Original paper

Five-year effectiveness of low-dose-rate brachytherapy: comparisons with nomogram predictions in patients with non-metastatic prostate cancer presenting significant control of intra- and periprostatic disease

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Abstract

Purpose: To assess the effectiveness of low-dose-rate (LDR) brachytherapy in patients with localized prostate cancer and to compare the outcome with predictions from Kattan and Partin nomograms at 60 months after seed implantation.

Material and methods: One thousand, one hundred and eighty-seven patients with localized prostate cancer at low-, intermediate-, or high-risk of progression received LDR brachytherapy using iodine-125 seeds with curative intent, applied as monotherapy or in combination with external beam radiation therapy (EBRT), and/or androgen deprivation therapy (ADT). At 60 months after seed implantation, data of 1,064 patients (1,058 alive + 6 who died of prostate cancer) were analyzed for biochemical progression-free survival (bPFS) based on prostate-specific antigen (PSA) levels using the Phoenix definition. Five-year bPFS probabilities were determined for various risk group classifications (d'Amico, Mt. Sinai, MSKCC/Seattle, NCCN). Outcomes were also compared to patient-individualized nomogram predictions of 5-year bPFS (Kattan 2002) and probability of organ-confined disease (Kattan 2002, Partin 2007).

Results: Overall, 93.3% (993/1,064) of the patients were free of biochemical progression within 5 years, while the average 5-year bPFS probability according to the Kattan nomogram was significantly lower (85%, $p < 0.001$). Outcomes were significantly better than Kattan nomogram predictions in the subgroup of patients with monotherapy as well as in patients additionally treated with EBRT. Comparison of the overall outcome with nomogram predictions for organ-confined disease (Kattan nomogram: 50%; Partin nomogram: 65%) revealed a significant probability of LDR brachytherapy to destroy periprostatic tumor spread ($p < 0.001$) in all risk group constellations, even in high-risk patients.

Conclusions: The results indicate high effectiveness of LDR brachytherapy in all risk groups, significantly better than predicted with the Kattan nomogram in most subgroups. The significant superiority of LDR brachytherapy compared to nomogram predictions of organ-confined disease suggests that LDR brachytherapy effectively controls both intra- and periprostatic disease.

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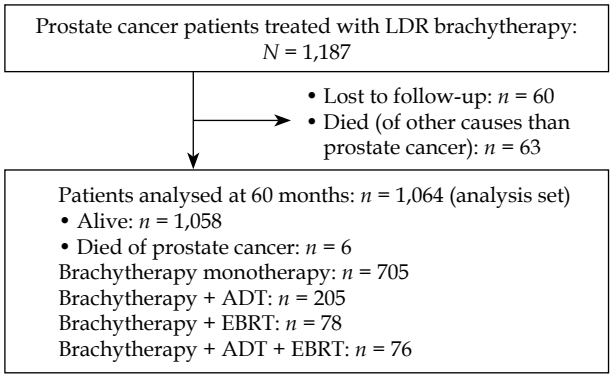
Purpose

Low-dose-rate (LDR) brachytherapy, controlled by transrectal ultrasound, is an established treatment option for non-metastatic prostate cancer of various stages. LDR brachytherapy has been known for almost 30 years [1,2,3,4,5,6], and is recognized as an appropriate treatment option in many relevant guidelines worldwide [7,8,9,10]. For early tumor stages (low-risk), LDR brachytherapy as monotherapy is the recommended therapeutic option. At favorable intermediate-risk of progression, LDR brachytherapy may be carried out as monotherapy, while at advanced intermediate-risk or at high-risk, it is typically combined with external beam radiation therapy (EBRT) and/or androgen deprivation therapy (ADT). Such multimodal therapy in locally advanced stages of prostate cancer has been recommended in several guidelines such as the European ESTRO/EAU/EORTC guidelines from 2000 [11], the European EAU-ESTRO-SIOG guidelines from 2017 [10] as well as those of the American Brachytherapy Society [7] and the National Comprehensive Cancer Network (NCCN) [9]. Efficacy of multimodal therapy at high-risk of progression has been evidenced in a recent randomized trial (ASCENDE RT) [12] and in a meta-analysis comparing different treatment options [2].

In spite of this evidence, long-term experience with LDR brachytherapy in non-metastatic prostate cancer has been sparse for a long time, in particular when applied in patients at higher risk of progression. In the current German S3 guidelines, multimodal treatment with LDR brachytherapy is not included as an established treatment option [8]. This calls for large-scale observational studies, because long-term evaluation of radiotherapeutic methods (such as LDR brachytherapy) is not easily amenable to randomized clinical trials [13]. A planned large-scale prospective randomized trial to compare four treatment options (including LDR brachytherapy) in low- and early intermediate-risk prostate cancer in Germany (PREFERE, clinicaltrials.gov: NCT01717677) had to be discontinued due to poor acceptance and recruitment.

The purpose of this retrospective observational cohort study was (a) to evaluate the long-term effectiveness of LDR brachytherapy as monotherapy, and in combination with EBRT and/or ADT, (b) to compare the outcome to Kattan nomogram predictions for 5-year outcome, and (c) to evaluate destruction of periprostatic tumor invasion by LDR brachytherapy. Control of periprostatic disease is known to be pivotal, at least after radical surgery. Pathologic specimens after radical prostatectomy show that already at intermediate-risk, the tumor penetrates and grows through the prostatic capsule in 30-50% of patients [14,15,16]. This tumor invasion is the most frequent reason for clinical relapse after radical surgery [17].



ADT – androgen deprivation therapy, EBRT – external beam radiation therapy, LDR – low dose rate

Fig. 1. Patient characteristics

Material and methods

Patient characteristics

This was a retrospective observational cohort study involving 1,187 patients, with non-metastatic prostate cancer (TXN0M0). The patients were treated with LDR brachytherapy between June 2002 and June 2010 at a specialized radiation oncology institution in Hamburg (Germany), in cooperation with numerous urological partner centers and hospitals.

Patient characteristics are displayed in Figure 1. In total, 1,187 patients with non-metastatic prostate cancer were accrued and treated with LDR brachytherapy. One hundred and twenty-three patients were lost to follow-up or died of other causes than prostate cancer in the course of 60 months. Six patients died due to systemic prostate cancer progression. Hence, 1,064 patients (1,058 patients alive plus 6 patients who died of prostate cancer) could be evaluated at 60 months after seed implantation (analysis set).

Patients were only included in the study if they received LDR brachytherapy with curative intent, i.e., within the first 180 days after initial histologic assessment of the tumor. Patients after active surveillance or watchful waiting were excluded. Each patient was treated with the best care option at the physician's discretion, according to guidelines [7,8,9,10,11]: either LDR brachytherapy alone or LDR brachytherapy in combination with EBRT, and/or ADT. In some cases, LDR brachytherapy was applied as monotherapy based on the patient's request, even though combination therapy was indicated.

LDR brachytherapy was performed with iodine-125 seeds as strands (S06 EZAG; 6711, Oncura) rather than loose seeds [18]. A transperineal procedure monitored by transrectal ultrasound was used, under continuous control of the z-axis by fluoroscopy until December 2005, exclusively ultrasound-based as real-time planning after December 2005. The D_{90} target dose was set to 160-180 Gy in patients with LDR brachytherapy as monotherapy, and 130 Gy in patients with multimodal therapy (reference dose: 145 Gy and 108 Gy, respectively). From 2007, the clinical target volume (CTV) was defined as the prostate contour surrounded by a clinical margin, according to the GEC/ESTRO/EAU recommendations from 2007 [19]. In multimodal therapy, EBRT was applied at doses between 45 and 50.4 Gy (1.8 Gy per day) to the prostate region, including the seminal vesicles, three months after implantation of the LDR brachytherapy seeds to avoid overdosage. Some patients received anti-hormonal therapy in neoadjuvant or adjuvant setting, with patient-individual medication and duration, here collectively reported as "ADT".

Duration of ADT was typically 2-6 months in the neoadjuvant, and 6-12 months in the adjuvant setting; no patient was treated with ADT for more than 2 years.

At baseline (prior to seed implantation), each patient was evaluated with respect to clinical and pathologic tumor stage, initial prostate-specific antigen (PSA) level, and Gleason score, and was classified into a prognostic risk group according to d'Amico [20], the risk definition commonly applied in Germany [8]. For further analysis, patients were also classified according to alternative definitions: Mt. Sinai [21], Seattle/Memorial Sloan-Kettering Cancer Center (MSKCC) [22], and NCCN criteria (clinical and biopsy-based/ histopathologic) [9].

For counselling of each patient, the preoperative Kattan nomogram [15] was employed to predict the likelihood that a patient remains free of PSA progression within 5 years. In addition, both the Kattan [15] and the Partin nomogram [16] were used to determine the patient-individual likelihood of organ-confined disease at the time of seed implantation.

The oncological remission status of each patient was determined 60 (± 3) months after starting LDR brachytherapy, to match the 5-year time frame of the Kattan nomogram predictions. Biochemical progression-free survival (bPFS) was determined using the Phoenix definition (PSA cut-off = nadir + 2 ng/ml, [23]). Patients who underwent any type of salvage therapy within the first 60 months were also considered relapsed. To allow for the comparison of patient outcomes and 5-year nomogram predictions, the analysis comprised only patients who were alive 60 months after seed implantation, and who were not lost to follow-up (analysis set).

Statistical analyses

As this study is observational, the statistical analysis is descriptive without corrections or modelling. Fisher's exact test (two-sided) was employed to assess whether the observed bPFS rates differed significantly from the mean probability of bPFS or organ-confined disease, as predicted with nomograms in the respective patients. Analysis was conducted with R, version 3.4.1, and was done in a hierarchical manner (for the entire cohort, then for each risk group, then for the treatment modality subgroups within each risk group). *P* values below 0.05 were considered statistically significant.

Results

In total, 93.3% of patients in the analysis set (993/1,064) remained free of biochemical progression within 5 years (Table 1). While the patients treated between 2002 and 2005 had a bPFS rate of 91.9%, the bPFS rate was clearly higher (94.4%) in the patients treated after 2005, demonstrating either improvements due to intraoperative online planning [24] or a learning curve of the institution.

A wide variety of patients was included in this study, ranging from low- to high-risk of progression with initial PSA levels between 0.155 and 85.5 ng/ml, tumor stages between T1a and T3a, and Gleason scores between 4 and 10. Patients were grouped according to risk factors in Table 1.

This analysis shows that bPFS rates did not markedly differ between clinical tumor stages (Table 1). In particular, bPFS rates were very similar for the stages cT2a, cT2b, and cT2c (93.9%, 89.4%, and 91.1%, respectively) even though the cT2c stage in the d'Amico classification defines a high-risk situation also when the other parameters are favorable [20]. Overall, similar results were obtained when patients were stratified according to their biopsy-based histopathological tumor stage (Table 1).

Table 1. Five-year biochemical progression-free survival (bPFS), listed according to risk factors

	Number of patients	5-year bPFS, *n* (%)
All patients (analysis set)	1,064	993 (93.3%)
Tumor stages (clinical)		
cT1a/b	6	6 (100%)
cT1c	580	548 (94.5%)
cT2a	198	186 (93.9%)
cT2b	132	118 (89.4%)
cT2c	146	133 (91.1%)
≥ cT3	2	0 (0%)
Tumor stages (biopsy-based, histopathologic)		
pT1a/b	10	10 (100%)
pT2a	422	404 (95.7%)
pT2b	287	267 (93.0%)
pT2c	344	310 (90.1%)
≥ cT3	1	0 (0%)
Initial PSA		
< 2 ng/ml	20	19 (95.0%)
≥ 2 and < 4 ng/ml	83	81 (97.6%)
≥ 4 and < 6 ng/ml	372	357 (96.0%)
≥ 6 and < 10 ng/ml	382	351 (92.0%)
≥ 10 and < 15 ng/ml	119	109 (91.6%)
≥ 15 and < 20 ng/ml	49	44 (89.8%)
≥ 20 ng/ml	39	30 (76.9%)
Gleason score		
≤ 5	119	112 (94.1%)
6	588	565 (96.1%)
7	308	274 (89.0%)
7a (3 + 4)	239	220 (92.1%)
7b (4 + 3)	69	54 (78.3%)
≥ 8	49	40 (81.6%)

bPFS – biochemical progression-free survival, PSA – prostate-specific antigen

When outcomes were analyzed by initial PSA levels, bPFS was around or above 90% in patient subgroups with initial PSA below 20 ng/ml, but below 80% when initial PSA was ≥ 20 ng/ml (Table 1). Additionally, patients were grouped according to their Gleason score before brachytherapy (Table 1). While Gleason scores up to 7a (3 + 4) were associated with 5-year bPFS rates above 90%, bPFS was 78.3% in the patients with Gleason score 7b (4 + 3). This lower rate of bPFS was predominantly resulting from tumor metastases in the spine and the pelvic bones, not local recurrence. In patients with Gleason scores ≥ 8, the bPFS rate was higher (83.3%), and all four patients with Gleason score 10 remained free of progression. None of the patients with a Gleason score of ≤ 6 have died of prostate cancer within 5 years, whereas systemic progress with death was seen in 6 patients with Gleason scores of 7a or higher.

When patients were classified in prognostic risk groups according to the d'Amico criteria [20], differences were evident with bPFS rates of 97.4%, 90.5%, and 87.4% for the patients at low-, intermediate-, and high-risk, respectively. Grouping the patients according to alternative prognostic models yielded very similar values (Table 2). This indicates that all the classification models are equally applicable to the patients in this study.

Five-year biochemical progression-free survival and comparison to Kattan nomogram predictions

To systematically evaluate the observed 5-year bPFS data, the outcome was compared to the probability of 5-year bPFS, as determined with established preoperative Kattan nomogram (Table 3). This nomogram represents an individualized assessment of a patient's risk of biochemical progression [15]. For the patients in the analysis set, the average 5-year bPFS as predicted with the Kattan nomogram was 85% (range, 23-99%). Statistical analysis revealed that the observed outcome was significantly better than calculated from the Kattan nomogram ($p < 0.001$).

In 910 patients (85.5%), LDR brachytherapy was applied without additional EBRT, either as monotherapy or in combination with ADT. Of these patients, 94.6% (861/910) were free of biochemical progression after 5 years, a rate which was significantly higher than predicted ($p < 0.001$, average 5-year bPFS probability according to Kattan nomogram: 85%). One hundred fifty-four patients (14.5%) received LDR brachytherapy plus EBRT and had a 5-year bPFS of 85.7% (132/154 patients), which also exceeded the average Kattan nomogram-based probability of 5-year bPFS (79%), although not significantly ($p = 0.09$).

Next, the outcomes were compared to the respective Kattan nomogram predictions for each prognostic risk group (Table 3). Since bPFS rates were comparable between risk group classification models (as evidenced in Table 2), one of them, the biopsy-based histopathologic NCCN classification, was chosen for further analysis because it is independent of digital rectal examination (thus less error-prone), and because the NCCN classification distinguishes two separate levels of intermediate-risk (favorable and unfavorable intermediate-risk), providing higher selectivity. Five-year bPFS was 96.6%, 95.3%, 87.9%, and 82.4% at low-, favorable intermediate-, unfavorable intermediate-, and high-risk, respectively. For patients at low- and intermediate-risk, the outcomes were significantly better than predicted ($p < 0.001$), while for the patients at high-risk, the superiority of the outcomes (5-year bPFS in 82.4% of patients) compared to the Kattan nomogram prediction (average 5-year bPFS, 70% of patients) was just below the level of statistical significance ($p = 0.091$).

Five-year biochemical progression-free survival rates comparison to probability of organ-confined disease

Further, the observed 5-year bPFS outcomes were related to nomogram predictions that disease is confined within the prostate capsule. For the total patient cohort, the observed 5-year bPFS of 93.3% was significantly higher ($p < 0.001$) than the average likelihood of organ-confined disease as determined with the Kattan nomogram (50%) or the Partin nomogram (65%).

The observed bPFS rates were significantly higher than the predicted likelihood for organ-confined disease for nearly all subgroups (risk groups according to the NCCN classification, treatment modality), except for high-risk patients without EBRT. This superiority was more pronounced in the comparison of the observed outcomes with the Kattan nomogram predictions, which always yielded lower values than the Partin nomogram. For the total cohort and for some subgroups, the difference between the two nomogram predictions themselves was also statistically significant (Table 4).

Table 2. Five-year biochemical progression-free survival (bPFS) in patients classified in the indicated prognostic risk groups. Values are numbers of patients free of progression within 5 years/ number of patients in the respective risk group, percentage in brackets

Prognostic risk group	Risk group classification				
	d'Amico	Mt. Sinai	Seattle/MSKCC	NCCN (clinical)	NCCN (pathologic)
Low-risk	483/496 (97.4%)	483/496 (97.4%)	538/558 (96.4%)	483/496 (97.4%)	309/320 (96.6%)
Intermediate-risk	335/370 (90.5%)	257/285 (90.2%)	312/343 (91.0%)	449/491 (91.4%)	608/653 (93.1%)
Favorable intermediate-risk	n.a.	n.a.	n.a.	324/350 (92.6%)	448/471 (95.1%)
Unfavorable intermediate-risk	n.a.	n.a.	n.a.	125/141 (88.7%)	160/182 (87.9%)
High-risk	173/198 (87.4%)	251/283 (88.7%)	141/163 (86.5%)	59/77 (76.6%)	75/91 (82.4%)

MSKCC – Memorial Sloan-Kettering Cancer Center, n.a. – not applicable, NCCN – National Comprehensive Cancer Network

Table 3. Five-year biochemical progression-free survival (bPFS) in the indicated NCCN risk groups and the indicated treatment modalities; comparison to 5-year bPFS predictions (Kattan nomogram). Statistical significance of the difference between observed bPFS rates and Kattan nomogram prediction: $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***); $p > 0.05$ is considered non-significant (n.s.)

	Number of patients	5-year bPFS, *n* (%)	Kattan nomogram prediction 5-year bPFS, mean (range)	*p* value, significance
All patients (analysis set)	1,064	993 (93.3%)	85% (23-99%)	< 0.001***
Brachytherapy without EBRT	910	861 (94.6%)	85% (23-99%)	< 0.001***
Brachytherapy + EBRT	154	132 (85.7%)	79% (24-98%)	0.093 (n.s.)
Low-risk	320	309 (96.6%)	89% (81-99%)	< 0.001***
Mono	267	256 (95.9%)	90% (81-99%)	0.011*
+ ADT	49	49 (100%)	88% (82-99%)	0.027*
+ EBRT	4	4 (100%)	93% (90-95%)	0.999 (n.s.)
+ EBRT + ADT	0	–	–	–
Intermediate-risk (all = favorable + unfavorable)	653	609 (93.3%)	84% (53-99%)	< 0.001***
Mono	423	398 (94.1%)	85% (60-98%)	< 0.001***
+ ADT	149	140 (94.0%)	81% (54-99%)	0.001**
+ EBRT	53	49 (92.5%)	86% (69-96%)	0.319 (n.s.)
+ EBRT + ADT	28	22 (78.6%)	87% (78-98%)	0.729 (n.s.)
Favorable intermediate-risk	471	449 (95.3%)	84% (54-98%)	< 0.001***
Mono	326	311 (95.4%)	85% (60-98%)	< 0.001***
+ ADT	108	105 (97.2%)	81% (57-91%)	0.001***
+ EBRT	26	25 (96.2%)	87% (69-94%)	0.241 (n.s.)
+ EBRT + ADT	11	8 (72.7%)	86% (81-93%)	0.999 (n.s.)
Unfavorable intermediate-risk	182	160 (87.9%)	85% (53-99%)	0.12 (n.s.)
Mono	97	87 (89.7%)	85% (53-97%)	0.359 (n.s.)
+ ADT	41	35 (85.4%)	81% (65-99%)	0.770 (n.s.)
+ EBRT	27	24 (88.9%)	87% (71-98%)	0.999 (n.s.)
+ EBRT + ADT	17	14 (82.4%)	88% (78-98%)	0.999 (n.s.)
High-risk	91	75 (82.4%)	70% (23-99%)	0.091 (n.s.)
Mono	15	13 (86.7%)	78% (23-99%)	0.999 (n.s.)
+ ADT	7	5 (71.4%)	71% (33-88%)	0.999 (n.s.)
+ EBRT	21	19 (90.5%)	74% (42-90%)	0.211 (n.s.)
+ EBRT + ADT	48	38 (79.2%)	64% (24-94%)	0.173 (n.s.)

ADT – androgen deprivation therapy, bPFS – biochemical progression-free survival, EBRT – external beam radiation therapy, n.s. – non-significant

Discussion

This study demonstrates high long-term effectiveness of LDR brachytherapy as monotherapy and in the multimodal setting, under real-world conditions, in a large patient cohort (1,064 patients) ranging from low- to high-risk of progression, and thus representing large heterogeneity of non-metastatic prostate cancer patients in the clinical practice.

The data presented here are essentially in line with those of similar studies conducted elsewhere. A study at Mount Sinai Medical Center (USA) concluded that LDR brachytherapy is an effective treatment option for patients with non-metastatic prostate cancer of all risk

Table 4. Five-year biochemical progression-free survival (bPFS) in the indicated NCCN risk groups and the indicated treatment modalities; comparison to Kattan and Partin nomogram predictions for organ-confined disease. Statistical significance of the difference between observed bPFS rates and Kattan nomogram prediction: $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***); $p > 0.05$ is considered non-significant (n.s.). The dagger (†) indicates that Kattan and Partin nomogram predictions were statistically significantly different ($p < 0.05$)

	Number of patients	5-year bPFS, *n* (%)	Organ-confined disease (Kattan), mean (range)	*p* value observed vs. predicted	Organ-confined disease (Partin), mean (range)	*p* value observed vs. predicted
All patients (analysis set)	1,064	993 (93.3%)	50% (2-83%)	< 0.001***	65% (6-93%)†	< 0.001***
Brachytherapy without EBRT	910	861 (94.6%)	54% (6-83%)	< 0.001***	69% (6-93%)†	< 0.001***
Brachytherapy + EBRT	154	132 (85.7%)	26% (2-71%)	< 0.001***	37% (6-93%)	< 0.001***
Low-risk	320	309 (96.6%)	64% (38-83%)	< 0.001***	79% (46-93%)†	< 0.001***
Mono	267	256 (95.9%)	64% (38-83%)	< 0.001***	79% (46-93%)†	< 0.001***
+ ADT	49	49 (100%)	64% (38-83%)	< 0.001***	79% (58-93%)	0.001*
+ EBRT	4	4 (100%)	68% (67-71%)	0.026*	82% (80-84%)	0.999 (n.s.)
+ EBRT + ADT	0	–	–-	–	–	–
Intermediate-risk (all = favorable + unfavorable)	653	609 (93.3%)	48% (6-83%)	< 0.001***	61% (12-93%)†	< 0.001***
Mono	423	398 (94.1%)	50% (13-83%)	< 0.001***	65% (12-93%)†	< 0.001***
+ ADT	149	140 (94.0%)	50% (6-81%)	< 0.001***	64% (17-99%)†	< 0.001***
+ EBRT	53	49 (94.2%)	35% (13-67%)	< 0.001***	44% (12-93%)	< 0.001***
+ EBRT + ADT	28	22 (78.6%)	32% (11-67%)	0.001**	39% (12-84%)	0.006**
Favorable intermediate-risk	471	449 (95.3%)	49% (6-83%)	< 0.001***	64% (12-93%)†	< 0.001***
Mono	326	311 (95.4%)	51% (13-83%)	< 0.001***	67% (12-93%)†	< 0.001***
+ ADT	108	105 (97.2%)	53% (6-81%)	< 0.001***	67% (17-93%)	< 0.001***
+ EBRT	26	25 (96.2%)	33% (13-67%)	< 0.001***	43% (12-84%)	< 0.001***
+ EBRT + ADT	11	8 (72.7%)	34% (15-55%)	0.198 (n.s.)	41% (12-69%)	0.387 (n.s.)
Unfavorable intermediate-risk	182	160 (87.9%)	43% (11-83%)	< 0.001***	55% (12-93%)†	< 0.001***
Mono	97	87 (89.7%)	49% (22-83%)	< 0.001***	65% (30-90%)†	< 0.001***
+ ADT	41	35 (85.4%)	42% (15-78%)	< 0.001***	55% (17-93%)	0.007**
+ EBRT	27	24 (88.9%)	36% (13-67%)	< 0.001***	45% (12-93%)	0.001**
+ EBRT + ADT	17	14 (82.4%)	30% (11-67%)	0.005**	37% (12-84%)	0.013*
High-risk	91	75 (82.4%)	23% (2-78%)	< 0.001***	37% (6-93%)	< 0.001***
Mono	15	13 (86.7%)	45% (8-78%)	0.050 (n.s.)	60% (6-93%)	0.215 (n.s.)
+ ADT	7	5 (71.4%)	39% (6-67%)	0.592 (n.s.)	55% (17-80%)	0.999 (n.s.)
+ EBRT	21	19 (90.5%)	19% (2-37%	< 0.001***	37% (11-69%)	0.001***
+ EBRT + ADT	48	38 (79.2%)	16% (3-71%)	< 0.001***	28% (6-78%)	< 0.001***

ADT – androgen deprivation therapy, bPFS – biochemical progression-free survival, EBRT – external beam radiation therapy, n.s. – non-significant

groups, including high-risk patients [25]. Similarly, another large-scale study in the USA determined excellent long-term outcomes with modern LDR brachytherapy in patients at low-, intermediate-, and high-risk [26]. For LDR brachytherapy as monotherapy, long-term benefits comparable to those described here have been reported across all risk groups in various regions of the world including UK [27], USA [5,28], France [29], China [30], and Japan [31]. Similarly to the results of this study, superior bPFS rates of brachytherapy compared to those predicted with

Kattan nomograms (pre and post-operative) have also been reported for a patient cohort in Israel, which was however smaller and mainly consisted of low-risk patients [32]. Overall, it can be concluded that international study results are transferrable to the standard of care in Germany.

The superiority of the observed 5-year bPFS rates compared to Kattan nomogram predictions was most significant in the monotherapy patients and those at lower risk. It is however remarkable that local control was also very good in advanced risk constellations, where relapse was typically due to systemic tumor spread rather than local progression. This may also argue in favor of PSA screening for early detection and early treatment of localized prostate cancer. We observed no death in patients with Gleason scores 5 or 6. At this stage, LDR brachytherapy as monotherapy is typically sufficient [7,8,9,10,33], which is also evidenced in this study.

The observed 5-year bPFS rates decreased gradually with increasing risk according to each of prognostic risk group definitions used. This indicates that the classification of patients into the risk groups was appropriate and accurate. Further, the usefulness of the two-separate intermediate-risk groups in the NCCN classification is highlighted by the observed 5-year bPFS rates, which differed considerably between the patients at favorable and unfavorable intermediate-risk (95.1% vs. 87.9%).

Individual risk factors (tumor stages, PSA levels, Gleason scores) however correlated less well with the observed outcomes, and thus appear to be less valuable than prognostic risk groups in the context of brachytherapy, at least in the timeframe of 5 years [34]. In particular, the tumor stage cT2c (tumor covering both lobes) was not associated with lower 5-year bPFS than cT2a or cT2b (tumor confined to ≤ 50 or > 50% of one lobe, respectively). While the stage cT2c defines a high-risk in some risk group definitions in the context of radical prostatectomy [20], this elevated risk was not confirmed in this study for patients with cT2c disease treated with brachytherapy.

Both intra- and periprostatic disease appear to be controlled well with brachytherapy. This is evidenced in this study by significant superiority of the observed bPFS rates, compared to Kattan and Partin nomogram predictions for organ-confined disease. This significant advantage was seen across all risk strata and in most treatment modalities, with the exception of high-risk patients without EBRT.

To the authors' knowledge, this is the first study, in which real-world data were assessed with respect to both the Kattan and the Partin nomogram and not just either of them. Interestingly, the Kattan nomogram values for the probability of organ-confined disease were consistently 10-15% below the respective Partin nomogram values, a difference that was statistically significant in the total cohort as well as in several subgroups. This possibly reflects differences in the characteristics of the patients used for establishment of the nomograms, and also differences in the extent of radical prostatectomy or histopathology performed at MSKCC in New York (Kattan nomogram) vs. Johns Hopkins University in Baltimore (Partin nomogram).

The nomogram predictions are derived from radical prostatectomy and describe the probability of organ-confined disease at the time of surgery. Hence, the finding that brachytherapy performed significantly better than in nomogram predictions can be interpreted as a potential advantage of brachytherapy over any kind of nerve-sparing radical prostatectomy [17]. This is consistent with a recent review that suggested better disease control with multimodal radiation therapy than surgery in high-risk patients, which implies that incomplete tumor resection after radical surgery may by itself be a cause for metastases [35]. Also, already a decade ago, small-scale randomized prospective trials showed that radical prostatectomy and LDR brachytherapy are similar in terms of long-term biochemical recurrence-free survival in low-risk prostate cancer [36,37]. Along similar lines, long-term follow-up data of the Surveillance, Epidemiology, and End Results (SEER) database including more than 240,000 patients with non-metastatic prostate cancer revealed that even in patients at highest risk, 8-year survival rates were comparable between radical prostatectomy (partially with adjuvant EBRT, 85.5%) and brachytherapy (85.1%), and much higher than with EBRT (78.8%) or no local treatment (50.2%) [38].

Especially in high-risk non-metastatic prostate cancer, achieving local control is paramount for long-term disease-free survival. In retrospective studies, there is evidence for a considerable long-term benefit when brachytherapy is combined with EBRT (with or without ADT) in men with high-risk prostate cancer, with benefits of multimodal brachytherapy compared to surgery alone or EBRT alone [2,35,39,40,41,42,43]. While several clinical trials have determined a bPFS benefit of EBRT + high-dose-rate brachytherapy over EBRT alone in patients at intermediate- and high-risk [44,45,46], only one large-scale prospective randomized trial has been conducted investigating LDR brachytherapy + EBRT vs. EBRT alone in patients with non-metastatic prostate cancer at elevated risk ("ASCENDE RT", [12]). ASCENDE RT showed that patients at intermediate- and high-risk were twice as likely to remain free of biochemical recurrence when EBRT was combined with LDR brachytherapy, performed with iodine-125 seeds similar to those employed in this study. The results presented in this study basically confirm the high effectiveness of brachytherapy in the context of clinical practice, also in patients at elevated risk.

It has to be noted that bPFS rates cannot be compared directly between the treatment modalities, as there is an inherent imbalance between patients in this respect: multimodal therapy is more frequently applied in patients with less favorable prognosis. To account for such inherent differences, bPFS rates were compared to the respective patient-individualized nomogram predictions, which served as reference. The results show a trend towards more pronounced superiority of brachytherapy when performed as monotherapy. Consistent with this, a recent systematic review stated that patients treated with brachytherapy have excellent long-term disease outcomes and do not further benefit from addition of ADT to brachytherapy at low- or favorable intermediate-risk [47], while patients at higher

risk appear to benefit from ADT in this setting [48]. This additional advantage of ADT in patients at higher risk was not seen in this study, possibly in part owing to patient-individual reasons, differences in disease severity, or low number of patients in the respective subgroups.

Since this study was an observational study, it has limitations like the lack of randomization of a control group. Further, PSA values may have fluctuated due to the antihormonal therapy in the first months or 2 years. Yet, such effects are negligible in the course of 60 months: influences of ADT (less than 2 years in each case) can be excluded, and "PSA bounces" after LDR brachytherapy are typically observed only within 6-24 months after seed insertion [49,50]; later rises in PSA indicate tumor progression rather than therapy-related alterations. Another limitation of this study is that patient-individual treatment choices might have confounded results. This potential source of bias was accounted for by using patient-individualized nomogram predictions as reference.

Conclusions

This study clearly demonstrates the benefit of LDR brachytherapy in terms of 5-year bPFS in one of the largest patient cohorts investigated so far in the context of clinical practice. The high effectiveness of LDR brachytherapy was observed across all risk groups. The outcomes of LDR brachytherapy were significantly better than expected on the basis of nomogram predictions for "organ-confined disease", suggesting that LDR brachytherapy with stranded seeds effectively controls both intra- and periprostatic disease.

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Disclosure

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