Definitive Conformal Radiotherapy for Localized Prostate Cancer: A Long-term Follow-up Study

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Abstract. *Background: The present study analyzed the clinical long-term outcome of patients with localized prostate cancer after definitive conformal radiotherapy with and without accompanying androgen deprivation (AD). Patients and Methods: From 1996 to 2000, 210 patients (median age: 69 years; range: 54-82 years) with a localized prostate cancer (T1/T2: 72%; initial PSA <10: 39%; Gleason <7: 65%) were treated at Hannover Medical School. Fourteen percent of the patients were classified as low risk (LR), 40% as intermediate risk (IR) and 43% as high risk (HR) according to the ASTRO consensus definition. All patients received a conformal radiotherapy of the prostate with a median total dose of 70.2 Gy (<65 Gy: 5%; 65-70 Gy: 36% and >70 Gy: 59%), 177 patients (84%) in combination with temporary AD (median duration 4 month). Biochemical failure after irradiation was defined as three consecutive serum PSA elevations in accordance to the ASTRO consensus statement from 1997. Long-term side-effects were evaluated on the basis of a standardized questionnaire. Results: The median follow-up was 5.2 years (0.94 to 9.41 years); 54 events (28%) were registered, and 41 patients (20%) were lost to follow-up. The 7-year overall survival (OS) was 75.6% without significant differences in the results regarding the three risk groups (LR: 84.6% vs. IR: 77.2% vs. HR: 73.5%). The 5- and 7-year biochemical disease free survival (bDFS) were 78.3% and 70.0% (LR: 84.6%/84.6% vs. IR: 75.5%/66.7% vs. HR: 77.7%/66.1%). Conclusion: This study confirms the findings of other investigators and encourages the continuation of risk-adapted treatment policy for localized prostate cancer modified by using higher radiation doses and long-term AD for selected patients with higher risk tumors.*

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Prostate cancer is the sixth most common cancer in the world and the most common male malignancy in Europe, North America and some parts of Africa (1). Since the late 1980s, the incidence of prostate cancer rose rapidly; therefore, in Europe 2.6 million new cases per year have been noted. This is in particular as a result of the establishment of prostate-specific antigen (PSA), which is presently the most important and clinically useful biochemical tumour marker for screening and monitoring of prostate cancer (2, 3).

In the 1990s, the treatment of prostate cancer changed towards risk-adapted multimodal treatment, particularly for high risk patients, and towards individualized treatment decisions concerning the type of local therapy taking into consideration patient's age and request, comorbidity, and innovations in surgical and radiotherapeutic techniques. As a result of this trend, radiotherapy has become more and more important (4, 5).

For prostate cancer patients treated with external beam radiotherapy (EBRT), pre-treatment serum PSA level, Gleason score (GS) and T stage have been described as major independent predictors of survival. Based on these three factors, the Radiation Therapy Oncology Group (RTOG) and, later, the American Society for Therapeutic Radiology and Oncology (ASTRO) have established three levels of risk in localized prostate cancer. According to this consensus definition, the low-risk group must fulfil all of the following criteria: pre-treatment PSA ≤10 ng/mL, GS ≤6 and T ≤2a; patients with a pre-treatment PSA level above 20 ng/mL, GS 8-10 or T stage greater than T2b belong to the high risk group; and all other patients fit in the intermediate group (6, 7).

The presented single institution study analyzed the long-term effects of definitive conformal EBRT alone and in combination with androgen deprivation in patients with localized prostate cancer coming from all three risk groups.

Patients and Methods

Between 1996 and 2000, 578 consecutive patients with prostate cancer were referred to Hannover Medical School's Department of Radiotherapy. One hundred and sixty-one patients (27.9%) received adjuvant irradiation after prostatectomy; a further 123

Table I. *Further reasons for exclusion from this analysis (n=84).*

Reason for exclusion	Number of patients
Other radiotherapy concept	27
Additional EBRT of the whole pelvis	22
Definitive brachytherapy (seeds)	5
Other treatment decision	23
Patient refused radiotherapy	11
Androgen deprivation only	9
Wait and see	3
Other reasons	34
Palliative intention (total dose <60 Gy)	4
Relapse after first-line treatment	15
Prostate cancer as second primary	15

patients (21.3%) already had metastases. Another 84 patients were excluded from this analysis for various other reasons as listed in Table I. Hence, a total of 210 out of these 578 patients (36%) were available for this observational study. All patients had a histologically proven localized prostate cancer without evidence of any type of metastasis (clinical stage, $T_{1\text{-}4}N_0M_0$, initial PSA <100 ng/mL). The patients' age ranged from 54 to 82 years with a median of 69 years. A summary of the clinical characteristics and treatment parameters is listed in Table II. All patients were treated definitively with three-dimensional conformal radiotherapy of the prostate with a median total dose of 70.2 Gy (range: 64.8 to 75.6 Gy). Linac-based radiotherapy was delivered by a conformal shaped four-field technique using 10 MV or 23 MV photons in daily fractions of 1.8 Gy, five times a week. Androgen deprivation (AD) was administered to 177/210 patients (84%); 88 had temporary AD (≤4 months in 53 cases and 4-12 months in 35 cases) and 28 had AD of >12 months, including 11 patients who received life-long anti-androgen treatment; 4 patients underwent an orchiectomy. Unfortunately, for 61 patients the duration of AD was indeterminable retrospectively. The median duration of AD for the 116 patients with known duration of AD was four months (range: 1 to 120 months).

All patients were followed up continuously every three months for the first two years and at 6-month intervals thereafter. The follow-up procedure included disease-specific history, treatment-related toxicity, digital rectal examination and PSA monitoring. Specific diagnostic procedures, such as bone scintigraphy, were performed when a relapse was suspected. PSA control during follow-up was carried out by the same laboratory for each patient, measuring the PSA levels with commercially available test kits.

Biochemical relapse (PSA failure) after irradiation was defined as three consecutive rises of serum PSA ≥0.4 ng/mL after achieving the nadir according to the ASTRO consensus statement from 1997 (8). The outcome was measured from the date of diagnosis (date of prostate biopsy) to the date of biochemical disease-free failure. Patients alive without evidence of disease were censored at the date of their last follow-up. Biochemical disease-free survival (bDFS) rates and overall survival (OS) rates were estimated with the Kaplan-Meier method using the statistical software package of the local clinical cancer registry. The log-rank test was used to evaluate differences in bDFS with a p=0.05 significance level; p-values <0.1 showed a trend for significance.

Table II. *Clinical characteristics of the 210 patients.*

	Number of patients without relapse	Number of patients with biochemical relapse	Number of patients with unknown relapse
Total number	139 (66.2%)	54 (25.7%)	17 (8.1%)
Age (years)			
<60	8 (5.8%)	4 (7.4%)	1 (5.9%)
60-69	63 (45.3%)	31 (57.4%)	8 (47.1%)
70-79	68 (48.9%)	18 (33.3%)	7 (41.2%)
≥80	0 (0.0%)	1 (1.9%)	1 (5.9%)
Stage			
T1	20 (14.4%)	7 (13.0%)	6 (35.3%)
T2	80 (57.6%)	28 (51.9%)	6 (35.3%)
T3	36 (25.9%)	18 (33.3%)	4 (23.5%)
T4	1 (0.8%)	1 (1.9%)	1 (5.9%)
Gleason score			
2-6	91 (65.5%)	30 (55.6%)	11 (64.7%)
7	31 (22.3%)	12 (22.2%)	2 (11.8%)
8-10	14 (10.1%)	12 (22.2%)	3 (17.7%)
Pre-treatment PSA			
<10 ng/mL	54 (38.9%)	16 (29.6%)	4 (23.5%)
10-20 ng/mL	55 (39.6%)	23 (42.6%)	6 (35.3%)
>20 ng/mL	26 (18.7%)	14 (25.9%)	6 (35.3%)
Risk group			
Low (Favourable)	22 (15.8%)	4 (7.4%)	3 (17.7%)
Intermediate	56 (40.3%)	24 (44.4%)	5 (29.4%)
High (Poor)	57 (41.0%)	26 (48.2%)	8 (47.1%)
Unknown	4 (2.9%)	0 (0.0%)	1 (5.9%)
Central axis dose (Gy)			
64-66	37 (26.6%)	15 (27.8%)	3 (17.7%)
67-69	20 (14.4%)	10 (18.5%)	2 (11.8%)
70-72	81 (58.3%)	29 (53.7%)	12 (70.6%)
73-75	1 (0.7%)	0 (0.0%)	0 (0.0%)
Androgen deprivation			
None	21 (15.1%)	8 (14.8%)	4 (23.5%)
≤4 months	36 (25.9%)	17 (31.5%)	0 (0.0%)
4-12 months	26 (18.7%)	8 (14.8%)	1 (5.9%)
>12 months	16 (11.5%)	8 (14.8%)	0 (0.0%)
Orchiectomy	3 (2.2%)	1 (1.9%)	0 (0.0%)
Unknown duration	37 (26.6%)	12 (22.2%)	12 (70.6%)
Post-treatment PSA nadir			
≤0.1 ng/mL	62 (44.6%)	17 (31.5%)	4 (23.5%)
0.11-0.49 ng/mL	29 (20.9%)	15 (27.8%)	2 (11.8%)
0.50-1.00 ng/mL	14 (10.1%)	9 (16.7%)	0 (0.0%)
>1.0 ng/mL	15 (10.8%)	7 (13.0%)	0 (0.0%)
Unknown	19 (13.7%)	6 (11.1%)	11 (64.7%)

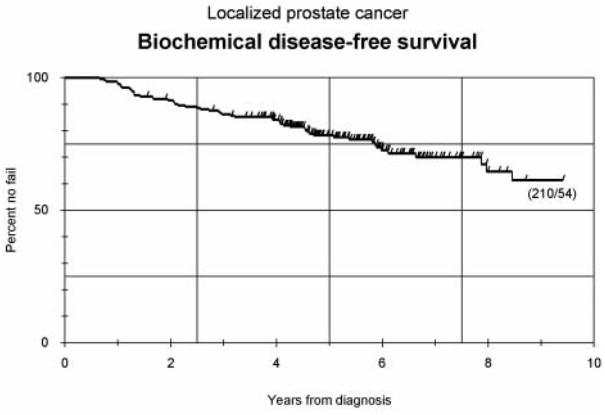

Figure 1. *Biochemical disease-free survival (bDFS) of all 210 patients.*

To assess the late toxicity, a questionnaire was sent to the 177 living patients with a feedback rate of 92% (n=163). It contained questions based on criteria defined by the RTOG/EORTC (9). To complete the results for toxicity, especially for the deceased patients, the urologists in attendance were consulted directly.

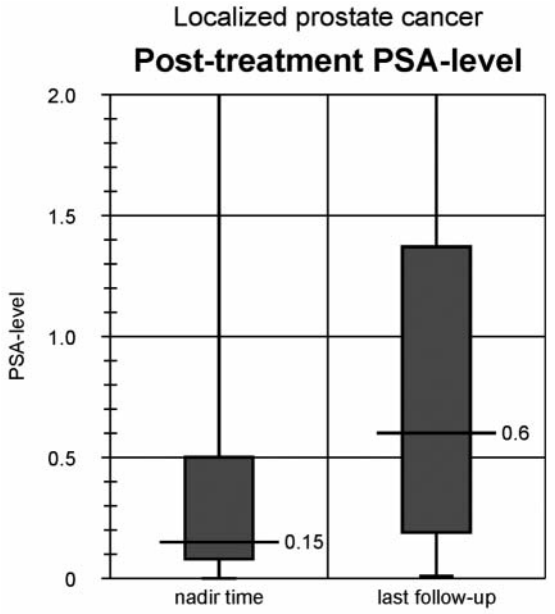

Figure 2. *Distribution of PSA levels (ng/mL) at time of nadir (n=174) and last follow-up (n=190).*

Results

Fifty-four patients (28%) experienced biochemical failure during the median follow-up period of 5.17 years (mean: 5.29 years; range: 0.94 to 9.41 years). Four of these patients developed hematogenous metastases shortly after the diagnosis of biochemical failure (PSA level at last follow-up: 3.54 ng/mL, 7.66 ng/mL; 308 ng/mL; and unknown in one case), upon which three passed away. A further two patients developed histologically proven local relapse (PSA level at last follow up: 1.0 ng/mL and 0.33 ng/mL). Thirty-eight patients (18%) died disease-free to date.

The estimated 5- and 7-year OS rates according to Kaplan-Meier analysis were 88.2% ±4.7% and 75.6% ±8.0%, respectively. The actuarial rate of bDFS for all of the patients is shown in Figure 1. At 5 and 7 years, the estimated bDFS rates were 78.3% ±5.9% and 70.0% ±7.7%, respectively.

The classification into the risk groups resulted in 14% low risk (n=29), 40% intermediate risk (n=85) and 43% high risk patients (n=91); 2% of the patients (n=5) could not be classified clear due to incomplete documentation in the patients' dossiers. Taking these risk groups into account, the 5- and 7-year OS rates were: low risk, 93.1% ±9.4% and 84.6% ±18.3%; intermediate risk, 89.6% ±7.1% and 77.2% ±12.2%; and high risk, 86.0% ±7.6% and 73.5% ±12.5%. The corresponding bDFS at 5 and 7 years were 84.6% ±14.5% (5- and 7-year value identical for low risk); 75.5% ±9.6% and 66.7% ±12.0% (intermediate risk); and 77.7% ±9.2% and 66.1% ±13.3% (high risk).

Figure 2 shows the PSA course after treatment for all patients. Eighty six percent of the patients reached a PSA nadir below 1.0 ng/mL; 47% a nadir of ≤0.1 ng/mL. The median PSA nadir after irradiation was 0.15 ng/mL (range: 0 to 10.0 ng/mL); median PSA at last follow-up was 0.6 ng/mL (range: 0 to 308 ng/mL).

The univariate analysis showed a significance for survival of low-risk *vs*. high-risk patients (p=0.048) but there was no significance for low-risk *vs*. intermediate-risk and intermediate-risk *vs*. high-risk patients. The significance for low-risk *vs*. high-risk remains so strong that taking high- and intermediate-risk *vs*. low-risk patients, significance is still found. But the low-risk group is a small group comprising only 29 patients.

In addition, the univariate analysis showed a strong tendency for significance for PSA nadir ≤0.1 ng/mL *vs*. >0.1 ng/mL and a further trend for significance for Gleason score ≤7 *vs*. >7. All other described and possibly important predictors had no significant influence on OS and bDFS in this patient population (Table III).

Of the 177 living patients who received the questionnaire, 163 answered it (feedback rate: 92%). The grading of the overall organ toxicity was based on the most serious of the assessed symptoms (*e.g.* miction frequency: all 1-2 hours=grade 2). The resulting late toxicity according to the RTOG criteria (9) is shown in Table IV. All in all, intermediate (grade 2) toxicity occurred in 14.1% of the patients (n=23) referring to the urogenital tract (GU) and in 3.1% (n=5) referring to the gastrointestinal tract (GI); a

Table III. *Significance of clinical and therapeutic parameters for bDFS.*

Parameter	bDFS (p<0.05=significant)
Patient age (years)	
<70 (n=113) *v.s.* ≥70 (n=97)	0.139
T stage	
T1/T2 (n=147) *v.s.* T3/T4 (n=61)	0.347
Gleason score	
<7 (n=132) *v.s.* ≥7 (n=74)	0.119
≤7 (n=177) *v.s.* >7 (n=29)	0.080
Pre-treatment PSA (ng/mL)	
<10 (n=74) *v.s.* ≥10 (n=130)	0.305
≤20 (n=158) *v.s.* >20 (n=46)	0.581
Central axis dose (Gy)	
<70 (n=87) *v.s.* ≥70 (n=123)	0.560
Risk group	
Low (n=29) *v.s.* intermediate (n=85)	0.119
Low (n=29) *v.s.* high (n=91)	0.048
Intermediate (n=85) *v.s.* high (n=91)	0.972
Low/intermediate (n=114) *v.s.* high (n=91)	0.513
Low (n=29) *v.s.* intermediate/high (n=176)	0.047
Androgen deprivation	
Applied (n=177) *v.s.* nothing (n=33)	0.489
≤4 months (n=53) *v.s.* >4 months (n=63)	0.346
PSA nadir (ng/mL)	
≤0.1 (n=82) *v.s.* >0.1 (n=92)	0.056
<0.5 (n=128) v.s. ≥0.5 (n=46)	0.293

severe (grade 3) GU toxicity was found in 4 patients (2.5%). No grade 3 GI toxicity nor grade 4 GU/GI toxicities occurred during the present follow-up interval.

Discussion

Prostate cancer continues to be a major health problem in developed countries. Approved approaches to prostate cancer include radical prostatectomy, radiotherapy, endocrine treatment and watchful waiting depending on the risk category (stage, Gleason score (GS), PSA). The literature does not provide clear-cut evidence for the superiority of surgery over radiotherapy, considering that both approaches differ in their side-effects. The definitive external beam radiotherapy (EBRT) is frequently employed in localized and locally advanced prostate cancer in which there is appreciable evidence that higher risk patients benefit from more intense therapy, *e.g.* by addition of androgen suppression to EBRT (4).

The stage-adapted results for RT show a 10-year prostate-specific survival of about 90%, 75% and 50% for low-risk, intermediate-risk and high-risk patients, respectively (10). Patients diagnosed with prostate cancer after 2000 can expect better outcomes from treatment than patients who were diagnosed in the 1980s and early 1990s; these improved outcomes are the result of stage migration, new technologies such as three-dimensional conformal radiotherapy and optimum use of androgen suppression (11).

Measurement of serum PSA has become the standard for determining treatment efficacy in men after definitive therapy for localized prostate cancer (12). After radical prostatectomy, it is clear that the serum PSA should decrease and remain within the undetectable range according to standard assays if a patient is to be considered cured (13). But the absolute serum PSA level associated with cure in patients treated with EBRT is much less clear. It is evident that serum PSA decreases immediately after EBRT in the majority of patients, but some patients will have an increasing PSA profile after irradiation, which indicates recurrent or persistent disease (14).

Some early reports have focused on the relationship between the PSA nadir after treatment and the subsequent disease course in individual patients. For example, a level of 1.5 ng/mL was chosen as the upper limit of normal by Hanks *et al.* (15) based on long-term information obtained from patients treated with RTOG protocols. Other investigators demonstrated that patients with a PSA nadir of less than 1 ng/mL following EBRT in particular experienced favourable bDFS rates within the first five years of observation. Moreover, multivariate analysis demonstrated that patients who had a PSA nadir of less than 1 ng/mL experienced improved bDFS independent of clinical stage, pre-treatment PSA and Gleason score (16). These results were also observed in the large RTOG and EORTC trials, which have used a PSA limit of 1 ng/mL.

It should be noted that a strong tendency for significant difference (p=0.056) was found in bDFS rate with respect to PSA nadir after RT and androgen suppression at the level of 0.1 ng/mL – the level of 0.1 ng/mL was selected because nearly half of the patients (47%) reached a PSA nadir of ≤0.1 ng/mL. This strong tendency for significance is not unexpected, because serum PSA does not always reflect the behaviour of the tumour if anti-androgen treatment has been initiated (12). In particular, androgen suppression can lead to low serum PSA levels although prostate cancer is present, so that the PSA nadir after combined treatment possibly cannot serve as a predictive factor, as seen in this study. However, significance for PSA nadir ≤0.1 ng/mL *vs.* >0.1 ng/mL is likely in a similar study, if a higher number of cases are compared.

In the present study, the estimated OS rates based on the risk groups at 5 and 7 years were 93% and 85% (low risk); 90% and 77% (intermediate risk); and 86% and 74% (high risk). The corresponding bDFS rates at 5 and 7 years were 85% and 85% (low risk); 76% and 67% (intermediate risk); and 78% and 66% (high risk).

The OS rates are 93%, 90% and 86% higher than the reported five-year outcomes in the 1989 patterns of care study for prostate cancer but this is not surprising due to the advances in diagnostics and therapy of the prostate cancer in

Table IV. *Graduated late toxicity after RTOG/EORTC.*

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Unknown
Questioned urogenital problems (n=163)						
Dysuria	146 (89.6%)	9 (5.5%)	5 (3.1%)	3 (1.8%)	0 (0.0%)	0 (0.0%)
Haematuria	154 (94.5%)	5 (3.1%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	3 (1.8%)
Pollakisuria	63 (38.7%)	79 (48.5%)	17 10.4%)	3 (1.8%)	0 (0.0%)	1 (0.6%)
Approximated max. urogenital toxicity	62 (38.0%)	74 (45.4%)	23 (14.1%)	4 (2.5%)	0 (0.0%)	0 (0.0%)
Questioned gastrointestinal problems (n=163)						
Bowel habits	104 (63.8%)	50 (30.7%)	2 (1.2%)	0 (0.0%)	0 (0.0%)	7 (4.3%)
Blennorrhoea	135 (82.8%)	23 (14.1%)	3 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.2%)
Pain	159 (97.5%)	1 (0.6%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	2 (1.2%)
Approximated max. gastrointestinal toxicity	94 (57.7%)	64 (39.3%)	5 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Chronic skin toxicity (n=163)	148 (90.8%)	14 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)

the past twenty years (17). The results for bDFS are similar to those of several studies of other investigators. Pisansky *et al*. found a bDFS at 3 years of 94% (low risk), 77% (intermediate risk) and 43% (high risk) (18). Valicenti *et al*. reported a bDFS at 10 years of 85% (GS 2-5), 79% (GS 6), 62% (GS 7) and 43% (GS 8-10) (19). In the present study GS 2-5 and GS 6 were merged to the low-risk, GS 7 to the intermediate-risk and GS 8-10 to the high-risk group. However, particularly for the high-risk group, slightly better results were found than those reported in the literature.

The bDFS in this study has been determined according to the ASTRO consensus statement from 1997, where three consecutive rises in PSA after RT are required for biochemical failure. This definition of biochemical failure, however, was a controversial issue in the past and is furthermore a surrogate only because all definitions of PSA failure after EBRT seem to revolve around a consistently rising PSA and ignore the fact that patients can have fluctuating PSA values (20).

Recently, the RTOG–ASTRO Phoenix Consensus Conference have recommended a new so-called "Phoenix" definition to define biochemical failure following radiotherapy with or without hormone ablation in men with clinically localized prostate cancer as "PSA nadir + 2 ng/mL". Using this new definition significantly changes the biochemical failure pattern compared with using the original ASTRO definition of biochemical failure, which incorporates backdating, resulting in an artificial flattening of Kaplan-Meier curves and overly favourable estimates when follow-up is short (21). The Phoenix definition reduces these artefacts and correlates with mortality, including overall mortality, so that the independence of this correlation from the use of neoadjuvant/adjuvant androgen deprivation supports the use of PSA nadir + 2 in prostate cancer clinical trials of RT with or without androgen deprivation (22).

In this study, the biochemical failure rate decreases from 25.7% (n=54) to 19.5% (n=41) when the Phoenix definition is used: 26 patients can retrospectively be classified as biochemical failure. Of these 26 patients, 57.7% (n=15) belong to the high-risk group, 34.6% (n=9) to the intermediate-risk and 7.7% (n=2) to the low-risk group. For 15 patients, the classification after Phoenix definition failed, because they received a salvage therapy before fulfilling the Phoenix criterion PSA nadir + 2. The remaining 13 patients were classified as biochemical failure after the ASTRO consensus statement from 1997 not fulfilling the new Phoenix definition and had not received a salvage therapy.

The most important clinical prognostic factors of disease outcome in prostate cancer which are proven to be useful in clinical patient management are pre-treatment serum PSA level, TNM stage grouping, histological grade as Gleason score, and surgical margin status if surgery has been performed. Further prognostic factors that have been extensively studied biologically and clinically but whose importance remains to be validated in statistically robust studies included tumour volume, histological type and DNA ploidy (23). The influence of the three main prognostic factors GS, T-stage and pre-treatment serum PSA level to the bDFS could not be shown in this analysis, probably because all patients were classified into the three above mentioned risk groups before tumour therapy started. Furthermore, patients at higher risk were treated more intensely than patients with low risk prostate cancer, as seen in Table V.

The only significances found in the univariate analysis were low risk compared with high risk (p=0.048) and intermediate/high risk (p=0.047), respectively. Even so, significant differences in bDFS between the intermediate-risk and high-risk group were not observed probably despite similar intense tumour therapy in most of the patients. One possible reason is that the Gleason score sum, a number

Table V. *Therapeutic parameters of the risk groups.*

	All (n=210)	Low risk (n=29)	Intermediate risk (n=85)	High risk (n=91)	Unknown (n=5)
Median dose	70.2 Gy	70.2 Gy	70.2 Gy	70.2 Gy	70.2 Gy
Radiation only	n=33	n=8	n=16	n=8	n=1
Radiation + short term AD (≤ 4 months)	n=53	n=6	n=23	n=23	n=1
Radiation + intermediate term AD (>4-12 months)	n=35	n=6	n=14	n=15	n=0
Radiation + long term AD (>12 months)	n=28	n=2	n=9	n=17	n=0
Radiation +AD with unknown duration	n=61	n=7	n=23	n=28	n=3

composed of two patterns recognized by their architectural arrangement, was not correctly determined in the earlier patients because of some inexperience of the pathologists resulting in an alteration of the clinical risk (24). Additionally, tertiary Gleason 5 tumours should be factored into the Gleason score sum immediately as there appears to be a shorter time to biochemical recurrence in these patients. Particularly in 2005, the International Society of Urology recommended that Gleason 3 + 3 or 4 + 3 tumours with tertiary pattern Gleason 5 be classified as Gleason 8 or 9, respectively (25). To further explore this issue, in 2007 Patel *et al*. studied 2370 men with clinical T1c-3b, N0, M0 prostate cancer who underwent definitive local therapy including EBRT alone and EBRT with 6 months of androgen deprivation. This study suggests, despite the short median follow-up time of 4.2 years, that Gleason 7 tumours with tertiary Gleason 5 pattern should be considered as Gleason 8–10 tumours for treatment purposes (26).

For PSA nadir (p=0.56) and Gleason score (p=0.080) univariate analysis showed a trend to significance. The role of the age of the patient *per se* as a significant prognostic factor in prostate cancer is reported for irradiated patients but it is still controversial (27, 28). This data does not support age as an independent factor for the bDFS.

From the treatment-related factors, the meta-analysis of five large RTOG trials had confirmed that the required irradiation dose is a strong independent predictor of failure in definitively irradiated patients (5). Particularly, a total RT dose of at least 72 Gy resulted in significantly improved outcome (29). Patients most likely to benefit from increasing doses seem to be those with poor risk features, *i.e.* pre-treatment PSA ≥10, GS ≥7 or T stage ≥T2b (10).

Numerous randomized trials also demonstrated a clinical benefit in terms of biochemical control, local and distant control, and overall survival from the addition of androgen suppression to external beam radiotherapy in intermediate- and high-risk patients. In 2000, Roach *et al*. (5) performed a meta-analysis of the recent five prospective randomised RTOG prostate cancer trials assessing the efficacy of short-term and long-term androgen suppression in terms of disease-specific and overall survival of 2200 men. They reported that patients with high-risk prostate cancer had an approximately 20% higher chance of survival at eight years with the addition of long-term androgen suppression. Most of the patients in these trials were irradiated with doses between 65 and 70 Gy so that the benefit of dose escalation particularly in patients treated with long-term androgen suppression has to be further validated. In the present study, however, significant better bDFS rates could not be found in higher-risk patients who received radiation doses exceeding 70 Gy in combination with short-term androgen deprivation.

In the present study, there was no higher rate of late rectal (GI) toxicity (RTOG/EORTC grade 2/3: 3%) and only a slight increased rate of late urogenital (GU) toxicity (RTOG/EORTC grade 2/3: 16%) as reported in the literature (30). However, there was an increased rate at obstructive GU complaints because approximately 30% of the patients had a diagnosed T3/4-tumour. Significant higher toxicity, particularly late bowel toxicity, as a result of the combination of radiotherapy with androgen suppression was not noted in this study in contrast to the first analysis of the Medical Research Council (MRC) RT01 study (31). It is likely that the increased late toxicity reported in the MRC RT01 trial is a result of the higher total dose (74 Gy) (32).

The used questionnaire is a good method for screening the late toxicity due to its high acceptance rate by the patients. A higher accuracy during the toxicity evaluation can be achieved by the fact that, with missing answers, patient contact takes place. In addition, the pre-therapeutic output findings should be initially noted.

In conclusion, there is strong evidence to support risk-adapted treatment of prostate cancer patients even if stratification into the known risk groups neglects other possible clinical prognostic factors. A moderate dose-escalation probably brings an additional benefit for the higher-risk patients treated with simultaneous androgen deprivation but a simultaneous androgen deprivation has – based on the literature data – a possible worsening influence on the toxicity in the setting of the dose escalated

radiotherapy. Hopefully, the ongoing trials will further define the role of endocrine treatment in more favourable risk patients treated with dose escalated radiotherapy.

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