Moderate Risk-Adapted Dose Escalation with Three-Dimensional Conformal Radiotherapy of Localized Prostate Cancer from 70 to 74 Gy

First Report on 5-Year Morbidity and Biochemical Control from a Prospective Austrian-German Multicenter Phase II Trial

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Purpose: Evaluation of late side effects and biochemical control (bNED) 5 years after three-dimensional radiotherapy with moderate, risk-adapted dose escalation.

Patients and Methods: From 03/1999 to 07/2002, 486 patients have been registered in the prospective Austrian-German multicenter phase II trial (AUGE). 399 (82%) localized prostate cancer patients (T1–3 Nx/N0 M0) were evaluated. The low- and intermediate-risk groups were treated with 70 Gy, the high-risk group with 74 Gy, respectively. Additional hormonal therapy (HT) was recommended for intermediate- and high-risk group patients. Late toxicity (EORTC/RTOG) and bNED (ASTRO and Phoenix) were prospectively assessed.

Results: Median follow-up was 65 months. Distribution concerning risk groups (low-, intermediate-, high-risk group) showed 29%, 50% and 21% of patients, respectively. HT was given in 87% of patients. The 5-year actuarial rates of late side effects grade ≥ 2 for 70 Gy/74 Gy were 28%/30% (gastrointestinal; p = 0.73) and 19%/34% (urogenital; p = 0,06). The 5-year actuarial bNED rate stratified by risk groups (low-, intermediate-, high-risk group) was 74%, 66% and 50% (ASTRO), and 81%, 80% and 60% (Phoenix), respectively. Within multivariate analysis T-stage and initial prostate specific antigen were significant factors influencing bNED (ASTRO) whereas Gleason Score and duration of HT were not.

Conclusion: Dose escalation within standard three-dimensional conformal radiotherapy (3D-CRT) up to a level of 74 Gy did not result in significantly increased gastrointestinal side effects, whereas urogenital side effects showed an increase close to significance. However, the total number of patients with severe toxicity was low. To achieve high tumor control rates with acceptable treatment-related morbidity, local doses of at least 74 Gy should be considered, in particular for intermediate- or high-risk patients applying 3D-CRT.

Key Words: Prostate cancer · 3D-CRT · Toxicity · bNED · Outcome

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Dreidimensionale konformale risikoadaptierte Radiotherapie des lokalisierten Prostatakarzinoms mit moderater Dosiseskalation von 70 auf 74 Gy. 5-Jahres-Resultate der prospektiven österreichisch-deutschen Phase-II-Multicenterstudie

Ziel: Bestimmung von Spätnebenwirkungen und biochemischer Kontrolle (bNED) nach risikoadaptierter Dosiseskalation im Rahmen einer prospektiven österreichisch-deutschen Phase-II-Multicenterstudie.

Patienten und Methodik: Von 03/1999 bis 07/2002 wurden 486 Patienten mit Prostatakarzinom (T1–3 Nx/N0 M0) gemeldet, und 399 (82%) kamen zur Auswertung. Patienten der Niedrig- und Intermediärrisikogruppe wurden mit 70 Gy, die Hochrisikogrup-

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pe mit 74 Gy bestrahlt (Tabelle 1). Eine begleitende Hormontherapie wurde für Patienten der Intermediär- und Hochrisikogruppe empfohlen. Spätnebenwirkungen (EORTC/RTOG) und bNED (ASTRO/Phoenix) wurden ermittelt.

Ergebnisse: Der mittlere Nachbeobachtungszeitraum betrug 65 Monate. Hinsichtlich der Risikogruppen (Niedrig-, Intermediär-, Hochrisikogruppe) fanden sich 29%, 50%, und 21% Patienten. Eine begleitende Hormontherapie erhielten 87% der Patienten. Detaillierte Patientendaten sind in Tabelle 2 aufgeführt. Die 5-Jahres-Raten an Spätnebenwirkungen Grad ≥ 2 für 70 Gy/74 Gy lagen bei 28%/30% (gastrointestinal; p = 0,73) und 19%/34% (urogenital; p = 0,06; Abbildungen 1 und 2). Die 5-Jahres-bNED-Raten entsprechend den Risikogruppen (Niedrig-, Intermediär-, Hochrisikogruppe) lagen bei 74%, 66% und 50% (ASTRO; Abbildung 3) bzw. 81%, 80% und 60% (Phoenix; Abbildung 4). In der multivariaten Analyse zeigten sich T-Stadium und initiales prostataspezifisches Antigen als signifikant bezüglich bNED (ASTRO) und Gleason-Score sowie die Dauer der Hormontherapie als nicht signifikant (Tabelle 4).

Schlussfolgerung: Die Dosissteigerung auf 74 Gy führt zu keinen signifikant erhöhten Raten an gastrointestinalen Spätnebenwirkungen. Die Rate an urogenitalen Spätnebenwirkungen ist hingegen erhöht. Insgesamt finden sich jedoch nur wenige schwere Grad-3-Spätnebenwirkungen (Tabelle 3). Um respektable Tumorkontrollraten (Abbildung 5) zu erreichen, sollte, vor allem für Patienten der Intermediär- und Hochrisikogruppe, eine lokale Dosis von zumindest 74 Gy appliziert werden.

Schlüsselwörter: Prostatakarzinom · 3D-CRT · Nebenwirkungen · Ergebnisse · bNED

Introduction

In the early 1990s, local doses < 70 Gy were standard in three-dimensional conformal primary prostate cancer treatment [37]. Since 1996, multiple prospective studies have been performed revealing a dose response [2, 21–23, 35] which resulted in a change of clinical practice by applying doses of 70–78 Gy during the last decade. Furthermore, new technologies, such as computerized treatment plan optimization, intensity-modulated radiotherapy (IMRT) and, most recently, image-guided radiotherapy (IGRT), have offered new possibilities for dose escalation [5, 6, 9, 11–13, 17, 19, 28, 31] enabling dose levels of ≥ 80 Gy [16, 30, 34]. Such doses are, in general, limited to prospective clinical studies performed by highly specialized radiotherapy centers, whereas in widespread daily clinical practice local doses so far applied range between 70–80 Gy. Despite various radiotherapy studies that were able to demonstrate a benefit in clinical outcome by dose escalation for localized prostate cancer [4, 7, 14, 16, 18, 20, 26–29, 33, 34, 38], the main limitation remains the risk of increased late side effects: gastrointestinal, in particular from the rectum, and also urogenital.

In 1999, the Austrian-German Phase II multicenter study applying 70 Gy and 74 Gy, respectively, was started. The hypothesis of this study was that a moderate increase of dose from 70 Gy to 74 Gy would result in a difference of grade ≥ 2 late gastrointestinal side effects which was hypothesized to be < 10%. The dose of 74 Gy was applied in high-risk patients, the dose of 70 Gy in low- and intermediate-risk patients. Secondary study endpoints were biochemical (bNED) and clinical control, late urogenital side effects and endoscopic evaluation for patients presenting with proctitis. This is the first report about late gastrointestinal and urogenital side effects and bNED at 5 years.

Patients and Methods

Protocol Entry Criteria and Patient Characteristics

Patients with histologically proven prostate cancer, tumor stage T1–3 Nx0 Mx0 and a maximum initial prostate specific antigen (iPSA) of 50 ng/ml were eligible. In case of iPSA > 30ng/ml, a bone scintigraphy was performed to exclude distant metastasis. Patients with metastases, signs of positive lymph nodes on CT and MRI and previous pelvic irradiation were excluded. The history of secondary cancer (except basalioma), Karnofsky Index < 80% and total femoral-hip endoprosthesis was not permitted. TNM staging was scored according to the American Joint Committee on Cancer 1997 guidelines. Informed consent was not regarded as necessary, as such doses were being used in clinical practice at various centers during this time period. Informed consent was only asked in case of an intervention due to rectoscopy. Between March 1999 and July 2002, 486 patients have been registered. 32 patients were excluded because they did not fulfill the study criteria (twelve patients with secondary cancer, ten patients received a higher dose, five patients had an iPSA > 50 ng/ml, three patients with positive lymph nodes, and two patients with bone metastasis). Four patients did not finish radiotherapy due to severe non-treatment-related disease, and 51 patients were not evaluated due to lack of complete follow-up data, resulting in 399/486 patients (82%) available for evaluation. Distribu-

Table 1. Definition of risk groups according to tumor differentiation, serum prostate-specific antigen (PSA), and grading/Gleason Score.

Tabelle 1. Einteilung der Risikogruppen entsprechend T-Stadium, prostataspezifischem Antigen (PSA) und histologischem Grading/Gleason-Score.

Tumor stage	≤ cT2a	≤ cT2b	cT3	Any T
PSA	≤ 10	< 20	< 20	20–50
G1 or Gleason 2–3	Low risk	Intermediate risk	High risk	High risk
G2 or Gleason 4–6	Low risk	Intermediate risk	High risk	High risk
G3 or Gleason > 6	Intermediate risk	Intermediate risk	High risk	High risk

tion in regard to treatment center showed 39 patients (10%) from Göppingen, 174 patients (44%) from Munich, eight patients (2%) from Tübingen, and 178 patients (45%) treated in Vienna, respectively.

Patients were divided into three risk groups according to tumor differentiation, pretreatment PSA and T-stage (low, intermediate, high risk; Table 1). A neoadjuvant hormonal therapy (HT) was recommended in the intermediate- and high-risk groups with a maximum duration of 12 months. HT consisted of either luteinizing hormone-releasing hormone (LHRH) agonist + antiandrogen or LHRH agonist alone.

Radiotherapy

The gross tumor volume/clinical tumor volume (GTV/CTV) was defined based on series of CT and MRI slices. The CTV included the prostate in the low-risk group and the prostate + the base of the seminal vesicles/seminal vesicles in the intermediate-/high-risk groups. All patients were treated with a four-field-box technique with individualized blocks and rectal balloon [10]. The low- and intermediate-risk groups were treated up to a total dose of 70 Gy and the high-risk group to 74 Gy (2 Gy per fraction). Dose was prescribed to the ICRU reference point with at least 95% of the planning target volume (PTV) receiving the prescribed dose [15]. The safety margin around the CTV was 10 mm in all directions except for the 74-Gy group where a 5-mm posterior margin was used for the first 8 Gy.

Toxicity and bNED

All measures of time were calculated from the last day of radiotherapy. During the first 3 years after radiotherapy patients were seen every 3–6 months and at least once a year thereafter. Follow-up included a complete history, physical examination, transrectal ultrasound, and serum PSA. Late gastrointestinal/urogenital side effects were prospectively documented using the EORTC/RTOG Score [3]. bNED was defined according to the ASTRO [1] and the Phoenix definition [25]. Furthermore, the start of HT after radiotherapy was regarded as biochemical failure.

Statistical Analysis

Assuming an increase of late gastrointestinal grade ≥ 2 side effects < 10%, a total of 330 patients would be necessary (error type II: $\beta = 85\%$, error type I: $\alpha = 5\%$; X^2 based on N-Query 2.0) – 399 patients are analyzed. Estimates of bNED and side effects were calculated using the Kaplan-Meier product-limit method, for side effects also crude rates were used. Univariate comparisons were performed using the log-rank test. The relative risks are summarized with hazard ratios and 95% confidence intervals from Cox regression models. For all analyses T-stage, iPSA, Gleason Score and duration of HT were treated as categorical variables, with the lowest category serving as reference category. In case of no HT, the duration was defined as 0 months. To evaluate the influence of treatment center, an additional multivariate analysis was performed including the treatment centers Göppingen, Munich, and Vienna. Patients from Tübingen were excluded because its covariates with T-stage would cause co-linearity. Analyses were done by the use of SPSS 15.0. All tests were two-sided; $p < 0.05$ was considered statistically significant.

Results

Patients

The median follow-up for all 399 patients was 65 months (2–110 months), and the median age was 71 years (51–85 years). Patients' characteristics are shown in Table 2. HT was administered in 347 patients (87%). In regard to risk group, 74% low-risk, 90% intermediate-risk and 96% high-risk group patients received HT. The proportion of patients receiving HT ≥ 12 months was small – it was 7% in the low-risk, 9% in the intermediate-risk and 10% in the high-risk group, with a median duration of 6 months, 7 months and 9 months, respectively.

Late Side Effects

The proportion of patients suffering from severe toxicity was low (Table 3). Late crude gastrointestinal side effects grade 2 and 3 could be detected in 23% and 2%, respectively. The 5-year actuarial rates of gastrointestinal side effects grade ≥ 2

Table 2. Patients' characteristics. PSA: prostate-specific antigen.

Tabelle 2. Patientencharakteristika. PSA: prostataspezifisches Antigen.

		Patients n (%)
T-stage	T1	114 (29)
	T2	230 (58)
	T3	55 (14)
Maximum PSA	≤ 10 ng/ml	228 (57)
	> 10 to < 20 ng/ml	126 (32)
	≥ 20 ng/ml	45 (11)
Grading	G1	90 (23)
	G2	252 (63)
	G3	39 (10)
	Unknown	18 (5)
Gleason Score	2–6	235 (59)
	7	78 (18)
	8–10	32 (8)
	Unknown	54 (14)
Grading and Gleason Score	Unknown	1 (0,3)
Risk group	Low	117 (29)
	Intermediate	199 (50)
	High	83 (21)
Hormonal therapy	Yes	347 (87)
	< 6 months	164 (47)
	6–12 months	156 (45)
	> 12 months	27 (8)

Table 3. Crude gastrointestinal and urogenital side effects (EORTC/RTOG) total and by radiation dose.

Tabelle 3. Gastrointestinale und urogenitale Nebenwirkungen (EORTC/RTOG): Gesamt und dosisbezogen.

Event type	Total (n = 399) n (%)	70 Gy (n = 316) n (%)	74 Gy (n = 83) n (%)
Gastrointestinal			
• Grade 0	240 (60)	192 (61)	48 (58)
• Grade 1	60 (15)	46 (15)	14 (17)
• Grade 2	91 (23)	71 (22)	20 (24)
• Grade 3	8 (2)	7 (2)	1 (1)
Urogenital			
• Grade 0	200 (50)	160 (51)	40 (48)
• Grade 1	125 (31)	102 (32)	23 (28)
• Grade 2	65 (16)	48 (15)	17 (20)
• Grade 3	9 (2)	6 (2)	3 (4)

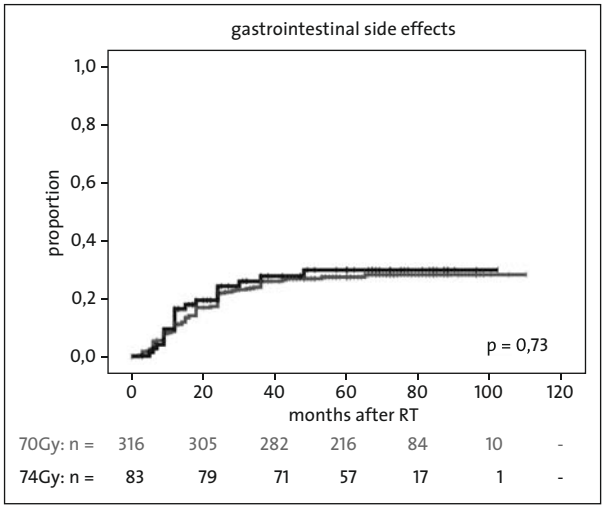

Figure 1. 5-year rate of gastrointestinal side effects grade ≥ 2 (EORTC/RTOG) according to dose: 28% (70 Gy, gray) versus 30% (74 Gy, black); p = 0.73.

Abbildung 1. 5-Jahres-Rate gastrointestinaler Nebenwirkungen Grad ≥ 2 (EORTC/RTOG): 28% (70 Gy, grau) versus 30% (74 Gy, schwarz); p = 0,73.

were 29% (total) and 28% (70 Gy) and 30% (74 Gy), respectively (Figure 1). No significant difference between the different dose levels could be detected (p = 0.73). Late crude urogenital side effects grade 2 and 3 could be detected in 16% and 2%, respectively. The 5-year actuarial rates of urogenital side effects grade ≥ 2 were 23% (total) and 19% (70 Gy) and 34% (74 Gy), respectively (Figure 2). This difference was close to significant (p = 0.06).

bNED

The 5-year actuarial bNED rate for all 399 patients was 65% using ASTRO and 77% using Phoenix definition, respectively. When bNED rates were stratified by risk groups (low-, intermediate-, high-risk group), the 5-year rate was 74%, 66% and 50% (ASTRO), and 81%, 80% and 60% (Phoenix), respectively. A significant difference between low-risk versus high-risk patients (ASTRO: p < 0.001; Phoenix: p = 0.001) and

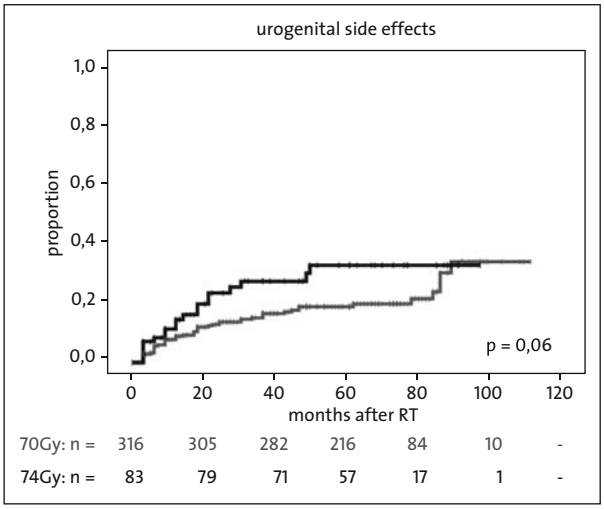

Figure 2. 5-year rate of urogenital side effects grade ≥ 2 (EORTC/RTOG) according to dose: 19% (70 Gy, gray) versus 34% (74 Gy, black); p = 0.06.

Abbildung 2. 5-Jahres-Rate urogenitaler Nebenwirkungen Grad ≥ 2 (EORTC/RTOG): 19% (70 Gy, grau) versus 34% (74 Gy, schwarz); p = 0,06.

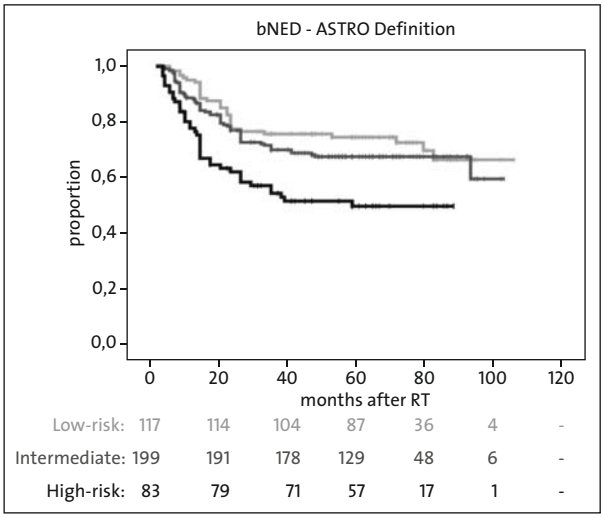

Figure 3. bNED (biochemical no evidence of disease, ASTRO) stratified by risk groups showing a significant difference between low-risk versus high-risk patients (p < 0.001) and intermediate- versus high-risk patients (p = 0.002). Light gray: low risk; gray: intermediate risk; black: high risk.

Abbildung 3. bNED (biochemisch rezidivfrei, ASTRO) nach Risikogruppe mit signifikantem Unterschied zwischen Niedrig- versus Hochrisikopatienten (p < 0,001) und Intermediär- versus Hochrisikopatienten (p = 0,002). Hellgrau: niedriges Risiko; grau: intermediäres Risiko; schwarz: hohes Risiko.

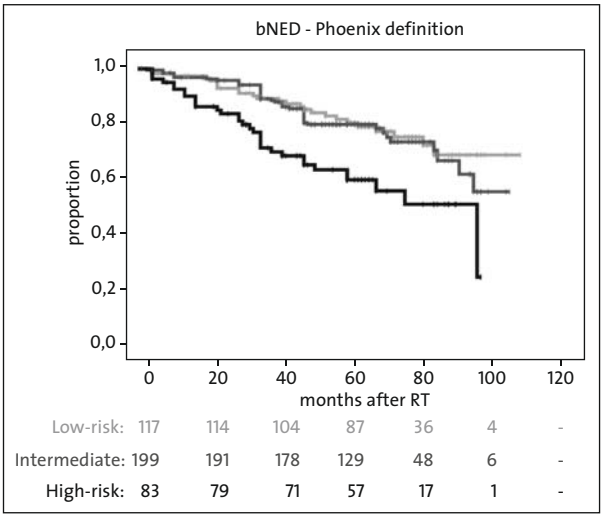

Figure 4. bNED (biochemical no evidence of disease, Phoenix) stratified by risk groups showing a significant difference between low-risk versus high-risk patients (p = 0.001) and intermediate- versus high-risk patients (p = 0.001). Light gray: low risk; grey: intermediate risk; black: high risk.

Abbildung 4. bNED (biochemisch rezidivfrei, Phoenix) nach Risikogruppe mit signifikantem Unterschied zwischen Niedrig- versus Hochrisikopatienten (p = 0,001) und Intermediär- versus Hochrisikopatienten (p = 0,001). Hellgrau: niedriges Risiko; grau: intermediäres Risiko; schwarz: hohes Risiko.

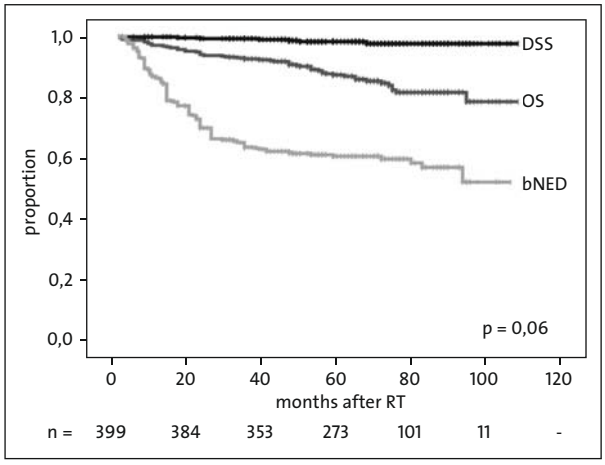

Figure 5. Disease-specific (DSS; black), overall (OS; gray), and biochemical survival (bNED, ASTRO; light gray).

Abbildung 5. Krankheitsspezifisches (DSS; schwarz), Gesamt- (OS; grau) und biochemisches Überleben (bNED, nach ASTRO; hellgrau).

intermediate- versus high-risk patients (ASTRO: p = 0.002; Phoenix: p = 0.001) was found using log-rank test (Figures 3 and 4). Within multivariate analysis T-stage and iPSA were significant factors influencing bNED (ASTRO) and T-stage was significant in regard to phoenix definition. Gleason Score and duration of HT were not significant (Table 4). In regard to treatment center, no significant influence was found performing separate multivariate analysis. At time of evaluation 347 (87%) patients were alive. 46 patients (12%) died due to non-prostate-cancer-related disease. Six patients (1.5%) died of prostate cancer after a median time period of 42 months – three high-risk and three intermediate-risk patients – resulting in an actuarial 5-year overall and disease-specific survival rate of 88% and 99%, respectively (Figure 5).

Table 4. Multivariate analyses (HR [CI] and p-values)) of potential predictors of bNED (ASTRO and Phoenix) with following covariates: T-stage, Gleason Score, iPSA, duration of HT. bNED: biochemical control; CI: confidence interval; HR: hazard ratio; HT: hormonal therapy; iPSA: initial prostate-specific antigen; RC: reference category.

Tabelle 4. Multivariate Analyse (HR [CI] und p-Wert)) bezüglich bNED (ASTRO und Phoenix) mit folgenden Kovariablen: T-Stadium, Gleason-Score, iPSA und Dauer der HT. bNED: biochemische Kontrolle; CI: Konfidenzintervall; HR: Hazard-Ratio; HT: Hormontherapie; iPSA: initiales prostataspezifisches Antigen; RC: Referenzkategorie.

		ASTRO HR (95% CI)	p-value	Phoenix HR (95% CI)	p-value
T-stage	T1	RC		RC	
	T2	0.52 (0.31–0.89)	0.016*	0.53 (0.28–0.99)	0.045*
	T3	0.53 (0.33–0.83)	0.006*	0.50 (0.29–0.87)	0.013*
Gleason Score	2–6	RC		RC	
	7	0.83 (0.55–1.26)	0.390	0.78 (0.48–1.26)	0.308
	8–10	0.95 (0.57–1.57)	0.828	1.04 (0.58–1.86)	0.904
iPSA (continuous)		1.02 (1.01–1.04)	0.007*	1.02 (1.00–1.04)	0.069
Duration HT (continuous)		0.98 (0.96–1.01)	0.211	0.99 (0.95–1.02)	0.411

*significant

Discussion

When this prospective Austrian-German multicenter study was designed in the 1990s, local doses of 66–70 Gy were standard in three-dimensional conformal definitive radiotherapy (3D-CRT) of prostate cancer in Austria and Germany. The aim of our study was to demonstrate that moderate dose escalation can be applied safely without a significant increase of toxicity. Depending on risk group, patients received 70 Gy or 74 Gy. Escalating the dose up to a level of 74 Gy did not result in a significant increase of severe grade 3 toxicity. We could not detect any significant difference regarding actuarial late gastrointestinal side effects grade ≥ 2 (p = 0.73; Figure 1). The actuarial 5-year rates were 28% (70 Gy) and 30% (74 Gy). The difference regarding actuarial late urogenital side effects was, however, close to significant (p = 0.06). The actuar-

ial 5-year rates were 19% (70 Gy) and 34% (74 Gy, Figure 2). A total of 84 patients (70 Gy) and 17 patients (74 Gy) reached a follow-up of ≥ 80 months. Longer follow-up is certainly necessary to arrive at a final judgment of this difference as observed at present – also taking the long period urogenital side effects need to evolve into account. Altogether, the absolute amount of grade ≥ 2 gastrointestinal and urogenital side effects is in line with literature data from prospective studies, e.g., with the recent report by Peeters et al. [20]. Within the randomized Dutch trial comparing 68 Gy versus 78 Gy, the 5-year rate of grade ≥ 2 gastrointestinal side effects was 27% versus 32% and regarding grade ≥ 2 urogenital side effects 41% versus 39%, without any increase detected.

In order to limit the amount of severe side effects, some dose-escalation trials include dose-volume constraints in particular for the rectum/rectal wall [16, 34]. Fiorino et al. recommended dose-volume constraints for the rectum of < 55% to receive 50 Gy, < 40% to receive 60 Gy, < 25% to receive 70 Gy, and < 5% to receive 75 Gy. By analyzing 1,132 patients, they were able to confirm these parameters to be predictive for rectal bleeding [8]. To reduce the probability of grade ≥ 2 side effects, patients receiving 74 Gy were treated, in our study, with a reduced posterior margin of 5 mm during the first four fractions (8 Gy) followed by a margin of 10 mm (66 Gy). Patients receiving 70 Gy were treated with a posterior margin of 10 mm during the whole treatment. Furthermore, it was recommended to limit the rectal volume receiving a dose of ≥ 60 Gy to 57% based on the data published by Wachter et al. [32]. The assessment of rectum volume parameters within a separate subgroup analysis of this study including 164 patients treated at the department in Vienna [24] found only 18 patients (11%) who did not fulfill the dose-volume constraints as recommended by Fiorino et al. [8]. Interestingly, only two out of these 18 patients were found to have grade 2 rectal toxicity – one patient receiving 70 Gy and another one 74 Gy.

To date, at least nine randomized trials on dose escalation for prostate cancer radiotherapy have been published [4, 14, 18, 20, 27–29, 33, 38]. The interpretation of their results remains, however, difficult for several reasons: the different definitions of risk groups, the different study endpoints, the different lengths of follow-up, the inclusion/exclusion of HT, and the different treatment modalities. The British MRC RT01 trial compared 64 Gy versus 74 Gy 3D-CRT including systematically (neo)adjuvant HT for 6–8 months [4]. According to the three risk groups (low, intermediate, and high), the 5-year bNED rates were 79%, 70% and 43% in the 64-Gy arm, compared to 85%, 79% and 57% in the 74-Gy arm, respectively. A significant improvement was detected for the entire study population. Our data are in accordance with the British trial taking into account that their definition of biochemical failure was comparable to the Phoenix definition. The question if even higher doses reaching a level beyond 80 Gy would result in increased tumor control rates with acceptable treatment-related morbidity has not been answered until now. The M.D. Anderson randomized trial found a significant increase in gastrointestinal toxicity (10-year incidence: 26% vs. 13%) comparing 78 Gy versus 70 Gy [18]. Zelefsky et al. found an increase in incidence of grade 2 urogenital side effects from 8% for patients treated to 70.2 Gy to 20% for those treated to 81 Gy [36]. By the use of new technologies or the combination of external-beam radiotherapy and high-dose-rate brachytherapy, local doses close to 80 Gy have already become current practice in specialized centers. However, the benefit of dose escalation has to be measured not only by improved bNED, tumor control and survival, but also the impact of dose escalation on treatment-related side effects has to be taken into account carefully to arrive at an appropriate balance between disease control and treatment-associated morbidity.

Conclusion

Dose escalation within standard 3D-CRT up to a level of 74 Gy does not result in significantly increased gastrointestinal side effects, whereas in regard to urogenital grade ≥ 2 side effects, an increase may be expected. Overall number of patients with severe toxicity (grade 3) is low. To achieve high tumor control rates with acceptable treatment-related morbidity, local doses of at least 74 Gy should be considered, in particular for intermediate- or high-risk patients applying 3D-CRT. In case of considering higher doses, the use of more advanced technology like IMRT and IGRT should be considered, which is expected to control in particular late gastrointestinal side effects.

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