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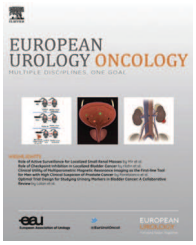

European Association of Urology

Defining the Most Informative Intermediate Clinical Endpoints for Predicting Overall Survival in Patients Treated with Radical Prostatectomy for High-risk Prostate Cancer

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Abstract

Background: Given the prolonged natural history of clinically localized, high-risk prostate cancer, there is a need for the identification of intermediate clinical endpoints (ICEs) to predict long-term overall survival (OS).
Objective: To explore the role of novel potential ICEs based on clinical follow-up to predict long-term survival in patients with high-risk prostate cancer.
Design, setting, and participants: Overall, 3507 patients treated at 12 tertiary referral centers between 1988 and 2016 were evaluated.
Intervention: Radical prostatectomy (RP) with extended pelvic lymph node dissection.
Outcome measurements and statistical analysis: The impact of biochemical recurrence (BCR) and clinical recurrence (CR) within 1, 3, 5, and 7 yr after surgery on the risk of OS was evaluated in multivariable Cox regression analyses. In patients with BCR, the impact of progression to CR within 6 mo and 1, 3, and 5 yr on long-term OS was investigated. Discrimination was assessed using Harrell's *c* index.
Results and limitations: Median follow-up for survivors was 76 mo. The 5- and 10-yr OS and cancer-specific survival rates were 94% and 81% versus 98% and 95%, respectively. On a time-varying multivariable analysis, BCR (hazard ratio [HR]: 1.02; 95% confidence interval [CI]: 1.00, 1.04) and CR (HR: 1.05; 95% CI: 1.03–1.07) emerged as predictors of OS ($p < 0.001$). The development of CR within 5 yr after surgery was the

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most informative ICE for predicting OS (*c* index: 0.74). In patients with BCR, progression to CR within 12 mo represented the most informative predictor for the subsequent risk of dying from all causes. Patients who developed BCR within 5 yr after RP and progressed to CR within 12 mo had a 10-yr OS rate of 47%. These results require prospective validation.

Conclusions: When predicting long-term survival in surgically treated high-risk patients, progression to CR within 5 yr of RP confers the highest discrimination with respect to other landmark points. In men experiencing BCR, progression to CR within the subsequent 12 mo achieved the highest discrimination. Further studies are needed to validate our findings.

Patient summary: We investigated the most informative intermediate clinical endpoints for predicting overall survival (OS). Occurrence of clinical recurrence within 5 yr after radical prostatectomy confers the highest discrimination to a model predicting OS.

1. Introduction

Prostate cancer (PCa) is the most common solid tumor in males and the sixth leading cause of death in western countries [1]. Up to one out of four patients diagnosed with PCa harbor high-risk disease [2]. Multimodal therapies including radical prostatectomy (RP) represent one of the possible treatment options according to all available guidelines [3–5]. Of note, RP is associated with relatively good oncological outcomes, where cancer-specific survival (CSS) rates range between 8% and 15% at long-term follow-up [6,7]. Given the prolonged natural history of surgically managed PCa patients, surrogate endpoints for predicting long-term overall survival (OS) are needed for two main reasons: (1) to tailor the optimal follow-up schedules and (2) to assess the efficacy of the implementation of novel treatments in future prospective studies [8,9]. Randomized controlled trials evaluating the oncological benefits of PCa therapies in patients with localized disease are often limited by relatively short follow-up, which can be inadequate to demonstrate the benefit of a given approach [10]. As such, these investigations might become obsolete by the time of their release and publication due to the rapidly changing paradigm of PCa treatment. On the contrary, identification of robust intermediate clinical endpoints (ICEs) to aid in predicting long-term survival would overcome these issues and facilitate completion of clinical trials. Although previous studies proposed time to metastases as a surrogate endpoint for predicting OS [8,9], they are limited by the inclusion of heterogeneous cohorts of patients, where none of these investigations specifically focused on high-risk disease treated with RP. In the face of such a paucity of data, we aimed to explore the role of the potential role of novel ICEs in predicting OS in a population of surgically managed high-risk PCa patients.

2. Patients and methods

2.1. Study population

Data from a multi-institutional database, including patients who underwent extended pelvic lymph node dissection (ePLND) and RP at 12 tertiary care centers, were retrospectively collected between 1987 and 2016. All patients included in our cohort had high-risk disease according to the D'Amico classification, namely, clinical stage ≥T2c and/or biopsy Gleason score >7 and/or preoperative prostate-specific antigen (PSA) >20 ng/ml [11]. Overall, 5291 patients with available follow-up data and pathological data on tumor stage, nodal involvement, surgical margins status, and Gleason score were included. Patients who received neoadjuvant treatments were excluded. We further excluded patients who received any adjuvant therapies such as androgen deprivation therapy (ADT; $n = 834$), radiation therapy ($n = 533$), or both ($n = 380$). For the study purposes, we excluded patients whose time to clinical recurrence (CR) corresponded to the time to biochemical recurrence (BCR; $n = 37$). Indeed, in these cases, de novo symptoms might have triggered patient check-up. The final patient population consisted of 3507 cases. The CONSORT diagram is displayed in Supplementary Figure 1.

2.2. Covariates and endpoints

Age at RP, preoperative PSA, year of surgery, pathological stage (T2 vs T3a vs T3b–T4), Gleason score (≤6 vs 7 vs 8–10), surgical margin status (negative vs positive), and lymph node invasion (absent vs present) were evaluated as covariates in our models. The primary endpoint was represented by OS, defined as the time from RP to the occurrence of death by any cause. CSS was defined as the time from RP to the occurrence of death due to PCa, whereas the time from RP to the occurrence of noncancer death was defined as other-cause mortality (OCM). BCR was defined as two consecutive PSA values ≥0.2 ng/ml after RP. CR was defined as positive imaging during follow-up, after the onset of BCR.

All patients were followed up until death or to the end of the study period. Vital statistics and cause of death were identified from death certificates or physician correspondence.

2.3. Statistical analysis

First, OS, BCR, and CR rates were computed according to the nonparametric Kaplan-Meier estimator. The inverse Kaplan-Meier method was used to estimate the median follow-up time for event-free patients. The CSS and OCM rates were estimated according to the cumulative incidence method in the presence of competing risks [12]. Second, we hypothesized that the occurrence of BCR and CR during the follow-up time were predictors of OS. Thus, in order to evaluate the role of the occurrence of CR and BCR in predicting OS, a multivariable Cox regression was generated. For this purpose, BCR and CR were considered as time-varying covariates. Specifically, the occurrence of BCR and CR was considered to be multiplicative with the analysis time. To allow for a better understanding

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of this interaction, the time scale was set as a multiple of 12 mo, whereas all the other analyses were performed on a unitary time scale based on months. All multivariable Cox regression analyses were fitted, adjusting for age at RP, preoperative PSA, year of surgery, pathological Gleason score, pathological stage, lymph node invasion, and surgical margins status. Landmark analyses evaluating patients alive and not censored at 1, 3, 5, and 7 yr after RP based on multivariable Cox regression models were used to assess the prognostic impact of intermediate endpoints (namely, BCR and CR) on subsequent survival at each time point of interest [9]. The intermediate endpoint status was assessed up to the landmark time (namely, 1, 3, 5, and 7 yr after RP). The discrimination of multivariable models was assessed by calculating the Harrell's concordance index (*c* index). We considered the model with the greater discrimination index to be most informative for the prediction of OS. The impact of intermediate endpoints (namely, BCR and CR) on OS within those landmark times was investigated after adjusting for the aforementioned covariates. The intermediate endpoints and the landmark time were defined a priori, and were based on clinical follow-up. Third, to identify the most informative endpoint in terms of progression to CR in patients with BCR ($\Delta_{recurrence} = t_{cr} - t_{bcr}$), we considered patients with BCR only, and among those, we evaluated the impact of the progression to CR within 6 mo and 1, 3, and 5 yr after the occurrence of BCR on OS. In this scenario, we considered the occurrence of BCR as the entry point (time zero, t_0) of the analysis, namely, $t_0 = t_{bcr}$.

Fourth, in order to identify the patients with the worst prognosis in terms of OS after RP, a new subgroup was defined combining information from the most informative endpoints in terms of BCR and progression to CR, according to the highest *c* index of the models.

Statistical analyses were performed using Stata 14 (StataCorp MP, College Station, TX, USA). All tests were two sided, with a significance level set at $p < 0.05$.

2.4. Sensitivity analyses

In order to verify the impact of the most significant endpoint in predicting OS, we repeated our analyses including also patients who received postoperative adjuvant therapies ($n = 1747$). This resulted in a final cohort of 5254 patients.

3. Results

3.1. Patients' characteristics and follow-up

Median (interquartile range [IQR]) age at surgery was 66 (60–70) yr, median (IQR) year of surgery was 2006 (1999–2010; Supplementary Table 1). The median (IQR) follow-up for survivors was 76 (26–119) mo. Overall, 452 patients experienced death by any cause; among them, 136 patients died from PCa. The 5- and 10-yr OS rates were 94% (95% confidence interval [CI]: 93–95%) and 81% (95% CI: 79–83%), respectively. The 5- and 10-yr CSS and OCM rates were 98% and 95% versus 96% and 87%, respectively (Fig. 1). Overall, 1287 patients progressed to BCR and 362 further progressed to CR. Median (IQR) time of progression to CR was 21.8 (2.6–64.0) mo (Fig. 2). The 5- and 10-yr BCR- and CR-free survival rates were 61% and 48% versus 92% and 85%, respectively.

3.2. Cox models with time-varying covariates

Occurrences of BCR and CR were treated as binary variables that varied with time (Table 1). The hazard ratio [HR] for BCR was 1.02 (95% CI: 1.00, 1.04; $p = 0.035$) for each unit increase in the time scale, which was set as 12 mo. In the case of CR, an augmented risk of dying persists for each unit time increase (HR: 1.05; 95% CI: 1.03, 1.07; $p < 0.001$).

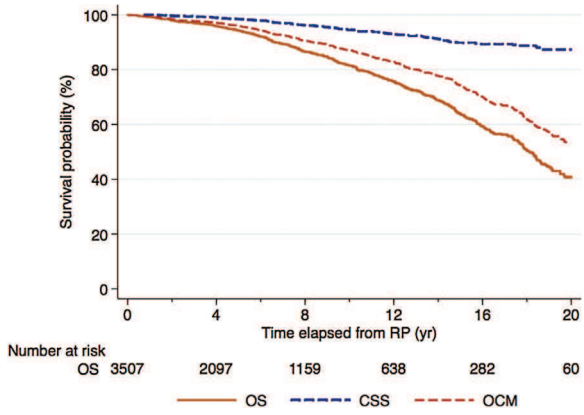

Fig. 1 – Probability of overall survival (OS) estimated with the Kaplan-Meier method and probability of cancer-specific survival (CSS) and other-cause mortality (OCM) estimated with the competing risks method. RP = radical prostatectomy.

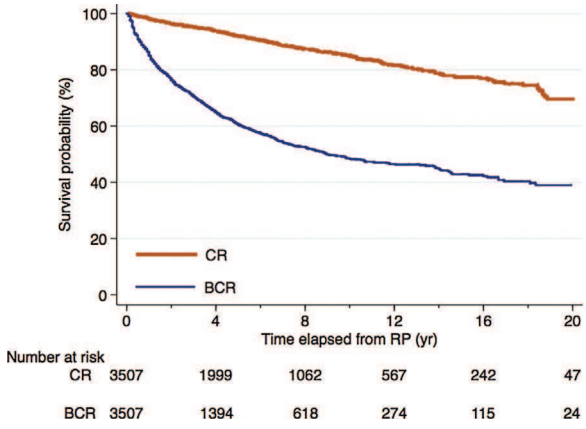

Fig. 2 – Kaplan-Meier estimates of freedom from biochemical recurrence and clinical recurrence. BCR = biochemical recurrence; CR = clinical recurrence; RP = radical prostatectomy.

3.3. Landmark analyses

Fig. 3 depicts the Kaplan-Meier curves illustrating the OS according to the landmark points and stratified according to the occurrence of BCR and CR within the landmark time. Overall, 3143, 2387, 1825, and 1359 patients were alive and not censored at 1, 3, 5, and 7 yr after RP, respectively, and were included in the landmark analysis. Table 2 displays the details for each intermediate endpoint in terms of BCR and CR.

On Cox multivariable analysis, the occurrence of BCR within each landmark time emerged as a predictor of OS; among these occurrences, the occurrence within 5 yr after RP produced the greatest benefit to the model in terms of *c* index (0.69; Table 3). Concerning CR, its occurrence within 1, 3, and 5 yr emerged as a predictor of OS. Among different time points, the CR within 5 yr after RP produced the

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Table 1 – Multivariable Cox regression analyses predicting overall survival, including biochemical recurrence and clinical recurrence as time-varying covariates.

Covariate	BCR			CR		
	HR	(95% CI)	*p* value	HR	(95% CI)	*p* value
Age	1.06	1.04, 1.08	<0.001	1.06	1.05, 1.08	<0.001
PSA	1.00	0.99, 1.00	0.2	1.00	0.99, 1.00	0.42
Year of surgery	0.99	0.97, 1.01	0.2	0.99	0.97, 1.01	0.4
Pathologic stage						
T2	1	Ref.		1	Ref.	
T3a	1.23	0.99, 1.54	0.06	1.28	1.03, 1.60	0.03
T3b–4	1.75	1.39, 2.19	<0.001	1.75	1.41, 2.17	<0.001
Pathological Gleason score						
≤6	1	Ref.		1	Ref.	
7	1.20	0.96, 1.50	0.1	1.17	0.94, 1.46	0.2
8–10	1.87	1.44, 2.43	<0.001	1.78	1.38, 2.30	<0.001
Surgical margin status						
Negative	1	Ref.		1	Ref.	
Positive	1.31	1.11, 1.60	0.002	1.27	1.06, 1.53	0.01
Lymph node invasion						
Negative	1	Ref.		1	Ref.	
Positive	0.96	0.71, 1.31	0.8	0.97	0.71, 1.31	0.8
BCR	1.02	1.00, 1.04	0.04			
CR				1.05	1.03, 1.07	<0.001

BCR = biochemical recurrence; CI = confidence interval; CR = clinical recurrence; HR = hazard ratio; PSA = prostate-specific antigen; Ref. = reference.

greatest improvement in the predictive accuracy of the model (*c* index: 0.74; Table 3).

3.4. *Defining the most informative* $\Delta_{recurrence}$

Among 1287 patients who progressed to BCR, 1153, 884, 674, and 508 were alive and not censored after 6 mo, 1 yr, 3 yr, and 5 yr, respectively, from the occurrence of BCR (Table 4). Among these patients, irrespective of time from RP to the occurrence of BCR, progression to CR within 12 mo of BCR yielded the highest predictive accuracy in terms of *c* index (0.70; Table 5). The Kaplan-Meier curves illustrating the OS according to the landmark points and stratified according to the progression to CR within the landmark time are depicted in Fig. 4. Finally, to identify the group with the worst prognosis, we combined the two most informative endpoints in terms of BCR and $\Delta_{recurrence}$ in a single category that was represented by the occurrence of BCR within 5 yr after RP and subsequent progression to CR within 12 mo. Overall, 127 patients fell into this category; 47 of them succumbed during follow-up. The 5- and 10-yr OS rates in this category were 78% and 47%, respectively; the log-rank test demonstrated a statistically significant difference between the survival functions ($p < 0.001$). The Kaplan-Meier curves depicting OS are shown in Fig. 5.

Table 2 – Number of patients alive and not censored at the landmark point and number of events, in terms of biochemical recurrence or clinical recurrence, from prostatectomy to the landmark point.

	1 yr		3 yr		5 yr		7 yr	
	Patients *n*	Events *n*	Patients *n*	Events *n*	Patients *n*	Events *n*	Patients *n*	Events *n*
BCR	3143	457	2387	873	1825	1086	1359	1184
CR	3143	55	2387	138	1825	203	1359	255

BCR = biochemical recurrence; CR = clinical recurrence.

3.5. *Sensitivity analysis*

To confirm our findings, we analyzed the entire cohort of 5254 patients, which included patients who underwent adjuvant ADT ($n = 834$), radiation therapy ($n = 533$), or both ($n = 380$). Detailed patient characteristics are provided in Supplementary Table 2. The OS curves and the BCR- and CR-free survival curves are provided in Supplementary Figures 2 and 3, respectively. On multivariable Cox

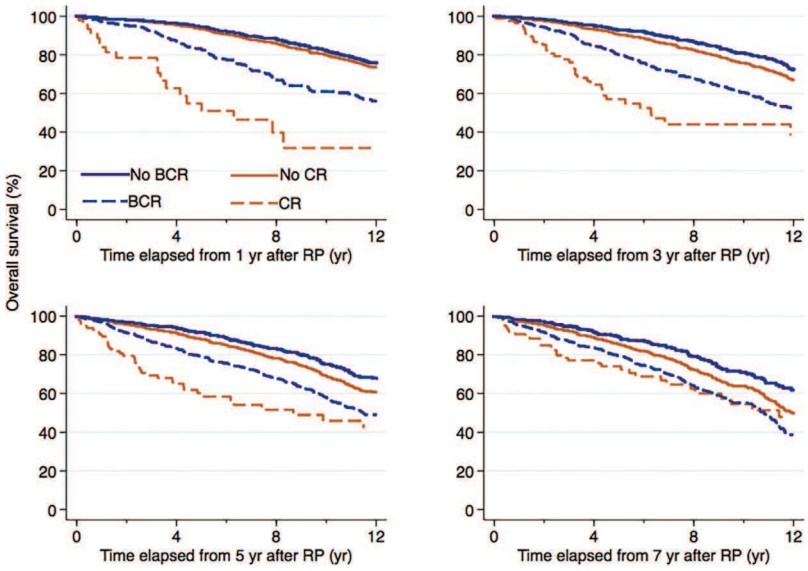

Fig. 3 – Kaplan-Meier estimates illustrating landmark analyses for overall survival, according to the development of biochemical recurrence (BCR) and clinical recurrence (CR) within 1, 3, 5, and 7 yr from radical prostatectomy (RP). RP = radical prostatectomy.

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Table 3 – Multivariable Cox regression analyses predicting overall survival, at different landmark points evaluating the impact of the different intermediate endpoints.

Model	HR	95% CI	*p* value	*c* index
BCR				
1 yr	1.71	1.37, 2.11	<0.001	0.682
3 yr	1.99	1.62, 2.43	<0.001	0.684
5 yr	1.76	1.42, 2.19	<0.001	0.687
7 yr	1.69	1.31, 2.18	<0.001	0.668
CR				
1 yr	6.37	3.96, 10.2	<0.001	0.720
3 yr	2.84	2.02, 4.00	<0.001	0.728
5 yr	2.04	1.47, 2.83	<0.001	0.737
7 yr	1.20	0.83, 1.74	0.3	0.686

BCR = biochemical recurrence; CI = confidence interval; CR = clinical recurrence; HR = hazard ratio.

Table 4 – Number of patients who developed biochemical recurrence and number of events, in terms of progression to clinical recurrence, for each intermediate endpoint at each landmark time.

	6 mo		1 yr		3 yr		5 yr	
	Patients *n*	Events *n*	Patients *n*	Events *n*	Patients *n*	Events *n*	Patients *n*	Events *n*
CR	1228	114	1153	144	884	214	674	261

CR = clinical recurrence.

Table 5 – Multivariable Cox regression analyses predicting overall survival in patients with biochemical recurrence (BCR), in order to identify the best intermediate endpoint in terms of progression from BCR to clinical recurrence.

Model	HR	95% CI	*p* value	*c* index
$\Delta_{recurrence}$				
6 mo	1.93	1.27, 2.82	<0.001	0.672
1 yr	1.77	1.27, 2.46	<0.001	0.696
3 yr	1.52	1.11, 2.07	0.009	0.664
5 yr	1.28	0.91, 1.80	0.2	0.645

CI = confidence interval; HR = hazard ratio; $\Delta_{recurrence} = t_{cr} - t_{bcr}$.

regression analyses, CR, fitted as a time-varying covariate, was confirmed as an independent predictor of overall mortality (OM; $p < 0.001$), with an HR of 1.08, on a 12-mo time scale (Supplementary Table 3). Overall, 903 patients died from any causes, 1979 experienced BCR, and 647 progressed to CR (Supplementary Table 4). The occurrence of CR within 5 yr after RP was confirmed as the most significant ICE for predicting OM (*c* index = 0.75; Supplementary Table 5). Supplementary Figure 4 displays the landmark analysis.

4. Discussion

RP with ePLND, either alone or as a part of a multimodal approach, represents one of the available treatment options for patients with high-risk PCa [13,14]. This approach is associated with good long-term oncological outcomes [6,7,15–18]. Overall, roughly 6% and 14% of high-risk patients die from PCa and from any causes at 10-yr follow-up [19]. Moreover, some of these patients succumb to their disease even after the 10-yr landmark [20]. As a consequence, relatively long follow-up is needed when assessing the efficacy of novel local or systemic treatments in prospective trials [8]. Therefore, the optimal duration of a trial testing novel therapies in the high-risk setting might be too long to provide practice-changing data for contemporary patients. As such, assessing the optimal ICE in this setting would be key to provide clinically meaningful information in a shorter time frame.

The current study represents the first investigation that sought to identify the most significant ICE in a large contemporary cohort of high-risk PCa patients managed with RP alone at several referral tertiary centers. Our findings suggest that progression to CR within 5 yr of surgery represents the most informative endpoint in predicting long-term survival. These observations have been confirmed by the inclusion, in our cohort, of the men who were treated in a multidisciplinary setting, where adjuvant therapies such as radiotherapy and/or ADT were administered. Concerning BCR, we have demonstrated that its occurrence within 5 yr of surgery is the most informative endpoint for predicting OS. We were also able to assess the most informative endpoint in terms of $\Delta_{recurrence}$, namely, time from BCR to CR. In patients who developed recurrence, progression to CR within 12 mo from the onset of BCR represented the most significant ICE for OS, irrespective of the time elapsed between surgery and BCR. Finally, we combined the information originating from the most informative ICE for BCR and $\Delta_{recurrence}$ in an effort to define a subcategory of patients with the worst prognosis. This category, which included patients who developed BCR within 5 yr of surgery and progressed to CR within 12 mo of BCR, harbored the most unfavorable prognosis at long-term follow-up, where the 10-yr OS rate did not exceed 50%.

For the evaluation of the most informative landmark point, we relied on the Harrell's *c* index, which is the ability of a model to discriminate between patients who actually experience the event and those who do not. In other words, the best model is the one the predicted probability of which is able to discriminate patients facing death (higher probability) from those surviving (lower probability) [21]. The *c* index depends on both the HR and the number of events that are considered within the landmark time. In our data, despite the high *c* index owing to the early recurrence, the most informative landmark time for predicting OS was the occurrence of CR within 5 yr. Even if this intermediate endpoint depicted a lower HR, the resulting predicted probability discriminates better than an earlier landmark time in predicting OS. This is in line with the findings of previous studies adopting a similar statistical analysis [9].

Previous studies sought to identify intermediate endpoints in PCa patients [8,9]. The ICECaP working group analyzed data from 19 clinical trials and showed that metastasis-free survival can be considered as a strong ICE

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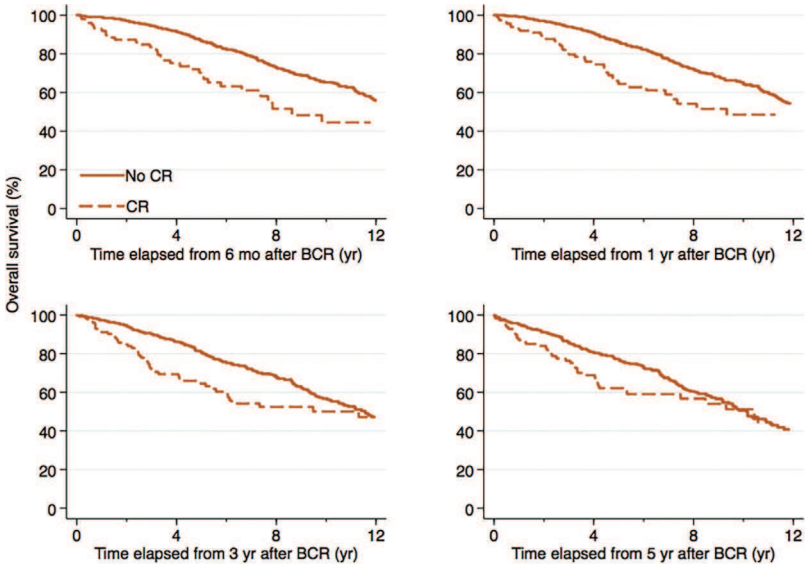

Fig. 4 – Kaplan-Meier estimates illustrating landmark analyses for overall survival, according to the progression to clinical recurrence (CR) within 1, 3, 5, and 7 yr from the development of biochemical recurrence (BCR).

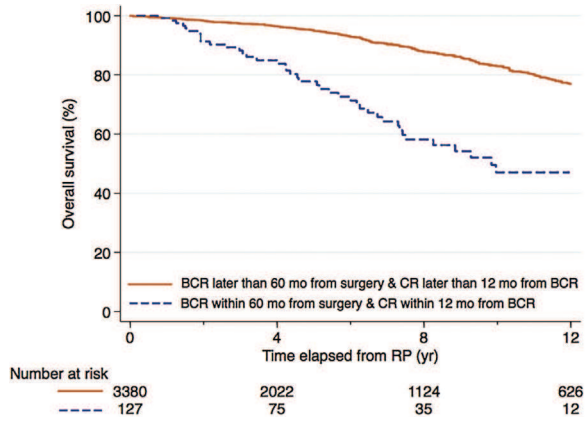

Fig. 5 – Kaplan-Meier estimates for overall survival, considering patients who developed biochemical recurrence (BCR) within 5 yr of surgery and progressed to clinical recurrence (CR) within 12 mo of BCR. RP = radical prostatectomy.

for predicting OS. However, the majority (90%) of patients were treated with radiation therapy [8]. As such, these observations are hardly applicable to patients treated with RP. More recently, Jackson et al. [9] demonstrated that progression to CR within 5 yr after postoperative radiotherapy represented the most informative endpoint when predicting OS at 10 yr in surgically managed PCa patients. These observations are in keeping with our findings, where the occurrence of CR within 5 yr after surgery represented the most informative endpoint predicting OS. However, while we focused our initial analyses on patients who did not receive any neoadjuvant or adjuvant treatment, up to one out of four patients evaluated by Jackson et al. [9] received neoadjuvant therapies or concurrent hormonal therapy at the time of postoperative radiotherapy. Therefore, findings by Jackson et al. [9] could not be generalizable to the entire spectrum of high-risk PCa patients treated with surgery. Our study represents the first of its kind in evaluating the role of a potential novel ICE in surgically treated high-risk patients. However, being the first in this regard represents the primary limitation to the generalization of our findings. In fact, more studies exploring and potentially confirming our results are needed to ultimately allow for establishing the surrogacy of the development of metastasis within 5 yr of RP and OS.

From a clinical standpoint, our results may help physicians in the identification of a category of patients who are at an increased risk of dying at long-term follow-up and, in turn, who would benefit from more aggressive local and systemic therapies at the time of recurrence. Moreover, our results could guide the design of novel trials assessing the efficacy of therapeutic approaches in the context of high-risk PCa. Although the identification of ICE should not replace the assessment of strong endpoints such as OS, these surrogate outcomes (namely, ICEs) can aid in the process of predicting the final results of

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prospective studies and, eventually, accelerating progresses within the field.

Despite several strengths, our study is not devoid of limitations. First, the data have been retrospectively collected and a prospective validation is warranted. Second, detection of CR and its timing depends on follow-up protocols and the imaging modality adopted. In this context, our study is limited by heterogeneous follow-up protocols. Moreover, the lack of details on the imaging modalities adopted prevented us to adjust our analyses for this potential confounder. Finally, patients were treated over a relatively long time period. During this time, advances in diagnostic and surgical techniques occurred. Similarly, interpretative changes applied to the grading system. This might, in part, limit the generalizability of our findings to contemporary high-risk patients.

5. Conclusions

The occurrence of CR within 5 yr of surgery represents the most informative ICE for predicting OS in men treated with RP for high-risk PCa. Moreover, in patients with BCR, progression to CR within 12 mo emerged as the most informative ICE. Further studies are needed to confirm our findings and ultimately allow for the evaluation of surrogacy of development of metastasis within 5 yr of RP and OS.

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: Martini, Gandaglia, Briganti.
Acquisition of data: Zaffuto, Bianchi, Cucchiara.
Analysis and interpretation of data: Gandaglia, Montorsi, Briganti.
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Critical revision of the manuscript for important intellectual content: Briganti, Montorsi.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.euo.2018.12.002.

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