Strahlenther Onkol 2012 · 188:410–416
DOI 10.1007/s00066-012-0081-8
Received: 24 August 2011
Accepted: 20 January 2012
Published online: 26 February 2012

M. Geier[1] · S.T. Astner[1] · M.N. Duma[1] · V. Jacob[2] · C. Nieder[3,4] · J. Putzhammer[1] · C. Winkler[1] · M. Molls[1] · H. Geinitz[1]

[1] Klinik und Poliklinik für Strahlentherapie und Radiologische Onkologie, Technische Universität München, München
[2] Klinik für Strahlenheilkunde, Universitätsklinikum Albert-Ludwigs-Universität Freiburg, Freiburg
[3] Department of Oncology and Palliative Care, Nordland Hospital, Bodø
[4] Institute of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø

Dose-escalated simultaneous integrated-boost treatment of prostate cancer patients via helical tomotherapy

Curative treatment of patients with localized prostate cancer comprises radical prostatectomy or radiation therapy. In external beam radiation therapy, dose escalation is currently investigated to improve outcomes. Several studies provide strong evidence for a dose–response relation of local tumor control, biochemical progression-free survival, and progression-free survival [3, 10, 18, 20, 25, 28, 35, 37].

Formerly published long-term results from a randomized phase III dose escalation trial conducted at the M.D. Anderson Cancer Center demonstrated a significant benefit after dose escalation to 78 Gy in terms of improved freedom from biochemical and clinical progression [18, 28]. Dose-escalation trials using conformal three-dimensional (3D)-radiation therapy showed that the additional anti-tumor effectiveness is accompanied by an increased treatment-related morbidity, i.e., gastrointestinal and genitourinary toxicity [3, 25, 28].

Intensity-modulated radiation therapy (IMRT) might counteract normal tissue toxicity correlated with conventional dose escalation [11]. For example, a large IMRT-based prostate cancer dose-escalation study initiated at the Memorial

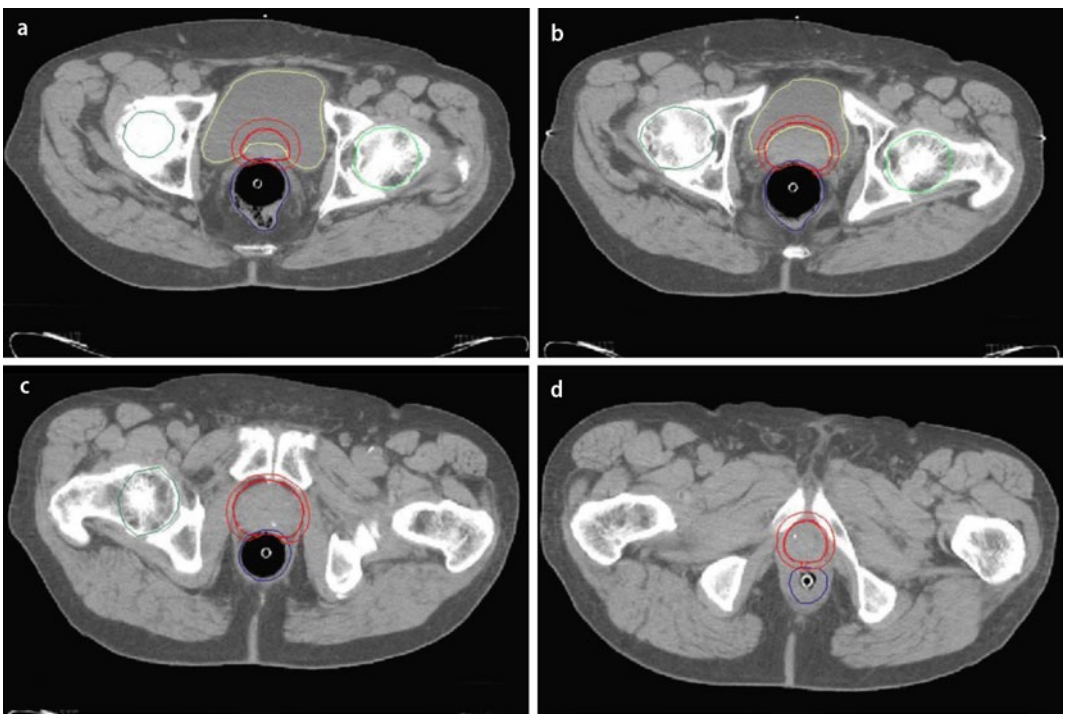

Fig. 1 ▶ **a**, **b**, **c**, **d** Examples for delineation of 70 Gy PTV1 (*orange*), 76 Gy PTV2 (*red*), and rectum with rectal balloon (*violet*), bladder (*yellow*) and femoral heads (*green*) on different slices of the planning CT in the craniocaudal direction

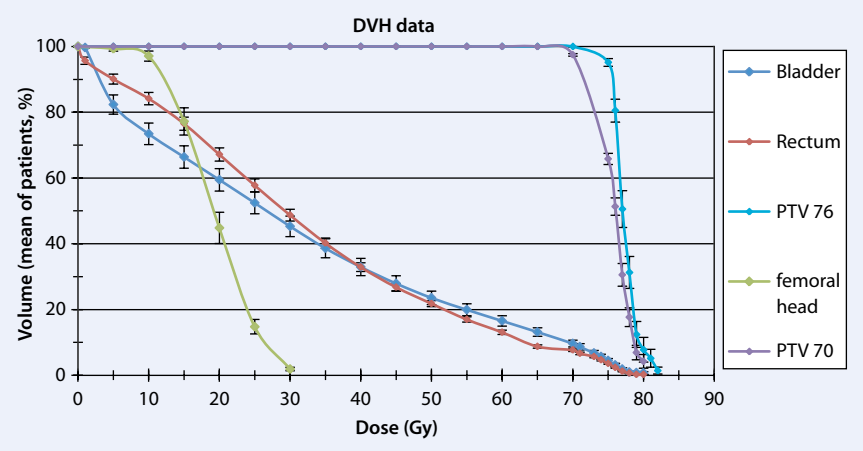

Fig. 2 ▲ Cumulative dose–volume histogram (*DVH*) using overall patients mean planning values and error bars for standard error of the means

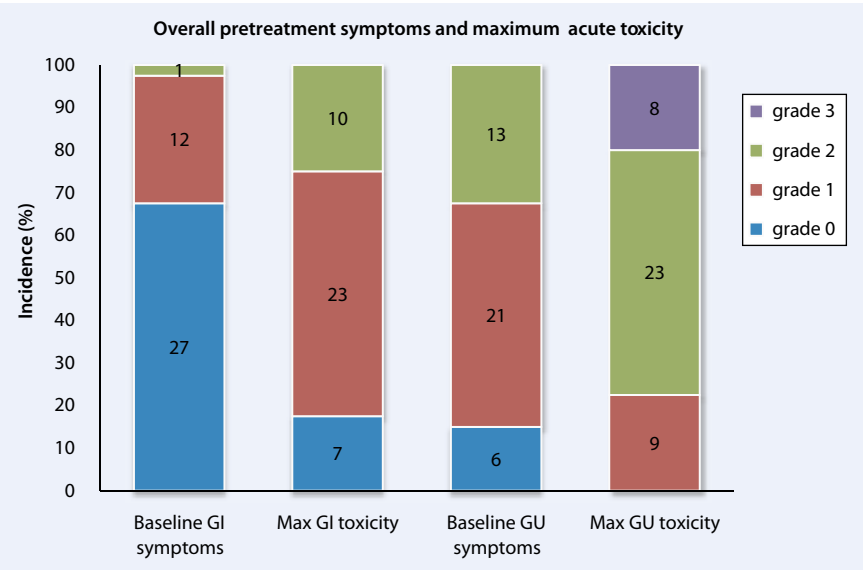

Fig. 3 ▲ Incidence of overall baseline (pretreatment) and maximum (onset during treatment) acute genitourinary (*GU*) and gastrointestinal (*GI*) symptoms encompassing the detailed symptoms shown in Tab. 4. Numbers in the bars display the number of patients with corresponding toxicity

Sloan-Kettering Cancer Center although not randomized reported a favorable toxicity profile in patients treated with IMRT as compared to those who had received 3D treatment, despite a further increase in the prescribed total dose [35, 36].

In principle, dose escalation can be achieved either by increasing the number of fractions at 1.8–2 Gy per fraction or by increasing the dose per fraction above 2 Gy (hypofractionation). The rationale for using increased doses per fraction is the assumed relatively low α/β ratio reported for prostate cancer. Due to this rather low α/β ratio of about 1–3 Gy [24, 29] prostate cancer cells are hypothesized to be especially susceptible to cell kill by hypofractionated radiotherapy [1]. As the α/β ratio for prostate cancer is also assumed to be lower than that for the rectal wall, hypofractionated radiation therapy should have the potential to improve the therapeutic gain and has consequently been adopted as a strategy to tackle prostate cancer [1, 7, 19]. This concept has been further extended by the simultaneous integrated boost (SIB) concept, where increased doses per fraction are selectively and simultaneously delivered to subvolumes of the target volume [14, 21, 32].

This report is on the acute toxicity and the dose–volume data of the first 40 patients treated at our department with helical tomotherapy using a moderately hypofractionated simultaneous integrated boost IMRT (SIB-IMRT) to a total dose of 76 Gy in 2.17 Gy per fraction applied to the prostate.

Patients and methods

Patients and treatment planning

Starting in February 2008, patients with intermediate risk, localized prostate cancer (cN0 cM0) were treated with SIB-IMRT at the tomotherapy unit in our department. Patients with intermediate risk prostate cancer were defined as (1) not having low-risk features (cT1, Gleason score < 7, and initial PSA ≤ 10 ng/ml) and (2) not having a risk of ≥ 20% of lymph node metastasis according to the Roach formula [30]. In selected cases, patients were treated with SIB-IMRT, even if they did not fulfill the above criteria for intermediate risk prostate cancer.

A CT scan of the pelvis from the iliac crest to the ischias tuberosities was performed in 5 mm slice thickness for treatment planning. Furthermore, a MRI scan was carried out and fused with the planning CT to optimize the definition of the prostatic volume [13]. The target volumes and organs at risk (OAR) were contoured in iPlan (BrainLAB AG, Feldkirchen, Germany). The gross tumor volume (GTV) comprised the prostatic gland and base of the seminal vesicles. The margins for the clinical target volume (CTV) accounting for microscopic extracapsular tumor spread were 5 mm in all directions except for the rectal interface with no additional safety margin. The planning target volume (PTV1) encompassed the CTV with a safety margin of 3 mm in all directions except for the craniocaudal direction with margins of 5 mm (◘ **Fig. 1**). The boost volume (PTV2) encompassed the prostatic gland only, with a safety margin of 3 mm in all directions except for the craniocaudal direction where it was 5 mm. The rectum (outer contour) was delineated from the anal verge to the start of the sigmoid colon. In addition, the following OARs were contoured: urinary bladder, femoral heads, sigmoid colon, and remainder of the bowel within 2–3 cm

Abstract · Zusammenfassung

Strahlenther Onkol 2012 · 188:410–416 DOI 10.1007/s00066-012-0081-8

M. Geier · S.T. Astner · M.N. Duma · V. Jacob · C. Nieder · J. Putzhammer · C. Winkler · M. Molls · H. Geinitz

Dose-escalated simultaneous integrated-boost treatment of prostate cancer patients via helical tomotherapy

Abstract

Purpose. The goal of this work was to assess the feasibility of moderately hypofractionated simultaneous integrated-boost intensity-modulated radiotherapy (SIB-IMRT) with helical tomotherapy in patients with localized prostate cancer regarding acute side effects and dose–volume histogram data (DVH data).
Methods. Acute side effects and DVH data were evaluated of the first 40 intermediate risk prostate cancer patients treated with a definitive daily image-guided SIB-IMRT protocol via helical tomotherapy in our department. The planning target volume including the prostate and the base of the seminal vesicles with safety margins was treated with 70 Gy in 35 fractions. The boost volume containing the prostate and 3 mm safety margins (5 mm craniocaudal) was treated as SIB to a total dose of 76 Gy (2.17 Gy per fraction). Planning constraints for the anterior rectal wall were set in order not to exceed the dose of 76 Gy prescribed to the boost volume. Acute toxicity was evaluated prospectively using a modified CTCAE (Common Terminology Criteria for Adverse Events) score.
Results. SIB-IMRT allowed good rectal sparing, although the full boost dose was permitted to the anterior rectal wall. Median rectum dose was 38 Gy in all patients and the median volumes receiving at least 65 Gy (V65), 70 Gy (V70), and 75 Gy (V75) were 13.5%, 9%, and 3%, respectively. No grade 4 toxicity was observed. Acute grade 3 toxicity was observed in 20% of patients involving nocturia only. Grade 2 acute intestinal and urological side effects occurred in 25% and 57.5%, respectively. No correlation was found between acute toxicity and the DVH data.
Conclusion. This institutional SIB-IMRT protocol using daily image guidance as a precondition for smaller safety margins allows dose escalation to the prostate without increasing acute toxicity.

Keywords

Prostate cancer · Intensity-modulated radiotherapy · Image-guided radiotherapy · Tomotherapy · Acute toxicity

Dosiseskalation aufgrund simultan integrierter Boost-Behandlung bei Prostatakarzinompatienten mittels helikaler Tomotherapie

Zusammenfassung

Ziel. Die Verträglichkeit des simultan integrierten Boost-Protokolls unserer Klinik als primäre Therapie für Patienten mit lokal begrenztem Prostatakarzinom sollte bezüglich der Akuttoxizität unter Berücksichtigung der individuellen DVH-Daten evaluiert werden.
Methoden. Untersucht wurden die ersten 40 Patienten mit intermediärem Risiko bei lokal begrenztem Prostatakarzinom, die mittels vorgestelltem SIB-IMRT-Protokoll mit helikaler Tomotherapie an unserer Klinik behandelt wurden. Die definitive Strahlentherapie bis zu einer Gesamtdosis von 76 Gy (Einzeldosis 2,17 Gy) erfolgte unter täglicher Bildanleitung („Image Guidance"). Das Planungszielvolumen (Prostata und Samenblasenbasis mit Sicherheitssaum) wurde mit 70 Gy (Einzeldosis 2 Gy) behandelt, während das Boostvolumen des simultan integrierten Boosts (Prostata mit 3 mm Sicherheitssaum bzw. 5 mm kraniokaudal) mit 2,17 Gy Einzeldosis therapiert wurde. Das erlaubte Dosismaximum im Bereich der vom Boostvolumen erfassten Rektumvorderwand entsprach den verordneten 76 Gy des Boosts. Die gastrointestinale und urogenitale Akuttoxizität wurden prospektiv mittels eines modifizierten CTCAE (Common Terminology Criteria for Adverse Events)-Scoringsystems evaluiert (Tab. 1). Die DVH-Daten der Patienten wurden mit den Akuttoxizitätsdaten korreliert.
Ergebnisse. Das vorgestellte SIB-Therapieprotokoll ermöglicht eine gute Rektumschonung, obwohl die verordnete Boostdosis als Dosismaximum im Bereich der Rektumvorderwand akzeptiert wurde. Die mediane Rektumdosis betrug 38 Gy. V65, V70 und V75 waren entsprechend 13,5%, 9% und 3% (Tab. 3). Neben drittgradiger Nykturie bei 20% der Patienten wurden zweitgradige gastrointestinale und urogenitale Nebenwirkungen bei 25% bzw. 57,5% der Patienten beobachtet (Fig. 3, Tab. 4). Signifikante Zusammenhänge zwischen den DVH-Daten und der Akuttoxizität konnten nicht gezeigt werden.
Zusammenfassung. Das vorgestellte SIB-IMRT-Protokoll mit täglicher Bildführng – als Voraussetzung für verkleinerte Sicherheitssäume – ermöglicht eine leicht hypofraktionierte, mäßige Dosiseskalation an der Tomotherapie ohne Erhöhung der Akutnebenwirkungen. Die chronische Toxizität ist Gegenstand laufender Nachbeobachtung.

Schlüsselwörter

Prostatakarzinom · Intensitätsmodulierte Strahlentherapie · Bildgeführte Strahlentherapie · Tomotherapie · Akuttoxizität

above the PTV1. A help structure (Rectum-76) containing the overlap of the PTV2 with the rectum and 3 mm anteriorly was created in order to limit the dose to this structure to ≤100% of the prescribed dose to PTV2. The prescribed dose was 70 Gy in 2 Gy per fraction to the PTV1 and 76 Gy in 2.17 Gy per fraction to the PTV2. The dose calculation was carried out with the inverse treatment planning system of Tomotherapy (Tomotherapy, Inc., Madison, WI, USA). The objective was to cover at least 95% of the PTV2 with 76 Gy (after the first 5 patients that were calculated to the median of the volume). The maximum dose should not exceed 107% of the prescribed dose. Assuming an α/β ratio of 3 or 1.5 for prostate cancer cells, the biologically 2-Gy equivalent dose for the prescribed dose of 76 Gy is 78.6 Gy_3 or 79.7 $Gy_{1.5}$, respectively [22].

Treatment planning contained no formal constraints for the remaining rectum and bladder doses, but high (volume receiving at least 60 Gy (V60) to volume receiving at least 76 Gy (V76)) and intermediate dose (volume receiving at least 35 Gy (V35) to volume receiving at least 59 Gy (V59)) rectal and bladder volumes were kept as low as possible by an iterative planning process.

Tab. 1 Toxicity score

Symptom	Grade 0	Grade I	Grade II	Grade III	Grade IV
Stool frequency	Normal	2–3 stools per day	4–6 stools per day, nocturnal, mild spasms	7–9 stools per day, severe spasms, incontinence	>10 stools, bloody stools
Constipation	None	>3 stools per week	>2 stools per week	>1 stool per week, subileus	>96 hours since last stool, ileus
Anal incontinence	None	Stool smear	Stress and urge incontinence	Full rectal incontinence	
Consistency	Normal	Doughy stool, minor addition of mucus	Liquid stool, addition of mucus or macroscopic blood	Aqueous stool, major mucus and blood addition	Life-threatening bleeding
Abdominal pain	None	Mild pain, treatment not indicated	Drug treatment indicated	Symptoms uncontrollable with drugs	
Urinary frequency	3–6x per day	Every 2–3 h, 6–8x per day	Every 1–2 h, 9–11x per day	More than every hour, >12x per day	
Nocturia	None	Every 4 h, 1–2x per night	Every 2–3 h, 3–6x per night	Every 1–2 h, >6x per night	
Urinary incontinence	None	Occasional (e.g., with coughing, sneezing)	Spontaneous, ≤2 pads per day	≥2 pads per day, total incontinence	
Urinary retention	None	Weakened urinary stream	Placement of urinary, suprapubic or intermittent catheter placement indicated	Elective operative intervention indicated	
Alguria	None	Mild pain, treatment not indicated	Drug treatment indicated	Symptoms uncontrollable with drugs	
Hematuria	None	Asymptomatic; clinical or diagnostic observations only	Gross hematuria; medical intervention infrequently indicated	Gross hematuria; continuous medical intervention indicated	Transfusion or cystectomy needed

Quality assurance

Treatment plans for all patients were checked through a plan quality assurance procedure prior to the first treatment. For that purpose, patient treatment plans were re-calculated for suitable phantoms using the tomotherapy planning software.

Treatment

All patients had neoadjuvant hormonal therapy 2–4 months before radiation therapy. Patients were immobilized for treatment in an individually shaped vacuum cushion. For immobilization of the prostate, an endorectal balloon was used.

After set-up, patients received a MV-CT prior to each treatment fraction. This daily image guidance using a MV-CT caused an additional dose of 1 cGy per CT scan, which was typically carried out from 2 cm above the PTV1 to 2 cm below the PTV1 in 6 mm slice thickness. After acquisition, the MV-CT was fused automatically to the planning CT scan. If necessary, this fusion was corrected manually to align the prostatic gland. After this correction, treatment time was approximately 4–5 min with a jaw of 2.5 cm and a pitch of 0.27.

Toxicity evaluation

Gastrointestinal (GI) and genitourinary (GU) symptoms were prospectively documented before, after 20 fractions, and at the end of radiotherapy. Toxicity was scored according to modified CTCAE version 3 criteria (**Tab. 1**).

Results

Patient and treatment characteristics

Patient and treatment characteristics are shown in **Tab. 2**. All patients received the prescribed treatment, except for neoadjuvant hormonal therapy in 4 patients due to intolerance. Treatment planning data (**Tab. 3**, **Fig. 2**) assessed for each patient showed good rectal sparing. High (V60–V76) and intermediate dose (V35–V59) rectal volumes were kept low with a median value of the volume receiving more than 65 Gy (V65) of 13.5%. The respective values for the V70 and V75 were 9% and 3%. At the same time, very good dose coverage of PTV1 and PTV2 was achieved, with median doses of 73.7 Gy and 77.0 Gy respectively.

Acute toxicity

Incidence of baseline and maximum acute GI and GU symptoms during treatment are provided in **Fig. 3**. No grade IV GI or GU toxicity was observed. Grade III GU side effects as seen in **Tab. 4** occurred in 20% of patients involving nocturia only and merely two of these eight patients had no baseline symptoms. Grade II GU toxicity was observed in 58% of patients. Regarding GI side effects, 25% patients reported grade II symptoms without any grade III toxicity (**Tab. 4**). No

Tab. 2 Patients' characteristics

Patients (n)	40
Median age (years, range)	72 (60–80)
Disease stage (n, %)	
T1	12 (30)
T2	28 (70)
T3	0 (0)
Gleason score (n, %)	
4	2 (5)
5	1 (2.5)
6	15 (37.5)
7	21 (52.5)
8	1 (2.5)
Median pretreatment PSA level (ng/ml, range)	7.7 (2.85–24.0)
Median prostate dose (Gy, range)	77.04 (75.81–79.51)
Neoadjuvant hormonal therapy (n, %)	36 (90)
Median duration (months, range)	3 (0–7)

Tab. 3 Dose statistics of the rectum, bladder, planning target volume 1 (***70 Gy PTV***) and planning target volume 2 (***76 Gy PTV***) concerning the mean dose (D_{mean}), maximum dose (D_{max}) and volumes (%) irradiated with at least 40 Gy (***V40***), 50 Gy (***V50***), etc.

Rectum									**70 Gy PTV**		
	D_{mean}	D_{max}	V40	V50	V60	V65	V70	V75	D_{mean}	D_{min}	D_{max}
Mean	38.1	78.4	39.9	26.6	16.9	13.1	8.7	3.6	73.5	63.4	78.0
Median	37.9	78.5	39.9	26.3	17.3	13.5	9.1	3.4	73.5	64.3	77.9
Min	23.3	75.2	20.2	14.9	9.0	5.2	2.2	0.2	70.9	60.1	75.3
Max	48.0	83.3	64.0	43.5	29.0	22.4	15.4	6.6	75.1	67.3	86.5
Bladder									**76 Gy PTV (SIB)**		
	D_{mean}	D_{max}	V25	V30	V40	V50	V60	V70	D_{mean}	D_{min}	D_{max}
Mean	31.1	78.7	53.2	46.1	33.6	24.0	16.9	9.6	77.1	72.3	79.4
Median	30.8	78.4	52.5	45.5	30.8	20.5	13.6	7.8	76.9	72.8	79.5
Min	14.1	76.6	19.9	17.2	11.6	7.6	4.7	2.0	75.5	66.6	76.8
Max	54.5	86.5	99.7	95.3	76.9	56.5	47.2	32.4	79.3	75.8	85.3

SIB simultaneous integrated boost.

significant correlation was found between dose–volume parameters of the OARs and maximum acute toxicity of the patients.

Discussion

We report the feasibility of an institutional protocol for definitive treatment of prostate cancer using SIB-IMRT with helical tomotherapy. Acute toxicity and dose–volume histogram (DVH) data were evaluated prospectively in a well-defined intermediate risk patient sample, whereas the risk stratification was performed with a modified scheme based on the D'Amico risk categories. The assessment of acute side effects showed low therapy related GU and GI toxicity in spite of modest dose escalation up to 76 Gy with 2.17 Gy per fraction and a permitted dose of 76 Gy to the anterior rectal wall. This is in line with other studies on dose escalation using IMRT [2, 9, 16, 36] or hypofractionated treatment of prostate cancer [19, 23, 26, 27, 33] and studies combining hypofractionation and dose escalation applying a SIB [5, 12, 14], although the dose to the anterior rectal wall was limited to lower doses in several of these studies as compared to our protocol, either by excluding the rectal overlap from the boost volume or restricting the allowed doses to the overlap regions at lower dose levels.

Guckenberger et al. [12], for example, reported on 100 prostate cancer patients in various risk groups that were treated with definitive conventional IMRT up to doses of 73.91–76.23 Gy with 2.31 Gy per fraction to the prostate and the base of seminal vesicles with safety margins of 5 mm without rectal overlap (PTV-2). PTV-1 encompassed the prostatic gland and the proximal 2 cm of seminal vesicles with a three-dimensional margin of 10 mm except for the posterior direction with 7 mm. In this volume, the total dose was restricted to about 58–60 Gy in 1.84 Gy fractions. According to the risk group, 25% of patients received treatment to the pelvic lymphatics with 46 Gy. The authors reported lower GU and GI side effects with symptoms ≥ grade II in 36% and 8%, respectively. Grade III GU toxicity was observed in only 1% of patients and no grade III GI side effects were seen.

Furthermore, Di Muzio et al. [4] also assessed SIB-IMRT, treating 60 prostate cancer at any stage to different doses with tomotherapy. A subgroup of 31 low-risk patients in their population was treated similar to our patient sample, but using a stronger hypofractionation in the SIB (71.4 Gy, 2.55 Gy per fraction to the prostate and margins of 8 mm, except in the cranial–caudal direction with a margin of 10 mm) and prescribing a lower total dose to the large PTV (61.6 Gy, 2.2 Gy per fraction to the prostate and the proximal portion of seminal vesicles). Overall, DVH data of that study are comparable to our study regarding the rectal D_{mean}. V40 and V50 are slightly lower in our data, whereas D_{max} and V65 are reported slightly lower by the Italian group. The last aspects can be most probably explained by the lower dose prescribed to the overlap volume between the SIB volume and the rectum in the Italian study (65.5 Gy, 2.34 Gy per fraction). Regarding bladder doses higher D_{mean}, V40 and V55 mean values can be found in the Italian trial compared our data, with a similar value for V60. Grade II and III GU toxicity, assessed with the RTOG score, was reported for 7/31 (22%) and 1/31 (3%) patients, respectively. No higher than grade I GI toxicity was observed.

As already mentioned, the lower GI toxicity observed in the two above presented studies compared to our results might be explained to some extent by providing a stronger dose limitation to the rectal overlap or even sparing the rectal overlap from the boost volume compared to our treatment protocol.

Tab. 4 Detailed incidence of gastrointestinal (*GI*) and genitourinary (*GU*) pretreatment symptoms and maximum acute toxicity during treatment

	Pretreatment symptoms (n, %)				Maximum toxicity (n, %)			
GI	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**
Frequency	34 (85)	5 (12.5)	1 (2.5)	0 (0)	19 (47.5)	17 (42.5)	4 (10)	0 (0)
Constipation	35 (87.5)	5 (12.5)	0 (0)	0 (0)	32 (80)	8 (20)	0 (0)	0 (0)
Anal incontinence	39 (97.5)	1 (2.5)	0 (0)	0 (0)	37 (92.5)	2 (5)	1 (2.5)	0 (0)
Consistency	37 (92.5)	3 (7.5)	0 (0)	0 (0)	18 (45)	20 (50)	2 (5)	0 (0)
Abdominal pain	39 (97.5)	1 (2.5)	0 (0)	0 (0)	28 (70)	8 (20)	4 (10)	0 (0)
GU	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**
Unrinary frequency	26 (65)	12 (30)	2 (5)	0 (0)	5 (12.5)	21 (52.5)	14 (35)	0 (0)
Nocturia	9 (22.5)	20 (50)	11 (27.5)	0 (0)	0 (0)	14 (35)	18 (45)	8 (20)
Urinary incontinence	35 (87.5)	2 (5)	3 (7.5)	0 (0)	28 (70)	4 (10)	8 (20)	0 (0)
Urinary retention	25 (62.5)	15 (37.5)	0 (0)	0 (0)	16 (40)	23 (57.5)	1 (2.5)	0 (0)
Alguria	38 (95)	1 (2.5)	1 (2.5)	0 (0)	19 (47.5)	18 (45)	3 (7.5)	0 (0)
Hematuria	39 (97.5)	1 (2.5)	0 (0)	0 (0)	35 (87.5)	4 (10)	1 (2.5)	0 (0)

On the other hand, Kassim et al. [15] showed that excluding the rectal overlap from the boost volume might result in a marked decrease of tumor control due to underdosages, as they reported on a planning study that assessed in each case two plans of 36 prostate cancer patients to a total dose of 78 Gy in 2 Gy per fraction to the boost volume once including and once excluding the rectal overlap, respectively.

Comparing the different GU toxicities of the above discussed studies including our own, aside from the different pretreatment symptoms, the use of different toxicity scores must also be considered and might explain the discrepancies to some extent. As can be seen in **Tab. 1**, nocturnal urinary frequency higher than 6 for example is classified as grade III toxicity in our modified score. In contrast to that, only GU symptoms requiring medical intervention are defined as grade III toxicity using the CTCAE score. Furthermore, most of the GU side effects were assessed more sensitively with our adapted score compared to the standard CTCAE or RTOG scores. Regarding this, the reported overall GU toxicity of our study is in the range of already published studies, since the only observed grade III symptom in the present trial was nocturia.

DVH data of the herein analyzed patient group compare favorably to the data of a patient sample that was treated previously with 3D conformal radiotherapy to doses of 74 Gy at our institution using 10 mm margins without daily image guidance [8]. Rectal V35, V50, and V65 in that sample were 47%, 35%, and 22% as compared to 48%, 27%, and 14%, respectively, in the present study.

The reduction of the safety margins in our study though was well considered, as these margins compensate for the extent of extracapsular spread, intrafractional motion during radiotherapy and uncertainties in contouring. Possible interfractional set-up errors are minimized in our protocol by daily MV-CT scans prior to radiation and are, therefore, not incorporated into the safety margins [38]. Regarding the extent of extracapsular spread, Schwartz et al. [31] found a range of extraprostatic tumor spread from 0–5.9 mm by analyzing 404 whole mounted prostatectomy specimens and stated a GTV to CTV margin of 5 mm sufficient to account for microscopic spread. For intrafractional motion, Kotte et al. [17], analyzing 427 patients with 11,426 prostate position verifications based on fiducial gold markers, calculated that a lower limit for margins of 2 mm would be sufficient to account for intrafractional prostate position shift with slightly larger margins in the craniocaudal direction. In contrast, Fiorino et al. [6], analyzing 410 MV-CTs of 17 prostate cancer patients treated with tomotherapy, reported margins of at least 5–6 mm being appropriate to compensate for intrafractional motion, IGRT intrinsic uncertainties, and interobserver variability with an estimated standard deviation of 1 mm for the latter two. In a recently published study, Wang et al. [34] assessed the intrafractional prostate motion of 59 patients with or without an endorectal balloon for prostate immobilization and showed that using an endorectal balloon 3 mm margins are sufficient to compensate for the prostate motion in 95% of treatment time compared to 5 mm in the non-endorectal group.

Considering these results our margins of at least 8 mm (5 mm GTV to CTV expansion regarding microscopic spread and 3 mm CTV to PTV extension including margins for intrafractional motion and uncertainties in contouring) in every direction except to the rectum as an anatomical barrier with 3 mm (no margin for microscopic spread) seem to be appropriate to minimize the risk of geographical miss, though not considering IGRT intrinsic uncertainty and interobserver variability with explicit margins.

Conclusion

These preliminary results regarding acute tolerability of this institutional treatment protocol for slightly hypofractionated prostate SIB-IMRT and IGRT with tomotherapy are promising. Assessing late toxicity, local control, and overall survival are issues of an ongoing study.

Corresponding address

Prof. Dr. H. Geinitz
Klinik und Poliklinik für Strahlentherapie und Radiologische Onkologie, Technische Universität München
Ismaninger Str. 22, 81675 München
Germany
hans.geinitz@lrz.tu-muenchen.de

Conflict of interest. The corresponding author states that there are no conflicts of interest.

References

1. Brenner DJ (2003) Hypofractionation for prostate cancer radiotherapy – what are the issues? Int J Radiat Oncol Biol Phys 57:912–914
2. De Meerleer G, Vakaet L, Meersschout S et al (2004) Intensity-modulated radiotherapy as primary treatment for prostate cancer: acute toxicity in 114 patients. Int J Radiat Oncol Biol Phys 60:777–787
3. Dearnaley DP, Sydes MR, Graham JD et al (2007) Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. Lancet Oncol 8:475–487
4. Di Muzio N, Fiorino C, Cozzarini C et al (2009) Phase I-II study of hypofractionated simultaneous integrated boost with tomotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 74:392–398
5. Dolezel M, Odrazka K, Vaculikova M et al (2010) Dose escalation in prostate radiotherapy up to 82 Gy using simultaneous integrated boost: direct comparison of acute and late toxicity with 3D-CRT 74 Gy and IMRT 78 Gy. Strahlenther Onkol 186:197–202
6. Fiorino C, Di Muzio N, Broggi S et al (2008) Evidence of limited motion of the prostate by carefully emptying the rectum as assessed by daily MVCT image guidance with helical tomotherapy. Int J Radiat Oncol Biol Phys 71:611–617
7. Fowler JF, Ritter MA, Chappell RJ, Brenner DJ (2003) What hypofractionated protocols should be tested for prostate cancer? Int J Radiat Oncol Biol Phys 56:1093–1104
8. Geinitz H, Thamm R, Keller M et al (2011) Longitudinal study of intestinal symptoms and fecal continence in patients with conformal radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 79:1373–1380
9. Ghadjar P, Gwerder N, Manser P et al (2010) High-dose (80 Gy) intensity-modulated radiation therapy with daily image-guidance as primary treatment for localized prostate cancer. Strahlenther Onkol 186:687–692
10. Goldner G, Dimopoulos J, Kirisits C, Potter R (2009) Moderate dose escalation in three-dimensional conformal localized prostate cancer radiotherapy: single-institutional experience in 398 patients comparing 66 Gy versus 70 Gy versus 74 Gy. Strahlenther Onkol 185:438–445
11. Guckenberger M, Flentje M (2007) Intensity-modulated radiotherapy (IMRT) of localized prostate cancer: a review and future perspectives. Strahlenther Onkol 183:57–62
12. Guckenberger M, Ok S, Polat B et al (2010) Toxicity after intensity-modulated, image-guided radiotherapy for prostate cancer. Strahlenther Onkol 186:535–543
13. Hentschel B, Oehler W, Strauss D et al (2011) Definition of the CTV prostate in CT and MRI by using CT-MRI image fusion in IMRT planning for prostate cancer. Strahlenther Onkol 187:183–190
14. Junius S, Haustermans K, Bussels B et al (2007) Hypofractionated intensity modulated irradiation for localized prostate cancer, results from a phase I/II feasibility study. Radiat Oncol 2:29
15. Kassim I, Dirkx ML, Heijmen BJ (2009) Evaluation of the dosimetric impact of non-exclusion of the rectum from the boost PTV in IMRT treatment plans for prostate cancer patients. Radiother Oncol 92:62–67
16. Keiler L, Dobbins D, Kulasekere R, Einstein D (2007) Tomotherapy for prostate adenocarcinoma: a report on acute toxicity. Radiother Oncol 84:171–176
17. Kotte AN, Hofman P, Lagendijk JJ et al (20007) Intrafraction motion of the prostate during external-beam radiation therapy: analysis of 427 patients with implanted fiducial markers. Int J Radiat Oncol Biol Phys 69:419–425
18. Kuban DA, Tucker SL, Dong L et al (2008) Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys 70:67–74
19. Kupelian PA, Willoughby TR, Reddy CA et al (2007) Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: Cleveland Clinic experience. Int J Radiat Oncol Biol Phys 68:1424–1430
20. Levegrun S, Jackson A, Zelefsky MJ et al (2002) Risk group dependence of dose-response for biopsy outcome after three-dimensional conformal radiation therapy of prostate cancer. Radiother Oncol 63:11–26
21. Li XA, Wang JZ, Jursinic PA et al (2005) Dosimetric advantages of IMRT simultaneous integrated boost for high-risk prostate cancer. Int J Radiat Oncol Biol Phys 61:1251–1257
22. Lordick F, Geinitz H, Theisen J et al (2006) Increased risk of ischemic bowel complications during treatment with bevacizumab after pelvic irradiation: report of three cases. Int J Radiat Oncol Biol Phys 64:1295–1298
23. Martin JM, Rosewall T, Bayley A et al (2007) Phase II trial of hypofractionated image-guided intensity-modulated radiotherapy for localized prostate adenocarcinoma. Int J Radiat Oncol Biol Phys 69:1084–1089
24. Nickers P, Hermesse J, Deneufbourg JM et al (2010) Which alpha/beta ratio and half-time of repair are useful for predicting outcomes in prostate cancer? Radiother Oncol 97(3):462–466
25. Peeters ST, Heemsbergen WD, Koper PC et al (2006) Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol 24:1990–1996
26. Pervez N, Small C, MacKenzie M et al (2010) Acute toxicity in high-risk prostate cancer patients treated with androgen suppression and hypofractionated intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 76:57–64
27. Pollack A, Hanlon AL, Horwitz EM et al (2006) Dosimetry and preliminary acute toxicity in the first 100 men treated for prostate cancer on a randomized hypofractionation dose escalation trial. Int J Radiat Oncol Biol Phys 64:518–526
28. Pollack A, Zagars GK, Starkschall G et al (2002) Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys 53:1097–1105
29. Proust-Lima C, Taylor JM, Secher S et al (2011) Confirmation of a low alpha/beta ratio for prostate cancer treated by external beam radiation therapy alone using a post-treatment repeated-measures model for PSA dynamics. Int J Radiat Oncol Biol Phys 79:195–201
30. Roach M 3rd, Hanks G, Thames H Jr et al (2006) Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 65:965–974
31. Schwartz DJ, Sengupta S, Hillman DW et al (2007) Prediction of radial distance of extraprostatic extension from pretherapy factors. Int J Radiat Oncol Biol Phys 69:411–418
32. Singh AK, Guion P, Sears-Crouse N et al (2007) Simultaneous integrated boost of biopsy proven, MRI defined dominant intra-prostatic lesions to 95 Gray with IMRT: early results of a phase I NCI study. Radiat Oncol 2:36
33. Soete G, Arcangeli S, De Meerleer G et al (2006) Phase II study of a four-week hypofractionated external beam radiotherapy regimen for prostate cancer: report on acute toxicity. Radiother Oncol 80:78–81
34. Wang KK, Vapiwala N, Deville C et al (2011) A study to quantify the effectiveness of daily endorectal balloon for prostate intrafraction motion management. Int J Radiat Oncol Biol Phys (in press)
35. Zelefsky MJ, Chan H, Hunt M et al (2006) Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. J Urol 176:1415–1419
36. Zelefsky MJ, Fuks Z, Hunt M et al (2002) High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. Int J Radiat Oncol Biol Phys 53:1111–1116
37. Zietman AL, Bae K, Slater JD et al (2010) Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95–09. J Clin Oncol 28:1106–1111
38. Zucca S, Carau B, Solla I et al (2011) Prostate image-guided radiotherapy by megavolt cone-beam CT. Strahlenther Onkol 187:473–478