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Impact of Postoperative Radiotherapy in Men with Persistently Elevated Prostate-specific Antigen After Radical Prostatectomy for Prostate Cancer: A Long-term Survival Analysis

Giorgio Gandaglia[a,b,†], *Stephen A. Boorjian*[c,†], *William P. Parker*[c], *Emanuele Zaffuto*[a,b], *Nicola Fossati*[a,b], *Marco Bandini*[a,b], *Paolo Dell'Oglio*[a,b], *Nazareno Suardi*[a,b], *Francesco Montorsi*[a,b], *R. Jeffrey Karnes*[c], *Alberto Briganti*[a,b,*]

[a] *Unit of Urology/Division of Oncology, URI, IRCCS Ospedale San Raffaele, Milan, Italy;* [b] *Vita-Salute San Raffaele University, Milan, Italy;* [c] *Department of Urology, Mayo Clinic, Rochester, MN, USA*

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Abstract

Background: Prostate cancer (PCa) patients with prostate-specific antigen (PSA) persistence after radical prostatectomy (RP) are at increased risk of mortality, although the natural history of these men is heterogeneous and the optimal management has not been established.
Objective: To develop a model to predict cancer-specific mortality (CSM) and to test the impact of radiotherapy (RT) on survival in this setting.
Design, setting, and participants: We identified 496 patients treated with RP and lymph node dissection at two referral centers between 1994 and 2014 who had PSA persistence, defined as a PSA level between 0.1 and 2 ng/ml at 6–8 wk after RP.
Outcome measurements and statistical analyses: A multivariable model predicting CSM was developed. We assessed whether the impact of postoperative PSA levels on survival differed according to baseline CSM risk. The nonparametric curve fitting method was then used to explore the relationship between baseline CSM risk and 10-yr CSM rates according to postoperative RT.
Results and limitations: Median follow-up for survivors was 110 mo. Overall, 49 patients experienced CSM. The 10-yr CSM-free survival was 88%. Pathologic grade group and pathologic stage were independent predictors of CSM (all $p = 0.01$). The association between CSM-free survival and PSA at 6–8 wk differed by the baseline CSM risk, whereby the effect of increasing PSA was evident only in patients with a CSM risk of $\geq$10%. Postoperative RT was beneficial when the predicted risk of CSM was $\geq$30% ($p = 0.001$ by an interaction test). Our study is limited by its retrospective design.
Conclusions: Increasing PSA levels should be considered as predictors of mortality exclusively in men with worse pathologic characteristics. Postoperative RT in this setting was associated with a survival benefit in patients with a CSM risk of $\geq$30%. Conversely, individuals with a CSM risk of $<$30% should be initially managed expectantly.
Patient summary: Not all patients with prostate-specific antigen persistence have a poor prognosis. Pathologic characteristics should be used to estimate the risk of cancer-specific mortality in these individuals and to identify patients who could benefit from postoperative radiotherapy.

† Both authors contributed equally.
* Corresponding author. Unit of Urology/Division of Oncology, URI, IRCCS Ospedale San Raffaele, Milan, Italy. Tel. +39 0226437286; Fax: +39 0226437286.
E-mail address: briganti.alberto@hsr.it (A. Briganti).

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1. Introduction

Radical prostatectomy (RP) is associated with excellent oncologic outcomes in patients with localized prostate cancer (PCa), with approximately 75% of such patients being free from recurrence at 10-yr follow-up [1–3]. Following surgery, prostate-specific antigen (PSA) is expected to become undetectable at approximately 6 wk postoperatively. However, up to 20% of patients with adverse pathologic characteristics fail to achieve an undetectable PSA after RP [4–8]. These individuals are at increased risks of recurrence and mortality compared with patients with initially undetectable postoperative PSA [4,7–10]. Considerable heterogeneity has been noted in the clinical outcomes of patients with PSA persistence after surgery [9,11]. A detectable PSA after RP has the potential to reflect persistent local or distant PCa cells not removed by surgery as well as benign prostatic tissue left behind during the procedure. While in the former case, timely administration of additional cancer therapies might improve oncologic outcomes [12,13], in the latter scenario, additional postoperative treatments may represent overtreatment and, thus, possibly expose these men to unnecessary side effects [14–16]. While subanalyses of prospective randomized trials have found a benefit to postoperative radiotherapy (RT) in men with PSA persistence [12,13], to date no study identified the optimal candidate for this approach in order to maximize oncologic benefit for those most likely to experience disease progression, while sparing the use of RT in those less likely to benefit from it.

We hypothesized that the impact of postoperative RT on disease progression and mortality varies according to an individual's risk of cancer-specific mortality (CSM). As such, we aimed at developing a novel predictive tool to identify patients with PSA persistence at a higher risk of CSM. We subsequently evaluated the impact of postoperative RT on CSM according to the risk of dying from PCa. We relied on a large contemporary cohort of patients with PSA persistence after RP treated at two high-volume tertiary referral centers.

2. Patients and methods

2.1. Population source

After Institutional Review Board approval, 982 patients treated with RP between 1994 and 2014 at two tertiary referral institutions (IRCCS Ospedale San Raffaele, Milan, Italy, and Mayo Clinic, Rochester, NY, USA) with available data on the first PSA value after surgery were identified. All patients had PSA persistence, defined as a PSA level of $\geq$0.1 ng/ml after RP. Among those, we selected patients who underwent a first PSA assessment between 6 and 8 wk after surgery (n = 612). Due to their increased risk of harboring distant metastases [17], patients with PSA levels >2 ng/ml at 6–8 wk after surgery (n = 100) were excluded from our analyses. Moreover, patients with incomplete pathologic data and pNx status were excluded from our study (n = 16). This resulted in a final cohort of 496 patients.

2.2. Covariates

All patients had complete data, including age at surgery, year of surgery, preoperative PSA, pathologic stage, pathologic grade group, surgical margin status, and lymph node invasion. Prostatectomy specimens were evaluated by high-volume, dedicated uropathologists. Postoperative RT was delivered to the prostate and seminal vesicle bed using previously described techniques [18–20]. Whole pelvis RT was administered to 7% and 80% of patients with pN0 and pN1 disease included in the postoperative RT group, respectively. Immediate androgen deprivation therapy (ADT) was defined as ADT administered within 90 d from surgery. The decision to administer postoperative RT $\pm$ ADT was based on the clinical judgment of each treating physician according to individual patient and cancer characteristics.

2.3. End points

The primary outcome of the study was CSM, which was defined as death from PCa. Other-cause mortality (OCM) was defined as death due to other causes. Follow-up time was defined as the time elapsed between surgery and CSM or last follow-up.

2.4. Statistical analyses

Our statistical analyses consisted of multiple steps. First, multivariable Cox regression analyses assessed predictors of CSM. Covariates consisted of pathologic stage, pathologic grade group, pN1 status, positive surgical margin status, and immediate ADT. The regression coefficients were then used to generate a model predicting 10-yr CSM. A leave-one-out cross validation was used to construct the Harrell c-index to assess discrimination of our novel model. The relationship between the predicted probability and the observed fraction of patients experiencing CSM at 10 yr was depicted using the calibration plot method.

Second, we assessed whether the impact of PSA level at 6–8 wk after surgery on CSM-free survival differed according to the risk of CSM. Locally weighted 10-yr Kaplan–Meier estimates by values of a continuous covariate (locally weighted scatterplot smoothing) method was used to graphically depict the relationship between PSA at 6–8 wk and 10-yr CSM-free survival in the overall population and after stratifying patients according to the median 10-yr CSM risk (<10 vs $\geq$10%) [21].

Third, we sought to assess whether the impact of postoperative RT was different by CSM risk. A multivariable Cox regression model predicting CSM was developed for patients who did not receive postoperative RT. The same covariates adopted in the nomogram developed for the overall population were used. The 10-yr CSM risk was calculated for each patient using the multivariate coefficients. We then tested an interaction with groups (postoperative RT vs no RT) and the probability of dying from PCa according to the newly developed model. The nonparametric curve fitting method was used to graphically explore the relationship between the risk of CSM and actual 10-yr CSM rates according to the administration of postoperative 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

Table 1 depicts clinical and pathologic characteristics of patients included in our cohort. Median age at surgery was 64 yr. When patients were stratified according to receipt of postoperative RT, significant differences were observed with regard to the year of surgery, preoperative PSA and risk group, pathologic grade group, pathologic stage, nodal status, positive surgical margin status, and PSA level at

Table 1 – Descriptive statistics of 496 patients with clinically localized prostate cancer treated with radical prostatectomy and extended pelvic lymph node dissection between 1994 and 2014, who experienced prostate-specific antigen (PSA) persistence

	Overall (n = 496)	No RT (n = 245, 49.4%)	Postoperative RT (n = 251, 50.6%)	p value
Year of surgery				
Median (IQR)	2004 (1998–2010)	2000 (1996–2009)	2005 (2000–2010)	<0.001
Age at surgery (yr)				
Median (IQR)	64 (58–68)	65 (59–69)	63 (57–67)	0.002
Preoperative PSA (ng/ml)[a]				
Median (IQR)	8.5 (5.5–14.3)	7.9 (5.1–13.5)	9.2 (5.9–15.2)	0.02
Preoperative D'Amico risk group (%)				
Low	81 (16)	50 (20)	31 (12)	<0.001
Intermediate	230 (46)	125 (51)	105 (42)	
High	185 (37)	70 (29)	115 (46)	
Surgical technique (%)				
ORP	409 (83)	207 (85)	202 (81)	0.1
RARP	87 (18)	38 (16)	49 (20)	
Grade group at final pathology (%)				
1	131 (26)	96 (39)	35 (14)	<0.001
2	115 (23)	50 (20)	65 (26)	
3	86 (17)	36 (15)	50 (20)	
4	46 (9.3)	21 (8.6)	25 (10)	
5	118 (24)	42 (17)	76 (30)	
Pathologic stage (%)				
T2	231 (47)	138 (56)	93 (37)	<0.001
T3a	124 (25)	52 (21)	72 (28)	
T3b	134 (27)	52 (21)	82 (33)	
T4	7 (1.4)	3 (1.2)	4 (1.6)	
pN1 (%)	114 (23)	42 (17)	72 (29)	0.01
Positive surgical margins (%)	246 (50)	88 (36)	158 (63)	<0.001
Number of removed lymph nodes				
Median (IQR)	9 (5–15)	9 (5–12)	9 (6–18)	0.06
Number of positive lymph nodes[b]				
Median (IQR)	2 (1–5)	2 (1–5)	3 (1–5)	0.4
First PSA after surgery				
Median (IQR)	0.3 (0.2–0.6)	0.2 (0.2–0.5)	0.3 (0.2–0.8)	0.001
ADT concomitant to RT (%)	58 (12)	–	58 (23)	NA
Immediate ADT without RT (%)	51 (10)	51 (21)	–	NA
Late ADT at progression (%)	204 (41)	71 (29)	133 (53)	<0.001

IQR = interquartile range; ADT = androgen deprivation therapy; ORP = open radical prostatectomy; RARP = robot-assisted radical prostatectomy; NA = not applicable; RT = radiotherapy.
ADT during RT in the RT group.
Immediate ADT after surgery in the no RT group.
Salvage ADT at progression.
[a] Missing in 32 patients.
[b] In node-positive patients.

6–8 wk after surgery (all $p \leq 0.02$). Moreover, although no differences were observed in the use of ADT immediately after surgery between patients in the no RT and postoperative RT groups (21% vs 23%; $p = 0.3$), the use of late ADT at progression significantly differed between the two groups (29% vs 53%; $p < 0.001$).

3.2. Uni- and multivariable analyses predicting CSM

Median follow-up for survivors was 110 mo (interquartile range: 98–121). Overall, 49 and 77 patients experienced CSM and OCM, respectively. The resulting 10-yr CSM-free survival rate was 88% (Fig. 1). At multivariable analyses, pathologic grade group ≥4 (hazard ratio [HR]: 2.72; 95% confidence interval [CI]: 1.43–5.14; $p = 0.01$) and pT3b/4 tumor stage (HR: 2.34; 95% CI: 1.21–4.49; $p = 0.01$) were independently associated with CSM (Table 2). Pathologic grade group, pathologic stage, nodal status, surgical margins, and immediate ADT were included in a model to predict the 10-yr CSM risk in patients with PSA persistence after RP. The coefficients to calculate the risk of CSM are depicted in Supplementary Table 1. A novel nomogram was then developed to facilitate individual estimation of the risk of CSM at 10-yr follow-up (Supplementary Fig. 1). At internal validation, the discrimination accuracy of this model based on pathologic characteristics and administration of immediate ADT was 67% in our cohort. Supplementary Figure 2 depicts the calibration plot.

3.3. Effect of PSA levels at 6–8 wk after RP on CSM

At univariable Cox regression analyses, the level of detectable PSA as measured at 6–8 wk after RP was significantly associated with the risk of CSM (HR: 1.72; 95% CI: 1.07–2.76; $p = 0.02$) for the overall cohort, such that we

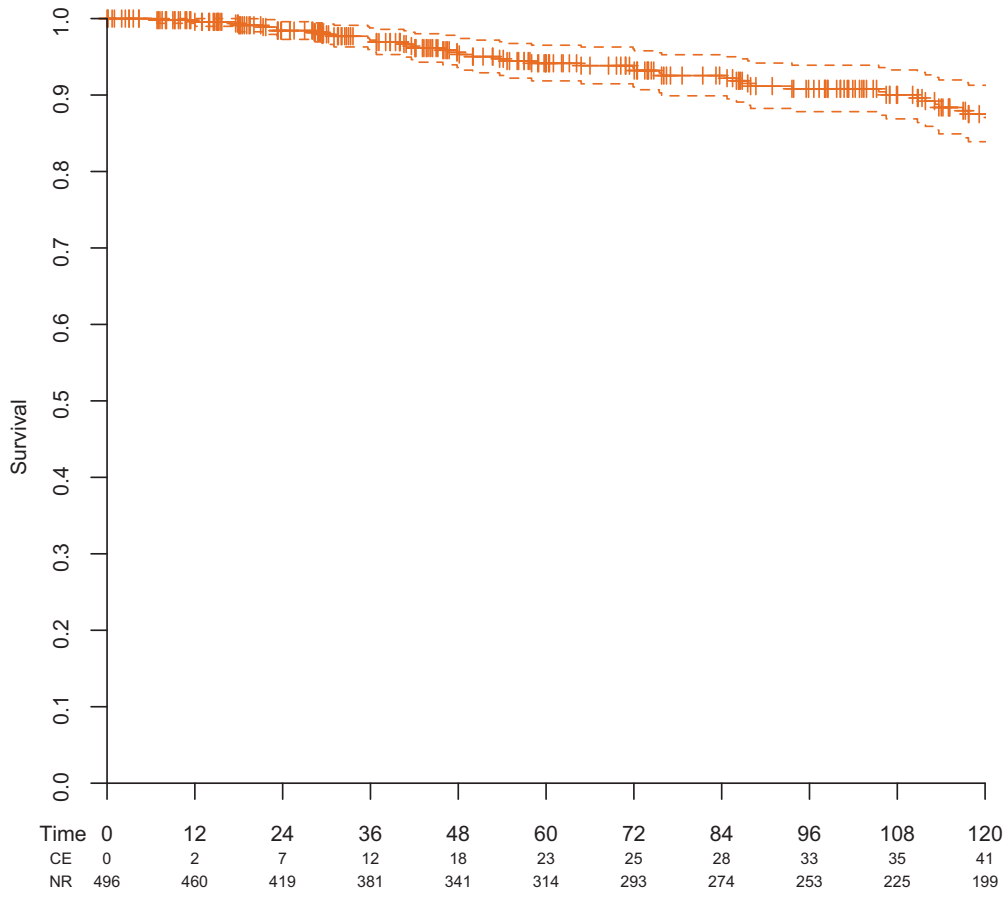

Fig. 1 – Kaplan–Meier analyses assessing time to cancer-specific mortality in patients with PSA persistence after radical prostatectomy in the overall population. PSA = prostate-specific antigen.

noted a progressive decrease in 10-yr CSM-free survival according to the level of the first PSA after surgery (Fig. 2A). Interestingly, however, when patients were stratified according to their predicted risk of CSM (<10% vs ≥10%), the association between CSM-free survival and PSA at 6–8 wk differed by the risk of CSM and was evident only among those with more aggressive disease. Conversely, increasing PSA levels at 6–8 wk after RP were not associated

Table 2 – Multivariable Cox regression analyses evaluating the risk of cancer-specific mortality in 496 patients treated with radical prostatectomy and extended pelvic lymph node dissection, who experienced postoperative prostate-specific antigen persistence

	Univariable analyses		Multivariable analyses	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age at surgery	1.03 (0.98–1.07)	0.2	–	–
Pathologic grade group				
≤3	1 (Ref.)	<0.001	1 (Ref.)	0.01
≥4	4.37 (2.44–7.72)		2.72 (1.43–5.14)	
Pathologic tumor stage				
T2-pT3a	1 (Ref.)	<0.001	1 (Ref.)	0.01
T3b/4	4.04 (2.29–7.09)		2.34 (1.21–4.49)	
Pathologic nodal status				
Negative	1 (Ref.)	<0.001	1 (Ref.)	0.4
Positive	3.23 (1.71–6.11)		1.44 (0.66–3.12)	
Positive surgical margins				
No	1 (Ref.)	0.01	1 (Ref.)	0.3
Yes	2.06 (1.13–3.68)		1.36 (0.72–2.56)	
Receipt of immediate ADT	2.97 (1.66–5.33)	<0.001	1.27 (0.62–2.59)	0.5

HR = hazard ratio; CI = confidence interval; ADT = androgen deprivation therapy; Ref. = reference.

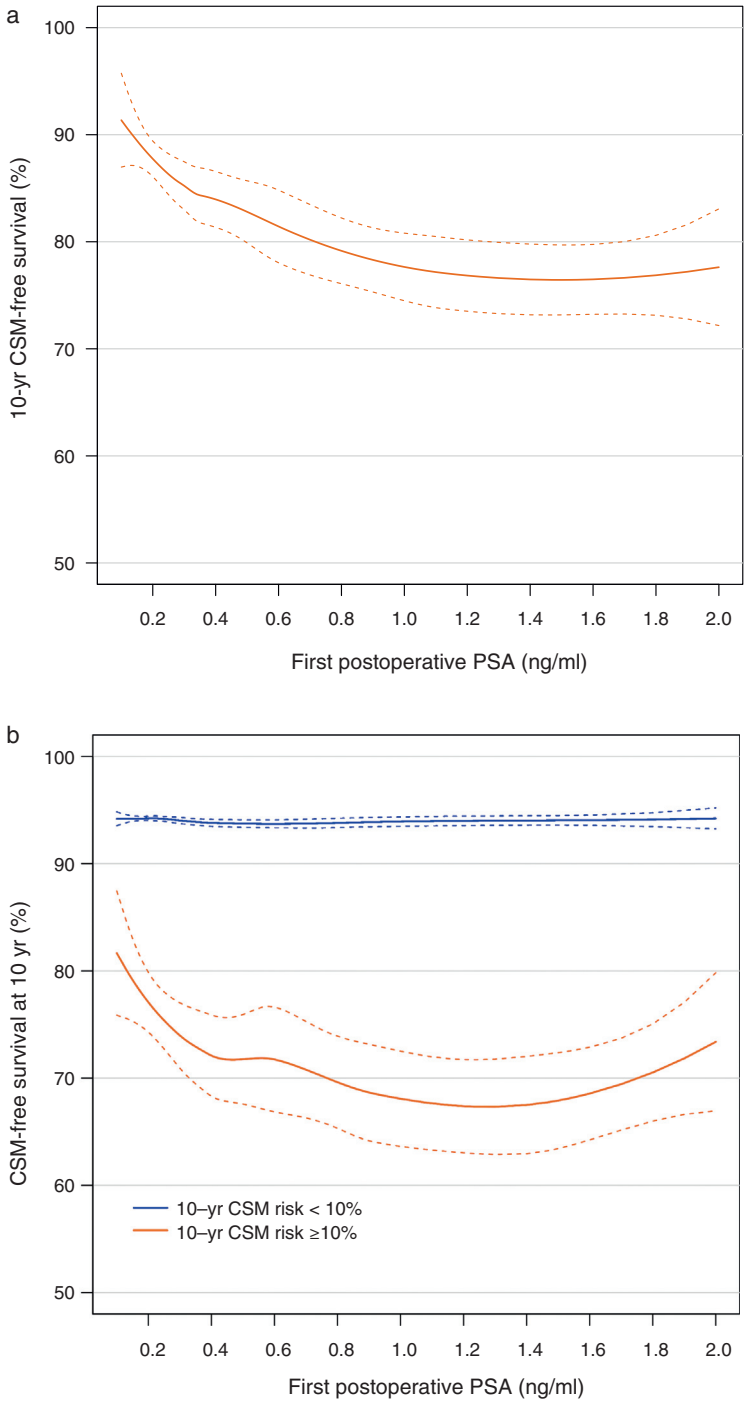

Fig. 2 – Cancer-specific mortality (CSM) rates at 10-yr follow-up plotted against the PSA level at 6–8 wk after radical prostatectomy (A) in the overall population and (B) after stratifying patients according to their nomogram-predicted 10-yr risk of CSM (<10% vs ≥10%). PSA = prostate-specific antigen.

with lower CSM-free survival among men with a risk of CSM of <10% (Fig. 2B).

3.4. *Association of postoperative RT with CSM*

Supplementary Table 2 shows the results of multivariable analyses predicting CSM in men who did not receive RT. The coefficients to calculate the 10-yr risk of CSM are depicted in Supplementary Table 3. The interaction test for the hypothesis that the impact of postoperative RT on CSM may vary according to the risk of CSM calculated on the basis of a multivariable model that included pathologic characteristics and receipt of immediate ADT was statistically significant ($p = 0.001$). The observed 10-yr CSM rates were then plotted against the predicted probability of CSM at 10-yr follow-up according to the administration of

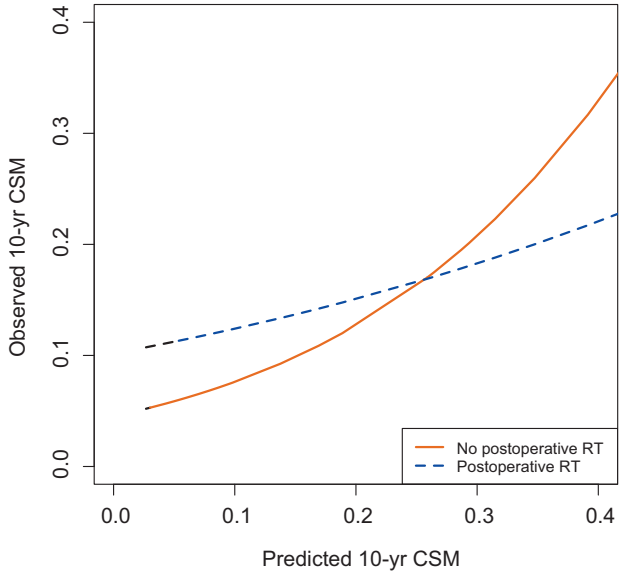

Fig. 3 – Cancer-specific mortality (CSM) rate plotted against nomogram-predicted probability of CSM at 10 yr after radical prostatectomy. Dashed red line indicates postoperative radiotherapy (RT). Solid red line indicates no postoperative RT.

postoperative RT (Fig. 3). Herein, we found that the receipt of postoperative RT was associated with a survival benefit only for those patients with a risk of CSM of ≥30%.

4. Discussion

Up to 20% of PCa patients experience PSA persistence after RP, defined as a PSA level ≥0.1 ng/ml 6 wk following surgery [4–8]. These individuals have been found to be at increased risks of disease recurrence and mortality [4,7–10]. Therefore, a role for additional cancer therapies such as RT in this setting has been proposed [4,12,13,22]. Nevertheless, it remains unknown whether all patients who fail to achieve an undetectable PSA level after RP would benefit from additional treatments to the same extent. Accurate patient selection is therefore necessary to identify those men who would most benefit from postoperative RT with regard to long-term oncologic control, while sparing possible treatment-related side effects among those patients who are unlikely to progress even in the presence of detectable PSA after surgery. With this background, we aimed both to assess the long-term outcomes of men with PSA persistence after RP, stratified by PCa pathologic features, and to evaluate the association of postoperative RT with survival according to the individual risk of CSM using a large multi-institutional cohort of contemporary patients.

Several results of our study are noteworthy. First, we demonstrated that the prognosis of men with PSA persistence is not invariably poor. In fact, approximately four out of five patients did not experience CSM at 10-yr follow-up. Moreover, we determined that higher pathologic grade group and the presence of pT3b/pT4 disease were associated with an increased risk of CSM. Of note, our results are in line with previous investigations reporting an association between pathologic characteristics and the risk of mortality in patients with PSA persistence [6,11]. Moreover, our analyses take advantage from the large sample size and relatively long follow-up, as well as from the inclusion of patients with detailed data on pathologic characteristics and administration of postoperative treatments. Importantly, we then developed a multivariable model to predict individual patients' 10-yr CSM risk. Our tool showed a discrimination accuracy of 67%. We next used this CSM risk prediction to test the impact of increasing PSA levels at 6–8 wk after RP on the risk of dying from PCa. Interestingly, we provide what is to our knowledge the first report that increasing postoperative PSA levels are associated with the risk of dying from PCa exclusively in men with a CSM risk of >10%. This was particularly evident when the PSA levels increased from 0.1 to 1.4 ng/ml. On the contrary, the slight improvement in the 10-yr CSM-free survival rates observed when the postoperative PSA levels increased from 1.4 to 2 ng/ml might be related to the relatively small number of patients with a CSM risk of >10% and high postoperative PSA levels. Of note, in men with more aggressive PCa pathology at RP, a detectable PSA at 6–8 wk might reflect the presence of persistent malignant prostatic cells either locally or in distant sites. Although novel imaging modalities such as prostate-specific membrane antigen positron emission tomography/computed tomography scan are characterized by relatively high detection rates in men with biochemical recurrence even at low PSA levels and might theoretically discriminate which of these patients harbored persistent local or distant disease [23], their role in the PSA persistence setting still needs to be clarified [2]. Similarly, none of the available studies on genomic classifiers addressed their impact in the identification of men with PSA persistence who should receive postoperative RT [24]. As such, our model based on pathologic characteristics might help clinicians in identifying patients more likely to have a local recurrence and who, therefore, would benefit from local salvage therapies. Of note, we showed that maximizing local disease control with RT was beneficial in men with a CSM risk of >30%. Given the limited number of patients and events in higher risk ranges, we were unable to test the role of postoperative RT in men with even higher risks of CSM. Conversely, in men with less aggressive disease (ie, organ confined disease and pathologic grade groups 1–3), PSA level did not impact cancer-specific survival. In these cases, PSA persistence might be a proxy of benign prostatic tissue left behind during RP, and the impact of competing causes of death would thereby be more pronounced. Further, these patients did not demonstrate a benefit from postoperative RT.

While data from several previous studies have supported a benefit for postoperative RT in patients with PSA persistence [4,12,13,22], no study to date has tested the effect of RT according to individual patient profile in this group of men. Such investigation is highly relevant, as it has also been shown that a subset of patients with PSA persistence never experience recurrence. For example, Rogers et al [11] demonstrated that more than one out of five men with PSA persistence who did not receive any

adjuvant treatment would be free from metastases at 10-yr follow-up. To address this void, we hypothesized that while postoperative RT might improve oncologic outcomes in some patients, it may represent an overtreatment in others. Our results support this hypothesis, as we found that postoperative RT was associated with decreased CSM only in men with more aggressive disease at RP. From a clinical standpoint, our model may thus assist clinicians in the identification of patients with a lower baseline risk of CSM, who therefore, should be initially managed expectantly. Conversely, men with a higher risk of CSM should be considered for additional postoperative treatments such as RT.

We recognize that our study is not devoid of limitations. First, although we adjusted our analyses for potential confounders, we cannot completely exclude an effect of selection bias. The indication to administer RT or ADT was not standardized, and varied according to the treating physician and patient preferences. Randomized controlled trials specifically designed to address the efficacy of postoperative RT in the setting of PSA persistence are needed to address this issue. Second, >40% of men not receiving postoperative RT received ADT, which may represent a confounding factor. Nonetheless, our predictive model accounted for the effect of immediate postoperative ADT. Third, the lack of a pathologic review might limit the validity of our findings. Nonetheless, all patients included in our study were evaluated by high-volume dedicated uropathologists at two tertiary referral centers. Fourth, the model predicting 10-yr CSM in men who did not receive RT exhibited suboptimal calibration characteristics at internal validation. This might be related to the relatively small number of events among patients who did not receive postoperative RT. Finally, the lack of data on PSA kinetics after surgery precluded us to adjust our analyses for this variable. However, our risk model to predict the 10-yr risk of CSM is based on readily available variables to the practicing clinician and should thereby assist in patient counseling and postoperative management.

5. Conclusions

Not all PCa patients with PSA persistence after RP have universally poor oncologic outcomes. Increasing PSA levels should be considered as predictors of mortality, exclusively in men with a risk of CSM of >10% defined by pathologic characteristics. Likewise, the benefits of postoperative RT on survival are restricted to those men with adverse pathology, indicating the opportunity for an individualized approach to treatment in these patients.

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: Briganti, Boorjian, Gandaglia.
Acquisition of data: Gandaglia, Parker, Fossati, Bandini, Dell'Oglio, Suardi.
Analysis and interpretation of data: Briganti, Gandaglia, Zaffuto.
Drafting of the manuscript: Gandaglia, Briganti, Boorjian.
Critical revision of the manuscript for important intellectual content: Briganti, Boorjian, Karnes, Montorsi.
Statistical analysis: Gandaglia, Zaffuto.
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Supervision: Briganti, Boorjian, Karnes, Montorsi.
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Appendix A. Supplementary data

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