RECENT ADVANCES IN DEFINITIVE RADIOTHERAPY FOR PROSTATE CANCER

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ABSTRACT

Definitive radiation therapy is a well-recognised curative treatment option for localised prostate cancer. A suitable technique, dose, target volume, and the option of a combination with androgen deprivation therapy needs to be considered. An optimal standard external beam radiotherapy includes currently the intensity-modulated and image-guided radiotherapy techniques with total doses of ≥76-78 Gy in conventional fractionation. Data from several randomised studies increasingly support the rationale for hypofractionated radiotherapy. A simultaneous integrated boost with dose escalation focused on a computed tomography/positron emission tomography or magnetic resonance imaging/magnetic resonance spectroscopy detected malignant lesion is an option to increase tumour control with potentially no additional toxicity. The application of a spacer is a promising concept for optimal protection of the rectal wall.

Keywords: Prostate cancer, positron emission tomography, magnetic resonance imaging, external-beam radiotherapy, intensity-modulated radiotherapy, image-guided radiotherapy, simultaneous integrated boost, hypofractionation, dose escalation.

INTRODUCTION

Standard curative treatment options for localised prostate cancer (PrC) are radical prostectomy (RP) or definitive radiation therapy. Equivalent biochemical recurrence rates have been frequently reported in the past.[1] Patients undergoing RP are more likely to have urinary incontinence and erectile dysfunction, while patients undergoing radiotherapy are more likely to have bowel problems.[2,3] Treatment decision is usually based on specific risk groups[4] (Table 1, including the author's suggestion for a radiotherapy treatment concept). Very low/low-risk patients and very high/high-risk patients are combined in low and high-risk groups, respectively, in most studies. A very low-risk group defines a group particularly well suited to active surveillance. The decision for a radiotherapy dose and target concept, and the decision for additional androgen deprivation therapy (ADT), are based on individual risk factors. Modern radiotherapy concepts result in favourable and improved results in comparison to older concepts,[5] even for high-risk patients, with 10-year prostate-specific survival rates of about 95% applying doses ≥75.6 Gy.[6,7]

RADIOTHERAPY TECHNIQUES

This review focuses on external beam radiotherapy (EBRT) for PrC, commonly administered as fractionated linear accelerator photon treatment. Conventional fractions are generally used, with 1.8-2.0 Gy daily fractions up to a total dose of 74-80 Gy. EBRT is based on a single treatment planning computed tomography (CT) with a specific prostate position, predominantly dependent on rectum volume (three-dimensional conformal radiotherapy [3D-RT]).[8] As a result of daily positioning uncertainties, inter and intrafraction prostate motion, safety margins need to be added around the prostate in the treatment planning process. Prostate (+/- seminal vesicles; +/- pelvic nodes) is defined as clinical target volume (CTV) with safety margins as planning target volume (PTV).

Image-guided radiotherapy (IGRT) techniques are a prerequisite for a precise prostate localisation

for every EBRT fraction and reduction of safety margins. Biochemical tumour control has been shown to be significantly lower for patients with larger rectum volumes in the treatment planning CT scans even if a posterior safety margin of 1 cm is considered without IGRT techniques.[9] Cone beam CT, ultrasound localisation with dedicated ultrasound imaging system, fiducial markers (intraprostatic gold markers, fiducial catheters) in combination with MV/kV portal imaging are used to correct patient set-up.[10,11] Higher technology fiducials include electromagnetic transponders, which transmit radiofrequency waves and require special localisation and tracking systems that track prostate motion during an EBRT fraction.[12] According to an evaluation of inter and intrafraction prostate displacements, safety margins of 9 mm/15 mm/10 mm versus 4 mm/4 mm/4 mm are required in the superior-inferior/anterior-posterior/lateral directions without versus with daily image guidance to assure treatment of PrC with an adequate precision.[13]

Intensity-modulated radiotherapy (IMRT) is an advanced 3D-RT technique, often regarded as the current standard technique for primary PrC EBRT, improving dose conformity and reducing the dose to organs at risk in comparison to conventional 3D-RT.[5] A multileaf collimator is required for IMRT. Leafs are either on constant positions (step-and-shoot IMRT) or they are moving during irradiation (dynamic IMRT). Terms such as VMAT (volumetric modulated arc therapy) or Rapid Arc are used for specific dynamic IMRT technologies with simultaneous rotation of the gantry and leafs, allowing the delivery of a treatment fraction within 1-2 minutes. Tomo Therapy®, Vero®, or CyberKnife® are specific linear accelerator technologies. A CyberKnife® (linear accelerator mounted on a robotic arm) is exclusively used for hypofractionated (high dose per fraction) or single dose (also known as radiosurgery) treatments.

Table 1: Prostate cancer recurrence risk definitions and corresponding radiotherapy concept.

Risk Group	Risk group definition	External beam radiotherapy concept	
Very low risk	Stage T1c Gleason score ≤6 PSA <10 ng/ml fewer than 3 prostate biopsy cores positive, ≤50% cancer in each core PSA density <0.15 ng/ml/g	dose	≥72-74 Gy
		target volume	prostate +/- base of semi-nal vesicles
Low risk	Stage T1-T2a Gleason score ≤6 PSA <10 ng/ml	ADT	no indication
Intermediate risk	Stage T2b-T2c or Gleason score 7 or PSA 10-20 ng/ml*	dose	≥76-78 Gy
		target volume	prostate + (base of) semi-nal vesicles
		ADT	+/- neoadjuvant/adjuvant ADT for 4-6 monts
High risk	Stage T3a or Gleason score 8-10 or PSA >20 ng/ml	dose	≥76-78 Gy
		target volume	prostate + (base of) semi-nal vesicles, risk adapted treatment of pelvic lmph nodes
Very high risk (locally advanced)	Stage T3b-T4	ADT	+ 2-3 years adjuvant ADT

*Patients with multiple adverse factors may be shifted into the next higher risk group.
PSA: prostate-specific antigen; ADT: androgen deprivation therapy.

DOSE ESCALATION

Several randomised EBRT dose escalation studies have been performed in the last few decades, demonstrating a biochemical and clinical recurrence free survival benefit for total doses of 74-78 Gy in comparison to doses of 64-70 Gy.[14,15] As the majority of patients were recruited in the 1990's, treatment consisted of conformal radiotherapy without IGRT. Dose escalation has been shown to significantly prevent biochemical failure in all risk groups in meta-analyses of randomised trials.[14,15] A meta-regression analysis demonstrates an advantage of 14% (82% versus 96%), 18% (71% versus 89%), and 19% (51% versus 70%) in low, intermediate, and high-risk patients, respectively, for the biochemical control after 5 years for doses of 80 Gy in comparison to 70 Gy.[14] However, high dose radiotherapy was associated with a significantly greater risk of late >Grade 2 gastrointestinal (GI) toxicity (hazard ratio 1.58 [1.24-2]; p<0.001[14] or 1.72 [1.42-2.08]; p<0.001[15]). No difference resulted in overall mortality rates (MRs) and PrC MRs. The 10-year-PrC specific MRs were 8.4% in the high dose versus 9.3% in the conventional dose arms.[15] Taking into account a usually slow progression of PrC, a longer followup will probably be required to demonstrate differences in survival rates in dose escalation trials. In an international salvage ADT trial, the time from salvage ADT to death was estimated at about 9 years, with only 17% of patients dying of PrC after 7 years.[16]

After a median follow-up period of 9 years, the MD Anderson dose escalation trial reported a significant disease-free survival benefit was reported in the group of patients with an initial prostate-specific antigen (PSA) >10 ng/ml (2% versus 15%; p=0.03) as well as in the group of high-risk patients (4% versus 16%; p=0.05).[6] As dose escalation increases biochemical tumour control, high doses of ≥76-78 Gy can be applied for all risk groups. The time to long-term salvage ADT is significantly delayed.[17] Higher toxicity rates must be weighed up against this benefit, so that modern radiotherapy techniques are particularly important in dose escalated treatment concepts. For older patients, especially low-risk patients or intermediate-risk patients with a PSA <10 ng/ml, lower doses of 70-74 Gy might be sufficient, as biochemical recurrence leads to a clinical recurrence in only a small percentage of patients. Dose escalation to ≥76-78 Gy can be generally recommended for intermediate and high-risk patients who are at greater risk of developing a metastatic disease.

TARGET VOLUME

CTV always includes the whole prostate. Focusing irradiation only on parts of the prostate is not useful as PrC is known to occur multifocally.[18] As only the proximal 2 cm are involved in >90% of patients,[19] the base of seminal vesicles should be included in the CTV in intermediate and high-risk patients. The elective irradiation of pelvic lymph nodes (PLNs) is discussed controversially. Whole pelvic radiotherapy (WPR) might improve outcomes of patients with PLN involvement by sterilising microscopic disease. An advantage in respect of biochemical recurrence-free survival in comparison to irradiation of the prostate only could be shown in a retrospective study after lymphadenectomy and histologically proven lymph node invasion in 415 patients[20] and in a large prospective randomised study with a total of 1,323 patients (radiation therapy oncology group [RTOG] 9,413, primary EBRT), particularly with neoadjuvant antiandrogen therapy.[21] PLNs were included for patients with an invasion risk of at least 15%. Smaller EBRT volumes encompassing only the true pelvis (or mini-pelvis) appear to be inadequate. Whole pelvic EBRT up to the level of the L5-S1 interspace was associated with improved progression-free survival rates in comparison to mini-pelvis EBRT or prostate only EBRT.[22] The studies that failed to show the benefit of PLN irradiation, RTOG 7,707 and GETUG-01,[23,24] did not use WPR as defined on the RTOG 9,413 study, did not consistently use antiandrogen therapy (AAT), and included relatively favourable patients. In large randomised studies demonstrating the benefit of long-term AAT for locally advanced PrC, PLNs were included in the target volume up to doses of 44-50 Gy.[25,26] Treatment concepts in these studies should be the basis for generally accepted standards.

ANDROGEN DEPRIVATION THERAPY (ADT)

EBRT with ADT has been shown to be associated with a survival benefit in comparison to ADT alone in randomised Phase III studies in patients with locally advanced PrC.[27,28] After a 10 year follow-up period, Widmark et al.[27] report an improvement of biochemical recurrence-free survival from 26% to 76%, disease-specific survival from 76% to 88%, and overall survival (OS) from 61% to 70%. Prospective

randomised studies have shown an OS advantage for EBRT with ADT in comparison to EBRT alone for patients with locally advanced or high-risk PrC. In the EORTC 22,863 study patients received a treatment with an LHRH (luteinising hormone releasing hormone) agonist for 3 years,[25] and in the RTOG 85-31 study indefinitely or until signs of progression.[26] Adjuvant AAT with bicalutamide (for a median time of 2 years) also resulted in an OS benefit in locally advanced PrC.[29] A short-term neoadjuvant ADT for 4 months was associated with a survival benefit for patients with larger local tumours (>25 cm^3) and a Gleason score 2-6 in the RTOG 86-10 study,[30] in another study for patients with a PSA >10 ng/ml and a Gleason Score ≥7.[31] High-risk patients benefit from longer ADT duration (3 and 2 years) in comparison to a shorter duration (4 and 6 months).[32,33]

RTOG 94-08 randomised patients with T1b-T2b tumours and a PSA <20 ng/ml to a short-term ADT of 4 months starting 2 months before EBRT versus EBRT alone. The largest overall and disease-specific survival benefit resulted in the group of intermediate-risk patients, with significant increase of 10-year OS from 54% to 61%. No benefit resulted for low-risk patients.[34] Thus, high-risk patients benefit from a longer ADT of at least 2-3 years. Intermediate-risk patients might benefit from short-term ADT of 3-6 months. Randomised studies must evaluate if this benefit still exists when higher doses of ≥76 Gy are used.[35] As ADT toxicity profile is well-known (hot flashes, impotence, osteoporosis, anaemia, weight gain, gynaecomastia, cardiotoxicity),[36] patients with comorbidities should be individually assessed in respect of ADT, especially long-term ADT.

HYPOFRACTIONATION CONCEPTS

Hypofractionated radiotherapy is defined by fraction doses of more than 2 Gy. Radiobiological PrC data and new advanced radiation therapy techniques with improved dose conformity are leading to an increasing number of hypofractionated treatments. Toxicity and tumour control after radiotherapy can be described by the linear-quadratic equation. An important parameter in this equation is the α/β ratio, which describes the sensitivity of normal tissues or tumours to fractionation in radiotherapy. Tumours with high α/β values are less able to repair injury between fractions than normal tissues with low α/β values, so small fractions allow recovery of normal tissues while killing tumour cells. The lower α/β ratio of PrC compared to the surrounding late-responding normal tissues (e.g. the rectal wall) lays the potential foundation for hypofractionation to improve tumour control without increasing the risk of late effects in normal tissues.[37]

Currently available Phase III studies indicate similar biochemical outcomes for the hypofractionated in comparison to conventionally fractionated treatment concepts (Table 2).[37-42] Toxicity results were also without statistically significant differences, particularly regarding long term toxicity,[37-42] though Pollack et al.[40] found worse urinary function after hypofractionated radiotherapy in the subgroup of patients with compromised urinary function before treatment.[40] Older studies, using doses below the current standard (60-64 Gy in 2 Gy fractions in the conventional arms) reported higher biochemical failure rates in the hypofractionated arms.[41,42] Several Phase I and II studies with extreme hypofractionation have been published, using fractions of 6-10 Gy up to total doses of 36-50 Gy.[43] Katz et al.[44] treated 477 patients. The majority received a total dose of 36.25 Gy in 7.25 Gy fractions. Biochemical control rates of ≥90% in low and intermediate-risk patients were reported after a median follow-up of 6 years. Phase III studies are currently recruiting. Extreme hypofractionation usually requires stereotactic techniques, including unique beam arrangements, stable immobilisation, motion control, and daily image guidance.

SIMULTANEOUS INTEGRATED BOOST TO INTRAPROSTATIC LESION

Focusing the dose escalation on the actual tumour has the potential to increase tumour control without increasing toxicity. Local PrC recurrence after primary EBRT usually originates in the location of the primary tumour, as demonstrated in studies comparing magnetic resonance imaging (MRI) before EBRT and at the time of recurrence.[45] MRI, magnetic resonance spectroscopy (MRS), and positron emission tomography (PET) with choline, acetate, or prostate-specific membrane antigen (PSMA) are suitable methods to localise intraprostatic lesions with an adequate sensitivity and specificity.[46,47] T2 weighted, diffusion-weighted, and contrast-enhanced sequences are the recommended key sequences for PrC detection and localisation in multiparametric MRI. MRS indicates the metabolism within the tissue.

Table 2: Randomised Phase III hypofractionation trials.

Reference	Patient number	Patient population	Median follow-up	Fractionation	Biochemical recurrence free survival
Lukka et al.[41]	936	Stage T1-T2 PSA <40 ng/ml	6 years	60 Gy/2 Gy	60%
				52.5 Gy/2.63 Gy	53%
Pollack et al.[40]	303	Intermediate and high risk	6 years	78 Gy/2 Gy	79%
				70.2 Gy/2.7 Gy	77%
Yeoh et al.[42]	217	Stage T1-T2	7 years	64 Gy/2 Gy	34%
				55 Gy/2.75 Gy	53%
Arcangeli et al.[38]	168	High risk	6 years	80 Gy/2 Gy	79%
				62 Gy/3.1 Gy	85%
Dearnaley et al.[39]	457	Stage T1-T3a, PSA <30 ng/ml	4 years	70 Gy/2 Gy	-
				60 Gy/3 Gy	-
				57 Gy/3 Gy	-
Hoffman et al.[37]	203	Stage T1-T3b PSA <20 ng/ml, Gleason score <10	6 years	75.6 Gy/1.8 Gy	-
				72 Gy/2.4 Gy	-

PSA: prostate-specific antigen.

High choline peaks indicate malignant areas, correlating to a higher ratio of cellular membranes per volume and a higher turnover of phospholipid membranes within the carcinoma.[46]

Molecular imaging by means of PET provides another method to study metabolic activity of tumours *in vivo*. PSMA has been used increasingly in recent years, tending to show a higher proportion of patients with suspected disease in comparison to other tracers.[47] The hybrid technology PET/CT reduces image fusion mismatches significantly. Studies comparing PET results with histological PrC specimens reported a specificity and positive predictive value between 80-90%.[48] Treatment planning studies applying ^{18}F-choline PET/CT, MRI/MRS, or angiotensin-converting enzyme PET-CT demonstrated a considerable potential for dose escalation to the macroscopic tumour with only minor changes of the dose to the organs at risk and normal tissue complication probability.[49,50] The opportunity for an improved adaptation of treatment plans for the individual patient results.

Clinical data on acute toxicity in a group of 118 PrC patients after dose escalation with a simultaneous integrated boost (SIB) technique to an MRI/MRS detected tumour (76 Gy median dose to PTV and 80 Gy median dose to gross target volume [GTV] prescribed) did not find an increase of severity or incidence of acute toxicity.[51] The additional SIB did not increase quality of life (QoL) changes in the acute phase or >1 year after radiotherapy in a QoL study.[52] Long-term results, including biochemical and clinical tumour control, have not been reported yet. Phase III studies are examining focal dose escalation up to 95.5 Gy, with doses of 76 Gy in 2 Gy fractions or 77 Gy in 2.2 Gy fractions to the whole prostate.[53]

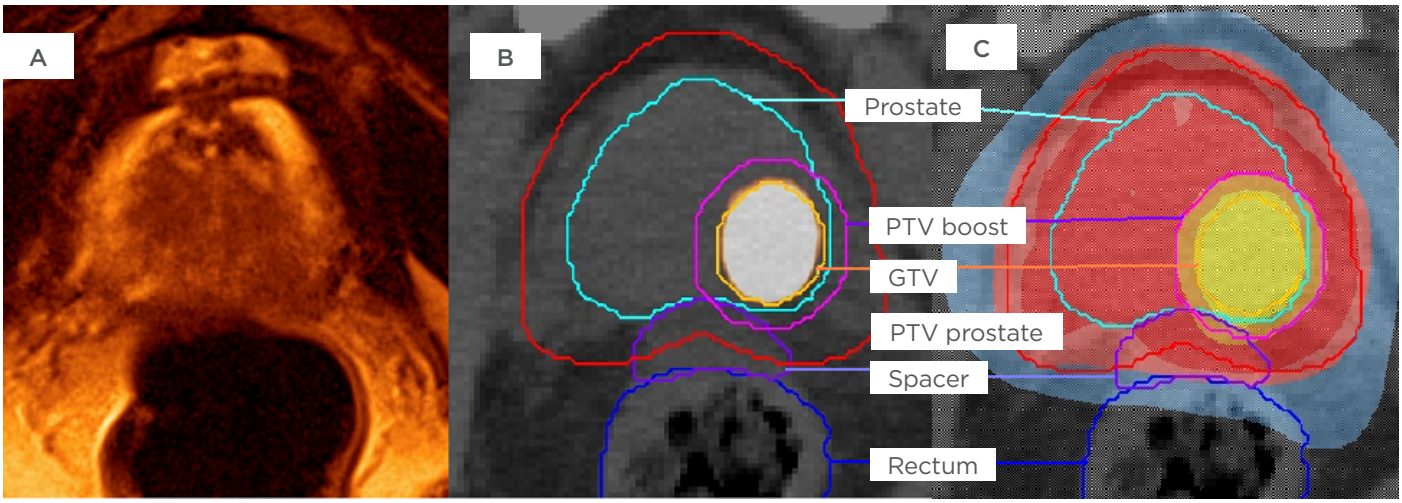

Figure 1: Simultaneous integrated boost to intraprostatic lesion with hydrogel spacer.
Tesla-2 weighted magnetic resonance imaging (A), prostate-specific membrane antigen positron emission tomography–computed tomography with spacer (B), isodose distribution with spacer and contours for treatment planning (C) in axial slices.
PTV: planning target volume; GTV: gross target volume.

SPACER APPLICATION

Rectum toxicity is the dose-limiting toxicity. Dose-volume correlations have been reported in many studies. Hyaluronic acid, human collagen, an inflatable balloon, or hydrogel are potential materials that have been used in clinical studies to create a prostate-rectum separation effectively.[54] The injection or implantation is performed under transrectal ultrasound guidance via the transperineal approach under local, spinal, or light general anaesthesia.[54] Spacer insertion is facilitated by a prior hydrodissection, helping to place the spacer between Denonvilliers' fascia and anterior rectal wall, using the same 18-gauge spinal needle. The implantation of a biodegradable balloon implies an incision of 3-5 mm and 1.5 cm depth.[55] A distance of about 1 cm results after spacer injection or placement, leading to significantly lower rectal doses. Injections of up to 20 ml of spacer volume usually created a space of 1-1.5 cm between the prostate and rectal wall.[56,57] Studies have shown stable spacer volumes during the radiotherapy period.[55,58]

Well-tolerated injection or implantation techniques and low rectal treatment-related toxicity have been demonstrated in prospective studies.[59,60] GI toxicity was evaluated in a group of 48 patients in a multi-institutional study. Only 12% of patients experienced Grade 2 acute GI toxicity (no patients with Grade 3 or higher toxicity) and 7% (two patients, one of them with Grade 1 at baseline already) experienced Grade 1 late GI toxicity within 12 months after treatment (no patients with Grade 2 or higher toxicity).[60] Long-term clinical results and the results of randomised studies are needed to better define the beneficial effect for the patient. Nevertheless, randomised trials are needed to define the benefit on the best level of evidence. The first randomised trial, evaluating the hydrogel spacer injection, has already closed patient accrual. An example for hypofractionated dose escalation to a simultaneous integrated boost with a hydrogel spacer is demonstrated in Figure 1. PrC was diagnosed in the left peripheral lobe in MRI and PSMA PET. A plan was calculated with a total dose of 78 Gy to the prostate in 2 Gy fractions, simultaneously 93.6 Gy in 2.4 Gy fractions to the intraprostatic lesion (GTV). Only 0.5% of the rectum volume was included within the 70 Gy isodose, so that extremely high doses can be delivered even to peripheral lesions without the risk of relevant rectal toxicity.

CONCLUSION

Radiobiological PrC data, technical advances in imaging techniques, treatment planning, and treatment delivery changed external beam radiotherapy standard concepts and led to new concepts that need to be evaluated in the near

future. The current standard implicates the delivery of a high conformal dose to the prostate with small safety margins, resulting from the application of daily image guidance. Hypofractionated radiotherapy is used increasingly, as data of prospective randomised trials are available with follow-up periods of several years. Extreme hypofractionation, definition of a simultaneous integrated boost with a focused dose escalation, and the application of a spacer to protect the rectal wall are promising concepts that need to be evaluated in randomised Phase III trials. They might develop to new standards, making radiotherapy a convenient treatment with low toxicity and high tumour control rates.

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