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ORIGINAL ARTICLE

Salvage radiation therapy following radical prostatectomy. A national Danish study

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ABSTRACT
Background: The purpose of this observational cohort study was to evaluate the outcome and prognostic factors following salvage radiotherapy (SRT) in a consecutive national cohort.
Material and methods: Between 2006 and 2010, 259 patients received SRT in Denmark. Patient- and cancer-related characteristics were retrospectively retrieved from patient charts. The primary end point was biochemical progression-free survival (b-PFS).
Results: At the end of follow-up, 51% of the patients displayed a prostate-specific antigen (PSA) level <0.1 ng/ml. The three-year b-PFS rate for the total cohort was 57.0%. Nearly half of the patients (44%) received androgen deprivation therapy (ADT) in combination with SRT. Positive surgical tumour margins ($p = 0.025$) and ADT ($p = 0.001$) were the only markers independently correlated with b-PFS. In patients who received SRT without ADT, both a pre-SRT PSA level ≤ 0.5 ng/ml ($p = 0.003$) and pathological tumour stage T1-T2 ($p = 0.036$) independently correlated with b-PFS. Moreover, a duration between radical prostatectomy (RP) and SRT ≤ 29 months ($p = 0.035$) independently correlated with b-PFS in patients treated with ADT in combination with RT.
Conclusions: In patients treated for biochemical failure after RP, positive surgical tumour margins and PSA levels ≤ 0.5 ng/mL at the time of SRT were associated with a favourable outcome. Despite less favourable tumour characteristics, patients receiving SRT and ADT demonstrated improved b-PFS, and in particular, patients with PSA levels >0.2 ng/ml benefitted from additional ADT.

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In Western countries, prostate cancer (PC) is the most common male malignancy [1]. The incidence of PC is rising, leading to an increased number of patients undergoing radical prostatectomy (RP). Approximately 15–25% of patients who undergo RP for clinically localised PC will experience biochemical failure [2,3] and for a large proportion of these patients, biochemical failure is the only sign of recurrent disease. One critical challenge is to verify whether these patients have local disease recurrence in the prostatic bed or distant metastasis, although current imaging techniques, including transrectal ultrasound (TRUS) with biopsies, fail to discriminate between these two types of failure, especially at early stages of disease [4–7]. However, patients with local failure are potentially curable when treated with salvage radiotherapy (SRT) after RP.

Previous studies have addressed the use of SRT in patients with biochemical failure after RP and demonstrated benefits from adjuvant radiotherapy (ART) compared to RP alone in patients with high-risk factors, either with or without additional ADT [8–15]. A number of prognostic factors have also been suggested to relate to outcome after SRT; these include the pre-SRT prostate-specific antigen (PSA) level, the Gleason score (GS) of the specimen, extra-capsular tumour extension, seminal vesicle tumour involvement, surgical margins, and lymph node metastasis. Previous studies have also reported a broad range of success rates in terms of biochemical progression-free survival (b-PFS) after SRT, varying from 10% to 50% [3,4,8,10].

Over the past ten years, SRT has become a generally accepted treatment in Denmark, for patients with local disease recurrence after RP. However, there have been no recommendations for the use of ADT in combination with SRT. The purpose of the present study was to characterise an unselected consecutive national cohort of patients undergoing SRT and identify clinical and pathological factors related to b-PFS.

Material and methods

This was a national retrospective analysis of all 259 patients who received SRT in Denmark during the five-year period between 2006 and 2010. The definition of biochemical failure after RP changed during the study period; early in the study period, this phenomenon was defined as an increase in PSA equal to or greater than 0.5 ng/ml, although this threshold was

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subsequently lowered to 0.2 ng/ml. None of the patients displayed evidence of distant metastases. The patients were treated at one of five radiotherapy centres in Aarhus, Herlev, Odense, Aalborg, and Copenhagen. Patient- and treatment-related factors were retrieved from the patients' medical charts at the Department of Oncology and Urology.

The patients underwent RP over a 10-year period between 1999–2009. In the beginning of the period all patients had a pelvic lymphadenectomy in the fossa obturaii, during the surgical procedure. Later in the period, only patients with intermediate and high-risk, according to the D'Amico risk criteria, had a pelvic lymphadenectomy. Only patients without lymph node metastases received later SRT

Before SRT, 115 patients received neoadjuvant ADT. The physician initiated ADT before radiotherapy on the basis of clinical judgement without standardised criteria. The patients were treated with a median dose of 69 Gy (range 66–74), with 2-Gy daily fractions to the prostatic bed and the location of the seminal vesicles, according to the Radiation Therapy Oncology Group (RTOG) guidelines [16]. Pelvic lymph nodes were not included in the target volume. The definition of SRT is the administration of radiotherapy to the prostatic bed in patients with biochemical failure after surgery but with no evidence of distant metastatic disease [16]. The patients made follow-up visits for clinical assessment and PSA testing one month after RT, followed by every 3–6 months for the following two years and annually thereafter.

The primary endpoint of this study was b-PFS after RT, which was defined as a serum PSA value of 0.2 ng/ml or higher, as confirmed using a second blood test. A number of potential prognostic factors, such as PSA level at the time of RP, pT-stage, status of the surgical margins, GS of the surgical prostate specimen, PSA nadir after RP, PSA level at the time of RT, combined treatment with ADT, time from diagnosis to RP, and time from RP to RT, were included in the analysis. The dates for biochemical failure in patients with a consistent PSA rise after RP or RT were registered as the dates of RP or RT, respectively.

Statistical analysis

The Kaplan–Meier method was used to evaluate b-PFS after RT, and differences between groups were tested with the log-rank test. B-PFS was calculated from the day ending SRT, and censoring was made at the date for the first blood test with a serum PSA value of 0.2 ng/mL or higher.

Multivariate Cox regression analysis was performed to identify prognostic factors that were independently associated with b-PFS. Only parameters that were significantly correlated with b-PFS in the univariate analysis were included in the multivariate model. All statistical tests were two-sided, with a statistical significance level of 0.05. The statistical analyses were performed with Stata version 12.0 (Stata, College Station, TX, USA).

Results

This study comprised 259 patients treated with SRT in Denmark. Nearly half (115; 44%) of the patients received ADT in combination with SRT, while 144 (56%) received SRT alone. The patient and tumour characteristics are shown in Table I.

Table I. Clinico-pathological, biochemical, and treatment characteristics.

Characteristics	Salvage radiotherapy No. (%)	SRT with ADT No. (%)	SRT without ADT No. (%)
Pre-RP PSA level (ng/ml)			
<10	87 (33)	31 (27)	56 (38)
≥10 to ≤20	106 (42)	51 (45)	54 (40)
>20	53 (20)	29(25)	24 (17)
Unknown	13 (5)	4 (3)	9 (5)
Pathologic Gleason score			
<7	50 (19)	30 (25)	20 (14)
7	142 (55)	55 (48)	86 (61)
8–10	59 (23)	25 (23)	34 (23)
Unknown	8 (3)	5 (4)	3 (2)
Surgical margin			
Tumor negative	82 (31)	31 (26)	50 (35)
Tumor positive	163 (64)	78 (69)	85 (60)
Unknown	14 (5)	6 (5)	8 (5)
Pathologic T-stage			
PT2	176 (68)	77 (67)	98 (69)
PT3a	44 (17)	21 (18)	23 (16)
PT3b	6 (3)	3 (3)	3 (2)
PT4	4 (1)	1 (1)	3 (2)
Unknown	29 (11)	13 (11)	16 (11)
PSA nadir (RP)			
<0·2 ng/ml	186 (72)	81 (72)	105 (73)
≥0·2 ng/ml	48 (19)	24 (20)	24 (17)
Unknown	25 (9)	10 (8)	14 (10)
Pre-SRT PSA (ng/ml)			
0·2	22 (8)	8 (4)	25 (17)
>0·2–0·5	80 (31)	23 (20)	57 (40)
≥0·5	122 (47)	72 (63)	49 (34)
Unknown	35 (14)	16 (14)	19 (13)
SRT dose (median; Gy)	68·0 (66·0–74·0)	68·0 (66·0–74·0)	70·0 (66·0–70·0)
Age at SRT (median; years)	66·0 (52·1–78.9)	65·7 (52·1–78.9)	66·2 (53·5–77·8)
Time from diagnosis to RP (median; months)	2.47 (0–73.5)	2.43 (0–45.0)	2.53 (0–73.5)
Time from RP to SRT (median; months)	30.4 (2.0–113.3)	34.1 ((2.0–108.8)	26.2 (2.5–113.3)
Follow-up duration, after SRT (years)	3·1 (0·7–6·6)	4·1 (1·8–6·6)	2·6 (0·7–6·5)

PSA, prostate-specific antigen; RP, radical prostatectomy; SRT, salvage radiotherapy.

Forty-eight patients demonstrated measurably elevated PSA levels three months after RP. The median time from diagnosis to RP was 2.46 months (range 0–73.5). The median time from RP to biochemical failure was 13.5 months (range 0–111.7), and the median time from biochemical failure to RT was 8.4 months (range 0.03–88.3).

In all patients treated with combined therapy, ADT was initiated before RT. Two-thirds of the patients treated with combined ADT and RT (74; 64%) received a gonadotropin-releasing hormone analogue, and the remaining patients were treated daily with 150 mg bicalutamide. The median duration of ADT was 15.0 months (range 0.3–85.9). Patients treated during the earlier period of the study (2006–2008) more frequently received ADT in combination with SRT (79; 30.5%) than did patients who were treated later (28; 10.8%) ($p<0.001$).

The median follow-up time after SRT was 3.1 years (range 0.7–6.6). At the follow-up visit three months after the completion of RT, 57 (22%) of the patients had a detectable serum PSA level ≥0.2 ng/ml. Biochemical failure was observed in 127 (49.0%) of the patients, including patients who never obtained a non-measurable PSA. The three-year b-PFS rate for the total cohort was 57.0% (95% CI 50–63) (Figure 1). For patients treated with ADT combination therapy, the three-year b-PFS rate was 68.0% (95% CI 59.0–76.2) compared with 47.8%

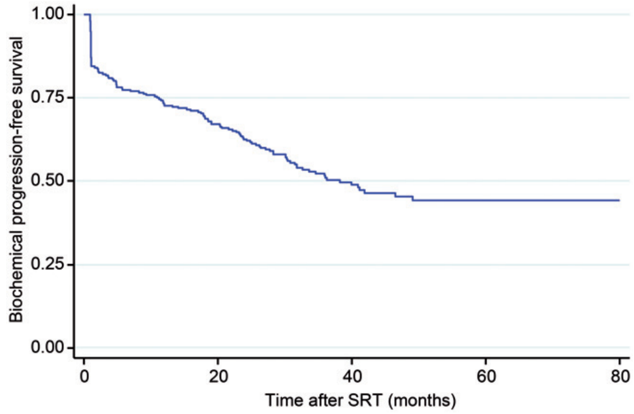

Figure 1. Kaplan-Meier estimates of b-PFS. Overall b-PFS. SRT, salvage radiotherapy.

Table II. A univariate analysis of clinical and pathologic predictive factors for biochemical progression-free survival in prostate cancer patients undergoing salvage radiotherapy after radical prostatectomy.

Parameter	No.	3-year b-PFS % (95% CI)	*p*-value[a]
Pre-RP PSA level (ng/ml)[b]			
≤12·6	127	53·0 (43·6–61·6)	0·2884
>12.6	117	47·0 (37·2–56·3)	
Pathologic Gleason score			
≤6	49	64.3 (48.9–76.1)	0·0703
≥7	200	48.0 (40.4–55.1)	
Surgical margin status			
Negative	81	41.0 (29.8–51.9)	0·0102
Positive	162	56.2 (47.6–63.8)	
Pathological tumor stage			
≤T2c	175	52.4 (44.2–60.0)	0·4071
≥T3a	54	48.5 (34.3–61.3)	
PSA nadir RP			
Undetectable	184	54.4 (46.6–61.7)	0·1898
Detectable	48	43.7 (28.3–58·0)	
Pre-SRT PSA level (ng/ml)[b]			
≤0·5	104	47.1 (37.0–56.6)	0·1688
>0·5	118	51.9 (41.7–61·2)	
Time from RP to SRT (months)[b]			
≤29	134	48.7 (39.7–57.2)	0·1871
>29	121	54.7 (44.8–63.5)	
Patient's age at SRT (years)[b]			
≤66 years	131	58.7 (49.4–67.0)	0·8789
>66 years	128	44.3 (34.8–53.3)	

ADT, androgen deprivation therapy; PSA, prostate-specific antigen; RP, radical prostatectomy; SRT, salvage radiotherapy.
[a]*p*-values are from Kaplan-Meier log-rank statistics; [b]Continuous variables were dichotomised at their median.

(95% CI 37.1–55.7) in patients receiving no ADT. Eleven of the patients with disease failure after RT demonstrated verified clinical failure; the remaining patients presented biochemical failure, with a PSA level ≥0.2 ng/ml serving as the only sign of failure. Three patients died from PC, and four patients died from causes not related to PC.

In a univariate analysis, positive surgical tumour margins ($p = 0.0102$) and concurrent ADT ($p < 0.001$) were significantly related to b-PFS (Table II). The Kaplan-Meier estimates are illustrated in Figure 2.

A stratified analysis was performed on patient groups treated with ($n = 115$) or without ($n = 143$) ADT. In patients treated with SRT alone, positive surgical tumour margins ($p = 0.0471$), pT ($p = 0.0041$), and pre-RT PSA levels ($p = 0.0008$)

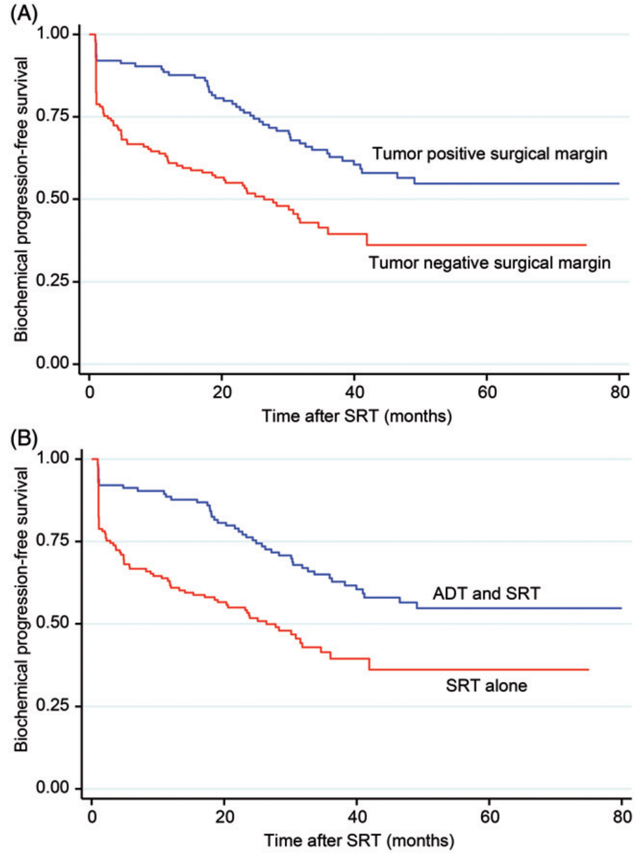

Figure 2. Kaplan–Meier estimates of b-PFS. (A) B-PFS according to surgical margin. (B) B-PFS according to ADT. ADT, androgen deprivation therapy; SRT, salvage radiotherapy.

were significantly related to b-PFS. In patients receiving ADT in combination with RT, we found that only the time between RP and SRT ($p = 0.0275$) were significantly related to b-PFS.

Cox proportional hazards multivariate analysis of the total cohort found that both positive surgical margins and ADT remained significantly related to b-PFS. Pathological tumour stage ($p = 0.036$) and a pre-RT PSA level ≤0.5 ng/ml ($p = 0.003$) were independent predictors of b-PFS in patients treated with SRT alone, whereas a time from RP to RT ≤29 months ($p = 0.035$) were related to b-PFS in patients treated with a combination of RT and ADT (Table III).

The addition of ADT was statistically correlated with a longer b-PFS in patients with pre-SRT PSA levels higher than 0.2 ng/ml, whereas the addition of ADT was non-significant for improved b-PFS in patients with pre-SRT PSA levels at 0.2 ng/ml (Figure 3).

Discussion

The ultimate goal of SRT is to eradicate residual tumour foci in patients with biochemical failure after RP. SRT has curative potential in patents with increasing PSA levels caused by local failure, whereas this therapy is of no benefit if this increased level is due to metastases. Although there are no published prospective studies demonstrating the efficacy of SRT, it is an accepted form of standard treatment for patients with biochemical failure after RP [9,17,18].

Table III. Cox proportional hazards analysis of factors estimating biochemical progression-free survival in prostate cancer after salvage radiotherapy following radical prostatectomy.

Variables	HR (95% CI)	SE	*p*-value
The whole cohort			
Surgical margin (tumor positive vs. negative)	0·66 (0·46–0·95)	0·122	0·025
Androgen deprivation therapy (with vs. without)	0·50 (0·32–0·75)	0·106	0·001
SRT without ADT			
Pathological tumor stage (T1-T2 vs. T3-T4)	0·56 (0·33–0·96)	0·154	0·036
Pre-SRT PSA level (≤0·5 ng/ml vs. >0·5 ng/ml)	0·48 (0·29–0·78)	0·121	0·003
SRT with ADT			
Time from RP to SRT (≤29 months vs. >29 months)	0·52 (0·28–0·95)	0·162	0·035

ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen; RP, radical prostatectomy; SRT, salvage radiotherapy.

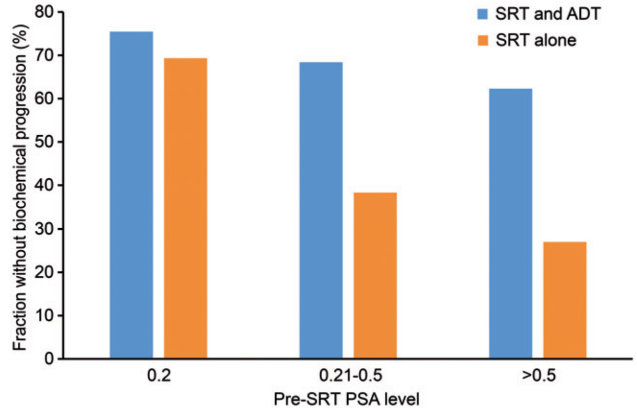

Figure 3. Three-year b-PFS and the impact of pre-SRT PSA levels on patients treated with concomitant ADT in combination with SRT and patients treated with SRT alone. ADT, androgen deprivation therapy b-PFS, biochemical progression-free survival; PSA, prostate-specific antigen; SRT, salvage radiotherapy. *p*-values are from Kaplan-Meier log-rank statistics: pre-SRT PSA level 0.2 (p =0.4990); pre-SRT PSA level >0.21–<0.5 (p =0.0252); pre-SRT PSA level ≥0.5 (p <0.001).

This study sought to address the efficacy of SRT in terms of b-PFS in an unselected consecutive national cohort of patients. During the study period, the number of patients treated with SRT increased by five-fold. This significant increase was caused by a number of factors, including an increasing number of patients diagnosed, a lower threshold for PSA levels before SRT and a general change in the approach and the development of national guidelines for the treatment of patients with biochemical failure after RP.

Recently, three prospective, randomised trials have shown a benefit from adjuvant radiotherapy (ART) in patients with pT3 or positive tumour margins after RP. In particular, patients receiving ART demonstrated an improved b-PFS compared to patients in the deferred arm [11–13], and one of these studies (the SWOG trial) even found improvements in metastasis-free survival following ART. However, one remaining question is when radiotherapy should be offered to these high-risk patients. The three previous studies all compared ART with SRT at a late time point in patients with a significant rise in PSA after RP. Therefore, the MRC RADICALS study, an ongoing, well powered, randomised controlled trial, will help answer important questions about the timing of radiotherapy in patients with factors related to a high risk for failure after surgery and the optimal use of ADT in combination with radiotherapy [19].

There are several important considerations regarding the administration of radiotherapy to patients after RP. The American Urological Association (AUA) and the American Society for Radiation Oncology (ASTRO) recommend that patients with adverse pathologic findings be treated with ART immediately following RP instead of waiting for biochemical or clinical failure [18].

As mentioned above, one critical issue in the early management of SRT is to determine whether an increasing PSA level is caused by a local failure in the prostatic bed or by distant metastases. Stephenson estimated the frequencies of local and distant failures and found an almost even distribution between these two failure sites [8]. TRUS-guided biopsy from the prostatic bed for the detection of local relapse demonstrates low sensitivity, and its use remains controversial and depends on the PSA level [20]. PET/CT 11C-choline also demonstrates low sensitivity, but this sensitivity was shown to increase considerably with PSA levels exceeding 1.0 ng/ml, resulting in a greater likelihood of identifying failures in the prostatic bed or lymph node or bone metastasis [21].

In a multivariate analysis of the entire cohort, we found that both the addition of ADT and positive surgical margins were independently associated with b-PFS (Table III). Nearly half of the patients in the present study received RT in combination with ADT, and stratified analysis showed that pre-RT PSA levels ≤0.5 ng/ml and pathological tumour stage T3-T4 were correlated with a favourable outcome in patients treated with RT without ADT. These data confirm that SRT should be administered at the earliest sign of biochemical failure after RP, especially in patients with pathological tumour stages of T3-T4. In the group of patients treated in combination with ADT, time between RP and SRT ≤29 months were correlated with a favourable outcome.

The time between surgery and radiation demonstrated an influence on b-PFS, which was clearly related to the pre-SRT PSA level. Additionally, as the salvage treatment strategy became more aggressive with time, the PSA threshold was lowered to 0.2 ng/ml, which automatically shortened the period between surgery and radiation.

In previous retrospective studies on SRT outcome, the following prognostic factors have emerged as favourable and related to a high response rate to SRT: pre-RP and pre-SRT PSA levels, PSA doubling time, the interval to PSA failure, GS, positive surgical tumour margins, seminal vesicle invasion, lymph node metastasis, and ADT administered in combination with SRT [3,4,8,10,22,23]. In particular, the multicentre study conducted by Stephenson et al. included 1540 patients and demonstrated a significant relationship between pre-SRT PSA levels and prognosis. In this study, the six-year disease-free survival rates were 48%, 40%, 28%, and 18% in patients with pre-SRT PSA levels <0.5, 0.5–0.1, 1–1.5, and >1.5 ng/ml, respectively [23]. These results are comparable with the current results showing that a pre-SRT PSA level ≤0.5 ng/ml and positive surgical tumour margins resulted in the most favourable outcomes. Thus, the addition of ADT seems to make these otherwise favourable factors less important.

The current study, as well as previous retrospective studies, showed a benefit in biochemical control with the addition of ADT to adjuvant or SRT treatment [10,24,25]. However, the optimal duration of and nature of ADT remain unknown; in this study, the median duration of ADT was 15.0 months. In previous adjuvant trials, the typical duration of ADT was six months. In our study, ADT was primarily administered before 2008, due to the existing guidelines. In general, patients who received ADT demonstrated higher pre-RP and pre-SRT PSA levels compared to patients who received SRT alone; therefore, these patients were expected to display a worse outcome (Table I), although they achieved more favourable b-PFS compared to those patients receiving SRT alone. Compared to patients treated with SRT alone, those treated with combination therapy had an improved three-year b-PFS for all pre-SRT PSA levels. In particular, patients with pre-SRT PSA levels >0.2 ng/ml benefitted from the additional ADT (Figure 3). To our knowledge, this is the first study to indicate such a PSA-dependent effect of ADT in patients treated with SRT.

Before recommending combined therapy to patients with PSA >0.2 ng/ml, we need a longer follow-up period, with overall survival as the primary endpoint. Furthermore the upcoming results of the prospective MRC RADICALS study, with standardised criteria for treatment with ADT will help answering questions about the optimal use of adjuvant ADT in combination with SRT.

The median follow-up period for this study was 3.1 years. With a longer follow-up, the increase in b-PFS may possibly translate into a survival benefit. In this study, we found a three-year b-PFS of 57%, which is relatively high compared with the rates reported in other studies, which range from 10% to 50% [3,4,8,10,22]. The inclusion of an unselected consecutive national cohort of patients receiving SRT over a five-year period was a clear strength of the current study, while one limitation was its retrospective study design and the changes in clinical practices made during the study period.

Conclusions

In a consecutive national cohort of patients treated for biochemical failure after RP, patients with positive surgical tumour margins and pre-SRT PSA levels ≤ 0.5 ng/ml demonstrated favourable outcomes. Despite less favourable tumour characteristics and longer follow-up periods, patients treated with combined SRT and ADT demonstrated b-PFS improvement; in particular, patients with PSA levels >0.2 ng/ml benefitted from additional ADT.

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