Combination of Dose Escalation with Technological Advances (Intensity-Modulated and Image-Guided Radiotherapy) Is Not Associated with Increased Morbidity for Patients with Prostate Cancer

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Purpose: The aim was to evaluate treatment-related morbidity after intensity-modulated (IMRT) and image-guided (IGRT) radiotherapy with a total dose of 76 Gy in comparison to conventional conformal radiotherapy (3DCRT) up to 70.2–72 Gy for patients with prostate cancer.
Patients and Methods: All patients were prospectively surveyed prior to, on the last day, as well as after a median time of 2 and 16 months after RT using a validated questionnaire (Expanded Prostate Cancer Index Composite). Criteria for the 78 matched pairs after IMRT vs. 3DCRT were patient age, use of antiandrogens, treatment volume (± whole pelvis), prognostic risk group, and urinary/bowel/sexual quality of life (QoL) before treatment.
Results: QoL changes after dose-escalated IMRT were found to be similar to QoL changes after 3DCRT in all domains. Only sexual function scores more than 1 year after RT decreased slightly more after 3DCRT in comparison to IMRT (mean 9 vs. 6 points; $p = 0.04$), with erections firm enough for intercourse in 14% vs. 30% ($p = 0.03$). Painful bowel movements were reported more frequently after 3DCRT vs. IMRT 2 months after treatment (≥ once a day in 10% vs. 1%; $p = 0.03$), but a tendency for higher rectal bleeding rates was found after IMRT vs. 3DCRT more than 1 year after RT (≥ rarely in 20% vs. 9%; $p = 0.06$).
Conclusion: Combination of dose escalation with technological advances (IMRT and IGRT) is not associated with increased morbidity for patients with prostate cancer.

Key Words: Prostate neoplasm · Intensity-modulated radiotherapy · Image-guided radiotherapy · Conformal radiotherapy · Quality of life

Strahlenther Onkol 2011;187:479–84
DOI 10.1007/s00066-011-2249-z

Verknüpfung einer Dosiseskalation mit technologischen Fortschritten (intensitätsmodulierte und bildgeführte Radiotherapie) ist bei Patienten mit Prostatakarzinom nicht mit erhöhter Morbidität assoziiert

Ziel: Ziel war die Analyse therapiebedingter Morbidität nach intensitätsmodulierter (IMRT) und bildgeführter (IGRT) Radiotherapie mit einer Gesamtdosis von 76 Gy im Vergleich zur konventionellen konformalen Radiotherapie (3DCRT) bis 70,2–72 Gy bei Patienten mit einem Prostatakarzinom.
Patienten und Methoden: Alle Patienten wurden prospektiv vor Beginn, am letzten Tag, median 2 Monate und 16 Monate nach RT mittels eines validierten Fragebogens befragt (Expanded Prostate Cancer Index Composite). Kriterien für 78 gematchte Paare nach IMRT vs. 3DCRT waren das Patientenalter, der Einsatz eines Antiandrogens, Zielvolumen (± Becken), prognostische Risikogruppe und Lebensqualität (LQ) beim Wasserlassen/Stuhlgang/Sexualität vor der Behandlung.
Ergebnisse: LQ-Veränderungen nach dosiseskalierter IMRT waren den LQ-Veränderungen nach 3DCRT in allen Domänen sehr ähnlich. Nur der Punktwert für die sexuelle Funktion fiel über ein Jahr nach der Behandlung nach 3DCRT etwas mehr als nach IMRT (durchschnittlich 9 vs. 6 Punkte; $p = 0,04$), mit ausreichender Erektion für Geschlechtsverkehr in 14% vs. 30% ($p = 0,03$). Schmerzhafter Stuhlgang wurde zwei Monate nach Therapie häufiger nach 3DCRT als nach IMRT berichtet (≥1-mal täglich in 10% vs. 1%; $p = 0,03$); jedoch fand sich über ein Jahr nach RT die Tendenz zu einer häufigeren Rate rektaler Blutungen nach IMRT als nach 3DCRT (≥ selten in 20% vs. 9%; $p = 0,06$).

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Received: December 13, 2010; accepted: April 8, 2011
Published Online: July 25, 2011

Schlussfolgerung: Die Verknüpfung einer Dosiseskalation mit technologischen Fortschritten (IMRT und IGRT) ist bei Patienten mit einem Prostatakarzinom nicht mit erhöhter Morbidität assoziiert.

Schlüsselwörter: Prostatakarzinom · Intensitätsmoduliert Radiotherapie · Bildgeführte Radiotherapie · Konformale Radiotherapie · Lebensqualität

Introduction

External beam radiotherapy (EBRT) is a well-established curative treatment for prostate cancer [8–10, 12, 19, 22]. Dose escalation has been shown to be associated with significantly improved biochemical control rates in several prospective randomized trials [25]. This benefit is compromised by the disadvantage of increased rectal toxicity. These trials were started more than 10 years ago, so that conventional conformal radiotherapy (3DCRT) was applied.

Major technical advances that are increasingly adopted for EBRT for localized prostate cancer are intensity-modulated radiotherapy (IMRT) [8, 12] and image-guided radiotherapy (IGRT) [22]. In comparison to 3DCRT, dose conformality can be improved using the IMRT technique [6, 14, 23]. The volume of organs at risk can be especially reduced within the high dose region.

The application of IGRT before each fraction for prostate localization is the crucial prerequisite for the reduction of safety margins to account for prostate motion. Posterior margins of 0.75–1.00 cm have been shown to be inadequate particularly for patients with initially larger rectum volumes – with decreased biochemical recurrence-free survival rates [5]. As reported in a recent publication, 1.5 cm posterior margins are needed without IGRT, whereas 0.4 cm are sufficient with daily IGRT [22].

The aim of this study is the comparison of health-related quality of life (QoL) changes after 3DCRT with total doses of 70.2–72 Gy versus dose-escalated IMRT up to 76 Gy. Matched pairs were selected to ensure two well comparable patient groups.

Patients and Methods

This prospective study was based on consecutive patients who were treated due to localized T1-3N0M0 prostatic carcinoma with 3DCRT in the years 2003–2007 and IMRT in the years 2006–2008. The treatment was based on a computed tomography (CT) scan in the supine position with a slice thickness of 5 mm. Patients were asked to have a full bladder for the planning CT scan and each radiotherapy fraction.

For 3DCRT, treatment plans were calculated using a four-field box technique with 15 MeV photons and a multileaf collimator. The PTV was required to be enclosed by the 90% isodose relative to the International Commission on Radiation Units and Measurements (ICRU) reference point [13] with a margin of 1.5 cm in the anterior/lateral and 1 cm in the craniocaudal and dorsal directions to the clinical target volume (CTV = prostate ± seminal vesicles). The total dose to the prostate in the reference point was 70.2–72 Gy at 1.8–2.0 Gy daily fractions. Treatment of the whole pelvis was performed in case of an estimated risk of lymph node involvement above 15% (according to Partin tables [17]) up to a total dose of 45–46 Gy at 1.8–2.0 Gy daily fractions using the 3DCRT technique for all patients.

For IMRT, 8 mm lateral/anterior, 5 mm superior/inferior, and 4 mm posterior margins were added to the CTV [22]. Inverse planning with a five field step-and-shoot IMRT technique and 15 MeV photons was used. The direct machine parameter optimization algorithm was applied for inverse planning with a 2 cm^2 minimum segment area, 5 minimum segment monitor units, and a maximum number of 70 segments. The dose to the PTV was prescribed to a reference point, as suggested by the ICRU for conformal radiotherapy [13]. The general relationship between ICRU reference and PTV mean doses in IMRT has been found to be similar to that in three-dimensional dose distributions [29]. Treatment planning objectives included a maximum dose of 50 Gy/70 Gy to 50%/20% of the rectum volume, a maximum dose of 55 Gy/70 Gy to 50%/30% of the bladder volume and a dose homogeneity of ± 5% within the PTV. The total dose to the prostate in the reference point was 76 Gy at 2.0 Gy daily fractions.

Table 1. Patient characteristics. PTV: planning target volume, PSA: prostate-specific antigen, *p < 0.01.

Table 1. Patientencharakteristika. PTV: Planungszielvolumen, PSA: prostataspezifisches Antigen, *p < 0,01.

	3DCRT	IMRT
Patient age (years), median (range)	71 (55–83)	72 (57–83)
PTV (cm^3), median (range)*	325 (60–627)	240 (70–537)
Whole pelvis, n (%)	16 (21)	16 (21)
Bladder volume (cm^3), median (range)	203 (41–784)	209 (55–763)
Rectum volume (cm^3), median (range)	115 (46–364)	87 (27–332)
Initial PSA (ng/ml), median (range)	7 (4–168)	6 (3–200)
Neoadjuvant hormonal therapy, n (%)	24 (31)	24 (31)
Duration of neoadjuvant hormonal therapy, median (range)	4 (1–77)	3 (1–66)
Adjuvant hormonal therapy, n (%)	12 (15)	10 (13)
Low risk, n (%) (no risk factors: PSA < 10 ng/ml; Gleason score < 7; cT-stage < 2b)	31 (40)	31 (40)
Intermediate risk, n (%) (single risk factor: PSA 10–20 ng/ml or Gleason score = 7 or cT-stage = 2b/c)	15 (19)	15 (19)
High risk, n (%) (two risk facors or PSA > 20 ng/ml or Gleason score > 7 or cT-stage > 2b/c)	32 (41)	32 (41)

IGRT was applied using the BAT® SXi system (B-mode acquisition and targeting) [22] after setup to external skin marks immediately before IMRT treatment. Sagittal and transverse images were captured. Contours from the planning CT scan were superimposed on the BAT images. When the images are aligned on the monitor, the computer reveals the couch shifts in three dimensions to bring the prostate into alignment with the original planning CT position.

Patients were surveyed prospectively before (time A), on the last day (B), and a median time of 2 months (range, 6 weeks–6 months) after (C), and 16 months (range, 12–20 months) after (D) radiotherapy using a validated questionnaire (same median intervals and ranges after 3DCRT and IMRT), the Expanded Prostate Cancer Index Composite (EPIC) [26, 28]. The questionnaire comprises 50 items concerning the urinary, bowel, sexual, and hormonal domains for function and bothersomeness. The multi-item scale scores were transformed lineary to a 0–100 scale, with higher scores representing better QoL.

Only patients with questionnaire results from both time A and time D were included in the analysis, resulting in an initial group of 362 patients after 3DCRT (whole pelvic treatment in 61 cases) [20, 21] and 78 patients after IMRT (whole pelvic treatment with IMRT as a boost in 16 cases, IMRT as a boost following 3DCRT up to a dose of 60 Gy in 44 cases, IMRT for the complete treatment in 18 cases). For each patient in the IMRT subgroup, a 3DCRT patient was matched according to the following criteria: age ± 5 years, use of antiandrogens, treatment volume (± whole pelvis), prognostic risk group, and urinary/bowel/sexual QoL (function score preferably ± 10 points) before treatment. Finally, 78 patients after 3DCRT and 78 patients after IMRT resulted for the evaluation including 78/78 (time A), 60/45 (time B), 78/69 (time C), and 78/78 (time D) questionnaires after 3DCRT/IMRT.

The questionnaire was given to the patients personally by one of the physicians at time A, B, and C. Patients presented in the department 6–10 weeks after the end of treatment. Missed questionnaires in the acute phase (time C) and questionnaires 1–2 years after radiotherapy (time D) were sent to the patients with a return envelope. If a questionnaire was not returned within 4 weeks, patients were contacted by telephone and were urged to complete it.

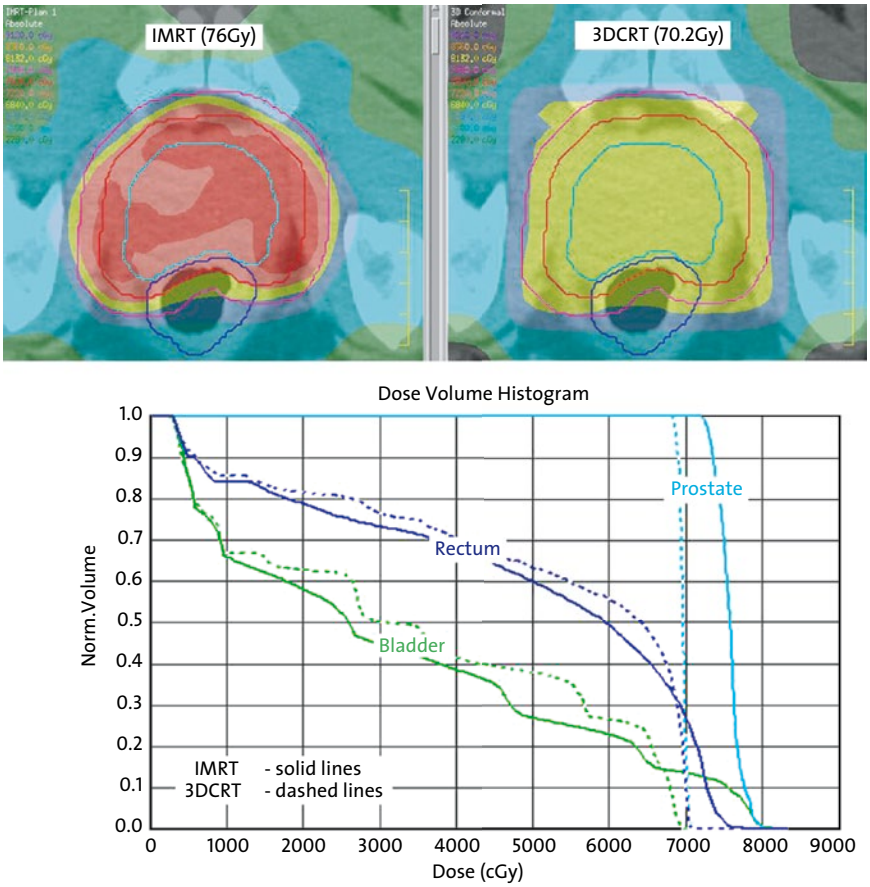

Figure 1. IMRT (*left*, prescription dose of 76 Gy) versus 3DCRT (*right*, prescription dose of 70.2 Gy) treatment plans with isodose lines in an axial CT slice and the dose–volume histograms for the prostate, rectum, and bladder.

Abbildung 1. IMRT (*links*, Verschreibungsdosis von 76 Gy) versus 3DCRT (*rechts*, Verschreibungsdosis von 70,2 Gy) Bestrahlungspläne mit Isodosen in einer axialen CT-Schicht und den Dosis-Volumen-Histogrammen für Prostata, Rektum und Blase.

Statistical analysis was performed using the SPSS 17.0 (SPSS, Chicago, IL), software. The Wilcoxon's matched-pairs test was applied to determine differences between the treatment groups and longitudinal changes in specific subgroups of patients, including a prostate-specific antigen (PSA) evaluation within 12 month after EBRT (biochemical recurrence = rise by ≥ 2 ng/ml above the nadir PSA). Contingency table analysis with the χ^2 test was performed to compare treatment groups with respect to categorical variables. All p values reported are two-sided; $p < 0.05$ is considered significant.

Results

Baseline patient characteristics were well balanced (Table 1). The PTV was considerably smaller in the IMRT group as a result of reduced safety margins around the prostate. 3DCRT and IMRT treatment plans are shown in Figure 1 (example for same patient) to demonstrate the crucial differences: (1) larger PTV in the 3DCRT plan; (2) larger rectal and bladder volumes in the

Table 2. Mean function scores before treatment and differences after treatment relative to baseline scores (quartiles in parentheses; negative differences indicate a quality of life improvement; *significant difference between treatment groups).

Tabelle 2. Mittlere Funktionswerte vor der Behandlung sowie Differenzen nach der Behandlung relativ zu den Ausgangswerten (Quartile in Klammern; negative Differenzen bedeuten eine Verbesserung der Lebensqualität; *signifikanter Unterschied zwischen den Untergruppen).

		Time A	Time A–time B	Time A–time C	Time A–time D	Significant differences		
						A vs. B	A vs. C	A vs. D
Urinary function score	3DCRT	94 (94;100;100)	15 (1;15;27)	3 (0;0;7)	0 (0;0;0)	+	+	–
	IMRT	92 (92;100;100)	14 (0;10;20)	2 (0;0;5)	–1 (0;0;1)	+	–	–
Bowel function score	3DCRT	94 (93;96;100)	19 (4;18;32)	6 (0;4;11)	4 (–4;0;7)	+	+	+
	IMRT	93 (92;96;100)	16 (4;14;25)	4 (–4;4;11)	2 (–4;0;7)	+	+	+
Sexual function score	3DCRT	31 (7;30;50)	11 (0;6;19)	5 (0;0;11)	9 (0;6;19)*	+	+	+
	IMRT	35 (16;32;52)	6 (0;1;14)	4 (–3;2;10)	6 (–2;3;19)*	+	+	+
Hormonal function score	3DCRT	87 (80;90;100)	3 (–5;0;10)	4 (–5;0;10)	–1 (–10;0;5)	–	–	–
	IMRT	88 (80;95;100)	4 (0;0;10)	0 (–8;0;5)	–1 (–10;0;5)	+	–	–

Table 3. Selected symptoms (*significant difference between treatment groups).

Tabelle 3. Ausgewählte Symptome (*signifikanter Unterschied zwischen den Untergruppen).

		Time A (%)	Time B (%)	Time C (%)	Time D (%)
Pain on urination	3DCRT	4	50	9	3
≥ once a day	IMRT	1	38	7	6
≥ Occasional urinary dribbling	3DCRT	36	48	39	40
	IMRT	36	48	38	36
Rectal urgency ≥ once a day	3DCRT	13	52	14	10
	IMRT	14	38	20	12
Bloody stools ≥ rarely	3DCRT	3	20	9	9
	IMRT	10	16	6	20
Painful bowel movements	3DCRT	1	16	10*	6
≥ once a day	IMRT	3	17	1*	4
Uncontrolled leakage of stool > rarely	3DCRT	4	20	18	13
	IMRT	4	16	12	7
No ability to have erections	3DCRT	28	51	43	47
	IMRT	24	38	37	42
Erections not firm enough for sexual intercourse	3DCRT	59	79	67	86*
	IMRT	62	65	67	71*
Lack of energy ≥ once a day	3DCRT	10	15	13	12
	IMRT	8	21	9	10

high dose region, but smaller rectal and bladder volumes in the medial and lower dose region in the IMRT plan.

Urinary, bowel, sexual, and hormonal function scores were similar in the 3DCRT versus IMRT groups before and after treatment (Table 2); the mean or median score changes did not differ > 5 points at any interval. The only statistical difference was found for the sexual function score changes at time D. Focusing only on patients without hormonal therapy, a statistical difference still remained (median sexual function score decrease of 13 vs. 6 points after 3DCRT vs. IMRT; p = 0.02). Median urinary and bowel function scores at time D were the same as the baseline scores. However, a bowel function score decrease of ≥ 7 points and a sexual function score decrease of ≥ 19 points resulted for 25% of patients in both subgroups at time D, respectively.

Percentages of selected symptoms are shown in Table 3. A statistically significant difference was found considering the percentage of patients reporting frequent painful bowel movements at time C (10% after 3DCRT vs. 1% after IMRT; p = 0.03). However, a tendency for larger rectal bleeding rates was found after IMRT at time D (≥ rarely in 20% after IMRT vs. 9% after 3DCRT; p = 0.06). A great or moderate problem with bloody stools was reported in 7% after IMRT vs. 1% after 3DCRT (p = 0.09). Focusing only on patients who did not report having any rectal bleeding before EBRT, 17% vs. 8% reported at least rare rectal bleeding after IMRT vs. 3DCRT (p = 0.08). Stool incontinence was less frequently observed after IMRT. In contrast to patients after IMRT, uncontrolled leakage of stool (> rarely) was reported significantly more often in comparison to the baseline percentage by patients after 3DCRT (p = 0.04).

Another statistically significant difference was found for the presence of erections not firm enough for sexual intercourse at time D with a considerably higher percentage after 3DCRT vs. IMRT (86% vs. 71%; p = 0.03), supporting the results for the sexual score differences at time D. Patients with erections firm enough for intercourse before treatment lost this ability in 35% after IMRT vs. 68% after 3DCRT (p = 0.03).

Median PSA values within 12 months after the end of EBRT were slightly lower after IMRT (1.7, 1.2, 0.9, and 0.8 ng/ml after 3, 6, 9, and 12 months, respectively; single biochemical recurrence) in comparison to 3DCRT (2.2, 1.1, 1.0, and 0.9 ng/ml after 3, 6, 9, and 12 months, respectively; three biochemical recurrences).

Discussion

The dose-limiting toxicity in the treatment for prostate cancer is the rectal toxicity [4]. Randomized dose-escalation trials have found similar urinary toxicity, but an increased rectal toxicity with higher doses after 3DCRT [25]. Rectal toxicity is associated with both the rectal volume within a particular dose level and the dose to a particular rectal volume [1–4, 7, 11, 16]. By increasing the total dose to the prostate and decreasing safety margins around the prostate, we have changed two parameters, hoping to improve the tumor control without increasing rectal toxicity. IGRT has been combined with every IMRT fraction. With the possibility to considerably reduce the PTV, IGRT is probably of greater value in comparison to IMRT.

It is too early to assess tumor control for the patients in this study, but QoL changes appear to be well comparable. In particular, no relevant differences were found within the urinary and hormonal domains. Patients after IMRT reported painful bowel movements less frequently 2 months after treatment in comparison to patients after 3DCRT, suggesting a faster relief of pain due to smaller rectum volumes within the high dose levels. Rectal bleeding was reported more frequently after IMRT (not reaching the level of statistical significance), suggesting the predominant effect of the total dose to even smaller rectal volumes on the development of rectal bleeding. Nevertheless, it has to be considered that IMRT has only been used as a boost after an initial dose of 60 Gy with the 3DCRT technique for the majority of patients in this study. Treatment toxicity can potentially be further decreased if IMRT is used throughout the total treatment.

Chronic effects several years after EBRT might have additional effects on QoL. In contrast to rectal bleeding, the cumulative incidence of stool incontinence has been shown to increase even after more than 5 years [2], so that further differences might be found after longer follow-up intervals. Specifically concerning incontinence, significantly higher percentages reporting uncontrolled leakage of stool in comparison to baseline were only found after 3DCRT, so that stool incontinence will unlikely occur more frequently in the IMRT group several years after EBRT. The reduction of treated volume, thus, also an improved protection of the anal sphincter, appears to be the crucial factor [27].

A comparable analysis, using QoL information from the patient's perspective, has not been published in the literature yet. Theoretical dosimetric and radiobiologic data suggest a significantly lower NTCP (normal tissue complication probability) after IMRT in comparison to 3DCRT for the rectum [15]. The largest patient series comparing 3DCRT vs. IMRT and doses ranging from 66–81 Gy was published in 2008 by Zelefsky et al. [30], using the National Cancer Institute's Common Terminology Criteria for Adverse Events. The risk of gastrointestinal toxicities was found to be significantly reduced for patients after IMRT (actuarial likelihood at 10 years for the development of at least grade 2 toxicity of 13% vs. 5%). Unfortunately, the actual symptoms leading to grade 2 or higher toxicities were not reported. Comparable to our finding reported in a recent publication [18], Zelefsky et al. [30] report acute symptoms to be important precursors of late toxicities.

The only domain with statistically significant differences concerning the actual scores was the sexual domain, with a significantly higher percentage of patients with erections firm enough for sexual intercourse more than 1 year after treatment. The total dose has not been found to affect erectile dysfunction rates in a dose-escalation trial comparing dose levels of 68 Gy and 78 Gy [24]. Erectile dysfunction has been defined as "problems with achieving or maintaining erections". It is not clear if differences existed for these patients concerning the ability for sexual intercourse or if a smaller PTV is responsible for the difference that was found in the present study. Nevertheless, taking into account the limited number of patients with erections firm enough for sexual intercourse before EBRT, further studies with larger patient numbers should be performed to verify these data.

Conclusion

The application of technological advances (IMRT and IGRT) for dose escalation is not associated with increased morbidity for patients with prostate cancer. Advantages found in this study were a faster relief of pain during bowel movements, not significantly increased stool incontinence relative to baseline levels, and better long-term erectile function.

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