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Clinical Investigation

Prostate-Specific Antigen Persistence After Radical Prostatectomy as a Predictive Factor of Clinical Relapse-Free Survival and Overall Survival: 10-Year Data of the ARO 96-02 Trial

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Summary

In the ARO 96-02 prospective clinical trial on lymph node–negative prostate cancer, 74 patients who retained a detectable prostate-specific antigen (PSA) after prostatectomy received salvage radiation therapy with 66 Gy.

Objective: The ARO 96-02 trial primarily compared wait-and-see (WS, arm A) with adjuvant radiation therapy (ART, arm B) in prostate cancer patients who achieved an undetectable prostate-specific antigen (PSA) after radical prostatectomy (RP). Here, we report the outcome with up to 12 years of follow-up of patients who retained a post-RP detectable PSA and received salvage radiation therapy (SRT, arm C).

Methods and Materials: For the study, 388 patients with pT3-4pN0 prostate cancer with positive or negative surgical margins were recruited. After RP, 307 men achieved an undetectable PSA (arms A + B). In 78 patients the PSA remained above thresholds (median 0.6, range 0.05-5.6 ng/mL). Of the latter, 74 consented to receive 66 Gy to the prostate bed, and

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They had a significantly increased risk of clinical progression and poorer overall survival than did men with an undetectable PSA who received adjuvant radiation therapy with 60 Gy or had a wait-and-see strategy. The impact of PSA persistence should be reevaluated in detail in a larger cohort.

SRT was applied at a median of 86 days after RP. Clinical relapse-free survival, metastasis-free survival, and overall survival were determined by the Kaplan-Meier method.

Results: Patients with persisting PSA after RP had higher preoperative PSA values, higher tumor stages, higher Gleason scores, and more positive surgical margins than did patients in arms A + B. For the 74 patients, the 10-year clinical relapse-free survival rate was 63%. Forty-three men had hormone therapy; 12 experienced distant metastases; 23 patients died. Compared with men who did achieve an undetectable PSA, the arm-C patients fared significantly worse, with a 10-year metastasis-free survival of 67% versus 83% and overall survival of 68% versus 84%, respectively. In Cox regression analysis, Gleason score $\geq$8 (hazard ratio [HR] 2.8), pT $\geq$ 3c (HR 2.4), and extraprostatic extension $\geq$2 mm (HR 3.6) were unfavorable risk factors of progression.

Conclusions: A persisting PSA after prostatectomy seems to be an important prognosticator of clinical progression for pT3 tumors. It correlates with a higher rate of distant metastases and with worse overall survival. A larger prospective study is required to determine which patient subgroups will benefit most from which treatment option.
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Introduction

For men with clinically localized prostate cancer, radical prostatectomy (RP) provides overall control rates: ie freedom from prostate-specific antigen (PSA) recurrence in 82% to 75% after 5 to 15 years, respectively (1). However, with high-risk factors, the figures may fall as low as 60% to 40% within 5 to 10 years (2, 3). The ARO 96-02 trial was conducted to evaluate the benefit of post-RP adjuvant radiation therapy (ART) in pT3-4 prostate cancer. In agreement with 2 other randomized studies, a significant result was that patients with positive surgical margins are likely to have an improved biochemical recurrence-free survival owing to the additional treatment (4-6). ARO 96-02 was unique among the 3 trials in defining "adjuvant" most strictly: patients would be included only if their PSA dropped below detection limits a few weeks after RP. Additionally, per-protocol lymph node dissection enabled an appropriate evaluation of the nodal status.

In patients whose PSA did not become undetectable, immediate radiation therapy was intended as salvage strategy. Recent studies on salvage radiation therapy (SRT) recommend treatment to be initiated as early as possible. In terms of biochemical progression, that would be at a PSA of 0.5 ng/mL or less (7-9). ARO 96-02 patients whose PSA remained detectable after RP provided an opportunity to further analyze the factors that may influence the prognosis after SRT for locally advanced disease. The current report aimed to assess the impact of post-PR PSA persistence on clinical progression and overall survival.

Methods

Study conditions

The ARO 96-02 trial (Fig. E1, available at www.redjournal.org) recruited its patients from 1997 to 2004. It aimed to compare ART with a wait-and-see strategy (WS) after RP (margins R0 or R1) in patients with pT3-4N0M0 prostate cancer. Tumor stages were determined according to the 1992 International Union Against Cancer criteria (10). Preoperatively, patients had histologically proven cT1-cT3N0 prostate cancer. They all underwent preoperative and postoperative PSA test, bone scan, and chest radiography. The protocol was approved by the local ethics committees of all 22 participating centers. Written informed consent was obtained from all patients.

Surgery and pathology

The operation consisted of open RP and pelvic lymphadenectomy (including the prostate gland and seminal vesicles). Nerve-sparing resection was allowed and performed at the discretion of the operating surgeon. The surgical specimen was fixed in formalin, and the resection margins were ink marked, completely. The prostate was sectioned from the distal margins to the bladder neck. R1 was stated if malignant cells were in direct contact with the labeled margins. The Gleason score was determined according to the original criteria (11). Two of the authors (R.G., S.S.) provided central pathology review.

Post-RP treatment

For organizational reasons related to the German health system, men were randomized to WS or ART before achieving a post-RP undetectable PSA, which was mandatory in these 2 study arms. At the time, PSA assays with a limit of 0.1 ng/mL were standard, whereas more sensitive test systems became common during the study period. Out of 388 randomized patients, 78 retained a detectable PSA after surgery (median, 0.6 ng/mL; range, 0.05-5.6 ng/mL) (Table 1). Four of these men refused radiation therapy. After stating biochemical progression, and with a median delay of 86 days after RP, the remaining 74

Table 1 Post-RP/pre-SRT serum PSA of 74 C-arm patients of the ARO 96-02 trial

Serum PSA, ng/mL	n
≤0.1	13
>0.1-0.2	6
>0.2-0.4	8
>0.4-0.6	9
>0.6-1.0	12
>1.0-2.0	13
>2.0-5.6	11
-	2

Abbreviations: PSA = prostate-specific antigen; RP = radical prostatectomy; SRT = salvage radiation therapy.

were irradiated according to the trial protocol. They received a median dose of 66 Gy to the prostate bed. Radiation therapy was applied with linear accelerators in a 3- to 4-field technique after computed tomography−based 3-dimensional (3D) planning (6). All patients (arm A = WS, arm B = ART, and arm C = SRT) were scheduled for follow-up: quarterly during the first 2 years; then twice yearly; and from year 6 onward, once every year.

Analysis

We report on clinical-relapse-free survival (cRFS), metastasis-free survival (MFS), and overall survival (OS). The terminating events for cRFS were local recurrence or systemic dissemination or death for any reason. Sole biochemical recurrence was not considered. Survival data were analyzed with the Kaplan-Meier method and log-rank test. Cox multivariable regression was performed, incorporating parameters that were at least borderline significant in univariate analyses. Information on early and late toxicity of the gastrointestinal (GI) and the genitourinary (GU) tracts was extracted from the follow-up documentation without explicit repeated inquiry.

Results

The patient characteristics are summarized in Table 2 (pT stages according to the original documentation). The data represent the best available information: reference pathology where available or else local pathology. The age distribution of the men did not differ between arms A + B and C. By contrast, the pre-RP PSA of arm C patients was significantly increased, their Gleason scores were higher, tumor stage was higher, positive margins were more frequent, and extraprostatic extensions were larger.

The median follow-up time in the 3 trial arms was 112 months. Figure 1 shows the Kaplan-Meier probabilities of cRFS in arm C. The 10-year rate was 63%. In univariate analysis, the C-arm patients had a significantly better cRFS with Gleason score <8 ($P = .0023$), pT < 3b ($P = .0076$), or an extraprostatic tumor extension <2 mm ($P = .0047$); resection margin status R0/1 was not a significant discriminator data not shown in detail. In 1 multivariable Cox regression model for cRFS in the C arm patients, a Gleason score >7, pT > 3a + b, and extraprostatic extension >2 mm were associated with hazard ratios of 2.8, 2.4, and 3.6, respectively. However, only the influence of the Gleason score was statistically significant (Table 3).

In the C arm, 7 (15%) of 48 patients whose data were available achieved an undetectable PSA after SRT. Forty-three men (58%) received hormone therapy (HT) because of recurrence. By treatment arm, the 5-year rates of not requiring HT were 84% (WS), 92%(ART), and 57% (C arm), respectively. Twelve men (16%) with post-RP persistent PSA experienced distant metastases; 23 (31%) died, 9 (12%) of them of prostate cancer. For comparison, in arms A + B, 63 (21%) men had HT, 20 (7%) experienced metastases, and 43 (14%) died, 15 (5%) of prostate cancer. MFS was significantly worse in the C arm than in patients whose PSA became undetectable after prostatectomy ($P = .00084$) (Fig. 2). Compared with the 10-year OS of 68% (58%-80%) in arm C, men with an undetectable post-RP PSA had significantly higher Kaplan-Meier estimates: 86% (80%-92%) in arm A ($P = .0024$) and 83% (76%-90%) in arm B ($P = .017$), respectively. The importance of achieving a post-RP undetectable PSA, irrespective of the consecutive management, is documented in Figure 3, where arms A + B show an OS of 84% (80%-89%), again better than arm C ($P = .0019$).

No cases of grade 3 or 4 acute toxicity were reported. Three men (6%) had Radiation Therapy Oncology Group grade 2 early bladder adverse events, and 5 had grade 2 GI tract side effects. Urethral stricture was reported for 1 patient. The most severe late effects were experienced by 5 patients (7%) with grade 3 and 2 patients (3%) with grade 2 bladder impairment. Absence of GU and GI tract late toxicity was reported in 50 (68%) and 59 (80%) patients, respectively. Overall, toxicity in arm C was slightly higher than in arm B, where the total dose was 6 Gy lower.

Discussion

Salvage radiation therapy is well established for men with biochemical recurrence, where it is specifically efficient if given before the PSA exceeds 0.5 ng/mL (12). However, comparably few data have been published so far specifically on patients with a persisting PSA after RP, and there is evidence that in these cases too, radiation therapy can enable a PSA-negative state (13). Since as PSA has a half-life of approximately 3 days, PSA levels should fall below detection limits within a few weeks after RP. A persisting PSA may result from normal tissue or local tumor cells that escaped resection or from distant metastases. Only in cases of residual local or locoregional tumor would radiation therapy provide a benefit.

Several publications have suggested a low impact of PSA persistence. In their 11-parameter nomogram predictive for biochemical progression of SRT patients,

Table 2 Patient characteristics in the ARO 96-02 trial

Trial arm, no. of patients	SRT, n=74	WS, n=159	ART, n=148	*P* value
Age ± standard deviation, y	63.9 ± 4.9	63.3 ± 5	64.4 ± 5.2	-
Range	53-72	51-75	50-77	-
Pre-RP PSA data available*	n=74	n=157	n=148	<.0001
Average ± standard deviation, ng/mL	23 ± 20	11.9 ± 10	12.9 ± 10.3	
Range	2.8-99	0.6-76.5	0.1-57.9	
≤4	2 (3%)	20 (13%)	12 (8%)	
4.1-10	14 (19%)	67 (43%)	66 (45%)	
10.1-50	53 (72%)	69 (44%)	67 (45%)	
>50	5 (7%)	1 (1%)	3 (2%)	
Gleason score data available*	n=71	n=159	n=148	<.0001
≤6	10 (14%)	57 (36%)	56 (38%)	
7	43 (61%)	86 (54%)	74 (50%)	
≥8	18 (25%)	16 (10%)	18 (12%)	
Staging data available*	n=74	n=159	n=148	.0002
<pT3a	1 (1%)	2 (1%)	4 (3%)	
pT3a	21 (28%)	74 (47%)	76 (51%)	
pT3b	14 (19%)	27 (17%)	23 (16%)	
pT3c	25 (34%)	43 (27%)	40 (27%)	
pT4a	13 (18%)	13 (8%)	5 (3%)	
Surgical margins data available†	n=74	n=159	n=148	.0055
R0	14 (19%)	62 (39%)	48 (32%)	
R1	60 (81%)	97 (61%)	100 (68%)	
Length of positive margins, median	7.4 mm	3.4 mm	2.8 mm	
Extraprostatic extension data available†	N=67	N=140	N=125	.0038
≤2 mm	26 (39%)	84 (60%)	72 (58%)	
>2 mm	41 (61%)	56 (40%)	53 (42%)	
Detailed lymph node data available	n=74	n=105	n=100	-
Lymph nodes resected per patient	8.2 ± 5.4	9.1 ± 5.1	8.9 ± 5.7	
Median (range)	7 (1-31)	8 (1-26)	8 (1-31)	
pN0	74 (100%)	159 (100%)	148 (100%)	
Pre-RP hormone therapy data available	n=74	n=159	n=148	-
Hormone therapy	8 (11%)	19 (12%)	16 (11%)	
No hormone therapy	66 (89%)	140 (88%)	132 (89%)	

Abbreviations: ART = adjuvant radiation therapy; PSA = prostate-specific antigen; RP = radical prostatectomy; SRT = salvage radiation therapy; WS = wait and see.

Where possible, reference pathology data are included ("best available information").

* Cochrane-Armitage test (exact), arms A + B (WS + ART) versus arm C (SRT).

† Fisher's exact test, arms A + B (WS + ART) versus arm C (SRT).

Stephenson et al (14) calculated a very small contribution from PSA persistence to the risk of SRT failure. To predict post-RP cancer-specific mortality, Eggener et al (15) used 8 parameters; PSA persistence is none of them. D'Amico et al (16) found that favorable conditions like a pre-RP PSA <10 ng/mL (rising slowly), nonpalpable cancer, and Gleason score ≤6 were associated with very slow post-RP PSA dynamics, such that a PSA initially persisting above 0.2 ng/mL would not exceed 0.25 ng/mL after 3.6 years.

Other data would rate the impact of PSA persistence higher. With a detectability limit of 0.1 to 0.15 ng/mL, Sengupta et al (17) found systemic progression and cancer-specific mortality to be significantly more frequent in 303 men with post-RP PSA persistence then in 2451 men who achieved an undetectable PSA. Using ultrasensitive assays with a PSA ≤0.05 ng/mL defined as undetectable, Eisenberg et al (18) reported on biochemical progression-free survival after prostatectomy. Over 5 years, 456 patients with an undetectable PSA fared significantly better than did 69 men with a persisting PSA (86% vs 67% recurrence-free survival, $P<.01$). Even within the high-risk group of R1 patients (n=91), retention of a detectable PSA correlated with a poorer outcome (50% vs 72%, $P=.07$). These were RP-only results: neoadjuvant HT or radiation therapy excluded men from this retrospective analysis, and secondary RP treatment was classified as an event.

Reviewing 240 men who underwent RP, Audenet et al (19) identified the early post-RP PSA level as a potential indicator of recurrence. Although in univariate analysis, 6 factors were associated with biochemical relapse, the multivariable test yielded 3 parameters that correlated significantly with the outcome: positive surgical margins ($P=.002$), pathologic stage pT ≥ 3 ($P=.001$), and a 6-weeks post-RP PSA ≥0.1 ng/mL ($P=.001$). However, in this retrospective study, the median follow-up time was only 44 months, and the PSA cutoff point of 0.1 ng/mL was

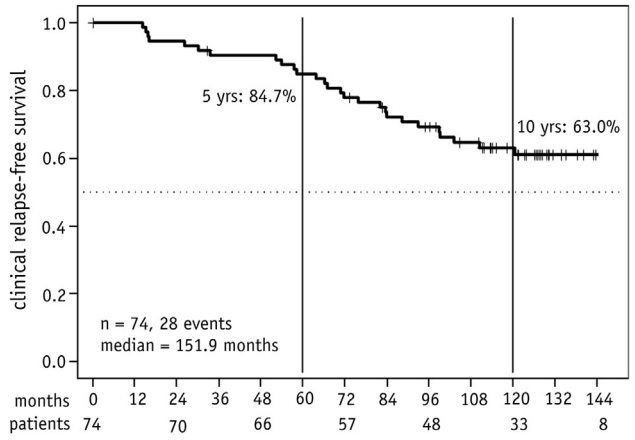

Fig. 1. Kaplan-Meier probability of clinical relapse-free survival of arm-C patients in the ARO 96-02 trial. Men who retained detectable prostate-specific antigen after prostatectomy received immediate salvage radiation therapy with 66 Gy. Numbers of patients at risk are indicated at the bottom.

arbitrary. Of course, reducing that cutoff point according to the growing sensitivity of PSA assays would increase the false-positive rates. In this context, contributions from residual benign prostate tissue to PSA recurrence have been questioned (20).

A straight comparison of published data on the impact of PSA persistence is hampered by heterogeneous study designs: With their slightly different definitions of PSA persistence, Eisenberg et al (18) reported a 5-year PSA relapse-free survival of 67%, whereas the estimate of Audenet et al (19) was 42%. Katz et al (21) observed 83% MFS 4 years after SRT. Johnson et al (22) reported on 250 SRT patients, 48 of whom also received androgen deprivation. They calculated a post-SRT 10-year MFS of 23% for men who had PSA recurrence earlier than 18 months after RP, and 10-year cancer-specific survival was 66%. Our C arm patients had a 10-year MFS of 67% and a cancer-specific survival of 88%, respectively, which is fairly good given their risk profile. For comparison, a cohort of 160 men who had no intervention for post-RP PSA persistence had 5-year and 10-year MFS probabilities of 49% and 22%, respectively (23). The overall survival among 291 patients with post-RP persisting PSA and no salvage therapy was 63% after 10 years, which was still 5% less than in our patients (24).

Of course, the impact of PSA persistence must not be regarded in isolation. Moreira et al (25) conducted an analysis on 697 patients after prostatectomy. More recent year of recurrence, center (out of 5), shorter disease-free interval, and Gleason score 8 to 10 predicted an increased probability of secondary treatment. Where data were available, also PSA doubling time was an indicator of a requirement for salvage therapy. All 3 disease-specific parameters had earlier been related to the risk of metastasis and prostate cancer death (26, 27). When compared with patients in arm A or B of the ARO 96-02 trial, men who retained a detectable PSA after prostatectomy had more or higher-grade risk factors suggestive of, and associated with, an unfavorable course of disease. This is well in agreement with an older report on the prognostic significance of a detectable post-RP PSA (17). Besides confirming high-risk factors, D'Amico et al (16) also determined favorable parameters like slow PSA kinetics both before and after RP, which correlated with clinically insignificant PSA failure (16). However, the comparison of the 3 ARO study arms underlines the importance of achieving an undetectable PSA after prostatectomy. PSA persistence was a negative predictor of metastasis-free and overall survival.

Although the ARO 96-02 trial focused on the comparison of ART versus WS in patients who achieved an undetectable post-RP PSA, the 74 C-arm patients with PSA persistence represent a valuable prospectively defined clinical cohort as well. In terms of Kaplan-Meier probability 12 years after immediate SRT, 37% of the C-arm patients had experienced a clinical relapse, and cancer-specific mortality was 14% by that time. By comparison, in the SWOG 8794 trial, high-risk N0 patients (extracapsular tumor extension, positive surgical margins, or seminal vesicle involvement) received immediate post-RP radiation therapy (60-64 Gy) or WS. In the radiation therapy arm, 14

Table 3 Multivariable analysis of factors influencing clinical progression-free survival in men receiving SRT for persisting PSA after prostatectomy

Factor*	Statistical parameter	Model 1 (n=71)	Model 2 (n=64)
Gleason score (best information) ≤7	Relative risk	2.96	2.81
	95% Confidence interval	1.35-6.51	1.15-6.86
	P	.0043	.023
T stage (best information) ≤pT3b	Relative risk	2.08	2.38
	95% Confidence interval	0.93-4.67	0.92-6.14
	P	.074	.074
Extraprostatic extension <2 mm	Relative risk	Not included	3.55
	95% Confidence interval		0.77-16.38
	P		.10

Abbreviations: PSA = prostate-specific antigen; SRT = salvage radiation therapy.
* Indicated factors are the reference group.

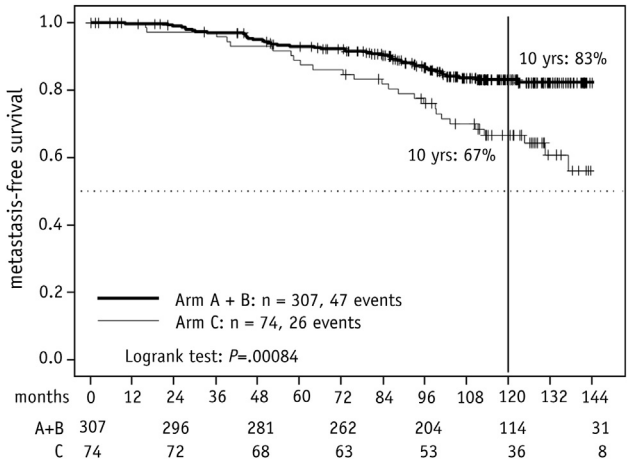

Fig. 2. Kaplan-Meier probability of metastasis-free survival of ARO 96-02 patients. Men with undetectable prostate-specific antigen (PSA) after radical prostatectomy had a wait-and-see strategy (arm A) or received adjuvant radiation therapy with 60 Gy (arm B). Men who retained a detectable PSA (arm C) received immediate salvage radiation therapy with 66 Gy. Numbers of patients at risk are indicated at the bottom.

of 190 men (7%) had experienced metastases during a median 10.2 years of follow-up; in the WS arm it was 30 of 184 men (16%). In both arms, the incidence increased with higher post-PR PSA values (28). Biochemical relapse occurred in 28 of 29 (97%) of the men who had a post-RP PSA >1.0 ng/mL, but it was emphasized that in the entire cohort the predominant treatment failure was local failure.

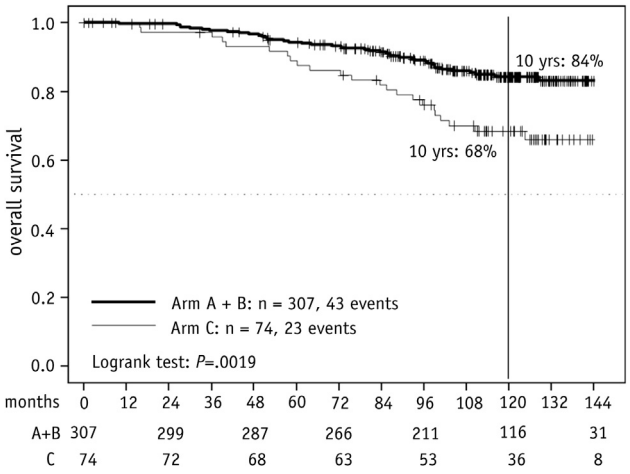

Fig. 3. Kaplan-Meier probability of overall survival of ARO 96-02 patients. Men with undetectable prostate-specific antigen (PSA) after radical prostatectomy had a wait-and-see strategy (arm A) or received adjuvant radiation therapy with 60 Gy (arm B). Men who retained detectable PSA (arm C) received immediate salvage radiation therapy with 66 Gy. Numbers of patients at risk are indicated at the bottom.

Thus, the new observation we have made is that PSA persisting after RP predicts an increased rate of clinically manifest progression over a long time and may therefore require a more aggressive treatment strategy.

Radiation therapy in the ARO 96-02 trial was conventional 3D conformal radiation therapy. With a median dose of 66 Gy, the treatment was well tolerated. In the ongoing trials RADICALS (Radiotherapy and androgen deprivation in combination after local surgery), RAVES (Radiotherapy - Adjuvant Versus Early Salvage), and GETUG 17 (Groupe d'Étude des Tumeurs Uro-Génitales) comparing ART vs (early) SRT, 64 to 66 Gy is still the standard dose. (29-31). With the use of more recent techniques such as intensity modulated radiation therapy, dose escalation should be feasible without increasing toxicity (32). However, patients with occult dissemination at the time of RP would have a benefit from at least additional HT, a strategy that is also addressed in RADICALS. It remains a challenge for the future to identify by improved imaging or by surrogate markers which patient will profit most from which treatment option. In the ARO trial, several C-arm patients had a post-RP PSA well above the recommended levels for "early" SRT. On the other hand, biochemical recurrence at low PSA levels may not always lead to clinical progression (12, 33).

Thus, a shortcoming of our study is the broad distribution of post-RP PSA levels. Regarding discussions of the right PSA level for early SRT (9, 34), our cohort is quite inhomogeneous; so also may be the men's prognosis after radiation therapy. The retrospective subgroups are too small to yield event numbers suitable for analysis. To overcome these problems, prospective studies should be conducted to ultimately allocate cases individually to the appropriate treatment strategy.

In conclusion, despite immediate SRT with 64 Gy, post-RP PSA persistence correlated with a poor prognosis, including worse overall survival. Patients with PSA persisting after RP are likely to benefit from early aggressive therapy. The broad distribution of post-RP PSA levels in the C arm does not allow reliable assessment of the optimal cutoff point for efficient SRT. Prospectively randomized clinical trials of SRT for PSA persistence are warranted.

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