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RESEARCH ARTICLE

Postoperative adjuvant and very early salvage radiotherapy after prostatectomy in high-risk prostate cancer patients can improve specific and overall survival

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Abstract

Purpose Adjuvant radiotherapy (ART) for biochemical relapse (BR) after radical prostatectomy (RP) showed increased disease-free survival (DFS) in three previous randomized trials. Retrospective phase II trials evaluated if early salvage RT (ESRT) is equivalent to ART. Our study aims to compare ART and ESRT to salvage RT.

Materials and methods We compared RP plus ART and ESRT versus SRT. Indication for RT was made by PSA determination after RP: ART when PSA ≤ 0.2 ng/ml, ESRT when PSA ≤ 0.3 after PSA rise from 0.0 to SRT PSA ≥ 0.3. The cause of death of each patients was analyzed, DFS, cause-specific survival (CSS) overall survival (OS) and metastasis-free survival (MFS) in relation to RT intention.

Results Between 1993 and 2008, 204 patients with a median age of 65 years (44–75) were treated. The median follow-up was 160 months (28.1–273.3). At diagnosis, 89.7% had localized clinical stages and 90.2% had Gleason (G) ≤ 7. The median PSA was 10 (range 4–101). The postoperative G was ≥ 7 in 66.2%; 56.4% had ≥ 2 positive margins; 29.4% received ART, 20% ESRT and 59.3% SRT. The DFS for ART, ESRT and SRT was 74, 56 and 39% with significant differences between the three groups ($p < 0.001$). ART + ESRT were combined versus SRT; for the DFS, the significant differences ($p < 0.001$) remained 67% versus 39%. Positive margins, pT3 and pre-RT PSA were significant factors on multivariate analysis. The CSS in the ART + ESRT group was 92 vs. 78% in the SRT group ($p < 0.05$). OS was 69% in ART + ESRT vs. 57% in SRT ($p < 0.05$). MFS was 82.7% in ART + ESRT vs. 67.4% in SRT.

Conclusions In this study the ART + ESRT presented benefits versus SRT in DFS, CSS, OS and MFS.

Keywords Postoperative radiotherapy · Biochemical relapse · Adjuvant radiotherapy · Early salvage and salvage radiotherapy

Introduction

Two previous randomized trials reported benefits in disease-free survival (DFS) with adjuvant radiotherapy (ART) versus wait-and-see in pT3N0 prostate cancer patients treated with radical prostatectomy (RP) [1, 2]. A third randomized trial also obtained benefits in metastasis-free survival (MFS) (71 vs. 61% $p = 0.016$) and overall survival (OS) (74 vs. 66% $p = 0.023$) at 10 years [3].

Nonetheless, the implementation of ART is limited despite the high level of evidence provided by these phase III trials. The main reason is that some specialists believe that ART may lead to overtreatment of patients with the potential risk of unnecessary RT toxicity. This is supported by a few non-phase III retrospective studies showing the

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same efficacy with early salvage postoperative radiotherapy (ESRT) versus ART [4].

These phase III trials were not designed to answer the question of whether ART can be deferred until an increase in PSA, equivalent to salvage RT (SRT), without compromising the oncologic outcome, because the comparative arm in the three trials was an observation arm. The open question is whether ART is better than or equal to SRT, especially if it is initiated early (ESRT) on confirmation of biochemical relapse (BR). Indeed, there is consensus that ESRT should be initiated before the PSA level exceeds 0.5 ng/ml [5].

To address these questions, we evaluated DFS, MFS, OS and cause-specific survival (CSS) at long-term follow-up using a single-institutional retrospective series of patients who underwent postoperative RT after RP with high-risk pathological factors (high Gleason, pathological margins, pT3 stage, etc). We hypothesized that ART or maybe very ESRT in this high-risk group of patients could provide better cancer control and survival than SRT. Since the three phase III trials were not designed to compare the grade of chronic toxicity between ART vs. SRT, we also retrospectively analyzed this fact in each group (ART, ESRT and SRT).

Materials and methods

We retrospectively studied all the patients treated with RP, referred to our department for RT, from 1993 to 2008. After obtaining review board approval, patient records were reviewed. All patients had histologically confirmed adenocarcinoma of the prostate. ART was defined as RT in patients with PSA ≤ 0.2 ng/ml, ESRT when PSA was ≤ 0.3 after an increase from the initial 0.0 ng/ml, and SRT when the PSA value was persistently ≥ 0.3 ng/ml at the first PSA evaluation after RP. The number of patients in the ART and ESRT groups was low compared to the SRT group, and they were, therefore, combined for comparison with the SRT group.

From 1993 to the end of 2005, RP consisted of open surgery and pelvic lymphadenectomy, while from 2006 to 2008 the vast majority of patients underwent RP by laparoscopy. The patients were from our university hospital (80%) as well as other hospitals (20%) (a total of 12 different urologists). We also included six patients from a study on the administration of docetaxel plus hormonotherapy (HT) before RP [6].

Patients were treated with linear accelerators (6 or 18 MV) at standard fractionation (1.8–2 Gy) with a median dose of 66 Gy (60–70). From 1999 to 2008 all the patients were treated with 3D planning (74%). Prior to 1999, 2D (26%) was performed. With 2D the median dose was 64 Gy (60–66). All the patients were treated by the same radiation oncologist.

The variables studied included: patient age, baseline PSA, stage and Gleason (G) at diagnosis (≤ 6, 7, ≥ 8), time from surgery to any kind of RT and pre-RT PSA levels. Pathological data included: stage (from pT0 to pN1), pathological (pG) score, surgical margin (negative vs. positive number) and tumor unilaterality or bilaterality, unifocality or multifocality in the surgical specimen and combination with HT. The end points were DFS, MFS, OS and CSS. All the study outcomes were measured from the date of surgery to address a potential lead-time bias.

Statistical analyses consisted of a non-parametric approach, median, and the Kruskal–Wallis test was used to compare variables among the radiation groups.

Univariate analysis was performed and comparison between curves was assessed by the log rank test. DFS, MFS, OS and CSS were obtained using the Kaplan–Meier method. Multivariate analysis with the Cox regression method was used to detect any potential variable with an effect on DFS, MFS, OS and CSS.

Results

The median age of the patients studied was 65 years (44–75). The median follow-up was 160 months (28.1–273.3). The median PSA was 10 (range 4–101), being ≤ 10 in 32%, > 11- ≤ 20 in 47.6% and > 21 ng/ml in 20.4%. At diagnosis, 89.7% were localized clinical stages (T1c, T2a, T2b and T2c), whereas the pathological stage was around 33%. Pathological findings showed a more advanced stage in more than 60% of the patients (Table 1), Baseline G score ≤ 6 in 56.4%, 7 in 33.8% and ≥ 8 in 8.4%. Postoperatively, these percentages changed to G ≤ 6 in 30.9%, 7 in 44.6% and ≥ 8 in 24.2%. Multifocal and bilateral pathological involvement was observed in 70.6% of patients, and 56.4% had two or more positive margins.

ART was administered to 29.4%, whereas ESRT and SRT were received by 20 and 59.3% of patients, respectively. The median time from surgery to radiation was 3.9 months (m) (2.7–5.2), 24.6 (13–36.3) and 23 (19–22.7) for ART, ESRT and SRT, respectively. Table 1 shows the comparison among the clinical and pathological characteristics of all the patients considering RT type, presurgical PSA values, pT and pN category, and positive/negative margins. The median age significantly differed ($p = 0.023$) between the ESRT group and the other groups, with the patients in the ESRT group being slightly older. There were also statistically significant differences with regard to the concomitant use of HT with RT. This combination was nearly 55% in the SRT group, being ≤ 5% in the other two groups. The main reasons to add neoadjuvant and concomitant HT to SRT were secondary in each case to decision of onco-urological committee and

Table 1 Characteristics of the patients

Characteristics	ART		ESRT		SRT		Statistics
Patients (204)	60	29.2%	22	10.8%	122	59.8%	Non-parametric test
Age							
Median	64		67		64.35		$p=0.023$
Range	44–75		58–74		49–75		
Presurgery PSA							
Median	10		9.5		11		ns
Range	4–98		5–18		4–101		
Pre-RT PSA							
Median	0.091		0.16		0.9		$p<0.001$
Range	0–0.2		0.01–0.3		0.3–10		
Concomitant HT + RTP	3	5%	1	4.5%	66	54.1%	$p<0.001$
pT category							ns
< p T3	12	20%	10	46.4%	47	38.5%	
p T3a	34	56.7%	10	45.4%	45	36.9%	
p T3 b	13	21.7%	2	9.1%	26	21.3%	
pN category							ns
p N1	1	1.7%	0	0	4	3.3%	
Margin							ns
Positive	55	91.7%	19	86.4%	96	78.7%	
Negative	3	5%	3	13.6%	16	13.1%	
Focality							ns
Unifocality	11	18.3%	4	18.2%	30	24.6%	
Multifocality	47	78.3%	18	81.8%	79	64.8%	
Laterality							ns
Unilaterality	11	18.3%	4	18.2%	30	24.6%	
Bilaterality	47	78.3%	18	81.8%	79	64.8%	
Gleason score							ns
≤6	12	20%	7	31.8%	42	34.4%	
7	36	60%	12	54.5%	43	35.2%	
≥8	12	20%	3	13.6%	35	28.7%	
Missing	2	3.3%	0	0	12	9.8%	

when PSA previous to RT was equal or superior to 0.9 ng/ml (also consensus decision of the committee).

Twenty patients presented grade 3–4 toxicity (13.3% after ART, 9.1% after ESRT and 8.2% after SRT) which was resolved (grade 1–2) with hyperbaric and/or surgical treatment, without any colostomy or cystectomy.

The DFS was 74, 56 and 39% for ART, ESRT and SRT, respectively, at a median follow-up of 160 m, with statistically significant differences among the three groups ($p<0.001$) (Fig. 1).On grouping the ART and ESRT patients together to have an equivalent number of patients for comparative analysis with the SRT group, DFS remained significantly different at 67% versus 39% ($p<0.001$)(Fig. 2). In the multivariate analysis positive margins, pT3 and pre-RT PSA were found to be significant factors for DFS ($p<0.001$).

During the follow-up period, 30 patients died secondary to prostate cancer: 5/81 patients in the ART + ESRT group versus 25/121 in the SRT group. The OS also significantly differed between the ART + ESRT and the SRT groups, with 69 vs. 57% ($p<0.05$), respectively (Fig. 3). At a median follow-up of 160 months, the CSS was higher in the ART + ESRT group than the SRT group (92 vs. 78%, $p<0.05$) (Fig. 4). At the end of follow-up, 59.4% of patients remained alive (120), 39% had died and 1.5% were lost to follow-up. MFS was 82.7% in the ART + ESRT group versus 67.4% in the SRT group (Fig. 5) ($p<0.01$). Overall, 41 (20%) patients developed distant M1 (bone or nodes). The ART + ESRT group presented a lower number of M1 than the SRT group (11 vs. 30).

Discussion

The timing of postoperative RT remains unclear in randomized studies. The three randomized clinical trials of postoperative RT after RP available at present found a benefit in

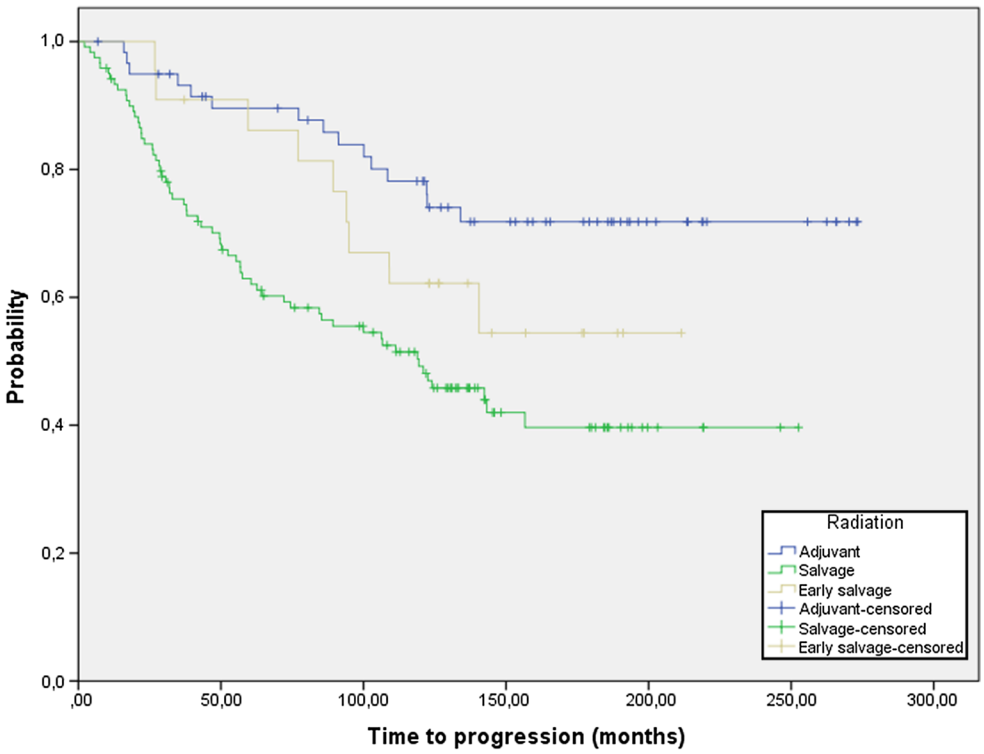

Fig. 1 Disease-free survival by postoperative intention to treat radiotherapy (adjuvant vs. early salvage vs. salvage)

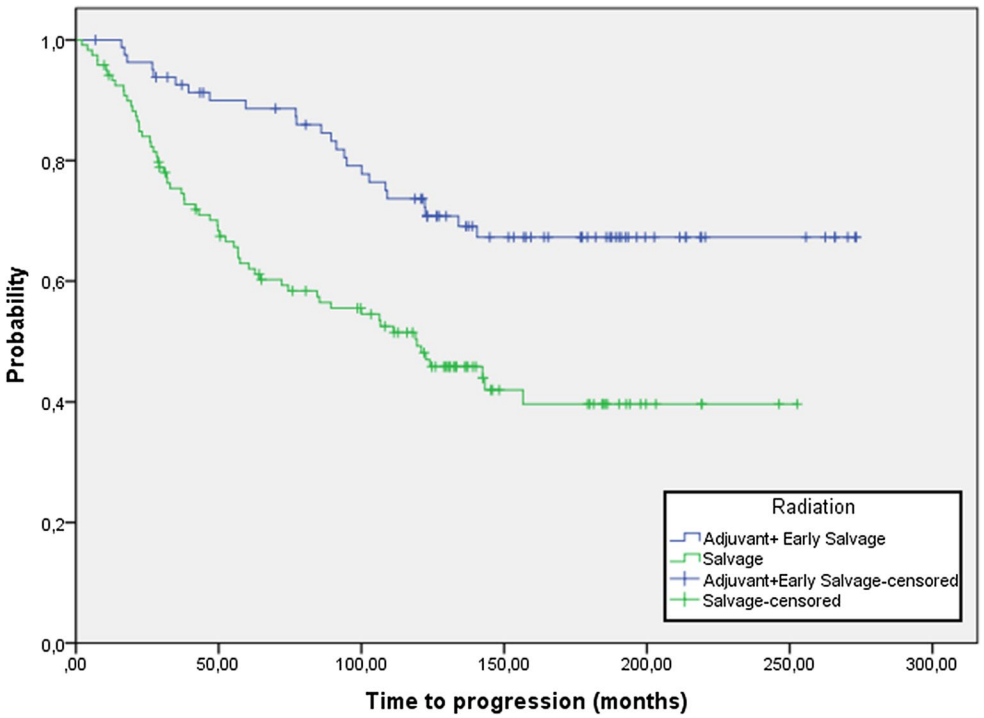

Fig. 2 Disease-free survival by intention to treat radiotherapy (adjuvant + early salvage vs. salvage)

DFS at 10 years with ART versus a wait-and-see approach, and only one trial found a benefit in MFS and OS. In all these trials, nearly one-third of patients in the ART arm had low PSA levels prior to ART and they received ESRT or SRT more than real ART. It is also important to point out that in postoperative RT some high risk factors are biologically correlated with the probability of local persistence versus systemic disease, and some correlate with any residual local disease. As each patient can present with different combinations of pathological factors, risk stratification for ART or SRT can be very complex. Another major criticism of these three phase trials was that nearly 40% of patients in the

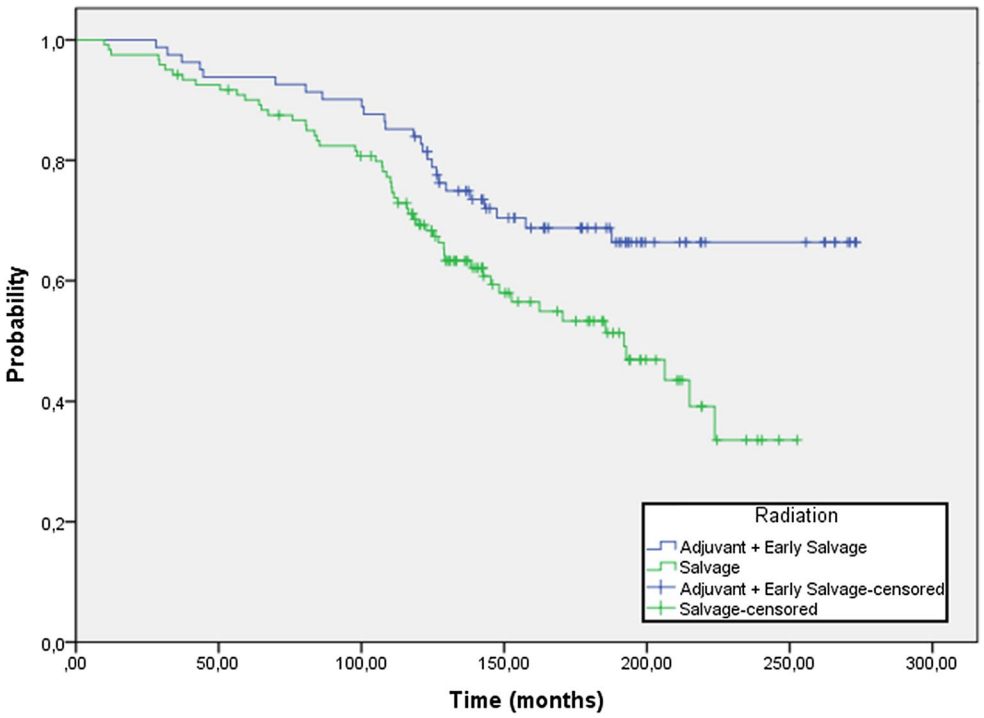

Fig. 3 Overall survival by intention to treat radiotherapy (adjuvant + early salvage vs. salvage)

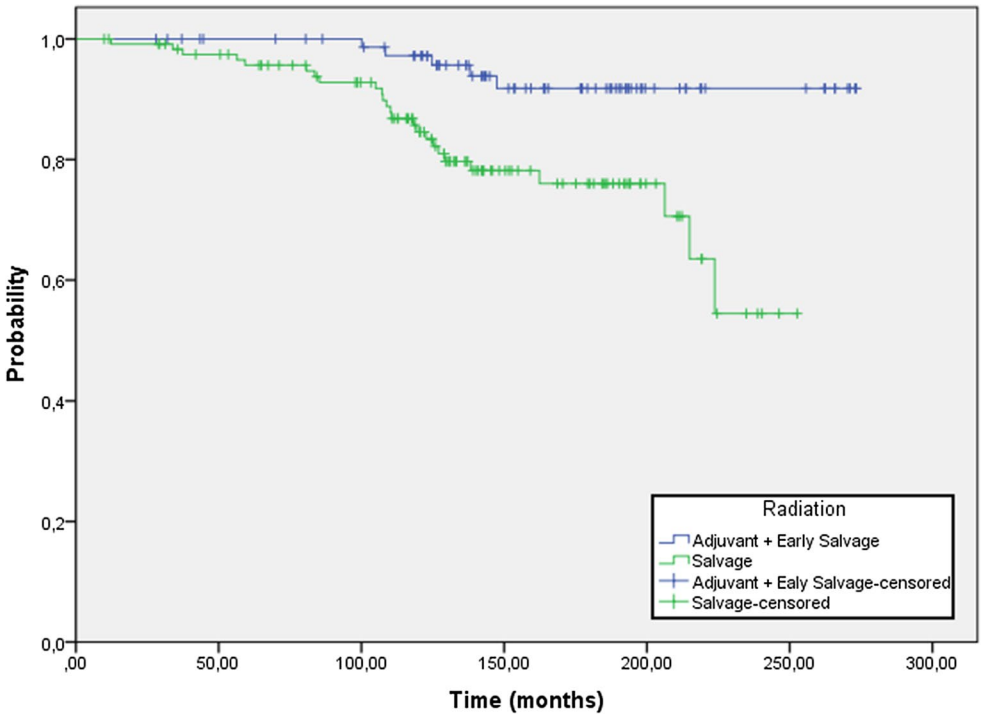

Fig. 4 Specific survival by intention to treat radiotherapy (adjuvant +early salvage vs. salvage)

wait-and-see arm never presented recurrence, indicating, as mentioned previously, possible overtreatment with ART in the study population, since some patients could have been cured by RP alone. The possibility of previous cure of prostate cancer with surgery alone cannot be ruled out in a few of the ART patients in our study, but it should be noted that this ART group had a larger combination of bad prognostic factors (more advanced stage, high Gleason score and more aggressive pathological involvement as shown in Table 1) than the other postoperative groups.

Previous phase II trials comparing ART with ESRT or SRT showed an increase of DFS with ART, but not of OS [7–9]. This may be due to a mixture of factors such as a smaller number of patients, a shorter follow-up, different end

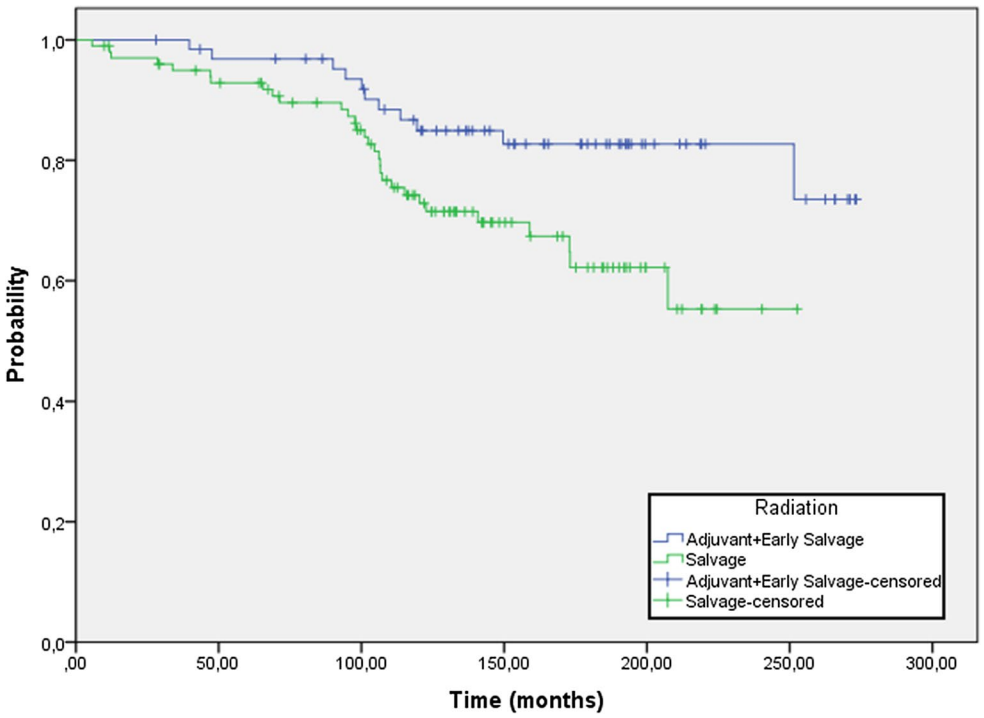

Fig. 5 Metastasis-free survival by intention to treat radiotherapy (adjuvant + early salvage vs. salvage)

points, and a large interval of PSA thresholds (0.0–1 ng/ml) prior to postoperative RT. In our series, the PSA interval in each group (ART, ESRT, and SRT) was very well defined and stratified to avoid this bias in the analysis. Another important aspect of our series was the long median follow-up, which, to our knowledge, is one of the longest in the literature to date.

Compared to the ESRT and SRT group in our series, the ART group showed a better DFS. This finding was supported by the presence of low PSA levels at the time of treatment initiation [10]. This observation was also found in a multi-institutional analysis, showing the best 5-year biochemical relapse-free survival (bRFS) in relation to the level of pre-RT PSA of 0.01–2.0 ng/ml (63% for 0.21–0.5 mg/ml, 54% for 0.51–1.0 ng/ml, and 43% for 1.01–2 ng/ml) [11]. The median PSA of our three groups was 0.091 ng/ml, 0.16 ng/ml and 0.9 ng/ml for ART, ESRT and SRT, respectively. Despite the very small differences among our median PSA levels, especially between ART and ESRT (0.091–0.16), the differences in DFS were statistically significant between these two groups. In concordance with the relationship between pre-SRT levels and the results of this treatment of note is a study including 894 patients which reported a rapid reduction in bRFS related to previous PSA values: the maximum obtainable bRFS (defined as 95% of the maximum) decreased by about 2.7 and 4.5% for each increment of 0.1 ng/ml for a G score <7 and ≥ 7, respectively [12]. In addition, the detrimental effect of an increase of PSA can never be fully compensated by increasing the doses, especially in patients with a $G \geq 7$ [13].

Recent randomized studies have described a better DFS and/or OS with the addition of HT to postoperative RT [14]. Although the combination of HT + RT favored the SRT group compared to the other groups (54.1% versus $\leq 5\%$) in our series, we found no benefit in any of the end points (DFS, OS, CSS or MFS).This result may be due to the short duration of HT (median administration of 6 months) in the SRT group. Another possible explanation may be that a large part of our study population that received concomitant HT to postoperative RT included patients in the SRT group, and a recent multi-institutional series with 525 patients and the use of concomitant HT in SRT for biochemical relapse after RP showed a reduction in the rate of metastases only in the ESRT group ($p = 0.046$) and in patients with high risk factors [15].

Achievement of the very important end points mentioned above in our study was obtained with radiation alone, especially ART and ESRT.

To our knowledge, this is the first study to find statistically significant benefits with ART and ESRT compared with SRT after RP in all the end points of DFS, MFS, OS and CSS. In addition, we provide a detailed description of PSA levels to stratify each group as well as information regarding bad prognostic factors (including a high Gleason score, stage pT3, positive margins, etc).

Our series provides some insights favoring the administration of ART and ESRT versus SRT after RP in high-risk patients. This favorable impact on end points of survival (OS, CSS and MFS) secondary to ART compared to ESRT has recently been demonstrated in a multi-institutional,

propensity score-matched cohort study including 1566 patients with adverse pathological factors undergoing RT post-RP [16]. The authors of this latter study performed a sensitive analysis in which the decreased risk of BR relapse associated with ART only lost statistical significance when more than 56% of patients in the ART group were assumed to have been cured by RP alone. These results suggest that the improved outcomes seen in the ART versus the ESRT group cannot be simply ascribed to more favorable clinicopathological features. In this study, ART was associated with a greater bRFS, MFS and OS compared with ESRT. All these end points were very similar to ours; however, it should be noted that the PSA levels in this important study on ART was < 0.1 ng/ml while the PSA levels in ESRT were 0.1–0.5 ng/ml. In our series, the PSA levels in ART and ESRT patients were ≤ 0.2 and ≤ 0.3 ng/ml, respectively, after a rise in PSA from 0.0. We believe that pre-postoperative PSA RT of > 0.3 ng/ml should be considered as SRT rather than ESRT. Indeed, patients with pre-postoperative PSA levels ≥ 0.2 ng/ml are at a higher risk of progression after SRT and the majority of patients with PSA ≥ 0.1 ng/ml after RP will progress to PSA ≥ 0.2 ng/ml [17]. Other authors such as Fossati et al. [18] also considered ESRT in patients with rising or persistently elevated PSA levels after RP defined as a PSA level > 0.1 ng/ml at 1 month after RP. These authors included 925 patients treated with SRT after RP in seven institutions. At a median follow-up of 8.0 years, 130 patients (14% of all the patients) developed distant metastases (M1). On multivariate analysis, the pre-SRT PSA level was significantly associated with M1 (hazard ratio; 1.6, $p < 0.0001$). MFS is a strong surrogate of OS as pointed out in a recent meta-analysis of 28 phase III trials including 28.905 patients [19].

There is scarce evidence in the literature, on the role of ART or ESRT in patients with less than a pT3 stage after RP who presented BR during follow-up. An important proportion of our patients presented BR: 20% (13 patients) in ART group, 46.4% (10 patients) in the ESRT group and 38.5% (47 patients) in the SRT group. According to the consensus guidelines of the American Urological Association and the American Society for Radiation Oncology, patients with less than a pT3 stage but with other important high risk factors (positive margins, plus a high Gleason score and > 0.1 ng/ml) should be informed about the benefits and risks of ART and real ESRT (< 0.3 ng/ml after progressive increase following RP) versus SRT [20].

Regarding the toxicity of postoperative RT, late grade 3 toxicity was observed in 1% of patients in a large retrospective multi-institutional analysis of patients receiving this treatment, whereas late grade 3 rectal toxicity was 0.4% [21]. Our results on toxicity differed greatly from these results with nearly 10% of late grade 3–4 urinary toxicity, with no statistically significant differences among the ART, ESRT or SRT groups. The previously mentioned three phase III trials reported limited information about late toxicity, while the rate of urethral stricture in the SWOG trial was very similar to that of our series (17.8% for ART vs. 9.5% in the observation arm). Although some of the patients in the observational arm received SRT at progression, it is essential to point out that urethral stricture could, in part, be associated with RP alone.

Nonetheless, our series has several limitations. The first is that we used a retrospective design with the well-known possible inherent selection bias. The second may be the long period of time from the first and the last patients of the series (1993–2008), which could also induce several important biases such as factors not analyzed in our study including the type of RT (2D vs. 3D, size of the radiation fields, nodes irradiation or not, and learning curve, among others). A third limitation is the scarce number of patients in ESRT group which led to combining this group with the ART group to perform the comparative analysis with SRT. The median pre-RT PSA values in the ART and ESRT groups were very similar (0.091–1.6), but the median time of ART and ESRT administration was very different (2.9 versus 20 months, respectively). This scarce number of ESRT patients did not allow analysis of the main end points in the three groups, with the exception of DFS which significantly differed among the three groups (ART vs. ESRT vs. SRT).

In conclusion, from the results of our analysis ART and ESRT (specifically considered increased from 0.00 to < 0.3) can produce a benefit in DFS, CSS, MFS and OS in patients with prostate cancer and several high-risk pathological factors after RP. Three phase III studies about the comparison between ART and ESRT/SRT are ongoing [22–24] and they clarified some important facts about role or ART or ESRT in relation to SRT and also the role of concomitant AD. Finally different high-tech improvements such as genomic biomarkers to best risk stratification [25] or novel imaging techniques for optimizing RT target coverage [26] can be very useful to improve results in this important population of patients.

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Compliance with ethical standards

Conflicts of interest All the authors not have any conflicts of interest.

Ethical approval Research involving Human Participants and/or Animals it is not performed.

Informed consent All the patients signed informed consent before postoperative radiotherapy.

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