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ARTICLE

Clinical

Effect of early salvage radiotherapy at PSA < 0.5 ng/ml and impact of post-SRT PSA nadir in post-prostatectomy recurrent prostate cancer

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Abstract

Background For patients with recurrent prostate cancer after radical prostatectomy (RP), salvage radiotherapy (SRT) offers a second chance of cure. European guidelines (EAU) recommend SRT at a PSA < 0.5 ng/ml. We analyze the efficacy of SRT given according to this recommendation and investigate the predictive power of the post-SRT PSA nadir.

Methods Between 1998 and 2013, 301 patients of two university hospitals received SRT at a PSA < 0.5 ng/ml (median 0.192 ng/ml, IQR 0.110–0.300). Patients, who previously received androgen deprivation therapy, were excluded. All patients had 3D-conformal RT or intensity-modulated radiotherapy (IMRT, $n = 59$) (median 66.6 Gy). The median follow-up was 5.9 years. Progression and overall survival were the endpoints.

Results After SRT, 252 patients re-achieved an undetectable PSA. In univariate analysis, pre-RP PSA ≥ 10 ng/ml, pT3-4, Gleason score (GS) 7–10 or 8–10, negative surgical margins, post-RP PSA ≥ 0.1 ng/ml, pre-SRT PSA ≥ 0.2 ng/ml and post-SRT PSA nadir ≥ 0.1 ng/ml correlated unfavorably with post-SRT progression. In a multivariable Cox model, pT3-4, GS 7–10, negative margins and a pre-SRT PSA ≥ 0.2 ng/ml were significant risk factors. If the post-SRT PSA was added to the analysis, it dominated the outcome (HR = 9.00). Of the patients with a pre-SRT PSA < 0.2 ng/ml, only 9% failed re-achieving an undetectable PSA. Overall survival in these patients was 98% after 5.9 years compared to 91% in patients with higher pre-SRT PSA (Logrank $p = 0.004$).

Conclusions SRT at a PSA < 0.2 ng/ml correlates significantly with achieving a post-SRT undetectable PSA (<0.1 ng/ml) and subsequently with improved freedom from progression. Given these overall favorable outcomes, whether additional androgen deprivation therapy is required for these men requires further study.

Introduction

Radical prostatectomy (RP) is one of the most common treatment options currently recommended for clinically localized prostate cancer (PCa). However, depending on risk factors such as an advanced pathological stage (pT3–4), a high Gleason score (GS 8–10) or positive surgical margins (R1), 50–80% of these patients experience biochemical recurrence [1]. After PSA recurrence, salvage radiotherapy (SRT) offers a second chance of cure. Overall, approximately 60% of the patients re-achieve an undetectable PSA after SRT, and 80% of these men are free from progression after 5 years [2, 3]. However, 40–70% of the patients initially responding to SRT, later develop re-increasing PSA values as biochemical evidence of progression of disease. The rate of these recurrences depends on pre-SRT parameters with the PSA as a major factor. European guidelines (EAU) recommend early SRT at a PSA < 0.5 ng/ml [4].

Recently, Stish et al. reported a retrospective study of 1.106 patients who have received SRT between 1987 and 2013 at a PSA ≤ 0.5 ng/ml compared with later treatment,

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with median follow-up of 8.9 years. Biochemical recurrences, distant metastases, and cause-specific mortality were significantly reduced with the earlier intervention. An observed advantage for overall survival was not significant. Besides the pre-SRT PSA, tumor stage and Gleason score were associated with all four endpoints while the post-SRT PSA was not analyzed as a potentially independent variable [5].

In fact, the post-SRT PSA appears to be a prognostic marker [6, 7]. A decrease below 0.1 ng/ml can be regarded as a first favorable treatment result. Failing such a response may identify SRT-patients who require an additional therapy at some time.

We analyzed the efficacy of SRT given according to EAU recommendation (PSA < 0.5 ng/ml) and investigated the predictive power of the post-SRT PSA nadir.

Methods

In this retrospective analysis, we included 301 patients of two university centers who received SRT for post-RP biochemical recurrence at a PSA < 0.5 ng/ml. The patients had RP between 1989 and 2011, 123 with negative surgical margins, 140 with positive margins, and 38 were Rx. All were stated node negative, 289 pN0 with median 10 nodes resected and 12 cN0 (lymphadenectomy not indicated). 26 patients (9%) previously received androgen deprivation therapy (ADT). Cases with ADT between RP and SRT were excluded. Table 1 summarizes the baseline patient characteristics.

After recurrence, the patients received SRT (1998–2013) with median 66.6 (range 59.4–72) Gy. All had 3D-conformal treatment, including 59 cases with intensity modulated radiotherapy (IMRT). In pT2-tumors and pT3a-tumors the planning target volume included the prostate bed and the basis of the former seminal vesicles. In pT3b-tumors, the bed of seminal vesicles was included, too. Regional pelvic lymph nodes were not irradiated.

The median follow-up was 5.9 years (max. 13.3 years)

Follow-up information was in part obtained through inquiry from the attending practitioners. The primary endpoint was post-SRT progression according to Stephenson's criteria: a rising PSA 0.2 ng/ml above the nadir or the initiation of ADT or clinical progression [2]. As laboratory standards varied during the reported period, we defined a PSA < 0.1 ng/ml as undetectable. Overall survival (OS) was a second endpoint in the analysis.

Table 1 Baseline characteristics of 301 prostate cancer patients receiving salvage radiotherapy for post-prostatectomy recurrence

Item	Patients
Pre-RP ADT	
Yes	26 (9%)
No	275 (91%)
Median pre-RP PSA (IQR)	9.64 (6.55–14.5) ng/ml
pT stage	
pT2	153 (51%)
pT3a	95 (32%)
pT3b	47 (16%)
pT4	4 (1%)
Missing data	2 (<1%)
Gleason score	
GS ≤ 6	125 (42%)
GS = 7	113 (38%)
GS = 8-10	61 (20%)
Missing data	2 (<1%)
Nodal state	Median 10 nodes resected
cN0	289 (96%)
pN0	12 (4%)
Surgical margins	
R0	123 (41%)
R1	140 (47%)
Rx	38 (13%)
Pre-SRT PSA	
Median (IQR)	0.192 (0.110–0.300) ng/ml
<0.03 ng/ml	4 (1%)
0.03–0.099 ng/ml	60 (20%)
0.1–0.199 ng/ml	91 (30%)
0.2–0.499 ng/ml	146 (49%)
SRT dose	
Median (range)	66.6 (59.4–72) Gy
Age at SRT	
Median (range)	66.1 (62.4–69.8) years

We used WinStat and SPSS for descriptive statistics, Kaplan–Meier analysis (Logrank-test) and multivariable Cox regression.

Results

After RP, 260 patients achieved a PSA in the undetectable range (<0.1 ng/ml), 41 had a persistent or rising PSA. First recurrence was stated in median 0.9 years after RP (IQR 0.3–1.9). The median time from RP to SRT was 1.6 years (IQR 0.7–2.3). After SRT, 252 patients re-achieved an undetectable PSA, 49 retained higher values. There were 92 s recurrences and 17 patients died (Fig. 1a).

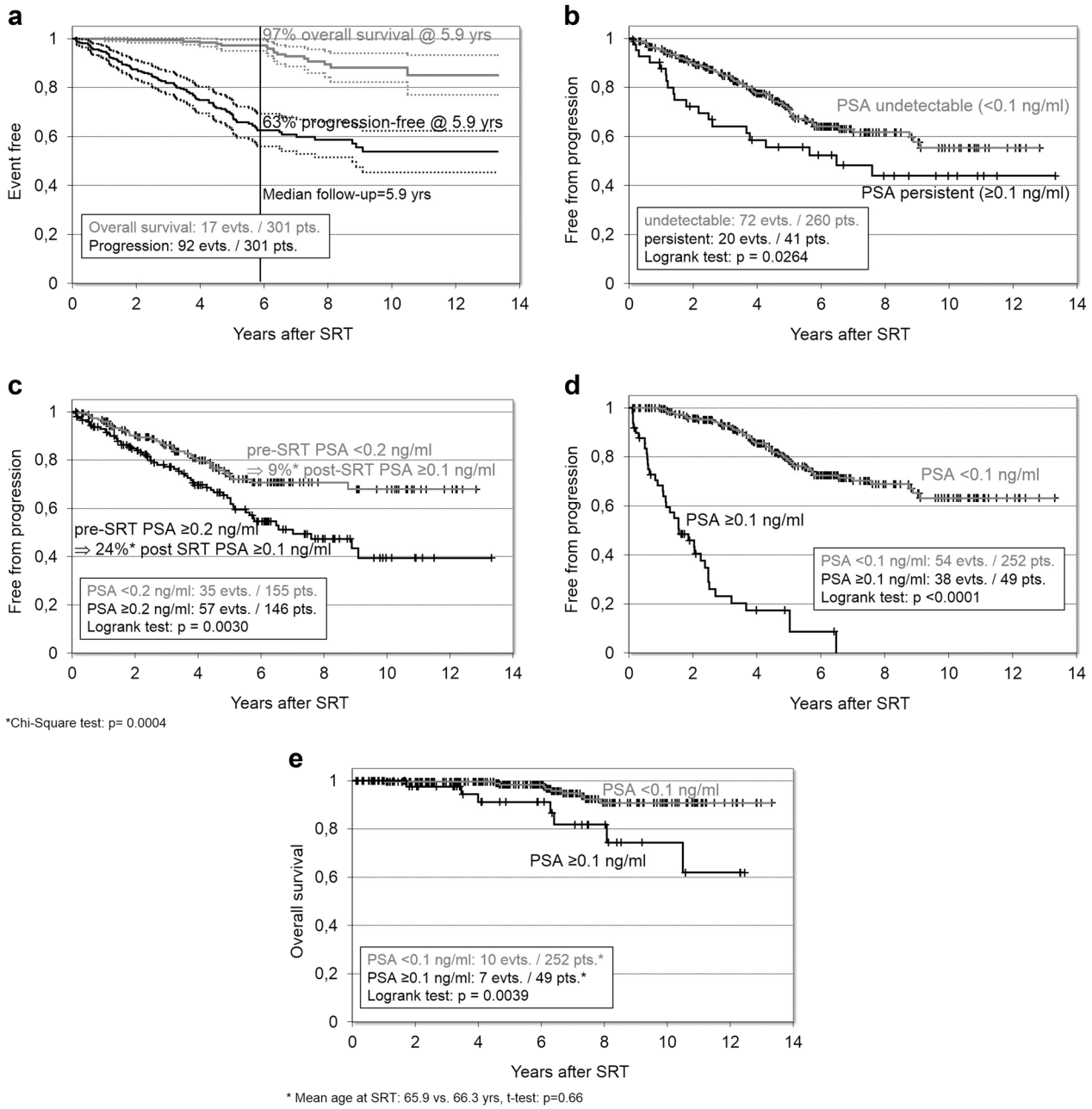

Fig. 1 **a** Overall outcome of salvage radiotherapy for post-prostatectomy recurrent prostate cancer. **b** Kaplan–Meier plot of post-SRT progression: Post-RP PSA undetectable vs. persistent **c** Kaplan–Meier plot of post-SRT progression: pre-SRT PSA < 0.2 vs. ≥0.2 ng/ml. **d** Kaplan–Meier plot of post-SRT progression: post-RT PSA < 0.1 vs. ≥0.1 ng/ml **e** Kaplan–Meier plot of overall survival: post-RT PSA < 0.1 vs. >0.1 ng/ml

In univariate analysis, the following parameters correlated unfavorably with post-SRT progression: pre-RP PSA ≥ 10 ng/ml, pT3-4, Gleason score (GS) 7–10 or 8–10, negative surgical margins (R0), post-RP PSA ≥ 0.1 ng/ml, pre-SRT PSA ≥ 0.2 ng/ml and post-SRT PSA nadir ≥ 0.1 ng/ml (Fig. 1b–d). There was no subgroup that did not benefit from SRT at PSA < 0.2 ng/ml (Table 2).

In backward excluding Cox regression analysis, pT3–4 (Hazard ratio HR = 2.29), GS 7–10 (HR = 2.52), negative margins (HR = 1.68) and a pre-SRT PSA ≥ 0.2 ng/ml (HR = 1.71) were significant risk factors. If the post-SRT PSA was added to that model, it dominated the outcome (HR = 9.00) (Table 3).

Of the patients with a pre-SRT PSA < 0.2 ng/ml, only 9% failed re-achieving an undetectable PSA; with a higher

pre-SRT PSA, 24% did so. The difference also had an impact on overall survival which was 98% vs. 91% after 5.9 years (Logrank $p = 0.004$) favoring men with a post-SRT PSA < 0.1 ng/ml (Fig. 1e).

Discussion

The optimal timing of radiotherapy after RP is still under debate [8, 9]. Three randomized prospective trials (SWOG 8794, EORTC 22911, and ARO 96-02) have shown a benefit for adjuvant radiotherapy (ART) compared with a wait-and-see strategy, and in the SWOG 8794 trial, not only biochemical progression but also overall survival was improved [1, 10, 11]. However, as salvage therapies in these trials are not well documented, even an indirect comparison of ART vs. SRT is hampered and so far, ongoing randomized trials (e.g., RADICALS) which directly compare the two strategies have not yet published results.

Recently, a multi-institutional, propensity score-matched cohort study reported on 1566 patients who underwent ART or early SRT at ten medical centers in the United States. ART, compared with early SRT, was associated with higher freedom from biochemical failure (12-year actuarial rates: 69% vs. 43%), freedom from distant metastases (95% vs. 85%), and overall survival (91% vs. 79%) [12].

Nonetheless, it is clear that ART but also SRT can be connected with overtreatment. In the observational arm of the ARO 96-02 trial, depending on risk factors, a quarter (R1 or pT3c) to half (pT3 R0) of the patients remained free from progression after 10 years [1].

The right setting for adjuvant versus early salvage radiotherapy is still under debate, with respect to the patients clinical characteristics [13, 14].

Recently, two randomized controlled trials compared SRT plus androgen deprivation therapy to SRT alone. The RTOG 9601 trial showed an improvement of overall survival for the combination of 2 years of bicalutamide and SRT after a median follow-up of 13 years. This improvement was restricted to patients with a pre-RT PSA ≥ 0.7 ng/ml [15]. The GETUG AFU-16 trial showed that after a median follow-up of 5 years, the addition of 6 months of goserelin to SRT improved progression-free survival [16]. Men with a pre-SRT PSA > 0.5 ng/ml had a 3-fold higher benefit in biochemical control compared with those with < 0.5 ng/ml. It is important to note that PFS is actually not suitable as primary endpoint when a GnRH agonist is given that directly affects the PSA.

In an observational cohort study of 259 patients from Denmark, a benefit from additional ADT was found in men, whose PSA exceeded 0.2 ng/ml [17], while its application seems to be controversial even in patients with macroscopic local recurrence [18].

However, in the setting of early salvage, the role of ADT remains debatable. In patients with a PSA level before SRT of < 0.7 ng/ml, additional ADT should not be routinely used but may be considered in patients with additional risk factors such as Gleason score ≥ 8 and negative surgical margins [19, 20].

In our cohort, early SRT at a PSA < 0.2 ng/ml correlates significantly with achieving a post-SRT undetectable PSA (0.1 ng/ml) and subsequently with improved freedom from progression. International guidelines recommend SRT at a PSA of 0.5 ng/ml or less [4]. The Mayo data are in full

Table 2 Subgroup analysis: Benefit from SRT at PSA < 0.2 ng/ml

Subgroup	*N*	FFP @ 5.9-years	Logrank *p*
Pre-PR PSA < 10 ng/ml	151	0.74 vs 0.62	0.0575
Pre-PR PSA ≥ 10 ng/ml	133	0.65 vs 0.50	0.0942
pT2	153	0.84 vs 0.63	0.0244
pT3-4	146	0.59 vs 0.46	0.0263
GS ≤ 6	125	0.84 vs 0.67	0.0779
GS ≤ 7	238	0.76 vs 0.61	0.0080
GS 7	113	0.65 vs. 0.55	0.0983
GS ≥ 7	174	0.59 vs. 0.45	0.0380
GS ≥ 8	61	0.49 vs. 0.26	0.1142
R0	123	0.71 vs. 0.42	0.0137
R1	140	0.73 vs 0.61	0.0477

Table 3 Multivariable Cox regression analysis of progression

	Model 1 (backward elimination)		Model 2 (inclusive mode)	
Risk factor	HR (95% CI)	*p*	HR (95% CI)	*p*
pT3–4	2.29 (1.36–3.86)	0.0020	1.45 (0.85–2.47)	0.1766
GS 7–10	2.52 (1.40–4.52)	0.0021	1.97 (1.13–3.42)	0.0165
Negative margins	1.68 (1.07–2.65)	0.0245	1.58 (0.99–2.53)	0.0542
Pre-SRT PSA ≥ 0.2 ng/ml	1.71 (1.08–2.72)	0.0219	1.45 (0.91–2.30)	0.1143
Post-SRT PSA nadir ≥ 0.1 ng/ml	Not included	–	9.00 (5.42–14.9)	<0.0001

Model 1 is based on parameters known before SRT. Model 2 only applies for post-SRT considerations of the prognosis. The post-SRT PSA nadir is a dominant predictor of the further course of disease

agreement with that cutoff [5]. However, with advancing laboratory techniques, today a rising PSA is detectable at much earlier stages.

Two multi-institutional retrospective studies from the United States that report on over 3100 patients, showed a benefit from early SRT at a PSA < 0.2 ng/ml vs. PSA 0.2–0.5 ng/ml vs. higher values [21, 22]. Different from the above cohorts, we report exclusively on node-negative cases (pathologically confirmed in 96%) without androgen deprivation therapy between RP and SRT.

A retrospective study on 716 patients with pT2–pT4 pN0 R0-1 adenocarcinoma of the prostate and undetectable PSA after RP examined the efficacy of SRT at PSA ≤ 0.5 ng/ml. At multivariable Cox regression analysis, pre-SRT PSA was significantly associated with biochemical recurrence after early SRT (HR 4.9; $p < 0.0001$) besides pT3, GS > 8 and negative margins (HR values 2.1–2.7). However the advantage from early SRT was highest in men with more unfavorable pathological features but less pronounced in men with lower-risk profiles [23].

Depending on the presence of risk factors, PSA values well below 0.1 ng/ml have already been suggested for the initiation of SRT [24]. Freedland et al. reported on a retrospective survey of 358 men undergoing RP between 1991 and 2001. For patients with a detectable postoperative PSA value from 0.11 to 0.2 ng/ml, the 1 and 3-year risk of PSA progression was 64% and 93%, respectively [25]. Taken together, the above data underline the potential of very early SRT, i.e., at a PSA < 0.2 ng/ml, to improve the prognosis of post-RP recurrent prostate cancer.

In a study on 448 patients, Jackson et al. found an increased risk of biochemical progression, distant metastases, cancer-specific, and overall mortality in men who retained a PSA ≥ 0.1 ng/ml after SRT. Additionally, a detectable PSA nadir within 6 months post-SRT was an unfavorable prognostic parameter. These patients are unlikely to have clinically localized disease and should be considered for initiation of systemic therapies [7]. In contrast to our cohort, the pre-SRT PSA was quite advanced (median 0.6 ng/ml) in that study. The potential of the PSA-nadir as a predictive factor for long-term outcome (all cause mortality) has similarly been reported for primary radiotherapy ± ADT [26].

Limitations of our analysis relate to the retrospective design. We had to accept inhomogeneous follow-up sequences and PSA detection became more sensitive during the reported period. To prevent bias, we defined a uniform range of undetectability, which does not reflect recent laboratory standards. Effects of the nadir below 0.1 ng/ml could thus not be determined.

The dose prescription varied considerably, including dose-escalation which was applied during a couple of years in patients whose PSA declined during the course of SRT. This would introduce bias in an analysis of the dose dependence of our endpoints, which doubtlessly exists. In addition, it must be noted that the endpoint PSA progression has some limitations [19]. Data on metastasis-free survival are not yet available.

Conclusions

Early SRT at a PSA < 0.2 ng/ml was favorable in the 301 patients and all analyzed subgroups. It correlated significantly with achieving a post-SRT undetectable PSA (<0.1 ng/ml), which has high predictive potential for improved freedom from progression. In patients who had SRT at a PSA < 0.5 ng/ml, an undetectable post-SRT PSA-nadir was the strongest predictor of freedom from progression and overall survival. Missing an undetectable nadir may help to identify patients, who can benefit from additional systemic treatment. The recommended PSA cut-off for SRT (<0.5 ng/ml) should be reconsidered.

Compliance with ethical standards

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

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