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CLINICAL INVESTIGATION **Prostate**

ACHIEVING AN UNDETECTABLE PSA AFTER RADIOTHERAPY FOR BIOCHEMICAL PROGRESSION AFTER RADICAL PROSTATECTOMY IS AN INDEPENDENT PREDICTOR OF BIOCHEMICAL OUTCOME—RESULTS OF A RETROSPECTIVE STUDY

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Purpose: Salvage radiotherapy (SRT) is commonly used to treat patients with biochemical failure after radical prostatectomy (RP). Retrospective series have demonstrated biochemical response in approximately 60–75% of patients, but only a significantly lower rate of patients achieves a response with a decrease of the prostate-specific antigen (PSA) to a value below the limits of detectability. Therefore, long-term response at 10 years is only about 20–25% in all of these patients. The purpose of this study was to determine prognostic factors with impact on achieving the undetectable PSA range after SRT and to define the role of this end point.

Methods and Materials: Between 1997 and 2004, 162 patients received SRT at the Charité Universitätsmedizin, Berlin. No patient had hormonal treatment before SRT and 90% of the patients (143) had a SRT dose of 66 Gy. We analyzed the impact of nine potential risk factors on achieving an undetectable PSA after RT and on biochemical relapse–free survival (bNED) after SRT.

Results: Median follow-up time was 41.5 months and median PSA pre-RT was 0.33 ng/mL. Calculated bNED for 3.5 years was 54%. A total of 60% of the patients achieved an undetectable PSA after SRT. Univariate analysis demonstrated statistically significant predictors of biochemical progression after SRT: Gleason score ($p = 0.01$), PSA pre-SRT ($p = 0.031$), tumor stage ($p = 0.047$), and persistent detectable PSA after RT ($p < 0.00005$). In multivariate analysis, margin status ($p = 0.017$) and PSA pre-SRT ($p = 0.002$) were significant predictors of an undetectable PSA after SRT. The most significant independent predictor of bNED was "PSA undetectable after RT" ($p < 0.0005$) with a hazard ratio of 8.4, thus leading to a calculated bNED at 3.5 years of 75% compared with only 18% for those patients, who did not achieve an undetectable PSA after SRT. The rate of severe Grade 3-4 side effects was below 2.5%.

Conclusions: The study represents one of the largest retrospective single-institution series of SRT for increasing PSA after RP in patients without any hormonal treatment before the initiation of SRT. Our findings suggest that achieving an undetectable PSA after RT is an important prognosticator for a high chance of cure and patients with a low PSA pre-SRT, positive surgical margins, and low tumor stage at the time of RP are best candidates for SRT.

Prostate cancer, Radical prostatectomy, Radiotherapy, Biochemical progression, Prostate-specific antigen.

INTRODUCTION

Radical prostatectomy (RP) with or without nerve-sparing techniques or radiation therapy are two of the existing first-line therapeutic options for patients with prostate cancer, with best results achieved in patients with organ confined disease. There are clearly defined risk factors predicting the outcome after RP (*i.e.*, Gleason score, prostate-specific antigen [PSA] level before surgery, tumor stage, infiltration of the seminal vesicles or positive surgical margins) (1–4). However, progression of the disease is a common event even in patients with good prognostic factors. A PSA increase of ≥0.2 ng/mL is a common definition of progression of the disease. It occurs in up to 50% of patients with pT3 tumors and this value ranges up to 70% in case of pT3 tumors with positive surgical margins (5, 6).

It remains uncertain whether a PSA increase after RP indicates isolated local disease, distant metastatic progression, or both (7). Therefore the best treatment for recurrent prostate

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cancer in patients with increasing or persisting PSA without clinical evidence of disease remains controversial. It is of major importance to distinguish in these patients local recurrence from distant metastasis to select the most appropriate treatment. Unfortunately, this is impossible in most cases. There are indicators for a higher likelihood of local recurrence as slow PSA progression, more than 1 year between RP and the increase of PSA or Gleason score <7, for example (8). On the other hand, there are also indicators suggesting metastatic disease as short PSA doubling time or Gleason score at RP from 8 to 10 (9, 10). Some authors tried to define combinations of risk factors. For example, patients with a combination of PSA <1 ng before RT, pre-RP Gleason score <7, and a long PSA doubling time after progression have a high risk of local disease (11). Recently, a predictive model of the outcome of RT for PSA progression after RP has been established (12).

Assuming a local nature of the underlying disease, salvage radiotherapy (SRT) of the prostatic bed has widely been used to treat patients in the absence of biopsy-proven local recurrence. An established standard is conformal radiotherapy to the prostatic fossa with a dose of about 66 Gy, aiming to irradiate the presumed local recurrence and hence to reduce the risk of a ''second wave of metastasis'' leading to clinical progression of disease (13). In the light of these well-known problems in detecting local recurrence in the prostatic bed, radiotherapy to the prostatic fossa is one of the rare therapies in which radiation oncologists irradiate without a histologic proof of tumor recurrence. Many authors were able to demonstrate, that SRT results in an initial treatment response with decreasing PSA values in up to 60–75% of the patients (14, 15). There is less information about the number of patients who achieved an undetectable PSA after SRT and the prognostic value of this end point on the one hand and the definition of ''undetectable'' PSA on the other. Threshold values of <0.3 ng/mL, <0.2 ng/mL, or even lower have been used (12). Many patients with decreasing PSA develop an increase of PSA later, thus indicating further progression of disease. Only about 20–30% of the patients remain without evidence of disease at 10 years (9). Therefore it is of relevance to define factors likely to predict patients with a good chance to respond best to SRT and to define subgroups of patients who will need additional therapy (*e.g.*, hormonal treatment or irradiation of the pelvic lymphatics) (12).

The purpose of our study was to analyze the prognostic factors of patients to achieve an undetectable PSA after SRT and to compare these results with the results of the irradiation of patients who did not achieve the undetectable PSA range after SRT.

METHODS AND MATERIALS

Between 1997 and 2004, 169 patients received SRT at the Charité Universitätsmedizin, Campus-Benjamin-Franklin, Berlin, for biochemical failure after RP. Seven patients were excluded from analysis. Six of them had hormonal treatment between RP and SRT and 1 patient was lost to follow-up. Therefore 162 patients with irradiation for the prostatic bed alone and without hormonal treatment after RP were investigated further.

Data were obtained retrospectively using the irradiation protocols and patient charts of the Departments of Radiation Oncology and Urology, Charité Universitätsmedizin, Campus-Benjamin-Franklin, Berlin, or at other referring urologic centers. At the beginning of SRT, no patient had clinical evidence of metastatic disease. However, in patients with PSA before start of SRT below 1 ng/mL no chest X-ray or radionuclide bone scan was done because of the inability of any standard diagnostic tool to detect such small amounts of malignant tissue although planning computed tomography scans were always examined to rule out metastatic disease or nodal involvement. Patients were treated with 18 MV photons using conformal radiotherapy techniques. In the case of pT2 tumors, the planning target volume was the prostatic bed including the bladder neck and periprostatic clips with a security margin of 1 cm. In the case of pT3 tumors, the bed of the seminal vesicles was included additionally into the target volume. A total dose of 66.6 Gy in 1.8 Gy daily fractions was delivered to the target volume in 87% of the cases. Overall, 19 patients received lower doses of 59.4–64.8 Gy early in the period under evaluation (Table 1). Regional pelvic lymph nodes were not irradiated. Side effects were scored using the Radiation Therapy Oncology Group and the European Organisation for Research and Treatment of Cancer) late-effect toxicity criteria. Because PSA values were measured in different laboratories, the lower detection limits varied from 0.03 to 0.1 ng/mL. Definition of complete biochemical response therefore was achieving a range of the PSA below the limits of detectability of the individual assay used; in all cases, this was below 0.1 ng/mL (Table 2). Biochemical failure after SRT was defined as three consecutive increases in PSA measurements (American Society for Therapeutic Radiology Oncology Criteria) or the start of hormonal treatment. The time to PSA failure after SRT was defined at the time interval from the start of SRT to the midpoint of the first two PSA increases after SRT.

PSA measurements were already performed during radiotherapy. Therefore we were able to detect increasing PSA values before SRT was finished. In those cases, the time point of biochemical failure was calculated using the same definition, but before the end of SRT.

Kaplan-Meier curves were used to demonstrate the PSA failure-free probability (16). Log–rank test was used for statistical comparison of the Kaplan-Meier curves. The Cox proportional hazards regression model was used for multivariate analysis to determine the association between clinicopathologic factors and PSA progression-free survival (17). Additionally potential risk factors of biochemical progression were investigated with a multivariate logistic regression analysis. We analyzed prognostic factors, including an undetectable PSA after SRT, PSA doubling time, Gleason score, tumor stage, PSA before start of SRT, infiltration of seminal vesicles, PSA preoperatively, positive or negative surgical margins, time between RP and SRT, age, and patients who achieved an undetectable PSA vs. patients with persistent PSA after RP.

Table 1. Radiotherapy dose

	Number of patients	%
Total dose salvage radiotherapy (Gy)		
59.4 Gy	5	3.1
63.0 Gy	6	3.7
64.8 Gy	6	3.7
65.8 Gy	1	0.6
66.0 Gy	1	0.6
66.6 Gy	142	87.7
68.4 Gy	1	0.6

Table 2. Undetectable range of prostate-specific antigen after salvage radiotherapy: comparison of all patients

Prostate-specific antigen range (ng/mL)	Number of patients (%)
<0.03	130 (80.2%)
≥0.03–<0.05	16 (9.9%)
≥0.05–<0.1	16 (9.9%)
<0.1	162 (100%)

Using all available PSA values, we calculated PSA doubling times by linear regression analyses of the log(PSA) for every patient. Continuous variables were dichotomized at their median for multivariate analyses. In a first round all previously mentioned variables were included into the regression models. Thereafter we reduced the number of variables including only those parameters with a significant or almost significant impact; therefore, not more than three variables were included in the second round of multivariate analyses.

To compare the results of this study with those of recently published series, we recalculated biochemical relapse free survival (bNED) and univariate analyses by using the definition of biochemical relapse proposed by Stephenson *et al.* (11). In this latter study, disease progression was defined as a serum PSA value of 0.2 ng/mL or more above the post-SRT nadir followed by another higher value, a continuous rise in the serum PSA despite SRT, initiation of systemic therapy after completion of SRT, or clinical progression.

RESULTS

Patients and tumor characteristics are shown in Table 3. The median age of the patients at start of RT was 66 years (range, 54–82 years). Preoperation PSA ranged from 2.33 ng/mL to 106.4 ng/mL, with a median of 12 ng/mL. Histologic data on eviscerated lymphatic tissue were available from 104 of 160 patients with pelvic lymph node dissection, with a median number of 8 lymph nodes (range, 0–28 nodes). The time from RP to the start of SRT was median 18.6 months and ranged from 1.6 months to 168 months. Pre-SRT PSA ranged from 0.034 ng/mL to 8.87 ng/mL; the median was 0.33 ng/mL. PSA doubling time between RP and start of SRT ranged up to 85.2 months, the median being at 4.99 months. A total of 87.1% of the patients had 66.6 Gy as total dose with a single dose of 1.8 Gy (Table 1). No patient had hormonal treatment before the start of or during SRT.

Table 3. Patients characteristics (n = 162)

	Median		Range
Age (y)	66		54–82
		Number of patients	(%)
Stage	pT_{2a}	18	11.1
	pT_{2b}	3	1.9
	pT_{2c}	57	35.2
	pT_{3a}	48	29.6
	pT_{3b}	29	17.9
	pT_4	3	1.9
	Unknown	4	2.5
Lymph node involvement	pN_0	160	98,8
	cN_0	2	1,2
Number of negative nodes, median (range)	8 (0–28)	104	65%
Margins (positive)	R_1	92	56.7
Margins (negative)	R_0	55	34
Margins (unknown)	R_x	15	9,3
Gleason score (<7)		83	53.1%
Gleason score (7–10)		73	43.2%
Unknown		6	3.7%
Prostate-specific antigen after radical prostatectomy	Undetectable	87	53.7
	Persistent	72	44.4
	Unknown	3	1.9

Table 4. PSA after SRT

	Number of patients	All patients (%) (n = 162)	Without patients with decreasing PSA (%) (n = 155)
Post-SRT PSA undetectable	93	57.4	60
Post-SRT PSA detectable	62	38.3	40
Post-SRT PSA decreasing, not in the undetectable range	7	4.3	/
Total	162	100.0	100.0

Abbreviations: PSA = prostate-specific antigen; SRT = salvage radiotherapy.

Median follow-up time after SRT was 41.5 months (range, 3.1–97.2 months), 3 patients died within the follow-up time; one death was related to prostate cancer. Five patients developed bone metastasis (3.1%). One patient had lung metastasis (0.6%), 1 had cutaneous metastasis (0.6%), and 1 patient had a local recurrence within the irradiation field. Median time from start of SRT to post-SRT PSA nadir was 6.75 months (range, 0–43.8 months).

After completion of SRT, 7 of 162 patients still had decreasing PSA levels at the time of analysis. Of the remaining 155 patients, n = 93 (60%) achieved a PSA nadir in the undetectable range vs. n = 62 (40%) with a detectable PSA nadir or a continuously rising PSA from the start of SRT (n = 3/62) (Table 4). During follow-up, these two groups of patients experienced a different development: we observed a biochemical or additional clinical progression in 69 of all 162 patients (42.6%). But in those patients with a PSA nadir below detection limit after SRT, only n = 21 (22.6%) showed a biochemical progression compared with 48 of 62 patients (77.4%) who did not achieve an undetectable PSA range. Calculated 3.5-year bNED for all patients was 54%. Calculated 3.5-year bNED for the group of patients with an undetectable PSA nadir was 75% and for the group with persistent detectable PSA 18% ($p < 0.00005$).

Univariate analysis of factors influencing bNED after SRT showed that, 4 of 11 preradiotherapy factors were statistically

Table 5. Univariate analysis of factors influencing freedom from biochemical progression (bNED) after SRT

	Log–rank test
PSA undetectable after SRT vs. not	$p < 0.00005$
Gleason score (≤6 vs. ≥7)	$p = 0.010$
PSA before start of SRT (≤0.5 vs. >0.5 ng/mL)	$p = 0.031$
Stage ($\leq pT_{2c}$ vs. $\geq pT_{3a}$)	$p = 0.047$
Seminal vesicles (positive vs. not)	$p = 0.056$
PSA doubling time before start of SRT (≤5.0 months vs. >5.0 months, median)	$p = 0.056$
Margins positive vs. negative	$p = 0.098$
PSA before RP (≤12 vs. > 12 ng/mL, median)	$p = 0.356$
Time from RP until start of SRT (≤18.6 months vs. >18.6 months, median)	$p = 0.433$
PSA undetectable post-RP vs. persistent PSA after RP	$p = 0.678$
Age (≤66 y vs. >66 y, median)	$p = 0.770$

Abbreviations: bNED = biochemical relapse–free survival; PSA = prostate-specific antigen; SRT = salvage radiotherapy; RP = radical prostatectomy.

significant predictors of outcome (Table 5). These factors were undetectable PSA after SRT ($p < 0.0005$), Gleason score ≤ 6 vs. ≥ 7 ($p = 0.01$), tumor stage ($\leq pT_{2c}$ vs. $\geq pT_{3a}$) ($p = 0.047$), and pre-SRT PSA level ($p = 0.031$) (Table 5). An investigation of predictive factors of clinical relapse-free survival was not done because the small number of events.

Multivariate analysis was done to investigate potential factors influencing the PSA decrease into the undetectable range after SRT and to detect factors predicting biochemical progression after SRT. In both cases, logistic regression analysis was used. Additionally, the Cox regression model was used to define independent factors of bNED. The investigated parameters were: patient age (≤66 vs. >66 years), PSA before RP (≤12 ng/L vs. >12 ng/mL, median) tumor stage (≤pT2c vs. ≥pT3a), seminal vesicle infiltration (positive vs. negative), margins (positive vs. negative), Gleason score (≤6 vs. ≥7), persistent detectable PSA vs. increase out of the undetectable range after RP, PSA doubling time before start of SRT (≤5.0 vs. >5.0 months), PSA before start of SRT (≤ 0.33 ng/mL vs. >0.33 ng/mL), and achieving an undetectable PSA after SRT (Table 6).

Using multivariate analysis with logistic regression for factors influencing an undetectable PSA after SRT, only pre-SRT PSA level (odds ratio 3.03, $p = 0.002$) and resection stage (positive margins) (odds ratio 0.41, $p = 0.017$) were found to be independent predictive factors. The most significant predictive factor of biochemical progression after SRT in both logistic regression and Cox regression was an undetectable PSA after SRT with an odds ratio of 11.51 ($p < 0.0005$) and a hazard ratio of 8.43 ($p < 0.0005$). Additionally, two factors showed a significant influence using the Cox regression model, one associated with a better and one associated with a worse outcome: tumor stage (≤pT2 vs. ≥pT3a) with a hazard ratio of 1.76 ($p = 0.025$) and PSA doubling time with a hazard ratio of 0.47 ($p = 0.003$).

Kaplan-Mayer estimates for remaining free of biochemical progression according to an undetectable PSA after SRT (Fig. 1), to initial tumor stage (Fig. 2) and to PSA before

Table 6. Multivariate analyses of factors influencing an undetectable PSA after SRT and biochemical progression (bNED) after SRT

	PSA undetectable after SRT (logistic regression)	Biochemical Progression after SRT (yes or no) (logistic regression)	Progression free-survival (bNED) (Cox regression)
Age (≤66 vs. >66 y)	NS	NS	NS
PSA pre-RP (≤ 12 vs. > 12 ng/mL)	NS	NS	NS
Tumor stage	NS	n.s. (p=0.052)	p=0.025 HR 1.76 CI 1.07–2.9
Seminal vesicle involvement	NS	NS	NS
Margin status (positive vs. negative)	p = 0.017 OR 0.41 CI 0.20–0.85	NS	NS
Gleason score	NS	NS	NS
PSA post-RP (undetectable vs. persistent)	NS	NS	NS
PSADT (≤5.0 months vs. >5.0 months)	NS	NS	p=0.003 HR 0.47 CI 0.29–0.78
PSA before SRT ≤0.33 vs. >0.33 ng/mL (median)	p = 0.002 OR 3.03 CI 1.48–6.2	NS	NS
PSA after SRT (undetectable vs. detectable)	—	p<0.0005 OR 11.51 CI 5.21–25.42	p<0.0005 HR 8.43 CI 4.80–14.82

Abbreviations: OR = odds ratio; HR = hazard ratio; PSADT = prostate-specific antigen doubling time; RT = radiotherapy; RP = radical prostatectomy; NS = not significant.

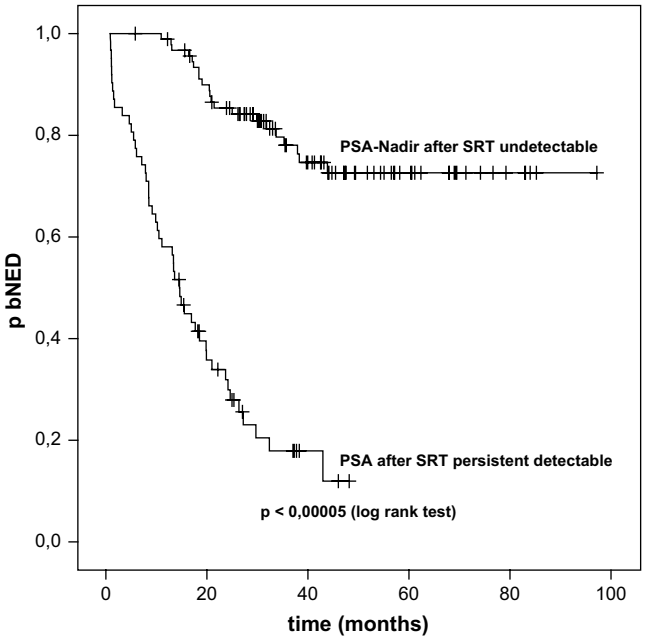

Fig. 1. Kaplan-Meyer estimates of biochemical relapse–free survival (bNED) survival after salvage radiotherapy (SRT). Comparison of patients who achieved an undetectable prostate-specific antigen (PSA) vs. not.

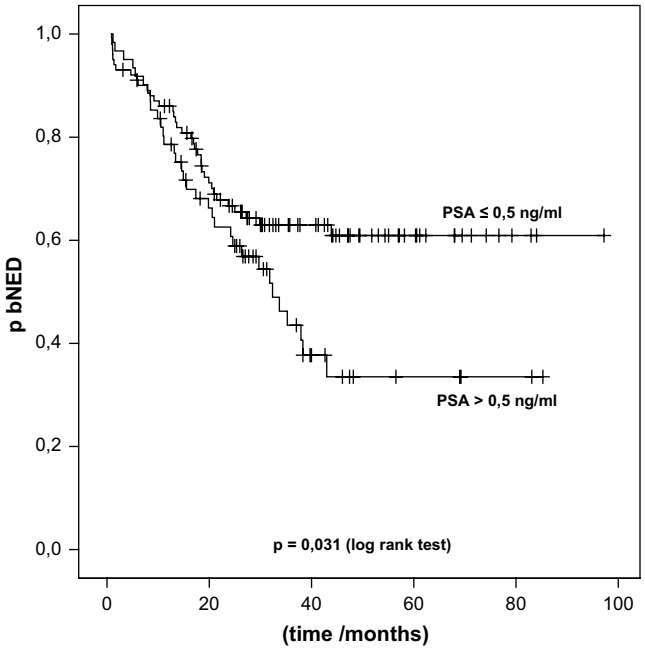

Fig. 3. Kaplan-Meyer estimates of biochemical relapse–free survival (bNED) for prostate-specific antigen (PSA) before start of salvage radiotherapy (SRT). Comparison of patients with a PSA ≤ 0.5 ng/mL vs. PSA > 0.5 ng/mL.

starting SRT (Fig. 3) illustrate these findings. An analysis of prognostic factors related to overall survival was not done.

Acute side effects of Grade 3 or 4 were not recorded. Eleven patients (6.8%) had RT-induced chronic complications ge;Grade 2. Five patients (3.1%) had complications associated with rectal symptoms (Grade 2 bleeding, tenesmus), 2 patients had Grade 2 (transient cystitis); however, 4 patients (2.4%) had Grade III late cystitis. Urethral stricture developed in 4 patients (2.8%).

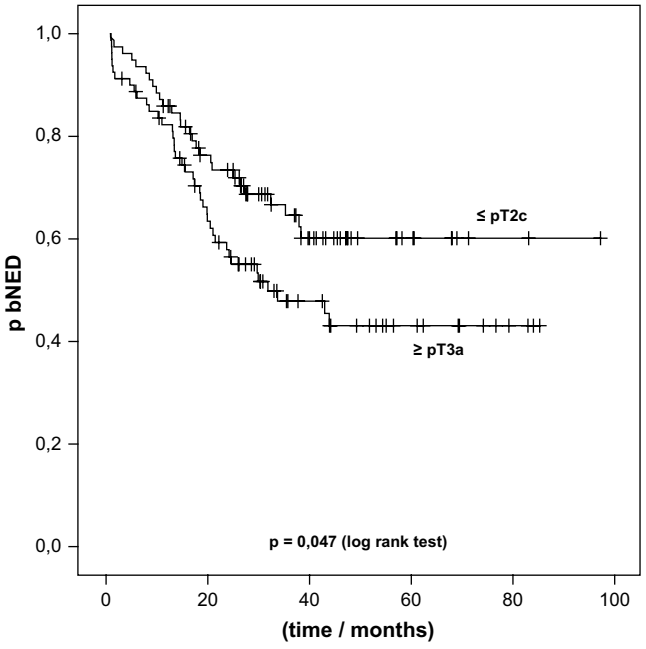

Fig. 2. Kaplan-Meyer estimates of biochemical relapse–free survival (bNED) survival according to tumor stage. Comparison of patients with stage ≤pT2c vs. ≥pT3a.

By using the definition of Stephenson *et al*. for disease progression (11), a clinical or biochemical relapse was detected in 61 patients during follow-up, with a calculated bNED of 58% at 3.5 years. Furthermore, univariate analyses revealed a significant impact on biochemical relapse–free survival for three variables: PSA undetectable after SRT ($p < 0.00005$), Gleason score ($p = 0.011$), and PSA before start of SRT (dichotomized at 0.5 ng/mL, $p = 0.012$).

DISCUSSION

Many retrospective studies describe the outcome of patients treated with salvage RT for both PSA increase and persistent PSA after RP (18–20). Up to now there have been no data from a prospective randomized trial for salvage RT after biochemical failure of RP. The present retrospective study with the analysis of 162 patients differs from most other studies because no patient had hormonal treatment before SRT—nearly 90% of the patients were treated homogeneously with 66.6 Gy and, of special interest, patients had careful follow-up to detect whether they patients achieved an undetectable PSA after SRT below 0.1 ng/mL, especially in more than 90% below 0.05 ng/mL. In most of the retrospective studies, the response rate is defined as decreasing of PSA, but not as achieving an undetectable PSA after SRT (21). In these circumstances, approximately 70–75% of patients had a decrease of their serum PSA. However, a substantial proportion of these patients, initially responding to SRT, later develop increasing PSA values as biochemical evidence of progression of disease again. Therefore only about 20–30%

of all patients have no progression of the disease at 8–10 years (9, 18). To the best of our knowledge, we are the first to demonstrate that achieving an undetectable PSA below 0.1 ng/mL is an independent highly significant predictor of long-term biochemical outcome.

Pazona *et al*. demonstrated in a retrospective series of 223 patients that patients with a complete response defined as <0.3 ng/mL (162 of 223) had a 5-year bNED of 55% compared with all patients (40%). The median follow-up was 50 months (9). However, a statistical comparison of these groups was not done and only 223 of 307 men were followed because most of these patients were irradiated in other parts of the United States. Additionally, the patients were treated inhomogeneously. The undetectable range (<0.3 ng/mL) in this series was relatively high compared with the undetectable range <0.05 ng/mL in more than 90% of our patients. Our data indicate that the definition of biochemical progression with a PSA of more than 0.3 ng/mL or more than 0.4 ng/mL as proposed by others (12) remains questionable.

There is a major controversy concerning the best time to start irradiation (*i.e*., the best PSA cutoff level). In former times, the recommended cutoff level was below 1.5 ng/mL (American Society for Therapeutic Radiology and Oncology), but a lower cutoff level was clearly correlated with a better biochemical outcome. For example, various cutoff points had been selected (8, 11, 14, 15, 22); for example, 1.5 ng/mL (14) or 1.1 ng/mL (22). More recent series recommended start of treatment at PSA levels <0.5 ng/mL (11). Our results, as with those of the other groups, suggest that patients with low pre-SRT PSA levels (*i.e*., <0.5 ng/mL) may be the ones who benefit most from salvage RT. Our data strongly indicate that a PSA <0.33 ng/mL was an independent prognosticator of achieving an undetectable PSA after SRT, thus giving the chance of a durable long-term response. On the other hand, the best level for start of irradiation remains uncertain as there is a risk for an overtreatment in case of benign glands only. Stephenson *et al*. suggested the best level being in between 0.2 ng/mL and 0.4 ng/mL (12), but the question remains unresolved. It seems possible that the ideal time of treatment could be the first detected and confirmed rise of the PSA value out of the undetectable range; however, this strategy would be associated with a growing proportion of patients being overtreated.

Interestingly, a reanalysis of the Southwest Oncology Group 8794 Trial (subgroup analysis of a randomized Phase III trial comparing adjuvant RT vs. ''wait and see'') demonstrated a clearly significant benefit for patients with a PSA level <0.2 ng/mL for bNED, local recurrence, and distant failure compared with a PSA level >0.2 ng/mL<1.0 ng/mL (23), thus raising the question of a superiority of adjuvant radiotherapy after RP for high-risk patients over the strategy of SRT at the time of PSA elevation (24). Three randomized Phase III trials demonstrated a nearly 20% absolute benefit in case of bNED for 60 Gy compared with ''wait and see'' only (25–27). Because there are no randomized data comparing adjuvant RT and SRT, the best time to start irradiation remains under discussion (28).

Positive surgical margins, indicating residual disease in the prostatic bed as the target for radiotherapy was a predictor of a better outcome after salvage RT in previous studies (11, 21). Our results correlate well with these studies. Positive surgical margin status was an independent prognosticator in multivariate analysis to achieve an undetectable PSA after SRT and also indicating a favorable outcome after 4 years of bNED. All these data support the active role of SRT to the prostatic fossa to reduce the risk of local recurrence in both adjuvant RT and SRT.

PSA doubling time (PSADT) is an important prognosticator of bNED as stated by Ward *et al*. (10). Our data, as did others, confirm these results. Using the median of PSADT in our patients (5 months), there was a clear significant benefit in terms of bNED for patients with a longer PSADT in multivariate analysis.

A major point of discussion is the best definition of progression after RT for an elevated PSA after RP. There are many different definitions by different authors, thus leading to problems with comparisons of the results (21). Our own definition followed the American Society for Therapeutic Radiology and Oncology guidelines (29), other authors used two consecutive increases of PSA after SRT (29, 30), or two consecutive increases from nadir (31, 32). Stephenson reported the results of a multi-institutional cohort with 1,540 patients from 17 North American tertial referral centers and defined progression as a PSA value of 0.2 ng/mL or more above the postradiotherapy nadir followed by another rise (11, 12). Others stated a single PSA value greater than 0.4 ng/mL at least 1 year after RT (10) as progression or not achieving a decrease to less than 0.3 ng/mL (with all patients starting with values higher than 0.3 ng/mL) (9). We compared our results using an additional analysis with the Stephenson definition and found no significant differences between both definitions in our own patients. However, there is an urgent need to find a uniform definition of biochemical progression after RT for elevated PSA after RP for better comparisons of the various reports.

The best RT dose in the case of elevated PSA after RP remains uncertain. Total SRT dose was associated with significantly improved bNED in some studies (21, 22). Total doses between 64 Gy and 66 Gy are commonly recommended (11). However, there is clear evidence in the case of definitive RT of prostate cancer, that doses beyond 72 Gy are needed to cure a macroscopic tumor burden (28). Our data suggest the high importance of achieving an undetectable PSA after SRT. However, the median follow-up of our patients remains too short to conclude that these patients durably remain free of tumor. Therefore it would be possible that 66.6 Gy is enough to achieve an undetectable PSA in many cases, but not enough for durable cure. It is noteworthy that our median PSA before start of SRT was low, only 0.33 ng/mL, suggesting the presence of only a small tumor. However, the median PSADT in our cohort of patients was short (5 months), which usually indicates a poor prognosis. The comparably favorable outcome may also be due to the relatively short follow-up time. Therefore a longer follow-up is necessary

to draw firm conclusions. Furthermore, pelvic lymph node dissection might have been more extensive in our series of patients with a median number of eight nodes compared with other reports, thus indicating a higher chance of freedom from pelvic lymph node metastasis at the time of radical prostatectomy. Presuming this, the source of a PSA increase after RP should be more often a local recurrence rather than a lymph node involvement.

SRT is generally associated with a low rate of severe acute and late side effects. Urinary incontinence in 0–5% of the cases, moderate proctitis in 0–10% and mild to moderate cystitis in up to 10% may result from this procedure (11, 14, 21, 33). Severe late effects are rare events affecting 3–6% or fewer of the patients (21). In our study, SRT was well tolerated with only a few severe effects: altogether, 4.2% had moderate proctitis or cystitis Grade 2. However, 4 patients (2.4%) had Grade 3 cystitis. Urethral strictures are not only occasionally associated with radical prostatectomy. Therefore our rate of 4 of 162 patients (2.4%) after RT after RP is neither uncommon nor solely attributable to SRT.

Several limitations of our study are noteworthy. *(1)* Our data represent a large retrospective series, but with all their inherent limitations. *(2)* There is an absence of a comparison group that did not receive RT for an elevated PSA. *(3)* We were not able to correlate these results with the clinical outcome (*e.g.*, metastasis-free survival) because the small number of patients with hematogenous metastases ($n = 7$, 4.3%). *(4)* We started irradiation even in patients with a PSA level below 0.2 ng/mL, thus indicating a potential overtreatment in a proportion of patients with possibly benign nature of low-level, gradual PSA recurrences. Therefore the decision to offer radiation therapy should be balanced against its potential side effects.

CONCLUSIONS

We were able to demonstrate the new information that achieving an undetectable PSA after SRT below at least 0.1 ng/mL, in most cases below 0.03 ng/mL, is a highly significant independent predictor of freedom from biochemical progression after RT for elevated PSA after RP. These patients should have the chance of a long-term durable response with no further treatment required. Additionally supporting this conclusion, positive margins and PSA level before start of RT were independent predictors of achieving an undetectable PSA after RT. PSADT and tumor stage were independent predictors of bNED. Further studies are warranted to support these findings.

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