IMRT to Escalate the Dose to the Prostate while Treating the Pelvic Nodes

Matthew L. Cavey[1], John E. Bayouth[2], Martin Colman[1], Eugene J. Endres[2], Giuseppe Sanguineti[1]

Background and Purpose: To assess and quantify the benefit of introducing intensity-modulated radiotherapy (IMRT) over conventional approaches to cover the pelvic nodes while escalating the dose to the prostate gland.
Material and Methods: The pelvic lymphatics were planned to receive 50 Gy at 2 Gy per fraction by four-field box (4FB) technique and standard field blocks drawn on digitally reconstructed radiographs (DRR), 4FB with field blocks according to the position of pelvic nodes as contoured on serial planning CT slices, or IMRT. The lateral fields included three different variations of field blocks to assess the role of various degrees of rectal shielding. The boost consisted in 26 Gy in 13 fractions delivered via six-field three-dimensional conformal radiotherapy (3DCRT) or IMRT. By the combination of a pelvic treatment and boost, several plans were obtained for each patient, all normalized to be isoeffective with regard to prostate-planning target volume (PTV-P) coverage. Plans were compared with respect to dose-volume histogram (DVH) of pelvic nodes/seminal vesicles-PTV (PTV-PN/SV), rectum, bladder and intestinal cavity. Reported are the results obtained in eight patients.
Results: Pelvic IMRT with a conformal boost provided superior sparing of both bladder and rectum over any of the 4FB plans with the same boost. For the rectum the advantage was around 10% at V70 and even larger for lower doses. Coverage of the pelvic nodes was adequate with initial IMRT with about 98% of the volume receiving 100% of the prescribed dose. An IMRT boost provided a gain in rectal sparing as compared to a conformal boost. However, the benefit was always greater with pelvic IMRT followed by a conformal boost as compared to 4FB with IMRT boost. Finally, the effect of utilizing an IMRT boost with initial pelvic IMRT was greater for the bladder than for the rectum (at V70, about 9% and 3% for the bladder and rectum, respectively).
Conclusion: IMRT to pelvic nodes with a conformal boost allows dose escalation to the prostate while respecting current dose objectives in the majority of patients and it is dosimetrically superior to 4FB. An IMRT boost should be considered for patients who fail to meet bladder dose objectives.

Key Words: IMRT · Whole-pelvis radiotherapy · Dose escalation

Strahlenther Onkol 2005;181:431–41
DOI 10.1007/s00066-005-1384-9

IMRT zur Eskalation der Prostatadosis bei Bestrahlung der Beckenlymphknoten

Ziel: Evaluation des Vorteils der intensitätsmodulierten Radiotherapie (IMRT) im Vergleich zu konventionellen Methoden, um bei Bestrahlung der Beckenlymphknoten die Prostatadosis zu eskalieren.
Material und Methoden: Für die Bestrahlung der Beckenlymphknoten wurde eine Gesamtdosis von 50 Gy, in Fraktionen von 2 Gy, geplant unter Einsatz einer „Vier-Felder-Box"-(4FB-)Technik mit Standard-Blöcken, von 4FB-Technik mit Blöcken entsprechend der in seriellen Planungs-CTs festgestellten Lage der Lymphknoten, oder der IMRT. Die lateralen Felder umfassten drei unterschiedliche Anordnungen der Blöcke, um die Rolle verschiedener Grade der Abschirmung des Rektums zu ermitteln. Der Boost bestand aus 26 Gy in 13 Fraktionen, die mittels dreidimensionaler Sechs-Felder-Radiotherapie oder mittels IMRT verabreicht wurden. Durch Kombination von Beckenbestrahlung und Boost wurden für jeden Patienten mehrere Planungen durchgeführt, die alle isoeffektiv für das Planungszielvolumen der Prostata (PTV-P) waren. Die Planungen wurden hinsichtlich der Dosis-Volumen-Histogramme (DVH) des Planungszielvolumens der Beckenlymphknoten/Bläschendrüsen (PTV-PN/SV), des Rektums, der Blase und des Bauchraumes verglichen. Vorgestellt werden die bei acht Patienten ermittelten Ergebnisse.
Ergebnisse: Die IMRT des Beckens mit einem konformalen Boost war hinsichtlich des Schutzes von Blase und Rektum allen 4FB-Planungen mit demselben Boost überlegen. Für das Rektum betrug der Vorteil rund 10% bei V70 und war noch größer bei niedrigerer Strahlungsdosis. Die Bestrahlung der Beckenlymphknoten war bei initialer IMRT voll ausreichend, indem ungefähr 98% des Volumens 100% der vorgesehenen Dosis erhielten. Ein IMRT-Boost bewirkte, verglichen mit dem konformalen Boost, eine wirksamere Abschirmung des Rektums. Der Vorteil war jedoch bei IMRT des Beckens mit konformalem Boost immer größer als bei 4FB-

[1] Department of Radiation Oncology, University of Texas Medical Branch, Galveston, TX, USA,
[2] Department of Medical Physics, University of Texas Medical Branch, Galveston, TX, USA.

Received: October 19, 2004; accepted: April 26, 2005

Technik mit IMRT-Boost. Außerdem war der Effekt eines IMRT-Boost mit initialer IMRT des Beckens für die Blase höher als für das Rektum (bei V70 rund 9% und 3% für Blase bzw. Rektum).
Schlussfolgerung: IMRT der Beckenlymphknoten mit konformalem Boost erlaubt bei der Mehrzahl der Patienten die Eskalation der Prostatadosis unter Berücksichtigung der Zieldosis und ist dosimetrisch der 4FB-Technik überlegen. Ein IMRT-Boost kommt in Betracht für Patienten, bei denen die Zieldosis der Blase nicht erreicht wird.

Schlüsselwörter: IMRT · Strahlenbehandlung des Beckens · Dosiseskalation

Introduction

Strategies to improve outcome in patients with prostate cancer undergoing definitive radiotherapy include escalation of radiotherapy total dose, the addition of androgen deprivation to radiotherapy, the coverage of pelvic nodes by the initial target volume, or any combination thereof.

Dose escalation has been shown to improve outcome predominantly in intermediate- to high-risk patients in both retrospective and prospective studies [16, 22, 29–31, 43, 49]. Similarly, there is enough evidence now to support the use of long-term androgen deprivation in selected patients [4, 15, 27]. The role of adding pelvic node treatment to standard-dose radiotherapy to the prostate has been recently addressed by RTOG study 9413 [34] after several retrospective and prospective studies, as summarized by Roberts & Roach [36], were unable to provide a definitive answer. Preliminary results suggest that for patients with a > 15% risk of involvement of pelvic lymph nodes, as defined by the Roach formula [35], including the pelvic nodes in the initial fields may provide some benefit [34].

Interestingly, for the same patient population, both androgen deprivation [34] and dose escalation [18, 23] seem to play an independent role from pelvic node coverage in ameliorating outcome; in other words, combining the three strategies may provide additional benefits over each alone.

However, whether combinations of these strategies can be implemented safely is not clear. Concerns arise from the fact that long-term adjuvant androgen deprivation has been associated with an increased incidence of gastrointestinal toxicity [4, 15, 38, 40, 46]. Although it is not an unequivocal finding [1, 3, 21, 41], some studies have also reported increased gastrointestinal/genitourinary (GI/GU) toxicity when whole-pelvis radiotherapy is added to standard-dose (≤ 70 Gy) radiotherapy to the prostate compared to prostate-only (PO) radiotherapy [25, 37].

Recent data on rectal tolerance to radiation therapy (XRT) show that the volume of rectum that receives both intermediate (50–65 Gy) and high (65–75 Gy) doses is independently correlated to rectal bleeding [8, 11, 12, 17, 32]. The inclusion of pelvic nodes in the initial clinical target volume (CTV) of a four-field box (4FB) can potentially expose more rectum to intermediate doses and "saturate" rectal tolerance before the dose escalation can occur.

Moreover, what happens to the rectum and bladder when a pelvic treatment is part of a dose escalation program has never been addressed in detail. In the present paper, this issue is quantified and compared in terms of changes in dose-volume histogram (DVH) of both bladder and rectum using different approaches to treating both the pelvic nodes and boosting the prostate, including conventional, conformal, and intensity-modulated radiotherapy (IMRT) techniques.

Material and Methods

In the present study, different approaches to include the pelvic nodes in the initial treatment volume were considered. The resulting dose distributions were compared in terms of the percent of volume of organ at risk (OAR) receiving a given dose. Each plan was isoeffective with respect to coverage of the planning target volume of the prostate (PTV-P), i.e., 100% of PTV-P received at least 95% of the prescription dose (V95 ≥ 100) for all strategies.

Patients and Volumes

Eight consecutive patients with biopsy-proven adenocarcinoma of the prostate referred to our department for radical radiotherapy were selected for this study. All patients had clinically prostate-confined disease without obvious extracapsular extension or positive pelvic nodes.

For the simulation procedure, the patient was placed in the supine position with alpha cradle immobilizing the lower extremities. The patients were instructed to present for simulation (and treatment) with an empty rectum; bladder had to be voided 0.5–1 h before simulation and each treatment.

First, urethrography was performed. On the conventional simulator table, the isocenter was placed at the midpoint between L5/S1 and the beak of the urethrogram in the craniocaudal direction, and behind the femoral heads in the anterior-posterior plane. Afterwards, a planning CT was obtained with the patient in the same position and with the isocenter position marked. Typically, 5 mm slice thickness is used from the top of iliac bone to at least 5 cm below the base of the penis; a slice thickness of 3 mm was obtained for the cross-sectional slices containing the prostate.

The CT data sets were transferred to the Philips Pinnacle^3 treatment planning system (Philips Medical Systems, Madison, WI, USA). Regions of interest (ROIs) and OARs were outlined by a radiation oncologist and reviewed by another and included the prostate (P), seminal vesicles (SV), pelvic lymph nodes (PN), bladder (B), rectum (R), in-

testinal cavity (IC), penile bulb, and the femoral heads. For the purpose of the present study, the last two OARs were disregarded.

The margins added to the prostate consisted of 1.3 cm anterior, right and left, 1 cm superior and inferior, and 0.8 cm in the posterior direction. The pelvic lymphatics included the obturator and hypogastric, internal and external iliac (from the bifurcation of the common iliac artery at the level of the top of the sacroiliac joints, to the point where the external iliac artery crossed the inguinal ligament), and the presciatic and presacral (anterior to the first and second sacral segments) nodes. In contouring the pelvic nodes, guidelines from Nutting et al. [24] and Chao & Lin [6] were utilized. The CTV-PN was expanded by 1 cm in all directions, while the seminal vesicles were expanded with margins equivalent to the prostate.

The entire bladder and its contents were outlined. The rectum was contoured from the anus to the rectosigmoid junction, as previously reported [13], again including its contents. Individual loops of small bowel and colon were not contoured, but rather the contents of the "intestinal cavity" were considered as the IC volume. On axial CT slices, its boundaries included the abdominal wall anteriorly and anterolaterally, the retroperitoneal and deep pelvic muscles posterolaterally, and the great vessels, vertebral bodies, sacrum and rectum posteriorly. In a craniocaudal direction, the first slice containing the iliac bone down to the last slice containing fat anterior to the bladder was contoured. The rectum, as previously defined, was excluded from the IC volume. No margin was added to the OARs.

Fields

The goal was to deliver 50 Gy to the pelvic nodes and seminal vesicles (PTV-PN) and 76 Gy to the prostate (PTV-P) at 2 Gy per fraction. The two phases were considered in a conventional, sequential way with a plan for the initial 50 Gy covering PN + SV + P and a boost to the P only for an additional 26 Gy.

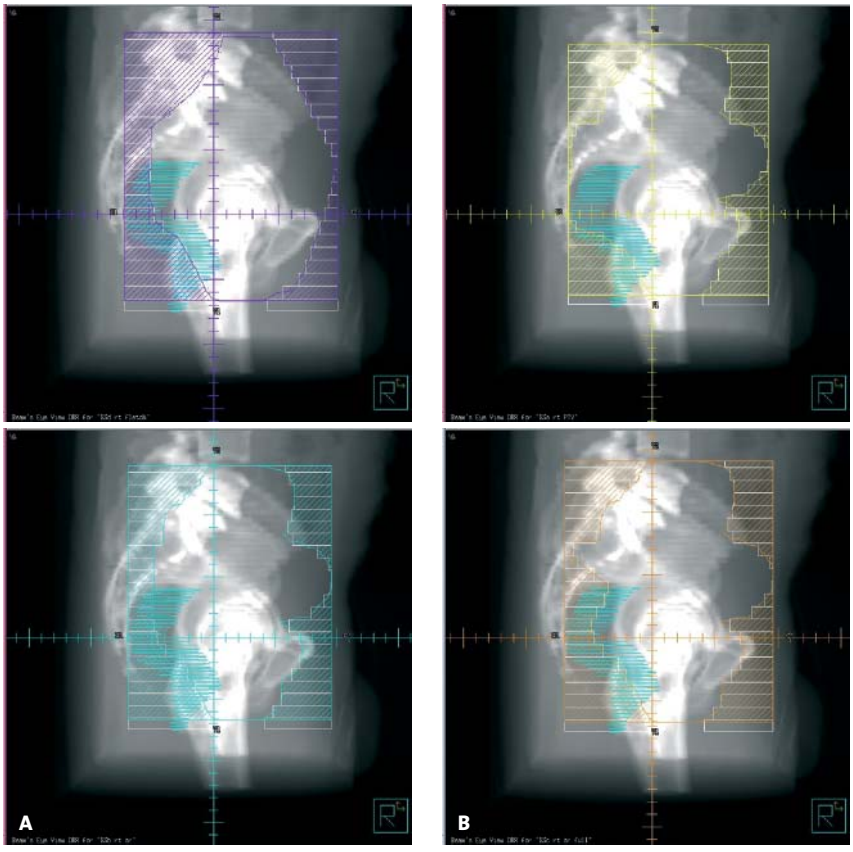

Figure 1a – Abbildung 1a

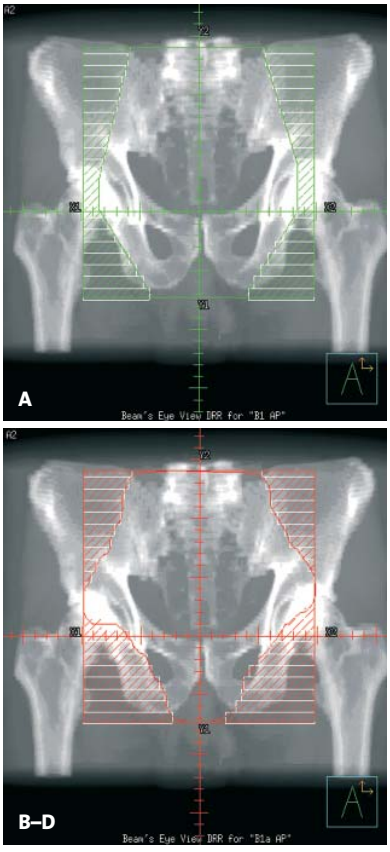

Figure 1b – Abbildung 1b

Figures 1a and 1b. Right lateral (a) and anteroposterior (b) DRRs of four-field box trials. Trial definition is reported in Table 1. It should be noted that the posterior/lower part of the lateral block is identical in all the fields and conformal to PTV-P coverage, while the posterior/upper part differs among B1, D1 and A1/C1.

Abbildungen 1a und 1b. Laterale (a) und anteroposteriore (b) digital rekonstruierte Radiogramme der 4FB- Bestrahlungsplanungen (Beschreibungen s. Tabelle 1). Zu beachten ist, dass der posteriore/untere Teil des lateralen Blocks in allen Feldern identisch ist und konformal der Bestrahlung des Planungszielvolumens der Prostata (PTV-P), während der posteriore/obere Teil Unterschiede zwischen B1, D1 und A1/C1 aufweist.

For the analysis in this study, the initial volume included both the PN and SV. For each patient, five different pelvic field plans and two different prostate boost plans were produced.

In general, three main approaches were investigated to cover the initial volume: "conventional" 4FB (trial A) with customized blocks drawn on digitally reconstructed radiographs (DRRs); three-dimensional conformal radiotherapy (3DCRT) 4FB (B, C, D) with blocks that "conformed" to PTV (PN + SV + P) on beam's eye view except at the posterior border of lateral fields, where various degrees of rectal shielding were utilized; and IMRT (E), covering the same volume as 3DCRT but with eight-field IMRT.

3DCRT fields were further divided according to the degree of rectal shielding on lateral fields: (1) *no* shielding (B), (2) *mid*-shielding (C), or shielding the anterior half of the rectum above the prostate PTV up to S2, and (3) *mid + upper* shielding (D), or shielding the anterior half of the rectum superiorly to the rectosigmoid junction. For the "conventional" (A) approach, once the blocks had been drawn on the DRR, part of rectum was shielded (as done in technique C). Field blocks for techniques A–D are illustrated in Figure 1 for one patient. The anteroposterior field was again drawn on DRRs without volumes (except for P) for trial A and according to PTV (PN + SV + P) for trials B–D (Figure 1).

It should be noted that geometric coverage of the prostate was identical for all the plans and took precedence over rectal shielding. In order to assure proper coverage, the edge of multileaf collimator (MLC) leaves was placed 8 mm from the edge of PTV. Moreover, the maximal x- and y-axis collimator settings from the 3DCRT fields were maintained in the other whole-pelvis trials.

The eight gantry angles selected for the inverse planning IMRT fields were coplanar and non-opposed at angles of 220°, 260°, 300°, 340°, 20°, 60°, 100°, and 140°. Field sizes were determined by the inverse planning system, but were initially set to allow exposure of the sum of all PTVs plus an additional margin of 1.5 cm.

Regarding the boost, two approaches were investigated: 3DCRT and IMRT. The 3DCRT used six fields at gantry angles of 240°, 270°, 300°, 60°, 90°, and 120°. The blocks were designed in the beam's eye view to expose the prostate plus margin again with an additional 8 mm margin for penumbra. No attempt was made to block the rectum at a given dose. For the IMRT boost plan, the field sizes were initially set to allow exposure of the prostate + margin with an additional 1.5 cm, but were ultimately determined by the inverse planning system.

Plans

The combination of these pelvic and boost plans resulted in the list of trials presented in Table 1. Again, all plans (pelvic and boost) were set to deliver the full prescription dose to 95% of the PTV-P. The method in which the two phases (pelvis and boost) were combined and optimized is as follows: 4FB plans (A–D) were created independent of boost technique, i.e., each field arrangement in Table 1 has the same monitor units regardless of boost plan. For a given patient, a plan was created for the 3DCRT boost and one for the IMRT boost. Each boost plan was adjusted slightly (< 1%) for each pelvic plan when matched to a particular pelvic plan in order to ensure V95 ≥ 100 for PTV-P.

Dose and dose-volume objectives were established for the two IMRT plans, the pelvic and boost. The IMRT boost plan was run first, based on published dose-volume objectives by Fiorino et al. [11], Zelefsky et al. [50], Huang et al. [17], and RTOG P0126 [32] as reported in Tables 2a and 2b. However, during the optimization process the planner may have adjusted the dose objectives to achieve a superior plan with the stated goal of achieving the lowest possible rectal DVH while maintaining the PTV prescription constraints.

For the IMRT pelvis plans, dose objectives for bladder and rectum were set slightly lower than those achieved by the IMRT boost plan in hopes to yield the "most optimal" plan. In addition, for the IMRT pelvis plan, in-house dose objectives were used for the intestinal cavity [39].

By convention, objectives for each plan, boost and pelvis IMRT, were based on a plan delivering 76 Gy in 38 fractions, even though only techniques F1

Table 1. Trials. 3DCRT: three-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy; P: prostate; PN: pelvic nodes; PTV: planning target volume.

Tabelle 1. Bestrahlungsplanungen. 3DCRT: 3-D konformale Radiotherapie; IMRT: intensitätsmodulierte Radiotherapie; P: Prostata; PN: Beckenlymphknoten; PTV: Planungszielvolumen.

Trial	PTV-PN Field arrangement	Comment	PTV-P Field arrangement	Total dose (Gy)
A1	Four-field box	Standard blocks;	3DCRT, six-field	26
A2		split rectum as C	IMRT, eight-field	26
B1	Four-field box	Drawn per PTV-PN;	3DCRT, six-field	26
B2		open on rectum	IMRT, eight-field	26
C1	Four-field box	Drawn per PTV-PN;	3DCRT, six-field	26
C2		split part up rectum	IMRT, eight-field	26
D1	Four-field box	Drawn per PTV-PN;	3DCRT, six-field	26
D2		split all up rectum	IMRT, eight-field	26
E1	Eight-field IMRT		3DCRT, six-field	26
E2			IMRT, eight-field	26
F1	None		3DCRT, six-field	76
F2			3DCRT, six-field	50
			IMRT, eight-field	26
G			IMRT, eight-field	76

Table 2a. Published dose-volume objectives for organs at risk (OARs). DVH: dose-volume histogram; ROI: region of interest.

Tabelle 2a. Veröffentlichte Dosis- und Volumen-Zielgrößen in Risikoorganen (OARs). DVH: Dosis-Volumen-Histogramm; ROI: Region of Interest.

ROI	Source [reference]	Dose (cGy)	% volume	Type
Rectum	RTOG (P0126) [32]	7,500	15	Max. DVH
		7,000	25	Max. DVH
		6,500	35	Max. DVH
		6,000	50	Max. DVH
	Huang et al.	7,800	5	Max. DVH
	(MDACC) [17]	7,560	15	Max. DVH
		7,000	25	Max. DVH
		6,000	40	Max. DVH
	Fiorino et al.	7,000	30	Max. DVH
	(AIRO) [11]	5,000	60	Max. DVH
Rectum overlap[a]	Zelefsky et al. (MSKCC) [50]	7,200		Max. dose
Bladder	RTOG (P0126) [32]	8,000	15	Max. DVH
		7,500	25	Max. DVH
		7,000	35	Max. DVH
		6,500	50	Max. DVH
	Huang et al.	7,000	25	Max. DVH
	(MDACC) [17]	6,000	35	Max. DVH
Bladder overlap[a]		7,600		Max. dose

[a] refers to the part of OAR that overlaps to the PTV

Table 2b. Dose-volume objectives used for treatment planning. DVH: dose-volume histogram; ROI: region of interest; PTV: planning target volume.

Tabelle 2b. Veröffentlichte Dosis- und Volumen-Zielgrößen für die Bestrahlungsplanung. DVH: Dosis-Volumen-Histogramm; ROI: Region of Interest; PTV: Planungszielvolumen.

ROI	Type	Target dose (cGy)	% volume	Weight
PTV76	Min. dose	7,200	X	30
	Min. dose	7,752	97	30
	Max. dose	7,980	X	30
PTV72	Max. dose	7,300	X	10
Prostate + margin	Min. dose	7,400	X	100
Rectum	Max. dose	7,500	X	1
	Max. DVH	7,250	13	1
	Max. DVH	6,900	20	1
	Max. DVH	6,050	28	1
	Max. DVH	5,200	37	1
	Max. DVH	4,800	43	1
	Max. DVH	3,800	60	1
Bladder	Max. DVH	7,700	8	0.1
	Max. DVH	7,450	18	0.1
	Max. DVH	7,280	23	0.1
	Max. DVH	6,900	30	0.1
	Max. DVH	6,000	45	0.1
	Max. dose	6,300	X	1
Intestinal cavity	Max. DVH	4,300	20	0.1
	Max. DVH	2,800	39	0.1
	Max. DVH	1,300	65	0.1
	Max. dose	7,750	X	0.1

Table 3. Selected Vx values for planning target volume of pelvic nodes/seminal vesicles (PTV-PN/SV; mean ± SD). Vx is the volume of a particular region of interest that receives x% of the prescription dose.

Tabelle 3. Ausgewählte Vx-Werte des Planungszielvolumens der Lymphknoten/Bläschendrüsen (PTV-PN/SV; Mittelwert ± SD). Vx ist das Volumen einer „Region of Interest", die x% der vorgesehenen Dosis erhält.

	V40 (%)		V47.5 (%)		V50 (%)		V60 (%)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A1	97.7	1.0	94.5	1.6	91.1	2.0	34.4	5.8
B1	100	0	100	0	99	0.7	37.1	6.0
C1	98.8	1.1	97.2	1.7	95.2	2.4	34.3	5.4
D1	97.3	2.2	95	2.9	92.7	3.5	33.8	5.1
E1	99.9	0.2	99.4	0.5	97.6	1.7	34.7	5.5

and G required all 38 fractions. Once each plan had been optimized, each trial in Table 1 was obtained by setting the appropriate number of fractions for each phase.

Data Management and Statistics

For each plan/patient, tabular differential DVH data was computed for each ROI. The data was then extracted from the planning system, converted into a Microsoft excel file, and recomputed as cumulative DVH data. For each ROI, both the mean DVH (± standard deviation [SD]) and the fraction of each ROI receiving a percent of a relevant prescribed dose, for the purpose of the present study, are reported. For PTV-PN coverage, V40 (or 80% of prescribed dose to target), V47.5 (95%), V50 (100%) and V60 (120%) were considered. Multiple intervals from V15 to V80 were considered for rectal and bladder dose.

Paired two-sided Student's t-tests were used for statistical comparison. Statistically significant difference was claimed for p-value < 0.05.

Results

Target Volume Coverage

First, the coverages of PTV-P and PTV-PN were examined according to the various initial techniques. Each of these trials used the same conformal boost but G. PTV-PN data are summarized in Table 3, and Figures 2 and 3 illustrate the mean DVH for all eight patients considered in this study for the most significant trials. With respect to PTV-P coverage, per initial assumption, all techniques were set to be isoeffective with regard to PTV-P coverage, delivering at least 95% of the prescription dose to 100% of the PTV-P volume (Figure 2). Regarding PTV-PN/SV coverage (Figure 3), the mean PTV-PN volume is 1,095 cm^3 (SD = 109 cm^3) or about six times greater than mean PTV-P volume and therefore, small changes along the y-axis are associated with a large effect on the absolute amount of the PTV that is included in a given isodose cloud.

When examining the 4FB trials (A–D, Figure 3a), the 3DCRT plan without rectal shielding (B1) shows a more com-

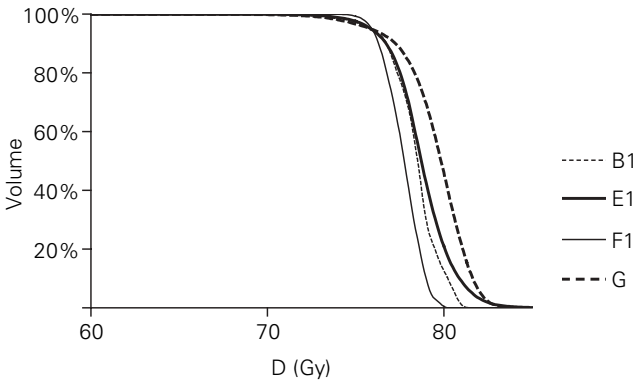

Figure 2. Dose-volume histogram of prostate-planning target volume according to different trials. For trial definition refer to Table 1.

Abbildung 2. Dosis-Volumen-Histogramme des Planungszielvolumens der Prostata entsprechend den verschiedenen Bestrahlungsplanungen (Beschreibungen s. Tabelle 1).

prehensive and significantly improved ($p < 0.05$) coverage of the target over other 4FB trials (A1, C1 and D1). Shielding the rectum on lateral fields of 4FB translated in underdosing part of PTV-PN volume that is proportional to the extent of shielding, as shown in Table 3. In the extreme scenario (D1 vs. B1), on average almost 3% and 6% more of PTV-PN volume falls outside of the 40 and 50 Gy isodose clouds, respectively. Comparing A1 and C1 (same degree of rectal shielding) shows that standard blocks results in decreased PTV-PN coverage of 1.1–4.1% in the V40–V50 interval over a three-dimensional conformal approach ($p < 0.05$).

Compared to the 4FB technique with rectal shielding (C1), IMRT to the pelvic nodes (E1) results in statistically improved ($p < 0.01$) coverage of the target in the 47.5–50 Gy interval, and a steeper gradient outside PTV-P producing a more conformal dose (Figure 3b) and a similar V60 (Table 3). Comparison between E1 and B1 reveals a slightly superior coverage of the target at V47.5 ($p = 0.014$) by B1 (both V40 and V50 are not statistically different), but this comes at the cost of a significantly higher V60 (Table 3, Figure 3b), as a result of a more conformal dose distribution with pelvic IMRT.

Introducing an IMRT as compared to a conformal boost had a negligible effect on prostate gland coverage (Figure 4a). However, as reflected by Figure 4b, the IMRT boost by increasing the conformity of dose to the PTV-P reduced V60 and V70 for PTV-PN.

Rectum

As expected, conforming fields to PTV-PN without shielding part of the rectum on the lateral fields (B1) exposes a large amount of rectum to low and intermediate doses (Figure 5a). However, even adding rectal shielding (A1, C1, D1) does not ensure that a plan meets dose-volume objectives for the rectum (Figure 5b).

Figure 5b also shows that including the pelvic nodes in the 4FB (A1, C1, D1) translated into an absolute increase in the percent of rectum getting 45 Gy, 55 Gy and 65 Gy of approximately 25–30%, 10–15% and 5–6%, respectively, as compared to PO radiotherapy (F1). At 70 Gy, although the difference was smaller (3–4%), it was still highly statistically significant.

Pelvic IMRT (E1) spares more rectum as compared to B1 (Table 4, Figure 5a). Moreover, considering both PTV-PN and rectal coverage, "initial" IMRT (E1) offers similar PTV coverage as compared to C1, but reduces rectal V50, V60, and V70 by 41.4%, 21.4%, and 14%, respectively (Table 4).

Figure 5c shows that a larger volume of rectum is included with E1 as compared to the PO techniques for doses < 55 Gy. Beyond this point, E1 is superior to PO 3DCRT (F1) and is not statistically different from PO IMRT (G) at 60 or 70 Gy.

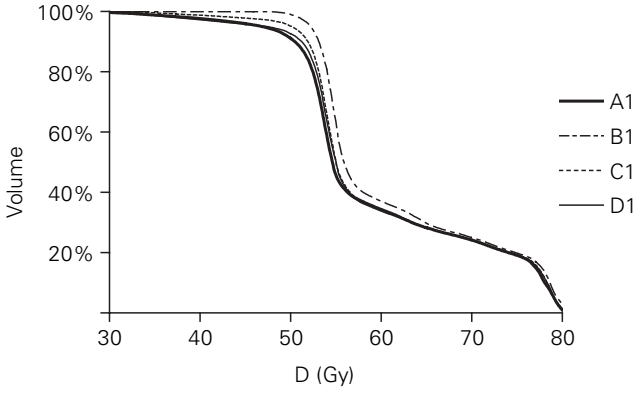

Figure 3a – Abbildung 3a

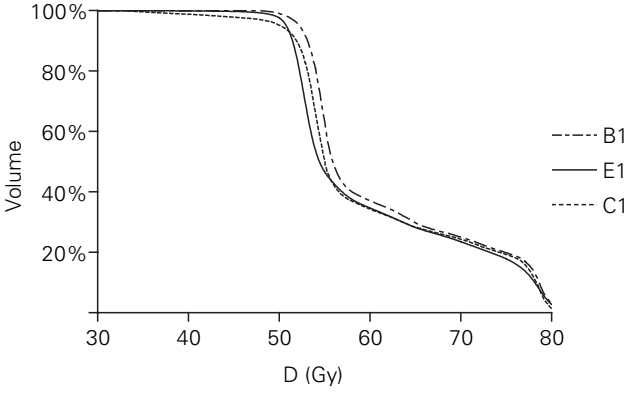

Figure 3b – Abbildung 3b

Figures 3a and 3b. Dose-volume histogram of planning target volume (pelvic nodes/seminal vesicles) according to different trials. For trial definition refer to Table 1.

Abbildungen 3a und 3b. Dosis-Volumen-Histogramme des Planungszielvolumens der Beckenlymphknoten/Bläschendrüsen entsprechend den verschiedenen Bestrahlungsplanungen (Beschreibungen s. Tabelle 1).

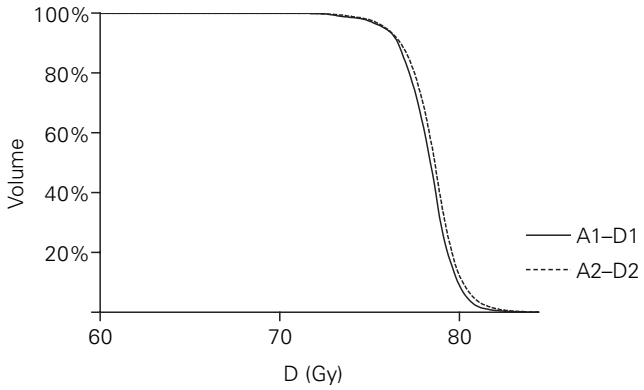

Figure 4a – Abbildung 4a

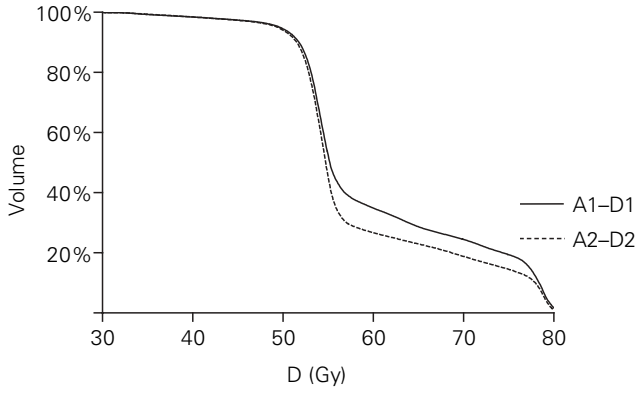

Figure 4b – Abbildung 4b

Figures 4a and 4b. Dose-volume histogram of (a) prostate-planning target volume and (b) planning target volume (pelvic nodes/seminal vesicles). Average of four-field box plans with 3DCRT (A1–D1) versus IMRT (A2–D2) boost. For trial definition refer to Table 1.

Abbildungen 4a und 4b. Dosis-Volumen-Histogramme a) des Planungszielvolumens der Prostata und b) des Planungszielvolumens der Beckenlymphknoten/Bläschendrüsen. Durchschnitt der 4FB-Planungen mit 3DCRT- (A1–D1) vs. IMRT-Boost (A2–D2). Beschreibung der Bestrahlungsplanungen s. Tabelle 1.

Using an IMRT instead of conformal boost for the trials including the pelvic nodes (Figure 6) reduces rectal V70 by approximately 7% and < 5% for the 4FB (A2–D2 vs. A1–D1) and IMRT (E2 vs. E1) trials, respectively. Interestingly, despite the benefit of an IMRT boost with 4FB pelvic treatment, E1 is consistently superior to A2–D2 at 65 Gy, 70 Gy and 75 Gy ($p = 0.009$, 0.011 and < 0.001, respectively).

Bladder

Trials with 4FB followed by 3DCRT (A1–D1) provided an average dose to bladder higher than that of initial IMRT to the pelvis with the same 3DCRT boost (E1, Figure 7). The difference between A1–D1 and E1 was up to about 30% at V50 (Table 5).

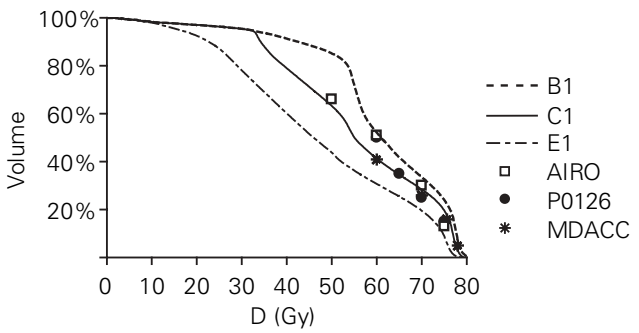

Figure 5a – Abbildung 5a

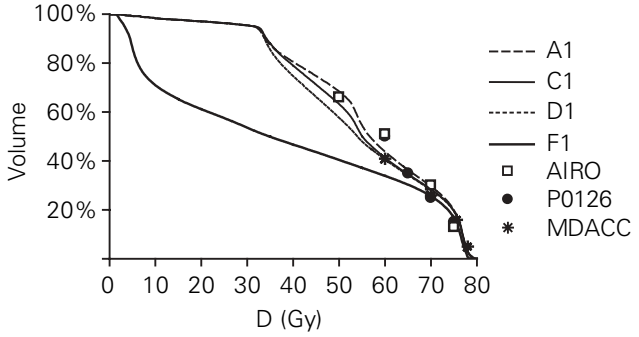

Figure 5b – Abbildung 5b

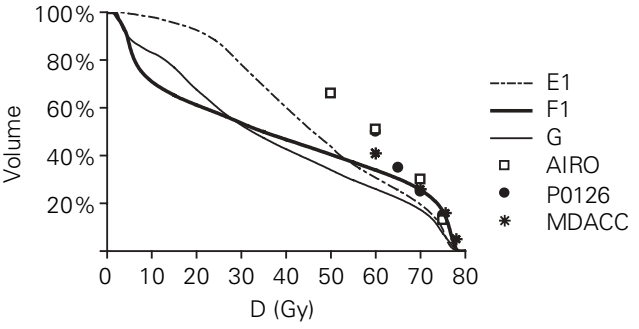

Figure 5c – Abbildung 5c

Figures 5a to 5c. Dose-volume histogram of rectum according to different trials. For definition of AIRO [11], P0126 [32] and MDACC [17] constraints refer to Table 2a. For trial definition refer to Table 1.

Abbildungen 5a bis 5c. Dosis-Volumen-Histogramme des Rektums entsprechend den verschiedenen Bestrahlungsplanungen. Zu AIRO [11], P0126 [32] und MDACC-Vorgaben [17] s. Tabelle 2a, Beschreibung der Planungen s. Tabelle 1.

As with the rectum, the coverage of pelvic nodes with any of the 4FB techniques (A1–D1) translated into a significantly larger portion of the bladder being irradiated over PO 3DCRT (F1). In particular, up to 40% more of the bladder was exposed to doses in the range of V30–50; at 60 Gy and 70 Gy, the absolute difference is around 20% and 15%, respectively. Interestingly, while pelvic IMRT (E1) included more bladder at low to intermediate doses than F1, the V65–75 values were

Table 4. Percent of rectal volume covered by each trial.

Tabelle 4. Prozentualer Anteil des Rektumvolumens, der bei den einzelnen Bestrahlungsplanungen erreicht wurde.

	A1		B1		C1		D1		E1		F1		G	
	Mean (%)	SD (%)	Mean (%)	SD (%)	Mean (%)	SD (%)	Mean (%)	SD (%)	Mean (%)	SD (%)	Mean (%)	SD (%)	Mean (%)	SD (%)
V15	97.7	5.0	97.7	5.0	97.7	5.0	97.7	5.1	95.6	6.1	65.3	11.6	76.9	6.1
V30	95.5	7.6	95.5	7.6	95.4	7.7	95.4	7.7	78.1	9.8	53.6	13.5	52.8	8.6
V45	74.7	14.3	88.6	9.6	71.2	7.8	66.2	12.7	51.5	9.1	43.6	13.2	38.4	8.0
V50	68.5	15.3	85.2	9.8	63.3	6.9	57.7	11.9	43.8	9.3	40.5	12.9	34.0	6.5
V55	54.6	16.1	71.8	14.2	50.1	9.3	48.0	10.5	36.3	10.1	37.2	12.5	29.7	5.1
V60	43.8	13.7	52.1	14.2	41.2	9.8	40.5	10.3	30.7	9.7	33.9	12.1	26.0	4.8
V65	36.4	12.5	41.8	13.6	34.6	10.0	34.3	10.3	25.5	8.9	30.3	11.5	22.1	4.6
V70	29.6	11.2	33.5	12.2	28.4	9.5	28.1	9.6	19.5	7.4	25.6	10.3	17.3	4.5
V75	19.8	9.2	24.0	9.9	19.6	7.5	19.3	7.4	8.9	3.7	16.5	8.5	7.3	6.2
V80	0.0	0.0	0.6	1.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

similar to F1. Figure 7 also shows that compared to PO IMRT (G), E1 and F1 included a larger volume of bladder in the high dose (65–75 Gy) region.

As shown in Figure 8, switching from a conformal to an IMRT boost for 4FB plans (A–D) allows at least 5% sparing of the bladder from V55 on. However, it is not until 65 Gy that the 4FB plans with IMRT boost (A2–D2) converge with E1 (pairwise comparison: 65 Gy: $p = 0.34$; 70 Gy: $p = 0.95$; 75 Gy: $p = 0.54$). On average, both E1 and A2–D2 plans are very close to the dosimetric constraints suggested by RTOG.

In terms of percent of organ spared at a given dose level, the advantage of an IMRT boost after initial pelvic IMRT (E2) was greater for the bladder than for the rectum: at 50 Gy, 60 Gy and 70 Gy the advantage was about 7%, 11% and 9%, respectively, while, as previously stated, it was always < 5% for the rectum.

Intestinal Cavity

As mentioned in the Material and Methods section, besides "usual" dose objectives, the following dose-volume objectives were utilized: V45 Gy ≤ 412 cm^3, V30 Gy ≤ 785 cm^3, and V15 Gy ≤ 1,279 cm^3. However, "sparing" of the intestinal cavity (and its contents) was not a primary objective of introducing IMRT for these patients. The results are graphically illustrated in Figure 9. C1 and D1 curves overlap B1 and have been omitted. E1 is similar or even worse than A1 and B1 up to 50 Gy,

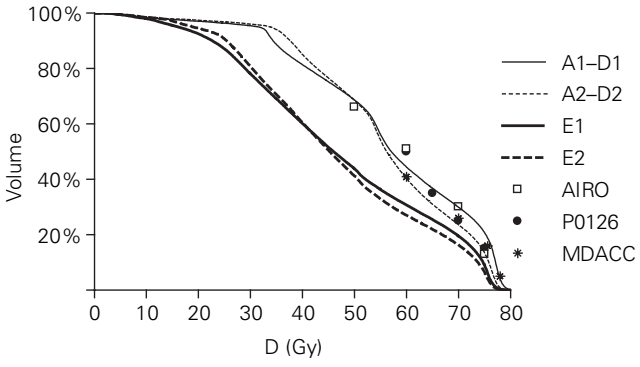

Figure 6. Rectal dose-volume histogram. Average of four-field box plans with 3DCRT (A1–D1) versus IMRT (A2–D2) boost compared with IMRT whole pelvis + 3DCRT (E1) or IMRT (E2) boost. For definition of AIRO [11], P0126 [32] and MDACC [17] constraints refer to Table 2a. For trial definition refer to Table 1.

Abbildung 6. Dosis-Volumen-Histogramme des Rektums. Durchschnitt der 4FB-Planungen mit 3DCRT- (A1–D1) vs. IMRT-Boost (A2–D2) verglichen mit IMRT des Beckens plus 3DCRT (E1) oder IMRT (E2). Zu AIRO [11], P0126 [32] und MDACC-Vorgaben [17] s. Tabelle 2a, Beschreibung der Bestrahlungsplanungen s. Tabelle 1.

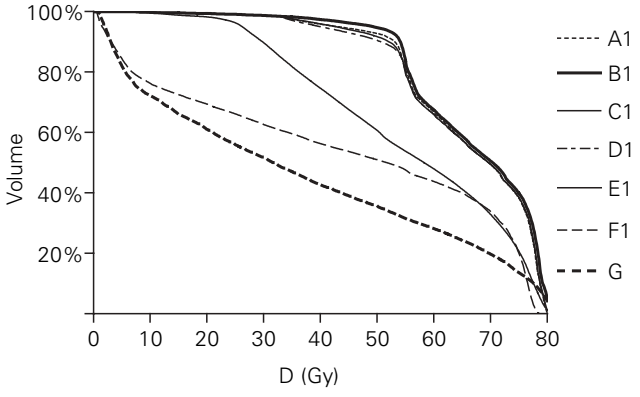

Figure 7. Mean bladder dose-volume histogram according to different trials. For trial definition refer to Table 1.

Abbildung 7. Durchschnittliches Dosis-Volumen-Histogramm der Blase entsprechend den verschiedenen Bestrahlungsplanungen (Beschreibungen s. Tabelle 1).

Table 5. Percent of bladder volume covered by each trial.

Tabelle 5. Prozentualer Anteil des Blasenvolumens, der bei den einzelnen Bestrahlungsplanungen bestrahlt wurde.

	A1		B1		C1		D1		E1		F1		G	
	Mean (%)	SD (%)	Mean (%)	SD (%)	Mean (%)	SD (%)	Mean (%)	SD (%)	Mean (%)	SD (%)	Mean (%)	SD (%)	Mean (%)	SD (%)
V15	99.6	1.1	99.6	1.1	99.6	1.1	99.6	1.1	98.8	3.3	72.5	21.2	66.2	20.9
V30	98.8	3.5	98.7	3.6	98.8	3.5	98.8	3.5	89.7	9.5	62.6	21.2	51.6	16.9
V45	94.5	12.6	96.2	6.5	94.1	12.3	92.9	15.5	67.6	17.3	53.7	19.5	39.0	12.7
V50	92.7	15.2	94.7	6.9	91.7	14.7	90.4	18.3	60.7	19.4	51.0	18.9	35.5	11.3
V55	80.7	23.5	83.8	17.9	79.5	23.4	80.3	22.4	53.8	20.6	47.6	17.9	31.6	10.3
V60	66.7	24.2	67.4	22.8	66.0	24.0	66.0	23.8	48.0	19.5	43.8	16.8	28.2	8.9
V65	57.6	22.4	58.8	21.5	57.5	22.3	57.4	22.1	41.2	17.5	39.9	15.5	24.3	7.5
V70	49.4	20.2	50.6	19.6	49.5	20.1	49.4	20.0	32.9	14.8	33.9	13.6	19.7	5.9
V75	38.2	16.5	39.9	16.3	38.5	16.5	38.4	16.2	20.7	10.6	19.9	8.0	13.6	6.4
V80	0.3	0.9	5.2	8.4	1.2	3.1	1.0	2.2	1.3	1.4	0.0	0.0	4.3	2.8

at which point there is small (≈ 5–10%) but statistically significant advantage in favor of E1 (A1 vs. E1, p = 0.007; B1 vs. E1, p = 0.001). Given the fact that the intestinal cavity volume is large (mean: 1,509.3; SD: 391.6 cm^3), the small advantage in favor of E1 may become clinically relevant for late complications.

Discussion

There is no definitive answer as to whether or not the pelvic lymphatics need to be treated for patients at > 15% risk of involvement. The matter has long been debated with both positive and negative retrospective studies summarized by Roberts & Roach [36].

Recently, Roach et al. reported the preliminary findings of RTOG randomized study 9413 addressing this issue in patients undergoing conventional dose (≈ 70 Gy) radiotherapy to the prostate [35]. Patients with whole-pelvis radiotherapy experienced a 4-year progression-free survival of 54.2% compared to 47% for patients treated on the prostate only [34]. These data, although preliminary, suggest that inclusion of pelvic nodes in the initial fields should be seriously taken into consideration in patients at significant risk of nodal involvement [28].

Interestingly, for the same group of patients, a recent retrospective study from Fox Chase suggests that radiation dose to the prostate is an independent predictor of biochemical control [17]. Additionally, the aforementioned RTOG study

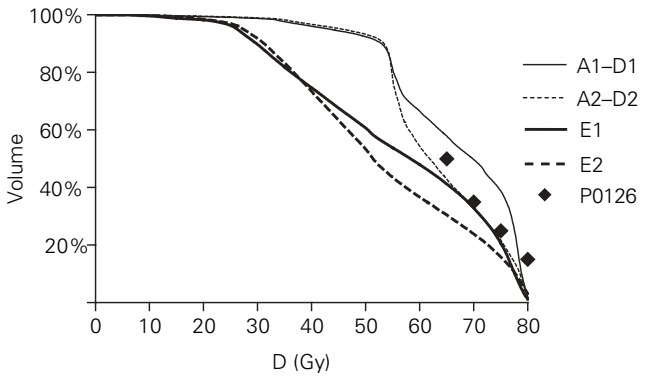

Figure 8. Bladder dose-volume histogram. Average of four-field box plans with 3DCRT (A1–D1) versus IMRT (A2–D2) boost compared with IMRT whole pelvis + 3DCRT (E1) or IMRT (E2) boost. For definition of P0126 [32] constraints refer to Table 2a. For trial definition refer to Table 1.

Abbildung 8. Dosis-Volumen-Histogramm der Blase. Durchschnitt der 4FB-Planungen mit 3DCRT- (A1–D1) vs. IMRT-Boost (A2–D2) verglichen mit IMRT des Beckens plus 3DCRT (E1) oder IMRT (E2). Zu P0126 [32] s. Tabelle 2a, Beschreibung der Bestrahlungsplanungen s. Tabelle 1.

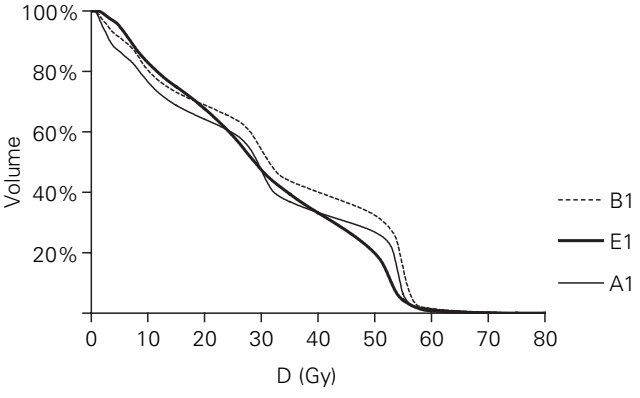

Figure 9. Mean intestinal dose-volume histogram according to three different trials. For trial definition refer to Table 1.

Abbildung 9. Durchschnittliches Dosis-Volumen-Histogramm des Darmes entsprechend den verschiedenen Bestrahlungsplanungen (Beschreibungen s. Tabelle 1).

suggests a role for neoadjuvant and concomitant androgen deprivation in addition to whole-pelvis radiotherapy [34]. In summary, while there is some evidence that extending initial fields may be worthwhile, other strategies may work equally as well and therefore the issue may be whether or not it is possible to combine the strategies safely in order to improve outcomes in this group of patients.

Some concerns about the compatibility of whole-pelvis radiotherapy and dose escalation arise from the present study. Figure 5a shows that each of the 4FB trials includes a larger amount of rectum in the intermediate and high dose interval compared to six-field PO radiotherapy. A similar scenario is true also for the bladder. On the other hand, while an IMRT boost added to initial 4FB can provide some benefit, the best results, in terms of both PTV coverage and bladder/rectum sparing, are achieved with pelvic IMRT. Notably, on average, results achieved with IMRT to pelvic nodes and conformal boost are always superior to 4FB followed by IMRT boost. Finally, an IMRT boost added to an initial IMRT plan can provide additional benefits, mainly in terms of bladder sparing.

The results of the present paper should be viewed and interpreted under the conditions initially set. If the pelvic lymphatics were treated to 45 Gy instead of 50 Gy and therefore the boost comprised a larger percentage of the total dose, then the relative benefit of an IMRT boost may be greater than in this study.

Additionally, further conformality of IMRT dose distribution might have been achieved by a simultaneous integrated boost (SIB) as described by Bos et al. [5]. However, in order to deliver the dose to PTV-PN and PTV-P in the same number of fractions, this would have introduced dose-fractionation issues and uncertainties in plan comparison [44].

Rectal shielding in proximity to the prostate gland as a means to improve rectal tolerance, even for only few fractions, was deliberately avoided. Although this has been a popular way to improve rectal tolerance and allow "safe" dose escalation [19, 48], coverage of PTV-P is affected as well, hampering the planned coverage of 95% of the volume.

Alternative field arrangements and differential field weighting could have been used for the boost and may have yielded better rectal sparing [2, 9, 26]. However, it should also be noted that based on the observed range of improvement from switching from plans with 3DCRT boost to those with IMRT boost (Figures 6 and 9), a modest improvement in the conformal boost would have had a limited effect on the rectal and bladder DVH.

Finally, when examining the bladder DVH results, it should be noted that patients had a half-empty bladder. Others have used much lower estimates for V40 and V65 that are consistent with a full bladder and the use of daily ultrasound for prostate localization [47].

Within prostate cancer radiotherapy, IMRT has been explored for its ability over 3DCRT to better conform to a concave-shaped volume such as the prostate [7, 10] and to better spare normal structures, including part of the bowel [14, 24] and even the penile bulb [42]. To our knowledge, however, the issue of dose escalation to the prostate while treating the pelvic lymphatics and the resultant bladder and rectal DVHs has not been studied in detail. While there is no doubt that there is a dosimetric advantage in using IMRT for treating the pelvic nodes, little is known to justify whether this is clinically worthwhile and cost-effective.

For example, in the studies that have reported rectal constraints (Table 2), most of the events are grade 2 toxicity [11, 17]; it has been shown that such toxicity has a modest impact on quality of life [20] and is transient [45]. Moreover, it has been reported that grade 2 and 3 rectal reactions may have a different radiobiological behavior with less severe reaction being linked to intermediate doses and more severe one to high dose regions along the DVH [33]. However, even taking into consideration this fact, it should be noted that pelvic IMRT is superior to 4FB across the entire rectal DVH, as shown in Figure 5. We believe that clinical testing of this approach within a prospective phase I–II study is warranted and such a study has been open at UTMB for patients with prostate cancer at significant risk of pelvic node involvement referred to us for definitive radiotherapy [39]. Based on the findings of the present study, pelvic IMRT followed by a conformal boost is our initial approach. An IMRT boost is considered particularly if the bladder DVH falls outside dose objectives.

References

1. Asbell SO, Caplan RJ, Perez CA, et al. Impact of surgical staging on evaluating the radiotherapeutic outcome in RTOG 77-06, a phase III study for T1b–T2b N0 M0 prostatic carcinoma. Int J Radiat Oncol Biol Phys 1995; 32:143.abstract.
2. Bedford JL, Khoo VS, Webb S, et al. Optimization of coplanar six-field techniques for conformal radiotherapy of the prostate. Int J Radiat Oncol Biol Phys 2000;46:231–8.
3. Bogner L, Scherer J, Treutwein M, et al. Verification of IMRT: techniques and problems. Strahlenther Onkol 2004;180:340–50.
4. Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997;337:295–300.
5. Bos LJ, Damen EMF, DeBoer RW, et al. Reduction of rectal dose by integration of the boost in the large-field treatment plan for prostate irradiation. Int J Radiat Oncol Biol Phys 2002;52:254–65.
6. Chao KS, Lin M. Lymphangiogram assisted lymph node delineation for patients with gynecologic malignancies. Int J Radiat Oncol Biol Phys 2002; 54:1147–52.
7. Corletto D, Iori M, Paiusco M, et al. Inverse and forward optimization of one- and two-dimensional intensity-modulated radiation therapy based treatment of concave-shaped planning target volumes: the case of prostate cancer. Radiother Oncol 2003;66:185–95.
8. Cozzarini C, Fiorino C, Ceresoli GL, et al. Significant correlation between rectal DVH and late bleeding in patients treated after radical prostatectomy with conformal or conventional radiotherapy (66.6–70.2 Gy). Int J Radiat Oncol Biol Phys 2003;55:688–94.
9. De Meerleer G, Vakaet L, DeGersem W, et al. Direct segment aperture and weight optimization for intensity-modulated radiotherapy for prostate cancer. Strahlenther Onkol 2004;180:136–43.
10. Fiorino C, Broggi S, Corletto D, et al. Conformal irradiation of concave-shaped PTVs in the treatment of prostate cancer by simple 1D intensity modulated beams. Radiother Oncol 2000;55:49–58.
11. Fiorino C, Cozzarini C, Vavassori V, et al. Relationships between DVHs and late rectal bleeding after radiotherapy for prostate cancer: analysis of a large group of patients pooled from three institutions. Radiother Oncol 2002;64:1–12.

12. Fiorino C, Sanguineti G, Cozzarini C, et al. Rectal dose-volume constraints in high-dose radiotherapy of localized prostate cancer. Int J Radiat Oncol Biol Phys 2003;57:953–62.
13. Fiorino C, Vavassori V, Sanguineti G, et al. Rectum contouring variability in patients treated for prostate cancer: impact on rectum dose-volume histograms and normal tissue complication probability. Radiother Oncol 2002; 63:249–55.
14. Gershkevitsh E, Clark CH, Staffurth J, et al. Dose to bone marrow using IMRT techniques in prostate cancer patients. Strahlenther Onkol 2005;181:172–8.
15. Hanks G, Pajak T, Porter A, et al. A phase III trial of the use of long term total androgen suppression following neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group protocol 92-02. J Clin Oncol 2003;21:3972–8.
16. Hanks GE, Hanlon AL, Schultheiss TE, et al. Dose escalation with 3D conformal treatment: five year outcomes, treatment optimization, and future directions. Int J Radiat Oncol Biol Phys 1998;41:501–10.
17. Huang E, Pollack A, Levy L, et al. Late rectal toxicity: dose-volume effects of conformal radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2002;54:1314–21.
18. Jacob R, Hanlon A, Horwitz E, et al. Role of prostate dose escalation in patients with > 15% risk of pelvic lymph node involvement. Int J Radiat Oncol Biol Phys 2005;61:695–701.
19. Lee WR, Hanks GE, Hanlon AL, et al. Lateral rectal shielding reduces late rectal morbidity following high dose three-dimensional conformal radiation therapy for clinically localized prostate cancer: further evidence for a significant dose effect. Int J Radiat Oncol Biol Phys 1996;35:251–7.
20. Lilleby W, Fossa SD, Waehre HR, et al. Long-term morbidity and quality of life in patients with localized prostate cancer undergoing definitive radiotherapy or radical prostatectomy. Int J Radiat Oncol Biol Phys 1999;43:735–43.
21. Lohr F, Dobler B, Mai S, et al. Optimization of dose distributions for adjuvant locoregional radiotherapy of gastric cancer by IMRT. Strahlenther Onkol 2003;179:557–63.
22. Lyons JA, Kupelian PA, Mohan DS, et al. Importance of high radiation doses (72 Gy or greater) in the treatment of stage T1–T3 adenocarcinoma of the prostate. Urology 2000;55:85–90.
23. Nguyen KH, Horwitz EM, Hanlon AL, et al. Does short-term androgen deprivation substitute for radiation dose in the treatment of high-risk prostate cancer? Int J Radiat Oncol Biol Phys 2003;57:377–83.
24. Nutting C, Convery D, Cosgrove V, et al. Reduction of small and large bowel irradiation using an optimized intensity-modulated pelvic radiotherapy technique in patients with prostate cancer. Int J Radiat Oncol Biol Phys 2000;48:649–56.
25. Perez CA, Lee HK, Georgiou A, et al. Technical factors affecting morbidity in definitive irradiation for localized carcinoma of the prostate. Int J Radiat Oncol Biol Phys 1994;28:811–9.
26. Pickett B, Roach M III, Horine P, et al. Optimization of the oblique angles in the treatment of prostate cancer during six-field conformal radiotherapy. Med Dosim 1994;19:237–54.
27. Pilepich MV, Caplan R, Byhardt RW, et al. Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy. Report of RTOG protocol 85-31. J Clin Oncol 1997;15:1013–21.
28. Pollack A. A call for more with a desire for less: pelvic radiotherapy with androgen deprivation in the treatment of prostate cancer. J Clin Oncol 2003;21:1899–901.
29. Pollack A, Smith LG, Eschenbach AC von. External beam radiotherapy dose-response characteristics of 1127 men with prostate cancer treated in the PSA era. Int J Radiat Oncol Biol Phys 2000;48:507–12.
30. Pollack A, Zagars GK. External beam radiotherapy for stage T1/T2 prostate cancer: how does it stack up? Urology 1998;51:258–64.
31. Pollack A, Zagars GK, Smith LG, et al. Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer. J Clin Oncol 2000;18:3904–11.
32. Radiation Therapy Oncology Group (RTOG). A phase III randomized study of high dose 3D-CRT versus standard dose 3D-CRT in patients treated for localized prostate cancer. Protocol P0126 (*www.rtog.org*).
33. Rancati T, Gagliardi G, Cattaneo GM, et al. Late rectal bleeding: fitting clinical data with different NTCP models. Int J Radiat Oncol Biol Phys 2003;57:Suppl:S392.
34. Roach M III, DeSilvio M, Lawton C, et al. Phase III trial comparing whole-pelvis versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. J Clin Oncol 2003;21:1904–11.
35. Roach M III, Marquez C, Yuo H, et al. Predicting the risk of lymph node involvement using the pre-treatment prostate specific antigen and Gleason score in men with clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 1993;28:33–7.
36. Roberts T, Roach M 3rd. The evolving role of pelvic radiation therapy. Semin Radiat Oncol 2003;13:109–20.
37. Rosen E, Cassady JR, Connolly J, et al. Radiotherapy for prostate carcinoma: the JCRT experience (1968–1978). II. Factors related to tumor control and complications. Int J Radiat Oncol Biol Phys 1985;11:723–30.
38. Sanguineti G, Agostinelli S, Foppiano F, et al. Adjuvant androgen deprivation impacts late rectal toxicity after conformal radiotherapy of prostate carcinoma. Br J Cancer 2002;86:1843–7.
39. Sanguineti G, Culp L, Pena J, et al. Acute small bowel and colon toxicity after pelvic IMRT for prostate cancer. ECCO 12. European Journal of Cancer Supplements; 2003;1(5):S268.
40. Sanguineti G, Marcenaro M, Franzone P, et al. Neoadjuvant androgen deprivation and prostate gland shrinkage during conformal radiotherapy. Radiother Oncol 2003;66:151–7.
41. Seaward S, Weinberg V, Lewis P, et al. Improved freedom from PSA failure with whole pelvic irradiation for high-risk prostate cancer. Int J Radiat Oncol Biol Phys 1998;42:1055–62.
42. Sethi A, Mohideen N, Leybovich L, et al. Role of IMRT in reducing penile doses in dose escalation for prostate cancer. Int J Radiat Oncol Biol Phys 2003;55:970–8.
43. Shipley WU, Verhey LJ, Munzenrider JE, et al. Advanced prostate cancer: the results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone. Int J Radiat Oncol Biol Phys 1995;32:3–12.
44. Sterzing F, Munter MW, Schafer M, et al. Radiobiological investigation of dose-rate effects in intensity-modulated radiation therapy. Strahlenther Onkol 2005;181:42–8.
45. Teshima T, Hanks GE, Hanlon AL, et al. Rectal bleeding after conformal 3D treatment of prostate cancer: time to occurrence, response to treatment and duration of morbidity. Int J Radiat Oncol Biol Phys 1997;39:77–83.
46. Vavassori V, Cozzarini C, Bianchi C, et al. Androgen deprivation and late rectal bleeding after radiotherapy for prostate carcinoma. Int J Radiat Oncol Biol Phys 2002;54:Suppl 1:109.
47. Xia P, Pickett B, Vigneault E, et al. Forward or inversely planned segmental multileaf collimator IMRT and sequential tomotherapy to treat multiple dominant intraprostatic lesions of prostate cancer to 90 Gy. Int J Radiat Oncol Biol Phys 2001;51:244–54.
48. Zelefsky MJ, Fuks Z, Happersett L, et al. Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. Radiother Oncol 2000;55:241–9.
49. Zelefsky MJ, Fuks Z, Hunt M, et al. High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. J Urol 2001;166:876–81.
50. Zelefsky MJ, Fuks Z, Hunt M, et al. High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. Int J Radiat Oncol Biol Phys 2002;53:1111–6.

Address for Correspondence
Matthew L. Cavey, MD
Department of Radiation Oncology
University of Texas Medical Branch
301 University Blvd.
Galveston
Texas 775555-0711
USA
Phone (+1/409) 772-2531, Fax 747-0025
e-mail: mlcavey@utmb.edu