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ORIGINAL ARTICLE

Combined-modality ^{125}J-seed-brachytherapy, external beam radiation and androgen deprivation therapy of unfavorable-risk prostate cancer: report of outcomes and side-effects

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Abstract

Purpose To analyze outcomes and complication rates in an unselected cohort of men with unfavorable (NCCN intermediate and high-risk) PCa receiving combined-modality radiation treatment (CRT).

Methods Patients received androgen deprivation therapy for 1 year and combined-modality radiation treatment (CRT) consisting of external-beam radiotherapy (EBRT, 59.4 Gy, 33 fractions) and ^{125}J seed-brachytherapy (S-BT, 100 Gy). Subgroups, including WHO group 3–5, and initial PSA (iPSA) < 20 and > 20 ng/ml were identified. Biochemical recurrence-free (BRFS), metastasis-free (MFS), cancer-specific (CSS) and overall survival (OS) were calculated at 5 and 10 years using the Kaplan–Meier method. Subgroups were compared using log-rank test and Cox proportional hazards regression. Urogenital and gastrointestinal side-effects were reported according to the CTCAE classification.

Results After a median of 6.9 years (range 2–13) calculated 5- and 10-year rates for the whole cohort of 425 men were 92.8% and 82.5% for BRFS, 95.1%, and 88.8% for MFS, 98.2%, and 95.1 for CSS, and 95.4%, and 80.1% for OS, respectively. Univariate (UVA) and multivariate analysis (MV) identified a group with unfavorable outcome with iPSA > 20 ng/ml, comprising 24% of all patients, in which 55% of recurrences, 54% of metastases and 71% of cancer-specific deaths occurred. Side-effects were limited, with < 5% of patients complaining of genitourinary and 0.5% of gastrointestinal AEs after 5 years.

Conclusion CRT is an excellent treatment option for men with unfavorable PCa. In a subgroup of patients with iPSA > 20 ng/ml further, possibly systemic, treatment options should be identified.

Keywords High-risk prostate cancer · Radiotherapy · Seed-brachytherapy · LDR-brachytherapy · Outcome research · Side-effects

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Introduction

Threat of prostate cancer recurrence, metastasis and death is largely attributable to a subgroup of patients with unfavorable prostate cancer (PCa), irrespective of treatment form [1–3]. Recent trials on combined-modality radiation treatment (CRT) of external-beam radiotherapy (EBRT) with a brachytherapy boost have shown that CRT is superior to EBRT alone in terms of improved biochemical control, local progression, distant metastases and survival [1, 4, 5], and appears at least equivalent to radical prostatectomy (RP) [5, 6], albeit at a higher rate of urogenital and gastrointestinal side effects.

We present outcome data of a group of unselected patients with unfavorable prostate cancer treated with CRT. In contrast to previous reports, our data show a low treatment-related morbidity. Except for patients with an initial PSA > 20 ng/ml, therapeutic effectivity was high in all subgroups.

Patients and methods

The protocol of this retrospective cohort analysis was approved by the ethical committee of the University of Luebeck. Men diagnosed between 2004 and 2017 with unfavorable PCa and deemed eligible for combination therapy with curative intend were identified. Every patient was seen independently by an urologist and by a radiotherapist and provided written informed consent in both institutions. Patient data were recorded independently at each institution, anonymized and entered into a shared database.

Before therapy, all patients underwent routine staging, including bone scan in all and CT scan in most of them, according to 2005 European Urology recommendations [7]. The initial PSA (iPSA) upon presentation with prostate cancer was documented. Patients with a follow-up less than 24 months or with iPSA > 100 ng/ml were excluded from evaluation.

For this evaluation, the recent National Cancer Comprehensive Network (NCCN) classification system [8] was applied, with PSA 10–20 ng/ml, Gleason 7 for intermediate, and PSA > 20 ng/ml, Gleason ≥ 8 for high-risk patients.

Treatment protocol included neoadjuvant androgen deprivation therapy (ADT) beginning before EBRT until 12 months after ^{125}J seed-brachytherapy (S-BT).

The most up-to-date radiation protocol was used whenever available. Three-dimensional conformal radiation therapy was used until 2009, followed by intensity-modulated radiation therapy (IMRT), which was enhanced by volumetric arc therapy (VMAT) and image-guided radiotherapy (IGRT) since 2012. Plans were calculated with Pinnacle planning system (Philips, MA, 01810, USA). EBRT was applied by Elekta Synergy machines (Elekta Instrument AB Stockholm, Sweden) and delivered at 59.4 Gy (33 fractions) to prostate and seminal vesicles and at 50.4 Gy (28 fractions) to the regional lymphatic area.

S-BT was performed according to guidelines [9] by an experienced urologist (either AB or PR) at 3 weeks after EBRT using the real-time intraoperative planning method [10], with Varian 7.0 as planning program (Varian Medical Systems, Palo Alto, USA). The prescription dose was 100 Gy.

Intraoperative and 6 weeks postoperative radiation doses were documented for quality control as proposed by Stock [11].

All involved institutions provided independent follow-up. Follow-up visits were appointed every 3 months for 2 years, every 6 months for another 2 years and yearly thereafter. Patients were evaluated with physical examinations, ultrasound examination, and PSA.

Biochemical recurrence was defined as 2 ng/ml PSA increase above a nadir value according to the Phoenix definition [12]. Metastatic disease was defined as bony, visceral, or lymph-node metastases on imaging. For lack of a standard definition, prostate cancer-specific death was rather stringently defined if the last PSA before death was > 10 ng/ml, if distant metastatic disease or if systemic antineoplastic therapy (other than androgen deprivation therapy, ADT) was documented before death.

Outcome measures were biochemical progression-free survival (BRFS), metastasis-free survival (MFS), prostate cancer-specific survival (CSS), and overall survival (OS). Covariates included age (≤ 70, > 70), WHO risk group, Gleason score, iPSA (< 10, 10 to ≤ 20, > 20 ng/ml), or date of treatment (≤ 2011 or thereafter).

The Kaplan–Meier product-limit method and the log-rank test were applied to estimate survival probabilities and compare survival, respectively. Univariate (UVA) and multivariate analyses (MVA) of predictors were performed using Cox proportional hazard regression. All analyses were performed descriptively, and *p* values are reported as descriptive measure for the strength of the evidence. Analyses were performed with SPSS v.24.0.

Treatment-related toxicity was evaluated by personal communication at each follow-up visit independently both by an urologist and a radiotherapist. The records of both institutions were evaluated, combined and graded using a combination of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3 and the Radiation Therapy Oncology Group late radiation morbidity scoring systems [13, 14].

Results

Clinical characteristics

Of the 508 patients treated, 83 were excluded from final evaluation for follow-up of less than 24 months ($n = 76$), or iPSA > 100 ($n = 7$). Median follow-up time for the cohort of 425 patients was 6.9 years (mean 7, range 2–13).

At presentation, the mean age was 69.4 years (range 41–86), the median iPSA was 10 ng/ml (mean 16.01, range 0.1–96.8). 60.7% and 39.3% of patients were attributable to NCCN intermediate and high-risk groups, respectively. Patient characteristics are shown in Table 1.

Adherence to treatment was high, with 94.8% of 425 men receiving the recommended neoadjuvant ADT. The number of patients not receiving the recommended ADT was too small for any meaningful subset analysis, therefore, their data remained in the total analysis.

Survival analysis

During follow-up, 10.4%, and 6.6% of patients had recurrence and metastases, respectively. 11.1% of patients died, with 3.3% attributable to PCa. Calculated BRFS rates were 92.8%, and 82.5% at 5 and 10 years, respectively. Corresponding data for MFS were 95.1% and 88.8%. Cancer-specific and overall survival rates were 98.2% and 95.1%, and 95.4% and 80.1% at 5 and 10 years, respectively (Table 2, electronic supplementary material). The NCCN high-risk group fared worse than the NCCN intermediate group.

Kaplan–Meier curves showed significant differences between intermediate and high NCCN risk groups with regard to BRFS ($p < 0.005$), MFS ($p < 0.005$), and CSS ($p = 0.002$) (Fig. 1).

Overall-survival differed between patients > 70 years and ≤ 70 years of age ($p = 0.03$). No difference was found in cancer-specific survival, suggesting co-morbidity as the cause of death.

High iPSA > 20 ng/ml was the most predictive factor for an adverse outcome, and was significantly associated with BRFS ($p = 0.005$), MFS ($p = 0.001$), and CSS ($p = 0.002$) (Fig. 2). In fact, harboring 24% of the whole cohort, after 10 years of follow-up this subgroup contained 55% of patients with biochemical recurrence, 54% with metastatic disease, and 71% of cancer-specific deaths.

On UVA iPSA (< 10 vs. > 20 ng/ml) and NCCN risk group (intermediate vs. high) were associated with BRFS, MFS and CSS. MVA did not discern between these risk factors, as iPSA > 20 ng/ml is a shared feature. There was no significant interaction between outcome and age or year of treatment (Table 3, electronic supplementary material).

Table 1 Patient characteristics (GS, Gleason score; iPSA, initial PSA; ADT, androgen-deprivation therapy)

Variable		Number (%)
Treated		508
iPSA > 100 ng/ml		7
Follow-up ≤ 24 months		76
Analyzed		425
GS	WHO Group	
6	1	34 (8%)
7a	2	144 (33.9%)
7b	3	158 (37.2%)
8	4	63 (14.8%)
9–10	5	26 (6.1%)
NCCN risk group		
Intermediate		285 (60.7%)
High		167 (39.3%)
iPSA (ng/ml)	Mean (range)	425
	16.1 (0.1–96.8)	
< 10		207 (48.7%)
10–20		115 (27.1%)
> 20		103 (24.2%)
ADT		425
< 6 months		11 (2.6%)
6–12 months		403 (94.8%)
> 12 months		11 (2.6%)
Age	69.6 (41–86)	425
< 50		5 (1.2%)
50–59		27 (6.4%)
60–69		158 (37.2%)
70–80		230 (54.1%)
> 80		5 (1.2%)
Age group		
≤ 70		226 (53.2%)
> 70		199 (46.8%)
Follow-up		
Months	85 (25–158)	
Years	6.9 (2–13)	
Recurrence		425
Yes		44 (10.4%)
No		381 (89.6%)
Metastases		425
Yes		28 (6.6%)
No		397 (93.4%)
Status		425
Alive		378 (88.9%)
Dead		47 (11.1%)
Cause		425
Dead of PCa		14 (3.3%)
Other cause		33 (7.8%)

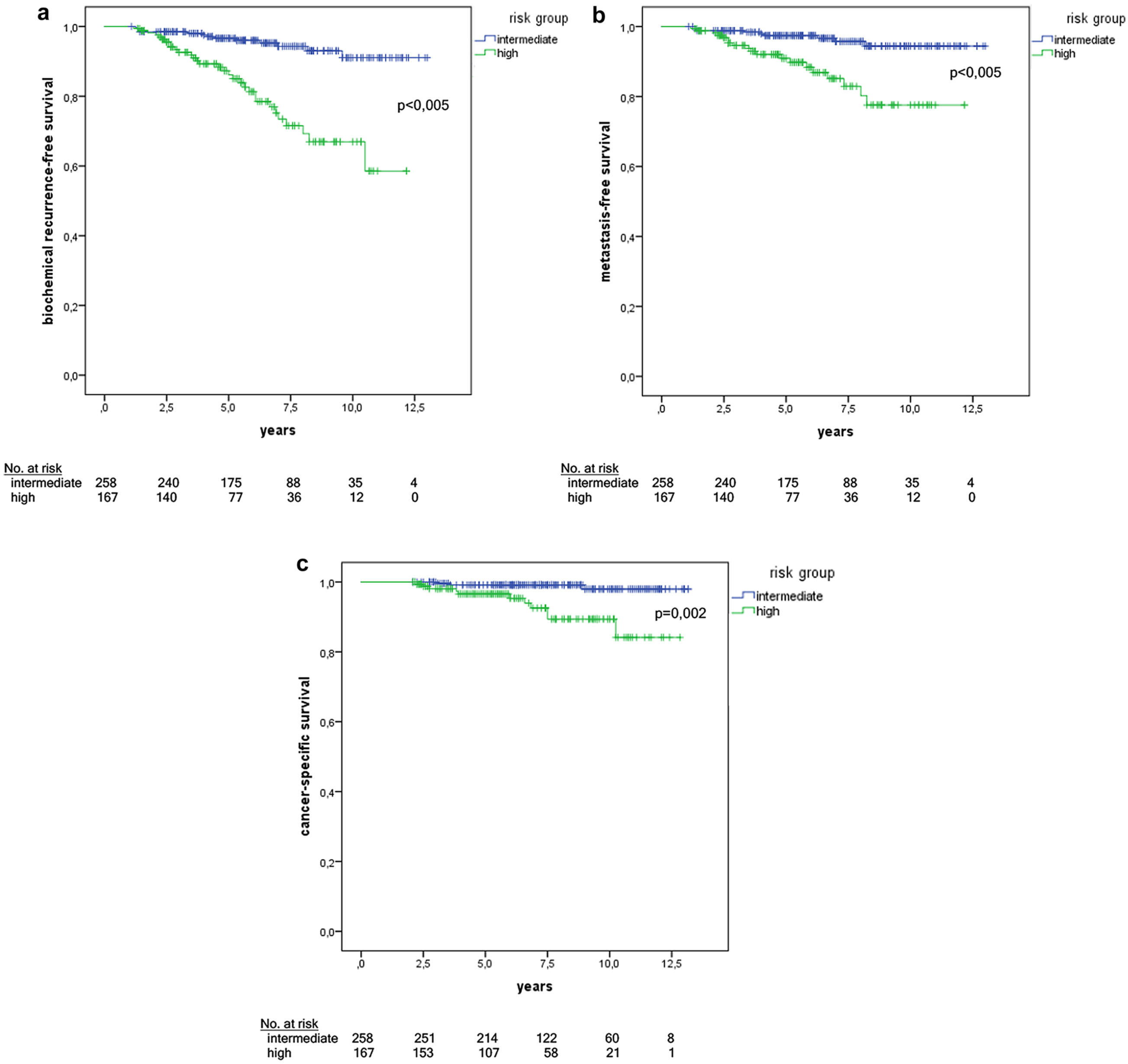

Fig. 1 Outcomes of NCCN intermediate-risk group vs. NCCN high-risk group with regard to **a** biochemical recurrence-free survival (BRFS), **b** metastasis-free survival (MFS), and **c** cancer-specific survival (CSS)

Treatment-related side-effects

There were no deaths related to complications of radiotherapy. With a mean intraoperative D90 of 126,9 Gy (range 106–166 Gy) (Table 4, electronic supplementary material), the cumulative incidence of grade ≥ 2 genitourinary (GU) morbidity was more prominent than grade ≥ 2 gastrointestinal (GI) morbidity ($p = 0.01$), but never exceeded > 20% of patients. Genitourinary side-effects, mostly of grade 1, were prominent in about 40% of patients at first follow-up after 3 months, declining over time thereafter, with < 5% of patients complaining of GU and 0.5% of GI events after 5 years (Fig. 3).

Discussion

The optimal treatment for unfavorable prostate cancer has not been defined precisely, with advocates for surgery and for radiation therapy likewise. The rate of secondary adjuvant radiation after radical prostatectomy (RP) is up to 20% in this patient group [15], and the success rate for EBRT

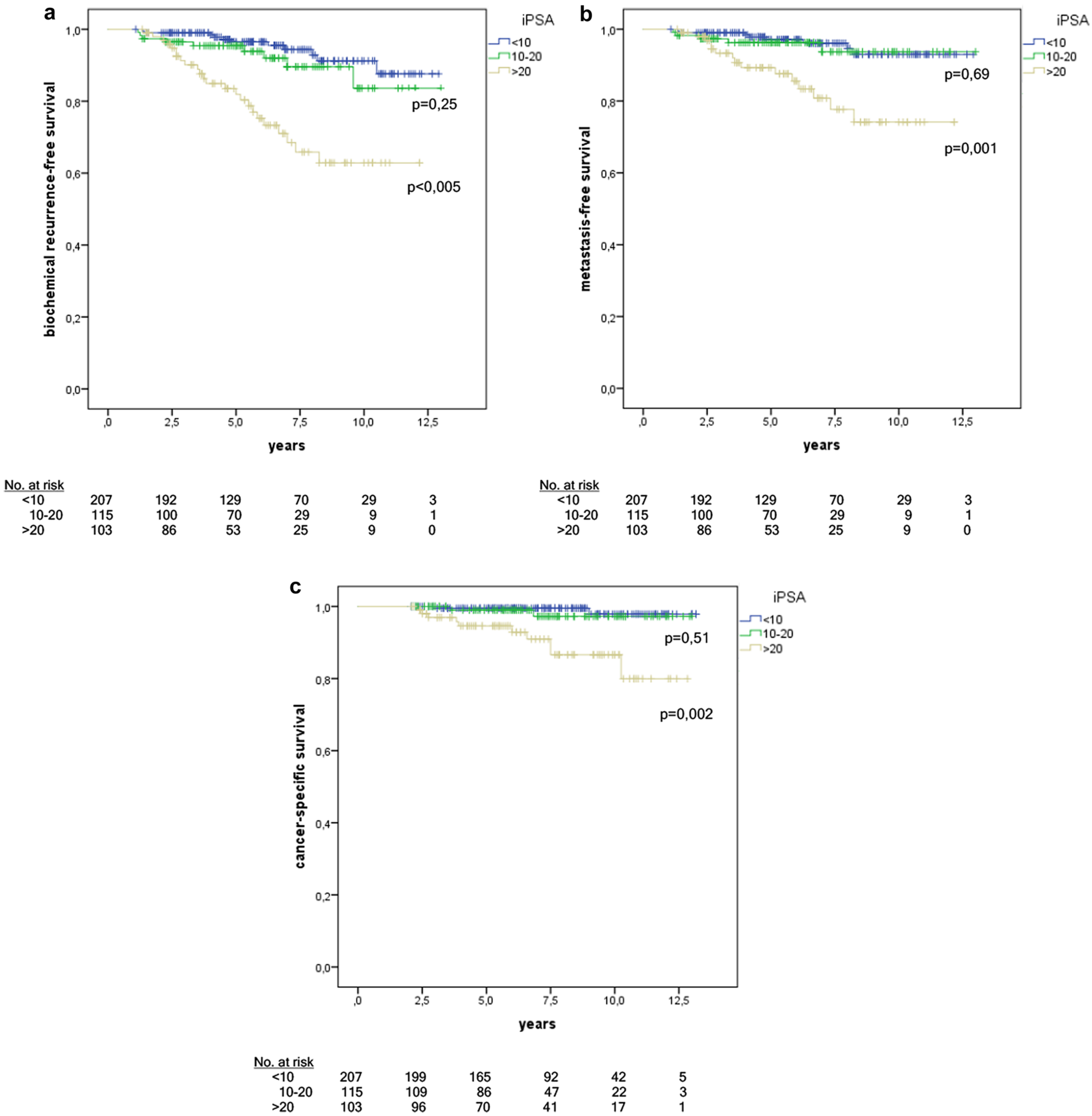

Fig. 2 Association of iPSA with **a** biochemical recurrence-free survival (BRFS), **b** metastasis-free survival (MFS), and **c** cancer-specific survival (CSS)

monotherapy differs largely [7]. After RP in high-risk prostate cancer, actual urological guidelines refer to 10- and 15-year CSS rates of 88% and 66%, respectively [16]. A recent trial on Gleason 9–10 prostate cancer reports on 5-year rates of distant metastasis after both RP and EBRT of 24%, and 5-year cancer–specific mortality rates of 12% and 13% after RP and EBRT, respectively [6].

Supposed reasons for this dilemma are twofold. Microscopic disease more than a few millimeters beyond the prostatic capsule has been shown common in men with high-risk PCa [17]. With RP, Briganti et al. found that roughly 60% of patients with high-risk PCa harbored non-organ confined disease [2], supporting the notion that extended-field therapies might be superior.

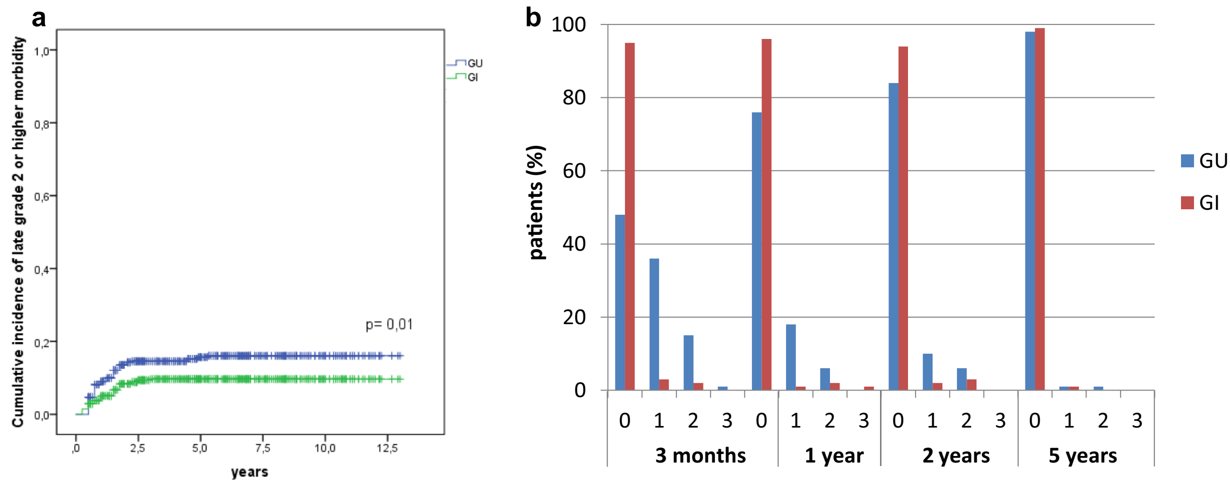

Fig. 3 Cumulative incidence (**a**) and rates (**b**) of late genitourinary (GU) and gastrointestinal (GI) CTCAE grade 0–3 adverse events

The concept of dose escalation by a local brachytherapy boost is intriguing, as combined-modality radiation therapy (CRT) provides dose escalation to the prostate far in excess of what can be achieved with EBRT alone. It is assumed that the biologically equivalent dose with CRT is over 200 Gy [18]. While CRT seems a well-suited option to address the limitation of any monotherapy in unfavorable patients, only recently long-term results of comparative clinical trials using CRT have been published. A SEER database study by Muralidhar et al. [3] evaluated cancer-specific survival rates among 45,078 patients with intermediate and high-risk PCa. They found a significant benefit for patients with unfavorable disease receiving CRT compared to EBRT alone ($p = 0.02$). In a recent study, Ennis et al. demonstrated comparable outcomes within the National Cancer Data Base in overall survival between RP and CRT [5], whereas inferior survival was seen after EBRT alone.

Two recent randomized trials demonstrated superior BRFS rates after CRT but failed to show significant improvements in distant metastasis or cancer-specific survival compared to EBRT alone [4, 19]. This gap in knowledge was recently closed by Kishan and coworkers from 11 institutions who found a robust association of CRT with better outcomes regarding MFS and CSS in very high-risk patients (Gleason ≥ 9) compared with both EBRT and, notably, RP [6].

These contributions on favorable outcomes after CRT together with well-documented supportive reports such as ours from unselected patient cohorts outside clinical trials may serve as a significant source of clinical guidance.

Biochemical recurrence antedates clinical progression by a median of 5–7 years [20], making long-term reports on metastases and survival critical. With a median follow-up of our cohort of 7 years, exceeding the median follow-up of the ASCENDE-RT trial by 0.5 years, our results appear valid and comparable to the published evidence. In comparison to the ASCENDE-RT trial [4], the majority of our patients were attributable to the NCCN intermediate risk group (NCCN intermediate ASCENDE-RT 30.7% vs. 60.7%; NCCN high ASCENDE-RT 69.3% vs. 39.3%). On the other hand, we rather over-estimated cancer-specific death by a wider definition based on clinical signs of progression before death. Furthermore, to account for PCa-unrelated deaths, we created a subset analysis of men younger and older than 70 years. This showed no difference in cancer-specific outcome, suggesting a correct estimate of the cancer-specific death cohort, which after 10 years was only 4.9%.

One dilemma of long-term retrospective analyses is a shift in arbitrary definitions. Several changes to risk classification [21, 22] occurred during the evaluation period. For analysis, patients were re-classified according to modern NCCN criteria. With regard to the ongoing debate on optimal treatment of intermediate-risk patients our results may serve as an argument for CRT. However, from a contemporary standpoint and with regard to the good results of monotherapeutic approaches [23], CRT therapy of intermediate-risk patients is regarded as overtreatment.

Even among the high-risk cohort, sub-cohorts with different mortality outcomes after radiotherapy can be identified [3]. In MVA, we recognized a distinct group of patients with an iPSA > 20 ng/ml with adverse outcome. Notably, this subgroup of patients was only recently added into WHO group III of the American Joint Committee on Cancer (AJCC) version 8 [24], supporting the relevance of our data. Consistent with our findings, the only risk factor predictive for treatment failure and metastasis in the series of Saad, using EBRT, was PSA ≥ 40 ng/ml [25]. Elevated PSA at time of diagnosis was also highly predictive for metastatic disease following RP [24, 26]. It can be assumed that PCa in this unfavorable subgroup already harbors distant micro-metastatic disease. Therefore, rather systemic (neo-)adjuvant therapy is deserved, as has recently been suggested in the GETUG 12 trial [27]. We caution, however, to use elevated PSA as an exclusion criterion since, as we have shown in our results, the majority of patients with high PSA still benefits from local curative treatment [26, 28, 29].

Good results from any treatment modality should be weighed against the possibility of harm. The vast majority of our patients reported side-effects CTC grade 1, which corresponds to irritative voiding symptoms treatable by alpha-blockers. Regarding the median age of the cohort, this medication is not unusual. Moreover, side-effects decreased continuously with no CTC $\geq$ grade 2 reported beyond 60 months after treatment. These findings confirm other reports on S-BT which showed that symptoms tended to peak initially, with near complete resolution by 4 years [30]. In our population with a consistently close and personal relationship between therapist and patient, side-effects were reported significantly lower than elsewhere. The ASCENDE-RT trial showed a higher incidence of side-effects in the CRT arm as compared to the EBRT arm [31]. This difference may in part be attributable to a higher dose of external beam radiation (ASCENDE-RT, 46 Gy in 23 fractions vs. 59.4 Gy in 33 fractions) and a lower prescription dose for the brachytherapy boost (ASCENDE-RT, 115 Gy stranded seeds vs. 100 Gy single seeds) than during the ASCENDE-RT trial. On contrary, in a SEER-based comparison among different radiotherapy modalities for prostate cancer, GI toxicity rates were lowest for brachytherapy [32]. Thus, CRT may offer an excellent risk to benefit ratio for prostate cancer patients, and counselling for curative therapy should include this treatment option.

Conclusion

CRT offers a good treatment option and an alternative treatment modality for men with unfavorable PCa, combining high long-term effectivity with low morbidity. In counselling for curative therapy this treatment option should be included. A subgroup of patients with iPSA > 20 ng/ml deserves further, systemic, treatment.

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Author contributions AB: protocol development, data analysis, manuscript writing and editing. KK: data collection, data analysis, manuscript editing. IRK: data analysis, manuscript editing. IR-N: manuscript editing. PR: manuscript editing. BB: protocol development, manuscript editing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent was not required.

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