EUROPEAN UROLOGY 71 (2017) 886–893

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Christopher J.D. Wallis, Raj Satkunasivam and Robert K. Nam on pp. 894–895 of this issue

Long-term Impact of Adjuvant Versus Early Salvage Radiation Therapy in pT3N0 Prostate Cancer Patients Treated with Radical Prostatectomy: Results from a Multi-institutional Series

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Article info

Article history:
Accepted July 20, 2016

Associate Editor:
Christian Gratzke

Keywords:
Prostatic neoplasms
Radiation therapy
Adjuvant
Salvage therapy

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Abstract

Background: Three prospective randomised trials reported discordant findings regarding the impact of adjuvant radiation therapy (aRT) versus observation for metastasis-free survival (MFS) and overall survival (OS) among patients with pT3N0 prostate cancer treated with radical prostatectomy (RP). None of these trials systematically included patients who underwent early salvage radiation therapy (esRT).
Objective: To test the hypothesis that aRT was associated with better cancer control and survival compared with observation followed by esRT.
Design, setting, and participants: Using a multi-institutional cohort from seven tertiary referral centres, we retrospectively identified 510 pT3pN0 patients with undetectable prostate-specific antigen (PSA) after RP between 1996 and 2009. Patients were stratified into two groups: aRT (group 1) versus observation followed by esRT in case of PSA relapse (group 2). Specifically, esRT was administered at a PSA level $\leq$0.5 ng/ml.
Intervention: We compared aRT versus observation followed by esRT.
Outcome measurements and statistical analysis: The evaluated outcomes were MFS and OS. Multivariable Cox regression analyses tested the association between groups (aRT vs observation followed by esRT) and oncologic outcomes. Covariates consisted of pathologic stage (pT3a vs pT3b or higher), pathologic Gleason score ($\leq$6, 7, or $\geq$8), surgical margin status (negative vs positive), and year of surgery. An interaction with groups and baseline patient risk was tested for the hypothesis that the impact of aRT versus observation followed by esRT was different by pathologic characteristics. The

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http://dx.doi.org/10.1016/j.eururo.2016.07.028

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nonparametric curve fitting method was used to explore graphically the relationship between MFS and OS at 8 yr and baseline patient risk (derived from the multivariable analysis).

Results and limitations: Overall, 243 patients (48%) underwent aRT, and 267 (52%) underwent initial observation. Within the latter group, 141 patients experienced PSA relapse and received esRT. Median follow-up after RP was 94 mo (interquartile range [IQR]: 53–126) and 92 mo (IQR: 70–136), respectively ($p = 0.2$). MFS (92% vs 91%; $p = 0.9$) and OS (89% vs 92%; $p = 0.9$) at 8 yr after surgery were not significantly different between the two groups. These results were confirmed in multivariable analysis, in which observation followed by esRT was not associated with a significantly higher risk of distant metastasis (hazard ratio [HR]: 1.35; $p = 0.4$) and overall mortality (HR: 1.39; $p = 0.4$) compared with aRT. Using the nonparametric curve fitting method, a comparable proportion of MFS and OS at 8 yr among groups was observed regardless of pathologic cancer features ($p = 0.9$ and $p = 0.7$, respectively). Limitations consisted of the retrospective nature of the study and the relatively small size of the patient population.

Conclusions: At long-term follow-up, no significant differences between aRT and esRT were observed for MFS and OS. Our study, although based on retrospective data, suggests that esRT does not compromise cancer control and potentially reduces overtreatment associated with aRT.

Patient summary: At long-term follow-up, no significant differences in terms of distant metastasis and mortality were observed between immediate postoperative adjuvant radiation therapy (aRT) and initial observation followed by early salvage radiation therapy (esRT) in case of prostate-specific antigen relapse. Our study suggests that esRT does not compromise cancer control and potentially reduces overtreatment associated with aRT.

1. Introduction

Despite the widespread use of prostate-specific antigen (PSA) screening over the last two decades, approximately 25% of contemporary patients treated with radical prostatectomy (RP) for localised prostate cancer (PCa) show locally advanced disease at final pathology in both European and American series [1,2]. These patients often present concomitant adverse pathologic features such as poorly differentiated disease and positive surgical margins, and they are at higher risk of recurrence and cancer-related death [3,4].

Two options essentially can be offered currently to pT3 node-negative PCa patients with undetectable postoperative PSA: immediate adjuvant radiation therapy (aRT) to the prostatic fossa or initial biochemical monitoring followed by early salvage radiation therapy (esRT) before PSA level exceeds 0.5 ng/ml [5,6].

The postsurgical management of these patients still represents a continuous matter of debate. Two main issues may be identified from the current literature. The first one relates to the lack of level-1 evidence in this field. Three randomised clinical trials compared aRT with initial observation in patients affected by locally advanced PCa [7–9]. However, the study design of these historical trials did not systematically include in the observational arm the patients who underwent esRT at a PSA level $\leq$0.5 ng/ml. Conflicting results emerged from these trials for the outcomes of metastasis-free survival (MFS) and overall survival (OS). The specific reasons for such a discrepancy might be related to the heterogeneity of patient populations and the lack of defined treatment protocols.

Second, the currently available evidence supporting the oncologic safety of salvage radiation therapy (sRT) is still based on retrospective studies [10–13]. A substantial proportion of patients who received salvage treatment in these retrospective studies had PSA values >0.5 ng/ml, whereas the PSA level at sRT was shown to be an important predictor of oncologic outcomes [14]. In these retrospective studies, the outcome was biochemical recurrence (BCR) following sRT, and the evaluation of hard clinical end points, such as clinical recurrence and survival, is still lacking [10–13].

To address these shortcomings, we evaluated MFS and OS at long-term follow-up using a multi-institutional series of pT3pN0 patients who underwent aRT versus initial observation followed by esRT in case of PSA relapse. We hypothesised that aRT was associated with better cancer control and survival compared with initial observation.

2. Materials and methods

2.1. Patient population

After institutional review board approval, we identified 764 patients treated with RP and pelvic lymph node dissection at seven tertiary referral centres between 1996 and 2009. Retrospective chart reviews were used at four institutions. All patients had histologically confirmed pT3pN0 R0–R1 adenocarcinoma of the prostate. No patient received any neoadjuvant or adjuvant hormonal therapy. All patients had an undetectable postoperative PSA (defined as <0.1 ng/ml).

Patients who were initially observed and then treated with sRT at a serum PSA >0.5 ng/ml were excluded from our analyses ($n = 127$). Patients with missing information on pathologic stage ($n = 24$), pathologic Gleason score ($n = 47$), or surgical margin status ($n = 56$) were likewise excluded. These selection criteria yielded 510 evaluable individuals with complete clinical, pathologic, and follow-up data.

Patients were stratified into two groups according to the postoperative management: aRT (group 1: $n = 243$; 48%) versus initial observation followed by esRT in case of PSA relapse (group 2: $n = 267$; 52%). Specifically, aRT was administered within 6 mo after RP to patients.

On the contrary, esRT was administered at a PSA level ≤0.5 ng/ml. The PSA relapse after surgery that led to esRT in group 2 was defined as postoperative undetectable PSA with a subsequent PSA increase within two or more determinations, according to the definition provided by the National Comprehensive Cancer Network (NCCN) guidelines [6]. Patients who did not develop PSA relapse in group 2 underwent oncologic follow-up that consisted of a PSA test every 3 mo for the first year, biannually between the second and the fifth years after surgery, and annually thereafter.

2.2. Radiation therapy technique

Radiation therapy consisted of local radiation to the prostate and seminal vesicle bed. All patients were treated with high-energy photon beams (10–25 MV) at conventional fractionation (1.8–2 Gy per fraction), with a median dose of 65 Gy (interquartile range [IQR]: 60–67). Conventional nonconformal treatment was delivered, and rectangular or minimally blocked beams were used. Alternatively, a three-dimensional conformal approach was used. The clinical target volume (CTV) was delineated on computed tomography (CT) images and included the prostatic fossa and periprostatic tissue. Clinical findings, presurgery CT scan, and surgical clips guided the clinicians to the CTV definition. The planned target volume was defined as CTV plus a 0.8- to 1.0-cm margin to account for organ motion and setup error.

2.3. Variable definition

Clinical data consisted of patient age at radiation therapy (RT), preoperative PSA level, time from surgery to RT, and pre-RT PSA level. Pathologic data included pathologic stage (pT2 vs pT3a vs pT3b or higher), pathologic Gleason score (≤6, 7, or ≥8), and surgical margin status (negative vs positive).

2.4. Outcome definition

The primary outcome of the study was distant metastasis. Distant metastases in bones, parenchymal organs, or soft tissues were identified by radiologic imaging and confirmed with biopsy per the treating clinicians' discretion. The secondary outcome of the study was OS. Follow-up time was defined as the time between RP and distant metastasis diagnosis or last follow-up (for the primary outcome), and the time between RP and patient death or last follow-up (for the secondary outcome).

2.5. Statistical analysis

Our statistical analyses consisted of three main steps. First, the Kaplan-Meier method was used to compare distant MFS and OS between the aRT and the observation followed by esRT cohorts. The log-rank test was used for the hypothesis that aRT provided better cancer control and OS compared with initial observation followed by esRT.

Second, multivariable Cox regression analysis tested the association between groups and oncologic outcomes. Covariates consisted of pathologic stage (pT3a vs pT3b or higher), pathologic Gleason score (≤6, 7, or ≥8), and surgical margin status (negative vs positive). The year of surgery was included in the multivariable model because the postoperative management of patients may vary over time.

Third, we tested the hypothesis that the impact of aRT versus observation followed by esRT differed by pathologic characteristics. As an example, aRT may provide better cancer control only in patients affected by locally advanced disease (eg, pathologic stage pT3b or higher), more aggressive disease (eg, pathologic Gleason score ≥8), and/or positive surgical margins. Therefore, we tested an interaction with groups (aRT vs observation followed by esRT) and baseline pathologic risk. The latter was derived by multivariable Cox regression analysis. The predictors consisted of pathologic stage, pathologic Gleason score, and surgical margin status. The nonparametric curve fitting method was used to explore graphically the relationship between distant MFS and OS at 8 yr after surgery and baseline patient risk.

All statistical analyses were performed using Stata software v.12.0 (StataCorp LP, College Station, TX, USA).

3. Results

Overall, 243 patients (48%) underwent aRT, and 267 (52%) underwent initial observation. Table 1 shows the comparative clinical and pathologic characteristics of patients. No statistically significant differences were observed between the groups in terms of age at surgery ($p = 0.3$), preoperative PSA level ($p = 0.6$), pathologic stage ($p = 0.13$), or pathologic Gleason score ($p = 0.3$). Conversely, patients who received aRT had a significantly higher rate of positive surgical margins compared with patients who underwent initial observation (74% vs 52%; $p < 0.0001$).

Median follow-up among patients who did not develop distant metastasis was similar between groups: 94 mo (IQR: 53–126 mo) and 92 mo (IQR: 70–136 mo), respectively ($p = 0.2$). In group 1, median time from surgery to aRT was 3 mo (IQR: 2–4 mo). In group 2, 147 patients experienced postoperative PSA relapse and subsequently received esRT. Median time from surgery to esRT was 25 mo (IQR:15–43 mo), whereas median PSA level at esRT was 0.2 ng/ml (IQR: 0.1–0.3 ng/ml).

Overall, 43 patients developed distant metastasis: 24 patients in group 1 and 19 patients in group 2, respectively. MFS at 8 yr was not significantly different between the cohorts: 92% (95% confidence interval [CI], 87–93) in group 1 versus 91% (95% CI, 84–95) in group 2 ($p = 0.9$) (Fig. 1). Similarly, OS survival at 8 yr was not significantly different between the two groups:

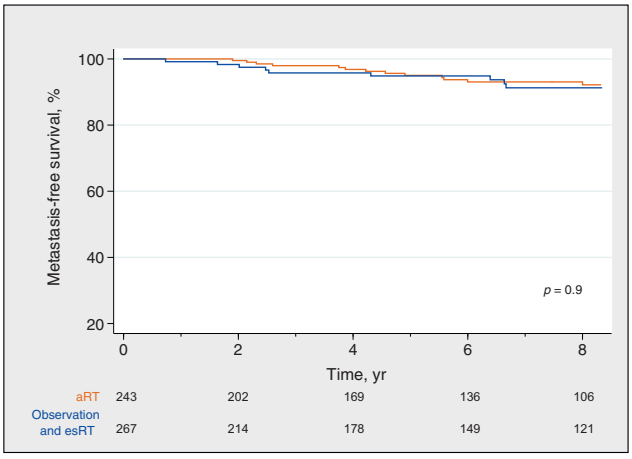

Fig. 1 – Kaplan-Meier plots depicting distant metastasis-free survival in 510 pT3pN0 prostate cancer patients treated at seven tertiary referral centres between 1996 and 2009, stratified according to postoperative management: adjuvant radiation therapy (orange line) versus observation followed by early salvage radiation therapy (esRT) in case of prostate-specific antigen relapse (blue line).
aRT = adjuvant radiation therapy; esRT = early salvage radiation therapy.

Table 1 – Descriptive characteristics of 510 pT3pN0 prostate cancer patients treated at seven tertiary referral centres between 1996 and 2009

Variables	Overall population n = 510 (100%)	Group 1: aRT n = 243 (48%)	Group 2: observation and esRT n = 267 (52%)	p value
Age at surgery, yr	64 (60–70)	64 (61–69)	65 (60–70)	0.3
Preoperative PSA, ng/ml	9.5 (6.2–15.1)	9.3 (6.2–15.8)	9.8 (6.3–14.8)	0.6
Pathologic stage, n (%)				0.13
pT3a	305 (60)	137 (56)	168 (63)	
pT3b or higher	205 (40)	106 (44)	99 (37)	
Pathologic Gleason score, n (%)				0.3
≤6	106 (21)	57 (23)	49 (18)	
7	267 (52)	120 (49)	147 (55)	
≥8	137 (27)	66 (27)	71 (27)	
Surgical margin status, n (%)				<0.0001
Negative	191 (37)	62 (26)	129 (48)	
Positive	319 (63)	181 (74)	138 (52)	
Time from RP to RT, mo†	4 (3–18)	3 (2–4)	25 (15–43)	<0.0001
PSA level at RT, ng/ml†	0.1 (0–0.3)	0 (0–0)	0.2 (0.1–0.3)	<0.0001
RT dose, Gy†	65 (60–67)	60 (60–65)	67 (66–67)	<0.0001
Follow-up, mo‡	94 (60–128)	94 (53–126)	92 (70–136)	0.2
Year of surgery, n (%)				<0.0001
1996–1997	52 (10)	9 (4)	43 (16)	
1998–1999	80 (16)	52 (21)	28 (10)	
2000–2001	97 (19)	66 (27)	31 (12)	
2002–2003	93 (18)	38 (16)	55 (21)	
2004–2005	58 (11)	23 (9)	35 (13)	
2006–2007	72 (14)	38 (16)	34 (13)	
2008–2009	58 (11)	17 (7)	41 (15)	

aRT = adjuvant radiotherapy; esRT = early salvage radiation therapy; PSA = prostate-specific antigen. RP = radical prostatectomy; RT = radiation therapy.
Data are stratified according to postoperative management: aRT (group 1) versus observation followed by esRT (group 2) in case of PSA relapse. All values are medians (interquartile range) or frequencies (proportions).
† Data reported only for patients who received radiation therapy.
‡ Follow-up reported for patients who did not develop distant metastases.

89% (95% CI, 78–94) in group 1 versus 92% (95% CI, 86–96) in group 2 (p = 0.9) (Fig. 2).

These findings were confirmed on multivariable Cox regression analysis (Table 2 and 3), in which observation followed by esRT was not associated with a significantly higher risk of distant metastasis (hazard ratio [HR]: 1.35; 95% CI, 0.63–2.86; p = 0.4) and overall mortality (HR: 1.39; 95% CI, 0.69–2.95; p = 0.4) compared with aRT.

We also tested whether the association of management approach with the risk of metastases and mortality were different according to specific pathologic characteristics. In particular, we tested an interaction between the groups (aRT vs observation followed by esRT) and baseline pathologic risk. The latter was derived by multivariable Cox regression analysis, in which the predictors consisted of

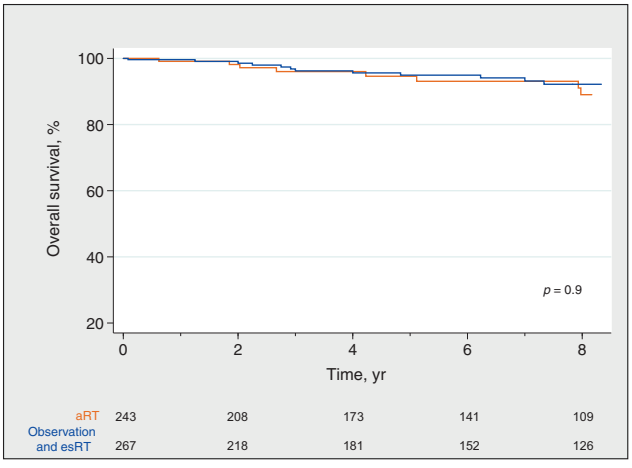

Fig. 2 – Kaplan-Meier plots depicting distant overall survival in 510 pT3pN0 prostate cancer patients treated at seven tertiary referral centres between 1996 and 2009, stratified according to postoperative management: adjuvant radiation therapy (orange line) versus observation followed by early salvage radiation therapy (esRT) in case of prostate-specific antigen relapse (blue line).
aRT = adjuvant radiation therapy; esR = early salvage radiation therapy.

Table 2 – Multivariable Cox regression analysis predicting distant metastasis in 510 pT3 pN0 prostate cancer patients treated at seven tertiary referral centres between 1996 and 2009

Predictor	HR	95% CI	p value
Year of surgery	1.12	1.02–1.23	0.014
Pathologic stage			
pT3a	1.00	Ref.	–
pT3b or higher	3.10	1.57–6.11	0.001
Pathologic Gleason score			
≤7	1.00	Ref.	–
≥8	3.50	1.80–6.80	0.0002
Surgical margin status			
Negative	1.00	Ref.	–
Positive	0.93	0.45–1.90	0.8
Group			
aRT	1.00	Ref.	–
Observation followed by esRT	1.35	0.63–2.86	0.4

aRT = adjuvant radiation therapy; CI = confidence interval; esRT = early salvage radiation therapy; HR = hazard ratio.

Table 3 – Multivariable Cox regression analysis predicting overall mortality in 510 pT3pN0 prostate cancer patients treated at seven tertiary referral centres between 1996 and 2009

Predictor	HR	95% CI	*p* value
Year of surgery	1.00	0.91–1.10	0.9
Pathologic stage			
pT3a	1.00	Ref.	–
pT3b or higher	2.81	1.38–5.74	0.005
Pathologic Gleason score			
≤7	1.00	Ref.	–
≥8	2.15	1.05–4.36	0.036
Surgical margin status			
Negative	1.00	Ref.	–
Positive	1.29	0.57–2.90	0.5
Group			
aRT	1.00	Ref.	–
Observation followed by esRT	1.39	0.69–2.95	0.4

aRT = adjuvant radiation therapy; CI = confidence interval; esRT = early salvage radiation therapy; HR = hazard ratio.

pathologic stage, pathologic Gleason score, surgical margin status, and year of surgery. The association between MFS and baseline patient risk was not significantly different by groups ($p = 0.9$ by an interaction test). A similar result was observed considering OS ($p = 0.7$ by an interaction test). These findings are illustrated in Figure 3 and 4, in which MFS and OS at 8 yr after surgery were plotted against baseline patient risk. We found that aRT and observation followed by esRT provided similar cancer control and survival regardless of PCa features.

Finally, we compared patient characteristics between the current study and the three published randomised clinical trials (European Organisation for Research and Treatment of Cancer [EORTC] 22911, ARO 96-02/AUO AP 09/95, and SWOG 8794). Notably, the three studies showed considerable heterogeneity of the patient populations included. For example, an undetectable postoperative PSA

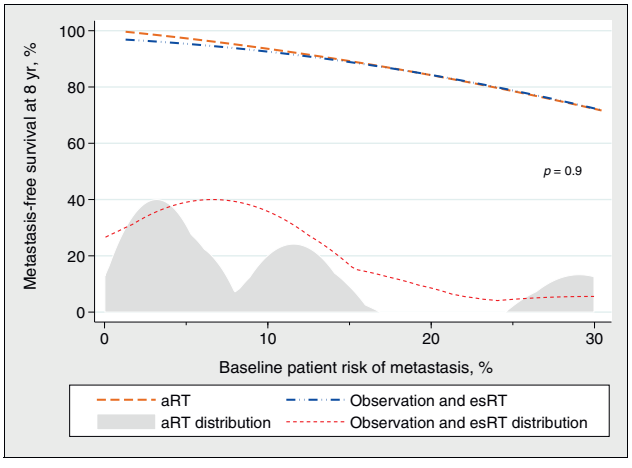

Fig. 3 – Distant metastasis-free survival at 8 yr after surgery plotted against baseline patient risk (derived from multivariable Cox regression analysis). Patients were stratified according to group: adjuvant radiation therapy versus initial observation followed by early salvage radiation therapy. Shaded area and dotted line represent the baseline patient risk distribution of groups 1 and 2, respectively.
aRT = adjuvant radiation therapy; esRT = early salvage radiation therapy.

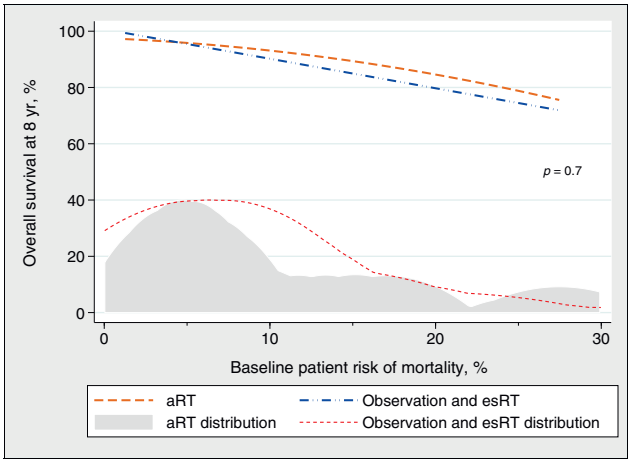

Fig. 4 – Overall survival at 8 yr after surgery plotted against baseline patient risk (derived from multivariable Cox regression analysis). Patients were stratified by group: adjuvant radiation therapy versus initial observation followed by early salvage radiation therapy. Shaded area and dotted line represent the baseline patient risk distribution of groups 1 and 2, respectively.
aRT = adjuvant radiation therapy; esRT = early salvage radiation therapy.

was required in the ARO 96-02/AUO AP 09/95 study only, whereas in the other two randomised trials roughly 30% of patients had a postoperative PSA >0.2 ng/ml. However, median age, preoperative PSA, and the rate of pT3a and pT3b disease in our series were essentially comparable with the other three studies (Table 4).

4. Discussion

Pathologically advanced PCa after RP is associated with worse oncologic outcomes because concomitant adverse pathologic features are often present [15,16]. Postoperative RT may improve disease control and patient survival when administered either immediately after surgery (aRT) or at PSA relapse (sRT) [9,13,17,18]. Three randomised clinical trials evaluated the impact of aRT on pT3pN0 patients, showing better biochemical outcomes at long-term follow-up. However, conflicting results were shown when clinical recurrence and patient survival were considered [7–9]. In contrast, previous retrospective studies showed an oncologic benefit for patients affected by BCR following RP treated with sRT [11,12,18,19].

The real relevant clinical question still remains whether postoperative RT should be administered in an adjuvant setting or could be postponed and reserved only for patients who will experience PSA relapse. According to the European Association of Urology and the NCCN guidelines, two options can be essentially offered to pT3 node-negative patients with undetectable postoperative PSA: immediate aRT to the prostatic fossa or initial biochemical monitoring followed by esRT before PSA level exceeds 0.5 ng/ml [5,6].

The hypothesis of the current study was that aRT provided better cancer control and OS compared with observation followed by esRT in pT3pN0 patients who

Table 4 – Comparison of patient characteristics between the current study and the previous three randomised clinical trials (EORTC 22911, ARO 96-02/AUO AP 09/95, and SWOG 8794)

Variables	Current study, *n* = 510		EORTC 22911 trial [7], *n* = 1005		ARO 96-02/AUO AP 09/95 trial [8], *n* = 307		SWOG 8794 trial [9], *n* = 425	
	aRT, *n* = 243	Observation followed by esRT, *n* = 267	aRT, *n* = 502	WS, *n* = 503	aRT, *n* = 148	WS, *n* = 159	aRT, *n* = 214	WS, *n* = 211
Median age, yr	64	65	65	65	65	64	64	65
Median preoperative PSA, ng/ml	9.3	9.8	12.3	12.5	9.7	9.4	<10: 47% ≥10: 53%	<10: 52% ≥10: 48%
Pathologic stage, *n* (%)								
pT2	0	0	17	16	3	1	*	*
pT3a	56	63	57	59	51	47	67	68
pT3b or higher	44	37	26	25	46	52	33	32
Gleason score, *n* (%)			Gx: 2	Gx: 1				
≤6	23	18	G1: 14	G1: 11	38	36	57	46
7	49	55	G2: 60	G2: 65	50	54	34	38
≥8	27	27	G3: 24	G3: 23	12	10	9	16
Surgical margin status, *n* (%)								
Negative	26	48	38	37	32	39	NA	NA
Positive	74	52	62	63	68	61	NA	NA
Postoperative PSA, ng/ml	<0.1: 100%	<0.1: 100%	≤0.2: 70% >0.2: 29%	≤0.2: 69% >0.2: 31%	<0.1: 100%	<0.1: 100%	<0.2: 65% ≥0.2: 35%	<10: 68% ≥10: 32%
Time from RP to RT, mo§	3	25	<4	NA	3	NA	<4	NA
Median PSA level at RT, ng/ml§	0.0	0.2	5.7	1.7	0.0	NA	NA	NA
Median RT dose, Gy§	60	67	60 (30 fractions)	NA	60 (30 fractions)	NA	60–64 (30–32 fractions)	NA
Median follow-up, mo	94	92	127		111	113	127	
Year of surgery, range	1996–2009		1992–2001		1997–2004		1988–1997	

aRT = adjuvant radiotherapy; EORTC = European Organisation for Research and Treatment of Cancer; esRT = early salvage radiation therapy; NA = not available; PSA = prostate-specific antigen; RP = radical prostatectomy; sRT = salvage radiotherapy; WS = wait and see.

§ Data reported only for patients who received radiation therapy.

* Proportion of pT2 R1 not specified (included in pT3a category).

achieved an undetectable postoperative PSA. Our results did not confirm that hypothesis because statistically significant differences in terms of distant metastasis and mortality were not observed between the groups. Several facets of our findings deserve attention.

First, these results corroborate the previous comparative study by Briganti et al, who found no significant difference between aRT and initial observation followed by esRT was found in terms of BCR [10]. However, the current study provides two main additional strengths: (1) The evaluated outcomes were distant MFS and OS, harder clinical end points compared with BCR; and (2) median follow-up was significantly longer compared with the previous study (93 vs 47 mo). These strengths were essential for the evaluation of these outcomes.

Second, baseline patient characteristics were comparable among groups. A similar proportion of advanced pathologic stage and high Gleason score were detected in both adjuvant and observational groups. At the same time, patients showed comparable age at surgery and preoperative PSA level. Conversely, a significantly different rate of positive surgical margin was observed between group 1 and 2 (74% vs 52%, respectively). However, positive margins did not affect the risk of distant metastasis at both univariable and multivariable analyses. When considering only patients who received esRT, the status of surgical margins (negative vs positive) did not significantly influence median time from surgery to esRT (29 mo; IQR: 15–43 mo) versus 23 mo (IQR: 14–44 mo; $p = 0.7$) and median PSA level at esRT (0.2 ng/ml; IQR: 0.1–0.3 ng/ml) versus 0.2 ng/ml (IQR: 0.1–0.3 ng/ml); $p = 0.4$. Similarly, it was not significantly associated with MFS (HR: 0.56; 95% CI, 0.18–1.76; $p = 0.3$). This finding was consistent with previous reports in which surgical margin status did not correlate with oncologic outcomes [12,20]. Taken together, these observations suggest that patient characteristics were substantially unlikely to alter our results.

Third, RT dose was significantly different between the two groups (60 vs 67 Gy; $p < 0.0001$). However, it was not associated significantly with the risk of distant metastasis at univariate analysis (HR: 0.98; 95% CI, 0.65–1.39; $p = 0.4$). The reason could be related to the relatively low dose administered in the salvage setting. Retrospective evidence indicates that oncologic outcomes following sRT are better by increasing radiation dose [21]. The hypothesis that dose escalation may improve biochemical outcome is currently under investigation by the SAKK–SWISS group for clinical cancer research that is randomising patients between 64 and 70 Gy (NCT01272050).

Fourth, the current study addressed a relevant clinical question recently investigated by three randomised clinical trials [7–9]. Conflicting results emerged from these studies regarding the risk of clinical recurrence. The main reason for such a discrepancy may be related to the inclusion criteria. The EORTC trial, in contrast to the other two studies, included a significant proportion of pT2 R1 patients, and

excellent prognosis was demonstrated for this category of patients [22]. An undetectable postoperative PSA was considered by the ARO study only; approximately 30% of patients had PSA persistence after surgery in both the EORTC and the SWOG trials. Finally, PSA level at RT was >0.5 ng/ml in a significant proportion of patients receiving salvage treatment in all three studies. The delay in sRT administration may have importantly affected patient prognosis because PSA level at RT was shown to be a crucial predictor of oncologic outcomes [11,12,14]. In contrast to the three trials just mentioned, in this study we included pT3pN0 patients who had achieved an undetectable postoperative PSA while sRT was administered at a PSA level ≤0.5 ng/ml. These inclusion criteria represent an important strength of the study. However, currently ongoing randomised trials (RADICALS NCT00541047 and RAVES NCT00860652) are needed to corroborate our findings.

Finally, we tested the hypothesis that the impact of aRT versus observation followed by esRT differed by pathologic characteristics. We found that aRT may be associated with an oncologic benefit only in patients with several adverse pathologic features at RP. However, a different impact of aRT according to pathologic characteristics was not observed. The reason may be related to the low number of patients with advanced and aggressive disease.

The current study has important clinical implications regarding postoperative RT administration. Approximately 40–50% of patients who were randomised to the observational arm in previous prospective randomised trials never recurred. Therefore, such patients would have been overtreated and exposed to treatment-related toxicity if aRT was administered in a blanket fashion following RP [23]. On the contrary, the restriction of esRT to only recurrent patients might potentially reduce overtreatment-related complications. Immediate aRT may potentially have a negative impact on functional outcomes recovery because urinary continence and sexual function recovery occurs mostly within the first 12 mo following surgery [24].

Despite its strengths, our study is not devoid of limitations. First, the relatively small size of the patient population may have influenced our results because the lack of significant differences among groups may be related to the number of patients included in the study. However, to the best of our knowledge, this is the first comparative study with stringent inclusion criteria evaluating distant metastasis and OS at long-term follow-up. Second, the retrospective nature of the study may also represent an important limitation. The decision whether to propose immediate postoperative aRT versus initial observation was left to the treating physician. This point may represent an important selection bias. However, as we previously specified, baseline patient characteristics were similar among groups, reducing the importance of such a selection bias. Finally, concomitant androgen-deprivation therapy was at the discretion of the referring urologist/radiation oncologist. Therefore, there was no standardised treatment schedule concerning type and duration of hormonal therapy. This may represent a further limitation of the study. However, a recent randomised trial did not show a significant survival benefit of goserelin in patients treated with sRT [25].

5. Conclusions

At long-term follow-up, no significant differences between aRT and esRT were observed in terms of MFS and OS. Our study, although based on retrospective data, suggests that a management approach to patients with adverse pathology at RP with initial observation and then esRT if biochemical relapse is diagnosed does not compromise cancer control and potentially reduces the overtreatment associated with a strategy of administering aRT to all such patients. The current ongoing randomised clinical trials are needed to corroborate our findings.

Author contributions: Nicola Fossati had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Tombal, Montorsi, Van Poppel, Wiegel.
Other (specify): None.

Financial disclosures: Nicola Fossati certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

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