliability of prostate localization. An analysis of in-slice deviations between observers also found the largest uncertainty for the seminal vesicles and the best agreement at the prostatic apex [25].

PTV Definition and Dose Prescription in Clinical Trials

A comparison of PTV concepts and dose prescription policies for dose escalation in radiotherapy of the prostate at leading US and European institutions reveals marked differences: A report on conformal treatment with up to 79 Gy from Fox Chase Cancer Center describes the use of 1 cm GTV to PTV margins in each direction [1]. Doses were prescribed, according to ICRU recommendations, to a point near the center of the target and variation of dose across the prostate was estimated to be 5%. The authors concede, however, that the 1-cm margin toward the rectum produced unacceptable rectal toxicity in the high-dose group and suggest a reduction of dose to the anterior rectal wall to 72 Gy by reducing this margin to 0–2.5 mm for the last part of the treatment [26]. Such a concept was already used at Memorial Sloan-Kettering Cancer Center where dose escalation to 81 Gy has been performed [2]: The PTV included the CTV plus a 10-mm margin except for only 6 mm at the prostate-rectum interface, added by another 5 mm circumferentially and 10 mm superiorly and inferiorly to account for beam penumbra. Doses were prescribed to the maximum isodose completely enclosing the PTV on three orthogonal planes through the isocenter, leading to up to 7% higher doses inside the PTV. In the highest dose group of 81 Gy, however, the rectum was completely blocked in all fields after 72 Gy.

A planning study from the University of Michigan, Ann Arbor, evaluated dose-volume histograms after prescription of up to 80 Gy to a PTV consisting of prostate ± seminal vesicles plus an 8-mm margin in each direction, covered by the 95% isodose [27].

In a hypofractionated concept of 70 Gy in 28 fractions of 2.5 Gy, the Cleveland Clinic Foundation applied margins of 4 mm posteriorly, 8 mm laterally and 5 mm in all other directions [21]. Dose prescription to isodose lines ranging from 82 to 90% resulted in mean prostate doses of 73.5–78.5 Gy and maximum doses of 77.4–84.5 Gy. In the multicenter dose-escalation trial RTOG 9406, 79.2 Gy were prescribed to the ICRU reference point in the central part of the PTV at the highest dose level, requiring coverage of at least 95% of the PTV by the prescription isodose [28]. An optional margin size of 5–10 mm was permitted around the prostate with or without seminal vesicles, depending on prognostic factors.

Table 2. Overview of minimum doses at the PTV surface in escalation of the prescribed dose as derived from the original publications; due to differences in dose prescription policy, 'dose-escalation' protocols may permit lower doses at the PTV surface than schedules considered 'conventional'

Institution	Stated prescribed dose, Gy	Minimum dose at the PTV surface, Gy
Fox Chase Cancer Center	79	75.1
Memorial Sloan-Kettering Cancer Center	81	81
Cleveland Clinic Foundation	70	70
Royal Marsden Hospital	74	66.6
University of Vienna	72	64.8

The Loma Linda University Medical Center has published data on proton or proton/photon treatment of the prostate with 74–75 cobalt gray equivalent (CGE) [29]. Their boost PTV included prostate and seminal vesicles plus a 1.2-cm margin in each direction. However, the dose prescription policy was not specified.

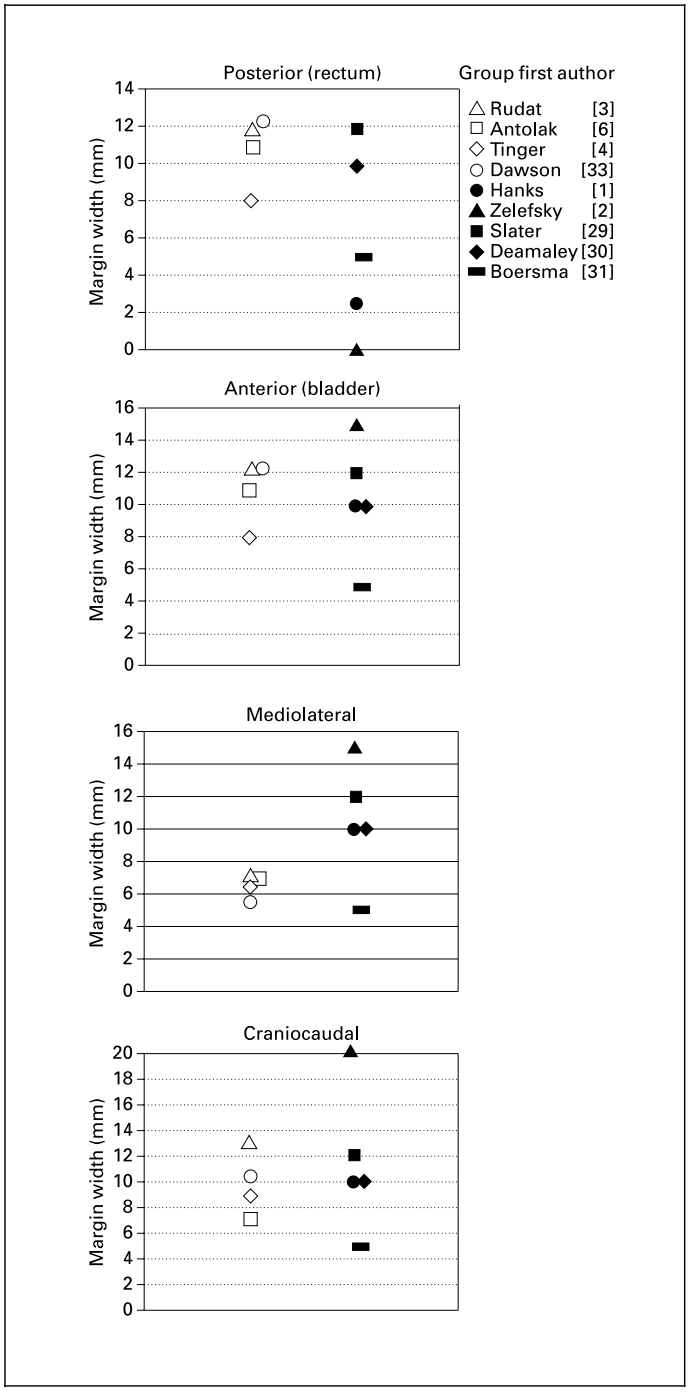
At the Royal Marsden Hospital, the standard of PTV definition in treatment up to 74 Gy has been extension of the prostate and seminal vesicle volume by 10 mm in each direction, requiring coverage of the PTV by the 90% isodose [30]. This was achieved in conformal therapy by creating blocks with a 6-mm margin from the PTV surface in beam's-eye view projection.

In a concept of concomitant treatment of the pelvis and a local prostate with/without seminal vesicle volume at the Netherlands Cancer Institute, the boost PTV treated up to 78 Gy was defined as the CTV expanded by 1 cm in each direction [31]. However, this margin was reduced to 5 mm after reaching 70 Gy, the prescribed dose being specified to the isocenter.

Finally, the University of Vienna, in treating the PTV encompassed by the 90% isodose to up to 72 Gy specified at the ICRU reference point, applied 1-cm margins around the GTV except for only 5 mm posteriorly. For reproducible distension of the organ, a rectum balloon is employed [32].

The resulting minimum doses inside the PTV for the highest-dose groups reported from the above institutions are summarized in table 2. Comparing GTV

Fig. 1. GTV to PTV margins as recommended by authors of setup and organ motion studies (left, open symbols) and as used for the final boost in dose-escalation trials (right, closed symbols).


Posterior (rectum)
Group first author
Rudat [3]
Antolak [6]
Tinger [4]
Dawson [33]
Hanks [1]
Zelefsky [2]
Slater [29]
Deamaley [30]
Boersma [31]
Margin width (mm)
Anterior (bladder)
Mediolateral
Craniocaudal

to PTV margins from the above studies with margin sizes recommended by studies looking at setup accuracy and organ motion reveals a discrepancy between theoretical assumption and clinical practice (fig. 1). Whereas some institutions have reduced the posterior margin for the final part of the treatment series below any recommendation for maximum protection of the rectum, the mediolateral margins used clinically appear very generous. This finding is based on the use of isotropic margins at many centers, neglecting the finding that the mediolateral setup error and, in particular, organ motion was minimal in most reports. Clinically used anterior and craniocaudal margins are, with some variation, in the range of recommended values.

Conclusion

Dose-escalation protocols in local radiotherapy of the prostate face the dilemma of maintaining adequate margins to assure treatment of the CTV, i.e. the prostate with or without seminal vesicles, while avoiding excessive doses to the organs at risk, in particular the rectum for which a steep dose-effect curve above 70 Gy has been demonstrated [1]. The institutions with the most experience in dose escalation seem to agree that the anterior rectal wall should not receive more than 72 Gy, no matter what margins may be required by setup and organ motion variability. Technical advances in various areas of radiotherapy planning and delivery have contributed to increased setup accuracy. While the ideal treatment position is still under debate, daily checks of patient setup, e.g. by portal imaging or ultrasound localization of the prostate, may eliminate the uncertainty introduced by setup variation. Organ motion is more difficult to influence: The use of a rectal balloon and consistent bladder filling (or voiding) may only reduce the uncertainty to some extent. The effect of inter-observer variation, however, has apparently not been taken into account in development of PTV concepts for dose escalation. The introduction of MRI into treatment planning may permit a clearer organ delineation and minimize this factor.

In conclusion, clinical experience has shown that the use of margins as proposed by authors of treatment variability, such as 10 mm toward the rectum, is not feasible in prostate treatment beyond 70 Gy. It seems advisable for each institution performing such treatment to first optimize its patient positioning and planning procedure, then measure the variability under such optimum conditions and define its own GTV to PTV margins. It appears reasonable to use the proposed margin size of 1.65 SD in each direction with a limit of total dose to the anterior rectal wall. While (anisotropic) margins may be individually defined for each institution, dose prescription should adhere to common criteria (ICRU), facilitating comparison of the results of different protocols.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 25–34

Inverse Planning and Intensity-Modulated Radiotherapy in Patients with Prostate Cancer

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Rationale for Dose Escalation in the Treatment of Prostate Cancer

For decades the standard approach for radiotherapy of prostate cancer used bony landmarks and positive and negative x-ray contrast of bladder and the rectum for localization and shaping of treatment portals. In contrast, three-dimensional (3D) treatment approaches the problem of localization with the full 3D information of CT. Advances in the imaging of prostate cancer led to a better definition of the target volume in three dimensions. Computer hardware and software technologies have been developed which allow the clinical use of image-based 3D radiation therapy planning. Linear accelerators are nowadays available which have advanced computer-controlled delivery and treatment verification features. These technical developments with 3D conformal radiotherapy (3D-CRT) improved the planning and treatment process substantially. Therefore, a highly individualized treatment can be delivered to a patient rather than standard solution of field shapes and beam angles. Another advantage is that the dose to critical structures is calculated and can be systematically compared to the clinical response in long-term studies in order to get more precise clinical data on the dose-response and the volume-response relationships in the various critical structures.

A growing number of clinical data have shown that the probabilities of tumor control and normal tissue complications after radiation therapy are dose-depen-

dent, and that the dose-response relationships may be rather steep sigmoid-shaped curves [1, 2]. The observation that tumor control curves are usually at lower dose levels relative to normal tissue toxicity curves provides the biological basis for curative radiotherapy [1–3]. Analysis of dose response is further complicated by uncertainties in tumor delineation, organ motion, and in patient positioning from day to day [4–12]. To compensate for these uncertainties, large safety margins have usually been added to the clinical target volume (PTV), extending into surrounding normal tissue, to decrease the risk of a marginal tumor underdosage. However, since the dose tolerance of critical normal organs is dependent on the volume of the irradiated tissue, the increase in normal tissues within the treatment volume constrains the treatment dose and consequently cure of the patients. This is the rationale of 3D-CRT [13, 14]. This approach uses volume information for tumor and normal organ segmentation, new algorithms for precise dose calculations, and computer-aided optimization to generate treatment plans that confine the prescribed dose to the tumor, while maximally excluding the adjacent radiosensitive normal structures.

The concept of 3D-CRT in the management of prostate cancer was validated by several groups in clinical studies [15–19]. A study of 743 patients with localized prostate cancer treated with 3D-CRT at memorial Sloan-Kettering Cancer Center [19] demonstrated that both the initial clinical response and the long-term tumor control were dose-dependent. The incidence of an initial complete response (PSA decreasing to 1.0 ng/ml) was 90% in patients receiving 75.6 or 81 Gy, as compared with 76 and 56% for those treated to 70.2 and 64.8 Gy, respectively ($p < 0.001$). The 5-year actuarial PSA relapse-free survival for patients with intermediate or unfavorable prognosis receiving 75.6 Gy was 78 and 53%, respectively, compared with 54 and 17%, respectively, for those treated to 70.2 Gy ($p < 0.05$). These results were confirmed by assessing of patients with postradiation biopsies obtained at 2.5 years after 3D-CRT, only 4% of patients receiving 81 Gy had evidence of active tumor, compared with 27, 36 and 57% for those receiving 75.6, 70.2 and 64.8 Gy, respectively ($p < 0.05$) [19, 20]. However, there was an increase in grade 2 rectal bleeding in patients receiving 75.6 Gy to 17%, from the 6% value observed in patients treated with 70.2 Gy ($p < 0.001$). While the overall rate of late grade 3 and 4 rectal and bladder toxicities was only 1.9%, analysis of dose-volume histograms (DVH) in patients receiving 75.6 Gy indicated that the rectal wall volume was significantly higher at each dose of the mean DVH for patients with rectal bleeding as compared with those who did not bleed ($p < 0.05$) [21]. There is clinical evidence that higher doses are essential for enhancing the local cure of prostate cancer patients. 3D-CRT techniques that more tightly confine the high-dose distribution to the PTV may be necessary to decrease the risk of rectal bleeding. However, even with 3D-CRT, rectal toxicity limits further increase of dose.

Dose Escalation with Inverse Planning and Intensity-Modulated Radiotherapy (IMRT)

One solution to produce more conformal dose distributions is inverse planning and dose delivery with intensity modulation (IMRT). In the following, the principle of IMRT is explained.

Inverse Planning

The standard approach of 3D treatment planning is that the planner chooses the treatment machine parameters interactively such as gantry angle, field size, etc. The method of virtual simulation helps in selecting the treatment parameters. The resulting dose distribution is then optimized in a trial-and-error approach by a variation of the treatment parameters until the desired coverage of target volume and sparing of radiosensitive structures is achieved. Therefore, the result of this approach may be time-consuming and depends strongly on the experience of the treatment planner.

A completely new approach to the solution of the treatment-planning problems, so-called 'inverse planning', was proposed at the end of the last decade [22]. The principal idea of inverse planning is to allow intensity variation within the different beams of a treatment technique (fig. 1). Interactive trial-and-error optimization of single beams is abandoned. Instead of this, a special software iteratively optimizes fluence distribution in the different beams until the desired conformal dose in the target volume is reached, on the condition that tolerance doses in critical organs are not exceeded [23].

Therefore, the crucial step in inverse planning is that the physician defines the dose which is to be applied in the target volume and dose which may be tolerated in the structures at risk. If such radiosensitive structures are close to the target volume, the desired doses may not be reached. In such situations the user has to define criteria in the software how to find the compromise of target coverage and sparing of structures in order to find the 'optimal' dose distribution. Therefore, inverse planning is a typical optimization problem.

Different optimization criteria and different strategies were developed in order to solve the inverse-planning problem: the group at the Karolinska Institute in Stockholm proposed to use optimization criteria based on biological models, while our group at the DKFZ favors purely physical criteria [22–24]. The group at the Royal Marsden Hospital in London implemented an optimization algorithm called 'simulated annealing' [25]. The principle of the algorithm is to randomly introduce small changes in the fluence pattern and to evaluate its effect on the dose distribution. Subsequently, the change in fluence pattern is kept if it improved and neglegted if the change impaired the dose distribution. Our group implemented a gradient-driven optimization procedure. The advantage of the

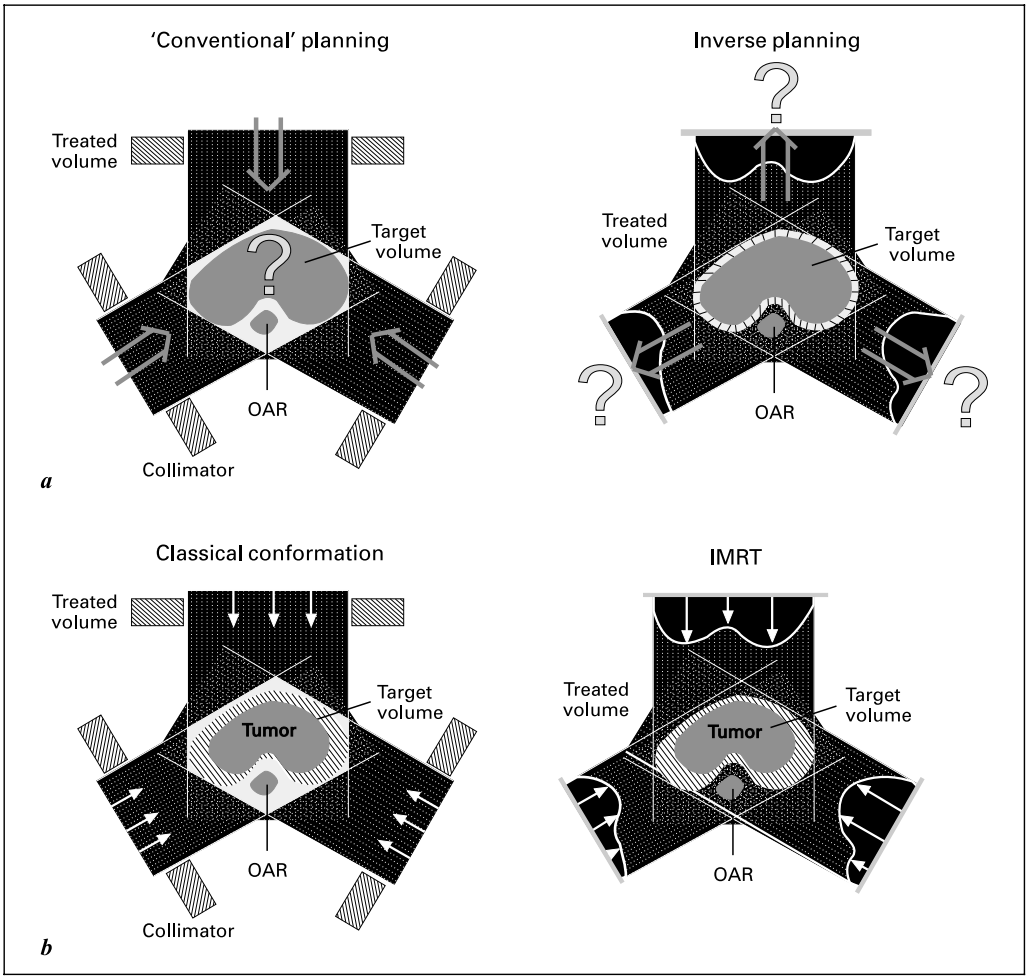


Fig. 1. a While in conventional planning a homogeneous fluence pattern (left) is used, the principle of inverse planning is to calculate an inhomogeneous fluence pattern (right) which generates the desired dose distribution in the patient. ***b*** IMRT is a method to generate fluence patterns in radiation fields. The superposition of the fields delivers the desired dose in the patient.

gradient driven algorithm is the higher speed which allows 'online' interaction with the optimization procedure. Both approaches are implemented in commercial inverse-planning tools.

From the theoretical point of view, the concept of inverse planning soon improved to be very powerful, especially for treatment planning of lesions with

challenging shape such as large base of skull tumors. It turned out in clinical practice that inverse planning requires also a trial-and-error approach during treatment planning until a class solution is found for a given indication. The class solution enables the planner to standardize inverse treatment and to shorten the time until the desired dose distribution is achieved. We have shown that inverse planning of large base of skull tumors produces superior results especially in large target volumes. An example of an inverse treatment plan is shown in figure 2. This plan was computed with our inverse-planning program KONRAD.

KONRAD uses the target volumes and organs at risk, designed with the conventional 3D treatment planning (in our case the TOMAS target delineation program within VOXEPLAN), but then has its own strategy to determine the treatment technique by using an iterative algorithm which was described by Bortfeld et al. [23]. DVH calculation and display are implemented as well as some basic viewing tools for 3D dose distributions. For a more elaborate evaluation of the dose distributions generated with KONRAD, the VIRTUOS module can be used. The program is described in detail in Preiser et al. [26]. The result of treatment planning is a fluence pattern which has to be generated by the treatment machine.

Intensity Modulation (IMRT)

After inverse planning the resulting fluence pattern has to be realized on the treatment machine. The techniques which have been recently developed in this context are called IMRT. In general, IMRT is very ill-defined because strictly spoken also wedges and missing tissue compensators, modulate the fluence of the beam. However, nowadays the term 'IMRT' should only be used in the context of inverse planning.

For radiotherapy with charged particles a very effective method of intensity modulation has been described, e.g. the magnetic scanning of pencil beams. For high-energy photons, however, the scanning beam idea cannot be applied: there is no physical way to directly deflect a photon beam. The most obvious way for the generation of an intensity-modulated photon beam therefore is to use x-ray compensators, or, as recently suggested by several groups, to apply computer-controlled MLCs. Two different techniques are currently being used: the first method, known as the step-and-shoot technique [27], generates an intensity-modulated beam for a fixed gantry angle by superposition of several static irregular-shaped fields. The beam has to be turned on and off for each subfield. The second is a dynamic method which produces intensity modulation by dynamic movement of the leaves while the beam for a static gantry angle is turned on all the time [28, 29].

Tomotherapy is another development in the context of intensity modulation. The idea here is to apply intensity-modulated beams by using a dynamic slit MLC

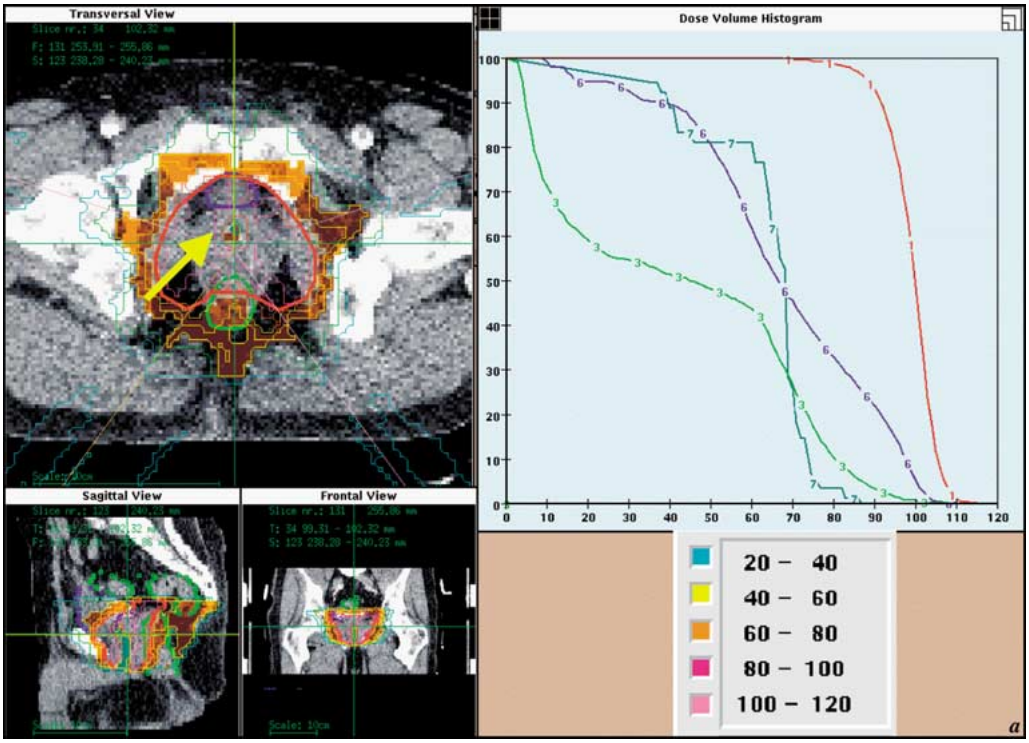
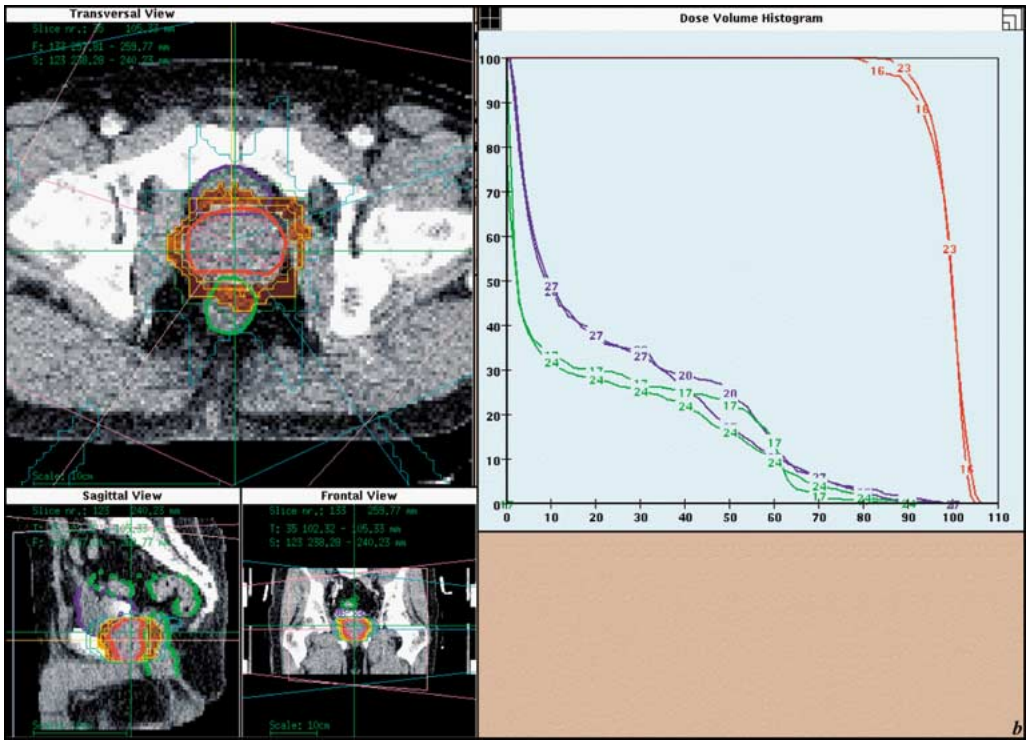


Fig. 2. Example of IMRT with step and shoot approach with inadequate large (***a***) and tight margins (***b***). This example demonstrates that IMRT cannot compensate for inadequate margins around the planning target volume. A special feature of IMRT is that it allows one to reduce the dose to structures within the target volume, e.g. the urethra (arrow in ***a***). The clinical role of this approach is currently under evaluation.

in a rotation-translation treatment technique. The disadvantage is that current technology only allows to treat the slices in a serial manner and large volumes may take a considerable time. Currently, similar to CT, spiral tomography is being developed.

Today, about 100 centers worldwide have IMRT capabilities with either using compensators, static or dynamic MLC or tomotherapy. However, the number of institutions with clinical IMRT programs is still limited. In our institute, we decided to start clinical studies with a step-and-shoot approach with a multileaf collimator in 1997.



Clinical Application of IMRT in Prostate Cancer

Treatment Planning

IMRT requires the same steps in preparation for treatment planning as 3D-CRT. Every step in the sequence of the treatment preparation and execution has to be optimized in order to achieve an optimal result.

Definition of the Target Volume and Critical Structures

The results of inverse treatment planning depend strongly on the shape of the target volume and the shape of the structures at risk. Therefore, it is crucial that the uncertainty of patient positioning and uncertainty in the definition of the different volumes is kept as low as possible. The disadvantage of a poorly defined target volume may not be overcome even by very sophisticated treatment-planning techniques. Figure 2 demonstrates the difference of two dose distributions in the same patient with tight and with wide safety margins. It is obvious that IMRT

is not capable of compensating for inadequate definitions of margins. And it is not possible to spare the rectum with inadequate margins.

Therefore, it is a necessity to image the target volume and the structures at risk properly. The definition of the prostate and the seminal vesicles is possible with sufficient accuracy on CT. There is some indication that MRI-based treatment planning may be able to increase the accuracy of target localization in prostate cancer patients and new methods such as MRS may allow a better definition of the macroscopic tumor volume.

Clinical Results

IMRT delivered with the step-and-shoot approach is routinely used in our clinic. The average length of the treatment sessions was 20 min and depends on the number of fields and number of intensity steps. This was also found by the Memorial Sloan-Kettering group. They reported an average treatment time of 18 min. Zelefsky et al. [19] note that the time to generate a treatment plan for 81 Gy to the prostate was even longer for forward planned radiotherapy than for IMRT.

In a recent paper the group at the Memorial Sloan-Kettering Cancer Center reported on the treatment of a stage T1c prostate cancer patient who planned part of his 3D-CRT course with an inverse planning algorithm that derived intensity-modulated beam profiles. When six such fields were combined isocentrically, the dose distribution and the DVH for the PTV indicated a significantly improved conformality and increased dose homogeneity than the plan produced by a conventional 3D-CRT technique [30]. The use of IMRT was motivated by the results of clinical studies that along with the improved local control with high-dose 3D-CRT, there was a higher incidence of late grade 2 rectal bleeding. More recently, Zelefsky et al. [31] updated the experience with IMRT in a large group of patients. Compared with conventional 3D-CRT, IMRT improved the coverage of the clinical target volume (CTV) by the prescription dose and reduced the volumes of the rectal and bladder walls carried to high-dose levels ($p < 0.01$), indicating improved conformality with IMRT. Acute and late urinary toxicities were not significantly different for the two methods. However, the combined rates of acute grade 1 and 2 rectal toxicities and the risk of late grade 2 rectal bleeding were significantly lower in the IMRT patients. The 2-year actuarial risk of grade 2 bleeding was 2% for IMRT and 10% for conventional 3D-CRT ($p < 0.001$). The authors have recently escalated the IMRT dose to 86.4 Gy and successfully treated 40 patients without an increase in acute toxicities [unpubl. data].

The urinary toxicity with IMRT was not reduced compared to the 3D-CRT. This finding may result from the parameters used in the inverse planning optimization program for the dose to the bladder wall. There is some indication that urinary symptoms from prostate radiotherapy may be associated with radiation-

induced damage to the urethra rather than the bladder [32]. It has been proposed that IMRT is capable of reducing the dose to the urethra. An example of such an approach is shown in figure 2. The dose to the urethra may be decrease by 20% with this technique. Whether IMRT can restrict the dose to the urethra without creating unacceptable cold spots in the PTV is unknown and has to be studied in future clinical trials.

Summary and Conclusions

Inverse planning and IMRT are methods with the potential to improve substantially clinical results in radiotherapy of prostate cancer. Available early clinical data demonstrate the feasibility and safety of high-dose IMRT for patients with localized prostate cancer and provide a proof-of-principle that this method improves dose conformality relative to tumor coverage and exposure to normal tissues.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 35–42

Radiotherapy after Radical Prostatectomy in Patients with Prostate-Specific Antigen Elevation

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Introduction

Prostate carcinoma is one of the most frequent malignant diseases affecting older men with increasing incidence. For clinical localized carcinomas without lymph node metastases, radiotherapy (RT) and radical prostatectomy (RP) represent two potentially curative, highly efficacious therapy options [3, 13, 16, 26]. After RP, which in the USA is routinely performed only for clinical stages T1–2, postoperative examination of T1/2a carcinomas revealed a pathologic stage T3/4 in up to 25% of the cases; this probability increases to over 40% in the case of a clinical T2b tumor [3]. In Germany, patients with clinical stage T3 carcinomas frequently undergo RP. In these patients, the probability of postoperative tumor growth beyond the organ is 70–80% due to considerable preoperative staging uncertainties [13]. Prostate-specific antigen (PSA) screening in the follow-up period has showed that in pathologic stage pT3a–b (capsular penetration, infiltration of the periprostatic adipose tissue and/or seminal vesicles) or pT4 (infiltration of adjacent organs) with or without positive margins, a PSA elevation out of the undetectable range can be expected within 3–5 years in 15–60% of the cases depending upon primary tumor extension [3, 14, 16].

In 35–54% of patients with PSA elevation after RP without a clinical correlate, vital tumor tissue was found by different examiners using punch biopsy from the urethrovesical anastomosis [11, 22]. There is no uniform urologic therapeutic concept for stage pT3/4 either with or without positive margins. Whereas some authors favor a wait-and-see strategy and possibly a delayed hormone therapy,

others advocate immediate hormone therapy [13, 26]. Adjuvant RT has been discussed as an alternative therapy, either once the PSA has increased out of the undetectable range [2, 24, 29] or in the case of punch-biopsy-proved local recurrence without distant metastases [23]. Technological developments over the past 10 years have led to significant improvements in radiooncology (especially three-dimensional treatment planning), which has made adjuvant RT increasingly attractive. Three-dimensional treatment planning can reduce acute as well as late side effects [5].

Percutaneous RT with Increasing PSA or with Persisting PSA after RP

The use of RT in cases of PSA elevation is problematic because it is simply not possible to primarily distinguish between local tumor progression and distant metastases. This is particularly the case when punch biopsies from the urethrovesical anastomosis are negative. Three studies have investigated the incidence of punch-biopsy-proved tumors in patients exhibiting either PSA elevation or 'persisting' PSA level after RP, in whom no radiologic evidence of local recurrence was found (including transrectal ultrasound). A tumor in the region of the anastomosis was revealed in 35–54% of the patients. Thus, the proportion of patients with a local tumor in the former prostate and seminal vesicle bed is probably even higher. These patients have a significantly higher risk of developing distant metastases and therefore have an unfavorable prognosis [11, 22, 23]. It is clear that the prevention of local recurrence, for example by adjuvant RT [20, 24] or by early therapy in the case of a small tumor volume, must be given the highest priority. On the one hand, there is the risk of overtreatment by irradiating patients who do not have a local tumor. This therapeutic concept is justifiable only if the rate of acute or serious side effects is low. On the other hand, a wait-and-see strategy makes little oncologic sense when the probability of local tumor growth is 40–50% [11, 22]. Whereas hormone therapy is palliative in nature (although frequently long term), percutaneous RT (for local tumor growth) seems to be a curative approach.

There has been an increase in the number of published studies on percutaneous RT for patients with PSA elevation out of the undetectable range or persisting PSA after RP (table 1), attesting to the importance of this clinical issue. The most critical questions are: In how many patients can an elevated PSA level after RP be reduced into the undetectable range by RT? And, in how many patients is the PSA level undetectable in the follow-up period? Probably only the latter patients have a curative chance. Also important is whether there are any predictive criteria for the probability of cure, because currently no data are available from randomized prospective studies.

Table 1. Patient series after RP with increase of PSA from the undetectable range or persistent PSA within the detectable range

Reference (first author)	Patients	PSA after RP undetectable	PSA after RP persistent	PSA after RT undetectable	PSA progression-free	Med. dose Gy	Follow-up (median) months
Cadeddu [3]	57	57		15/57 (26%) at least 2 years		50–75	40
Coetzee [5]	45	30			20/30 (67%)	66–70	40
			15		3/15 (20%)		11
Forman [7]	47				31/47 (64%)	(66)	36
Kaplan [9]	39				17/39 (44%)	60–70	25
Link [13]	25	13		10/13	7/13 (53%)		18
			12	5/12	1/12 (9%)		18
Morris [15]	48	18		12/18 (67%)	56%		30
			30	21/30 (70%)	40%		32
Pisansky [20]	166				PSA < 0.3; 46%	(64)	52
Schild [22]	27				59%	(64)	25
Wu [31]	53			16/53 (30%)	12/53 (23%)	(61.2)	15
			38		10/38 (26%)		

[1] In 7 cases PSA unknown.

Results of RT in Patients with PSA Elevation Out of the Undetectable Range or Persisting PSA after RP

A significant proportion of the increased PSA levels can be reduced into the undetectable range again by RT. The results vary between 30 and 70% depending on patient selection [4, 6, 14, 18, 28, 29] (table 1). The pooled data from six large studies show a PSA decrease into the undetectable range or below 0.2 ng/ml after RT in 133/239 patients (55%) [4, 6, 12, 14, 28]. The study groups under Coezee [5], Forman [7], Link [13], and Morris [1] obtained concurring results, showing 64–69% of the patients with PSA levels decreasing again into the undetectable range. Such considerable fluctuations between 30 and 70% attest to the critical role of patient selection, a factor that needs further research.

Several groups report 40–50% lasting stable PSA remissions also after median follow-up periods up to 60 months [4, 14, 16]. Other authors observed only 22–26% lasting complete remissions [2, 28] (table 1). The patient selection practiced by these two authors may have negatively influenced the results. Wu's group [31] reported on 53 patients, more than half of whom had persisting PSA levels after RP and a possibly worse prognosis. Cadeddu et al. [3] reported on the

Table 2. Influence of PSA before start of RT as indicator of treatment failure

Reference (first author)	Patients PSA undetectable after RT	PSA before RT, ng/ml	Patients PSA undetectable after RT	PSA before RT, ng/ml	PSA undetectable after RT, %	Follow-up (median) months
Forman [7]	24/29	<2	6/18	>2	83 vs. 33	36
Morris [15]		<1.7		>1.7	66 vs. 29	32
Schild [22]		<1.1		>1.1	78 vs. 18	25
Wu [31]	14/27	<2.5	2/26	>2.5	52 vs. 8	15

results of Walsh's group, a surgeon with outstanding experience. The local recurrence rate would be lower in patients treated by such a surgeon compared to a surgeon with less experience. Because patients from the entire USA and Europe are referred to him, they usually received irradiation therapy in their native cities, which involved the use of many different doses and techniques. Hence the results must be interpreted with caution [2].

The target volume of the RT is the prostatic bed using three-dimensional treatment planning. To minimize toxicity, the pelvic lymphatic drainage pathways are not irradiated [27]. The majority of authors favored a dose between 63 and 70 Gy, with a single dose of 1.8–2 Gy [26]. The best results (30/47 or 64% of patients in the undetectable range after a median of 36 months) were reported by Forman et al. [7]. In their study group the total dose was a median of 66 Gy (ranging to 70 Gy). In an additional 20% of the patients, the PSA levels decreased but not into the undetectable range. This level can remain stable for years. Whether these patients benefit from RT remains uncertain, but is rather unlikely.

Predictive Criteria for RT Response

The PSA value before beginning irradiation treatment is particularly significant: When it was <2.5 ng/ml, 52% (14/27) of patients attained the PSA undetectable range compared to 8% (2/26) with levels >2.5 ng/ml [28]. Comparable data were also reported by Forman et al. [7]: 24/29 (83%) of patients with a PSA level <2 ng/ml but only 6/18 (33%) with a level >2 ng/ml again attained the undetectable range again after RT. Similar results were reported by Morris et al. [15], who used the measure 1.6 ng/ml. The optimal PSA level before beginning irradiation treatment has not been definitively clarified (table 2). These data are strongly arguments against a 'wait-and-see strategy' while the PSA increases, because dur-

ing this time a local tumor, which possibly could be cured by a local treatment, can turn into a systemic progression. The PSA level should not exceed 2 ng/ml because then the rate of distant metastases significantly increases. The PSA level should be as low as possible before RT is starting.

Another factor to be clarified is whether a persisting PSA value, which postoperatively never decreases into the undetectable range, is equal in significance to a postoperative increase out of the undetectable range or whether it is a sign of systemic metastasizing, as some authors maintain [12, 28]. Current data support both the latter and the former views, but the relevant studies involve only small patient groups. Whereas Link et al. [13] observed a complete remission only in 9% (n = 12) of patients with persisting PSA, a complete remission occurred in 60% (n = 13) of patients with late elevation. Similar results were reported by Coetzee et al. [5]: 20% (n = 15) versus 80% (n = 30) of patients with late elevation out of the undetectable range. The study data from Carg and Morris contrast sharply with these. Among 67 patients with persisting PSA levels, 65% attained the undetectable range, precisely the same rate found among 59 patients with late elevation [14]. In view of these data, we do not feel that it is justified at this time to exclude patients from RT who exhibit persisting PSA after RP.

Relevant for patient selection is the time interval between RP and PSA elevation out of the undetectable range. When this period was less than 1 year, the rate of complete remission after RT was only 6% (1/16); it increased to 27% (12/44) and 44% if the interval was greater than 3 and 5 years, respectively [2]. Similar results were also reported by other authors [8, 9].

Various authors have also tried to localize tumor recurrence by analyzing the PSA doubling time. Whereas Partin et al. [17] concluded that a short doubling time (i.e., about 4 months) indicated distant metastases rather than local tumor growth, others could not confirm this observation [2].

To sum, there are currently no clear predictive criteria for implementing RT. However, the above-mentioned points can aid in making the best decision currently possible.

Acute and Late Side Effects

Of particular importance for a therapy without histologic confirmation is a justifiably low rate of side effects. As the literature data results attest, doses of RT up to 66.6 Gy given with three-dimensional treatment planning are rarely associated with serious long-term side effects of grade III/IV (according to the RTOG-EORTC grading system) in relation to the rectum and bladder, that is, with a probability of <3%. Syndikus's group [23] reported grade III/IV side effects in relation to bladder function; however, they did not distinguish between cystitis

and incontinence, and patients who only underwent RP also had a high rate of grade III side effects. Although total doses of 50–56 Gy were moderate, the median single dose was 2.76 Gy. This was possibly the reason for the increased rate of serious bladder side effects [20, 25]. When the postoperative RT was performed in a 3-dimensionally planned, 3- or 4-field-box technique with individual shaped fields to spare the bladder and rectum, RTOG grade I/II side effects occurred in up to 25% of the patients. They did not have a significantly negative impact on quality of life [26]. Formenti et al. [8] investigated the rate and degree of incontinence and impotence after nerve-sparing RP with or without adjuvant RT. Unfortunately, the follow-up examination comprised only a questionnaire, which has inherent weaknesses. No difference was found between 72 patients who underwent both RP and RT and 138 patients who underwent only RP when the total dose was 45–54 Gy. In a randomized study of 100 patients, after 24 months there was no difference in the number of completely continent patients between the group receiving 60 Gy and the group under observation [21]. In case material from the Mayo Clinic, the side effects in 60 adjuvant, postirradiated patients were not significantly different from those of 220 patients who did not receive adjuvant RT [26]. When the dose exceeded 70 Gy, however, the rate as well as the degree of side effects increased markedly [23, 24].

Conclusion

As a rule, RT can be offered to patients with PSA elevation out of the undetectable range or persisting PSA after RP as long as distant metastases have not been detected (bone scintigraphy). In 30–70% of these patients the PSA decreased into the undetectable range; in about 40–50% of these patients the PSA remained stable after 5 years. This patient group could have a curative chance with RT that otherwise would not exist. In any case, hormone therapy remains an alternative treatment for PSA elevation. Patients who appeared to benefit significantly from RT were those with PSA elevation more than 1 year after RP, those whose PSA level was <2 ng/ml before beginning RT, and those with a PSA doubling time of more than 6 months. Due to the limited data, patients who do not fall into one of these categories cannot justifiably be excluded from RT until the results of randomized studies are available. The rate of serious side effects is low, therefore confirming the suitability of this approach. It is imperative that the patient is precisely informed beforehand and understands that he is agreeing to a therapy that is not beneficial in 30–50% of the cases. At this time RT appears to be the only curative chance for this patient group.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 43–48

Is Radiotherapy of Pelvic Lymph Nodes Successful in Prostate Cancer?

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Introduction

Approximately 30% of patients with prostate cancer primarily present with locoregional lymph node involvement. Many physicians consider positive lymph nodes to be unequivocal evidence of systemic disease and have advocated deferred or palliative treatment. Either surgery or radiotherapy are locally restricted treatment strategies. It is likely that the majority of prostate cancer patients with positive lymph nodes also have occult distant metastases. Therefore, from a surgical viewpoint, lymphadenectomy prior to radical prostatectomy is regarded as a pure staging procedure with no curative effect. Compared to surgery, radiotherapy offers an either additional treatment option to increase surgical safety margins or a single treatment modality with larger treatment volumes. Recent reports with local conformal radiotherapy limited to the prostate gland with irradiation doses of >70 Gy stated high biochemical tumor control rates [1]. In multivariate analyses a strong overall effect of dose on the biochemically disease-free survival was seen. On the other hand, late gastrointestinal toxicity after pelvic irradiation correlated to a dose of >50 Gy and to the organ-specific dose-volume load. In a retrospective dosimetric analysis, treatment plans were reconstructed after conformal radiotherapy for prostate cancer in long-term follow-up patients [2]. Late rectal bleeding correlated to a greater fractional rectal volume exposed to high doses (70.2 or 75.6 Gy). Late small bowel toxicity was studied in 218 patients with prostate cancer treated by primary radiotherapy [3]. The total actuarial complication rate after 5 years for all grades was 24% and for severe complications 1.8%. Among treatment-related risk factors, only the irradiation of the whole pelvis, compared to the prostate gland alone, showed a significant correlation to late

gastrointestinal toxicity. What is at least the role of radiotherapy in the treatment of nodal disease located along the iliac or periaortic vessels? Considering the effect of tumor volume on treatment efficacy in radiation treatment, published data should be reviewed separately for either suspected, biopsy-proven or macroscopically evident lymph node disease.

Review of the Literature

Treatment of Suspected Lymph Node Disease in Prostate Cancer

From 1976 to 1983 the RTOG conducted the only two actually published large phase III trials of extended field irradiation in case of suspected nodal disease. The first RTOG 75-06 trial was designed to test the value of elective periaortic irradiation in patients with tumor extension beyond the gland but limited to the pelvis [4]. A total of 448 eligible patients with either a stage C or a stage A2/B carcinoma with evidence of pelvic lymph node disease were included in the analysis. After a median follow-up of 4.3 years, no statistical difference in overall or disease-free survival was observed. Compared with the effect of delayed hormonal therapy, there is no indication for elective treatment of the periaortic region in patients with positive pelvic nodes. RTOG 77-06 was designed to test the value of elective pelvic irradiation in patients without evidence of spread beyond the prostate [5]. Between 1978 and 1983 a total of 449 patients entered the trial. No better survival nor an improved cause-specific survival was found. Several bugs in the trial (dose, treatment volume, surgical staging [6–9]) led to several sub-analyses and, based on re-analysis, it was concluded that this trial was unable to answer the question.

A four-arm prospective randomized RTOG trial (94-13) was designed to determine the effect of whole pelvic irradiation and total androgen suppressive hormone therapy on outcome in patients at high risk for nodal disease. Patients whose calculated risk of lymph node involvement was greater than 15% were enrolled and randomized. The risk calculation was based on nomograms which considered the initial PSA value, the Gleason score and stage of disease. This trial is closed. Published data should be awaited. To evaluate the risk calculation model, which forms the basis of this RTOG trial, a retrospective analysis was performed at the University of California in 1998 [10]. A total of 201 patients were defined as being at high risk for lymph node involvement. 117 had whole pelvic irradiation and 84 had prostate irradiation alone. High-risk patients who received whole pelvic irradiation had a significantly improved median freedom from PSA failure time (34.3 vs. 21 months). Multivariate analyses revealed the type of irradiation being the most significant independent predictor of outcome for this patient group.

Treatment of Biopsy-Proven Lymph Node Disease in Prostate Cancer

A number of older reports describing the effect of treatment on patients with biopsy-proven positive nodes are based on clinical endpoints and cannot be used with confidence in the PSA era (since 1985). But it has been suggested that the extent of pelvic lymph node disease found at pelvic lymph node dissection (PLND) may be useful in determining which patients are likely to have a benefit from either radical surgery and/or additional radiotherapy. Smith et al. [11] evaluated 73 prostate cancer patients with pelvic nodal metastases found at PLND. Patients with only one positive node had a superior 5-year progression-free survival (44%) than either those patients with multiple microscopically positive nodes (27%) or with grossly positive nodes (15%). Kramer et al. [12] stated that the time to failure was longer in patients with one positive node than in those with more extensive nodal disease (21.5 vs. 13.7 months). The impact of minimal lymph node disease – micrometastasis < 5 mm in one unilateral lymph node – was prospectively evaluated by Schmid et al. [13] on a series of 132 consecutive patients. All patients had additional radiotherapy after PLND. Patients with only minimal lymph node disease had a disease-free survival similar to lymph node-negative patients.

A sub-analysis of the RTOG 75-06 trial, published in 1998, covered 90 long-term follow-up patients with biopsy-proven pelvic lymph node disease [14]. At 10 years, 29% of them were alive and only 7% had clinically no evidence of disease. Biochemical evidence of no disease was obtained in 2 of the 5 long-term survivors. In the limited sample, 2 of 39 patients with 1–2 positive lymph nodes and none of the 25 patients with more than 2 nodes were cured.

At a time when many physicians have been convinced that therapies directed against lymph node disease are only palliative, the re-analysis of the RTOG 75-06 trial presented new evidence that 7.4% of patients with biopsy-proven lymph node disease remained free of disease at 10 years. Advocates of nodal treatment were confirmed in their hypothesis that a population of patients who have modest amounts of nodal metastatic disease could benefit from effective regional therapies.

Further reports included hormonal management as combined modality treatment. Based on the idea of spatial cooperation and direct interaction, simultaneous hormonal therapy may be able to either decrease the distant metastases rate and increase the local effectiveness of irradiation.

Several single institutions' retrospective reviews described surprisingly favorable data. Wiegel and Bressel [15] reported in 1994 disease-free survivals of 83% at 5 years and 63% at 10 years for patients with microscopic nodal involvement. Sands et al. [16] reported in 1995 a 100% PSA-free serum level at 4 years. Either patient number (27 patients) and median follow-up was limited (25 months). Whittington et al. [17] analyzed the data of 66 patients. The overall

survival at 5 and 8 years was 94 and 84%, the clinical disease-free survival was 85 and 67% and the biochemical disease-free survival was 78 and 47%.

A national prospective randomized trial of standard external beam irradiation plus immediate androgen suppression versus external beam irradiation alone was initiated in 1985 by the RTOG (85-31) [18]. Those patients with radiotherapy alone had hormonal therapy at the time of biochemical relapse. A total of 173 patients with biopsy-proven lymph node disease were included. The biochemically disease-free survival after 5 years was significantly improved by combined treatment (55 vs. 11%). Estimated disease-specific survival at 5 years was 82% for the radiation and immediate hormonal therapy group and 77% for the radiation-alone group.

Conclusion

In the modern era of prostate cancer treatment, open or laparoscopic lymphadenectomy is able to detect nodal involvement and allows for stratification into curative or palliative treatment intent. The use of PSA serum levels makes data analysis of disease-free status more reproducible. Considering published data, there is no decisive answer to clear the role of radiotherapy in suspected or proven regional lymph node involvement from prostate cancer.

There is a subgroup of patients who will benefit from elective pelvic lymph node irradiation. What is the amount of regional lymph node disease which separates between curative and palliative treatment? Published data from mono-institutional experience could demonstrate that patients with minimal lymph node involvement had the same chance for cure than patients with negative lymph node disease. Furthermore, patients had a benefit from using extended radiotherapy portals if the risk of lymph node involvement exceeded a certain risk level. Is it a 10, 15 or 20% risk level? Nomograms help to estimate the risk of nodal metastases in individual clinical presentation of prostate cancer. Partin et al. [19] published in 1993 nomograms, obtained from mono-institutional experience, where 11% of the patients had pathologically identified lymph node metastases. In 1997, Partin et al. [20] compiled clinical and pathological data from three major centers and again generated nomograms that predict pathological staging at prostatectomy. In this compiled multi-institutional study, obtained with 12 surgeons, the incidence of lymph node metastases was 5%. For patients with the same pretreatment criteria the newer nomograms predicted much lower probabilities of lymph node involvement than the earlier nomograms. This may reflect different scoring techniques, for example in detecting capsular penetration or seminal vesicle involvement. But at least differences in the total number of removed lymph nodes either by open or laparoscopic lymphadenectomy and the quality of patho-

logical examination of the specimen preclude a decisive assessment of the clinical evidence of suspected lymph node disease.

Patients with proven regional lymph node disease should be considered for a combined treatment approach. Looking on both the dose-effect relation and the dose-volume effect in radiation therapy, additional hormonal therapy improved the efficacy in term of local control and distant metastases rate. The increased amount of clonogenic tumor cells needs higher doses or the simultaneous use of radiation sensitizer while at the same time the increased risk for distant metastases needs systemic treatment. Published data from mono- and multi-institutional trials are encouraging.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 49–65

Hormone Therapy in Advanced Prostate Cancer

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Introduction

In 1941, Huggins and Hodges [1, 2] showed that elevated levels of serum acid and alkaline phosphatase in prostate cancer patients decreased after castration and estrogen therapy. This decrease was associated with an improvement of cancer complaints. Since this pioneering work, which was honored with the Nobel Prize in 1966, antiandrogen therapy has been established as the therapy of choice in advanced prostate cancer. However, since that time surprisingly little progress has been achieved in the hormonal manipulation of tumor cells. It is only recently that new treatment modalities have been investigated.

Male androgens are mainly produced by the Leydig cells of the testis (90–95% of all testosterone produced). A minor proportion derives from metabolization of adrenal androgens (5–10%). The androgen production is under a negative feedback control via hypothalamus and hypophysis.

As prostate and prostate cancer cells are androgen-dependent, androgen deprivation leads to a reduction of tumor volume of 30–40% [3]. Tumor-related pain can be ameliorated, obstructive micturition problems improve [4] and the power as well as the sense of well-being can be positively influenced [5, 6].

Although some cures have been reported [7, 8], antiandrogen therapy is a palliative therapy. It is the therapy of choice in advanced prostate cancer. However, the duration of the response is limited. In patients having metastatic disease, time to clinical progression varied between 18 and 24 months. The progression is thought to be due to the growth of a subpopulation of tumor cells which are hormone-independent. Death occurs on average in 30–36 months [9]. To improve

Table 1. Hormone-ablative therapy of prostate cancer: surgery and medications

Surgical castration
Orchiectomy
Subcapsular orchiectomy
Medical castration
Estrogens
Diethylstilbestrol p.o.
Polyestradiol phosphate s.c.
Luteinizing hormone-releasing hormone antagonists (LHRH antagonists)
Luteinizing hormone-releasing hormone analogues (LHRH analogues)
Buserelin
Leuprorelin
Goserelin
Antiandrogens
Pure antiandrogens
Flutamide
Nilutamide
Biclutamide
Steroidal antiandrogens
Cyproterone acetate
Megestrol acetate

antiandrogen therapy, the following aspects are still being investigated. Which is the best androgen deprivation therapy? When to start antiandrogen therapy? Is monotherapy or combination therapy better? Is a continuous therapy necessary or is an intermittent treatment also effective? Which role does neoadjuvant hormone therapy play preceding radiation and operation? Is there a place for adjuvant hormone therapy after operation or radiation?

In this article, various aspects of hormone therapy will be addressed. Different therapeutic options for antiandrogen therapy exist (table 1).

Monotherapy

Orchiectomy

Bilateral orchiectomy was introduced in clinical practice by Huggins and Hodges [2] in 1941. One year later, Riba [10] proposed the bilateral subcapsular orchiectomy removing only the endocrine active tissue and not leaving behind an empty scrotum for cosmetic reasons. Both techniques are equally effective in

reducing testosterone levels [11]. They both lower serum testosterone levels to 5–10% (0.2 ng/ml) of the precastration level [12]. The main side effects of castration are loss of libido and erectile function, as well as hot flushes. Surgical complications as hematoma and infection are rare. Orchiectomy is the least expensive long-term therapy and independent of patient's compliance. However, it is irreversible and by many patients not accepted for psychological reasons. Having the choice between operation and medical treatment, the majority of patients will prefer initially the medication because it is less invasive and not mutilating [13].

Estrogens

Dose-dependently, estrogens suppress luteinizing hormone-releasing hormone (LHRH) secretion of the hypophysis. Gonadotropin and testosterone secretion decrease to castration levels [12, 13]. The VACURG studies showed diethylstilbestrol (DES) to be an effective medical castration with no differences in terms of progression and survival as compared to orchiectomy [14]. In higher doses (3–5 mg/day) DES causes serious cardiovascular side effects including myocardial infarction, stroke and thromboembolism. Lower doses (0.2–1 mg/day) are not able to suppress testosterone completely and the progression-free survival and overall survival is not as good as in orchiectomy [6, 14]. Similar results are found for polyestradiol phosphate, a parenteral estrogen. 160 mg/month of polyestradiol phosphate was less effective than surgical castration and a dosage of 240 mg/month was as powerful as medical castration (LHRH analogue) but causes more cardiovascular side effects [15, 16].

Luteinizing Hormone-Releasing Hormone Analogues

LHRH analogues cause overstimulation of the hypophysis. After an initial increased release of gonadotropin the luteinizing hormone secretion ceases and the testosterone level falls to castration level. There was no difference in survival and progression rate between LHRH and surgical castration; side effects are comparable as well [17–19]. The stimulated testosterone production in the first 2–3 weeks can lead to an accelerated tumor growth with increased PSA levels (flare phenomenon). Especially in symptomatic patients with an advanced metastasizing tumor this can cause an exacerbation of symptoms (clinical flare), trigger complications and lead to death [20]. Biochemical and clinical flare can be prevented by adding an antiandrogen one week prior or at the time when LHRH medication starts [21, 22].

Antiandrogens

Antiandrogens block the testosterone receptor and have no intrinsic activity. There are two different types, namely pure antiandrogens and steroidal antiandrogens.

Steroidal antiandrogens suppress LHRH and gonadotropin secretion. Testosterone decreases gradually. Today only cyproterone acetate plays a part in antiandrogen therapy of the prostate. Its efficacy was shown in randomized studies against DES [23]. A comparison study between cyproterone acetate and orchiectomy has not been published. Loss of libido and erectile function are the most important side effects of cyproterone acetate therapy. Hepatotoxicity and cardiovascular events are also rarely reported, especially when using higher doses [24].

Pure antiandrogens also block the testosterone action on receptors in the central nervous system and block the negative feedback mechanism of testosterone on hypothalamus and hypophysis. This leads to elevated levels of gonadotropins and testosterone in the circulating blood. Libido and erectile function are usually not affected. An additional side effect, probably due to elevated estrogen levels, is gynecomastia in 40% of patients. Often patients also suffer from nausea, vomiting and diarrhea. Different medicaments have been well investigated, such as flutamide, nilutamide and biclutamide – the latter causes few side effects compared to the other two [24, 25].

Orchiectomy, LHRH agonists and estrogens are equivalently effective in preventing progression and survival. Estrogen therapy is not first choice because of possible cardiovascular side effects. The monotherapy with antiandrogens is effective in treatment of advanced prostate cancer. Whether it is of the same therapeutic value as orchiectomy or LHRH therapy in terms of survival has to be proven in the future. Biclutamide monotherapy with 150 mg/day and higher doses is currently being investigated. Preliminary results indicate similar efficacy in patients without metastatic disease [26] and significant health-related quality-of-life advantages compared to orchiectomy [27] (table 2).

Combined or Maximal Androgen Blockade

Surgical castration and medical castration with an LHRH agonist block the testosterone production of Leydig cells. Nevertheless, low serum testosterone levels are still detectable. This remaining testosterone is derived from the adrenal androgens. In 1983, Labrie et al. [35] proposed that an additional antiandrogen therapy could improve the prognosis of advanced prostate cancer. This concept is called combined or maximal or total androgen blockade (MAB). The issue of MAB is still controversially discussed in the literature. However, most of the studies conducted failed to show a survival benefit for MAB. This fact is strongly supported by a meta-analysis of 25 MAB studies by The Prostate Cancer Trialists' Collaborative Group (5,710 patients with a median follow-up of 40 months), which could not find any difference in survival compared to either medical or

Table 2. Comparison of different monotherapies (a = advanced prostate cancer; M1 = metastasized prostate cancer)

Reference	n	Medicaments tested	Results/conclusions
Soloway, 1991 [28]	164 M1	Orchiectomy LHRH agonist (goserelin)	No differences in terms of time to treatment failure or time to disease progression
Waymont, 1992 [29]	250 a+M1	DES LHRH agonist (goserelin)	No difference in terms of time to treatment failure and survival; DES should no longer be used
Robinson, 1995 [30]	328 M1	Orchiectomy DES 1 mg/day orchiectomy + cyproterone acetate	No difference in time to metastatic progression and overall survival between the treatment arms; more cardiovascular deaths in the DES group
Boccon-Gibod, 1997 [31]	104 M1	Flutamide 250 mg t.i.d. Orchiectomy	No differences in terms of progression-free survival or survival
Chang, 1996 [32]	92 M1	Flutamide 250 mg t.i.d. DES 1 mg tid	No differences in terms of overall response rate but significantly longer time to treatment failure and longer survival for DES
Bales, 1996 [33]	586 a	Bicalutamide 50 mg/day Castration (orchiectomy or LHRH)	Bicalutamide monotherapy at 50 mg/day appears inferior to castration in overall objective and subjective response rates
Iversen, 1998 [26]	480 a	Biclutamide 150 mg/day Orchiectomy	Similar survival outcome; significant benefits with respect to sexual interest and physical capacity for biclutamide
Tyrell, 1998 [34]	1453 a+M1	Biclutamide 150 mg/day Orchiectomy	Biclutamide is less effective than castration in patients with M1 disease but shows a benefit in terms of quality of life and subjective response (no conclusive data on M0 disease)
Pavone-Macaluso, 1986 [23]	210 a+M1	Cyproterone acetate 250 mg/day DES 1 mg t.i.d. Medroxyprogesterone acetate 100 mg b.i.d.	No differences in terms of progression-free survival or survival between cyproterone acetate and DES; more cardiovascular side effects in the DES group; shorter survival time in the medroxyprogesterone group
Mikkola, 1998 [15]	444 a+M1	Polyestradiol phosphate (240 mg/month) Orchiectomy	No difference in inhibiting disease in patients with advanced prostatic cancer (T3–4 M0 and T1–4 M1); there were more cardiovascular complications in polyestradiol patients
Lukkarinen, 1998 [16]	236 a+M1	Polyestradiol phosphate (240 mg/month) LHRH agonist (goserelin)	In locally advanced (M0) and histologically well- or moderately-differentiated tumors, LHRH agonist therapy was considerably more effective than estrogen as regards time to progression of the carcinoma; in metastatic (M1) and histologically poorly-differentiated tumors both methods gave similar results

surgical castration alone [36]. Clinically important parameters such as symptom relief and length of symptom-free survival were not analyzed. Another meta-analysis summarizing seven studies with a total of 1,056 patients compared orchiectomy with and without nilutamide indicated an advantage for MAB in terms of pain relief, tumor markers and time to progression. An improved survival could not be shown [37]. A comparison between orchiectomy with and without flutamide in 1,387 metastatic prostate cancer patients by Eisenberger et al. [38] in 1998 showed no survival difference.

Three studies reported a survival benefit for MAB. The SWOG Intergroup Study 0036, which compared LHRH with and without leuprolide in metastatic prostate cancer, showed a significant survival benefit for the MAB group. The median survival was 35.01 months in MAB patients compared to 27.9 months ($p = 0.039$) in patients treated only with the LHRH agonist [39]. This study has been criticized because the flare phenomenon, which was not inhibited by a antiandrogen, could have influenced the results in the LHRH group. A subgroup analysis revealed that survival benefit was limited to patients with favorable prognosis (good performance and minimal disease) [40]. But 5-year survival curves seemed too narrow (a p value was not published) [41]. The EORTC Protocol 30853 reported a survival benefit of 7 months for the MAB group treated with goserelin and flutamide [41, 42]. In this study an increased proportion of patients with a more favorable prognosis may have been included in the MAP group. Dijkmann et al. [43], who tested the same medications as Bertagna et al. [37] in their meta-analysis, found a significant improvement of survival for MAB over orchiectomy alone.

Currently, there appears no justification for long-term use of MAB in advanced prostate cancer on a routine basis. Nevertheless, there may be patients who benefit from this regime. To prevent the flare phenomenon, short-term androgen therapy should be prescribed at the beginning of an LHRH therapy (table 3).

Early versus Deferred Therapy

The indication for hormone-ablative therapy in symptomatic advanced prostate cancer was established almost 60 years ago. Because the efficacy of hormonal therapy is of limited duration, the time when to start this therapy in asymptomatic patients was an object of debate for a long time. The first analysis of VACURG studies [5, 14], which compared early vs. delayed DES therapy, did not find any survival benefit for the immediately treated patients. A retrospective study comparing survival of advanced prostate carcinoma patients before (1937–1940) and after (1942–1943) hormonal therapy was introduced indicated no differences

Table 3. Comparison between monotherapy and combined antiandrogen therapy (a = advanced prostate cancer; M1 = metastasized prostate cancer)

Reference	n	Medicaments tested	Results/conclusions
Crawford, 1989, 1990, 1992 [39–41] (SWOG 0036)	602 M1	LHRH agonist leuprolide LHRH agonist leuprolide + flutamide	Significant difference in time to progression (+2.6 months) and median survival (+7.3 months) in favor of the MAB group
Denis, 1993, 1998 [42, 44] EORTC 30853	327 M1	LHRH agonist goserelin LHRH agonist goserelin + flutamide	Significant difference of median survival (27.1 vs. 34.4 months) in favor of the MAB group
Bertagna, 1994 [37] Meta-analysis	1056 M1	Orchiectomy + nitulamide Orchiectomy + placebo	The combination of nilutamide and orchidectomy has a beneficial effect on pain of metastatic origin, levels of tumor markers, the objective response of disease and the time to disease progression; no difference in survival
Dijkman, 1997 [43]	457 a	Orchiectomy + nitulamide Orchiectomy	With long-term follow-up of patients with advanced prostate cancer, the combination of nilutamide and orchiectomy has significant benefits in interval to progression and improved survival compared to orchiectomy and placebo
Robinson, 1995 [30] EORTC 30805	328 M1	Orchiectomy vs. DES 1 mg/day vs. Cyproterone acetate 150 mg/day	No differences in progression rates and overall survival
Boccardo, 1997 [45]	220 a+M1	Biclutamide 150 mg Goserelin + flutamide	No differences in terms of progression-free survival or survival
Eisenberger, 1998 [38]	1378 M1	Orchiectomy + flutamide Orchiectomy	No differences in terms of survival

[46]. Based on these results, deferred hormonal therapy was the therapy of first choice for a long time. The side effects of hormonal therapy were delayed for several months, while tumor progression was possible and not considered a great danger.

A critical re-evaluation of the VACRUG data by Sarosdy [47] in 1990 considering the larger proportion of cardiovascular death in immediately treated patients revealed a tumor-specific death rate of 3% for early treated patients vs. 8.4% for patients with deferred treatment.

From 1985 until 1993, 938 patients with locally advanced or asymptomatic metastasized prostate cancer were randomized for immediate (n = 469) vs. deferred hormonal therapy (n = 465; orchiectomy or LHRH analogue) by the Medi-

cal Research Council Prostate Cancer Working Party Investigator Group. The median time to deferred treatment was 9 months in metastasized disease and 27 months in localized disease. Tumor-associated complications were significantly more frequent in the deferred group: pathological fractures 11 vs. 21, spinal cord compression 9 vs. 23, ureteric obstruction 33 vs. 55 and extraskeletal metastases 37 vs. 55 patients, respectively. Although not significant, these complications seemed to be most frequent in metastatic disease. 141 of deferred patients compared to 65 of the immediately treated men needed a TURP during follow-up ($p < 0.005$). The tumor-specific survival after 5 and 10 years was significantly better in the immediate-therapy group: 150 vs. 136 patients and 11 vs. 5 patients, respectively. This difference was found in the entire study population and in patients without metastatic disease, but not in patients having metastases [48].

In 1999, Messing et al. [49] published a prospective randomized study on immediate vs. deferred hormonal therapy (orchiectomy or LHRH analogue) in 98 nodal-positive patients after radical prostatectomy. After a median follow-up of 7.1 years, a significantly lower death rate in favor of the immediate treatment (14.9 vs. 35.3%) was found.

Patients with a small tumor load and/or without metastatic disease seem to benefit from an immediate hormonal treatment in terms of survival. In metastatic disease no survival benefit has been proven yet, but it is evident that tumor-specific complications of metastatic prostate cancer can be positively influenced by immediate hormonal treatment.

Intermittent versus Continuous Androgen Deprivation

Androgen deprivation induces programmed cell death (apoptosis) of the androgen-dependent prostate carcinoma cells and subsequently causes a reduction of tumor volume of 30–40% in 60–80% of patients [3, 50]. At the same time, androgen deprivation exerts pressure on prostate cancer cells to become hormone-independent [51]. Moreover, hormone-insensitive cells may overgrow the hormone-sensitive cell population. The rationale for intermittent androgen deprivation is the assumption that apoptosis occurs faster than the selection of androgen-independent tumor cells.

The Shionogi tumor of the mouse is an experimental model for prostate carcinoma. Androgen deprivation lets the tumor shrink. After some days the tumor becomes hormone-resistant resulting in new tumor growth. Intermittent hormone therapy was simulated by castration, transplantation of the shrunk tumor into a second mouse and castration of this animal after tumor growth. With this procedure, time to hormone resistance was significantly longer (147 days instead of 51 days as compared to a single castration) [52].

Preliminary clinical studies indicated that intermittent estrogen therapy [53] and intermittent combined androgen blockade [52, 54, 55] can cause repeated tumor regression after hormonal therapy was stopped. In the therapy-free interval, patients reported improved sense of well-being and a recovery of libido. In men having normal erections before treatment, erectile function recovered in 90% within 3 months [53]. The mean duration of one cycle varied between 21 (first cycle) and 13 (fourth cycle) months and decreased with the number of cycles. The proportion of therapy-free time was between 40 and 48% of the follow-up time [54]. Patients with a small tumor load (pT1b, PSA relapse after radical prostatectomy and/or radiation) were found to have a therapy-free time of up to 58% [56]. In the same study no development of hormone resistance was seen during a follow-up of at least 2.5 years [56]. The following independent parameters are associated with a prolonged therapy-free interval: undetectable PSA during 1 year under hormone deprivation, isolated PSA relapse after curative treatment and normalized testosterone serum levels (>150 ng/dl) 4 weeks after therapy has ceased [57]. Patients with localized prostate cancer and patients with PSA relapse without clinically detectable disease have a better prognosis under intermittent hormone-ablative therapy than these on continuous treatment [58, 59].

A decrease of PSA into the normal range (<4 ng/ml) under hormonal deprivation therapy is also related with a superior outcome than a PSA remaining >4 ng/ml. The median survival time was 40 vs. 18 months [54, 60]. A favorable response to the initial hormonal treatment seems to be an important condition for the intermittent hormonal therapy. The therapy pause can be initiated after the stable normalization of PSA after 24–36 weeks. Therapy should be resumed when PSA has increased to 10–20 ng/ml [54, 58].

Advanced prostate cancer can be treated by intermittent hormonal therapy, although efficacy has not yet been proven in prospective studies. Side effects are reversible during therapy pauses, thus leading to an increased quality of life. Costs of this therapy modality are lower. Whether intermittent hormone-ablative therapy can improve the progression-free survival or the overall survival is not clear yet and must be proven by prospective randomized trials.

Adjuvant and Neoadjuvant Hormonal Therapy in Advanced Prostate Cancer

Adjuvant Hormonal Therapy following Radical Prostatectomy

A great number of patients with early-stage prostate cancer develop local or systemic progression and/or die from the disease despite receiving therapies with primary curative intent. Identification of high-risk patients and additional therapeutic options (e.g. adjuvant hormonal or radiotherapy) is therefore necessary.

The most commonly cited predictors of disease progression after radical prostatectomy have been the presence of high-grade disease (Gleason score ≥ 8), capsular perforation, positive margins [61], seminal vesicle invasion, lymph node metastases and a detectable postoperative PSA.

First experiences with adjuvant hormonal therapy (DES) for patients with prostate cancer were reported in a Veterans Administration study in 1967 [14]. This therapy did not find further application because of the excessive mortality due to cardiovascular side effects. Recent retrospective studies using other forms of hormone therapy for patients with node-positive disease report that there may be a benefit in terms of tumor-specific and overall survival for early hormonal therapy in such patients [62–64].

In a randomized prospective study, Messing et al. [49] have reported that an immediate antiandrogen therapy after radical prostatectomy and pelvic lymphadenectomy, in patients with node-positive prostate cancer, improves survival and reduces the risk of recurrence. In this study, 98 men who underwent radical prostatectomy and pelvic lymphadenectomy with positive lymph nodes were randomly assigned to receive immediate antiandrogen or to be followed until disease progression. After a median follow-up of 7.1 years, 3 of 47 men who received immediate antiandrogen therapy and 16 of 51 men ($p < 0.01$). In the observation group had died because of prostate cancer. Moreover, at the time of the last follow-up, 36 men in the immediate treatment group (77%) and 9 men in the observation group (18%) were alive and had no evidence of recurrence and no detectable serum PSA ($p > 0.001$).

The role of adjuvant hormonal therapy in patients with a extracapsular extension at surgery is at the moment not clear. However, an interim analysis of an open, randomized controlled trial of adjuvant flutamide 250 mg t.i.d. has shown a significantly improved progression-free survival at 4 years in the antiandrogen-treated group (90 vs. 69%; $p = 0.0029$) [65]. At the Mayo Clinic a series of 2,423 radical prostatectomy patients with a pT3 stage PCa were treated with an adjuvant antiandrogen therapy. They had an event-free 15-year survival of 77.3% [66]. Although an adjuvant therapy seems to be a valuable approach for pT3pN0pM0 prostate cancer, other parameters as quality of life, duration of therapy and toxicity have still to be assessed.

Adjuvant Hormonal Treatment following Radiation Therapy

The studies by Bagshaw et al. [67] and Hanks et al. [68] have shown that the long-term results of external beam irradiation alone for local advanced PCa were not satisfying due to the high risk of local relapse and/or distant metastasis. Since then the role of adjuvant hormonal therapy has been subject of several studies and there is now increasing evidence of a benefit in terms of both disease-free survival and overall survival.

In the RTOG (Radiation Therapy Oncology Group) 85-31 Trial [69], 977 men with clinical or pathological stage T3 or T4 M0 PCa with or without lymph node involvement were randomized between prostate and pelvic irradiation with either adjuvant LHRH analogues beginning the last week of radiation therapy or started at relapse. With a follow-up of 4.5 years there was a significant reduction in clinical local failure of disease, from 32% on radiotherapy alone to 17% with LHRH analogue treatment ($p < 0.001$), improvement of biochemical control of disease from 17 to 49% ($p < 0.001$), reduction of distant metastases from 29 to 19% ($p < 0.001$) and a statistically not significant improvement of 5% in survival. In the EORTC (European Organisation for Research and Treatment of Cancer) 22863 Trial [70], 415 patients with poorly differentiated T1/T2 disease or T3/T4 tumor were included. Patients were randomized to receive radiotherapy with an LHRH analogue or pelvic radiotherapy alone. Hormonal treatment consisted of oral cyproterone acetate 50 mg t.i.d. for 1 month started a week prior to radiotherapy and s.c. injection of an LHRH agonist every 4 weeks for 3 years. 401 patients were evaluable and the median follow-up was 45 months. A significant difference was observed in overall survival, 79% in favor of the combined treatment versus 62% for radiotherapy alone ($p < 0.001$) and in relapse-free survival 85 vs. 48% ($p < 0.001$). Local recurrence-free survival was 97 vs. 77% ($p < 0.001$), survival without clinical or biochemical evidence of relapse 81 vs. 43% ($p < 0.001$) and metastasis-free survival was 98 vs. 56% ($p < 0.001$). The Medical Research Council has reported results of a three-arm study comparing radiotherapy, orchiectomy and combined modality treatment radiotherapy with orchiectomy [71]. 277 patients were randomized and results show a significant lengthening of time for the development of metastases in the orchiectomy group. Moreover, there was a gain in local control and survival, with about 10% improvement (without statistical significance) in overall survival in the combined orchiectomy and radiotherapy group. Although further prospective trials with a longer follow-up assessing of quality of life as well as disease-related endpoints are needed, the use of adjuvant hormonal therapy must be considered in the future in clinical practice.

Neoadjuvant Hormonal Treatment Prior to Radical Prostatectomy

Since the development of reversible androgen deprivation, its use for a short period of time before radical prostatectomy has been advocated by many urologists without clear and definitive proof of its advantage. Most authors report a reduction of 30–50% of the prostate size; the reduction is less pronounced with hormonal monotherapy than with maximal androgen blockade [3, 72]. The influence of neoadjuvant hormonal therapy on the operability is controversial. Some authors have suggested that through the observed decrease in size, surgery would be facilitated. However, most authors have not found any clear advantage of such therapy [73]. It has also been suggested that the longer patients received

hormonal therapy prior to surgery, the more fibrosis was observed around the prostate. Clinical downstaging has been mentioned in several studies but has not been confirmed on pathological examination in the majority of cases [72, 74]. In a European multicentric prospective randomized study, pT2 tumors were statistically more significant in the neoadjuvant group than in the group without neoadjuvant therapy (48 vs. 24%, $p < 0.01$) [75]. In contrast, for clinical T3 tumors there was no statistically significant difference between both groups with respect to the final pathological stage [76]. Trachtenberg [76] pointed out that in recent series there was no significant downstaging in patients with clinical T3 disease. The major diagnostic difficulty is associated with the interpretation of specimens after hormonal treatment, indeed apparent pathological downstaging could be the result of histological changes in tumor cells making them difficult to recognize as persisting cancer cells. Another controversial aspect of neoadjuvant therapy is the effect on tumor grade. Downgrading has been described by several authors, in contrast other authors did not observe downgrading at all and paradoxically upgrading has also been reported. The only clear consensus upon effect of neoadjuvant therapy before radical prostatectomy is the reduction in the rate of positive margins in clinical T2 tumors in 20–50% of radical prostatectomy specimens. In patients with clinical T3 tumors, the effect of neoadjuvant hormone therapy on positive surgical margins is less clear.

Definitive conclusions about the merits of neoadjuvant hormonal therapy prior to radical prostatectomy will have to wait until large-scale randomized controlled prospective studies provide relevant data on timing and type of therapy, on clinical progression and disease-free survival.

Neoadjuvant Hormonal Therapy Prior to Radiotherapy

The absence of overlapping toxicity, the high response rates to androgen suppression and the facility with which the prostate is included in radiotherapy portals makes the prostate an ideal site for chemoradiation. Since radiation and hormonally mediated apoptosis appear to be induced by different mechanisms, their interaction may well be synergistic. Prostate size reduction by hormonal suppression prior to conformal radiotherapy allows higher doses to the tumor. A number of retrospective studies have demonstrated a reduction in the failure rates when androgen suppression is combined with radiotherapy. In the RTOG 86-10 Trial [77], 471 patients with stage cT2b-c, T3 and T4M0 PCa were randomized to receive hormonal therapy (flutamide 250 mg tid and an LHRH analogue) immediately (a month prior to radiotherapy and during irradiation) or in the event of relapse. With a median follow-up of 4.5 years there was no difference in overall survival, whereas at 5 years, progression-free survival had improved from 36 to 15% ($p < 0.001$). The rate of local relapse had declined (71 vs. 46%, $p < 0.001$) and so had the rate of metastases (41 vs. 34%, $p = 0.09$). Laverdiere et al. [78] random-

ized patients to radiotherapy alone (group 1), radiotherapy plus neoadjuvant combined androgen blockade (CAB) for 3 months prior to radiation therapy (group 2) or neoadjuvant CAB (3 months) plus CAB during radiotherapy plus 6 months of adjuvant CAB (group 3). At 24 months the positive biopsy rates were 69, 29 and 6% for groups 1–3, respectively. These and other studies suggest an enhanced effect of radiation and CAB in terms of local control, time to distant failure, disease-free survival and biopsy-negative rate. However, we must await the completion of several prospective randomized trials which should allow us to assess also the ideal patient for such a treatment.

Conclusion

Since the introduction of orchiectomy in the therapy of advanced prostate cancer in 1941, no improvement of survival has been achieved despite different new therapy modalities. Therefore, ameliorating side effects and quality of life has become an important issue of hormonal therapy in recent years. In particular, pure antiandrogens and intermittent androgen deprivation therapy are promising alternatives with few side effects. However, equivalence in terms of survival compared to orchiectomy and LHRH agonists has to be proven in further studies. Moreover, the role of antiandrogen therapy in addition to radical prostatectomy or radiation is not clearly defined yet. Today, castration by bilateral orchiectomy or by LHRH agonist remains the gold standard in hormonal therapy of advanced prostate cancer.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 66–71

Intermittent Androgen Ablation as a Treatment for Prostate Cancer

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Introduction

In 1941, Huggins and Hodges [9] introduced the permanent androgen withdrawal as first-line treatment for advanced cancer of the prostate (CaP). At present this is still the standard of care in the therapy of metastatic CaP. However, despite a high initial response rate of about 80%, a relapse occurs in more than 50% of the patients after an average time of 2 years. It was found that surgical or medical castration results in a median progression-free survival of 12–33 months and a median overall survival of 23–37 months in patients with CaP and bone metastases [6]. For still undefined reasons the apoptotic process induced by androgen ablation fails to eliminate the entire malignant cell population. Furthermore, after a variable period of time, progression inevitably occurs with increasing prostate-specific antigen (PSA) levels and an androgen-independent growth.

However, owing to the high response rate and frequency of profound remissions induced by continuous androgen ablation, there was little incentive to examine the less obvious physiological changes that accompanied androgen ablation and affected sense of well-being. In addition to loss of libido and potency, the adverse effects on bone (osteoporosis), muscle (atrophy), breast (gynecomastia), blood (anemia), lipids (low high-density lipoprotein) and mood (depression) remain a source of distressing clinical symptoms [7].

Androgen Dependence and Independence

Normal conditions for prostatic growth are established by three levels of androgen-mediated regulation: (1) positive effects on initiation of DNA synthesis and cell proliferation; (2) negative or inhibitory effects that limit the number of

cells in the prostate, and (3) apoptosis, a form of controlled cell death that occurs in the prostate when androgens are withdrawn. Androgen dependence is the clinical manifestation of apoptosis after androgen withdrawal in both normal and malignant tissues [3]. In the early stages of CaP only the form of androgen-mediated regulation that limits the number of cells in the prostate is missing. As the other two mechanisms are still functioning, androgen ablation has the double effect of triggering apoptosis and inhibiting DNA synthesis and cell proliferation. The ability to undergo apoptosis is acquired as a feature of differentiation under the influence of androgens. Therefore, in the absence of androgens, it is impossible for dividing cells to differentiate and become pre-apoptotic again [1, 3]. This explains why recurrent tumor growth is characterized by androgen independence. Improved control over progression to androgen-independence may be accomplished by intermittent hormonal therapy. It was postulated [8, 11] that the replacement of androgens even in small amounts would have a conditioning effect on surviving cells allowing them to converse or regain desirable traits of differentiation and implied that long periods of hormone deprivation accelerated progression towards autonomous growth.

The tumor best suited for studies on castration-induced cell death is the Shionogi carcinoma, a transplantable mouse mammary tumor that is androgen-dependent and closely mimics the clinical course of CaP in response to treatment. Bruchovsky et al. [4] and Akakura et al. [1] studied this tumor, which rapidly grows in the presence of androgens, undergoes apoptotic regression when androgens are removed and then gradually progresses to a hormone-refractory state. In the experiments, the tumor was transplanted into a succession of male mice, each of which was then castrated when tumor weight reached approximately 3 g. After castration, when the tumor had regressed to 30% of its initial weight, it was transplanted into a noncastrated male mouse. This cycle of transplantation-castration was repeated 5 times. The time to the onset of androgen independence was 147 ± 25 days for animals subjected to intermittent androgen suppression. In contrast, in animals treated by one-time castration, the time to the onset of androgen independence was a mean of 51 ± 3 days. These results demonstrate that apoptotic potential can be reintroduced several times by cyclic replacement and withdrawal of androgens.

Early Clinical Observations

Early attempts to minimize side effects of therapy with estramustine phosphate and diethylstilbestrol (DES) led to the administration of these estrogenic drugs on an intermittent basis with no apparent risk to the patient. Vahlensieck et al. [12] studied the intermittent administration of estramustine phosphate and

Table 1. Clinical studies of phase II intermittent androgen blockade [summarized in 13]

Author	Patients	Stage of disease
Goldenberg	47	A-D2
Higano	22	B-D2
Oliver	20	M0–M1
Theyer	60	NxM0–M+
Grossfeld	47	N0M0
Horwich	16	N+M0–N+M+
Bruchovsky	110	PSA relapse following RTX
Crook	54	Local and distant failure following definitive therapy
Kurek	44	PSA relapse following RPV; pT1b

noted no change in the rates of remission, stabilization and progression. Klotz et al. [10] investigated the intermittent regulation of testosterone with cyclic administration of estrogenic hormone. An improved quality of life was achieved and no adverse effects on survival were apparent.

Clinical Studies

More recently, several phase II clinical trials have been reported [summarized in 13]. Most of the studies have used maximal androgen blockade during the treatment intervals, which are typically 8 months in length. PSA has been used as a surrogate marker of disease reactivation during off-treatment intervals, generally with a threshold of 10 ng/ml for restarting treatment. However, the results are difficult to interpret because of the heterogeneity of the series as the studies concern small patient populations distributed in different stages (i.e. local, locoregional, metastatic). Furthermore the types of hormone treatment differed considerably (DES; antiandrogens – biclutamide, flutamide, cyproterone acetate (CPA); luteinizing hormone-releasing hormone agonist (LHRH-A) goserelin, leuprolide). A summary of these studies is given in table 1.

Neither of these reports included a formal quality-of-life (QoL) assessment. Bales et al. [2] have reported on QoL assessments in the first cycle of treatment for men receiving intermittent androgen ablation. While off treatment, 42% of men noted an improvement in energy and 50% reported no change, hot flushes disappeared in 60% and decreased in 33%, libido increased in 75% and erections

Table 2. Ongoing phase III studies on intermittent androgen blockade

1.	Phase III randomized study comparing intermittent versus continuous androgen suppression for patients with prostate-specific antigen progression in clinical absence of distant metastases following radiotherapy for prostate cancer (CAN-NCIC-PR7; CAN-NCIC-JPR7; EU 99013; SWOG-JPR7) Study coordinated by J.M. Crook
2.	Phase III randomized study comparing intermittent versus constant androgen combined androgen deprivation (bicalutamide and goserelin) in stage IV prostate cancer responsive to such therapy (SWOG-9346; CAN-NCIC-JPR8; CLB-9594; INT-0612; CAN-NCIC-PR) Study coordinated by M.H.A.A. Hussain
3.	Phase III study of intermittent MAB versus continuous MAB international study (South European Uro-Oncological group – SEUG) Study coordinated by C. da Silva
4.	Studies conducted by the German Cancer Society
4.1.	Phase III study of intermittent MAB versus continuous MAB in patients with PSA progression following radical prostatectomy (AP 06/95; EC507) Study coordinated by U.W. Tunn
4.2.	Phase III study of intermittent MAB versus continuous MAB in patients with metastatic prostate cancer (N+ and/or M+) (AP 17/95) Study coordinated by J.E. Altwein
4.3.	Phase III study of intermittent MAB versus continuous MAB in patients with prostate cancer and bone metastases (AP 19/96; EC 210) Study coordinated by J.M. Wolff
4.4.	Phase III study of intermittent AB versus continuous AB in patients with metastatic prostate cancer over the age of 70 years (AP 20/97) Study coordinated by H. Vogler and L. Weissbach

improved in 62%. Interestingly, only 35% reported an overall improvement in well-being. However, early data from the ongoing SEUG phase III study reported by Da Silva et al. [5] showed no difference in QoL and subjective response between intermittent adrogen ablation and continuous androgen ablation.

The accumulating clinical experience indicates that androgen deprivation can be used intermittently with treatment cycles of approximately 8 months' duration and variable treatment intervals. Patients with local or biochemical failure after curative treatment such as radical prostatectomy or radiotherapy have a longer median survival, tend to have longer off-treatment intervals and develop hormone resistance less rapidly. Therefore, they may be a more appropriate population for this form of treatment. However, several questions remain unanswered. The effect of intermittent androgen ablation on overall survival remains un-

known. As some patients seem to benefit more from this approach selection criteria need to be defined. The issue of testosterone recovery in the off-treatment intervals should be addressed and QoL formally measured employing valid instruments. Therefore, the results of ongoing well-designed randomized trials (table 2) of sufficient power are needed to clarify these points.

Conclusion

At present, CaP continues to be one of the most common malignancies in European men and still a large number of patients present with advanced disease at the time of diagnosis. The current standard of care for metastatic cancer of the prostate is permanent androgen withdrawal. However, this therapy is only palliative. Patients treated with permanent androgen blockade usually relapse and die secondary to prostate cancer's ability to progress to an androgen-independent state of growth. Recently, based on experimental and preclinical studies, intermittent androgen ablation has been discussed to be a potential alternative to permanent androgen blockade. Through the cycling of reversible androgen suppression, there appears to be recovery of apoptosis and subsequent slower progression to an androgen-independent state. At present several prospective randomized trials are under way to test intermittent androgen ablation as an alternative treatment in various stages of cancer of the prostate. However, until the results of these trials are available, this approach remains experimental.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 72–80

Controversies in Chemotherapy of Prostate Cancer

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Introduction

Chemotherapy is currently not a curative option in therapy of prostate cancer. Therefore, application of chemotherapy is restricted to advanced disease, e.g. the hormone refractory stage [for review, see 1–3]. The therapeutic goal in this situation is palliation, not cure. Once the tumor progresses despite hormone ablation, the average survival is approximately 9–12 months [1]. Therapeutic options available for advanced disease include secondary hormonal manipulations, such as antiandrogen withdrawal [4], analgesics [5], steroids [6], radioisotopes [7], and – for spinal cord compression – palliative radiotherapy or neurosurgery [8].

Considering the various palliative options available [for review, see 9] it can be well questioned whether chemotherapy is really useful in this situation. Earlier studies indicated response rates of approximately 8.7% [for review, see 10]. The reasons for this apparent failure of chemotherapy to achieve responses in the majority of patients are not completely understood at present. Compared to other types of cancer, response criteria are far less clearly defined in prostate cancer. Standard criteria for measuring response to therapy, such as bi-dimensionally measurable disease, are available only in a 10–20% of patients with metastastic prostate cancer. Moreover, these patients probably consitute a subpopulation with inferior prognosis.

Therefore, prostate-specific antigen (PSA) is used as a surrogate marker for response to therapy. Decrease of PSA to levels of $<50\%$ 8 weeks after therapy has been found to be a prognostic factor for survival by some [11] but not by others

[12]. Recently, guidelines have been issued for using PSA as a marker of response in clinical trials for chemotherapy of prostate cancer [13]. One must be aware of the fact that several factors can modify serum levels of PSA leading to false results, such as saw palmetto extracts used for therapy of BPH or Chinese herbal extracts such as PC-SPES used for therapy of advanced prostate cancer. It has been shown with drugs aiming at proliferation of prostate cancer, such as carboxyamido-triazole inhibitor [14, 15] or suramin [16] or the angiogenesis inhibitor TNP-470 [17] that changes in PSA do not always reflect growth inhibition. Therefore, additional surrogate markers such as quality of life or pain have also been accepted as indicators of therapeutic response to chemotherapy. Based on these response criteria some new chemotherapy regimens have been found to be active in patients with metastatic prostate cancer.

Suramin

Suramin is a polysulfonated naphthylurea that has long been used for human trypanosomiasis. Recently, it has been introduced to therapy of metastatic prostate cancer due to its inhibitory activity to several growth factors believed to be involved in the growth of prostate cancer, such as fibroblast growth factor [18] and gonadotropin [19]. Results of initial clinical trials suggested activity in metastatic prostate cancer [20].

Significant side effects of suramin therapy reported were adrenal suppression, polyneuropathy [21] and ocular symptoms [12]. In order to avoid unnecessary side effects, therapy is calibrated to serum levels of 300 μg/ml [22]. Moreover, hydrocortisone is added due to adrenal suppression. Experience recently reported by Hussain et al. [23] suggests that 46% of the patients experienced unacceptable toxicity, with 1 treatment-related death in 59 patients. In this study, no objective or partial responses were seen, whereas 53% of the patients had stable disease. More favorable results were reported by Garcia-Schurmann et al. [24], who treated 27 patients with hormone and chemotherapy refractory metastatic prostate cancer. One third of the patients had a >50% reduction of PSA and/or alkaline phosphatase with an average survival of 495 days; 48% had stable disease with an average survival of 341 days.

Corticosteroids

Prednisone in a dose of 10 mg b.i.d. has been found to achieve a PSA decline of at least 50% in 34% of the patients treated. Fourteen percent of the patients had a PSA decline lasting 6 months or more. Median survival was 12.8 months [25].

Low-dose dexamethasone has also been found to have activity in patients with metastatic prostate cancer: in a retrospective study [6], PSA reduction of >50% and important symptomatic improvement was experienced by the majority of patients; 35% had radiographic evidence for reduction of metastatic lesions.

Mitomycin

With a median time to progression of 5–10 months and significant side effects, antitumor activity of mitomycin C – an antitumor antibiotic – was found to be disappointing [26]. A combination with a blocker of adrenal testosterone – aminoglutethimide – was not more effective than mitomycin alone [27]. In an adjuvant setting, the use of mitomycin C was not recommended due to its significant impact on quality of life [28].

Mitoxantrone

Mitoxantrone is a topoisomerase II inhibitor and intercalates with the DNA. With a small number of patients, Otto et al. [29] found no complete response, partial responses in 12%, but improvement of symptoms in 60%. Tannock et al. [30] randomized 161 patients with symptomatic hormone-resistant prostate cancer to either receive prednisone alone or in combination with mitoxantrone. The endpoint of their trial was a palliative response which was defined as a two-point decrease in a pain scale without an increase in analgesic medication that was maintained for two consecutive evaluations 2 weeks apart. Twenty-nine percent of the patients responded to mitoxantrone/prednisone in terms of pain reduction as compared to 12% treated with prednisone alone ($p = 0.1$). Response duration was more than double in the group with combination therapy ($p < 0.0001$). General quality of life was significantly improved in patients receiving combined therapy [31]. Overall survival, however, was identical in the two groups. This finding was confirmed in a study published by Kantoff et al. [32]. They could not see a significant difference in quality of life, which could at least partly be explained by the fact that a third of their patients were asymptomatic at the beginning of the study, whereas in the study published by Tannock et al. [30], pain was a criterion for inclusion in the study.

Based on the published series, the combination of mitoxantrone/prednisone does not improve survival but may be helpful for pain reduction. It was for this reason that the Food and Drug Administration (FDA) of the US approved the combination of mitoxantrone and prednisone for palliative treatment of hormone-resistant prostate cancer.

Table 1. Activity of estramustine phosphate, alone or in combination

Regimen	n	PSA ↓, %	OR, %	Authors
Estramustine alone	63	n.a.	19	[33]
(pooled phase II data)	4			
Estramustine + vinblastine	36	31	61	[48]
Estramustine + etoposide	56	58	45	[36]
Estramustine + vinorelbine	25	48	0	[34]
Estramustine + vinorelbine + etoposide	25	56	32	[35]

Estramustine Phosphate

Estramustine phosphate is a carbamate ester conjugate of estradiol and nor-nitrogen mustard. Activity of estramustine phosphate includes disruption of microtubules, inhibition of *p*-glycoprotein and interference with the assembly of the nuclear matrix.

Analysis of pooled data derived from 18 phase II studies with 634 patients revealed objective responses in 19% of the patients [33]. Since estramustine phosphate interferes with the microtubules, it has been combined with other microtubule inhibitors such as vinblastine, vinorelbine or etoposide (table 1).

In two phase II trials, estramustine phosphate was combined with vinorelbine for therapy of hormone-resistant prostate cancer. Twenty-three out of 48 patients (48%) responded as evidenced by a decline of PSA serum levels [34]. Response duration was, however, 3 months only [35].

In a phase II study, Dimopoulos et al. [36] combined oral estramustine phosphate with oral etoposide. Fifteen out of 33 patients with measurable soft tissue disease had objective responses, 5 of them had complete responses. A decline of PSA serum levels of >50% was found in 58% of the patients included. Their results were confirmed by Pienta et al. [37] who found 53% partial responses in measurable lesions and 39% PSA response with this combination.

In a phase III trial including 201 patients, the combination of estramustine phosphate plus vinblastine was compared to vinblastine alone. Overall survival did not differ significantly between the two groups (11.9 vs. 9.2 months). However, time to progression and PSA decline were significantly improved in the group that received the combination of the two drugs [38]. Therefore, the combination of estramustine phosphate with microtubule inhibitors would warrant further investigation. Results of clinical trials with combinations of estramustine phosphate and taxanes are reported below.

Table 2. Activity of taxanes, alone or in combination

Regimen	n	PSA ↓, %	OR, %	Authors
Paclitaxel alone	23	17	4	[39]
Docetaxel alone	35	45	20	[41]
Estramustine + paclitaxel	34	53	44	[44]
Estramustine + docetaxel	18	39	25	[45]
Estramustine + docetaxel + prednisone	40	69	23	[46]

Taxanes

The taxanes, paclitaxel and docetaxel, the active constituents of taxol and taxotere, stabilize microtubules thereby inhibiting the dynamic reorganization of the microtubule network. Taxanes have been found to be active in a variety of cancers including prostate cancer (table 2).

Initial results with paclitaxel as a single agent at 135–170 mg/m^2 every 21 days were disappointing [39]. When paclitaxel was injected at a weekly dose of 150 mg/m^2, Trivedi et al. [40] achieved objective responses in 27% and a PSA decline of $\geq$ 50% in 39% of the patients.

Docetaxel as a single agent at 75 mg/m^2 every 21 days has been found to achieve a PSA decline of 50% and more in 65% of the patients [41]. When measurable lesions were considered, response rate was 28% with 1 complete response. Using the same dose, Friedland et al. [42] observed a 50% or greater PSA reduction in 38% of their patients.

The rationale for combining taxanes with other drugs acting on the microtubules has been that these substances share the same target but do not have overlapping toxicities. Since animal experiments suggested a synergistic activity of estramustine phosphate and paclitaxel [43], this combination was used in a phase II clincal trial yielding 44% objective responses and PSA decrease of $\geq$ 50% in 53% of the patients [44].

Combining estramustine phosphate with docetaxel yielded a >50% decline of PSA in 7/18 patients treated [45]. The combination of docetaxel, estramustine phosphate and hydrocortisone was even more effective: in a phase II study by the Cancer and Leukemia Group B, 23% objective responses in measurable disease and a PSA decline of 50 or more percent in 69% of the patients were observed [46]. Similar data were recently reported based on a phase I study [47].

Conclusions and Future Directions

Therapy for metastatic hormone-resistant prostate cancer remains a challenge. A significant improvement of survival has not been demonstrated with any of the new regimens introduced during the past few years. Thus far, chemotherapy continues not to be a curative option for therapy of metastatic hormone refractory prostate cancer. Regimens have been defined that offer symptom relief and/or improvement of quality of life, such as mitoxantrone/prednisone. Moreover, activity in a significant proportion of the patients in terms of PSA reduction has been specifically demonstrated for combinations of estramustine phosphate and taxanes.

Studies currently in progress focus at combination of drugs proven to be active in phase II trials, such as a phase I trial employing estramustine, docetaxel and carboplatin which is currently being conducted at Harvard University [#98238, http://cancercare.harvard.edu/scripts/mgwms32.dll] or the Cancer and Leukemia Group B study combining estramustine, docetaxel, carboplatin, and granulocyte colony-stimulating factor [http://www-calgb.uchicago.edu/]. Moreover, combined regimens such as docetaxel/estramustine phosphate and mitoxantrone/prednisone are being compared in ongoing studies ([1]; SWOG #9916; http://192.238.19.16/visitors/ViewProtocolDetails.asp?ProtocolID = 61). In phase III studies theses improvements will hopefully prove to extend survival of the patients in the future.

There will also be new fields for chemotherapy in prostate cancer such as neoadjuvant therapy in high-risk patients before radical prostatectomy (Dana Farber trial #99193 [http://cancercare.harvard.edu/scripts/mgwms32.dll]. The new enthusiasm about the role of chemotherapy in prostate cancer will hopefully translate into clinical benefits for the patients in the near future.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 81–86

Adjuvant Hormone Therapy in Locally Advanced and Localized Prostate Cancer: Three EORTC Trials

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Introduction

In the pre-PSA era, the clinical results of conventional irradiation for locally advanced prostate cancer have shown that high clinical stages are associated with a worse prognosis [1]. Treatment failures occur both within and outside the pelvis. The objective of adjuvant hormonotherapy is twofold: to decrease the occurrence of distant metastases due to subclinical deposits at the time of diagnosis and to reduce the risk of local relapse within the irradiated volume by inhibiting repopulation during irradiation [2]. A long-standing controversy surrounds the optimal timing of hormonotherapy for patients with asymptomatic locally advanced prostate cancer treated by radiotherapy: Should adjuvant hormone therapy be given prior and during radiotherapy (neoadjuvant treatment), or should it be started during radiotherapy and continued for a period of time after radiotherapy (adjuvant treatment) and for how long should the (neo)adjuvant hormone deprivation therapy be administered? As far as overall survival is concerned, recent results of randomized trials from the Radiation Therapy Oncology Group (RTOG) and the European Organization on Treatment and Research on Cancer (EORTC) plead in favor of adjuvant hormonal therapy [2–5]. Another and complementary strategy to improve local control and survival is to use three-dimensional conformal radiotherapy (3-DCRT) which enables radiation oncologists to adapt the isodose as closely as possible to a customized target volume and to escalate the dose, by using both multileaf collimator and multibeam ballistics [6].

Since 1987, the EORTC Genito-Urinary and Radiotherapy Groups have set up trials aiming at comparing various strategies of radiotherapy and hormonotherapy for localized and locally advanced prostate cancer with respect to: (1) overall survival and clinical disease-free survival clinically and biochemically defined; (2) quality of life with the EORTC core questionnaire QLQ C 30 which is a well-validated and accepted instrument to measure various domains that constitute quality of life, and (3) cost-effectiveness.

Trials

Published Trial: EORTC Trial 22863

In the period 1987–1995, 415 patients under 81 suffering from locally advanced prostate cancer, were randomly allocated between radiotherapy in combination with 3 years of combined androgen deprivation and radiotherapy alone, followed by the same hormonotherapy in case of relapse. The trial was closed in December 1995 due to ethical reasons: the combination arm was superior to radiotherapy alone. Planning target volume I was the whole pelvis and planning target volume II, prostate and seminal vesicles. The whole pelvis was irradiated with a four-field technique. Planning target volume II was irradiated with either the same technique or with three fields. In both arms, 50 Gy were delivered to the pelvis in 5 weeks, and 70 Gy in 7 weeks to the prostate and seminal vesicles. Hormonotherapy was given by a monthly subcutaneous injection of Zoladex® (goserelin acetate), started on the first day of irradiation, and continued for a period of 3 years; the LHRH analogue was combined with an antiandrogen starting 1 week before the Zoladex injection to prevent the transient rise of testosterone. With a median follow-up of 65 months, hormonotherapy has resulted in an increase of 5-year local control from 79 to 97% ($p < 0.001$) and clinical disease-free survival from 40 to 75% ($p < 0.001$); this has led to a significant increase in 5-year overall survival from 62 to 78% ($p < 0.001$) in favor of the combined modality treatment [3].

Ongoing Trial: EORTC 22961

The objective of this trial is to assess whether it is feasible to reduce the duration of adjuvant androgen deprivation from 3 years to 6 months without impairing overall survival. By reducing the duration of the treatment, it is hoped to improve the quality of life of these patients by reducing the side effects of the androgen deprivation treatment. In particular, hot flushes and fatigue should be reduced and sexual function should be better preserved. This latter point is particularly important since patients with locally advanced prostate cancer of the late nineties have less tumor burden and are younger than those of the mid eighties. In

addition, if androgen suppression is initially given for 6 months and thus stopped prior to tumor progression due to overgrowth by androgen-independent cells, any subsequent tumor growth would still allow hormonal treatment of the proliferation of androgen-dependent stem cells [7].

The EORTC equivalence trial 22961 [8] was initiated in April 1997. All patients staged cT1c-T2a-b/N1 or pN1 and cT2c-T4/N0-1 (PSA < 150 ng/ml) are eligible to the trial. They receive external irradiation for 5 weeks, followed by a pelvic boost given for 2 weeks and a 6-month combined androgen blockade initiated at the onset of external irradiation; 3-DCRT is recommended. Then, the patients are randomly allocated to receive either no further treatment (watchful waiting) or a 2.5-year continued hormonal treatment with the LHRH analogue (Decapeptyl®, Triptoréline) given every 3 months. The 5-year survival rate in the reference arm is estimated to be 80%. Equivalence is defined as a relative risk not greater than 1.35, which corresponds to a decrease of the 5-year survival rate from 80% to no less than 74%. Based upon that hypothesis, a total of 275 deaths need to be observed to test the equivalence with a power of 80% (b = 0.2), and a one-sided type I error rate of 5% (a = 0.05). To observe those events, a projected total number of 966 patients should be randomized (483 in each arm) over a period of 5 years. As of June 2000, 679 patients were registered and 465 were randomized, the average entry rate is 29 patients/month.

Trial to Be Launched EORTC 22991

The aim of this trial is to demonstrate that combining 3-DCRT and a short-term immediate and combined hormonal treatment in localized prostate cancer cT1-2a N0 M0 (PSA < 50 ng/ml) can improve disease-free survival as compared to 3-DCRT alone by increasing local control and decreasing distant metastases. 3-DCRT enables physicians to escalate the dose to the tumor without increasing acute and late toxicity. For Zelefsky et al. [9], the 5-year actuarial PSA relapse-free survival is dose-dependent and is significantly improved in patients with intermediate and unfavorable prognosis receiving > 75.6 Gy ($p < 0.05$). A dose comparison study between conventional irradiation (70 Gy) and 3-DCRT (78 Gy) has been started at the M.D. Anderson Cancer Center; preliminary results show that for patients with stage cT1-2 disease (including cT2b) and a PSA > 10 ng/ml, the 4-year NED rates were 55% with the 70-Gy patients and 93% for 78-Gy patients ($p = 0.003$) [10]. In EORTC 22991, three dose levels are allowed – 70, 74, 78 Gy – and each institution will commit to using one dose schedule for all the patients throughout the whole course of the study. In view of the better prognosis of the patients recruited in this trial and with regard to the shorter duration of the hormonal treatment given to the patients, a 5-year clinical and biochemical defined disease-free survival of 70% is assumed for the 3-DCRT-only arm. In order to detect a relative difference of 40% (HR = 0.714) from 70 to 77% with a two-sided

log-rank test at the 5% significance level and 80% power, the protocol requires 800 patients, recruited over a period of 5 years with 5 additional years of follow-up before the analysis. A total of 240 events need to be observed for the analysis to be carried out [11].

Discussion

With respect to locally advanced prostate cancer, two trials of the RTOG support a long-term adjuvant hormonal treatment. Protocol 85-31 [4] was devoted to adjuvant androgen suppression with goserelin acetate in patients classified as cT1-2 with regional lymph node involvement, cT3 regardless of regional lymph node status or pT3 after radical prostatectomy. Goserelin acetate was started at the end of the radiotherapy and continued indefinitely. With a median follow-up of 4.5 years, there was an increase of the local control ($p < 0.0001$), distant metastases-free rate ($p < 0.001$) and disease-free survival ($p < 0.001$). In patients with centrally reviewed tumors with a Gleason score of 8–10 there was a difference in actuarial 5-year survival in favor of the adjuvant goserelin arm ($p = 0.03$). In protocol 92-02 [5] patients with cT2c-T4 tumors and PSA <150 ng/ml received goserelin acetate and flutamide 2 months before and 2 months during radiation and were randomized to no further therapy or to 24 additional months of goserelin acetate alone. With a median follow-up of 4.8 years, the long-term androgen deprivation treatment arm significantly improved the disease-free survival ($p = 0.0001$), local control ($p = 0.0001$), time to distant metastasis ($p = 0.001$), time to biochemical failure ($p = 0.0001$) and showed a favorable trend for disease-specific survival ($p = 0.07$). All these studies of radiation treatment alone or in combination with androgen deprivation in patients with locally advanced prostate cancer have been criticized, since a hormone treatment-only arm was missing. An ongoing NCI Canada trial addresses the role of hormonal treatment alone in locally advanced prostate cancer comparing maximum androgen blockade versus maximum androgen blockade plus pelvic irradiation in clinical stage cT3-4, N0, M0 [12]. Taking into account the experience gathered from locally advanced breast cancer it is very likely that the best results will be achieved by the combined treatment which has a positive impact both on local control and survival [13].

With regard to localized prostate cancer, a short-term adjuvant androgen suppression to radiation therapy could possibly improve the results of local control, as suggested by the Quebec trial [14]. The aim of this study was to investigate whether combining MAB with conventional external beam therapy (up to 64 Gy) improves the rate of positive biopsies and serum PSA levels compared to radiation therapy alone. Patients were randomly allocated between radiotherapy alone

(group 1), 3 months of neoadjuvant MAB followed by radiotherapy (group 2), or MAB 3 months prior to, during, and 6 months after radiotherapy (group 3). Seventy-four percent of these men had cT1-2 tumors, 88% Gleason 2–6, and 77% PSA values <20 ng/ml. At 12 months, 62% of group 1 patients showed persistent disease in one biopsy from the previous malignant site of the prostate, versus 30 and 4% in groups 2 and 3, respectively ($p = 0.00005$). At 24 months, 65, 28 and 5% showed residual disease for groups 1, 2 and 3, respectively ($p = 0.00001$). With regard to the PSA serum levels, there was a difference between the three groups ($p < 0.0001$) at 12 months, which was no longer significant at 24 months between groups 2 and 3. These data should be looked at with great care, because PSA response and biopsy results are not considered endpoints for a phase III trial in prostate cancer. Pathologic evaluation of biopsy results after hormonal therapy is difficult and sampling error could also play a role. PSA can, at the best, be considered a surrogate endpoint; so hard endpoints of such studies (progression-free survival, overall survival and disease-specific survival) should be awaited before drawing definite conclusions. A support for this treatment approach is the breast cancer model, studying combined tamoxifen and radiotherapy which increased local control and survival in localized tumors <1 cm with a negative axillary clearance, with respect to radiotherapy alone [15], but the duration of hormonal treatment was longer than the one which is proposed for prostate. In the latter, the hormonal treatment cannot be prolonged too long in these good prognosis patients with a relatively long survival, due to the impact of the treatment on the quality of life, e.g. hot flushes, asthenia and the modification of the sexual life.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 87–98

Neoadjuvant Androgen Suppression and External Beam Radiation Therapy

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Introduction

When localized prostate cancer is treated with radiation, a significant proportion of patients will, if rebiopsied, show evidence of locally persistent or regrowing tumor [1]. This persistence is significant, not only as a cause of local treatment failure, but it also appears to be a source of subsequent metastasis and cancer-related death [2]. Improving local control is therefore essential for radiation oncologists and a major focus of contemporary research.

One of the basic tenets of therapeutic radiation oncology is that the tumor cell kill is proportion to the radiation dose prescribed [3]. The relationship between tumor control probability (TCP) and radiation dose is sigmoid with the slope of the curve and its 'take-off' point reflecting the intrinsic radiation sensitivity of the tumor cells (fig. 1). It is therefore clear that improved local tumor control can be achieved by increasing the delivered radiation dose. This has been shown to be true in a host of experimental and clinical situations. A recently reported randomized trial has now clearly shown that the same situation exists for prostate cancer [4]. Unfortunately, dose escalation carries some risks because of increased doses to the healthy normal tissues surrounding the tumor. Despite the efforts of clinicians to use more conformal radiation techniques, dose escalation still carries a risk of rectal bleeding and bladder damage [5]. For this reason, dose escalation is still viewed with concern by radiation oncologists, particularly those practicing in the community. An alternative is required and neoadjuvant androgen suppression (NAS) seems to fit the bill.

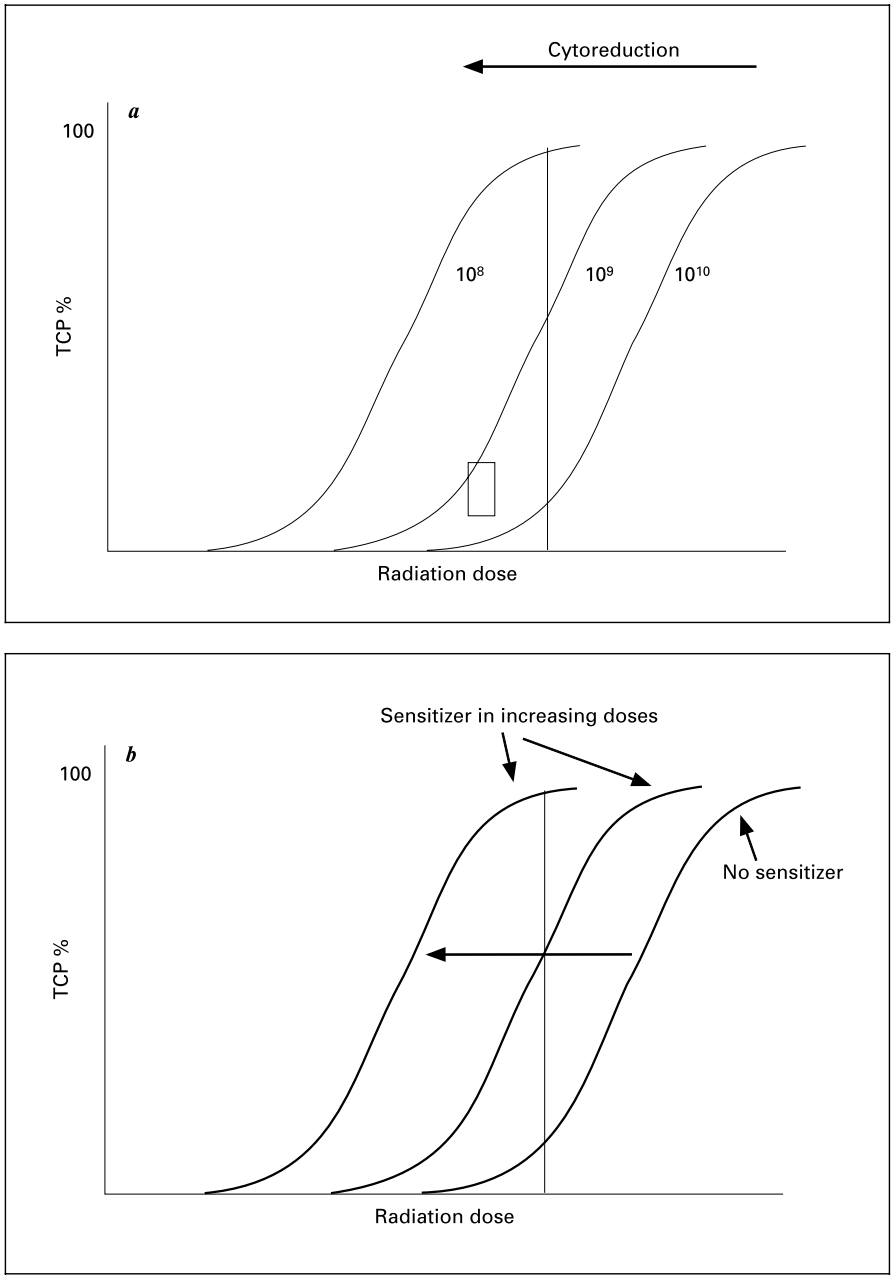

Fig. 1. The sigmoid dose-response relationship between therapeutic radiation dose and the probability of local tumor eradication (tumor control probability = TCP) may be influenced by tumor cell number (***a***) and by tumor cell sensitization (***b***).

The case for using NAS with radiation therapy is strong. It is built on theoretical, experimental and clinical foundations and has, over the last 5 years, entered routine oncologic practice.

Theoretical Evidence

Those advocating dose escalation are essentially seeking to climb the sigmoid dose-response curve on the assumption that it is steep and a small incremental increase in dose will cause a significant increase in TCP. A safer theoretical approach would be to reduce the number of clonogenic target cells within the tumor. Smaller and smaller tumors have curves set further and further to the left. Thus, by reducing tumor clonogenic cell number, the same radiation dose will give a higher TCP (fig. 1a). This is the principle of 'debulking', an additive interaction as used in many different situations in oncology. It underlies the use of 'lumpectomy' before radiation in breast cancer and transurethral resection before radiation in bladder cancer. Androgen deprivation, by inducing apoptosis and reducing clonogen cell number, theoretically offers a form of nonsurgical debulking. Significant improvements in TCP usually require a reduction in tumor volume of at least one order of magnitude.

Potential gains in TCP can also come if the dose-response curve for a given number of clonogens is shifted to the left by an increase in the overall sensitivity of the tumor cells to radiation. This process of 'radiation sensitization', a synergistic interaction, is also employed routinely in modern oncology (fig. 1b). Cisplatinum is routinely used to sensitize head and neck, gynecologic and bladder tumors. The problem with cisplatinum is its propensity to sensitize normal tissues as well as tumor and this does rather reduce the therapeutic advantage. If androgen suppression could sensitize tumor cells to radiation it would be specific to prostatic tissues as, to our knowledge, the integrity of rectum and bladder is not influenced by androgen levels. It is attractive to speculate that radiation and androgen deprivation may have, through apoptosis, a common final pathway for at least some component of their respective cell kills. This raises the possibility of mutual enhancement.

These, however, are theoretical gains. Theoretical concerns also exist. It is known that tumor cell killing by radiation may be dependent upon the cell cycle [6]. Certain phases of the cell cycle, particularly G2M, are more sensitive than others such as G0 [7]. Any tendency of androgen deprivation to freeze cells in a noncycling resting phase could, therefore, be deleterious. Equally, some forms of radiation-induced DNA damage require the progression of tumor cells into mitosis for their expression. Any delay could potentially allow the intrinsic DNA repair mechanisms a greater chance to complete their task.

Experimental Evidence

Cytoreduction

It has been known for over 50 years that cancer-related symptoms disappear when patients are castrated and that the prostate involutes and tumor clinically regresses. The assumption has been that some degree of tumor cell death has occurred. In the available rodent model systems, several different situations can be obtained. Dunning rat tumors do not regress but simply grow more slowly. LNCaP and PC3 human tumor xenografts may stabilize in size or regress somewhat. The Shionogi mouse mammary tumor regresses in volume by a factor of at least 10. Bruchovsky et al. [8] demonstrated that the number of clonogens within a Shionogi tumor is reduced by approximately two logs after castration. The mechanism is rapid apoptosis. It is not so easy, however, to imagine a reduction in tumor clonogen number in the other tumor examples. One could simply postulate a scenario in which cell proliferation had slowed.

Which situation obtains in situ in humans is not known for certain but histologic evidence from several randomized trials supports the idea of cytoreduction. In the Quebec randomized trial, tumor volume was, on the average, reduced from 2 to 1.5 cm^3 by 3–6 months of NAS [9]. The positive margin rates were considerably lower as was the incidence of multifocal disease. Gleave et al. [10] have shown that the time to maximal tumor regression in humans is approximately 8 months.

Synergistic Cell Killing

Meyn et al. [11, 12] have shown that apoptosis commonly occurs after the irradiation of various murine adenocarcinomas. Apoptosis has, likewise, been demonstrated to follow androgen deprivation in a number of androgen-sensitive rodent systems. Joon et al. [13] have used the Dunning tumor system and shown low rates of spontaneous apoptosis, and apoptosis after castration or low-dose radiation (<2% of cells). When castration was performed 3 days prior to radiation, however, the apoptotic rate rose in a supra-additive fashion to over 10%. This was not seen if the castration followed radiation. This system therefore raised the possibility of synergy and also pointed out a potential sequence and timing dependence of the interaction.

Our laboratory further examined the Shionogi tumor system performing large-scale trials to determine the tumor control probability under different situations [14, 15]. The TCD_{50} (radiation dose needed to, on the average, control 50% of these tumors) fell significantly if castration and radiation were performed synchronously as compared to radiation used alone (fig. 2). This might represent a sensitizing interaction. If castration was performed and radiation not given for a week until maximal tumor regression had occurred, the TCD_{50} fell yet further.

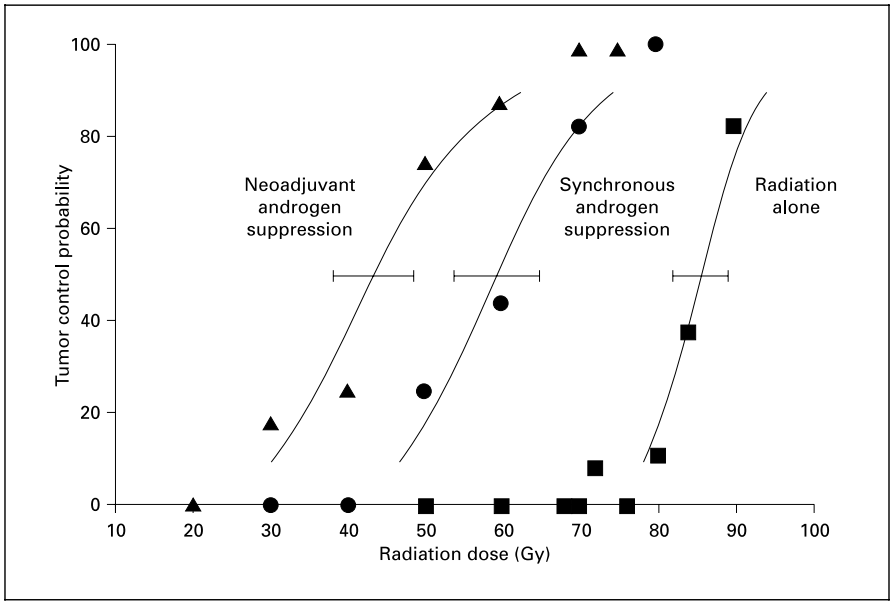

Fig. 2. Dose-response curves for the androgen-sensitive Shionogi mouse adenocarcinoma irradiated in vivo. The curves are pulled to the left when androgen deprivation is given with radiation. The best response is seen when radiation is deferred until the tumors have maximally regressed after androgen suppression [14, 15].

This additional fall could represent the advantage from cytoreduction. It is significant that far less benefit was seen if the castration followed the radiation (adjuvant therapy). While adjuvant therapy might have significant advantages in terms of controlling systemic disease, it did not, in this system at least, greatly enhance local control. If we waited until the tumors had acquired androgen independence and had regrown to their original size, then all advantage was lost and the TCD_{50} was back to its original value. It was also noted that not all Shionogi tumors regressed to the same degree. Those that regressed less had significantly higher TCD_{50} values.

These experiments generated some hypotheses for clinical testing in clinical trials. Firstly, that local control can be improved by NAS and that the improvement could be maximized by waiting for maximal tumor regression before delivering radiation. Secondly, that the response to NAS might predict the response to radiation and perhaps be used as a way of selecting patients for this or other more aggressive treatments.

Concerns

Despite this attractive experimental data, several genuine concerns exist. The first is that apoptosis has not been shown to convincingly occur after radiation of the human prostate cancer cell line LNCaP, at least by techniques so far used. This might make the appealing notion of synergy less possible. It has also been shown in several systems that cell cycling is essential for the classical form of postmitotic radiation-induced cell death. Indeed, Wazer et al. [16] have shown that the drug tamoxifen, which arrests breast cancer cells in G0, can reduce the tumor cell killing after clinically relevant doses of radiation. Garzotto et al. [17] have taken the argument further and used caffeine as a mitogen to stimulate dividing cells and enhance radiation-induced cell death. Apoptosis is dramatically demonstrated in normal prostatic epithelium and the presumption had been that it also occurs in tumor derived from that epithelium. It must, however, differ to some degree as though comparable genes are switched on it is a slower process, less complete, and followed by regrowth and androgen resistance. Indeed some have studied human prostate cancer cell lines and seen very little apoptosis after androgen deprivation. This would undermine both the possibility of cytoreduction and of synergy.

It is therefore possible that in any tumor a balance may exist between factors promoting and factors protecting against radiation cell kill and that the scales must be tipped in the correct fashion to obtain the desired effect. This may explain the sequence dependence of some of the positive interactions seen in the experimental models.

A recent study by Rittmaster et al. [18] attempted to answer the question as to whether apoptosis induction or proliferation repression was the dominant process following NAS. They analyzed radical prostatectomy tissue obtained from men who either had or had not undergone NAS. No difference was seen in the proliferative index as measured by Ki-67 or Mib-1 antibodies. No difference was seen in a measure of early apoptosis, the TUNEL assay. When they measured tissue transglutaminase, a measure of later apoptosis, there was, however, clear evidence of its induction by NAS. This again emphasizes the potentially critical aspect of timing in any interaction between NAS and radiation.

Clinical Evidence

Biological Gains

A great deal of phase II study data has accumulated over the last 5 years to show genuine clinical gains from NAS prior to radiation. A compelling study by Zelefsky et al. [19] reported on men treated at the Memorial Sloan-Kettering Cancer Center in a series of radiation dose-escalation studies. Attempts were made to

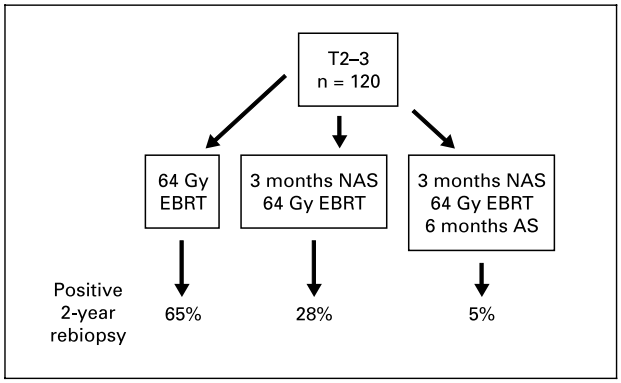

Fig. 3. The probability of a positive prostate rebiopsy in the Quebec randomized trial [20].

biopsy the palpably normal prostates of men 2 or more years after therapy. The dose-response curve was once again demonstrated with positive rebiopsies seen substantially less often once radiation doses exceeded 75 Gy. The likelihood of a positive rebiopsy was less for every given radiation dose level if NAS had been given in advance. The same study also showed that the likelihood of being free from a rising PSA level at 4 years was strongly predicted by whether or not the patients had a profound response to the NAS in terms of preradiation PSA nadir.

Two randomized trials have studied the question. The first was from Quebec and reported by Laverdiere et al. [20]. In this study, relatively small numbers of men with T1–3 prostate cancer were randomized to receive 64 Gy radiation, 3 months of NAS and 64 Gy, or 3 months NAS followed by 64 Gy and a further 6 months of AS (fig. 3). The difference in the rates of positive rebiopsy at 2 years was profound with substantially lower positive rates in those treated with androgen deprivation.

The landmark trial has been that from the Radiation Therapy Oncology Group (RTOG 86-10) [21]. In this trial, nearly 500 men with locally advanced tumors were randomized to either conventional dose radiation or the same radiation preceded by 2 months of androgen suppression with goserelin and flutamide and accompanied by 2 months more (fig. 4). At the 8-year mark a clear improvement in local control, biochemical disease-free survival, and metastasis-free survival has become apparent [22]. The latest analysis will also show the first evidence of an overall survival benefit. Whatever the biologic mechanism, it is clear

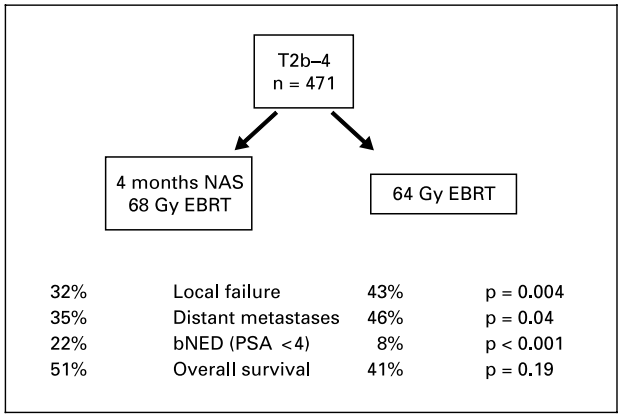

Fig. 4. RTOG 86-10: 8-year data from a randomized trial to assess the efficacy of NAS prior to external beam radiation in locally advanced prostate cancer [22].

that a positive clinical interaction has taken place between NAS and external beam radiation.

Technical Gains

While scientists have aimed for a biological advantage from the combination of NAS and external radiation, clinicians have exploited a technical advantage. High radiation doses are associated with an increase in normal tissue damage, particularly rectal bleeding. In a randomized trial performed at the Massachusetts General Hospital in the 1980s, 32% of men treated with 77 Gy developed rectal bleeding as compared with only 12% of those treated with a conventional dose [23]. The probability of bleeding was predicted not only by dose but by the volume of rectum receiving the high dose. Though conformal techniques were used in an attempt to keep down the rectal volume incorporated, many patients had bulky T3 tumors and thus rectum could not be spared without sparing tumor. Zelefsky et al. [24] have published data on 22 patients with large prostates simulated before and after 3 months of NAS. After the NAS there was a median reduction in the target volume (prostate ± seminal vesicles ± a margin for microscopic extension) of 25%. The median rectal volume receiving >95% of the target dose was correspondingly reduced by 25% and the high-dose bladder volume by 50%.

The technical advantage of downsizing allows either reduced morbidity for a fixed radiation dose or it may allow a higher radiation dose to be delivered for a given level or morbidity that is judged acceptable (fig. 5).

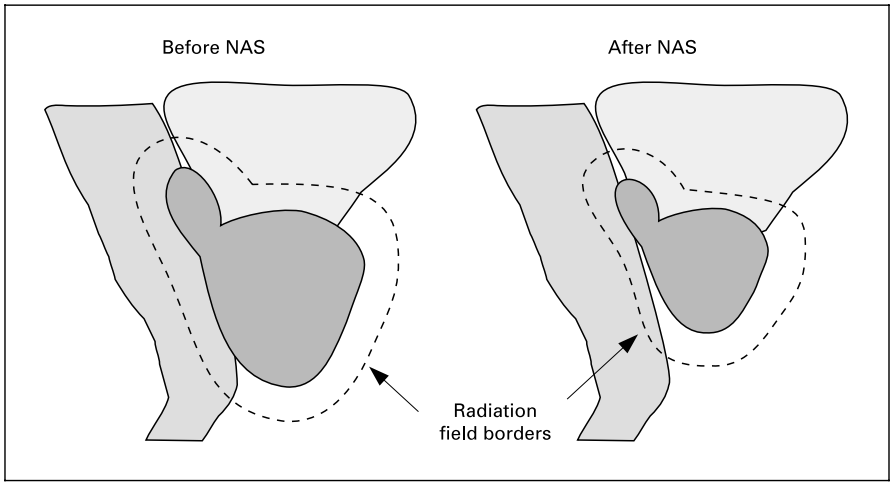

Fig. 5. NAS by shrinking the prostate may allow a reduction in the volumes of normal tissue treated by radiation when conformal techniques are used.

Remaining Questions and Concerns

Duration of NAS: Animal models suggest that delaying radiation until the time of maximal response to NAS will maximize the benefit. A Canadian group and the RTOG are both exploring 3 versus 8 months of NAS in trials recently opened.

Role in early stage disease: Though there may be benefit in T1–2 tumors, the advantage may be small due to the relatively high rates of local control already attained and due to the recent improvements in outcome that result from 3D conformal treatment planning. The cost and morbidity of a short course of NAS may not therefore be justified. Again this question is being addressed by the RTOG in a randomized trial that had closed having accrued over 1,600 patients. We are still approximately 2 years away from a first report.

NAS and brachytherapy: A short course of NAS is commonly given when the prostate volume exceeds 40–50 cm^3 in an effort to make the brachytherapy more successful (better tumor coverage and less pubic arch shielding) and safer (fewer seeds, lower central doses, and less urinary retention). The technical advantages are clear but a biological advantage has been assumed following the success with external beam radiation. This may have been a mistake. Early data from the Seattle group [Dr. John Sylvester, pers. commun.] suggests that if one stratifies

for prognostic factors, those who received NAS prior to either palladium or iodine brachytherapy fare worse in terms of 5-year biochemical disease-free survival. Two explanations are possible:

(1) As the prostate and its cancer involute, they shrink away from any extracapsular tumor like a boat linked by a rope to the dock as the tide goes down. Thus the post-NAS implant would be insufficient to treat extracapsular cancer cells at their most radial extent. This geographic misconception does not seem plausible when one considers that most extra-capsular disease is within 3 mm of the prostatic capsule.

(2) The nature of cell killing by low dose-rate brachytherapy is poorly understood. The relative balance of apoptosis and postmitotic killing is unknown. Whatever the mechanism, low-dose brachytherapy cell kill appears very sensitive in cell cycle issues and to proliferation. As the dose rate falls there is generally less cell kill for a given radiation dose because of the repair of sublethal damage and because undamaged cells may still proliferate increasing the surviving fraction [6]. Paradoxical effects may actually be seen at very low doses when some unchecked proliferation may bring cells into more sensitive phases of the cell cycle (the 'inverse dose-rate effect'). The dose rate is very heterogeneous across any implant with rates on the surface of the sources being substantially higher than those just a few millimeters away. In addition, dose rates differ greatly between the 1st and the 50th posttreatment day because of radiation decay. There is therefore plenty of time and opportunity for both positive and negative interactions to take place between the radiation and the NAS. The findings of the Seattle group sound a warning and clearly need to be tested in other data sets.

Conclusions

The technical advantage of NAS prior to external beam radiation is not in doubt. There is sound clinical evidence that a biological advantage also exists that has been demonstrated in randomized trials. The mechanisms of the benefit remain elusive and may be more complex than the current simple theories of cytoreduction and apoptosis. Manipulating the duration and timing of the NAS may increase this advantage. Such strategies are currently being explored. Extrapolation of these findings to low dose-rate brachytherapy may, however, be premature.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 99–105

Quality of Life following Radical Prostatectomy

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Introduction

Complete removal of malignancy is the mainstay in case of localized prostate cancer. Following the principles of Halsted, radical prostatectomy implicated excision of the prostate and seminal vesicles as well as surrounding tissue to obtain negative surgical margins. The perioperative morbidity was considerable, patients were uniformly impotent and a significant percentage was severely incontinent.

Since the early eighties the improved knowledge of pelvic functional and structural anatomy radical prostatectomy resulted in a technically safe operation with less morbidity. The appropriate selection of patients in terms of comorbidity and small tumor burden has led to an almost zero operative mortality and better cancer control rate. Moreover, urinary incontinence seems to be a lesser problem as reported previously. Refinements in intraoperative technique allowed the preservation of cavernosal nerves responsible for erectile function in appropriately selected younger patients with low volume disease. Additional measures such as removing the indwelling catheter as early as possible, short hospitalization, pelvic floor training to gain continence as early as possible, provision of erectile aids are all meant to reduce morbidity and improve health-related quality of life (HRQOL).

Competing means for local control of cT1 and cT2 prostate cancer such as external beam high-dose radiotherapy, HDR brachytherapy or iodine seed implantation can be offered. Each modality may have a different outcome in

terms of long-term survival, cancer recurrence, severity of side effects and impact on HRQOL. Until now, none of these treatment options were compared to each other in randomized trials. A clear statement regarding the superiority of one of these treatment options in respect of cancer control cannot be made. Most of the HRQOL reports deal with cross-sectional retrospective data after treatment providing the patients' HRQOL at a given time. Time of evaluation differs in most studies significantly within a given collective, but also differs to various reports published. Longitudinal data collection will be more meaningful since it facilitates the assessment of changes with time and moreover it enables to determine the likelihood of the return of HRQOL to pretreatment level. Limited information has been published until now about individual change of HRQOL following radical prostatectomy. Furthermore, it is important to note that different questionnaires are used to assess the severity of side effects and HRQOL indicating that a simple comparison of data is not possible. Moreover, prostate cancer-specific questionnaires are rarely used. Although we know about these drawbacks of our present HRQOL data, the information we already have at hand should be used in counselling patients in the pretreatment situation rather than reflecting on anecdotal professional experience.

The main side effects of radical prostatectomy are urinary incontinence and impotence. The impact on HRQOL will be discussed in this article based on personal results and the published literature.

Urinary Incontinence

Urinary incontinence (UI) following radical prostatectomy occurs in 5–74% depending on the definition of UI, method of evaluation, independence of the investigator, questionnaire vs. interview vs. chart review and center of excellence vs. multicenter survey. The impact on HRQOL was not assessed until recently. Herr [1] evaluated 50 patients 1–5 years following radical prostatectomy. All of the patients he evaluated experienced some degree of incontinence (at least 3 pads daily) but were free of cancer. The patients were investigated using a self-designed questionnaire considering the degree of incontinence and its global impact on activities of daily living and satisfaction regarding the results of the operation. The questionnaire was validated by retesting in 20 patients and demonstrated well to excellent reliability. Most of the patients (63%) were moderately to severely upset about their incontinence and some (24%) reported limitations in their physical activity compared to the preoperative situation. Interestingly, 53% of patients who underwent surgery 5 years earlier would not undergo radical prostatectomy again because of this side effect. This percentage was much lower (17%) in patients who were 1–3 years postoperatively. This finding suggests that with

longer follow-up, persistent incontinence may dampen earlier enthusiasm of having a successful operation.

Braslis et al. [2] used FLIC, POMS and a self-designed symptom inventory to evaluate 51 patients who have had a radical prostatectomy at least 12 months before. 61% of patients stated that they had no problem with incontinence, but 39% regarded incontinence as a problem. Six (12%) patients were significantly irritated. There was an inverse correlation between patient's incontinence and self-perceived physical and psychological well-being. Increased confusion, depression and anger were also significantly associated with incontinence. The impact of the diagnosis cancer, the regular medical attendance, incontinence, erectile dysfunction and the fear of dying may all be associated with an increased hardship score evaluated by the FLIC QOL questionnaire.

At our institution we evaluated 169 patients who had undergone radical prostatectomy 6–121 months (mean 32) earlier in regard to incontinence and HRQOL using the ICS urinary symptoms questionnaire and the EORTC-QLQ-C30. No leakage (38.7%), occasional leakage (48.8%) or occasional leakage with stress (3.0%) was reported by 90.5% and these patients were generally considered as completely continent. But already these minor degrees of urinary leakage were a significant problem in 11.0% of them. Moreover, the general perception of well-being was negatively influenced not only by urinary incontinence itself, but also by the severity of the symptom (measured by bother score) (fig. 1). Considering the different specific aspects of HRQOL, it became evident that bothersome incontinence had a negative impact on daily physical activity.

Using the database of the United States military health care system, Kao et al. [3] mailed a modified questionnaire which was initially designed by Fowler et al. to 1,396 patients who had undergone radical prostatectomy at five military medical centers by multiple surgeons. The analysis of 1,013 questionnaires showed that incontinence was present in 65.6% (any urinary leakage which warranted protection) and had significant impact on quality of life (818 patients evaluated).

Whereas the above-mentioned reports were the result of cross-sectional studies, Litwin et al. [4] performed a longitudinal study on 90 patients who underwent a radical prostatectomy and were followed by self-administered questionnaires at intervals of 3 months through 1 year. They used the RAND 36-Item Health Survey and the University of California, Los Angeles Prostate Cancer Index. There was a steady improvement in urinary function and decrease in urinary bother, but only 61 and 69% reached the baseline respectively. In spite of this, 90% or more of the patients reached the baseline in all other domains such as general health perception, physical and social function after a mean period of 5 months. This study provides relevant data based on reliable and validated instruments and follow-up over 1 year. Although these results have to be confirmed by other investigators, we

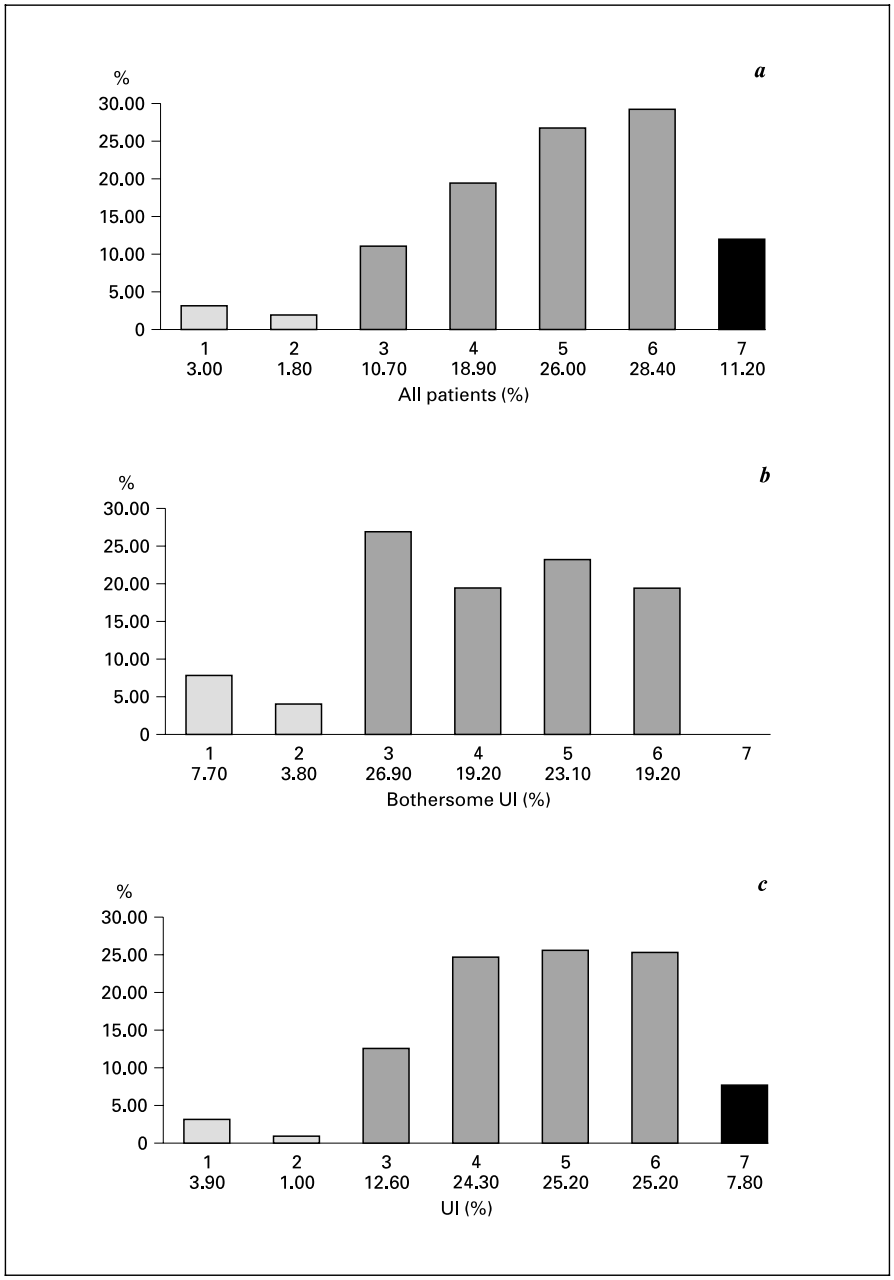

Fig. 1. Charts showing self-related QOL on a 7-item scale with 1 being the lowest and 7 meaning excellent. ***a*** All patients with radical prostatectomy. ***b*** Patients with urinary leakage only. ***c*** Patients with bothersome urinary leakage only.

can already use this information to reassure our patients that after a mean time of 6 months, 90% of patients will experience in most aspects the same quality of life as prior to surgery.

Stanford et al. [5] conclude in their survey that after 18 or more months, 8.4% of patients were incontinent, with men aged 75–79 having a significantly higher incidence of urinary incontinence than younger men.

Sexual Function

The term sexual function includes not only erection but also aspects such as frequency of sexual activity, sexual desire, ability to achieve orgasm and others. After standard radical prostatectomy most of the patients are impotent. Applying so-called nerve-sparing procedures, erectile function may be preserved in a considerable number of patients. Compared to publications on incontinence and HRQOL, even less robust information can be extracted from the present literature.

Braslis et al. [2] and Litwin et al. [4] report that sexual function was diminished significantly after prostatectomy, but only a minority [2] or an unknown percentage of patients had undergone a nerve-sparing procedure. Only 30% of patients in Litwin et al. [4] study reached the baseline in sexual function after a follow-up of at least 12 months. The QOL scores for sexual function were significantly diminished.

Fossa et al. [6] used the EORTC-QLQ-C33 and the PAIS questionnaire for 96 patients in whom a nerve-sparing procedure has been attempted. The impotence rate increased from 18% preoperatively to 78% after prostatectomy. Sexual function score was impaired compared to an observation group, but there was no significant correlation of impaired sexual life to global quality of life.

In a recent study performed by Gralnek et al. [7], 145 patients who underwent a radical prostatectomy were evaluated by means of RAND-36 and UCLA prostate cancer index. In 46 of them a nerve-sparing procedure was performed. In 22 (39%) the erectile function was preserved. The sexual function score and bother score was significantly better than in those in whom the procedure had failed. Importantly in patients with failed nerve-sparing procedure who used erectile aids the sexual function was significantly lower compared to the group of patients who had spontaneous erections sufficient for intercourse. Nevertheless, the sexual bother score was similar in both groups. Only 9% of all patients were less than satisfied with the treatment, impaired sexual function and freedom from disease were the most frequent causes.

Comparative Studies

There are at least three cross-sectional studies using established and validated HRQOL instruments to compare the effects of radical prostatectomy to radiotherapy. Lim et al. [8] used FLIC and POMS to evaluate 135 patients who had either undergone prostatectomy (89) or external beam radiotherapy (46). The mean score for incontinence and sexual function was significantly worse for the prostatectomy group, whereas bowel problems were worse in the radiotherapy group. Interestingly, the perception of incontinence as a big problem was more often noted in the radiotherapy group. Similar results were reported by Shrader-Bogen et al. [9] for a larger group of patients and using different instruments such as FACT-G and PCTO-Q. However, the overall FACT-G summary score as well as the functional well-being (subscale) were not affected after age adjustment. In contrast to these two studies, Fossa et al. [6] did not show any differences comparing radiotherapy with prostatectomy using EORTC-QLQ-C33, I-PSS (urinary symptoms) and PAIS (sexual function). However, radiotherapy patients displayed the highest mean scores for global quality of life. In a logistic regression analysis, severity of urinary tract symptoms and amount of fatigue were the only independent factors which had influence on quality of life.

Recently, Brandeis et al. [10] compared prostatectomy to brachytherapy and healthy controls. They used the same instruments as Litwin et al. [4]. Only physical function scored better for the prostatectomy group regarding the general HRQOL domains. As in previous studies, urinary function was in favor of brachytherapy, whereas bowel function scores were decreased in the brachytherapy group. Prostate cancer index sexual function and bother were equivalent in the prostatectomy and brachytherapy group and worse than in controls.

Conclusions

In summary: radical surgery means complete eradication of cancerous tissue. In case tumor is left behind, local recurrence as well as metastases can only be prevented in a minor percentage of patients by adjuvant measures. Whereas in the first years patients focus on survival, later impairment of quality of live becomes an essential issue later in those remaining without tumor recurrence. Incontinence and sexual dysfunction are the main side effects, which have a significant influence on HRQOL. Since radical prostatectomy for localized prostate cancer is only one of the possible treatment options, the patient has to be informed about the incidence of different side effects and their possible impact on HRQOL of the individual. Appropriate and honest counselling will have a significant influence on the well-being of the patient after completing therapy. Prospec-

tive longitudinal studies are essential to determine the impact of different treatment on the individual HRQOL. Centers of excellence may have better results than reported in surveys, therefore technical skills, selection of patients, counselling and appropriate support are important to improve outcome for the general population. Moreover, every center should evaluate its own patients instead of referring to reports in the current literature. Finally, we should be aware of the fact that the questionnaires we use at present may only partially provide insight into functional disabilities. For sexual function in particular, questionnaires should not substitute a structured and detailed interview.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 106–117

Outcome of Patients Undergoing Radical Cystectomy for Invasive Bladder Cancer

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Introduction

Since the early sixties, radical cystectomy has become the treatment option of choice in the management of high-grade invasive bladder cancer [1]. Improved surgical technique and modern perioperative care has lowered the perioperative complications rate from approximately 35% reported prior to 1970 to less than 10% in more recent series and lowered the operative mortality rate from nearly 20% to less than 2% [2, 3]. Moreover, in the last decade, bladder replacement has become the standard method of urinary diversion [4]. The requirements for an ideal intestinal bladder substitute are low pressure, adequate capacity, and a high compliance, which provides continence and voluntary control of voiding without residual urine [5]. These criteria are best met by orthotopic ileal reservoirs [6]. Perioperative mortality rates in large cystectomy series with simultaneous orthotopic bladder substitution range from 1 to 3.8% [5–7]. Other early and late postoperative complications are usually classified as reservoir-related or not related to the bladder substitute. The frequency of such complications may be substantial [5–7], especially in elderly patients with a higher comorbidity. However, long-term survival rates and function of orthotopic bladder substitutes following radical cystectomy are excellent [6, 8].

Pelvic lymph node dissection (PLND) and radical cystectomy are considered to be the optimal therapy for invasive bladder cancer and are regarded to be superior to radiation therapy or organ-conserving surgery with regard to local tumor control and ultimate cure of cancer [9]. Supporters of bladder preservation strategies are considering combined modality therapy as a reasonable alternative to radical cystectomy [10]. However, the best bladder preservation strategies lead to

elimination of bladder cancer in the short term in 10–20% and 50–80% of patients with T3 and T2 cancers, respectively, while later recurrences in the bladder are seen in 40–60% [9]. This review scopes the results of contemporary cystectomy and the outcome in regard of overall and disease-specific survival rates. The pathological classification used in this analysis is based on the 1992 version of the TNM staging system [11]. T stage was defined as clinical tumor stage, whereas pT stage was defined as the pathological tumor stage assessed from the cystectomy specimen.

The Crucial Role of Clinical versus Pathological Staging of Bladder Cancer

Transurethral ultrasound, CT and MRI imaging can be used to assess clinical tumor stage prior to surgery, but clinical staging of bladder cancer is related to a significant staging error. Preoperative evaluation by CT or MRI scan has yielded unsatisfactory results in regard of accurate T staging and lymph node involvement prediction in early series [12–15]. CT and MRI imaging have limited success in distinguishing between superficial and muscle-invasive disease. Consequently, several groups have reported high rates of understaging for clinically organ-confined tumors. Pagano et al. [16] reported an overall staging error of 44%. Thirty-five percent of T1 or carcinoma in situ lesions and 55% of T2 tumors were clinically understaged in this series. Lerner et al. [17] also reported significant problems with understaging of muscle-invasive but clinically organ-confined tumors. Sixty-eight percent of T2 and T3a tumors were finally staged pT3b or greater. Frazier et al. [18] compared clinical and pathological tumor stage and found that 40.9% of patients had a higher pathological stage than clinical predicted stage. On the other hand, the rate of overstaging was 19.5% for clinically superficial disease (Cis, Ta and T1) and 10.3% for muscle-invasive or non-organ-confined tumors (T2, T3a, T3b and T4). Another 14.1% of patients had no evidence of residual tumors in the final pathology. This overstaging may be in part explained by repeated pre-cystectomy transurethral resections and neoadjuvant chemotherapy that rendered the patient free of tumor or led to downstaging of tumors in the cystectomy specimen. A recently analyzed series with data of 686 patients [19] also revealed an overall clinical staging error of approximately 70%. Clinical staging by TURBT, CT or MRI scans led to overstaging in 19.5% of patients and clinical understaging was present in 49.9% of patients. Again, clinically organ-confined T2 and T3a lesions had a high proportion of understaged tumors (66.6 and 71.6%, respectively). Taken together, these data indicate that clinical staging is unsatisfactory despite powerful imaging techniques like CT and MRI scan. This inaccuracy does gain even more importance in view of the poor

survival rates of patients that have developed non-organ-confined tumors. Inaccurate clinical staging may in some patients lead to a delay until definitive surgery for invasive transitional cell carcinoma. More recent imaging series suggest that sensitivity and specificity for differentiating superficial and muscle-invasive tumors using MRI or CT scan imaging have improved [20, 21]. However, staging of pelvic lymph nodes in bladder cancer by CT or MRI scan is still unsatisfactory [22, 23]. Whether the improvement of these imaging modalities really translates in a better clinical decision-making still needs to be determined.

Radical Cystectomy for Superficial Invasive Disease

Approximately 75–85% of patients with newly diagnosed bladder cancer will present with disease confined to the mucosa (Ta or Cis) or submucosa (T1). Of these, 75% will recur, but only 10–15% will advance to muscle-invasive disease [24]. The remaining 15–25% of patients have primarily muscle-invasive disease with or without positive nodes. The management of patients with superficially invasive bladder cancer is controversial among urologists. Many centers advocate conservative management for patients that present with high-grade transitional cell carcinoma extending into submucosal tissue (T1) and even for patients with superficial muscle-invasive tumors (T2a). Others do suggest early cystectomy in patients with carcinoma in situ or high-grade tumors associated with lamina propria invasion or multifocal high-grade lesions, because as many as 50% of T1 grade 3 lesions will ultimately progress to muscle-invasive disease [24, 25]. The decision toward conservative therapy or immediate radical cystectomy depends on the clinical staging of the tumor and is therefore influenced by the high rate of false negative results in regard of invasion depth [16]. As clinical characteristics associated with recurrence and progression, failure of intravesical chemotherapy and endoscopically uncontrollable disease have been identified [26, 27]. In a recent analysis of high-risk patients that were treated initially with transurethral resection alone or combined with intravesical BCG, Cookson et al. [28] demonstrated that these patients are at a lifelong risk for development of progression. BCG did not prevent progression in patients with high-risk transitional cell carcinoma. One third of these patients are at risk to die from bladder cancer. Dinney et al. [29] recently reported in a retrospective analysis that patients with T1 bladder cancer have a high risk of recurrence (41%) and progression (25%). However, the analysis did not demonstrate an advantage for early cystectomy as definitive therapy for patients with T1 bladder cancer.

On the other hand, results of early radical cystectomy for patients with aggressive superficial bladder tumors are associated with a high overall and disease-specific survival (see table 1). Malkowicz et al. [30] reported in 1990 the

Table 1. Five-year survival rates following radical cystectomy and PLND in patients with superficial or muscle-invasive bladder cancer stage pT3a or less and negative nodes

Group (first author)	Year	Ref.	pT stage	Patients	5-Year survival, %
Skinner[a]	1988	3	pT2	Not stated	83
			pT3a		69
Malkowicz[a]	1990	30	pT0, pTa	12	100
			pCis	40	85
			pT1	14	80
			pT1/pCis	41	78
			pT2	22	76
			pT2/pCis	26	87
Pagano[a]	1991	16	pT2	58	63
			pT3a	Not stated	67
Frazier[b]	1993	18	pCis, pTa, pT1	126	82
			pT2	90	64
Amling[b]	1994	31	pTa	11	88
			pCis	19	100
			pT1	91	76
Freeman[b]	1995	32	≤pT2	120	84
Geschwend[b]	1997	19	pCis	34	96
			pT1	45	92
			pT2	121	82
			pT3a	74	71
Hautmann[b]	1998	8	pT2, pT3a	85	89
Bassi[a]	1999	52	pT0	16	94
(lymph node			pCis	46	78
involvement not stated)			pTa, pT1	49	69
			pT2	67	63
			pT3a	70	53

[a] Actuarial survival.
[b] Disease-specific survival.

results of 160 patients with bladder cancer stage pT2 or less. The 5-year actuarial survival rate for the respective stages at 95% confidence intervals were 100% for pT0/pTa tumors, 80% for stage pT1, 85% for patients with pure carcinoma in situ and 76% for stage pT2 tumors, respectively. Amling et al. [31] analyzed 220 patients with clinical high-grade or recurrent Ta, Cis or T1 disease and found an operative mortality rate of 2.3% and a cancer-specific survival rate of 88, 100, 80

and 76% at 5 years for patients with pTa, pCis, pT0 and pT1 disease, respectively. Freeman et al. [32] reported a series of 182 patients with clinically superficial bladder cancer stage Ta, Cis or T1. 34% of these patients were upstaged in the cystectomy specimen pathology to muscle-invasive disease or metastatic tumors. Only half of the tumors remained organ-confined in the pathology specimen. The median survival for patients with tumors that remained superficially invasive in the final pathology ($\leq$ pT2/pN0) was 10.2 years compared to a median survival of only 6.9 years for tumors that were upstaged to deep invasive or non-organ-confined disease ($\geq$ pT3a $\pm$ pN+). The calculated disease-specific 5- and 10-year survival rate for patients with superficial tumors was 83.6 and 77% respectively in this series. Accordingly, an analysis of 79 cystectomy patients with pure carcinoma in situ or pT1 disease that were treated at Memorial Hospital [19] had disease-specific 5- and 10-year survival rates of 96% for patients with pure carcinoma in situ and 91.7 and 83% for pT1 tumors respectively. The histologic grade seems to influence survival of these patients with superficial pT1 tumors. Due to stage progression and clinical understaging of superficial bladder tumors, early cystectomy with orthotopic bladder replacement was advocated by Freeman et al. [32] to improve survival for patients with aggressive superficial bladder tumors. Moreover, not only stage progression and understaging but also development of micrometastatic disease due to delayed treatment may impact on survival. Analysis of cancer-related survival of patients that had early or delayed cystectomy for muscle-invasive disease demonstrated a significant impact of the interval from first presentation with invasive disease until definitive cystectomy was performed. Time from diagnosis of invasive disease until cystectomy can influence disease-specific survival following radical cystectomy [8, 33]. Additionally, Hautmann and Paiss [8] could demonstrate that patients with delayed cystectomy had a significantly higher number of previous TUR-Bs and/or intravesical or systemic chemotherapy approaches.

Radical Cystectomy for Organ-Confined and Non-Organ-Confined Invasive Bladder

The pathologic stage of the primary tumor translates directly into the curability of bladder cancer. Jewett [34] first subdivided muscle-invasive cancers into superficial, stage B1, and deep, stage B2. The 5-year survival rate for patients with stage A and B1 tumors was 74% compared to 3% for stage B2 and C. Ritchie et al. [35] observed that any degree of muscle penetration adversely affected survival, with almost identical 5-year survival rates following cystectomy for pathologic stage B1 and B2 tumors (39.9 and 40.4%, respectively). Subsequent refinements in staging were based upon more precise correlations between the depth of inva-

sion of a bladder tumor and its prognosis. The recently updated 1997 TNM classification underlines even more the important distinction between organ-confined ($\leq$ pT2b) and non-organ-confined tumors ($\geq$ pT3a) in terms of disease-specific survival.

In 1990, Malkowicz et al. [30] reported results of 160 patients with bladder cancer stage pT2 or less. The 5-year actuarial survival rate for stage pT2 tumors was 76% in this series. Pagano et al. [16] reported findings in node-negative patients with 5-year overall survival rates of 63 and 31% for stage pT2 and pT3 tumors, respectively. A significant difference in the survival was observed in stage pT3 tumors by dividing tumors confined to the bladder (pT3a) from those extending through the bladder wall (pT3b) with an overall 5-year survival rate of 67 and 22%, respectively. Analyzing cancer-specific survival, Frazier et al. [18] reported 5- and 10-year survival rates of 82 and 71% respectively for pT1 tumors and 64 and 48% respectively for pT2 tumors. Hautmann and Paiss [8] analyzed 85 patients that had radical cystectomy and orthotopic urinary diversion for pT2 and pT3a disease and found a favorable 5-year disease-specific survival rate of 89% for this subset of patients. Analysis of patients that had radical cystectomy at Memorial Hospital [19] showed disease-specific 5- and 10-year survival rates of 91.7 and 83% respectively for pT1 tumors, 81.9 and 74.8% respectively for pT2 tumors and 70.5 and 64.5% respectively for pT3a lesions. Disease-specific survival at 5, 7 and 10 years for any organ-confined tumor stage was significantly higher compared with non-organ-confined tumors ($p < 0.0001$). The summarized results of overall or disease-specific survival rates for patients with organ-confined disease and negative nodes analyzed in recent series are shown in table 1.

In sharp contrast, the probability of survival decreases rapidly when the primary tumor penetrates the bladder wall and invades the perivesical fat or adjacent structures such as prostate, vagina, uterus or rectum. Whitmore and Marshall [36] reported 5- and 10-year survival rates of 17 and 5.6% for 42 patients with pT3b tumors treated with radical cystectomy and pelvic lymph node dissection. More recently, Skinner and Lieskovsky [3] reported a 5-year actuarial survival rate of 29% for pathological stage pT3b tumors. Recently, Pagano et al. [16] updated the results from their institution demonstrating 5-year survival rates of 67, 22 and 21% in patients with stage pT3a, pT3b and pT4 tumors. Frazier et al. [18] reported a disease-specific 5- and 10-year survival rate of 39 and 23% for pooled pT3 and pT4 lesions. Unfortunately, these results did not differentiate between pT3a and pT3b or pT4a and pT4b lesions. Patients that had radical cystectomy and orthotopic bladder replacement for pT3b or pT4 tumors experienced a 5-year disease-specific survival rate of 53% [8]. The summarized results of historical and recently published series are shown in table 2, with older series reporting poorer 5-year survival rates of approximately 20%.

Table 2. Five-year survival rates following radical cystectomy and PLND in patients with bladder cancer stage pT3b or more and negative nodes

Group (first author)	Year	Ref.	pT stage	Patients	5-Year survival, %
Whitmore	1962	36	pT3b	42	17
			pT4a	9	0
Richie	1975	35	pT3b	23	20
Pearse	1978	37	pT3b	Not stated	20
Bredael	1980	38	pT3b	24	25
			pT4	11	18
Giuliani	1985	39	pT3[a]	61	11
			pT4[b]	18	0
Skinner	1988	3	pT3b	Not stated	29
Pagano	1991	16	pT3b	Not stated	22
			pT4	40	21
Wishnow	1991	40	pT3b	48	58
			pT4	21	49
Frazier	1993	18	pT3a, pT3b, pT4	240	39
Gschwend	1997	19	pT3b	128	44
			pT4aCis/ducts	17	74
			pT4aStroma	45	51
			pT4b	29	26
Hautmann	1998	8	pT3b, pT4	50	53
Bassi	1999	52	pT3b	72	33
(lymph node involvement not stated)			pT4a[c]/pT4b	49	28

[a] Stage pT3 defined as deep muscle invasion.
[b] Stage pT4 defined as extravesical disease.
[c] Stage pT4a defined as direct extension into the prostate.

Impact of Regional Lymph Node Involvement

Regional lymph node status has consistently been found to be one of the strongest predictors of survival. Cystectomy candidates found to have positive pelvic lymph nodes at the time of PLND are generally regarded to have a poor prognosis, but considerable variation exists among the reported survival rates (table 3). While previous series report rather dismal outcomes [41], contemporary analyses have demonstrated that radical surgery in combination with PLND may in fact provide favorable long-term survival in some cases and that patients most

Table 3. Incidence and survival of patients with nodal metastases following radical cystectomy and PLND

Group (first author)	Year	Ref.	Period	Patients	pN+	Strata	Survival >5 years, %
Whitmore	1962	36	1940–55	230	55 (24%)	Overall	4
Dretler	1973	42	1955–67	302	54 (13%)	Overall	17
Reid	1976	46	1966–74	135	24 (18%)	Overall	26
Bredael	1980	38	1964–73	174	26	Overall	4
Smith	1981	41	1966–77	662	134 (20%)	pN1	17
						pN2	5
						pN3	5
						pN4	0
Skinner	1982	47	1971–79	153	36 (24%)	Overall	35
Zincke	1985	48	1960–80	–	57	Overall	10
Wishnow	1987	49	1983–85	130	18 (14%)	–	–
Grossmann	1988	50	–	–	10	pN1	40
(followed only 40 months)					11	pN2, 3	9
Roehrborn	1991	51	1971–86	280	42 (15%)	pN1	23
						pN2, 3	18
Lerner	1993	17	1971–89	591	132 (22%)	<pT3b	50
						≥pT3b	18
Vieweg	1994	43	1980–88	688	193 (28%)	<pT3b	51
						≥pT3b	17
						pN1	33
						pN2	22
						pN3	0
Bassi	1999	52	1982–94	369	78 (21%)	Overall	15

likely to benefit from radical surgery are those with favorable stage and/or with limited or microscopic lymph node involvement [17, 43–45]. In a detailed analysis of node-positive cystectomy candidates, 1-, 3-, 5- and 10-year survival rates were reported to be 67, 33, 25 and 21% respectively [45]. Survival appears to be a function of the extent of local disease with actuarial 5-year survival of 52% for bladder confined (pT0–pT3a), and 17% for tumors extending outside the bladder wall (pT3b–pT4b) ($p < 0.001$). Survival also seems to be inversely related to the extent and bulk of the tumor in the regional pelvic nodes. Among patients with involvement of a single lymph node (pN1), 33% survived 5 years, whereas only

22% with pN2 (2–5 lymph nodes involved) disease and no patient in the pN3 category (multiple nodes >3 cm) survived 5 years ($p < 0.0006$) [45]. Similarly, Lerner and Skinner [17] reported about actuarial 2-, 3-, 5- and 10-year survival rates of 61, 46, 35 and 24% respectively, when 1–5 lymph nodes were found to be positive for cancer. However, when 6 or more nodes were involved, prognosis was unfavorable with 44, 23, 17 and 17% ($p = 0.012$). Thus, the pT category of the primary tumor in addition to nodal tumor burden (pN category) become important stratification variables in determining who may or may not benefit from radical surgery and may influence the surgeon's decision as to proceed with cystectomy when lymph node involvement becomes evident. Many other clinical and pathological factors that may predict risk of relapse and survival in node-positive patients have been analyzed; however, no further factors have been consistently found to be significant survival predictors in node-positive disease.

In summary, pT category, pN category and distant metastases are the main factors determining outcome in patients with node-positive bladder cancer. PLND and radical cystectomy appear to benefit a small but significant number of patients with node-positive bladder cancer and should be performed especially in cases wherein the tumor is still confined to the bladder wall. Based on the experience reported in the literature, an overall cure rate of about 25% can be expected. Since PLND renders every fourth patient tumor-free, a planned cystectomy should not be abandoned in the face of microscopic lymph node metastases at frozen section. However, grossly enlarged nodes (pN3) generally indicate a poor prognosis. In these patients, radical surgery alone is unlikely to be curative and it is hypothesized that adjuvant treatment options appear to be necessary to improve survival. However, this needs to be tested in properly designed clinical trials. So far, only few controlled preliminary studies for these therapies have demonstrated a significant survival benefit in patients with low tumor burden in an adjuvant setting [53–55]. Till today, no prospective randomized study has convincingly demonstrated that systemic chemotherapy impacts on long-term survival of these patients.

Conclusions

The distinction of pathologically invasive but organ-confined tumors from those that penetrate into the perivesical fat, into adjacent organs or in regional lymph nodes is a crucial prognostic determinant. Staging by the currently used TNM system is highly accurate in predicting prognosis with pT stage and nodal involvement as strong independent predictive variables. Radical cystectomy has proven to be a definitive curative option for organ-confined epithelial bladder cancer. However, for non-organ-confined cancer, cure can be achieved in only

about one third of patients that have extension of disease in either perivesical tissue or with minimal nodal disease. Although local recurrence rates have dropped remarkably with improved surgical technique, the unsatisfactory survival rate for patients with non-organ-confined disease needs to be improved by additional treatment modalities like adjunct chemotherapy. Due to subclinical micrometastasis at the time of surgery, systemic treatment is required in addition to surgery to optimize patient's survival in the future. The reviewed data underline the importance of conducting randomized studies to test the true efficacy of established and new adjunct therapies in combination with radical cystectomy, preferably for this latter subgroup of patients.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 118–130

Invasive Bladder Cancer: Organ Preservation by Radiochemotherapy

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Introduction

The optimal treatment for invasive bladder cancer has been a subject of continuous controversy. In the United States as well as in Europe, the usual approach has been radical cystectomy. Sophisticated techniques for urinary diversion have been developed to improve patients' quality of life. However, even a neovesica cannot substitute for the patient's original bladder. Over the last decades, multimodality organ-sparing treatment has become the standard of care for many malignancies, including anal cancer, prostate cancer, laryngeal cancer, soft-tissue carcinomas, among others. Therefore, the question arises as to whether primary cystectomy can be replaced by an organ-sparing treatment option for bladder cancer without compromising survival. When used alone, neither transurethral resection of the bladder tumor nor chemotherapy or radiation alone results in significant local control. The rational to combine concurrent chemotherapy and radiation is twofold. First, radiation-sensitizing properties of certain cytotoxic agents, in particular cisplatin and 5-fluorouracil, may increase cell killing in a synergistic fashion, resulting in a higher likelihood of achieving total eradication of tumor in the bladder. Second, up to 50% of patients with muscle-invasive bladder cancer harbor occult widespread tumor metastases, which would be left untreated by local treatment alone. Several groups have reported the value of combined modality therapy, including transurethral resection, radiation therapy and concurrent

systemic chemotherapy [3–5, 8, 10, 13, 16]. With these programs, cystectomy has been reserved for patients with incomplete response or local failure following trimodality treatment. We present a 18-year experience with our bladder-sparing approach and report on predictive and prognostic factors influencing survival and bladder preservation.

Patients' Characteristics and Treatment Protocol

Between May 1982 and May 1999, a total of 400 patients suffering from invasive bladder cancer were treated with either radiotherapy (RT) alone or concomitant radiochemotherapy (RCT) after initial transurethral resection (TURB). For analysis, 33 patients were excluded due to nonurothelial cancer (14 patients), insufficient therapy (minimal target dose to the bladder <45 Gy, 13 patients) or T1 cancer without at least one risk factor (6 patients). Risk factors for T1 cancer were defined as tumor grade 3/4, residual tumor after initial TURB, associated Tis, multifocality, a tumor diameter >5 cm or multiple recurrences. All patients were free of distant metastases at the time of onset of RT/RCT. Lymph node metastases (detected by computed tomography or ultrasound), multiple TURBs prior to RT/RCT, or poor general condition with contraindications for radical cystectomy were not exclusion criteria. Patient's and tumor characteristics are shown in table 1.

Treatment was commenced by TURB aimed at maximal reduction of the tumor mass. The protocol scheme is depicted in figure 1. Residual tumor was assessed histologically by biopsies from all resection margins: R0 indicated microscopically complete TURB, R1 microscopic tumor residual, R2 macroscopic tumor residual. T category and grade were assessed according to the TNM classification of 1992 (UICC). RT was initiated 4–8 weeks after initial TURB using 10-MV photons and a 4-field box technique with individually shaped portals and daily fractions of 1.8–2.0 Gy on 5 consecutive days. A median dose of 54 (range 45–69.4) Gy was applied to the bladder, the pelvis was irradiated with a median dose of 45 (range 40–59.4) Gy. Seventy-nine patients additionally received a median dose of 45 (range 16.2–54.4) Gy to the para-aortic lymph nodes. A total of 120 patients were treated by RT alone. Since October 1985, chemotherapy has been given simultaneously with RT. CT was applied in the first and fifth week of RT and consisted of cisplatin (25 mg/m^2/day) in 126 patients, carboplatin (65 mg/m^2/day) was administered in 87 patients with decreased creatine clearance (<50 ml/min) or congestive heart disease. Since 1993 a combination of cisplatin (20 mg/m^2/day) and 5-fluorouracil (5-FU; 600 mg/m^2/day) was applied to 34 patients. Full-dose chemotherapy was received in 149 patients, i.e., the prescribed doses of cisplatin, carboplatin and 5-FU were administered in the first

Table 1. Patients and tumor characteristics (n = 367)

Male/female	285/82
Age (median and range), years	67 (31–93)
T category	
T1 (high risk)	76
T2	80
T3	184
T4	27
Grading	
G 1/2	170
G 2/3	196
Unknown	1
R status after 1st TURB	
R0	93
R1	127
R2	145
Rx	1
Lymph node metastases	
cN0	339
cN+	26
cNx	1
Invasion of lymph vessels	
Yes	168
No	176
Unknown	23
Associated carcinoma in situ	
Yes	68
No	255
Unknown	44
Multifocal tumor	
Yes	108
No	252
Unknown	7

and at least 75% in the second cycle. In 75 patients, the doses had to be reduced due to hematotoxicity or nephrotoxicity. However, for analysis of the impact of chemotherapy on the different endpoints, all patients were included ('intent-to-treat analysis').

Six to eight weeks after completion of RT/RCT, the response quality was evaluated by deep TURB of the former tumor bed. In case of histologically proven complete response, patients were followed at 3-month intervals, including cys-

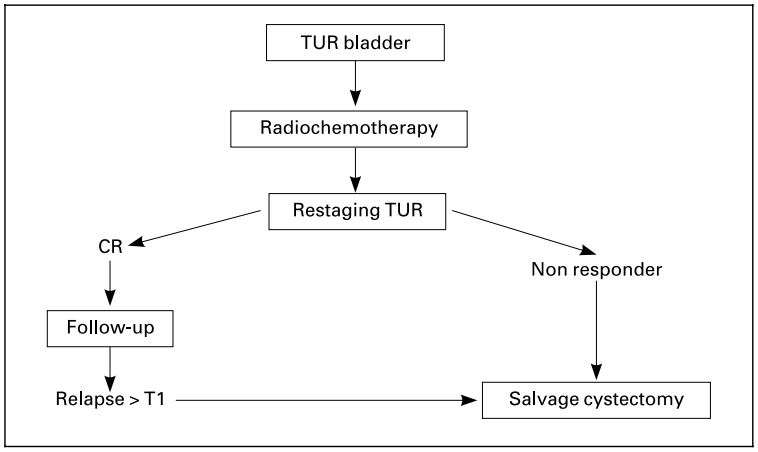

Fig. 1. Treatment scheme for patients with invasive bladder cancer at Erlangen University.

toscopy and biopsies of all suspected areas. In case of residual invasive tumor or invasive recurrent tumor, salvage cystectomy was recommended.

All patients were followed up until May 1999. At the time of analysis, the median follow-up for all surviving patients was 57 (range 3–179) months. Sixty-nine patients have been followed up 5 years and more. Survival rates were calculated according to Kaplan-Meier, differences were tested for statistical significance by the log rank test. Multivariate analyses were performed using logistic regression analysis (initial response) and the Cox model (censored data). The following factors were tested for predictive and prognostic impact on initial response, local control, distant metastases and survival rates: age, R status after initial TURB, T category, grade, invasion of lymph vessels, associated carcinoma in situ, multifocality of the tumor, evidence of pelvic lymph node metastases, RT vs. RCT, and RCT with cisplatin-based regimens vs. RCT with carboplatin.

Results

Initial Response

Initial TURB provided a curative resection (R0) in 25.3% (93 of 367 patients). As shown in figure 2, a complete remission (CR) at restaging TURB was achieved in 269 patients (73%). After RT alone, CR was 61% (71 of 117 patients), after RCT 81% (198 of 244 patients). CR rate was highest after RCT with combined 5-FU/cisplatin (88%, 30/34 patients) and cisplatin (85%, 105/123 patients),

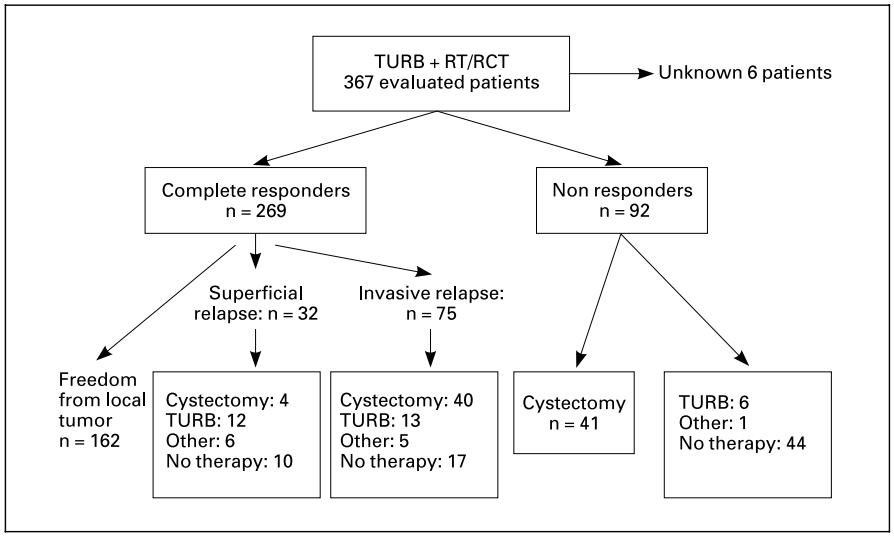

Fig. 2. Outcome of patients with complete and incomplete response to combined modality treatment.

Table 2. Predictive factors for initial response

	Univariate	Multivariate
Age	0.01	NS
Grade 1/2 vs. 3/4	NS	–
R status after 1st TURB	<0.0001	<0.0001
T category	<0.0001	0.0002
RT vs. RCT	0.0001	0.005
RCT-cis/5-FU vs. RCT-carbo	0.008	0.03

and lowest after carboplatin (72%, 63/87 patients). The impact of therapy modality on initial response was confirmed by multivariate analysis (table 2). RCT was more effective than RT alone ($p = 0.005$) and cisplatin-containing regimens more effective than RCT with carboplatin ($p = 0.03$). The strongest impact on initial response, however, could be demonstrated for R status after initial TURB ($p < 0.0001$) and T category ($p = 0.0002$). In univariate analysis also pelvic lymph node status was significantly associated with CR ($p = 0.006$). None of the other histopathologic factors revealed predictive value for initial response.

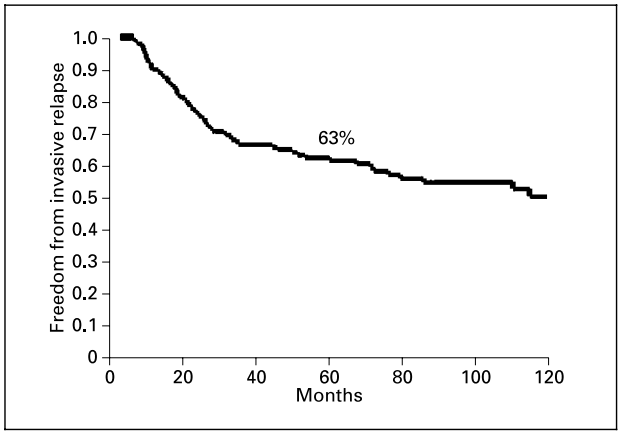

Fig. 3. Freedom from invasive relapse for patients with complete response after RT/RCT.

Local Control with Preserved Bladder

Among 269 patients who had no evidence of disease at restaging TURB, 162 have been continuously free of tumor in their bladder and 33 experienced a non-invasive relapse (fig. 2). Thus, 5- and 12-year rates of freedom from invasive bladder recurrence was 63 and 52% (fig. 3). Interestingly, none of the established histopathologic markers, including R status and T category, nor the treatment strategy (RT vs. RCT) did predict for an invasive treatment failure once CR had been achieved by primary treatment. However, invasion of lymph vessels and, in particular, multifocality of the primary tumor were significantly related to a higher risk for invasive relapse (table 3).

Salvage Cystectomy

Eighty-five patients (23%) underwent salvage cystectomy: 41 of 92 nonresponders and 44 of 269 patients with initial complete response (fig. 2). It should be noted that in 51 patients with invasive persistent disease after RT/RCT and in 35 patients with invasive local recurrences, salvage cystectomy could not be performed due to poor general health or advanced age, which were not exclusion criteria for our treatment nor for this analysis. Median time between end of RT/RCT and cystectomy for nonresponders was 6.6 (2.5–28) months, for patients with invasive relapse 26 (9.6–114) months. Cause-specific survival at 5 years for patients after early cystectomy (nonresponders) was 20%, for patients after salvage cystectomy for invasive recurrence 60% ($p = 0.001$), indicating the curative potential of salvage cystectomy for relapsed patients after CR, and the poor over-

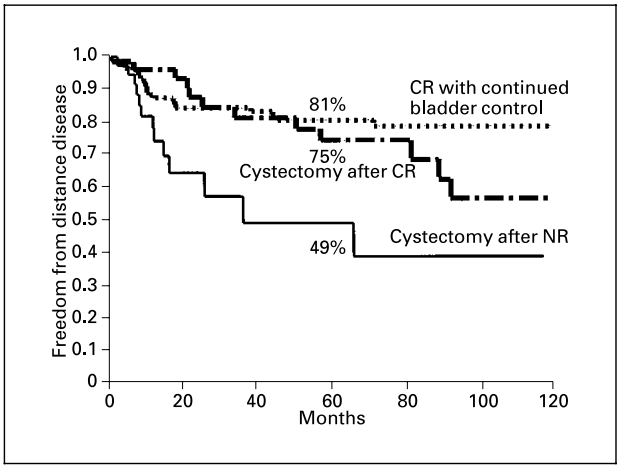

Fig. 4. Freedom from distant metastases for patients with continued bladder control and for patients who underwent cystectomy after complete response (CR) or as nonresponders (NR), respectively.

all prognosis for patients with nonresponding, thus biologically less favorable tumors, even when salvage cystectomy could be performed.

Distant Metastases

Distant metastases have been diagnosed in 84 patients with an actuarial rate of 29 and 38% at 5 and 10 years, respectively. After CR with continued bladder control, the 5-year rate of developing distant metastases was 20% (fig. 4). In patients who were complete responders after RT/RCT but experienced a local failure that required salvage cystectomy, this rate was 25% at 5 years. In patients, however, with nonresponding tumors who had undergone immediate cystectomy, more than 40% developed distant metastases within the first to years (fig. 4). Interestingly, concurrent systemic chemotherapy had no impact on the development of distant disease, neither for the whole group of evaluated patients (n = 367) nor for patients with CR after RT/RCT (n = 275). Prognostic factors for distant disease are shown in table 3: only T category and lymph node metastases were independently related to this endpoint.

Survival and Bladder Preservation

Overall survival and cause-specific survival for all patients was 48 and 53% at 5 years and 29 and 39% at 10 years, respectively. Of all surviving patients, 80% maintained their own and well-functioning bladder (44% at 5 years and 32% at

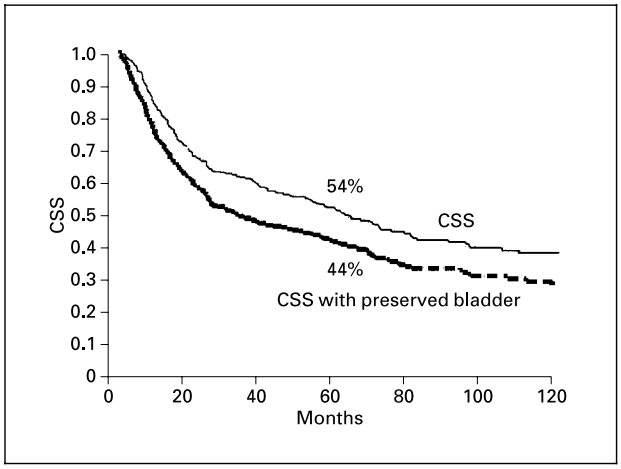

Fig. 5. Cause-specific survival for all patients. In the lower plot, salvage cystectomy was taken as an additional event.

Table 3. Prognostic factors for local control and distant metastasis

	Local control (no invasive relapse after CR)		Distant metastasis	
	univariate	multivariate	univariate	multivariate
R status after 1st TURB	NS	–	0.002	NS
T category	NS	–	0.002	0.008
Lymph node metastases	NS	–	0.003	0.006
Lymph vessel invasion	0.05	NS	0.03	NS
Multifocality	0.01	0.04	NS	–

10 years; fig. 5). Cause-specific survival after 5 and 10 years was 40 and 30% for RT, 53 and 38% for RCT-carboplatin, 64 and 48% for RCT-cisplatin and 76% at 5 years for RCT-cisplatin/5-FU. The strongest impact on CSS was noted for R status after initial TURB and T category (fig. 5, 7). An independent value in multivariate analysis was also confirmed for treatment mode (RT vs. RCT), age and grade (table 4). For the endpoint cause-specific survival with preserved bladder, only R status and T category remained significant in multivariate analysis.

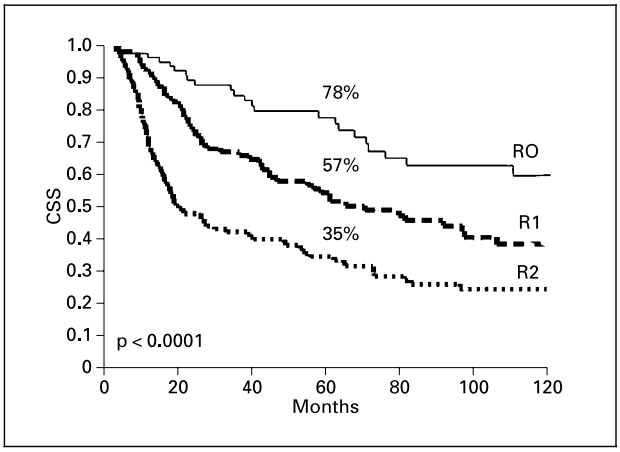

Fig. 6. Cause-specific survival for all patients according to R status after 1st TURB.

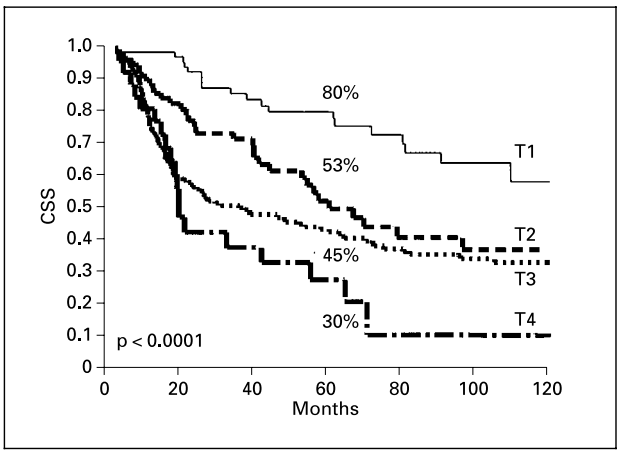

Fig. 7. Cause-specific survival for all patients according to T category after 1st TURB.

Acute and Late Toxicity

Typical acute radiation-induced side effects, such as transient urocystitis and enteritis, were easily managed by symptomatic treatment. Thirty-one percent of the patients receiving CT experienced WHO grade III and 2% grade 4 hematologic toxicity. One patient experienced tumor bleeding during RCT and underwent immediate cystectomy. In 2 patients, late gastrointestinal toxicity WHO

Table 4. Prognostic factors for cause-specific survival (with preserved bladder)

	CSS		CSS with preserved bladder	
	univariate	multivariate	univariate	multivariate
Age	0.007	0.01	NS	–
Grade 1/2 vs. 3/4	0.04	0.03	0.03	NS
R status after 1st TURB	<0.0001	0.0003	<0.0001	0.0001
T category	<0.0001	0.006	0.0002	0.02
Lymph node metastases	0.03	NS	0.03	NS
Lymph vessel invasion	0.007	NS	0.003	NS
RT vs. RCT	0.001	0.02	NS	–

grade IV occurred. One patient died after resection of the damaged intestinal loop perioperatively. The second patient suffered from necrotizing enteritis. He underwent resection and is free of complications. Three patients underwent cystectomy due to shrinking bladder following multiple TURBs before RT.

Discussion

Treatment of invasive bladder cancer remains a triple challenge: (1) the eradication of local disease; (2) the elimination of potential micrometastases, and (3) the maintenance of the best quality of life possible without compromising survival. Mounting evidence is now arising that bladder preservation by combined modality treatment with salvage cystectomy reserved for local failures results in long-term cure and overall survival similar to the best cystectomy-based series [11]. Moreover, approximately 80% of long-term survivors maintain their own normal functioning bladder. The understandable concern of urologists about an organ-sparing treatment has been addressed in this and in a number of other recently published series: (1) Radiation and concurrent chemotherapy provide complete response in more than 80% of tumors. Durable local control without distant metastases is achieved in the majority of these patients. (2) Salvage cystectomy with continent diversion can still be performed when it is proven to be necessary and still has a curative potential. (3) The irradiated preserved bladder functions well with only three cystectomies being necessary due to shrinking bladder within our observation period of 18 years. In this regard, it is important to stress that cystectomy due to shrinking bladder exclusively occurred after multiple TURBs preceding definitive RT, which is a clear risk factor for late complica-

tions after RT. Thus, it is recommended that combined modality treatment should be administered by dedicated multimodality teams making selective organ preservation therapy in invasive bladder cancer a medically reasonable alternative to radical cystectomy.

As more experience is acquired with organ-sparing treatment, it is clear that future directions of clinical and basic research will focus on two main topics: (a) the optimization of the treatment modalities, including incorporation of new cytotoxic agents, and (b) the proper selection of patients who will most probably benefit from the respective treatment alternatives. As demonstrated in our study, clinical criteria helpful in determining patients for bladder preservation include such variables as early tumor stage and a TURB as thorough as safely possible. These two factors revealed the strongest impact on initial response and long-term cure. Radiation with concurrent chemotherapy not only increased the rate of complete remission from 61% by RT alone to 81%, but was also associated with a significantly improved cause-specific survival. Carboplatin appeared to be less effective than cisplatin, with the combination of cisplatin and 5-FU being most efficacious. The safety profile and feasibility of this more aggressive regimen has been published in detail elsewhere [2]. It is noteworthy that the improved survival rate with combined RCT compared to RT alone was primarily an effect of the higher initial response rate. However, as TURB has also become more radical in recent years and total tumor resection (R0) is now attempted whenever feasible, the contribution of either treatment intensifications to improved local control and survival cannot be determined. Interestingly, the addition of chemotherapy did not show any impact on the development of distant metastases in our study, which is also reflected in the contradictory, albeit mostly negative results of adjuvant and neoadjuvant chemotherapy in cystectomy-based series [7, 9, 14]. Several new active chemotherapeutic agents, particularly gemcitabine [15] and the taxanes [1], may show promise in the treatment of transitional cell carcinoma and should also be incorporated in bladder-sparing approaches [6], especially in patients with a high likelihood for developing distant disease (advanced T stage, lymph vessel invasion, lymph node metastases).

To further optimize patient selection, it should be of pivotal interest to recognize the 20% or so of patients who do not respond to RCT. In our study, these patients showed a cause-specific survival rate of only 20%, even when salvage cystectomy could be performed, and more of 40% developed distant metastases within the first 2 years. Evidently, these tumors have a biologically less favorable profile and prompt cystectomy, possibly combined with more aggressive adjuvant chemotherapy, might be more effective in these patients. However, tumor heterogeneity is so great in bladder cancer that conventional histopathologic classification is inadequate for predicting the response to RCT for individual lesions. Translational research to identify molecular markers that may better identify a

tumor's true malignant potential as well as its response to specific cytotoxic therapies are sorely needed. We have recently published an immunohistochemical study in 70 patients with invasive bladder cancer, who were uniformly treated by RCT within our bladder-sparing protocol [12]. A high rate of spontaneous apoptosis and a high rate of proliferation, as measured by the Ki-67 labeling index, were significantly related to initial complete response and better local control with bladder preservation. Furthermore, in this present study, we identified 'multifocality of the tumor' as a risk factor for invasive relapse in patients who have achieved complete response at primary treatment. This may indicate that multifocality of the tumor is associated with transitional cell epithelium having a high propensity to develop recurrent or secondary carcinoma. This subgroup of tumors may also be better treated by prompt cystectomy; at least a close follow-up with regular cystoscopies is mandatory in patients with multifocal tumor who seek bladder preservation. Further studies are necessary to select tumors less likely to respond to or recur after RCT. However, we anticipate that translational research will further identify tumor subtypes with a high predictive value for success of bladder-preserving therapy. Based on these data, a multiparametric predictive assay would allow early choice of the best treatment regimen and therefore avoid unnecessary morbidity associated with cystectomy or RCT. Thus, both strategies would no longer be competitive, but complementary.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
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Radiation, Chemotherapy and Transurethral Surgery: An Organ-Sparing Alternative to the Radical Cystectomy

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Introduction

Bladder cancer is the fourth most common cancer amongst men and the eighth most common amongst women in the USA, with around 54,000 new cases and 8,000 bladder cancer deaths per year. The incidence increases with age and the median age at diagnosis in most series is 64–68 years, with less than 1% occurring in patients under the age of 40 years. Males are affected at least 3 times as often as females. The majority of cases in the western world are of transitional cell origin [1].

Bladder cancer represents a wide spectrum of diseases that can be grouped into three major categories: superficial; invasive (of the bladder wall), and metastatic. These tumors differ in their clinical behavior, their prognosis, and their primary management. For a superficial tumor the goal is to prevent superficial relapses as well as to prevent progression to an incurable stage. For metastatic disease the issue is one of choosing the most effective palliation. This review will concentrate on those with muscle-invading tumors. Here the issues are: which patients need radical removal of the bladder (cystectomy) for cure; which can be successfully cured without the need for radical surgery, and who is at such a risk for occult metastatic disease that adjuvant chemotherapy is necessary to boost the chance for cure.

Table 1. Organ conservation: the oncologic standard of the 1990s

Breast carcinoma
Anal carcinoma
Laryngeal carcinoma
Esophageal carcinoma
Limb sarcomas
T2–3 bladder carcinoma

Treatment Options in Muscle-Invading Bladder Cancer

The treatment for patients with muscle-invasive disease can be broadly divided into those that spare the bladder and those that involve removing it. In the USA and Germany the most common treatment is the surgical removal of the entire organ, its adnexae, and the regional lymph nodes: the radical cystectomy. The standard bladder-sparing treatment over the last three decades has been external beam radiation therapy. In the USA, radiation has been recommended a primary treatment only for patients judged 'unfit' for cystectomy on the basis of age, comorbid conditions, or disease extent. At least in part because of these negative selection criteria the reported retrospective series employing radiation alone are inferior to those reported with radical surgery [2–9]. The difference may also be due to two other factors. First, approximately 15% of patients are excluded from treatment by radical surgery because at the time of operation previously unrecognized extensive extravesical tumor is found. Thus in cystectomy series, but not in radiation series, some patients with locally metastatic tumors are excluded. Secondly, in most radiation series radiation was employed as a single modality. This we now recognize to be a vastly inferior form of treatment when compared with combined modality therapy. The latter aims to enhance the action of radiation by prior tumor debulking and concomitant sensitization with chemotherapy. During the last decade multimodality organ-sparing treatment has become the standard of care for many solid malignancies (table 1). The most strikingly successful advances have been seen in cancers of the breast, anus, esophagus, head and neck where radical surgery is routinely avoided. Multimodality therapy with organ preservation is now a realistic and competitive option for those patients with invasive bladder cancers who wish to avoid the rigors of a radical cystectomy.

When assessing the safety and efficacy of a bladder-conserving approach, the standard against which it must always be measured is the radical cystectomy. Pelvic recurrence rates are between 5 and 30% in reported series depending upon the clinical stage of the primary tumor [5, 7–9]. Overall 5-year survival figures are between 45 and 60%. Attempts to improve the outcome have taken two thrusts. The first is to make the loss of the native bladder more socially acceptable to patients, and the second is an attempt to increase cure rates by combining surgery with chemotherapy.

Following a radical cystectomy, the urinary flow from the ureters is directed into a conduit (usually an ileal loop) or into a conduit reservoir as a bladder substitute. In the standard ileal loop (Bricker) procedure the urine drains directly from the ureters into a segment of isolated ileum and then to the skin surface where it is collected at the stoma in an external bag. No internal reservoir is created. For continent diversions, bowel segments are created and used as reservoirs that are either intermittently catheterized by the patient through the abdominal wall stoma or are anastomosed to the urethra (the orthotopic neo-bladder) allowing the patient a chance of voiding more naturally [5]. Although continent diversions are becoming more popular, they are still only performed on a minority of patients undergoing radical cystectomy for muscle-invading tumor. They are also not without their problems such as enuresis, stenosis, mucosuria, alkalosis and progressive renal impairment. Revision procedures are common. Interestingly, in the largest reported series looking at quality of life, patient satisfaction was no higher with continent diversions, particularly the neo-bladder, than with the old-fashioned ileal conduit [10]. This probably reflects the raised expectations that such surgery brings and which is not easily satisfied. Continent diversions have proved seductive to surgeons who feel that they represent a significant step up for their cystectomy patients in terms of quality of life. Nevertheless, whatever the skill of the surgeon, a urinary diversion must always be inferior to a preserved, functioning, tumor-free bladder.

Patients with muscle-invading tumors have high rates of occult micrometastases (up to 50%) at the time of cystectomy and these usually manifest themselves over the subsequent 3 years. Adjunctive chemotherapy has therefore been widely studied in an attempt to reduce this rate. It may either be given prior to surgery (neoadjuvant), a sequence that delays definitive surgery but may have the advantage of facilitating it by tumor shrinkage, or it may be given after (adjuvant). Three randomized trials have failed to demonstrate any survival benefit from single- or multiple-agent neoadjuvant combinations when added to cystectomy [8, 11, 12]. Similarly a meta-analysis of several randomized trials showed no benefit from a neoadjuvant approach either [13]. By contrast, the Nordic Cooperative

Bladder Study 1 [14] has recently been updated and now reports a survival benefit at 5 years of 12% by the addition of two cycles of cisplatinum and doxorubicin in stage T3–4 patients receiving preoperative radiation and cystectomy. None of the randomized trials evaluating postcystectomy single-agent chemotherapy have shown any survival benefit [4]. Three randomized trials of multidrug adjuvant chemotherapy, all from single institutions (and all with some criticisms of trial design), have not shown a significant improvement in recurrence-free survival [15–17]. Many medical oncologists currently recommend adjuvant chemotherapy for patients with adverse pathologic features – the justification coming from their ability to delay, if not prevent, relapse.

Though chemotherapy may ultimately improve the outcome from radical cystectomy, it does not help to make surgery more attractive than the bladder-sparing alternatives. Indeed, one of the putative advantages of radical surgery, that it is a single-stage procedure and thus less complex, expensive, and time-consuming than the bladder-conserving alternatives, now disappears.

Bladder-Conserving Approaches

Randomized Comparisons of External Beam Radiation with Radical Cystectomy

External beam radiation has in Europe, and formerly in the USA, been the standard alternative to radical surgery. Implicit in its use is the understanding that should recurrence occur within the bladder, salvage by cystectomy remains feasible and, if appropriate, will be attempted. The fear of the urologic community has been that deferring definitive surgery and reserving it for relapse gives a second opportunity for metastases to occur and compromises survival. By 1985, four randomized trials had compared cystectomy (with preoperative radiation) with external beam radiation therapy with cystectomy reserved for those with persistent or recurrent bladder cancer (table 2). In 1977, Miller [18] reported the results of a randomized trial from the M.D. Anderson Hospital for patients with large T3 tumors. Of 35 patients randomized to receive primary cystectomy, 45% survived 5 years compared to 22% for the 32 patients receiving primary radiation. This is the only trial that reported a statistically significant survival advantage to immediate cystectomy. This trial has been criticized because only patients with large T3 tumors were entered who, as we now know, were unlikely to be cured by radiation as monotherapy. The Urologic Cooperative Group from the United Kingdom reported a much larger trial of 187 randomized patients. The recently updated results [19] report 5- and 10-year survival patients for the 98 patients randomized to immediate cystectomy as 39 and 19%, while for the 91 patients randomized to radiation therapy with salvage surgery the comparable

Table 2. Randomized trials of irradiation that did or did not defer radial cystectomy for salvage of recurrence

Treatment	Patients	Clinical stage	5-Year survival %	10-Year survival %	Present distant metastases
M.D. Anderson Hospital [18]					
50 Gy + cystectomy	35	T3	46	–	–
60 Gy + salvage cystectomy	32	T3	22	–	–
UK Cooperative Group [19]					
40 Gy + radical cystectomy	98	T3	39	19	–
60 Gy + salvage cystectomy	91	T3	28	15	–
National Danish Trial [20]					
40 Gy + radical cystectomy	88	T3	29	–	34
60 Gy + salvage cystectomy	95	T3	23	–	32
National Bladder Cancer Group[a]					
40 Gy + radical cystectomy	37	T2–T4a	27	–	38
60 Gy + salvage cystectomy	35	T2–T4a	40	–	31

[a] S.D. Cutler, pers. commun. 1983.

figures were 28 and 15%. The differences were not statistically significant. Analysis of outcome at 5 years by subgroups within this randomized trial (even though such an analysis may be statistically inappropriate) identified that women had a statistically insignificant trend towards a survival benefit if randomized to radiation. Likewise, men who were less than 60 years of age had a survival advantage if randomized to immediate surgery. In 1991 [20] the Danish National Bladder Cancer Group also reported no statistical survival difference in overall survival in the two arms of their study. The median follow-up was 50 months for 183 patients. The local/pelvic failure rate was, however, significantly lower in the group randomized to receive immediate cystectomy (7%) compared with those randomized to receive radiation therapy alone (35%). Twenty-seven of the patients with persistent or recurrent tumor underwent salvage cystectomy. The incidence of metastatic disease was similar in both groups, 32 and 34% at 5 years. The National Bladder Cancer Group performed a randomized trial of 72 patients [S.D. Cutler, pers. commun. 1983]. There was no difference in the 5-year survival rate nor the rate of distant metastases for patients randomized to immediate cystectomy (27 and 38% respectively) compared to those undergoing primary radia-

Table 3. Muscle-invading bladder cancer; success rates of bladder preservation with monotherapy

Treatment	Evaluated series	Total patients	Percent with bladder, free of invasive recurrence
Transurethral resection alone[a] [23, 24]	2	331	20[b]
Radiation therapy alone[c] [25–29]	5	949	41
Chemotherapy alone[c] [30] (cisplatin + methotrexate)	1	27	19

[a] Used selectively as monotherapy, most patients at these centers had cystectomy.
[b] Intravesical drug therapy often used for noninvasive recurrent tumors.
[c] No transurethral resection of tumor.

tion therapy with cystectomy only for recurrence (40 and 31% respectively). The median follow-up period in that study was 66 months. In the two trials that reported the incidence of distant metastases, there was no increased rate among those patients receiving radiation with deferred cystectomy for salvage [21]. The Memorial Sloan-Kettering Cancer Center also reported that deferring cystectomy in patients treated with the neoadjuvant chemotherapy regimen M-VAC (methotrexate, vinblastine, adriamycin, and cisplatinum) did not alter the overall survival at 5 years using both univariate and mutlivariate analyses [22].

Advances in Bladder-Preserving Approaches with Combined Modality Therapy

When used alone for muscle-invading disease, transurethral resection and chemotherapy provide durable local control in less than 20% of patients (table 3) [23, 24]. External beam, while controlling approximately twice that proportion, still falls far short of the ideal and leaves the need for salvage cystectomy a probability not a possibility [25–29]. As a consequence, the last decade has seen much interest in combined modality approaches to improve local control modeled on the paradigms successfully developed in anal and breast cancer. There is a double rationale for combining chemotherapy, radiation and limited surgery. First, local control may be enhanced by the cytoreduction prior to radiation. Both surgical debulking (transurethral resection) and cytotoxic drug therapy may achieve this. In addition, certain cytotoxic agents, in particular cisplatinum and 5-fluorouracil (5-FU), are capable of sensitizing tumor tissues to radiation if given concomitant-

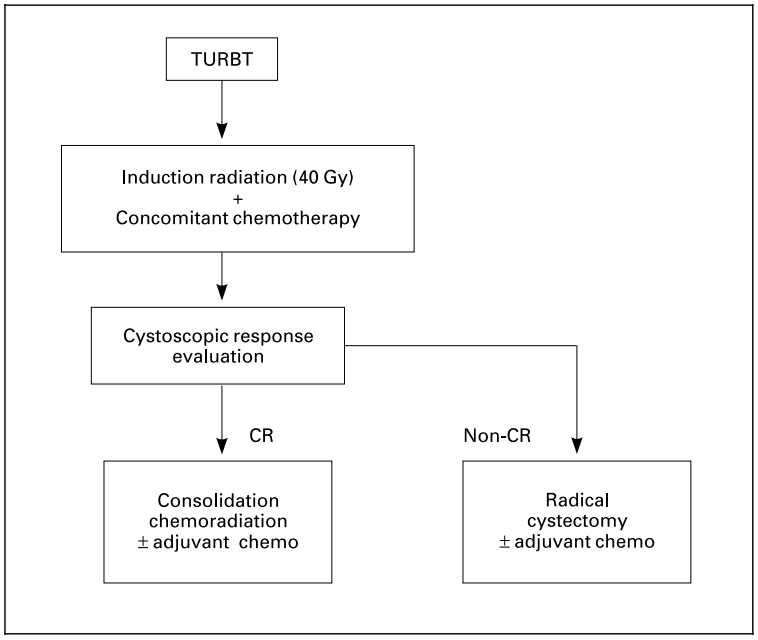

Fig. 1. A schema for an organ-conserving approach to the management of muscle-invading bladder cancer.

ly, thus increasing cell kill in a synergistic fashion. Second is the problem of occult metastatic disease that is not solved by any local therapy, no matter how aggressive. The identification of effective drugs that can be used in an adjuvant or neoadjuvant setting is one of the priorities in this field.

It is now clear that combining chemotherapy, radiation and transurethral resection (trimodality therapy) is a highly effective approach in carefully selected patients. The key to the success of such a program is the selection of patients for bladder conservation on the basis of their initial response to therapy. Bladder conservation is reserved for those who have a clinical complete responding when evaluated at a midpoint in therapy (fig. 1). These patients, approximately two thirds of the total, receive consolidation chemoradiation and then are followed indefinitely with regular cystoscopic examinations (table 4). Incomplete responders at this midpoint are encouraged to undergo cystectomy before their disease can progress and before they have received radiation doses that might make the continent diversion surgery more difficult and prompt cystectomy in those whose invasive tumor persists or recurs. For patients of similar age and with matched

Table 4. Muscle-invading bladder cancer; complete response rates after monotherapies and combined modality therapies

Treatment	Evaluated series	Total patients	Percent complete responses
Radiation therapy alone [26, 27, 31, 32]	4	721	45
Chemotherapy alone [33–38]	6	301	27
TURBT + chemotherapy [39–42]	4	225	51
TURBT + chemoradiotherapy [43–46]	4	218	71

TURBT = Transurethral resection of tumor.

Table 5. Recent results of TURBT and chemotherapy concurrent with radiation

Series	Induction treatment	Patients	5-Year survival %	5-Year survival with bladder preservation, %
Dunst [49]	TURBT, cisplatin and XRT	79	52	41
RTOG, 1993 [45]	Cisplatin and XRT	42	52	42
Kachnic [50]	TURBT, MCV, cisplatin and XRT	106	52	43
RTOG, 1997 [51]	TURBT, ± MCV, cisplatin and XRT	123	49	38
Paris, 1997 [48]	TURBT, 5-FU, cisplatin and XRT	120	63	–

XRT = External beam irradiation; MCV = methotrexate, cisplatin; TURBT = transurethral resection of tumor.

clinical stage of disease, trimodality therapy gives overall survival rates comparable to any reported in radical cystectomy series (40–63% at 5 years) (table 5). In addition, these selective bladder-preserving approaches have resulted in approximately 80% of the long-term survivors maintaining a normal functioning bladder.

Although a variety of drugs and different radiation dose schedules have been used, the highest clinical complete response rates (or a T0 bladder response) are

achieved in patients who receive concurrent chemotherapy rather than sequential treatment. One of the clearest examples of the success of concurrent chemoradiation for bladder preservation was reported in a study from the University of Paris [47, 48]. Transurethral resection of the bladder tumor (TURBT) followed by concurrent cisplatinum, 5-FU and accelerated radiation was used initially as a precystectomy regimen. The first 18 patients demonstrated no residual tumor on cystoscopic evaluation and re-biopsy, but all underwent cystectomy in accordance with the study design. None had any tumor in the cystectomy specimen. Thus a 100% complete response was truly achieved in patients who had been clinical complete responders. In previous studies of TURBT and M-VAC chemotherapy, only 50% of those judged clinical complete responders proved to be tumor-free at cystectomy. Thus, the addition of radiation improves the correlation between clinical complete responder and pathologic complete responder and makes the selection of patients for bladder conservation on the basis of clinical response a safer option. This has been borne out in practice. The likelihood of surviving 5 years with the native bladder was 38–43% after trimodality therapy (around 80% of those alive) compared with 20% (40% of those alive) for TURBT and chemotherapy alone. In one series from the University of Florida [53], radiation was only given to half of those receiving chemotherapy and TURBT – the results were correspondingly inferior (18% bladder preservation at 5 years). Trimodality therapy results in higher rates of bladder preservation but not a higher survival rate than treatment with transurethral resection and chemotherapy alone. This is likely due to the fact that with both approaches, patients are followed closely with surveillance cystoscopy and prompt salvage cystectomy performed on relapse.

The University of Paris group (see above) changed policy and began to use clinical complete response as a justification for bladder conservation. In a larger and more mature series of 120 patients, 77% had a clinical complete response after trimodality therapy [48]. Those who had not had a complete response underwent immediate radical cystectomy. The 5-year survival rate was 63%. At the University of Erlangen, 93 patients treated with maximal TURBT plus radiation and concurrent cisplatinum had clinical complete response rates of 85% [49]. Five-year overall survival was 61%, with 47% retaining a functioning bladder at 5 years.

At the Massachusetts General Hospital we have reported our experience with 106 patients treated with trimodality therapy using concurrent cisplatinum chemotherapy and daily radiation to a dose of 40 Gy [50]. In some cases, depending upon the era and departmental protocol, this was preceded by MCV neoadjuvant chemotherapy. The 70 clinical complete responders received consolidation radiation to a total dose of 65 Gy together with further sensitizing cisplatinum. Immediate radical cystectomy was performed on 13 patients who were less than complete responders and 6 who were unable to tolerate the induction chemoradiation.

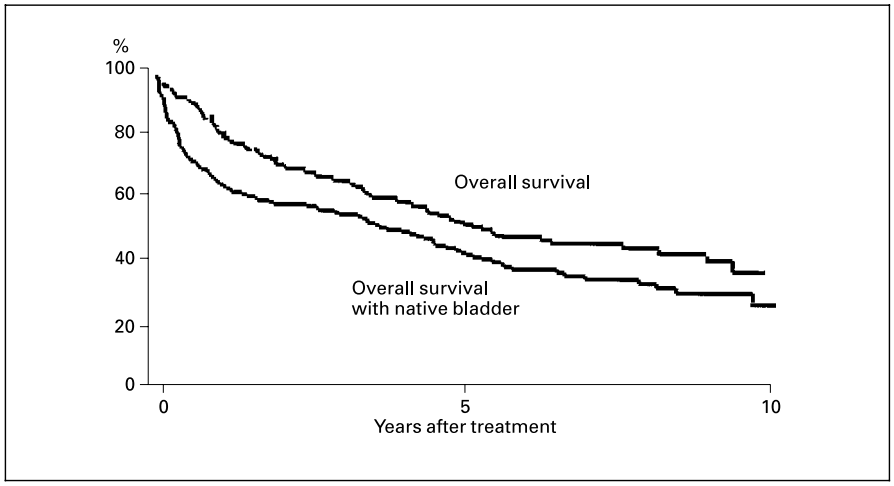

Fig. 2. Long-term results for 162 patients with T2–4 transitional cell carcinoma of the bladder treated on a series of protocols from 1986 to 1995 at the Massachusetts General Hospital.

The overall survival rate for all 106 patients in this prospective study was 52%, disease-specific survival 60%, and 5-year overall survival with an intact bladder 42%. Median follow-up was 4.4 years with 40 patients being followed for greater than 5 years. No cystectomies were performed for radiation-related bladder injury. A new analysis of this series is currently being performed with longer follow-up (6.1 years) and expanded to include all 162 patients treated on protocol between 1986 and 1985 confirms these original findings (fig. 2). It also shows that even those with quite advanced disease (T3–4a) maintain 5- and 8-year survival rates comparable to surgical series (48 and 39%) [52].

The Radiation Therapy Oncology Group (RTOG) has carried out two separate pilot trials of concurrent cisplatinum and radiation. These two studies, one combining with MCV chemotherapy, confirmed in multiple centers the original reports from single institutions that survival did not appear to be compromised by a careful approach that selects patients for bladder conservation on the basis of their response to induction trimodality therapy. Most recently the RTOG has reported the results of a randomized trial to assess the long-term efficacy of neoadjuvant MCV chemotherapy prior to cisplatinum and radiation [51]. With a median follow-up of 60 months, the 5-year overall survival rate was 49%: 48% in those receiving MCV and 49% in those who did not. There was no significant improvement in metastasis-free survival or freedom from invasive bladder

relapse. The absence of any benefit, coupled with the toxicity of this drug combination (only 67% completed protocol treatment), has led many investigators away from neoadjuvant therapy and towards the development and testing of new drugs.

Twice-a-day (accelerated) radiation regimens may be more effective than once-a-day regimens in their ability to induce and maintain a complete response [54]. We recently reported a pilot study from our institution evaluating the use of twice-a-day radiation in conjunction with cisplatinum, 5-FU and a TURBT. The clinical complete response rate was 77% and, with a median follow-up of 32 months, the overall survival and survival with a functioning bladder at 3 years were 83 and 78% [55]. When compared with our previous experience using once-a-day radiation and cisplatinum as the only radiation sensitizer, the results appear improved. This is now being tested in a prospective multicenter study organized within the RTOG. The RTOG is also to begin testing taxotere in combination with cisplatinum as a radiation sensitizer.

Responding to Concerns of the Bladder-Conserving Approach

Though surgical oncologists in nonurologic fields have embraced the concept of organ preservation as a laudable goal, the urologic community remains cautious and it is worthwhile addressing the specific concerns of this group.

Urologists have long held the view that prompt removal of the bladder maximizes the chance of cure. This is because bladder preservation risks a local relapse, possibly unresectable, from which metastases may arise. In answer to this one needs only point to the randomized trials comparing immediate with deferred cystectomy with comparable survival in all arms (table 2). The argument that surgery has now improved and that an advantage would now be seen with the contemporary cystectomy is refuted by the survival figures being reported by the many centers using contemporary trimodality therapy. The success of the trimodality approach lies, in part, in its recognition of the need for prompt salvage cystectomy in any patients with residual or recurrent disease.

Urologists have felt that local control is poor with radiation and that uncontrolled pelvic disease is a common and disastrous event. It is true that local control rates of 40% in historic series using radiation alone are vastly inferior to those achieved by radical surgery. Patients whose bladders are selected for conservation following a trimodality approach, however, have invasive relapse rates of only 9–17% over 5 years. At our institution only 36% of the 162 patients entering our protocols ended up requiring cystectomy. The majority of these were performed early for incomplete response. Because of this prompt intervention only 9.9% of the total developed the misery of uncontrolled pelvic tumor, a number similar to series employing immediate radical cystectomy.

Urologists also point out that bladder cancer is often associated with a field change and that the patient remains at risk of superficial relapse. We agree, and the risk of superficial relapse is reported at between 9 and 28% over 5 years. At our institution it was 26% with the majority being CIS. 69% of superficial relapses were in the same geographic region as the original invasive tumor. It has been our experience, however, that these tumors respond well to TURBT and intravesical agents such as BCG. Only 4 of 22 treated patients followed for a median of 3.9 years required subsequent treatment. The overall survival for those with a superficial relapse was no worse than for those who did not have such a relapse. A superficial relapse should not, in our opinion, be any more an indication for immediate cystectomy than a de novo superficial tumor.

Quality of life is a contentious issue. There is widespread belief that an irradiated bladder is prone to bleeding and contracture and becomes functionally worthless. In a case-controlled questionnaire study performed by Lynch et al. [56], there was no significant difference in bladder function between patients who were complete responders following 60 Gy radiation and matched individuals who had received no radiation at all. It is of note that in the three largest reports on trimodality therapy the need for cystectomy for a bladder complication is less than 1%. Good functional results are in part the consequence of sensitizing chemotherapy that some groups have used to reduce the delivered radiation dose below 60 Gy. They are also the consequence of improved technique (fractionation and partial bladder boosts) and improved radiation delivery (high-energy linear accelerators and 3-D conformal therapy). Kachnic et al. [57] evaluated 21 women treated at the Massachusetts General Hospital on our protocols. All reported satisfactory subjective urinary outcomes. It is also of note that 71% reported no decline in the satisfaction of sexual intercourse. A separate study showed that approximately 50% of men maintain unassisted sexual function, a value higher than is achieved after cystectomy [58]. There is undoubtedly systemic toxicity that accompanies the chemotherapy, but now that chemotherapy is routinely given as an adjuvant after cystectomy, this is a problem shared by both approaches to muscle-invading cancer.

The final concern is that treatment is complicated and costly. It is certainly true that trimodality requires the close cooperation of urologists, medical oncologists and radiation oncologists. Multimodality cancer clinics are now becoming commonplace in the USA providing a perfect setting for coordination of this treatment. Trimodality therapy is costly and, in addition, carries hidden costs such as the 36% who require cystectomy and the remainder who need regular cystoscopic re-evaluation. It must be noted, however, that the radical cystectomy also carries hidden costs such as the adjuvant chemotherapy commonly given and the 25–30% of patients who have either a prolonged hospitalization or require subsequent hospitalization for re-operation. We feel that to use cost-saving as a

justification for radical surgery is to skate on ethically thin ice. In the year 2001, cost-saving is not an appropriate reason to perform a mastectomy on a woman with localized breast cancer. It is an equally inappropriate reason to remove the bladder.

Conclusions

Bladder-preserving treatment for invasive bladder cancer in patients selected by the response of the tumor to induction TURBT, concurrent chemotherapy and radiation offers rates of long-term survival comparable to those achieved with immediate cystectomy-based approaches. The bladder-preserving strategy is less effective in achieving local control among those with very advanced cancers (T4b and those with associated hydronephrosis), but may still be a useful preoperative strategy. In 20–30% of patients cured of their muscle-invading tumor, a new superficial tumor will develop. These appear to be as responsive to conservative intravesical measures as a de novo superficial tumor. Bladder-preserving treatment almost always results in a normally functioning bladder without incontinence or hematuria.

The breast cancer model, so successfully adopted by multimodality teams across the USA and Western Europe, has, over the last two decades, limited the use of the mastectomy to women with locally advanced disease and to those who desire it. Bladder cancer now stands where breast cancer stood 20 years ago. We look forward to an organ-conserving approach being widely offered as a safe and reasonable alternative to the radical cystectomy over the coming years.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 147–150

T1G3 Bladder Cancer – The Case for TUR and BCG

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Superficial bladder cancer includes tumors confined to the epithelium (Ta) carcinoma in situ (CIS) and tumors that invade the lamina propria (T1). The primary treatment of these tumors is transurethral resection (TUR). Unfortunately, TUR alone does not solve the problem of recurrence and progression in the majority of superficial bladder tumors. Thus, adjuvant therapy is employed according to the prognosis of the specific tumor.

Traditionally, prognosis was thought to be influenced by tumor stage as well as by tumor grade [1]. Consequently, T1G3 bladder cancer was labeled with the highest risk of recurrence (60–80%) and progression (30–46%) [2]. In more recent publications, however, tumor grade emerges as the single most important prognostic factor: In a multivariate analysis of 1,529 patients with primary superficial bladder cancer, Millan-Rodriguez et al. [3] calculated odds ratios for progression and mortality. Grading with an odds ratio of 19 for progression and 14 for disease-specific mortality was by far the most important factor, compared with concomitant CIS (2.1 for progression, 3 for mortality), multiple tumors (2.0 for progression) and tumor size >3 cm (1.7 for progression). In this series, tumor stage did not alter prognosis.

Similarly, 15-year disease-specific survival of patients with high-grade superficial tumors was evaluated by Herr [4]. All patients had one or more courses of BCG. 15-year disease-specific survival was 74% for TaG3 tumors and 62% for T1G3 tumors ($p = 0.3$). Herr concludes that all high-grade tumors have a lifelong risk of progression and death of disease and must be managed accordingly.

What then is the optimal management of these tumors? There is wide consensus that TUR alone is inadequate to control high-grade bladder cancer. How-

Table 1. Recurrence and progression rates following BCG treatment of high-risk superficial bladder cancer

Reference	n	Follow-up months	Recurrence rate, %	Progression rate (muscle invasion), %	Progression rate metastasis, %	Death of disease, %
Seretta, 1996 [9]	50	52	32	6	6	–
Pfister, 1995 [10]	26	54	50	27	–	7
Cookson, 1992 [11]	86	59	9	7	–	–
Eure, 1992 [12]	30	39	34	3	3	–
Samodai, 1991 [13]	62	46	20	0	0	–
Boccon-Gibod, 1991 [14]	47	–	36	21	–	–
Klän, 1996	109	78	39	13	–	–

ever, an ongoing controversy exists if T1G3 tumors should be managed conservatively (i.e. TUR + adjuvant BCG) or by primary cystectomy. Papers claiming primary cystectomy being the treatment of choice [5, 6] often do not clearly state what kind of adjuvant treatment – if any – patients in the 'conservative' group received. Comparison with contemporary BCG series is therefore difficult. On the other hand, some reports on BCG treatment include G2 and G3 tumors [7, 8], again making comparison difficult. This fact plus the large inter-observer variability in the assessment of bladder cancer grading may account for the wide range of progression rates in recent BCG series (table 1).

Numerous phase III studies have addressed the question if BCG is superior to intravesical chemotherapy. In a recent review, Dalbagni and Herr [15] conclude that mitomycin is effective in papillary tumors, but BCG is superior to intravesical chemotherapy for the management of CIS and high-risk tumors. The problem in all these studies is however, that they include Ta and G1 and 2 tumors. To our knowledge, no study has so far compared the effect of BCG and chemotherapy in T1G3 tumors only.

As has been mentioned, G3 tumors seem to impose a lifelong risk of tumor recurrence and progression, thus reflecting the malignant potential of the bladder mucosa in this setting. Only few long-term data are available. Herr found a 62% disease-specific survival after 15 years in one series [4] and a 60% progression-free survival after 15 years in another series [16]. No comparative data are available with any other treatment modality. However, looking at the data there is obvious room for improvement. Long-term progression and survival rates reflect the fact that the effect of a single course of BCG is limited by time. Consequently,

varying maintenance schedules have been suggested. The most widely used is a 3-weekly maintenance protocol administered every 3 months for 3 years. In a recent report [17] on a prospectively randomized study by the SWOG (again including Ta and CIS), recurrence-free survival and worsening-free survival was significantly better in the maintenance group when compared with the single-course group.

In conclusion: BCG adjuvant therapy is currently suggested as standard adjuvant treatment of high-grade superficial bladder cancer [18]. 15-year data show survival rates >60%. No comparative long-term data with other therapy regimens have been reported. Cystectomy might be an alternative as primary treatment and is widely accepted as secondary treatment in short-term recurrent disease. The effect of BCG treatment seems to be temporary. Most recent data suggest maintainance therapy to be superior to a single-course schedule. The long-term recurrence and progression potential of the bladder mucosa in high-grade bladder cancer has to be addressed by any new therapeutic approach.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 151–158

Radiochemotherapy for T1G3 Bladder Cancer

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Introduction

Superficial bladder cancer carries a relatively favorable prognosis in most cases. Noninvasive papillary tumors (Ta) and superficially infiltrating cancers with high or moderate differentiation (T1G1–2) can often be managed successfully by transurethral resection. However, a subset of tumors behaves aggressively. The treatment recommendations for high-risk superficial bladder cancers differ widely. Some authors go on to favor radical cystectomy whereas most of the recent series propose an organ-preserving approach [1, 6, 14].

Natural Course of Superficial Bladder Cancer

Superficial bladder cancer demonstrates a broad spectrum of biological aggressiveness. After transurethral resection, up to 90% of the patients with high-risk tumors recur. The risk of recurrence[1] mainly depends on the presence of

[1] The term 'recurrence' is used in the literature on bladder cancer for all intravesical tumors detected after therapy of the primary tumor irrespective of site, T-category or grade of the recurrence and irrespective of the recurrence-free interval. With regard to the biological behavior of other cancers, e.g. breast cancer, recurrences therefore probably not only include true local recurrences of the primary tumor but also – and in the long run mainly – new secondary cancers.

Table 1. Patterns of recurrence in superficial bladder cancers after 20 years of follow-up [data from 7]

Tumor stage/ grade	n	No recurrence	Superficial recurrence %	Recurrence with progression, %	Death from bladder cancer, %
TaG1	22	27	59	14	14
TaG2–3	55	31	55	15	11
T1G2	41	19	49	32	22
T1G3	58	7	48	45	36

Table 2. Progression rate and cancer-related deaths over a period of 15 years in 48 patients with T1G2–3 bladder cancers (41 × T1G3, 7 × T1G2) treated with transurethral resection ± BCG [data from 6]

Years of follow-up	Patients at risk	Progression	Death from bladder cancer
0–5	48	17 (35%)	12 (25%)
5–10	31	5 (16%)	2 (6%)
10–15	26	3 (12%)	1 (4%)
Total	48	25 (52%)	15 (31%)

infiltration (Ta vs. T1), differentiation grade (G1–3) and the presence of other risk factors, e.g. multifocality and associated Tis [6, 7]. Up to half of the patients have progression in case of recurrence with a higher T-category and/or poorer differentiation grade as compared to the primary lesion. Patients with progression are at high risk of dying from bladder cancer.

Some recent series have analyzed the outcome of patients with superficial cancers after more than 10 years of follow-up. Holmang et al. [7] analyzed the patterns of recurrence in patients with Ta and T1 cancers (table 1). They found a high frequency of recurrences and a substantial number of cancer-related deaths in T1G2 and T1G3 tumors. There was no significant difference between both groups. These results prove that T1G3 carries an unfavorable prognosis with regard to other superficial cancers, but T1G2 seemed to have a comparably poor

Table 3. Treatment outcome after conservative treatment of T1G3 bladder cancers with transurethral resection (TUR) ± BCG with regard to length of follow-up (n.d., not determined) [data from 6]

Group (first author)	n	Treatment	Follow-up years	Progression rate, %	Deaths from bladder cancer, %
Eure, 1992 [4]	30	TUR + BCG	<5	17	n.d.
Cookson, 1992 [3]	16	TUR + BCG	<5	19	n.d.
Pansadoro, 1995 [11]	50	TUR + BCG	<5	12	n.d.
Zhang, 1996 [16]	23	TUR + BCG	<5	35	22
Hurle, 1996 [8]	51	TUR + BCG	<5	14	12
Sarkis, 1993 [12]	43	TUR	10	51	30
Holmang, 1995 [7]	58	TUR	20	45	36
Herr, 1997 [6]	48	TUR + BCG	15	52	31

outcome in the long run although time to recurrence may be longer than in T1G3 cancers. This finding is important with regard to the question how to define a high-risk subgroup within the population of patients with superficial cancers. Probably, T1G3 is not the only risk group.

Herr [6] analyzed the patterns of failure in T1G3 bladder cancers during a 15- to 20-year follow-up period (table 2). He found recurrences with tumor progression and cancer-related deaths even after 15 years and recommended lifelong surveillance of patients with high-risk superficial bladder cancer.

Intravesical therapy with mitomycin C or bacillus Calmette-Guérin (BCG) after transurethral resection can significantly reduce the frequency of recurrences but it mainly reduces favorable recurrences [9]. There is only a small effect of intravesical therapy on progression of the disease. Moreover, it remains unclear whether adjuvant treatment with BCG results in a survival benefit especially in the long run. Most of the series with adjuvant BCG treatment have limited follow-up up to 5–8 years which with regard to late recurrences may be insufficient. Table 3 demonstrates that the effect of intravesical therapy after 10 years is doubtful. The American Urological Association has recently published treatment recommendations for superficial bladder cancer on the basis of a meta-analysis of studies with intravesical therapy. According to this analysis, all types of drugs may reduce the rate of recurrence and intravesical therapy is therefore recommended for T1 and high-grade Ta tumors after transurethral removal of the tumor. However, the recommendations include the remark that there is no effect of intravesical therapy on long-term progression [13].

Theoretical Background for the Use of Radiotherapy

Biology of High-Risk Superficial Bladder Cancer

With regard to tumor biology, three different causes for recurrences of high-risk superficial bladder cancer have to be distinguished: (1) Residual tumor cells in the surroundings of the primary tumor may be left within the bladder mucosa after macroscopic complete transurethral resection and may cause local recurrences in the primary tumor region. (2) High-risk superficial bladder cancer may often be considered as a multifocal disease with the whole bladder epithelium as risk organ for the development of new (secondary) cancers. (3) The primary tumor may be clinically understaged and has already invaded into the deep muscle wall or spread to regional lymph nodes. This understaging error probably lies in the range of 20–30%. These cell deposits are surely not adequately treated by intravesical installation therapy. This fact may explain why intravesical chemo- or immunotherapy reduces the risk of superficial but not of deep muscle-invasive recurrence.

Arguments for the Use of Radiotherapy

As long as cells after transurethral resection remain only in the superficial mucosa, they may theoretically be treated by intravesical cytostatics or immunotherapy. It is, however, questionable whether deep tumor cell deposits can be reached. These cells, on the other hand, can adequately by treated with radiotherapy. Urothelial cancers are sensitive to radiation and the radiosensitivity is comparable to squamous cell cancers of the head and neck region. The doses necessary to control microscopic disease lie in the range of 45–50 Gy. These doses are far below the tolerance dose of the bladder (about 60 Gy for whole bladder irradiation) and can therefore be administered to a large volume with minimal risks of severe side effects. Therefore, external radiotherapy, especially if delivered with modern treatment techniques, offers a good chance to successfully control microscopic bladder cancer.

Treatment Results with Radiotherapy

Historical Series

Most of the radiotherapy series in the literature mainly contain patients with muscle-invading cancers and only few superficial tumors. Moreover, the referral of a patient with superficial cancer to radiotherapy probably reflects some kind of negative selection with regard to prognostic factors such as age, general condition, resectability or recurrence. The results in these series should therefore be interpreted carefully.

Table 4. Impact of interstitial radiotherapy on prognosis in T1 bladder cancer: results from the University of Rotterdam [15]

	TUR only	TUR + interstitial radiotherapy	
Number of patients	143	196	
Intravesical recurrences			
In the primary tumor region	66 (46%)	21 (11%)	
Outside the primary tumor region	41 (29%)	14 (7%)	
Total number of recurrences	107 (75%)	35 (18%)	
Muscle-invasive recurrences	32 (22%)	6 (3%)	
Ten-year survival	38%	76%	p = 0.0002

The best results have been achieved at the University of Rotterdam with interstitial implants [2, 15]. In this prospective series, patients with T1 cancers with a tumor diameter of <5 cm underwent transurethral resection of the tumor and subsequent local irradiation of the tumor area in the bladder wall by an interstitial radium implant. The definitive local control rate was 82% and the 10-year survival rate 76% (table 4). These figures are at least as good or better than most of the series in the literature supporting that, if radiotherapy is routinely used and not restricted to unfavorable subgroups, the results are probably better than with adjuvant intravesical therapy.

University of Erlangen Series

The largest series with T1 cancers treated with radiotherapy or radiochemotherapy according to current treatment standards comes from the University of Erlangen. At this institution, 83 patients with T1 cancers (primary or recurrent) received radio(chemo)therapy from January 1982 through July 1999 [C. Rödel, pers. commun., unpubl. 2000]. The treatment group consisted of selected patients with a high risk for recurrence and indications for radiotherapy were: unradical transurethral resection, tumor diameter >5 cm at the base of the tumor, G3, multifocal disease, associated Tis or multiple recurrences. The cause-specific survival of the whole population was 80% after 5 years and 58% after 10 years, the overall survival 71 and 45%, respectively. Salvage cystectomy for persistent or recurrent tumors was performed in 20% of the patients and 87% of the 5-year survivors and 82% of the 10-year survivors had a preserved bladder (table 5). The only prognostic factor for survival and local control was the completeness of the transurethral

Table 5. Treatment results with TUR + radiotherapy/radiochemotherapy in 83 patients with high-risk superficial bladder cancer: results from University of Erlangen [C. Rödel, pers. commun., unpubl. 2000]

	5-Year results	10-Year results
Overall survival, %	71	45
Cause-specific survival, %	80	58
Bladder preservation in survivors, %	87	82

Table 6. Impact of adjuvant intravesical therapy or radiotherapy after TUR on patterns of recurrence and time to progression in T1G3 bladder cancer: prospective, nonrandomized data from the Dutch South Eastern Bladder Cancer Study [10]

Treatment	n	Time to recurrence months	Recurrences without progression, %	Recurrences with progression, %
TUR only	48	11	48	27
TUR + BCG or TUR + MMC	51	19	30	25
TUR + XRT	17	25	18	17
		$p < 0.05$	$p < 0.05$	

resection prior to radiotherapy. In this series, 45 patients had T1G3 cancers and the results in T1G3 cancers were not different from the rest of the study population.

The survival figures in this series are comparable to the results of other large series using TUR ± intravesical therapy or radical cystectomy. Because of the different selection criteria in most of the series, the results with regard to survival are difficult to interpret. However, this study demonstrates the efficacy of radiotherapy with regard to organ preservation. To our knowledge, there is no other series with a comparably high rate of organ preservation in long-term survivors beyond 5 years.

Efficacy of Radiotherapy as Compared to Intravesical Therapy

There are no randomized trials addressing the question of whether radiotherapy is as effective or superior to current intravesical treatment options. However,

the Dutch South Eastern Bladder Cancer Group has recently presented data in 127 patients with T1G3 cancers [10]. This series is the largest group of T1G3 cancers that has ever been published in a single series. External radiotherapy with 50 Gy was one treatment option and 17 patients received radiotherapy. Radiotherapy was as effective as intravesical BCG or mitomycin C and yielded (in absolute figures) the best results (table 6).

A Statement for Radiotherapy in a Muldimodal Treatment Concept

Most superficial bladder cancers can be managed by transurethral surgery. However, a relevant subset of patients are at very high risk for recurrent and progressive cancers over a long period. About 30% of patients with T1 tumors will ultimately die from urothelial cancer. Current treatment options include early cystectomy or the goal of organ preservation by adjuvant intravesical therapy after transurethral resection. Patients who are at high risk of failing the goal of organ preservation by intravesical therapy are currently treated by cystectomy. Adjuvant radiotherapy offers an additional option with a high change of cure and bladder preservation.

The rationale for the use of radiotherapy in a multimodal treatment concept with the goal of cure and organ preservation results from: (a) theoretical basis for radiotherapy depending on the biological behavior of the disease; (b) patterns of tumor recurrence and progression after transurethral resection and intravesical therapy, and (c) proven efficacy of radiotherapy in prospective series.

Radiotherapy is currently indicated in patients with superficial cancers and high risk for recurrence with progression, especially in those with multiple risk factors. The ultimate value of radiotherapy in comparison with other treatment options, however, should be determined in randomized trials.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 159–165

The Technique of ^{125}I Permanent Implants

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Radical prostatectomy and external beam radiotherapy are the most common curative modalities employed in the treatment of early-stage prostate carcinoma. Recently, transrectal ultrasound-guided brachytherapy has gained popularity as an additional treatment option for patients with early-stage disease [1–4]. The introduction of ^{103}Pd sources, biplanar ultrasound probes, preloaded needles, sources embedded in vicryl suture, anchoring needles and fluoroscopy led to a dramatic increase of implants (over 48,000 implants in the USA during the last year) [5].

The goal of localized treatment is to achieve either a conformal dose distribution restricted to the prostate gland while hot spots should not exceed the tolerance level for uretral stenosis. Optimization procedures are based on different loading techniques. High or low activity seeds, palladium or iodine seeds, or rapid strands are available [6–9] to further optimize dose conformity and dose homogeneity while sparing the urethra. These different optimization tools for permanent seed implant allow a complex adjustment of dose application. Unfortunately the traits of conformity and uniformity are not complementary in prostate brachytherapy [10, 11].

Implant Design

Most institutions do a uniform seed implant, to place the sources within the prostate gland at a regular 1-cm spacing in all directions. In an effort to prevent delivering unnecessarily large doses to the surrounding tissue, one possibility is to restrict placement of the sources inside the gland but avoid placing sources in the urethra, a central structure.

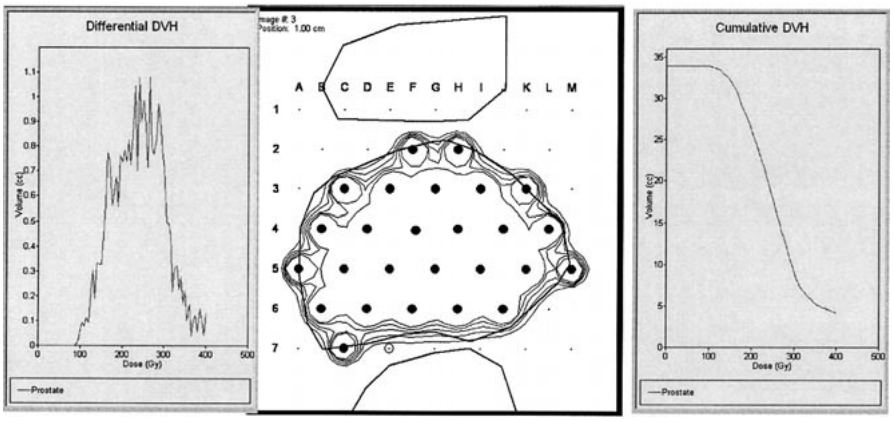

Fig. 1. Uniform implant low activity ^{125}I seeds.

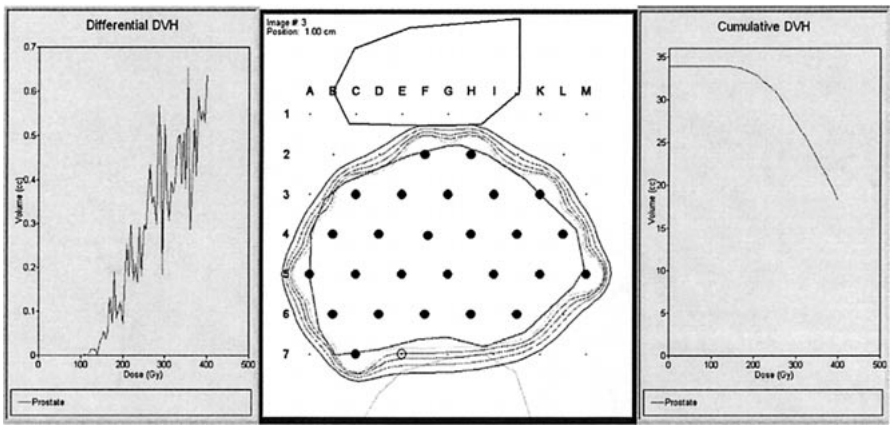

Fig. 2. Uniform loading high activity ^{125}I seeds.

Displayed in figure 1 is a slice through the center of the spherical prostate with isodoses displayed, a dose trace or a dose profile along the line displayed on the slice and a dose-volume histogram (DVH) for the prostate with this loading. The reference dose for this implant is 145 Gy and is one of the isodose lines displayed. The DVH has the calculated volume and the prostate DVH displayed. As can be seen from figure 1, the reference isodose line for the central slice does

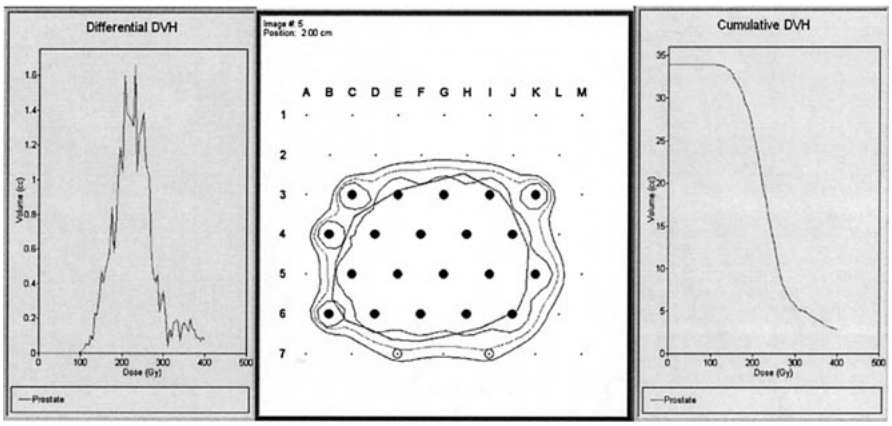

Fig. 3. Uniform loading with low activity ^{125}I seeds outside.

not cover the gland. The dose trace does not show any hot spots. The DVH for the entire implant is equally informative, with the volume dropping from 100% well before the reference dose value.

If we wish to retain uniform loading, we are now left with two choices, either increase the activity of the isotope to cover the gland or place sources outside the gland. Figure 2 shows the results of trying to increase the activity on the former plan.

Increasing the activity of the sources has produced highly unsatisfactory results. The isodose curves demonstrate almost full coverage of the gland with the 360-Gy isodose value. The dose profile shows doses in the central gland that exceed 450 Gy. Although the DVH does not begin to drop off after the reference dose, it does not fall quickly enough with almost 40% of the gland receiving doses >400 Gy.

Figure 3 is much improved. The isodose lines, at least on this slice, show adequate coverage of the gland. Although the ratio of the dose at the center of the gland to that at the periphery is high, no part of the dose profile shows >270 Gy on this slice, the DVH confirms the gland is adequately covered with none of the gland receiving >360 Gy. One might be concerned about the dose to the periprostatic neurovascular bundle with this arrangement, or possibly some other structure outside the gland, but in general this plan looks promising. The problem of course is one of placement. Sources outside the gland tend to migrate. One solution to this dilemma is to use Rapid Strand (sources in Vicryl suture) to help anchor these sources in place. Another is to retain the goal of placing sources inside the gland and explore peripheral loading.

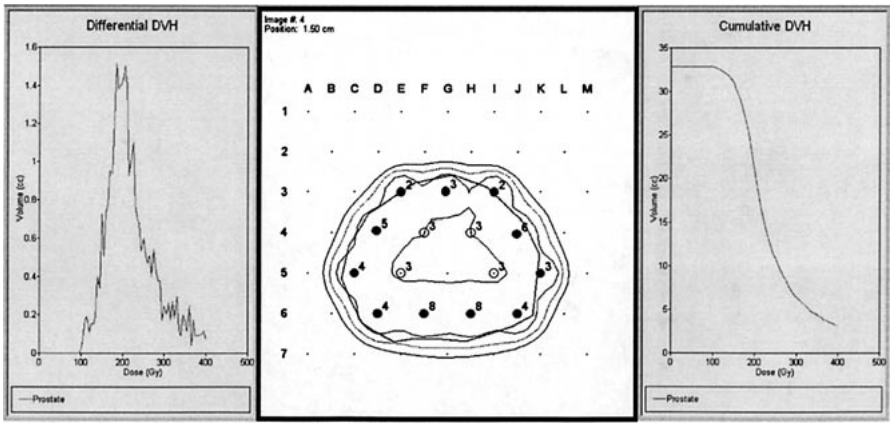

Fig. 4. Peripheral loading low activity ^{125}I seeds.

Figure 4 outlines the results of a peripherally loaded implant. This was done with sources placed on or near the periphery of the gland in all three dimensions. The peripherally loaded implant shows the best distribution so far. Coverage of the gland is excellent, both from the isodose curves and the DVH. The dose in the center of the gland from the dose profile sufficiently spares the urethra, but not less than the prescription dose. None of the gland receives >400 Gy and this is in the periphery – a very tempting plan indeed.

Once again though, the problem is placement. An implant designed like this is difficult to execute. Sources placed at the edge of the gland are the most difficult to place and have the most tendency to wander. To make the situation worse, and this is the crux of the matter, misplacement or movement of two or three sources close to each other in this situation drastically changes the dose distribution – most likely in a region of tumor cells.

Liking the distribution associated with peripheral placement, but clinging to the efficacy of the uniform implant has resulted in the modified peripheral implant. This hybrid starts off with either a uniform or a peripheral distribution and moves toward the other. At our institution we begin with a uniform implant and remove enough sources from the center of the gland to cool off the urethra and place enough sources at the periphery of the gland to push the isodoses away from the prostate far enough to provide the desired margin. Figure 5 shows the results of such a treatment plan. We have found that this approach has resulted in a plan that is achievable with an acceptable level of uniformity.

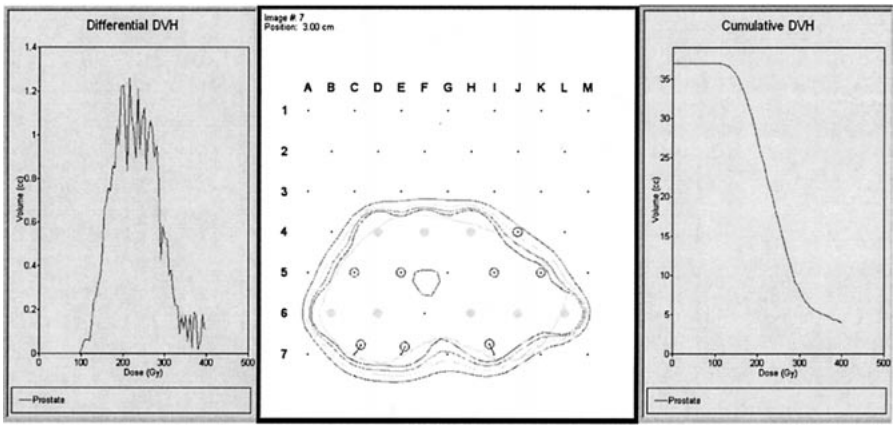

Fig. 5. Modified peripheral loading with high activity ^{125}I seeds.

Implant Quantifiers (Dosimetric Evaluation and Reporting)

All implant quantifiers are derived from the DVH. With only a few exceptions these quantifiers fall into one of two categories, a descriptor of implant conformity or a descriptor of implant uniformity. Because they are generated from the DVH, implant quantifiers can be either structure-based or calculation volume-based [12, 13].

Evaluation of postimplant dosimetry is typically carried out in three separate steps: (a) examination of isodose distribution; (b) generation of the DVH, and (c) determination of dose uniformity and dose conformity indices. These three aspects of dosimetric evaluation provide complementary information for assessing the quality of an implant. A two-dimensional isodose distribution should be generated on multiple slices throughout the prostate and in other areas of concern. Outline of the prostate and any adjacent critical structures as determined by tomographic imaging should be superimposed on the isodose distribution. Such isodose plots offer the most direct assessment of dose coverage, because the location of any underdosage in the prostate can be evaluated based on supplemental clinical judgment. It is recommended that at least the following set of isodose lines be generated as a percentage of the prescription dose: 200, 150, 100, 90, 80 and 50%. Generation of the DVH of the prostate is recommended. The most common format is the cumulative DVH, which shows the percent volume (or total volume) of the prostate that receives greater than or equal to a given dose. A less commonly used representation, the differential DVH (DDVH), displays the relative volume of the prostate that receives a given dose. The full width at half maximum

(FWHM) of the DDVH is a measure of the uniformity of the dose distribution. It is generated on the DDVH by taking the peak volume value, dividing by two, and drawing a horizontal line on the graph. The dose where the line first hits the rising curve is subtracted from the dose represented by the last intersection of the line and the falling curve, giving the FWHM. A larger value implies a wider range of doses or a less uniform dose distribution. A smaller value thus reflects a more uniform dose distribution. The unit for FWHM is gray (Gy).

Typically, the DDVH peaks at a dose that is higher than the prescription dose. The spread of the peak is a useful indicator of dose homogeneity [14, 15]. A smaller spread indicates greater dose uniformity. It is recommended that the following be reported to allow adequate evaluation of postimplant dosimetry and to allow correlation with clinical outcome: (1) The values of D_{100}, D_{90} and D_{80} (the dose that covers 100, 90 and 80% of the prostate, respectively). (2) The values of $V_{200,}$ $V_{150,}$ V_{100}, V_{90} and V_{80} (the fractional volume of the prostate that receives 200, 150, 100, 90 and 80% of the prescribed dose, respectively). (3) The total volume of the prostate (in cm^3) obtained from postimplant dosimetry. (4) The number of days between implantation and the date of the imaging study used for dosimetric reconstruction. (5) The urethral and rectal doses.

Looking on conformity, in our opinion the modified peripheral technique with high activity ^{125}I seeds is the best way to perform an implant for an experienced user. Less seeds and needles will reduce the damage to the gland and consecutively the side effects. In terms of economics, it is cheaper as well. The efficacy in terms of dose delivery of the different techniques should be evaluated in further trials.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 166–170

Interstitial Brachytherapy with Permanent Seed Implants in Early Prostate Cancer

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Brachytherapy as a technique of radiotherapy can be done by the implantation of sealed radioactive isotopes directly into the organ affected by the tumor. With regard to brachytherapy, the prostate is localized in an accessible region of the body just like certain gynecological structures, e.g. the uterine cervix. Transperineal access is easy and the prostate gland can be reliably distinguished from the surrounding organs at risk. This was recognized as early as 1911 when the first trials were carried out [1], but at the time it was not possible to position the implants accurately because the required technical equipment was not yet available. During the 1980s, TRUS (transrectal ultrasound), computed tomography and advanced treatment planning systems were introduced and their combination provided much better technical options [2–7].

Real-time TRUS and the introduction of closed perineal access resulted in the establishment of brachytherapy as an easy and expedient method which does not require hospitalization. Suitable patients can be offered a comfortable and effective treatment modality now which preserves a good quality of life.

Published Data; Tumor Control

Since the implementation of PSA (prostate-specific antigen) as a tumor marker in carcinoma of the prostate, the effect of treatment for prostate cancer is monitored by the measurement of PSA levels during follow-up. The PSA level for defining biochemical disease-free status is still not interpreted uniformly.

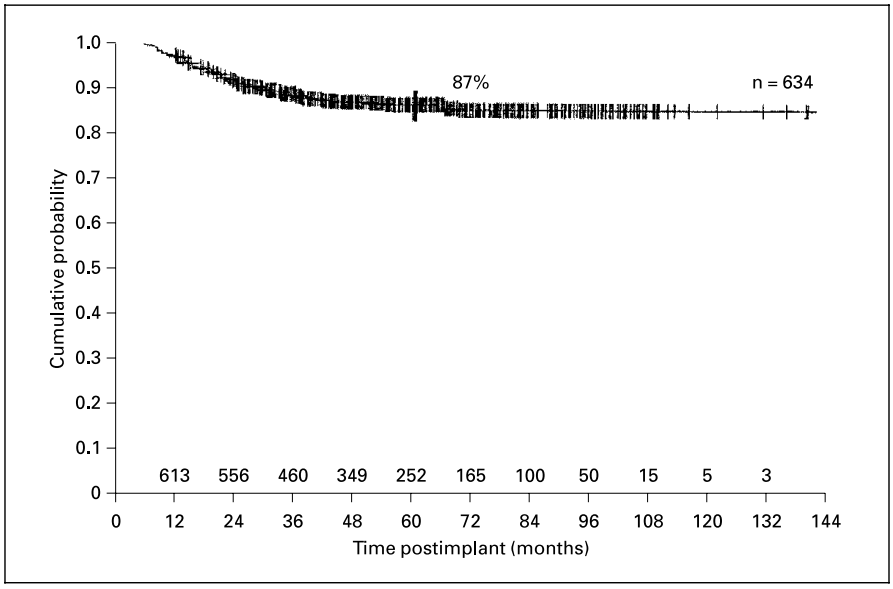

Fig. 1. Freedom from biochemical progression in 634 patients.

The sequence of PSA nadir after seed implantation was found to be equally good compared to the surgery group for those patients with favorable prognostic parameters (initially PSA < 10 ng/ml; Gleason score < 7) by all groups. In patients with higher initial PSA levels the outcome is less favorable. The reasons for this seem to be twofold, either the risk of extracapsular disease and/or the different techniques of implantation applied.

Consistent data could be demonstrated by the Seattle group (fig. 1). 634 patients were evaluated. PSA checks were carried out and end-points were set in accordance with the consensus statements of the ASTRO (American Society for Therapeutic Radiology and Oncology) [8, 9]. The patients in this trial had stage T1–T2 tumors, the Gleason score was ≥ 7 in 20% of the patients and the median PSA value was 11 ng/ml.

Impressive results could be demonstrated after stratification of biochemical and pathological risk factors (fig. 2). The biochemical disease-free survival after seed implantation seems to be equal to the outcome after radical prostatectomy and conformal radiotherapy with doses between 70 and 75 Gy in patients with PSA level < 10 ng/ml and Gleason score < 7 [10, 11]. This indicates that brachytherapy can yield excellent results if carried out by experienced specialists (table 1) [12].

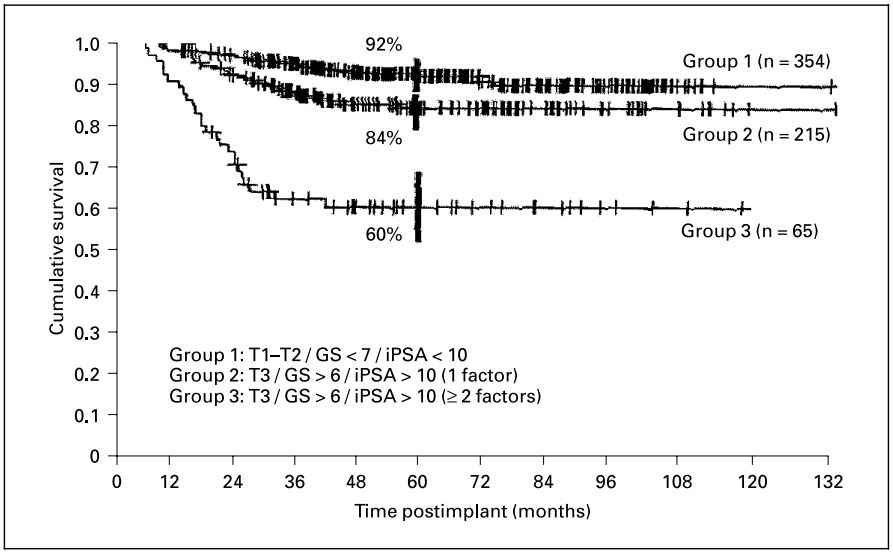

Fig. 2. Biochemical disease-free survival and risk factors.

Table 1. Biochemical disease-free survival

Study (first author)		Medical follow-up months	PSA, ng/ml			
			0–4	4–<10	11–<20	20+
Dattoli [4]	102	38	82	82	85	70
Grado [5]	490	47	88	88	72	57
Ragde [6]	320	56	95	87	77	65
Wallner [7]	92	36	100	80	45	39

Morbidity

Minor acute side effects after implantation resulting from the surgical procedure are more likely (about 50%). Most patients complain of symptoms related to the genitourinary tract [13–16]. Short-lasting urinary retention and moderate dysuria occur in 5–10% of all patients [13–15]. Reports of late effects include: An incidence of some degree of incontinence between 3 and 15% [15]. Rectal bleed-

ing is observed in 3–6% of patients if brachytherapy alone is applied and in 6–10% if it is combined with EBRT. 75–85% are potent with short-term follow-up. However, there is evidence that about 40–50% of the patients will be impotent at 5 years. Since data on late effects are scarce, various prospective studies on quality of life after seed implantation are presently being conducted [17–19].

Summary and Conclusion

Excellent clinical results after permanent seed implantation have been reported by various centers in large cohorts of patients. However, all of these had extensive experience in this special field of radiotherapy and the follow-up time is too short for definite conclusions. The fact that this option of treatment can be carried out on an outpatient basis and that it allows to get the patient back to normal as far as social environment and work are concerned, has led to wide acceptance of this particular mode of therapy. Therefore, permanent seed implantation is a possible treatment option for localized prostate cancer and can be offered to patients with T1–T2a tumors, PSA levels of <10 and a Gleason score of <7. By using permanent seed implantation in these selected patients, it seems possible to achieve results comparable with surgery alone or percutaneous, 3D-planned radiotherapy.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 171–176

Interstitial Hyperthermia Using Thermoseeds in Combination with Conformal Radiotherapy for Localized Prostate Cancer

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Introduction

Cancer of the prostate is the most frequent cancer of men in the United States and was estimated to be the second leading cause of death from cancer in the male population in 1996 [1]. Standard therapy for localized prostate cancer is radical prostatectomy. For stage T1–2 cancer, tumor control of 95% has been observed, but the last 10 years have also shown that the majority of patients with stage T3 cancer have not been optimally treated with radical surgery. The risk of local progress in following stage T3 disease has been found to vary between 11 and 83% (follow-up of 10 years) [2].

Antiandrogen therapy as a systemic therapy with a palliative therapeutic approach should not be considered in stage T3 tumors in the absence of positive lymph nodes and distant metastases because curative therapeutic alternatives are available. Radical prostatectomy was the only curative therapeutic approach before modern irradiation techniques were developed. With the clinical use of high-energy radiation sources, HDR techniques and an optimization of the radiation schedule, irradiation became an alternative method for the treatment of prostate cancer. Besides the excellent results of tumor control, the high morbidity of radical prostatectomy such as incontinence (23%), impotence (90–

100%) and urethral strictures (10%) led to a search for alternative therapeutic methods.

After standard radiation therapy with a 5-year follow-up, up to 90% of the patients had still tumor cells in their prostatic tissue specimens [3]. The risk of local tumor recurrence following radical prostatectomy is in the range of 12–26% [2]. The optimal method for high-dose radiation therapy is the interstitial approach. Interstitial radiation guarantees a homogeneous dose distribution with high doses in the prostate and reduced complications in the surrounding organs. This makes interstitial radiation a useful alternative tool for the treatment of localized prostate cancer.

The variety of radionuclides that are used for brachytherapy differ in their amount of radiated energy, half-time and tissue radiation depth. Radioisotopes can be permanently implanted into the prostate, such as gold-198, palladium-103 or iodine-125. Another method of interstitial radiation is the afterloading technique with iridium-192 [4]. For stage T3 tumors, only gold-198 and iridium-192 with their radiation characteristics proved to be effective. In the past, iodine-125 did not seem to achieve persistent local tumor control due to low tissue radiation depth and inhomogeneous distribution [5]. However, the latest publications report better local control which is due to a better patient selection [6].

The disadvantages of radiotherapy are the radiation-induced tissue damage and the few therapeutic possibilities for the treatment of radiation-related injuries. The symptoms of radiation cystitis are quite similar to the cystitis of bacterial origin, however, they are more difficult to treat. Patients suffer from urgency, dysuria, frequency and nycturia. Hematuria and bladder tamponades are major complications.

Beside cystitis, proctitis can be observed in a number of patients treated with interstitial radiation. Spasms, rectal bleeding and fecal urge leading to incontinence are the most common symptoms. Stenoses of the rectum with extended necrosis and fistulae between bladder, vagina or urethra have occurred. The incidence of radiation-induced complications varies between 1 and 5% for the bladder and 5 and 10% for the urethra. An innovative therapeutic approach for the treatment of prostate cancer is interstitial hyperthermia in combination with percutaneous radiation therapy, using implantable cobalt-palladium thermoseeds, which generate heat by induction in a magnetic field [7].

Combination of Hyperthermia and Radiation

Hyperthermia is known to enhance the effects of irradiation due to its additional cytotoxicity (from 42.5 to 43 °C) and sensitization (from 40.5 to 41 °C). There is no difference in the thermosensitivity of benign and malignant tissue.

However, hyperthermically mediated cytoxicity is enhanced under microenvironmental conditions such as reduced perfusion, acidosis and reduced cell metabolism. These conditions are common in radioresistant solid tumors.

Normal tissue tolerates higher temperatures between 41 and 44 °C due to physiological regulation. The absence of regulatory mechanisms in malignant tissue can cause extended tissue damage (necrosis) in the same temperature range. The question how hyperthermia leads to cellular death is not yet fully understood. An inhibition of cellular repair mechanisms, an enhanced direct cytotoxicity in radioresistant phases of the cell cycle (G2-, S-phase), damage to the cell membrane and the cytoskeleton have been observed [8].

Changes of cell metabolism are related to glycolysis, Krebs cycle, oxidative phosphorylation and lipid metabolism. In vivo hyperthermic temperatures are the result of exogenous energy administration and endogenous energy absorption. Invasive methods of hyperthermia applications have been studied on cancer of the uterus and the cervix since the beginning of this century [9]. In the mid-1980s, clinical studies using hyperthermia protocols were started [10, 11].

There are several advantages of interstitial invasive techniques of hyperthermia application compared to noninvasive approaches: (1) exactly defined energy application in the tumor with protection of benign tissue; (b) more effective local therapy; (c) homogeneous energy distribution and (d) compact measured matrix and better representation of invasively measured temperatures.

The combination of hyperthermia and radiation in the treatment of malignant tumors is based on a variety of experimental in vitro and in vivo data which have proved the synergistic effects of the two treatment modalities.

Material and Method

We planned a phase II trial to determine the efficacy of interstitial hyperthermia in combination with conformal radiotherapy for localized prostate cancer. All patients underwent laparoscopic lymphadenectomy to exclude lymphatic involvement. Cobalt-palladium thermoseeds were used to achieve interstitial hyperthermia. The curie temperature was 55 °C.

The patients were placed in the lithotomy position on a urologic table equipped with fluoroscopy. The implantation of seeds was performed under transrectal ultrasonic guidance and fluoroscopy. Seeds were placed homogeneously with 1 cm distance to each other and risk organs like urethra and rectum. We also placed one seed into each seminal vesicle. A total of 6 weekly, 1-hour thermal treatments (42–45 °C) were given to each patient. Foley catheters with indwelling thermocouples were placed to monitor urethral and rectal temperature throughout the procedure (fig. 1). All treatments utilized a patented coil system (Ablation Technologies, San Diego, Calif., USA). Patients initially were seated in a chair above the coil system. To optimize application of the magnetic field, we changed the coil system to a table, the patients directly in the magnetic field instead of above it. On the days of

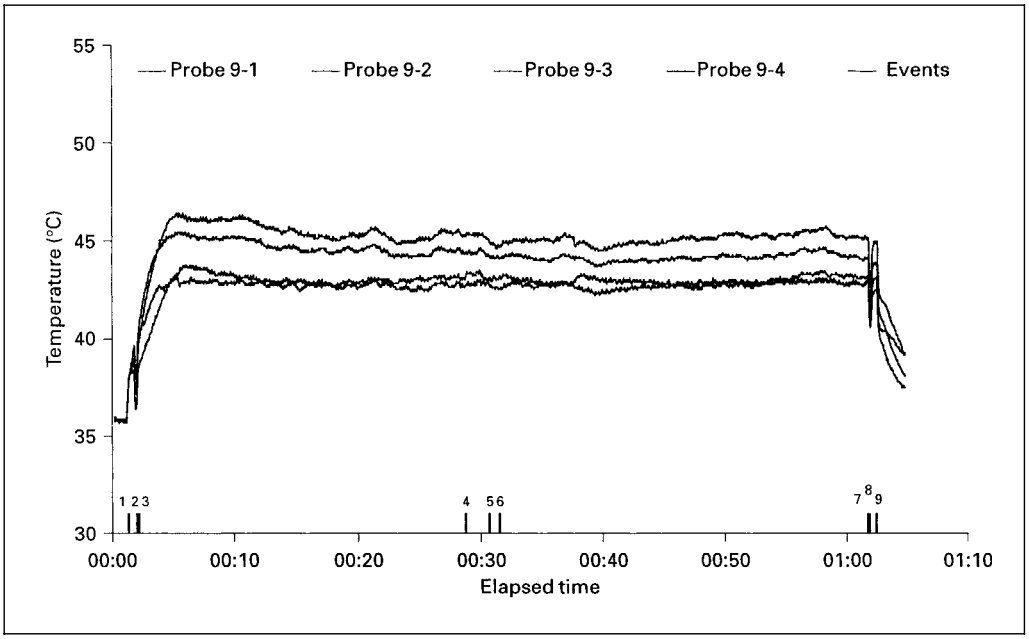

Fig. 1. Intraprostatic temperature during the hyperthermia session.

hyperthermia therapy, simultaneous fractionated (1.8 Gy/day) conformal radiotherapy of 68.4 Gy was delivered. There was a 2-hour interval between hyperthermia and the radiation session.

Criteria of inclusion were: T3 G1–3 adenocarcinoma of the prostate; T1–2, G1–3 prostate cancer with operative risk factors and patient's therapeutic wish.

Criteria of exclusion were: metastasis; antiandrogen therapy longer than 4 months; previous irradiation of the pelvis; pacemaker; metal implants and bladder outlet obstruction.

Results

Forty-one patients were treated between July 1997 and April 2000. The mean follow-up was 6 ± 6.4 months (range 0–24). Sixteen patients had clinically T3 tumors, 23 patients had T2 and 2 patients had a T1c tumor. All cancers had Gleason score 4–7. Mean age of the patients was 66 years (range 53–77). We placed an average of 30 thermoseeds (range 15–80) uniformly into the whole prostate. The therapy was well tolerated. No grade III or IV (RTOG) complications were observed during treatment. One patient had acute retention requiring supra-

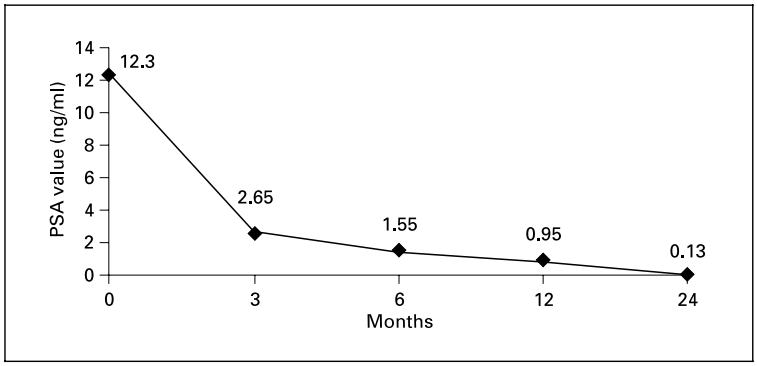

Fig. 2. PSA follow-up (median values) after treatment.

pubic diversion for 1 month after treatment and developed necrotic tissue in the prostate requiring a transurethral resection. The initial median PSA value was 12.3 ng/ml, which regressed after 3 months to 2.65 ng/ml, after 6 months to 1.55 ng/ml, after 12 months to 0.95 ng/ml and was stable after 24 months with 0.13 ng/ml (fig. 2). Of the biopsies performed 1 year after treatment, 67% were negative.

Conclusion

Combination of interstitial hyperthermia with conformal radiotherapy is a promising innovative treatment option for prostate cancer.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 177–182

High-Dose Rate Brachytherapy – The Charité Experience

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Introduction

The outcome of localized prostate cancer depends on local control. The probability of achieving local tumor control depends on numerous factors, such as tumor stage, grading, Gleason score and prostate-specific antigen (PSA) level, to mention just the major factors. The most common treatment for cT1 and cT2 prostate cancers is radical prostatectomy. Catalona and Smith [1] reported in a study with a follow-up of 7 years after radical retropubic prostatectomy a progression-free survival for stage cT1 of 79% and for stage cT2 tumors of 66%. In another report, overall survival rates at almost 10 years' follow-up was 78% for cT1 and 75% for cT2 tumors [2]. In a recent study, Martinez et al. [3] found for external beam irradiation versus radical prostatectomy no difference in terms of biochemical control and cause-specific survival at 7 years for patients with low-risk prostate cancer.

The optimal treatment for T3 tumors is still controversially discussed. There is evidence that 8–29% of T1 tumors and 30–60% of T2a,b tumors, which have been clinically staged T1 or T2 preoperatively, already show a transcapsular tumor spread in the pathologic specimen after radical prostatectomy [4–6]. Other studies have demonstrated a relationship of PSA level or Gleason score and the probability of seminal vesicle involvement after biopsy or radical prostatectomy [7–9].

The development of novel radiotherapy techniques in the last decade has opened the possibility to apply external beam radiotherapy at dose levels of 72 to

>80 Gy without detrimental complication rates. Particularly, 'intensity modulated radiotherapy' (IMRT) based on 'inverse treatment planning' will play a major role in dose escalation studies in the future. Another approach has been the combination of external beam irradiation and interstitial high-dose rate brachytherapy (HDR-BT). This treatment approach uses the HDR-BT as boost and likewise the external beam component can be reduced considerably. In terms of the biological effective dose (BED), this combination can as well as IMRT achieve doses in the range of 75–85 Gy.

With the introduction of PSA, diagnosis, treatment and follow-up of prostate cancer have changed dramatically. The PSA determination allows for a better comparison between different therapeutic strategies. We evaluated the combination of 2 × 9 Gy HDR-BT and external beam radiotherapy to a total dose of 45–50.4 Gy in terms of local tumor control as well as acute and late toxicity with special reference to T3 tumors.

Methods

Between December 1992 and December 1997 we treated 230 patients with localized prostate cancer (cT1-cT3), who had no lymph node metastasis staged by laparoscopic pelvic lymph node dissection. One hundred and thirty-four patients had a T3 tumor, 80 patients had a T2 tumor, and 16 patients had a T1 tumor. One hundred and thirty-nine patients were diagnosed to have intermediate-differentiated lesions (G2 cancer), 53 well-differentiated (G1 cancer), and 38 undifferentiated lesions (G3 cancer).

For all patients, pretreatment PSA levels, biopsy-proven prostate cancer, Gleason scores and an initial T-stage determination were available. A bone scan was performed in patients with PSA levels ≥ 10 ng/ml. Patients with laparoscopically proven lymph node metastasis were excluded from this treatment. All patients received a combination of HDR-BT and 3D conformal external beam irradiation.

Interstitial radiotherapy was administered using an iridium-192 HDR source in remote control technique. We placed 15–24 hollow needles uniformly into the prostate using a 7.5-MHz transrectal ultrasound probe (Combison 330 ultrasound, Kretz AG, Zipf, Austria) for control of needle positioning, using transversal and longitudinal sonographic sections [10]. Interstitial radiation of the prostate was carried out twice with a 1-week interval using a HDR iridium-192 source (nominal activity 10 Ci). Between October 1992 and December 1993, the interstitial dose was 10 Gy given in two fractions. We decreased the dose to 9 Gy per application after December 1993 [11].

Brachytherapy was combined with external beam radiotherapy. The fraction size was 1.8 Gy. Between October 1992 and December 1993, the total dose was 40 Gy. We increased the total dose to 45 Gy for cT1 and cT2 tumors and 50.4 Gy for cT3 tumors from January 1994 on. We also modified the management of the interstitial treatment, namely (a) the single interstitial radiation dose was decreased; (b) the needle-to-urethra distance was increased with a minimum of 1 cm, and (c) the distance to the anterior rectal wall was increased using a balloon on the transrectal ultrasound probe.

Digital rectal examination, transrectal ultrasound and PSA level determinations were regularly done during follow-up. Prostate biopsies were taken at 12 and 24 months after therapy. Complications were recorded according to RTOG-EORTC grading system [12]. Progression was defined by ASTRO criteria and stated if PSA values increased in three subsequent serum probes [13]. The Friedman and Wilcoxon tests were used for PSA value analysis. Kaplan-Meier and log rank statistics were used for survival analysis.

Results

The mean age of all patients was 67.3 years (range 49–83) and median follow-up time was 40.2 ± 19.6 months. The initial median PSA value was 12.8 ng/ml, which constantly regressed during the follow-up with 0.98 ng/ml at 12 months and 0.13 ng/ml after 60 months ($p \leq 0.001$). 47.2% of all patients reached a PSA level of <0.5 ng/ml. Progression-free survival depended on the initial PSA level. Patients with PSA levels ≤10 ng/ml had a significantly better progression-free survival than those with PSA values >10 ng/ml ($p = 0.01$). All patients with a T1 tumor survived free of progression at 5-year follow-up. The corresponding values for T2 and T3 tumors were 77.6 and 69.6%, respectively ($p \leq 0.04$). The progression-free survival for G1 tumors was 72%, for G2 tumors 69% and for G3 tumors 50%, respectively ($p = 0.08$).

Forty-one patients had progressive disease; 21 developed local disease, 12 systemic disease (skeleton), and 8 both. The treatment was well tolerated by all patients. No grade 4 (RTOG) acute complication occurred. Three patients had an episode of hematuria, which responded to conservative treatment. Only 10% of patients continued with elevated urinary frequency and dysuria after 3 months. Late sequelae grade 4 (RTOG) was observed in 6 patients (2.6%), 5 of whom developed a rectourethral fistula after rectal ulcerations requiring colostomy. One patient developed a ureter stenosis (0.4%). Grade 3 late sequelae occurred in 37 patients (16.1%). 12.2% (28 patients) developed urethral strictures and 3.9% (9 patients) became incontinent. Of these, 28 and 33% respectively had preirradiation urethral surgery in their medical history.

Discussion and Conclusion

The combined interstitial and 3D conformal external beam radiotherapy is a highly efficient treatment for locally advanced prostate cancer, especially for T3 patients. Evaluation of the lymph node status is a prerequisite for an accurate selection of patients. Initial PSA level, stage and grade are important prognostic factors.

A significant decrease of PSA levels during the 5-year follow-up can be achieved ($p \leq 0.001$). We observed a progression-free rate of 100% for T1 prostate cancer patients, 77.6% for T2 and 69.6% for T3 patients in the 5-year follow-up study using the ASTRO definitions. The initial PSA value is an important marker to determine outcome of radiotherapy [14–16]. In our series, patients with an initial PSA < 10 ng/ml had a significantly better progression-free 5-year survival compared with patients with PSA levels > 10 ng/ml.

Several different sources for interstitial radiotherapy are available. Iodine-125 or palladium-103 are low-dose rate sources, which show high tumor control probabilities for small tumors with good differentiation only in several reports. These sources are however not successful for tumors with capsule penetration, high pretreatment PSA or lower differentiation [14, 17, 18]. Gold-198 and iridium-192 are suitable for larger tumors with lower differentiation. With gold-198, 76% 5-year survival rates for T3 tumor could be achieved [19]. Iridium-192 can be delivered in low- and high-dose rate techniques. The longest follow-up of patients treated with the HDR technique was published in 1999 by Kovacs et al. [20] who found a 5-year overall and disease-specific survival of 83 and 94% respectively. This agrees well with our findings of 5-year overall and disease-specific survival of 93 and 98% respectively.

Unfortunately many reports work with different definitions of local control (i.e. based on biopsy results) which is one of the main problems when comparing different series. The criteria published by ASTRO are useful and allow a comparison between different treatment approaches. Therefore, we defined local control in our study according to these ASTRO criteria, which are primarily based on the follow-up of PSA levels.

When our study started in 1992, there was no data available about toxicity concerning HDR-BT. Although the rates of late sequelae with high-dose rate brachytherapy are comparable with those of low-dose brachytherapy reported in the literature [21], this issue is of major importance when regarding quality of life. In 1997, Borghede and Hedelin [22] showed the dose-dependent efficacy and toxicity of HDR therapy. Recently, Martinez et al. [23] found an actuarial grade 3 late complication rate of 9.3% in a group of 142 patients who underwent a combined HDR-BT and external beam radiotherapy treatment. Although their numbers of late toxicity events are lower than our results, their median follow-up is 2.1 years and this has to be regarded with caution as it is known that a considerable amount of late radiation toxicity occurs years after therapy. We observed that most of our patients with grade 3 and grade 4 late sequelae had either undergone TURP or urethrotomy within 1 year before or after HDR-BT. Sandhu et al. [24] reported a significant increase of urethral strictures in patients undergoing external beam radiotherapy who had TURP prior to therapy compared to those who did not [24]. Although these data cannot be directly transferred because of different thera-

py strategies, the results along with our own findings strongly suggest that patients with prior urological surgery are at higher risk to develop high grade late complications and may be bad candidates to receive this treatment.

Randomized studies are needed to compare HDR-BT with conformal external radiation therapy and other radiation therapy modalities, not only with respect to survival but also concerning late reactions and complications of normal tissue.

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Wiegel T, Heicappell R, Miller K, Hinkelbein W (eds): Controversies in Uro-Oncology.
Front Radiat Ther Oncol. Basel, Karger, 2002, vol 36, pp 183–190

Anatomy-Related and Transrectal Sonography-Guided Interstitial High-Dose Rate Brachytherapy Combined with Elective Irradiation of the Pelvic Lymphatics for Localized Prostate Cancer: The Kiel Experience

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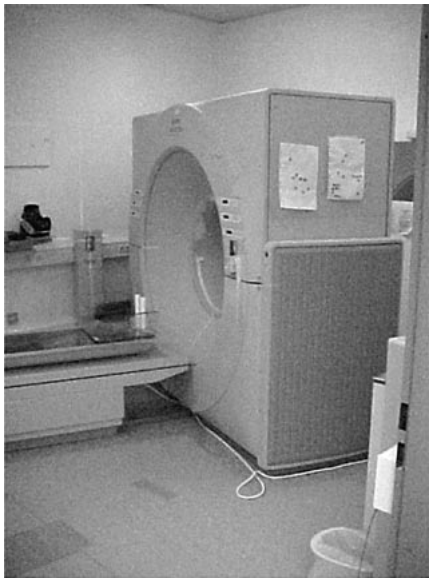
Introduction

The controversy regarding radiation versus prostatectomy for localized prostate cancer has been debated for many years, especially with the advent of nerve-sparing surgical procedures. This prospective study was designed to register the outcome of patients treated by combined high-dose rate brachytherapy (HDR-BT) for substantial local dose escalation and elective external beam radiation of the pelvic lymphatics in men with localized prostate cancer staged T1b-3 according to UICC (Union International Contre le Cancer) [1].

Material and Methods

One hundred and ninety-nine consecutive patients with localized prostate cancer (T1b-T3N0M0) were treated from February 1986 to October 1997 with a combined protocol using external beam elective irradiation of the lymphatics in the small pelvis and interstitial conformal HDR-BT for significant local dose escalation in the prostate [2, 3].



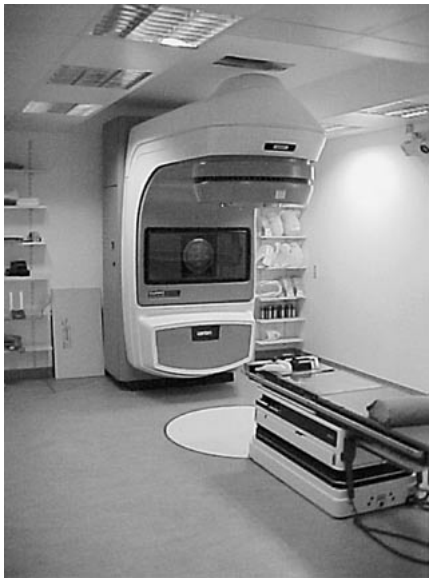


Fig. 1. CT scanner with laser localization divice.
Fig. 2. 15-MV accelerator.

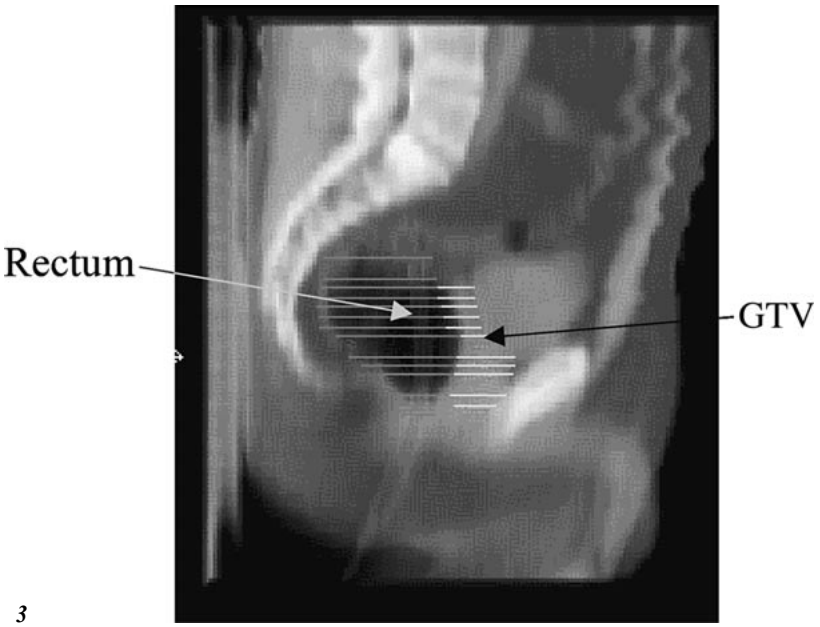
Teletherapy Protocol

The external beam radiotherapy was computed tomography (CT)-based planned and applied using a 15-MV beam from a linear accelerator (fig. 1, 2). The gross tumor volume (GTV) for the teletherapy was defined as the prostate and the seminal vesicles (fig. 3). The clinical target volume (CTV) was enlarged to the locoregional pelvic lymphatic region. The treatment was delivered in supine position with a bilateral 120° arc technique, skipping 60° anterior and posterior vectors. A four-field 'box' technique was introduced in 1991. The small pelvis was treated to 50 Gy with a dose limitation in the prostate to 40 Gy using intensity modulation of the beam by individually customed compensators. Patients were treated daily, 5 days/week with a dose of 2.0 Gy/day. Doses were planned, applied and reported according to the ICRU Report 50 recommendations [4].

BT Protocol

The implant geometry was related to the peripheral zone of McNeal [5]. The high-dose fall gradient in the surrounding tissue was aimed to assure an optimal protection of rectum, urethra and bladder for low morbidity. The high-dose volumes as defined by ICRU Report 58 [6] were used to implement the intended boost-in-boost therapy strategy.

Fig. 3. CT reconstruction: GTV and critical organ rectum.
Fig. 4. TRUS image and definition of CTV 1 = McNeal peripheral zone.



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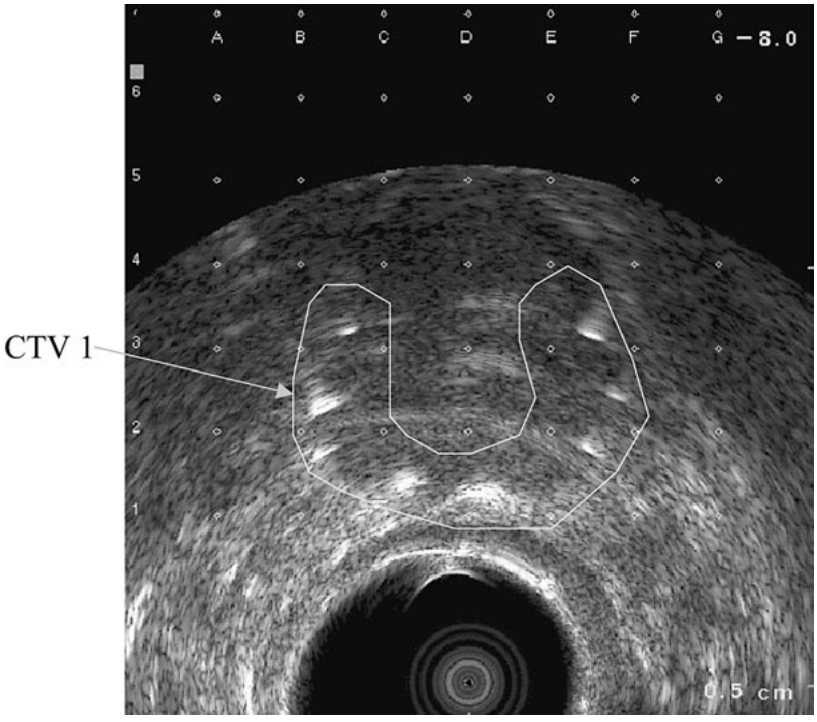

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The prostate was carried to the cumulative dose of nominal 70 Gy by transrectal ultrasound (TRUS)-planned conformal interstitial HDR-BT. An iridium-192 stepping source from an afterloader with an initial activity of 370 GBq was used. BT was applied in two fractions incorporated in the external beam treatment schedule.

For the BT the CTV definition differentiated a CTV 1 and a CTV 2. The CTV 1 (fig. 4) was defined in the peripheral zone of the prostate according to McNeal [5]. The CTV 2 included the entire prostatic gland.

The planning target volume (PTV) encompassed especially in T3 lesions the CTV with a small margin of 2–3 mm to take into account possible extracapsular disease. The minimum target dose (MTD) at the periphery of the planning target volume 1 (PTV 1) according to the ICRU Report 58 [6] was 15 Gy/fraction and was considered as reference dose. The MTD for the PTV 2 was ca. 9 Gy/fraction. The implant geometry required for the treatment of the described volumes can be termed as curved, single plan implant according to ICRU Report 58.

The overall treatment time was 6–7 weeks. Biological equivalent dose (BED) for the treatment was calculated as a total dose of 115 Gy regarding the 15-Gy BT isodose line which covered the peripheral zone of the prostate including 20–40% of that volume which received 20-Gy fraction dose with a BED of 135 Gy (boost-in-boost strategy). Biochemical failure was defined according to the ASTRO Consensus Panel. Instead of Gleason scores (GS), the WHO-Mostofi system [7] was used for histologic typing (grade 1 = GS 0–4, grade 2 = GS 5–7, grade 3 = GS 8–10).

Results

Treatment results were analyzed according to different prognostic groups with respect of initial PSA value and WHO-Mostofi tumor grading (G). Group I (n = 57): PSA < 10, G1–2 (GS < 7); group II (n = 24): PSA 10–20, G1–2 (GS < 7); group III (n = 31): PSA > 20, G1–2 (GS < 7); group IV (n = 18): PSA < 10, G3 (GS > 7), group V (n = 13): PSA 10–20, G3 (GS > 7); group VI (n = 29): PSA > 20, G3 (GS > 7). In 27 cases the pretreatment PSA was not known. The median follow-up in the groups was 74, 81, 56, 68, 75 and 70 months, respectively. In group I the percentage of T2b–T3 cancers according to UICC 1992 was 70.1%; in group II 87.5%, in group III 80.6%, in group IV 83.3%, in group V 84.6%, and in group VI 86.2%, respectively. The median initial PSA in the different groups was 6, 14.1, 33.6, 5, 14.6 and 38.6 ng/ml, respectively. In group VI, patients with PSA > 40 ng/ml represented 50% of the cases. The median Mostofi grading was calculated in group I: 2 (GS 5–7), in group II: 2 (GS 5–7), in group III: 2 (GS 5–7), in group IV: 3 (GS 8–10), in group V: 3 (GS 8–10) and in group VI: 3 (GS 8–10), respectively. However, the number of patients in some subgroups of the cohort was under 25. Therefore, 5 years' actuarial clinical survival was primarily calculated for groups I, III and VI. Actuarial clinical failure (CF) rate was 1.8% for group I, 12.9% for group III and 34.5% for group VI, respectively. bNED (bio-

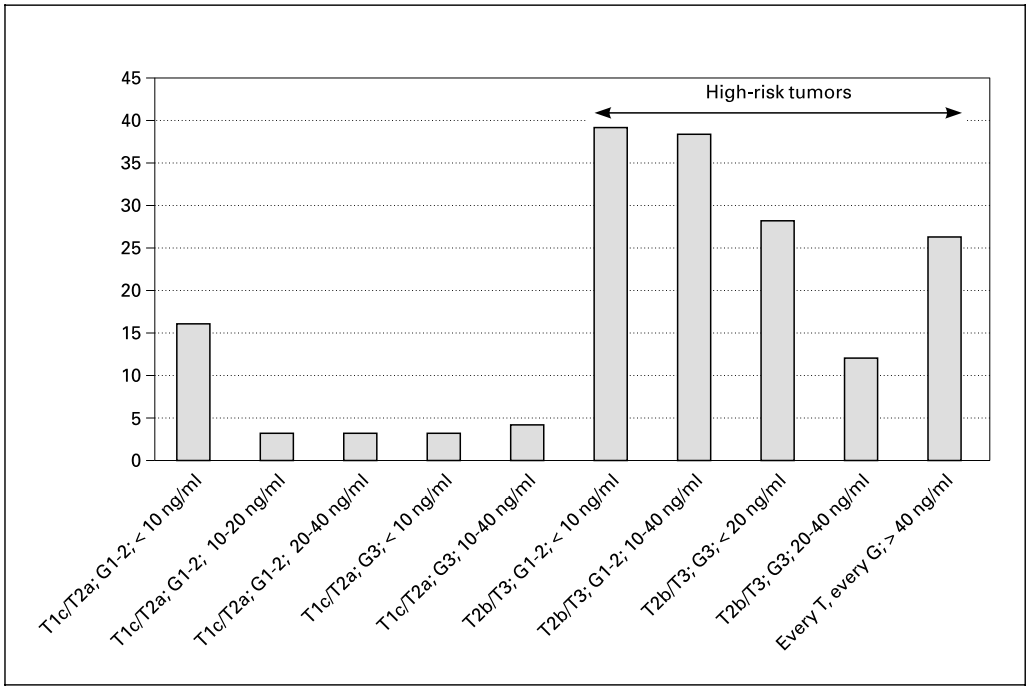

Fig. 5. Cumulative incidence: prognostic group II.

Table 1. Patient characteristics according to prognostic group I

Initial PSA/grading	n (n = 172)	T1/T2a %	T2b/T3 %	Median PSA grading	Median Mostofi	5-year bNED, %
<10 ng/ml/G1–2	57	29.9	70.1	6	2	94.7
10–20 ng/ml/G1–2	24	12.5	87.5	14.1	2	(83.3)
>20 ng/ml/G1–2	31	19.4	80.6	33.6	2	67.7
<10 ng/ml/G3	18	16.7	83.3	5	3	(72.2)
10–20 ng/ml/G3	13	15.4	84.6	14.6	3	(76.9)
>20 ng/ml/G3	29	13.8	86.2	38.6	3	38

WHO G1–2 = Gleason score (GS) <7; WHO G3 = Gleason score (GS) >7.

Table 2. Patient characteristics according to prognostic group II

Initial PSA/grading T-stage	n (n =172)	T1c %	T2a %	Median PSA grading	Median Mostofi	5-year bNED, %
T1c/T2a; G1–2; <10 ng/ml	16	6.25	93.75	3.6	2	
T1c/T2a; G1–2; 10–20 ng/ml	3	0	100	13.1	2	
T1c/T2a; G1–2; 20–40 ng/ml	3	0	100	23.8	1	
T1c/T2a; G3; <10 ng/ml	3	33	66	7.6	3	
T1c/T2a; G3; 10–40 ng/ml	4	0	100	21.2	3	
		T2b-c	T3			
T2b/T3; G1–2; <10 ng/ml	39	62.5	37.5	6.4	2	92.5
T2b/T3; G1–2; 10–40 ng/ml	38	42.1	57.9	18	2	84.2
T2b/T3; G3; <20 ng/ml	28	46.4	53.6	8.4	3	75
T2b/T3; G3; 20–40 ng/ml	12	58.3	41.7	24.5	3	
Any T, any G; >40 ng/ml	26	69.2	30.8	73.6	3	34.6

WHO G1–2 = Gleason score (GS) <7; WHO G3 = Gleason score (GS) >7.

chemical and clinical nonevidence of disease) was observed in group I: 94,7%; in group III: 67,7% and in group VI: 38%. Disease-free survival (DFS) was 98.2% in group I, 87.1% in group III and 65.5% in group VI, respectively. Overall survival (OS) was 82.5% in group I, 67.7% in group III and 62.1% in group VI, respectively. The results are detailed in table 1.

The patients were also grouped according to three prognostic variables: initial PSA, T-stage UICC 1992 [8] and WHO-Mostofi grading (fig. 5: prognostic groups II). Survival rates were calculated in subgroups with a sufficient number of patients. In patients with T2b/T3, G1–2, PSA < 10 (n = 39, median PSA 6.4 ng/ml, median Mostofi score 2) we observed a CF of 2.5%; bNED in 92.5%, DFS in 97.5% and OS in 85%. Patients with T2b/T3, G1–2, PSA >10 < 40 (n = 38, median PSA 18 ng/ml, median Mostofi score 2) showed CF in 15.8%, bNED in 84.2%, DFS in 84.2% and OS in 73.7%. In the cohort of T2b/T3, G3, PSA < 20 (n = 28, median PSA 8.4 ng/ml, median Mostofi score 3) CF was found in 21.4%, bNED in 75%, DFS in 78.6% and OS in 71.4%.

In the patient group with any T, any G, PSA >40 ng/ml (n = 26, median PSA 73.6 ng/ml, median Mostofi score 3) we found CF in 26.9%, bNED in 34.6%, DFS in 73% and OS in 69.2%, respectively. The results are detailed in table 2.

Table 3. Five-year bNED survival in men with prostate cancer: comparison of treatment methods

Prognostic group	Institution	Treatment method	n	Median PSA ng/ml	5-Year bNED, %
PSA >20 ng/ml, G1–2	Fox Chase	3D conformal	101	Not reported	32
	Baylor	Prostatectomy	34	31.0	54
	Kiel	HDR-BT/teletherapy	31	33.6	68
PSA 10–20 ng/ml, G3	Fox Chase	3D conformal	61	Not reported	62
	Baylor	Prostatectomy	90	13.2	73
	Kiel	HDR-BT/teletherapy	13	14.6	(76.9)

These data suggest strongly that the combined HDR-BT and teletherapy treatment method is especially suitable for high-risk prostate cancer patients as defined in the above prognostic groups.

Late grade 3 radiation toxicity according to the EORTC (European Organization for Research and Treatment of Cancer)/RTOG (Radiation Therapy Oncology Group) score side effects were observed in 2.3% for the genitourinary and 3.8% for the gastrointestinal system, respectively. No higher-grade side effects were registered.

Conclusion

The results confirm that local dose escalation using anatomy-related perineal TRUS-guided interstitial HDR-BT is a safe and effective treatment in men with localized prostate cancer. The therapy-related late toxicity is low. The 5-year bNED survivals in high-risk tumor groups were between 75 and 92.5%. An initial PSA value >40 ng/ml might be considered as noncurative with a 5-year bNED survival of 34.6%. However, the DFS and OS survival in this cohort was 73 and 69.2%, respectively. Furthermore, the 5-year bNED survival in the high-risk groups initial PSA >20 ng/ml, G1–2 and PSA 10–20 ng/ml, G3 was 67.7 and 76.9%, respectively. In comparison with the Kiel data, Kernen and Miles [9] reported 5-year bNED survival of 54 and 73% following prostatectomy in these prognostic groups. The Fox Chase center [10] reported 5-year bNED survival rates of 32 and 62% following 3D conformal radiotherapy for these patient groups. The results are detailed in table 3.

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