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Prostate cancer

The PSA-response to salvage radiotherapy after radical prostatectomy correlates with freedom from progression and overall survival ☆

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ABSTRACT

Background and purpose: In a retrospective analysis, we examined factors influencing the outcome of prostate cancer (PCa) patients receiving salvage radiotherapy (SRT) for PSA recurrence after radical prostatectomy (RP).

Material and methods: 306 patients received 3D-conformal SRT at a median pre-SRT PSA of 0.298 ng/ml. Post-SRT progression was defined as PSA ⩾0.2 ng/ml above nadir and rising further, or hormone treatment, or clinical recurrence. Data were analyzed with the Kaplan–Meier method and multivariable Cox regression.

Results: Application of SRT at a PSA <0.2 ng/ml correlated significantly with achieving a post-SRT PSA nadir <0.1 ng/ml and with improved freedom from progression (median follow-up 7.2 years). The post-SRT nadir <0.1 ng/ml correlated significantly with less recurrences and with better overall survival. In multivariable Cox analysis restricted to pre-SRT parameters, a pre-SRT PSA ⩾0.2 ng/ml had the strongest impact (hazard ratio 2.4) on progression. If the post-SRT PSA nadir was included in the model, then failing the nadir was the most important risk factor (hazard ratio 8.1).

Conclusions: Early SRT at a PSA <0.2 ng/ml is a favorable treatment option for post-RP biochemical recurrence. It correlated with a post-SRT PSA-nadir <0.1 ng/ml which was associated with improved freedom from progression and overall survival.

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Radical prostatectomy (RP) is one of the first-line therapy options for prostate cancer (PCa). The best results are obtained with organ-confined disease. Recurrence correlates with risk factors such as extraprostatic tumor extension, a high Gleason score, positive surgical margins, a short PSA doubling time and also post-RP persistence of PSA [8,25]. Numerous models are available to predict the probability of relapse. Upon validation, their accuracy ranges around 80% [4,16,22].

Clinical recurrence is usually preceded by PSA progression [20]. Therefore, initiating salvage radiotherapy (SRT) upon biochemical evidence of disease is now backed up by national and international guidelines. However, the appropriate PSA level to trigger SRT is not yet defined uniformly [8,10,24]. SRT allows around 60% of the patients to re-achieve an undetectable PSA. Similar to post-RP recurrence, the failure-rates after SRT can be assessed from the pattern of risk factors [1,12,21]. The parameters that influence the individual outcome after SRT reflect the whole course of disease, e.g. pre-RP PSA, surgical margins, PSA before radiotherapy or the treatment dose. There is also evidence that achieving a post-SRT PSA nadir between <0.03 and <0.1 ng/ml is a favorable prognostic marker [5,9,26].

Despite the considerable body of original data and meta-analyses, the optimal condition to initiate SRT is still unclear. Specifically, the definition for the first biochemical relapse is under discussion. Stephenson et al. observed freedom from progression after six years in 48% of the patients with a pre-SRT PSA up to 0.5 ng/ml but only 26% in men with a higher PSA [21]. One review suggested two PSA measurements ⩾0.4 ng/ml as the most accurate indicator of clinically significant disease [19]. A cut-off at 0.28 ng/ml distinguished high risk (39%) and low risk (22%) of post-SRT biochemical recurrence [17]. According to a matched-pair comparison, SRT at a median PSA of 0.22 ng/ml yielded results nearly identical with adjuvant radiotherapy [2]. European Guidelines suggest that SRT might be initiated, at PSA levels of 0.1–0.3 ng/ml, if a continuous PSA increase has been documented [7].

In the present paper, we report on the long-term outcome of SRT patients with a median/maximum follow-up of 7 and 14 years,

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respectively. The patients were treated homogeneously for pN0 (95%)/cN0 (5%) disease. They represent one of the largest cohorts in this field. We focus on the pre-SRT PSA and on the patients' PSA response to salvage treatment as parameters that influences long-term biochemical recurrence and overall survival.

Methods and materials

Patients and clinical variables

Between 1997 and 2007, 306 prostate cancer patients received salvage radiotherapy for post-RP recurrent disease at the Charité University Hospital Berlin. Radical prostatectomy had been carried out between 1989 and 2006. All patients had cN0 (5%) or pN0 (95%) tumors with median 8 (0–28) nodes resected. SRT was applied based on 3D planning with 1 cm security margins. The prescribed dose to the prostatic fossa (plus the seminal vesicles for pT3 tumors) was 66.6 Gy in the early years; from 2004 on, patients whose PSA decreased during SRT ($N = 66$) received 70.2 Gy [18]. The overall applied dose range was 59.4–70.2 (median 66.6) Gy. The post-SRT PSA follow-up information was mostly obtained through inquiry from the attending practitioners. Due to the retrospective character of our data-bank analysis, the comparability of PSA doubling times was questionable. We did not use this parameter.

While PSA detection limits varied between laboratories, we defined the undetectable PSA range as <0.1 ng/ml. We report retrospectively, with a median follow-up of 7.2 (max. 14.4) years. Table 1 summarizes the baseline characteristics of the patients.

Table 1
Clinical characteristics of 306 prostate cancer patients who received SRT.

Item	Patients
Median age at RP (range)	63 (43–77) years
Pre-RP hormonal treatment*	
Yes	40 (13%)
No	264 (86%)
Missing data	2 (<1%)
Median pre-RP PSA (range)	10.4 (0.54–107) ng/ml
pT stage	
pT2	165 (54%)
pT3a	84 (27%)
pT3b	50 (16%)
pT4	3 (1%)
Missing data	4 (1%)
Lymph node status	
cN0	14 (5%)
pN0 (median 8 nodes resected)	292 (95%)
Surgical margins	
Negative (R0)	109 (36%)
Positive (R1)	165 (54%)
Unknown (Rx)	32 (10%)
Gleason score	
GLS $\leqslant$ 6	148 (48%)
GLS = 7	96 (31%)
GLS = 8–10	61 (20%)
Missing data	1 (<1%)
Pre-SRT PSA median (range)	0.298 (0–8.9) ng/ml
< 0.03 ng/ml	3 (1%)
0.03–0.199 ng/ml	108 (35%)
0.2–0.499 ng/ml	86 (28%)
0.5–0.99 ng/ml	50 (16%)
1.0–4.99 ng/ml	53 (17%)
5.0–8.9 ng/ml	6 (2%)

RP = radical prostatectomy, PSA = prostate specific antigen, SRT = salvage radiotherapy.
* Patients with anti-androgen treatment between RP and SRT were excluded from the analysis.

Statistical methods

Post-SRT progression was defined according to Stephenson et al. [21]: Events terminating post-SRT freedom from progression were primarily biochemical recurrence defined as a rising PSA, 0.2 ng/ml above the post-SRT nadir or as persistently rising PSA; also, the application of hormone therapy (HT) was defined as progression. Patients with HT between RP and SRT were excluded from the analysis. There were too few events for a reasonable analysis of clinical progression and cancer specific mortality. The endpoint for overall survival (OS) was death from any reason. Data were analyzed using SPSS and WinStat. The Kaplan–Meier statistics with log-rank test and Cox regression analysis were used to quantify the influence of disease and treatment related parameters on freedom from progression and OS.

Results

After prostatectomy, 234 patients had achieved a PSA below 0.1 ng/ml (undetectable range), 64 had PSA persistence with higher values; for 8 patients, only the PSA at recurrence and/or pre-SRT PSA were available. Recurrences occurred in median after 9.5 months (interquartile range IQR 3.7–24.6 months) post-RP. The median delay from recurrence to SRT was 8.3 months (IQR 2.8–20.0 months). Radiotherapy was given at a median PSA of 0.298 ng/ml (IQR 0.143–0.723 ng/ml, also see Table 1). After SRT, 221 patients achieved a PSA nadir <0.1 ng/ml, 85 retained higher values. In median, patients had 17 PSA follow-ups (IQR 9–24). Post-SRT recurrence was stated in 134 cases.

Table 2 summarizes the univariate analyses of parameters influencing progression. The Kaplan–Meier curves for post-SRT progression depending on pre-SRT PSA are shown in Fig. 1. At the median follow-up of 7.2 years, the probability for freedom

Table 2
Summary of univariate analyses of parameters influencing post-SRT progression in 306 patients.

Parameter	Free from progression*	Logrank test
Pre-SRT PSA		
<20 ng/ml	0.507 (0.434–0.580)	$p = 0.3485$
$\geqslant$20 ng/ml	0.423 (0.253–0.593)	
Stage		
pT2	0.575 (0.489–0.661)	$p = 0.0032$
pT3–4	0.410 (0.319–0.501)	
Gleason score		
GLS $\leqslant$ 6	0.627 (0.538–0.715)	$p < 0.0001$
GLS $\geqslant$ 7	0.380 (0.295–0.465)	
Surgical margins		
R0	0.439 (0.335–0.544)	$p = 0.0821$
R1	0.549 (0.463–0.636)	
Post-RP PSA		
<0.1 ng/ml	0.547 (0.475–0.619)	$p = 0.0030$
$\geqslant$0.1 ng/ml	0.336 (0.211–0.461)	
Pre-SRT PSA		
<0.2 ng/ml	0.677 (0.580–0.773)	$p < 0.0001$
$\geqslant$0.2 ng/ml	0.400 (0.322–0.477)	
SRT dose**		
<70 Gy	0.460 (0.391–0.528)	$p = 0.0083$
70.2 Gy	0.678 (0.539–0.816)	
Post-SRT PSA nadir		
<0.1 ng/ml	0.670 (0.599–0.740)	$p < 0.0001$
$\geqslant$0.1 ng/ml	0.018 (0.000–0.053)	

RP = radical prostatectomy, PSA = prostate specific antigen, SRT = salvage radiotherapy.
* Kaplan–Meier estimates with 95% confidence intervals at the median follow-up of 7.2 years are indicated.
** Patients receiving 70.2 Gy were selected based on an intra-SRT PSA decline.