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Use of Concomitant Androgen Deprivation Therapy in Patients Treated with Early Salvage Radiotherapy for Biochemical Recurrence After Radical Prostatectomy: Long-term Results from a Large, Multi-institutional Series

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Abstract

Background: Hormonal manipulation concomitant to salvage radiotherapy (SRT) given for biochemical recurrence (BCR) after radical prostatectomy (RP) improved outcomes in two randomized trials. However, neither of these studies focused on men treated at low prostate-specific antigen (PSA) levels.
Objective: To test if the impact of androgen deprivation therapy (ADT) on metastasis in patients undergoing early SRT varies according to prostate cancer (PCa) features.
Design, setting, and participants: A total of 525 patients received SRT at PSA levels $\leq$2 ng/ml.
Outcome measurements and statistical analyses: Multivariable Cox regression analyses assessed factors associated with metastasis. We tested the hypothesis that the impact of ADT varied according to the risk of metastasis. An interaction with groups (concomitant ADT vs no ADT) and the probability of distant metastasis according to a newly developed model was tested. A nonparametric curve explored the relationship between the risk of metastasis and 10-yr metastasis rates according to ADT.
Results and limitations: Median PSA and radiotherapy dose were 0.42 ng/ml and 66 Gy, respectively. Overall, 178 (34%) patients received ADT. At a median follow-up of 104 mo, 71 patients experienced metastasis. Grade group $\geq$4 (hazard ratio [HR]: 1.66; 95% confidence interval [CI]: 1.01–3.30), pT3b/4 (HR: 2.61; 95% CI: 1.51–4.52), and dose (HR: 0.82; 95% CI: 0.76–0.89) were associated with metastasis. The impact of ADT

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differed according to the risk of metastasis calculated using a multivariable model ($p = 0.01$). This was confirmed when considering patients treated with early SRT ($p = 0.046$), where ADT was associated with a reduction in the rate of metastasis only in eSRT; patients with more aggressive characteristics (ie, pT3b/4 and grade group $\geq$4, or pT3b/4 and PSA at eSRT $\geq$0.4 ng/ml).
Conclusions: The beneficial effect of ADT concomitant to eSRT varied significantly according to disease characteristics, such that only men with more aggressive PCa features benefit from ADT in the eSRT setting for BCR after RP.
Patient summary: The oncological benefits of concomitant androgen deprivation therapy (ADT) in patients undergoing salvage radiotherapy (SRT) vary according to pathological characteristics. Only patients with more aggressive disease characteristics seemed to benefit from the use of hormonal manipulation at the time of early SRT. Conversely, the potential side effects of ADT could be spared in patients with low prostate-specific antigen levels and favorable pathological features.

1. Introduction

A non-negligible proportion of prostate cancer (PCa) patients undergoing radical prostatectomy (RP) will experience biochemical recurrence (BCR) [1,2]. These individuals are at an increased risk of metastasis and, eventually, of dying from PCa [3]. Salvage radiotherapy (SRT) represents the only curative treatment option associated with durable cancer control when delivered in an early setting (namely, eSRT) [4,5]. Two randomized controlled trials (RCTs) demonstrated that concomitant hormonal manipulation at the time of SRT improved oncological outcomes [6,7]. However, the generalizability of these findings might be limited by four main reasons:

1. None of the two studies focused exclusively on eSRT (namely, radiotherapy [RT] administered at prostate-specific antigen [PSA] levels <0.5 ng/ml), which is currently recommended by clinical guidelines [1,5,8–13]. Moreover, a systematic review recently showed that the benefit of hormonal manipulation varies according to pre-SRT PSA [14]. In this context, the RTOG 9601 trial was initially restricted to men with baseline PSA between 0.5 and 4 ng/ml, and those with a PSA between 0.2 and 0.5 ng/ml were considered eligible only after the initiation of the trial.
2. Inclusion of heterogeneous cohorts. For example, more than 10% of patients included the RTOG 9601 trial received SRT for PSA persistence after surgery, which is a risk factor for adverse oncological outcomes after SRT [15].
3. Use of a composite end point evaluated at intermediate follow-up [6]. While in the RTOG 9601 trial the primary end point was overall survival, in the GETUG 16 study the outcome was represented by progression-free survival at a median follow-up of 5 yr.
4. Both studies excluded men treated at higher radiation doses. Despite the lack of available level 1 evidence data supporting the role of dose escalation in the salvage setting, radiobiological models support the use of higher doses [16,17].

To overcome these limitations, we tested the impact of concomitant androgen deprivation therapy (ADT) in a contemporary cohort of men receiving SRT at low PSA levels for BCR after RP. We hypothesized that the beneficial effect of ADT might be limited to patients with more aggressive disease characteristics.

2. Patients and methods

2.1. Study population

After Institutional Review Board approval, 706 patients who received SRT for recurrent PCa after RP between 1996 and 2009 at six tertiary referral institutions were identified. All patients had an undetectable first PSA after surgery (defined as <0.1 ng/ml). All patients received SRT due to BCR after RP, which was defined as a PSA increase within two or more determinations [12]. Patients were excluded if they had missing PSA values at the time of SRT ($n = 38$), missing data on the administration of concomitant ADT ($n = 34$), and undergone previous ADT ($n = 40$). This resulted in a final population of 594 patients. We then focused on node-negative patients ($n = 558$). Owing to their increased risk of metastases [18], patients with PSA levels at SRT >2 ng/ml were excluded. This resulted in a study cohort of 525 patients.

2.2. Covariates

All patients had available data on preoperative PSA, pathological stage, surgical margin status, pathological grade group, RT dose and fields. Prostatectomy specimens were evaluated by high-volume, expert uropathologists. Central pathology review was not performed.

2.3. RT technique

Postoperative RT was delivered to the prostate and seminal vesicle bed at a median (interquartile [IQR]) dose of 66 (65–71) Gy using previously described techniques [8,19,20]. Whole-pelvis RT was administered to 112 patients (21%). The median (IQR) dose delivered to the pelvic nodal area was 50 (50–51) Gy. The decisions to irradiate the pelvic lymph node area and administer concomitant ADT were based on the clinical judgment of each treating physician according to individual patient and cancer characteristics.

2.4. End points

The primary outcome of the study was distant metastasis after SRT. Metastases in the pelvic and retroperitoneal lymph nodes, bones, parenchymal organs, or soft tissues were identified by conventional

imaging, as previously reported [19]. Follow-up time was defined as the time elapsed between SRT and the onset of metastasis or last follow-up.

2.5. Statistical analyses

Our statistical analyses consisted of different steps. First, Kaplan–Meier analyses assessed time to distant metastasis. Second, multivariable Cox regression analyses assessed variables associated with the risk of distant metastasis. Third, we tested whether the association between concomitant ADT and distant metastasis was different according to disease characteristics. A multivariable Cox regression model for metastasis-free survival based on pathological stage, grade group, positive margins, and PSA at SRT was developed exclusively in patients who did not receive concomitant ADT (n = 347). The risk of experiencing metastasis at 10 yr was then calculated for each patient using the multivariate coefficients. We tested an interaction with groups (concomitant ADT vs no ADT) and the probability of distant metastasis according to the newly developed model. The nonparametric curve fitting method graphically explored the relationship between the 10-yr risk of metastasis calculated using the novel model and observed metastasis rates according to the administration of concomitant ADT. In particular, we plotted the predicted metastasis rates against the observed rates at 10-yr follow-up after stratifying patients according to concomitant ADT at the time of SRT. We then repeated our analyses in patients who received eSRT (n = 316). Patients more likely to benefit from ADT at the time of eSRT were identified using the risk of 10-yr metastasis calculated according to the regression coefficients. Finally, we hypothesized that the impact of concomitant ADT might vary according to RT dose or fields. An interaction test was used to assess whether the potential benefit of ADT on the risk of metastasis varied according to dose or the administration of whole-pelvis RT.

All statistical tests were performed using the R statistical package v.3.0.2 (R Project for Statistical Computing, www.r-project.org). All tests were two sided, with a significance level set at <0.05.

3. Results

3.1. Baseline characteristics

Median (IQR) age at surgery was 64 (60–64) yr (Table 1). Median (IQR) PSA at the time of eSRT was 0.42 (0.24–0.72) ng/ml. When patients were stratified according to concomitant ADT, significant differences were observed with regard to positive surgical margins and RT dose (all $p \leq 0.001$; Table 1). Moreover, the use of concomitant ADT significantly differed according to the center and ranged between 11% and 58% (p = 0.001).

3.2. Outcome analyses

Median follow-up for survivors was 104 mo (IQR: 97–112). Overall, 71 patients were diagnosed with distant metastasis. The 10-yr metastasis-free survival rate was 88% (Fig. 1). Higher pathological stage and grade group as well as lower RT dose were each associated with a significantly increased risk of metastasis (all $p \leq 0.04$; Table 2). When considering patients treated with eSRT (n = 316), pathological stage, grade group, and dose were confirmed as independent predictors of metastasis (all $p \leq 0.04$; Supplementary Table 1). We then assessed predictors of metastasis in patients who did not receive ADT. Pathological stage and PSA at the time of SRT were each associated with a significantly increased risk of metastasis (all $p \leq 0.04$; Table 3). The impact of concomitant ADT on the risk of 10-yr distant metastasis differed according to the predicted risk of metastasis based on the multivariable model

Table 1 – Descriptive statistics of 525 patients with clinically localized prostate cancer treated with early salvage radiotherapy (SRT) for biochemical recurrence after radical prostatectomy

	Overall (n = 525)	No ADT (n = 347, 66%)	Concomitant ADT (n = 178, 34%)	p value
Age at surgery (yr)				
Median (IQR)	64 (60–64)	64 (59–68)	66 (62–71)	0.1
Preoperative PSA (ng/ml)				
Median (IQR)	8.6 (6.0–13.4)	8.4 (6.0–12.5)	9.0 (5.7–15.0)	0.3
Grade group at final pathology (%)				
1	203 (39)	132 (38)	71 (40)	0.5
2	148 (28)	106 (30)	52 (24)	
3	92 (17)	58 (17)	34 (19)	
4	53 (10)	33 (9)	20 (11)	
5	29 (5)	18 (5)	11 (6)	
Pathologic stage (%)				
T2	300 (57)	208 (60)	92 (52)	0.06
T3a	176 (34)	113 (33)	63 (35)	
T3b/T4	49 (9)	26 (7)	23 (13)	
Positive surgical margins (%)	220 (42)	161 (46)	59 (33)	0.001
Time from surgery to RT				
Median (IQR)	27 (14–54)	29 (16–56)	29 (15–51)	0.4
PSA at SRT (ng/ml)				
Median (IQR)	0.42 (0.24–0.72)	0.40 (0.23–0.70)	0.50 (0.26–0.90)	0.1
Dose (Gy)				
Median (IQR)	66 (65–71)	66 (65–66)	70 (66–74)	<0.001
Irradiation of the pelvic nodal area (%)	112 (21)	76 (22)	36 (20)	0.3
ADT duration (mo)	–	–	15 (10–29)[a]	
Follow-up (mo)				
Median (IQR)	104 (97–112)	94 (81–106)	147 (138–156)	0.001

ADT = androgen deprivation therapy; IQR = interquartile range; PSA = prostate-specific antigen; RT = radiotherapy.
[a] Data available for 110 patients.

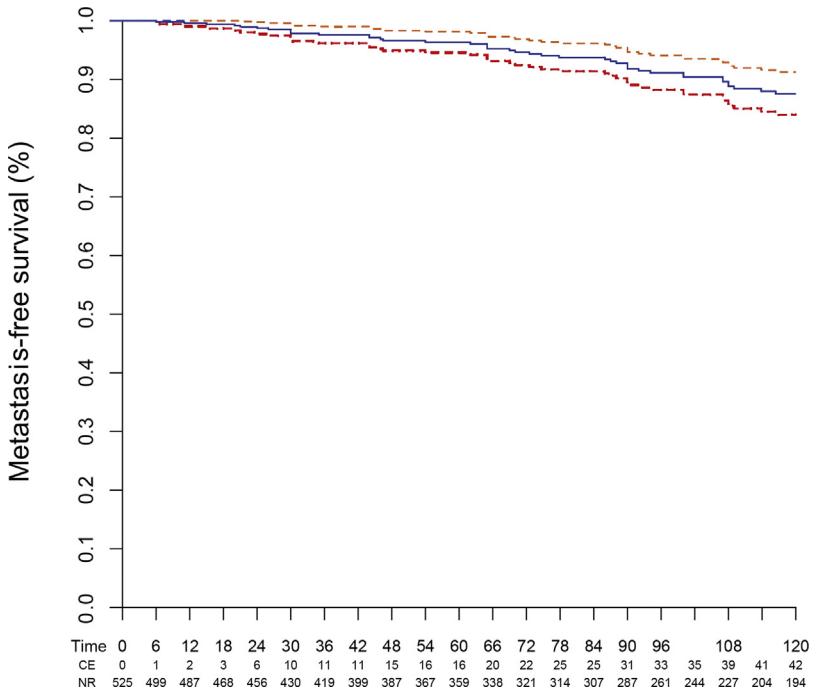

Fig. 1 – Kaplan–Meier analyses depicting the 10-yr distant metastasis–free survival in patients treated with early salvage radiotherapy.

Table 2 – Multivariable Cox regression analyses evaluating the risk of distant metastasis in 525 patients treated with early salvage radiotherapy (SRT) for biochemical recurrence after radical prostatectomy

	Univariable analyses		Multivariable analyses Model 1[a]		Multivariable analyses Model 2[b]	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
PSA at SRT	1.32 (1.04–2.27)	0.03	1.19 (0.69–2.04)	0.3	1.28 (0.75–2.19)	0.3
Pathologic grade group						
≤3	1 (Ref.)	0.02	1 (Ref.)	0.044	1 (Ref.)	0.041
≥4	1.86 (1.03–3.39)		1.79 (1.02–3.30)		1.66 (1.01–3.03)	
Pathologic tumor stage						
T2-pT3a	1 (Ref.)	0.001	1 (Ref.)	<0.001	1 (Ref.)	0.001
T3b/4	3.68 (2.15–6.31)		3.51 (2.05–6.09)		2.61 (1.51–4.52)	
Positive surgical margins						
No	1 (Ref.)	0.2	1 (Ref.)	0.6	1 (Ref.)	0.7
Yes	0.75 (0.46–1.23)		0.89 (0.53–1.43)		0.89 (0.54–1.49)	
Dose	0.84 (0.78–0.90)	<0.001	–	–	0.82 (0.76–0.89)	<0.001
Whole-pelvis RT	0.71 (0.36–1.38)	0.7	–	–	2.06 (0.95–4.47)	0.1

CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen; Ref. = reference; RT = radiotherapy.
[a] Model including only baseline PSA at SRT and pathologic covariates.
[b] Model including radiotherapy details.

($p = 0.01$ by an interaction test). In particular, the administration of concomitant ADT was associated with a reduced rate of distant metastasis exclusively in patients with more aggressive disease characteristics (Fig. 2). This was confirmed when we restricted our analyses to patients treated in the early salvage setting ($p = 0.046$). In particular, concomitant ADT was associated with a benefit in terms of metastasis exclusively in patients with pT3b/4 and grade group ≥4 or pT3b/4 and PSA at eSRT ≥0.4 ng/ml. Finally, we did not observe an interaction between the administration of concomitant ADT and RT doses or whole-pelvis RT in the overall population and when considering patients treated with eSRT (all $p \geq 0.3$).

4. Discussion

Two prospective RCTs demonstrated that hormonal manipulation improved oncological outcomes after SRT [6,7]. In the RTOG 9601 trial, Shipley et al [7] randomized 760 patients with PSA persistence or recurrence to 24 mo of bicalutamide or placebo concomitant to SRT. The administration of bicalutamide improved overall survival at a median follow-up of 13 yr. Similarly, the GETUG-AFU 16 trial randomized 743 patients who experienced BCR to SRT alone or SRT plus short-term ADT and demonstrated that the addition of ADT reduced the 5-yr progression rates [6]. Despite providing high level of evidence, generalizability of these results to

Table 3 – Uni- and multivariable Cox regression analyses evaluating the risk of distant metastasis in patients treated with early salvage radiotherapy (eSRT) for biochemical recurrence after radical prostatectomy who did not receive concomitant androgen deprivation therapy (*n* = 347)

	Univariable analyses		Multivariable analyses	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
PSA at SRT[a]	1.08 (1.03–1.19)	0.02	1.09 (1.01–1.18)	0.03
Pathologic grade group				
≤3	1 (Ref.)	0.03	1 (Ref.)	0.4
≥4	1.83 (1.03–4.14)		1.80 (0.83–7.32)	
Pathologic tumor stage				
T2-pT3a	1 (Ref.)	<0.001	1 (Ref.)	0.01
T3b/4	6.99 (2.95–16.5)		6.09 (1.96–18.9)	
Surgical margin status				
Negative	1 (Ref.)	0.7	1 (Ref.)	0.5
Positive	0.91 (0.41–2.05)		1.69 (0.35–8.04)	

CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen; Ref. = reference.
[a] Per increase of 0.1 ng/ml.

contemporary patients remains suboptimal. Both studies included a non-negligible proportion of men treated in a late salvage setting, which does not represent the standard of care for men treated with SRT [1,5]. This is crucial when considering that reduced BCR-free survival was observed even in patients treated at PSA levels <0.2 ng/ml [21]. Moreover, in the GETUG-AFU 16 study, the greatest effect of concomitant ADT was evident on biochemical progression only. However, it is well known that even in the salvage setting, not all patients who experience BCR will eventually die from PCa [22]. Therefore, these results, being potentially associated with a certain risk to overtreat some patients using concomitant ADT, should be interpreted carefully. Moreover, both studies excluded patients treated at higher SRT doses, where biological models support the role of higher doses in men with recurrence after RP [16,17]. We tried to overcome these limitations even though using a retrospective approach, and we aimed at assessing whether the impact of concomitant ADT varied according to individual risk profiles in a cohort of men receiving SRT at low PSA levels. We hypothesized that salvage RT alone administered at adequate doses might achieve optimal cancer control in patients with more favorable disease characteristics treated at low PSA levels regardless of the use of ADT. This would have important clinical implications since a non-negligible proportion of patients would be spared ADT and its related side effects [23]. On the contrary, those who would really benefit from this combined approach would be men with more aggressive disease.

We observed a significant interaction between the administration of ADT and the baseline risk of metastasis calculated according to a multivariable model. We found that concomitant ADT was beneficial only in those with more aggressive features, namely, pT3b/4 and grade group ≥4 or pT3b/4 and PSA at eSRT ≥0.4 ng/ml. Although subgroup analyses of RCTs should be interpreted with caution, our results are in line with those reported by the RTOG 9601 study, where patients with grade group 4–5 disease, positive surgical margins, and higher PSA levels at SRT appeared to experience the highest benefit in terms of survival from the addition of bicalutamide [7,14]. In particular, hormonal manipulation seemed to be beneficial

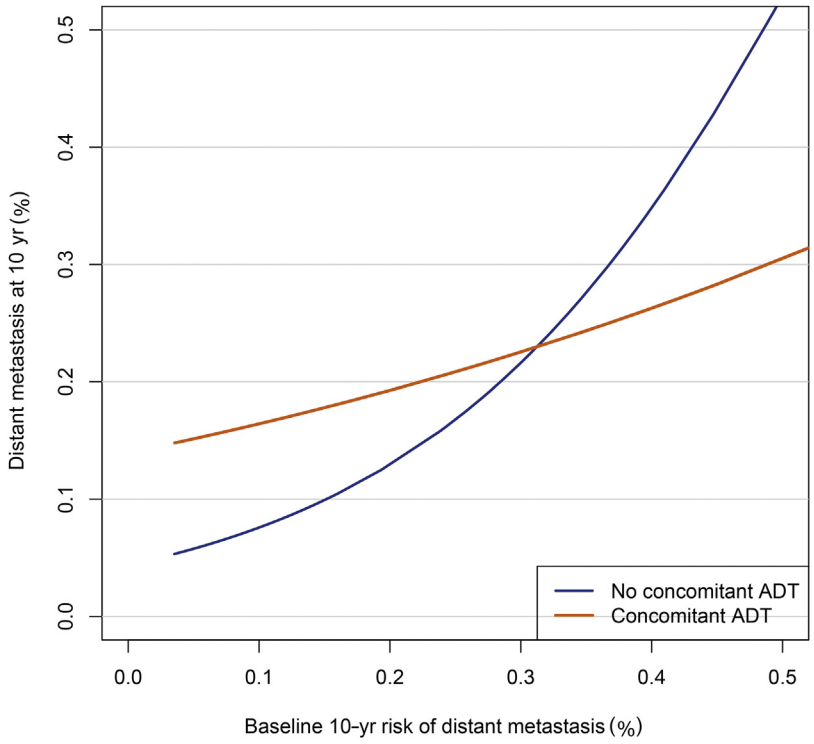

Fig. 2 – Distant metastasis-free survival rates at 10-yr follow-up after salvage radiotherapy plotted against the baseline risk of 10-yr distant metastasis.

in terms of overall survival exclusively in men with PSA ≥0.7 ng/ml. Moreover, bicalutamide improved metastasis-free survival only in patients with a pre-SRT PSA of ≥1.5 ng/ml [7]. Similarly, in the GETUG 16 study, patients with a PSA of ≥0.5 ng/ml at the time of SRT were more likely to benefit from ADT [6]. This is consistent with the observations of our study, where higher PSA levels contributed to the identification of patients who might benefit from ADT. By contrast, the lack of impact of positive margins on the risk of metastasis might be related to the administration of higher doses as well as to a more timely use of SRT, which might result into better local disease control [7,14,16,24]. Finally, our results are in line with those reported by a recent systematic review and framework for the use of hormone therapy concomitant to SRT, where the authors conclude that patient, tumor, and treatment factors should be taken into account when considering the use of hormone manipulation in individuals undergoing SRT [14]. The observation that the impact of concomitant ADT varied according to disease aggressiveness supports the hypothesis that the potential benefit of adding ADT to SRT might be related to an effect on subclinical metastatic disease outside the radiation field rather than to a failure of RT in maximizing local disease control [6,25,26]. This concept is also reinforced by the observation that, although patients receiving high-dose RT had improved oncological outcomes at long-term follow-up, the impact of the administration of concomitant ADT on the risk of distant metastasis did not vary according to RT dose or fields. In other words, the detrimental effect of aggressive disease characteristics could not be compensated by increasing doses or extending radiation fields [17]. As such, men treated at higher RT doses and/or with whole-pelvis RT also seemed to benefit from concomitant ADT. However, such a homogeneous effect of ADT regardless of dose and fields of SRT may be due to the retrospective design of our study. Indeed, only 31% and 21% patients received >70 Gy and whole-pelvis eSRT based on the discretion of each treating physician. This may have introduced unknown confounders, which cannot be accounted for in our multivariable models.

Despite several strengths, our study is not devoid of limitations. First, the retrospective nature of our study might have introduced a selection bias, where patients with more aggressive characteristics might have been considered for additional cancer therapies immediately after surgery. This might also explain the lack of association between grade group and the risk of metastasis observed in patients who did not receive concomitant ADT. Similarly, the effect of unmeasured confounders might explain the higher rates of metastasis observed in men receiving concomitant ADT with less aggressive disease as compared with their counterparts who did not receive hormonal manipulation. Under this light, we cannot exclude that the benefit of concomitant ADT on metastasis in patients with more aggressive features might be even more pronounced than that observed in our analyses. Second, the decision to administer concomitant ADT and follow-up protocols were based on the judgment of each physician and differed according to the treating institution. Third, doses and fields of SRT were not standardized. Owing to the relatively small number of events, we were not able to adjust our analyses for a center effect. Fourth, a small number of deaths from PCa ($n = 20$) precluded us to evaluate cancer-specific mortality. Finally, a lack of biological data such as genomic profiling prevented us to test the impact of concomitant ADT according to more comprehensive scores, which may potentially be helpful in the selection of men who are candidates for concomitant ADT at the time of eSRT [27]. Despite these limitations and the retrospective design, our study is the first report aiming at addressing the impact of concomitant ADT exclusively in patients treated with SRT for BCR after RP at low PSA levels.

5. Conclusions

We reported the first study aimed at identifying the best candidates for concomitant ADT at the time of eSRT. We found that oncological benefits associated with concomitant administration of ADT in patients undergoing eSRT significantly varied according to individual patient risk profiles. Only men with more aggressive disease seemed to benefit from ADT concomitant to eSRT. Therefore, our results support a tailored use of ADT in these men, which would also allow for decreasing potential ADT-related side effects, provided that these patients are treated in an early salvage setting.

Author contributions: Alberto Briganti 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.

Study concept and design: Gandaglia, Fossati, Montorsi, Briganti.
Acquisition of data: Colicchia, Battaglia, Chorda, Gandaglia, Fossati.
Analysis and interpretation of data: Fossati, Gandaglia, Zaffuto, Briganti, Montorsi.
Drafting of the manuscript: Gandaglia, Briganti, Montorsi.
Critical revision of the manuscript for important intellectual content: Briganti, Montorsi, Karnes, Boorjian, Bossi, Seisen, Cozzarini, Di Muzio, Wiegel, Shariat, Goldner, Joniau, Haustermans, De Meerleer, Fonteyne, Ost, Van Poppel.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2017.11.020.

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