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ORIGINAL ARTICLE

Prediction of survival outcomes following postoperative radiotherapy after radical prostatectomy for prostate cancer

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ABSTRACT

Background: To evaluate predictive factors for survival outcomes after post-prostatectomy radiotherapy.

Material and methods: In the years 2003–2008, 324 patients have received postoperative radiotherapy a median time of 14 months after radical prostatectomy. All patients have been treated up to 66.0–66.6 Gy in 1.8–2.0 Gy fractions. Predictive factors were analyzed at two stages, using a multivariable Cox regression analysis: (1) based on factors known before radiotherapy and (2) based on prostate-specific antigen response after radiotherapy.

Results: Median follow-up after radiotherapy was 121 months. Prostate-specific antigen before radiotherapy, pN1 and Gleason score remained predictive factors for disease-free (hazard ratio, HR of 6.0, 2.3 and 2.5) and overall survival (HR of 2.8, 2.0 and 1.6) in multivariable analysis. Prostate-specific antigen levels increased despite radiotherapy in 27% of patients in the first six months. Failed response following salvage radiotherapy and prostate-specific antigen doubling time at the time of biochemical recurrence were predictive factors for disease-free (HR of 2.8 and 7.3; $p < .01$) and overall survival (HR of 2.2 and 2.6; $p < .01$).

Conclusion: To reach the best survival outcomes following prostatectomy, salvage radiotherapy should be initiated early with low prostate-specific antigen levels, especially in patients with higher Gleason scores. Patients not responding to radiotherapy and/or patients with a short prostate-specific antigen doubling time after radiotherapy are candidates for early additional treatments.

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Introduction

In Europe, prostate carcinoma is the most common cancer in men [1]. Various therapy options exist such as radical prostatectomy (RP), definitive radiation therapy, brachytherapy, active surveillance and watchful waiting [2]. Within five years following RP approximately 15–28% of men might suffer from biochemical recurrence (BR) of prostate cancer (PCa) [3,4]. Prostatic fossa radiotherapy (RT) following RP is the treatment of choice for BR administered as salvage radiotherapy (SRT) [5,6]. The likelihood of recurrence is plainly elevated by the presence of pathological risk factors such as positive surgical margins (SM+), seminal vesicle invasion (SVI) and extraprostatic extension (EPE) [7–10]. It is not known if these factors are determining survival outcomes.

Three randomized controlled trials (RCT) showed adjuvant radiotherapy (ART) improves significantly biochemical recurrence-free survival (BRFS) in comparison to RP alone in case of pathological risk factors (R1 resection, stage T3a or T3b) [11–13]. Nevertheless, physicians frequently choose a prostate-specific antigen (PSA) follow-up alone in spite of these risk factors, as SRT might have the same survival outcomes and spare possible RT-related toxicity [14,15].

Several studies have evaluated predictive factors for BRFS after postoperative RT for PCa [5,16]. Five-year BRFS after SRT was proven to decrease with higher PSA level at the time of SRT [5]. SRT is best to be administered at low PSA values [6,17,18] as five-year BRFS was found to decrease by 18.3% per 1 ng/ml PSA level increase [5]. Further factors identified include pathologic tumor stage, Gleason score (GS) and surgical margin status [16].

Follow-up periods of around five years were too short to analyze survival outcomes. The primary aim of this study was to evaluate long-term disease-free and overall survival (OS) outcomes in a patient population treated with the same technique and dose in a single centre.

Material and methods

Patients

In the years 2003–2008, 324 patients have received a postoperative RT after RP. Baseline patient characteristics are

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Table 1. Baseline patient characteristics ($n = 324$).

Median patient age (IQR) at RP (years)	64 (61–68)
Median patient age (IQR) at RT (years)	67 (63–71)
Median time (IQR) between RP and RT (months)	14 (6–42)
Median PSA (IQR) before RP (ng/ml)	10 (6–18)
Median PSA (IQR) nadir after RP (ng/ml)	0.1 (0–0.3)
Median PSA (IQR) before RT (ng/ml)	0.5 (0.1–1.5)
pT3–T4 at RP (%)	62
Gleason score 8–10 at RP (%)	30
pN1 at RP (%)	7
ADT combined with RT (%)	33
CCI >4	39%
Coronary heart disease	10%
Diabetes	6%

IQR: interquartile range; RP: radical prostatectomy; RT: radiotherapy; PSA: prostate-specific antigen; ADT: antiandrogen therapy; CCI: Charlson Comorbidity Index.

presented in Table 1. Antiandrogen treatment has been frequently applied in case of risk factors postoperatively (median period of six months). In patients with PSA <0.1 ng/ml, 0–<0.5 ng/ml, 0.5–<1.5 ng/ml and >1.5 ng/ml, ADT has been applied in 61%, 30%, 20% and 24%, respectively. The Charlson Comorbidity Index (CCI) [19] was calculated as a scale that considers both patient age (starting at 50 years of age, each decade is counted as an extra point) and comorbidities.

Treatment

All patients have been treated with a three-dimensional conformal technique with single fractions of 1.8–2.0 Gy up to a total dose of 66.0–66.6 Gy. The planning target volume was required to be enclosed by the 90% isodose relating to the ICRU (International Commission on Radiation Units and Measurements) reference point [20] with a margin of 1.5 cm in the anterior/lateral and 1 cm in the craniocaudal and dorsal directions to the clinical target volume (i.e., prostatic fossa). Three-dimensional treatment plans with a four-field box technique and 15 MeV photons were applied. Pelvic lymph nodes were treated only in pN1 patients up to a total dose of 50.4 Gy.

Informed consent for the treatment carried out, elicitation, anonymization and evaluation of data was obtained from all patients. This study has been implemented in accordance with the ethical principles determined in the Declaration of Helsinki.

Follow-up

Regular follow-up evaluation was performed by the referring urologist, usually at least every three months in the first two years, every six months up to five years and then at least once a year. Follow-up data (laboratory, clinical results and medication) were collected in our department using patient and urologist questionnaires, additionally phone calls and also personal visits at the urologist's or general practitioner's practice.

BR after RT was defined as a PSA level rise exceeding 0.4 ng/ml or the initiation of ADT after RT. The level of 0.4 ng/ml for post-SRT progression has also been used in other studies, for example, Ghadjar et al. [21,22]. A PSA rise >0,4 ng/ml followed by a spontaneous decrease to pre-bounce level or lower was not rated as BR but as bounce phenomenon. In case of metastases or a PSA level of >10 ng/ml at the time of death, PCa was assumed to be the cause of death.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 25.0 software. Prostate-specific antigen doubling time (PSADT) was calculated by using the last PSA value before a PSA rise and the following PSA value according to the following formula: PSADT = [LN(2) × (date 1 – date 2)]/[LN (PSA2) – LN (PSA1)] [23]. For the PSADT before the beginning of RT, the last two values were usually taken into account, with the initial PSA required to be at least 0.1 ng/ml. PSADT before RT was only available for 176 patients.

The Kaplan–Meier methodology was used to assess the BR, local failure, metastases, disease-specific (death related to PCa) and OS rates in the overall population, as well as according to specific factors. The log-rank test was used to compare the free survival rates by these factors. Uni- and multivariable Cox proportional hazards regression analyses to assess factors potentially associated with survival outcomes were computed. Only significant factors in univariable analysis were considered in the forward stepwise multivariable analysis.

The following variables known before the beginning of RT were taken into account: GS (≤7 or G1–G2 vs. 8–10 or G3; grading only from older specimens without reported GS), pathological T stage (T2 vs. T3–T4), pathologically LN+ (N0 vs. N1); resection margins (R0 vs. R1), time between prostatectomy and RT (< vs. ≥median; 14 months), postoperative PSA nadir (< vs. ≥median; 0.1 ng/ml), PSA before RT (< vs. ≥median; 0.5 ng/ml), PSADT before RT (< vs. ≥median; 6 months) and combination of ADT with RT. As PSADT could be calculated in only 54% of patients (see above), it has not been considered in the multivariable analysis. Additionally to disease-related factors, CCI [19] was taken into account for OS analysis.

In a second analysis, PSA-associated factors based on response after RT were tested for the association with survival outcomes: failed PSA response (PSA not dropping within the first six months after RT) and PSADT in case of a recurrence. All p-values reported are two-sided; $p < .05$ is considered significant.

Results

Median follow-up after the end of RT was 121 months. 10-year BR-, local recurrence-, metastasis-free, disease-specific survival (DSS) and OS rates in this patient population were 41%, 96%, 79%, 84% and 69%. Within the follow-up period BR, local recurrence, metastases, death related to PCa and death overall resulted in 144, 12, 73, 47 and 100 patients, respectively. In univariable Cox regression analysis (Table 2), several factors proved to be significant predictors for a BR

Table 2. Univariable Cox regression analysis.

Factor	Hazard ratio	95% confidence interval	*p*-value
Biochemical failure			
Gleason score 8–10 vs. ≤7	3.2	1.8–5.7	<.01
T stage 3–4 vs. 2	2.5	1.2–5.1	.02
R0 vs. R1	1.7	1.2–2.3	<.01
pN1 vs. pN0	2.3	1.4–3.8	<.01
Time between RP and RT ≥14 vs. <14 months	3.2	1.8–5.7	<.01
Postop. PSA nadir ≥0.1 vs. <0.1 ng/ml	2.2	1.1–4.4	.03
PSADT before RT <6 vs. >6 months	2.3	1.1–5.1	.04
PSA before RT ≥0.5 vs. ≤0.5 ng/ml	5.2	2.4–11.1	<.01
Antiandrogen treatment no vs. yes	1.5	1.1–2.1	.02
Local failure			
T stage 3–4 vs. 2	7.0	0.9–54	.06
Metastases			
Gleason score 8–10 vs. ≤7	2.5	1.5–4.1	<.01
T stage 3–4 vs. 2	2.4	1.3–4.5	<.01
R0 vs. R1	1.9	1.1–3.3	<.01
pN1 vs. pN0	2.9	1.4–5.9	<.01
PSADT before RT <6 vs. >6 months	2.6	1.3–5.1	<.01
PSA before RT ≥0.5 vs. ≤0.5 ng/ml	3.7	2.1–6.7	<.01
Disease-specific survival			
Gleason score 8–10 vs. ≤7	3.2	1.8–5.7	<.01
T stage 3–4 vs. 2	2.5	1.2–5.1	.02
R0 vs. R1	1.7	1.2–2.3	<.01
pN1 vs. pN0	3.3	1.5–7.0	<.01
Postop. PSA nadir ≥0.1 vs. <0.1 ng/ml	2.2	1.1–4.4	.03
PSADT before RT <6 vs. >6 months	2.3	1.1–5.1	.04
PSA before RT ≥0.5 vs. ≤0.5 ng/ml	5.2	2.4–11.1	<.01
Overall survival			
Gleason score 8–10 vs. ≤7	2.0	1.1–2.8	<.01
T stage 3–4 vs. 2	1.8	1.1–2.8	.02
R0 vs. R1	1.7	1.1–2.6	.02
pN1 vs. pN0	2.4	1.3–4.3	<.01
Time between RP and RT ≥14 vs. <14 months	1.5	1.1–2.3	.03
PSA before RT ≥0.5 vs. ≤0.5 ng/ml	2.6	1.7–4.0	<.01
CCI >4 vs. ≤4	2.9	1.9–4.3	<.01

RP: radical prostatectomy; PSA: prostate-specific antigen; PSADT: prostate-specific antigen doubling time; RT: radiotherapy; CCI: Charlson Comorbidity Index.

after post-prostatectomy RT: higher GS, higher pathological T stage, pathologically LN+, negative surgical margins (SM−), longer time between prostatectomy and RT, higher postoperative PSA nadir, higher PSA before RT, lower PSADT before RT and the absence of an ADT.

The only significant factor for a local recurrence was the pathological T stage based on the RP specimen, with 10-year local recurrence-free survival of 99% in T2 vs. 94% in T3–T4 tumors ($p = .03$ in log-rang test). Factors significantly predicting metastases, DSS and OS in univariable analysis were a higher GS, higher pathological T stage, pathologically LN+, SM− and a higher PSA before RT. The highest hazard ratios consistently resulted for the GS, pathologically LN + and PSA-level before RT. These three factors remained significant for predicting survival outcomes in multivariable analysis (Table 3).

Including CCI in the multivariable analysis, CCI, pathologically LN+, PSA-level before RT and T stage were found to have a significant impact for OS, as higher GS was diagnosed more often in patients with higher CCI (GS of 8–10 in 37% patients with CCI > 4 vs. 28% with CCI ≤ 4).

Ten-year OS was 88% with a PSA <0.1 ng/ml and GS ≤7, but only 33% with a PSA >1.5 ng/ml and GS >7. Kaplan–Meier OS curves after stratification according to pre-RT PSA (quartiles in this patient population) are presented in Figure 1, with 10-year OS rates of 85%, 77%, 65% and 50% in patients with a PSA <0.1 ng/ml, 0.1–<0.5 ng/ml, 0.5–<1.5 ng/ml and ≥1.5 ng/ml, respectively ($p < .01$).

PSA levels increased following RT in 27% of patients in the first six months. A failed response and PSADT at the time of BR were both found to be predictive factors for metastases, DSS and OS in multivariable analysis (Table 4). 10-year OS of patients without PSA response was 57% vs. 74% in patients who responded to RT with dropping PSA levels ($p < .01$). Kaplan–Meier OS curves after stratification according to PSADT (quartiles in this patient population) are presented in Figure 2, with 10-year OS rates of 81%, 73%, 56% and 39% in patients with a PSADT ≥12 months, ≥6–12 months, ≥3–6 months and <3 months, respectively ($p < .01$).

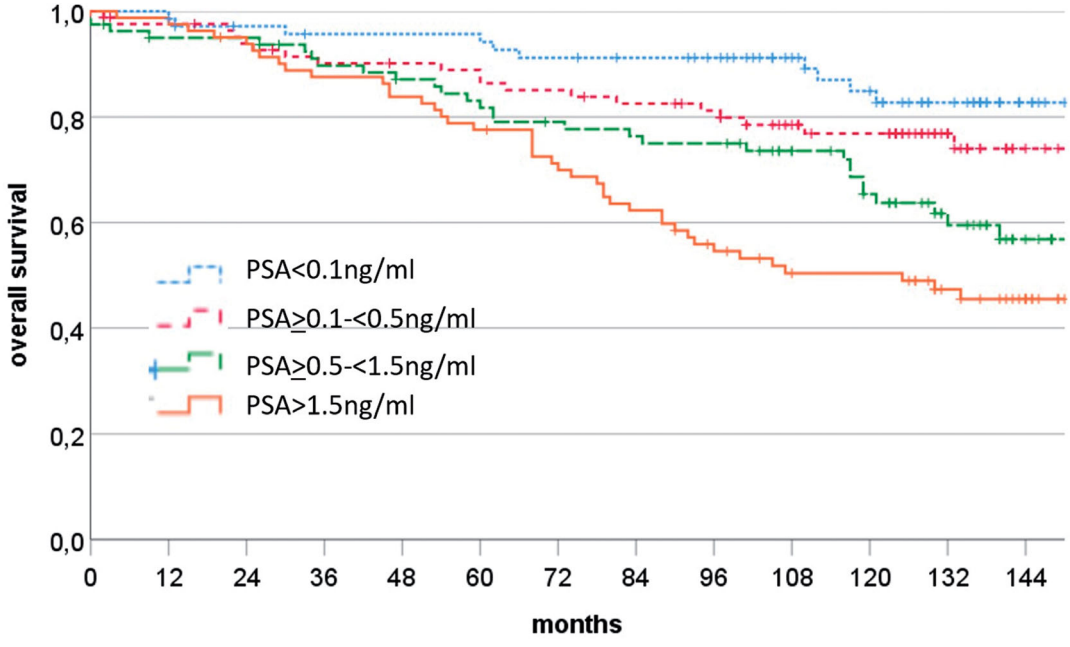
Discussion

We have conducted a retrospective study with a median follow-up of 10 years and a focus on OS. Such long-term surveys are rare, but only those enable an authentic assessment of predictive factors for OS outcomes. Only OS does not rely on specific definitions, specific diagnostic methods or interpretations. At the time of treatment for our study, 3D conformal RT was the standard for PCA radiation, nowadays IMRT is state of the art [2].

Table 3. Multivariable Cox regression analysis.

Factor	Hazard ratio	95% confidence interval	*p*-value
Biochemical failure			
Gleason score 8–10 vs. ≤7	1.5	1.1–2.1	.02
T stage 3–4 vs. 2	1.5	1.1–2.1	.04
R0 vs. R1	1.6	1.1–2.4	<.01
PSA before RT ≥0.5 vs. ≤0.5 ng/ml	3.5	2.4–5.1	<.01
Metastases			
Gleason score 8–10 vs. ≤7	1.9	1.1–3.2	.01
T stage 3–4 vs. 2	2.0	1.1–3.8	.03
PSA before RT <0.5 vs. ≥0.5 ng/ml	3.7	2.1–6.7	<.01
Disease-specific survival			
Gleason score 8–10 vs. ≤7	2.5	1.3–4.6	<.01
pN1 vs. pN0	2.3	1.0–5.3	.05
PSA before RT ≥0.5 vs. ≤0.5 ng/ml	6.0	2.6–13	<.01
Overall survival (without CCI)			
Gleason score 8–10 vs. ≤7	1.6	1.1–2.5	.04
pN1 vs. pN0	2.0	1.1–2.5	.02
PSA before RT ≥0.5 vs. ≤0.5 ng/ml	2.8	1.8–4.4	<.01
Overall survival (with CCI)			
T stage 3–4 vs. 2	1.6	1.0–2.6	.05
pN1 vs. pN0	2.3	1.2–4.3	<.01
PSA before RT ≥0.5 vs. ≤0.5 ng/ml	2.7	1.7–4.3	<.01
CCI >4 vs. ≤4	2.6	1.7–3.9	<.01

PSA: prostate-specific antigen; RT: radiotherapy; CCI: Charlson Comorbidity Index.



patients at risk

<0.1ng/ml	71	70	66	64	64	63	61	59	56	45	39	29	13
≥0.1-<0.5ng/ml	86	80	76	72	71	68	67	64	61	51	46	28	13
≥0.5-<1.5ng/ml	80	74	74	68	65	61	57	56	55	47	39	27	14
>1.5ng/ml	82	79	75	70	67	62	55	49	41	35	35	26	18

Figure 1. Kaplan–Meier overall survival curves after stratification according to pre-radiotherapy PSA ($p < .01$).

In this patient population, antiandrogen treatment in combination with RT has been usually applied postoperatively in case of risk factors as a neoadjuvant treatment (median period of six months). Adverse factors included positive surgical margins, T3 stage, high pre-RP PSA values and a high GS. An immediate postoperative ADT is not based on evidence from the literature. However, as Shipley et al. [24] found in their randomized trial the application of ADT to SRT results in improved rates of long-term overall, disease-specific and metastasis-free survival, especially in case of more aggressive tumors. Risk factors include a higher GS, high PSA levels or positive surgical margins. Unfortunately, we cannot confirm the results of this study as ADT has only rarely been prescribed additionally to SRT in case of higher PSA levels in our patient population. In our analysis, only an impact for reducing biochemical failure rates in univariable analysis was found for antiandrogen treatment.

Our data proved a higher GS (≥8), a higher pathological T stage (T3–T4), SM− and a higher pre-RT PSA (≥0.5 ng/ml) to be significant predictors for BR after postoperative RT in

multivariable analysis. Our observations are substantiated by several studies [14,16,25,26]. Briganti et al. [16], who developed a nomogram predicting five-year BR, also reported a higher GS (≥7), a higher pathologic T stage (T3a, T3b) and higher pre-RT PSA to be significant predictors. Contrary to our results, the authors of this study found SM + to be significantly associated with BR. This finding might be due to their study design requiring favorable conditions such as undetectable PSA levels after RP, pre-RT PSA ≤0.5 ng/ml and lymph node-negative PCa, and therefore lacking more adverse features which might alter the association of surgical margin status and BR [16].

There are multiple studies which deal with pre-RT PSA levels as predictive factors and found higher levels associated with worse BR rates [5,17,18,27]. Accordingly, EAU Guidelines recommend a PSA level of ≤0.5 ng/ml for SRT [28].

A systematic review including 25 studies found five-year BRFS decrease by 18.3% per 1 ng/ml PSA level increase [5] and King [27] describes that a 0.1 ng/ml PSA level increase causes a BRFS loss of circa 4%. These study results [5,17,27] are in line with our findings.

Tendulkar et al. [29] conducted a study with a median follow-up of five years after SRT found improved BRFS and metastasis-free survival rates by administration of early SRT at low PSA levels. They evaluated the pre-RT PSA levels more closely and observed the BRFS rate to decrease and the distant metastasis-rate to increase with increasing pre-RT PSA levels. For example, a five-year BRFS rate of 71% and 37% was found in case of SRT at a PSA level of 0.01–0.2 ng/ml and >2 ng/ml, respectively. These findings correlate with our analysis which however comprises a significantly longer period of observation and therefore assesses the even more important aspect of survival. Our 10-year OS rates are dependent on the pre-RT PSA level as well. For example, an OS rate of 85% and 50% was found in patients with a pre-RT PSA level of <0.1 ng/ml and ≥1.5 ng/ml, respectively (Figure 1).

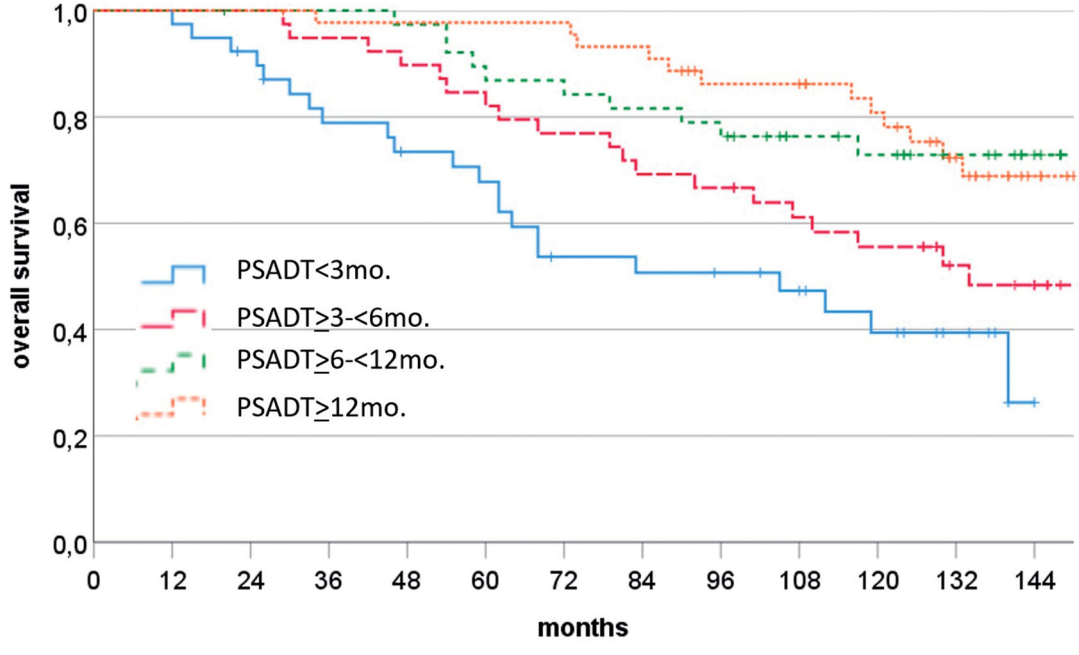
Moreover, we found a higher GS to be a significant predictor for BRFS, DSS, metastases and OS. Tendulkar et al. [29] highlight the predictive role of a high GS in their analysis and demonstrate simultaneously how the administration of SRT at lowest possible PSA levels can improve the outcome even of those patients at risk. Thus, particularly in patients with poorly differentiated tumors, SRT at lowest possible PSA levels is of great importance.

As we conducted a long-term follow-up, we were able to assess survival outcomes, presenting DSS and OS rates in our study population of 84% and 69%, respectively. Three factors

Table 4. Multivariable Cox regression analysis for PSA-related post-radiotherapy factors.

Factor	Hazard ratio	95% confidence interval	*p*-value
Metastases			
No PSA response	2.3	1.3–4.0	<.01
PSADT <6 vs. ≥6 months	3.0	1.7–5.2	<.01
Disease-specific survival			
No PSA response	2.8	1.5–5.3	<.01
PSADT <6 vs. ≥6 months	7.3	3.0–17	<.01
Overall survival			
No PSA response	2.2	1.3–3.6	<.01
PSADT <6 vs. ≥6 months	2.6	1.5–4.3	<.01

PSA: prostate-specific antigen; PSADT: prostate-specific antigen doubling time.



patients at risk													
>12 mo.	45	44	44	43	43	43	43	41	35	34	31	30	12
≥6 - <12 mo.	39	38	38	38	37	34	32	31	29	23	21	16	10
≥3 - <6 mo.	39	38	38	37	35	32	30	27	26	22	20	14	11
<3 mo.	39	35	35	29	26	24	18	17	16	13	10	6	0

Figure 2. Kaplan–Meier overall survival curves after stratification according to PSA doubling time (PSADT) during a biochemical recurrence after radiotherapy ($p < .01$).

known before RT, namely GS, LN + and pre-RT PSA level as well as two factors based on PSA response after RT, namely failed PSA response after RT and PSADT at BR proved to be significant predictors in multivariable analysis. Taking into account CCI, GS did not remain significant in the multivariable model.

Trock et al. [15] conducted a study with a median follow-up of six years after biochemical and/or local recurrence following RP and found that SRT at PSA levels ≤2 ng/ml leads to significantly increased DSS compared to SRT at PSA levels >2 ng/ml. Stish et al. [30] examined DSS a median time of 8.9 years after SRT in patients with detectable PSA after RP, also identifying higher pre-RT PSA levels (>0.5 ng/ml) to be an unfavorable predictor, not reaching statistical significance for OS. Our findings corroborate the pre-RT PSA level to be an unfavorable prognostic factor for DSS even in the range of lower PSA levels, supporting the relevance of current recommendations [28]. Likewise confirming our results, Stish et al. [30] found a higher GS (≥7 and ≥8) to be a significant risk factor for DSS and OS, respectively. LN + was significantly predictive for DSS only in univariable analysis in their study. This might be due to the small portion of LN + patients (1%), in contrast to 7% in our study population.

The findings of Abdollah et al. are in line with our results as the authors identified GS ≥8 and LN + to be predictive factors for DSS in multivariable analysis. In this trial, it has also been reported that ART significantly improved DSS and OS in patients with a GS ≥8 and the presence of one more risk factor (pT3b/T4 stage or LN+) [31]. Likewise, Thompson et al. [32] showed that ART reduced the risk of metastases and improved survival in pT3N0M0 PCA patients, with a greater benefit of ART in patients with GS ≥7.

We found a short PSADT before RT (<6 months) to be a predictive factor for BR, DSS and metastases in univariable analysis. Confirming our findings, a recent review [33] found a short PSADT to be the major adverse prognostic factor for survival in patients with RP as primary treatment. The authors describe a significant relationship between a short PSADT (≤12 months) and overall mortality, PCA-specific mortality as well as distant metastases.

However, not only the PSADT before RT but also in case of BCR following RT is of prognostic relevance. In our analysis, patients with shorter PSADT (<6 months) following RT experienced worse survival outcomes in multivariable analysis. As shown in Figure 2, the shorter the PSADT, the lower the OS rates.

Therefore, those patients should be considered for additive early treatments. The same applies to patients not responding to RT within six months, as non-response depicts a significant predictor for metastases, DSS and OS in multivariable analysis as well. Likewise, Jackson et al. [34] observed that patients with a continuously rising PSA after SRT were at highest risk for distant metastases, PCA-specific death and decreased OS.

In addition, they saw an increased probability for BR, distant metastases, PCA-specific death and lower OS rates in case of a post-RT PSA nadir of ≥0.1 ng/ml. These patients are even more at risk if they experience their nadir <6 months after SRT. The importance of the response behavior to RT is also underlined by Geinitz et al. [35] who report lower OS and DSS rates as well as higher rates of distant metastases in case of a post-RT PSA nadir >0.05 ng/ml. A study by Bartkowiak et al. [36] found patients with a post-SRT PSA nadir <0.1 ng/ml to experience a better OS and lower metastases rates. In addition, the authors of this study observed that early SRT at a PSA level of <0.2 ng/ml was associated with a post-SRT PSA of <0.1 ng/ml, which again underpins the importance of timely administration of SRT in order to achieve best possible outcomes.

A close follow-up within the first six months after SRT for patients with risk factors such as a high GS in order to assess PSA kinetics seems to be reasonable to detect the non-responders and patients at risk with a short PSADT and elevated nadir. Those patients are candidates for early additional therapies.

To reach the best survival outcomes following RP, SRT should be initiated early with low PSA levels, especially in patients with histologically poorly differentiated tumors. Patients with higher PSA levels and high GS will most likely benefit from a simultaneous ADT. Patients not responding to RT and/or patients with a short PSADT during BR are candidates for early additive systemic treatments.

Disclosure statement

No potential conflict of interest was reported by the authors.

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