



Toxicity and risk factors after combined high-dose-rate brachytherapy and external beam radiation therapy in men ≥ 75 years with localized prostate cancer

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Abstract

Purpose Combined high-dose-rate brachytherapy (HDR-BT) and external beam radiation therapy (EBRT) is a favorable treatment option in non-metastatic prostate cancer. However, reports on toxicity and outcome have mainly focused on younger patients. We aimed to determine toxicity and biochemical control rates after combined HDR-BT and EBRT in men ≥ 75 years.

Methods From 1999 to 2015, 134 patients aged ≥ 75 years (median 76 years; 75–82 years) were identified. Patients received 18 Gy of HDR-BT (9 Gy/fraction on days 1 and 8) with an iridium-192 source. After 1 week, supplemental EBRT with a target dose of 50.4 Gy was started (delivered in 1.8 Gy fractions).

Results Median follow-up time was 25 months (0–127 months). No severe (grade 4) gastrointestinal (GIT) or genitourinary (GUT) toxicities were observed. In 76 patients (56.7%), 3D conformal radiation therapy (CRT) and in 34.3% intensity-modulated radiotherapy (IMRT) was applied. CRT-treated patients were at a 2.17-times higher risk (hazard ratio [HR]: 2.17, 95% confidence interval [CI]: 1.31–3.57, $p=0.002$) of experiencing GUT. GIT risks could be reduced by 78% using IMRT (HR: 0.22, 95% CI: 0.07–0.75, $p=0.015$). Patients with a higher T stage (T2c–3a/b) were less likely to experience GIT or GUT (HR: 0.49, 95% CI: 0.29–0.85, $p=0.011$ and HR: 0.5, 95% CI: 0.3–0.81, $p=0.005$, respectively).

Conclusion HDR-BT/EBRT is a well-tolerated treatment option for elderly men ≥ 75 years with a limited number of comorbidities and localized intermediate- or high-risk prostate cancer. IMRT should be favored since side effects were significantly reduced in IMRT-treated patients.

Keywords Brachytherapy · Prostate cancer · Old patients · Biochemical recurrence · External beam radiotherapy

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Toxizität und Risikofaktoren nach kombinierter Hochdosis-Brachytherapie und perkutaner Bestrahlung bei Männern ≥ 75 Jahren mit lokalisiertem Prostatakarzinom

Zusammenfassung

Hintergrund Die Kombination aus HDR-(high-dose-rate)-Brachytherapie (BT) und externe Strahlentherapie (ERBT) ist eine vorteilhafte Behandlungsoption beim nichtmetastasierten Prostatakarzinom. Die Berichte über die Nebenwirkungen und den Therapieausgang beschäftigen sich zumeist mit jüngeren Patientenkollektiven. Ziel der Analyse war die Evaluation der Toxizität und der biochemischen Kontrollrate bei Patienten ≥ 75 Jahren, die sich einer kombinierten HDR-BT/EBRT unterzogen haben.

Methoden Von 1999–2015 wurden 134 Patienten ≥ 75 Jahren (Median 76 Jahre; 75–82 Jahre) identifiziert. Die Patienten erhielten 18 Gy einer HDR-BT (9 Gy/Fraktion an Tag 1 und 8) einer Iridium-192-Quelle. Die EBRT mit einer Zieldosis von 50,4 Gy (Einzeldosis von 1,8 Gy) begann nach einer Woche.

Ergebnisse Das mediane Follow-up betrug 25 Monate (Spanne 0–127 Monate). Es bestanden keine schwerwiegenden akuten (Grad 4) gastrointestinalen (GIT) oder urogenitalen (GUT) Nebenwirkungen. Bei 76 Patienten (56,7 %) kam die 3-D-konformale Bestrahlung (CRT) und in 34,3 % die intensitätsmodulierte Radiatio (IMRT) zum Einsatz. Bei CRT-behandelten Patienten bestand ein 2,17-fach erhöhtes Risiko (Hazard-Ratio [HR]: 2,17; 95 %-Konfidenzintervall [KI]: 1,31–3,57; $p=0,002$) für GUT. Das GIT-Risiko konnte um 78 % bei der IMRT reduziert werden (HR: 0,22; 95 %-KI: 0,07–0,75; $p=0,015$). Bei Patienten mit einem höheren T-Stadium (T2c–3a/b) bestand eine geringere Wahrscheinlichkeit GIT oder GUT zu erleben (HR: 0,49; 95 %-KI: 0,29–0,85; $p=0,011$ bzw. HR: 0,5; 95 %-KI: 0,3–0,81; $p=0,005$).

Schlussfolgerung Die kombinierte HDR-BT/EBRT ist eine sichere und gut verträgliche Behandlungsoption für ältere Männer ≥ 75 Jahren, die wenige Komorbiditäten und ein lokal begrenztes, mittel- bis hochgradiges Prostatakarzinom aufweisen. IMRT-Techniken sollten bevorzugt werden, da sich hierdurch die Nebenwirkungen signifikant reduzieren lassen.

Schlüsselwörter Brachytherapie · Prostatakarzinom · Ältere Patienten · Biochemisches Rezidiv · Perkutane Bestrahlung

Introduction

Prostate cancer is the most common tumor entity among males in Europe [9] and accounts for 9.5% of all new cancer cases in the United States [19]. Prostate cancer in the U.S. occurs more often between 65 and 74 years (median age: 66 years) [19]. In contrast, data from the United Kingdom indicate that the incidence peak is found between 75 and 79 years, followed by a subsequent decrease in the 80–94-years age group, before rising again in men ≥ 90 years [4]. In the future, more men ≥ 75 years are likely to be affected by prostate cancer due to demographic changes.

The introduction of prostate-specific antigen (PSA) screening has favored the diagnosis of early-stage diseases [7]. However, as comorbidities are often part of an ageing population with a longer life expectancy, choosing treatment options in patients ≥ 75 years may be controversial. Curative treatment options for localized prostate cancer include radical prostatectomy, monotherapy by means of external beam radiation therapy (EBRT) or interstitial brachytherapy, the combination of both possibilities, as well as active surveillance [15, 20]. In patients ≥ 75 years, physicians are often confronted with several comorbidities, so that radical prostatectomy is often connected with increased morbidity. Also, according to the current European guidelines on the treatment of patients with intermedi-

ate- and high-risk prostate cancer, a life expectancy of at least 10 years is compulsory for radical prostatectomy or radiotherapy [18].

The combination of high-dose-rate brachytherapy (HDR-BT) and EBRT is a favorable treatment option in cases of non-metastatic prostate cancer [11, 12, 14, 24]. There are several reports on the analysis of toxicity and outcome after combined HDR-BT/EBRT. However, these authors focused on younger patients with a mean/median age ranging from 66.4 to 68 years [2, 13]. Data on elderly patient cohorts ≥ 75 years are still very limited [27]. To our knowledge, this is the largest analysis which evaluates how combined HDR-BT/EBRT is tolerated among patients ≥ 75 years. The aim of this study was to determine toxicity and biochemical control rates after combined HDR-BT/EBRT in men ≥ 75 years.

Methods

Patient population

From December 1999 till November 2015, 134 patients aged ≥ 75 years (median 76 years; range 75–82 years) were identified who underwent combined HDR-BT/EBRT due to localized prostate cancer at the Department of Radiotherapy and Radiooncology of the University Medical Center

Hamburg-Eppendorf. All of these patients gave their written informed consent.

Inclusion criteria:

- Age of ≥ 75 years at the beginning of treatment
- Biopsy-confirmed adenocarcinoma of the prostate
- Prostate volume ≤ 60 ml and no symptoms of urinary retention

Exclusion criteria:

- Known involvement of regional lymph nodes and/or the presence of distant metastases
- Patients where anesthesia not possible

Assessment of clinical parameters

For prostate cancer risk assessment, all patients were classified into three risk categories according to the risk-adapted guidelines of the National Comprehensive Cancer Center (NCCN) [25]: 1) low risk: Gleason score (GS) ≤ 6 and PSA < 10 ng/ml and cT stage T1–2a; 2) intermediate risk: GS 7 or PSA 10–20 ng/ml or cT2b–2c; and 3) high risk GS 8–10 or PSA > 20 ng/ml or cT3–4.

Comorbidities were assessed by Charlson comorbidity index (CCI) [5]. Side effects were classified according to the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) [6].

Follow-up examinations were carried out 6–8 weeks and 8 months after the end of therapy. Subsequent follow-up was performed annually. Acute toxicities were classified as occurring within 3 months or at the first follow up after the completion of radiotherapy. According to Phoenix criteria, biochemical recurrence was defined as PSA increase ≥ 2 ng/ml above nadir [23].

Radiotherapy

HDR-BT was performed under general or spinal anesthesia. Treatment modalities were previously described by Schiffmann et al. [26]. Patients received 18 Gy of HDR-BT (9 Gy/fraction on days 1 and 8) with an iridium-192 source. After 1 week, supplemental EBRT of the prostate and the seminal vesicles started. The target dose for EBRT was 50.4 Gy (in 1.8 Gy fractions). Initially, a three-dimensional conformal technique (3D-CRT) was used. Since 2012, all patients have been treated with intensity-modulated radiotherapy (IMRT) and, in a few cases, TomoTherapy® (Accuray® Sunnyvale, CA, USA) was employed due to anatomical particularities.

Statistical analysis

Parameters are given in absolute and relative frequencies. In normally distributed data the mean and standard deviation were determined. Otherwise, the median with interquartile range (IQR) was evaluated. Shapiro-Wilk test was used for the assessment of normal distribution. Two related non-parametrical samples were compared by Wilcoxon signed-rank test and Chi-squared test (χ^2 test) was applied in case of categorical variables. The Friedman test was utilized for one-way repeated analyses of variance by ranks in non-parametrical datasets. Survival analysis was performed by Kaplan–Meier survival curves with corresponding logrank test. Cut-off values were determined by calculating the Youden index from receiver operating characteristic curve statistics (ROC). To evaluate risks of gastrointestinal (GIT) and genitourinary (GUT) toxicities, parameters were tested with univariate Cox regression analysis. Only covariates with $p < 0.05$ were then entered into a multivariate logistic Cox regression model ($p = 0.05$) to receive the overall prediction model.

Statistical calculation was conducted with SPSS Statistics 24 software (IBM Inc. SPSS Statistics, Armonk, NY, USA).

Results

All treated patients exhibited a good functional status (ECOG 0–1). Most patients presented with intermediate-risk prostate cancer and a median CCI of 3 (range 2–6). Most men suffered from hypertension, while 14 patients (10.4%) had also had a second neoplasm other than prostate cancer. In 76 patients (56.7%, $n = 125$), external beam percutaneous therapy was performed by means of 3D-CRT, while in 34.3% IMRT was applied. Irradiation of pelvic lymph nodes was reported in 18 patients (16.7%, $n = 108$). Past transurethral resection of the prostate had occurred in 7 cases (5.6%, $n = 125$) and androgen deprivation therapy (ADT) in 52 patients (41.3%, $n = 126$). Patient characteristics are summarized in Table 1.

Clinical parameters and evaluation of acute therapy-related toxicity

In 87 patients (69%, $n = 126$), no skin toxicity occurred. No grade 3 skin toxicity was observed. Considering GIT, most patients reported mild diarrhea and increased frequency of bowel movement (grade 1 in 53.5%). However, in two cases, grade 3 GIT occurred. During EBRT, in one of these patients, irradiation had to be paused at 36 Gy due to transrectal blood loss. Mild GUT was observed in 71 patients (55.9%, $n = 127$). Mostly patients reported on nycturia and

Table 1 Patient characteristics

Characteristics	<i>n</i>	%	Mean (\pm SD)/median (IQR)
<i>Age (years)</i>			76 (75–82)
<i>Baseline PSA value (ng/ml)^a</i>	–	–	7.9 (2.59–47)
PSA <10	84	63.2	6.2 (2.59–9.4)
PSA 10–20	38	28.6	12.03 (10–19.7)
PSA >20	11	8.3	32.14 (\pm 8.48)
<i>Gleason score^a</i>			
<7	24	18	6 (3–6)
7	82	61.7	–
>7	27	20.3	9 (8–10)
<i>T stage</i>			
T1c	35	26.1	–
T2a–b	50	37.3	–
T2c–T3a/b	48	35.8	–
Tx	1	0.7	–
<i>Risk assessment</i>			
Low risk	9	6.7	–
Intermediate risk	83	61.9	–
High risk	42	31.3	–
<i>Comorbidities</i>			
Hypertension	59	44	–
Diabetes mellitus type 2 (without end organ damage)	11	8.2	–
Peripheral vascular disease	8	6	–
Cerebrovascular or transient ischemic attack	7	5.2	–
Congestive heart failure	7	5.2	–
Rheumatic or connective tissue disease	7	5.2	–
Neoplasm other than prostate cancer	14	10.4	–
<i>Involved technique</i>			
3D-conformal irradiation	76	56.7	–
IMRT	46	34.3	–
TomoTherapy (Accuray®, Sunnyvale, Ca, USA)	3	2.2	–
Data not available	9	6.7	–

Data given as *n* (%) or mean \pm SD, median (IQR). In 18 patients, in which irradiation of pelvic lymph nodes was performed, 9 patients received IMRT and 7 received 3D-CRT

IMRT Intensity-modulated Radiotherapy

^a*n* = 133

Table 2 Clinical parameters in brachytherapy

	BT 1	BT 2	<i>p</i> -value
Volume of prostate gland (cm ³)	39.7 (17–66.8)	41.5 (\pm 11.4)	<0.001
Maximal rectum dose (Gy) during BT	3.08 (1.12–6.7)	2.79 (\pm 0.89)	0.001
Number of trocar needles	19 (10–24)	19 (10–24)	<0.001

Data given as mean \pm SD or median (IQR)

BT Brachytherapy

on increased frequency of urination. In all subgroups, no grade 4 toxicity was reported.

The volume of the prostate gland was measured before each BT session. In our patient cohort, a significant difference between the glandular volume of the first (me-

dian: 39.7 cm³) and the second BT fraction (mean: 41.5 cm³; *p* < 0.001) was found. The average cumulative maximal rectum dose was 5.88 (\pm 1.81) Gy. The rectum dose was significantly lower in the second BT session (*p* = 0.001). Clinical parameters in brachytherapy are summarized in Table 2

Table 3 Acute and late therapy-related toxicity

	RTOG				<i>n</i>	<i>p</i> -value
	Grade 0	Grade 1	Grade 2	Grade 3		
Acute skin toxicity	87 (69)	35 (27.8)	4 (3.2)	–	126	<0.001
Acute GI toxicity	37 (29.1)	68 (53.5)	20 (15.7)	2 (1.6)	127	<0.001
Acute GU toxicity	33 (26)	71 (55.9)	19 (15)	4 (3.2)	127	<0.001
Late skin toxicity	104 (90.4)	8 (7)	3 (2.6)	–	115	<0.001
	118 (98.3)	1 (0.8)	1 (0.8)	–	120	<0.001 (0.02 ^a)
Late GI toxicity	88 (76.5)	21 (18.3)	5 (4.3)	1 (0.9)	115	<0.001
	103 (85.8)	13 (10.8)	4 (3.3)	–	120	<0.001 (0.02 ^a)
Late GU toxicity	67 (58.8)	36 (31.6)	10 (8.8)	1 (0.9)	114	<0.001
	93 (77.5)	23 (19.2)	3 (2.5)	1 (0.8)	120	<0.001 (<0.001 ^a)

Data is given in absolute and in relative (%) frequencies. Late toxicity grading is subdivided in results of the first (*upper row*) and in the results of the last available follow-up (*lower row*)

RTOG Radiation Therapy Oncology Group, GI gastrointestinal, GU genitourinary

^aValues in brackets define *p*-values after testing the aforementioned subgroups against each other

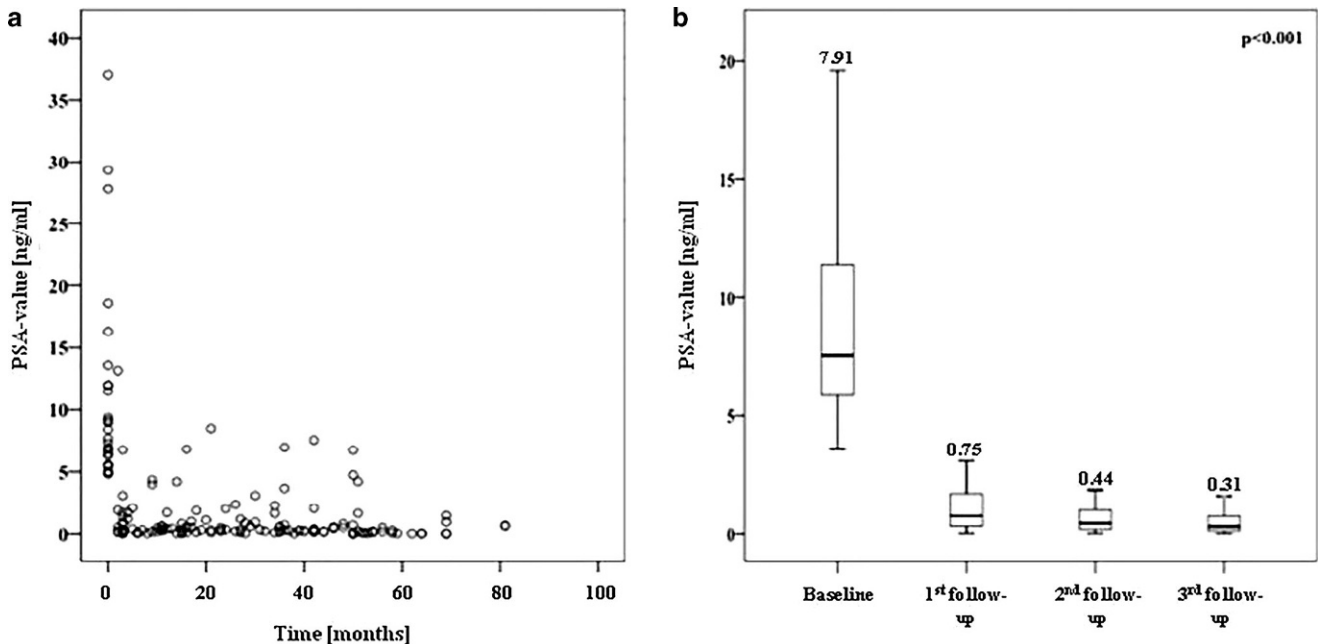


Fig. 1 Scatter diagram **a** shows the course of PSA values for the first five follow-up (*FU*) examinations. Boxplot diagram **b** demonstrates a significantly reduced post-therapeutic PSA value. Numbers over the box plots are the corresponding medians. The first three *FU* are shown as an example

and acute and late therapy-related toxicities are shown in Table 3.

Follow-up

In our patient cohort, median follow-up time was 25 months (range 0–127 months).

Biochemical response was evaluated by comparing the pre- and post-therapeutic PSA course. Fig. 1 shows significantly reduced post-therapeutic PSA values ($p < 0.001$). Considering all noted follow-up examinations (up to 16 fol-

low-up examinations in 2 patients), no significant difference in PSA values was observed ($p = 0.453$). Biochemical relapse was found in 12 patients (10.3%, $n = 117$) after a median time interval of 22 months (range 1–87 months). Overall biochemical relapse is demonstrated in Fig. 2. Considering different prostate cancer risk categories, no significant differences were found between the three subgroups ($p = 0.484$; Fig. 3). Fig. 3 also shows patients in whom ADT was started prior to combined HDR-BT/EBRT and those who did not receive ADT before HDR-BT. In our

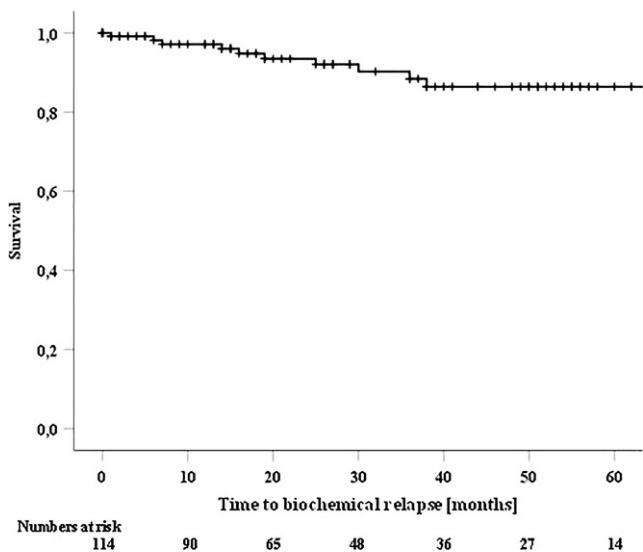


Fig. 2 Kaplan–Meier plot demonstrating overall biochemical relapse

patients, no significant differences were found between the aforementioned groups ($p=0.527$).

For evaluating late therapy-related toxicity, data from the first and the last available follow-up were compared. Considering the last available follow-up, significantly more patients presented with no late toxicities in all subgroups (grade 0; $p<0.001$). Only in one case, late GUT grade 3 was reported. Table 4 summarizes late toxicities at these two timepoints.

Risk assessment

In univariate and in multivariate logistic regression analysis, both T stage and the used technique (3D-CRT vs. IMRT vs. TomoTherapy [Accuray®, Sunnyvale, Ca, USA]) were identified as being predictors for developing GIT and GUT. Patients who were treated with 3D-CRT were at a 2.17-times higher risk (hazard ratio [HR]: 2.17, 95% confidence interval [CI]: 1.31–3.57, $p=0.002$) of experiencing GUT than their counterparts who received IMRT or TomoTherapy. Considering GIT, risks could be reduced by 78% using IMRT (HR: 0.22, 95% CI: 0.07–0.75, $p=0.015$). In our population, patients with a higher T stage (T2c–3a/b) were less likely to experience GIT or GUT showing a risk reduction by 50% (HR: 0.49, 95% CI: 0.29–0.85, $p=0.011$ and HR: 0.5, 95% CI: 0.3–0.81, $p=0.005$, respectively). All other tested covariates did not significantly impact on risk status (see Table 4 and 5). Skin toxicity was very mild. Therefore, no risk stratification occurred.

Discussion

This retrospective study focused on patients ≥ 75 years who underwent a combined HDR-BT/EBRT due to localized prostate cancer. Other studies have mainly examined younger patients [16]. Between 2004 and 2010, Soumarova et al. [27] examined 20 patients at a median age of 77 years who underwent a combined HDR-BT/EBRT. They reported on acute GUT and GIT in 60 and 25%, respectively. Despite their comparatively limited number of patients, the authors

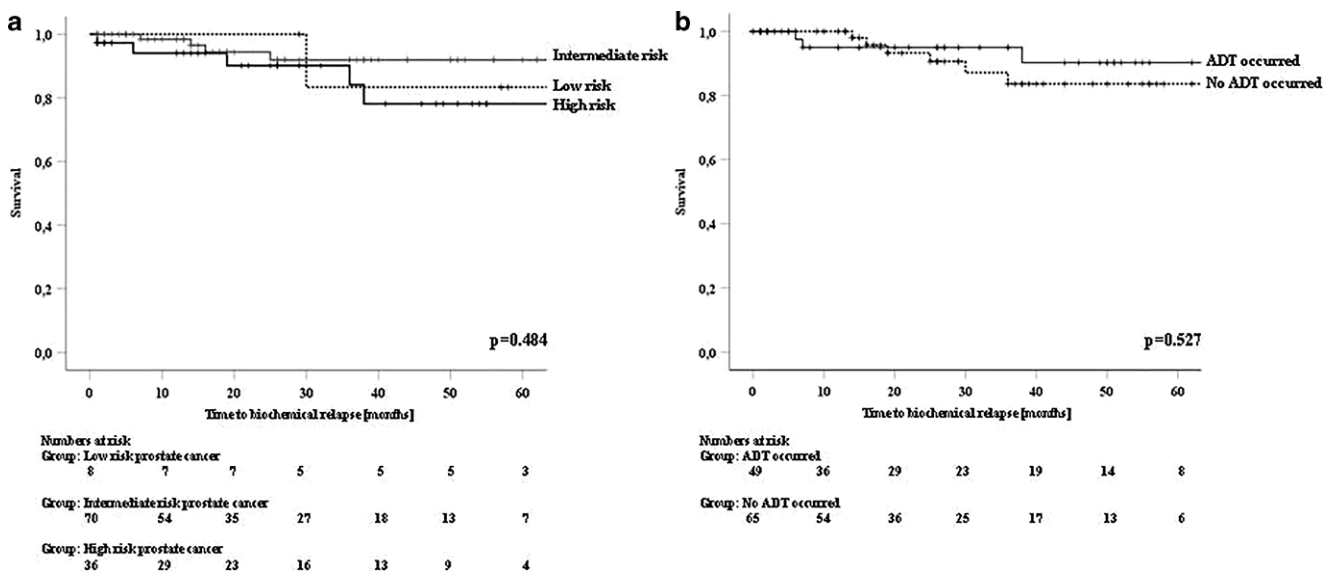


Fig. 3 Kaplan–Meier diagram in **a** demonstrates biochemical relapse in patients with different prostate cancer risk categories ($p=0.484$). Pairwise comparison of subgroups did not show significant differences. Kaplan–Meier survival plot in **b** distinguishes between patients in whom androgen deprivation therapy (ADT) was started prior to combined high-dose-rate brachytherapy and external beam radiation therapy (HDR-BT/EBRT) and those who did not receive hormone deprivation ($p=0.527$)

Table 4 Univariate and multivariate Cox regression analyses of different covariates for the incidence of gastrointestinal toxicity (all grades)

Gastrointestinal toxicity						
Covariates	Subset	<i>n</i>	Univariate analysis		Multivariate analysis	
			HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Age (years)	<76.5 vs. ≥76.5	116	1.4 (0.9–2.18)	0.132	–	–
PSA (ng/ml)	>20 vs. <10, 10–20	116	1.66 (0.63–4.33)	0.303	–	–
Gleason score	7 vs. <7, >7	115	0.54 (0.26–1.13)	0.1	–	–
T stage	T2c–3a/b vs. T1c, T2a/b	116	0.53 (0.32–0.9)	0.02	0.49 (0.29–0.85)	0.011
CCI	3 vs. 2, 4, 5	116	1.31 (0.46–3.71)	0.609	–	–
Cumulative rectal dose (Gy)	<6.525 vs. ≥6.525	112	1.06 (0.66–1.69)	0.821	–	–
Used RT technique	IMRT vs. 3D-conformal RT vs. TomoTherapy (Accuray®, Sunnyvale, Ca, USA)	113	0.23 (0.07–0.78)	0.018	0.22 (0.07–0.75)	0.015
Involved structures	Prostate + SV vs. additional pelvic lymph nodes	96	0.91 (0.47–1.74)	0.906	–	–
Reported TUR-P	Yes vs. no	109	1.49 (0.6–3.69)	0.395	–	–
ADT	Yes vs. no	111	0.94 (0.6–1.48)	0.798	–	–
Number of trocar needles (mean/patient)	17 vs. 10–16, 18–24	108	0.1 (0.01–1.03)	0.053	–	–

CCI Charlson comorbidity index, RT radiotherapy, TUR-P transurethral resection of the prostate, ADT androgen deprivation therapy, IMRT intensity-modulated radiotherapy, SV seminal vesicles, HR hazard ratio, CI confidence interval

Table 5 Univariate and multivariate Cox regression analyses of different covariates for the incidence of genitourinary toxicity (any grade)

Genitourinary toxicity						
Covariates	Subset	<i>n</i>	Univariate analysis		Multivariate analysis	
			HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Age (years)	<76.5 vs. ≥76.5	116	1.14 (0.75–1.75)	0.535	–	–
PSA (ng/ml)	>20 vs. <10, 10–20	116	1.42 (0.61–3.31)	0.418	–	–
Gleason score	7 vs. <7, >7	115	0.6 (0.29–1.26)	0.179	–	–
T stage	T2c–3a/b vs. T1c, T2a/b	116	0.55 (0.34–0.88)	0.014	0.5 (0.3–0.81)	0.005
CCI	4 vs. 2, 3, 5	116	0.46 (0.21–1.01)	0.053	–	–
Cumulative rectal dose (Gy)	<6.525 vs. ≥6.525	112	0.88 (0.55–1.4)	0.58	–	–
Used RT technique	3D-conformal RT vs. IMRT, TomoTherapy (Accuray®, Sunnyvale, Ca, USA)	113	2.0 (1.23–3.27)	0.005	2.17 (1.31–3.57)	0.002
Involved structures	Prostate + SV vs. additional pelvic lymph nodes	96	0.92 (0.49–1.73)	0.804	–	–
Reported TUR-P	Yes vs. no	109	0.84 (0.26–2.66)	0.761	–	–
ADT	Yes vs. no	111	0.88 (0.56–1.36)	0.56	–	–
Number of trocar needles (mean/patient)	17 vs. 10–16, 18–24	108	0.12 (0.01–1.15)	0.065	–	–

CCI Charlson comorbidity index, RT radiotherapy, TUR-P transurethral resection of the prostate, ADT androgen deprivation therapy, IMRT intensity-modulated radiotherapy, SV seminal vesicles, HR hazard ratio, CI confidence interval

stated that combined HDR-BT/EBRT was a safe and well-tolerated procedure. When dealing with elderly patients, some authors question the benefit of curative treatment options. However, Alibhai et al. concluded that especially older men with moderately or poorly differentiated tumors and a limited number of comorbidities benefit due to prolonged (quality-adjusted) life expectancy [1]. 93.2% of our patients suffered from an intermediate or high-risk tumor. Therefore, it is likely that especially this risk group recorded a therapy-related benefit.

In comparison to Soumarova et al., we observed almost the same percentage of patients who suffered from acute GUT grade 1 (55.9%). Conversely, in our cohort, more patients presented with acute GIT (grade 1 in 53.5%) which later resolved; the long-term course did not show grade 3 GIT on the last available follow-up examination.

Boehm et al. [3] evaluated predictors for biochemical recurrence and overall survival in patients treated with combined HDR-BT/EBRT (group 1) and patients who underwent radical prostatectomy (RP). These authors stated that RP (without additional ADT) offered a comparable response rate to HDR-BT and EBRT. Schiffmann et al. [26] examined 392 patients of whom 56.4% were treated with additional ADT to combined HDR-BT/EBRT. Interestingly, ADT improved biochemical control in high-risk prostate cancer, while in intermediate-risk patients, additional ADT did not reduce the risk of biochemical relapse. We did not notice advantages concerning biochemical control in ADT-treated patients.

We found two predictors of risk for GIT and GUT. The use of 3D-CRT doubled the risk for GUT of any grade. Likewise, the introduction of IMRT led to a risk reduction of 78% for therapy-related GIT. Although only 10 patients were evaluated by Nutting et al. [21], they also stated that IMRT may reduce therapy-related toxicity [10, 28].

Today, the advantages of IMRT over 3D-CRT are obvious. However, data on this specific patient cohort (e.g., elderly males after combined HDR-BT/EBRT) are still lacking. Also, effects may vary due to differences in BT protocols among different radiooncologic centers.

Interestingly, in our cohort, patients with a higher T stage (T2c–3a/b) were less likely to experience GIT or GUT of any grade. Faria and coauthors [8] assessed acute and late toxicity in 105 high-risk prostate cancer patients after hypofractionated irradiation delivered with IMRT and ADT. Within their cohort, acute GIT or GUT grades ≥ 2 were limited (17% each). Severe side effects occurred in 4 patients, 1 patient with GIT and 3 patients with GUT grade 3). However, statistical results of two different treatment methods, e.g. combined HDR-BT and EBRT vs. hypofractionated EBRT, cannot be transferred to one another due to biophysical and radiobiological differences. Nevertheless, in comparison to their low- and intermediate-risk counter-

parts, we assume that combined HDR-BT and EBRT in high-risk cancer patients does not result in a higher risk of experiencing severe GIT or GUT.

Pinkawa et al. [22] evaluated dose–volume-related factors in 64 patients who underwent HDR-BT (2×9 Gy) as a boost to EBRT. They stated that dose limitations of 15 Gy to the urethra and 6 Gy to the rectal mucosa were recommendable to minimize dose–volume-related side effects in BT. Our measured rectal doses fit these dose constraints. Nevertheless, in our patient cohort, measured rectal doses during BT were not a statistically significant predictor of GIT (HR: 1.06, 95% CI: 0.66–1.69, $p=0.821$).

The main limitation of this study is its retrospective design. However, to our knowledge, this is the largest retrospective analysis mainly focusing on this age category. Another limitation relates to the interobserver-related differences, as patients were examined by different investigators during the treatment. Moreover, detailed information on the period of ADT administration was partly missing and not accessible in all cases. Finally, our analysis only included a Kaplan–Meier analysis on biochemical recurrence. Information on metastases-free, cancer-specific, and overall survival is missing. Still, biochemical relapse serves as a screening parameter to indicate tumor progression [17].

Conclusion

Although HDR-BT has been practiced over several decades, data on elderly patients ≥ 75 years are still very limited. In summary, we consider combined HDR-BT/EBRT to be a well-tolerated treatment option for older males with a modest number of comorbidities and localized intermediate- or high-risk prostate cancer. IMRT technique should be favored.

Conflict of interest A. Löser, B. Beyer, C.O. Carl, B. Löser, Y. Nagaraj, T. Frenzel, C. Petersen, A. Krüll, M. Graefen, and R. Schwarz declare that they have no competing interests.

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