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Predictors of Castration-Resistant Prostate Cancer After Dose-Escalated External Beam Radiotherapy

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Abstract

Purpose—Castration-resistant prostate cancer (CRPC) is a near uniformly fatal form of prostate cancer; however, information on time to development and predictors for progression to CRPC is limited. We report a detailed longitudinal study for development of CRPC in men initially treated with external beam radiotherapy (EBRT).

Materials and Methods—During 1991–2008, 2478 patients with clinically localized prostate cancer were treated with dose-escalated EBRT at a single institution. The primary objective was to determine predictors of CRPC among men who failed definitive EBRT and progressed to salvage androgen-deprivation therapy (ADT). CRPC was defined as castrate levels of testosterone (<50 ng/dL) with progressive biochemical or radiographic disease.

Results—For the entire cohort (n=2478), the 10-year cumulative incidence rate for developing CRPC was 9.9%. For those that progressed to salvage ADT (n=362), the 7-year cumulative incidence rates for developing CRPC from time of salvage ADT was 33.7%. Amongst this cohort, multivariable analysis demonstrated that PSA doubling-time (continuous; hazard ratio [HR], 0.98 [0.97–0.99], $p<0.001$), higher Gleason score (HR, 1.96 [1.12–3.43]; $p=0.034$), and duration of ADT at time of EBRT (continuous; HR, 1.02 [1.01–1.03]; $p=0.007$) were associated with development of CRPC.

Conclusions—This represents the first report of predictors of CRPC for patients treated with modern dose-escalated EBRT. We demonstrate that among the minority of patients not initially cured after EBRT, those treated with longer-course ADT have higher rates of resistance to the re-introduction of ADT. Future trials will need to test this cohort with more aggressive or alternative forms of salvage therapies.

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INTRODUCTION

Until recently, the paradigm for the treatment of metastatic prostate cancer principally focused on targeting the androgen receptor.[1–3] This was accomplished most often with first-generation androgen-receptor antagonists in conjunction with chemical castration using luteinizing-hormone-releasing hormone (LH-RH) agonists. Unfortunately, as has been demonstrated with essentially all targeted therapies, acquired resistance develops, and tumor progression inevitably occurs.[4–8] In prostate cancer this condition is termed castration-resistant prostate cancer (CRPC), and is one of the most devastating forms of the disease, with a median survival of approximately 18 months.[9]

Since 2009, five new therapies have gained Food and Drug Administration approval for the treatment of CRPC.[1, 2, 9–11] Despite these powerful new therapies, CRPC remains uniformly fatal. Understanding which patients are predisposed to rapidly develop CRPC is imperative to provide at earlier timepoints alternative therapeutic strategies that may delay or prevent this outcome. However, limited information exists regarding clinicopathologic factors that predict for rapid development of CRPC.

The void of information on predictors of CRPC is longstanding, and for several reasons it is unlikely to be available through traditional prospective clinical trials or population-based studies. First, as only approximately 10% of all primary prostate cancer patients progress to requiring salvage androgen-deprivation therapy (ADT)[12], exceptionally large trials with long-term follow-up are necessary to have sufficient patient numbers to study this cohort. Secondly, of the select clinical trials of localized prostate cancer of sufficient size with long-term follow-up, all used older external beam radiotherapy (EBRT) doses and techniques that lack modern applicability.[13, 14] Thirdly, post-hoc analyses of recent trials in patients with CRPC have consisted of heterogeneous therapy of the primary disease and lack detailed pretreatment clinical staging and treatment records.[1, 2, 9–11] Lastly, population-based studies do not routinely have access to serum markers (prostate-specific antigen [PSA] and testosterone) and serial radiographic imaging results to determine, using strict criteria, the development of CRPC. To overcome these obstacles, we report the first detailed retrospective analysis of predictors of CRPC for a large uniform cohort of men initially treated with modern dose-escalated EBRT for localized prostate cancer.

MATERIALS AND METHODS

Patient Selection and Pretreatment Staging Evaluation

This study was conducted after approval from the institutional review board at Memorial Sloan Kettering Cancer Center. From 1991 to 2008, 2,718 patients with prostate adenocarcinoma were treated with dose-escalated EBRT (75.6–86.4 Gy) at our institution. Inclusion criteria consisted of histologic confirmation by a dedicated urologic pathologist, confirmation of localized prostate cancer by negative clinical pelvic lymph node staging with either computed tomography (CT) or magnetic resonance imaging, and detailed information regarding the use and duration of ADT at time of EBRT and at time of relapse; 2,478 men met the inclusion criteria and form the initial study cohort.

Pretreatment evaluation was risk adapted, but all patients received pelvic imaging, baseline pretreatment PSA testing, and a physical exam consisting of a digital rectal exam. Patients at higher risk for metastatic disease underwent a bone scan. Risk groups were defined according to the National Comprehensive Cancer Network (NCCN) risk-stratification system.[15]

Treatment

EBRT techniques have been described previously.[16, 17] Briefly, EBRT was delivered daily for 42 to 48 fractions in 1.8 Gy/fraction with 15 MV photons. All patients underwent CT-based simulation with custom immobilization. Per our institutional guidelines at time of treatment of the present cohort, no patients received elective pelvic lymph node radiation.

ADT was administered at the discretion of the treating radiation oncologist. In general, our common recommended clinical practices for offering ADT are for cytoreductive therapy, short-term ADT with neoadjuvant and concurrent therapy, and long-term ADT with neoadjuvant, concurrent, and adjuvant ADT. ADT primarily consisted of an LH-RH agonist, and a short course (30 days) of an androgen-receptor antagonist (to prevent a testosterone surge). Patients who experienced biochemical progression after EBRT (nadir plus 2 ng/mL) underwent salvage therapy at the discretion of the treating physician (Supplementary Table 1). Salvage ADT was the most common form of therapy used at time of relapse, and generally consisted of an LH-RH agonist with variable use of other forms of ADT (i.e. androgen receptor antagonists, adrenal steroid synthesis inhibitors, and 5-alpha reductase inhibitors). Continuous androgen deprivation (in contrast to intermittent therapy) was standard at our institution during the time period of this study.[18, 19]

Study objectives

The primary objective of the study was to determine predictors for the development of CRPC. CRPC was defined using the Prostate-Specific Antigen Working Group definition as castrate levels of testosterone (<50 ng/dL) in conjunction with progressive biochemical (3 rises) or radiographic disease (with or without biochemical progression).[20] By this definition, to be classified as having CRPC state, castrate levels of testosterone must be present; therefore, only those treated with salvage ADT were included in these analyses. Multivariate models included only 262 of the 362 eligible patients secondary to incomplete covariate information (specifically, PSA-doubling time [PSA-DT]).

Secondary objectives included determining time to CRPC for 1) patients who progressed to use salvage ADT, and 2) among the entire cohort. For men who progressed to use salvage ADT, time to CRPC was defined from the initiation of salvage ADT until the development of CRPC. Amongst the entire cohort of patients, the time to CRPC was defined from the time of completion of EBRT plus 6 months until development of CRPC using the landmark method.[21] This method was chosen as 37 patients completed ADT prior to the end of EBRT; hence 2,441 patients were included in these analyses. Predictors of development of CRPC for this larger cohort were not analyzed as most men in this group did not experience a biochemical failure, nor were treated with salvage ADT, and by definition could not develop CRPC.

Co-variable definitions

Co-variables included clinical T-stage (American Joint Committee on Cancer, 7th edition), Gleason score, baseline PSA, EBRT dose, and year of treatment (five chronological categorical groups). Percent positive cores were dichotomized into greater or less than 50% positive cores. The post-treatment PSA-DT calculations were performed from the date of the PSA nadir to the date of biochemical failure, and were defined as the reciprocal of the slope of the ordinary least-squares regression line of the base 2 logarithm of the PSA versus time. As ADT use and duration are joint decisions based upon the patient and the treating oncologist(s), discrete categorical treatment intervals were not observed and ADT use was analyzed as a continuous variable (Supplementary Fig 1).

An additional model based on Freedland et al (an analysis of patients with biochemically recurrent disease post-prostatectomy and reported predictors of cancer specific survival) was generated using their three prognostic variables, PSA-DT, Gleason score, and time from initial EBRT to biochemical failure.[22] However, this model did not demonstrate prognostic significance of their pre-defined PSA-DT cut points, or time from EBRT to biochemical failure. Hence our original pre-planned model was utilized (Supplemental Table 2).

Statistical methods

The associations between factors and the risk of CRPC were evaluated using competing-risks analyses. The risk of CRPC was estimated using a cumulative-incidence function that accounted for death without CRPC as a competing event. Cumulative-incidence comparisons of CRPC across subgroups were performed using a k-sample test. The Fine and Gray method was utilized for multivariate analyses.

As there is no prior information for predictors of developing CRPC for men who received EBRT, multiple covariates were incorporated to comprehensively panel predictors for subsequent treatment failure with salvage ADT. As 10 covariables were tested in the univariate model, to maintain an alpha of 0.05, a traditional p value of 0.05 would yield approximately a 40% probability of falsely rejecting the null hypothesis. For this reason, to correct for multiple testing, significance for univariate analyses was set using Bonferroni modeling with a p value of 0.005 to yield an approximate 5% probability of falsely rejecting the null hypothesis. For multivariate analysis, it was decided *a priori* to include prognostic variables that have shown to impact recurrence rates even if not significant on univariate analysis, which included T-stage, year of treatment, EBRT dose, and percent positive cores. [23, 24] Statistical significance for multivariate analysis, which inherently adjusts the p value, was two-sided and used a 5% significance level (p 0.05).

A statistical assumption was applied that exposure to salvage ADT was continuous after the initiation until development of CRPC. This is secondary to continuous salvage ADT being preferred at our institution. Hence, duration of salvage ADT was not considered as a time-dependent variable. Statistical analyses were performed using R (version 3.0.1; R Development Core Team) with the “survival” and “cmprsk” packages.

RESULTS

Baseline patient and treatment characteristics are outlined in Table 1. Of the 2,478 men in the study cohort, 566 (23%), 1,144 (46%), and 768 (31%) were categorized as low-, intermediate-, and high-risk by NCCN criteria, respectively. A total of 1,248 (50.4%) received upfront ADT at time of definitive EBRT; within this latter cohort of ADT-treated patients, 158 (28%), 489 (43%), and 601 (78%) were classified as having low-, intermediate-, and high-risk disease, respectively. 557 (22.5%) men in total experienced a biochemical failure after definitive therapy, of which 362 (14.6%) were treated with salvage ADT at time of relapse, and 191 (7.7%) ultimately developed CRPC.

The median follow-up of the entire cohort was 8.2 years, and the 5- and 10-year cumulative incidence rates for developing CRPC were 3.5% and 9.9%, respectively (Fig 1a). For patients with low-, intermediate-, and high-risk disease, the 10-year cumulative incidence rates were 1.2%, 8.0%, and 18.1% ($p<0.001$), respectively (Fig 1b).

Among the 362 patients who developed a biochemical failure and were treated with salvage ADT, the median follow-up from time of salvage ADT was 6.6 years, and the 3-, 5-, and 7-year cumulative incidence rates for developing CRPC from time of salvage ADT were 10.6%, 21.0%, and 33.7%, respectively (Fig 2a). For patients with low-, intermediate-, and high-risk disease, the 5-year cumulative incidence rates for CRPC from time of salvage ADT were 10.0%, 16.0%, and 25.2% ($p=0.02$), respectively (Fig 2b).

On univariate analysis, significant predictors ($p=0.005$) for the development of CRPC from time of salvage ADT included NCCN risk group, Gleason score, PSA-DT, and duration of ADT use at time of EBRT (Table 2). On multivariate analysis (Table 3) significant independent predictors of CRPC from time of salvage ADT included higher Gleason scores (Gleason 6 as reference; Gleason 7 (4+3) (HR, 1.85 [95%CI 1.05–3.28]; $p=0.034$); Gleason score 8–10 (HR, 1.96 [1.12–3.43]; $p=0.034$)), longer PSA-DT (HR, 0.98 [95%CI 0.97–0.99]; $p<0.001$) and duration of ADT at time of EBRT (HR, 1.02 [95%CI 1.01–1.03]; $p=0.007$).

DISCUSSION

The present analysis provides important information for patients and their physicians to understand features that predispose an individual to have an increased risk for the development of CRPC following definitive external beam radiation therapy. This study to our knowledge is the first series assessing predictors of CRPC amongst a large cohort of men uniformly treated with modern dose-escalated radiotherapy from time of diagnosis until transformation to CRPC. We demonstrate that, for patients who experience relapsed prostate cancer after definitive radiotherapy, prior ADT use predicted for more rapid progression to CRPC in those reinitiated on ADT for salvage therapy.

An estimated 85% of men with prostate cancer ultimately succumb to nononcologic causes of death, and the vast majority never experience a biochemical failure after definitive therapy.[25] Therefore, an approach was undertaken to assess for accurate predictors of CRPC solely among men who failed definitive EBRT and progressed to requiring salvage

ADT. On multivariate analysis, other than Gleason score, traditional clinical and pathologic features at time of diagnosis no longer were independently predictive for the development of CRPC. This suggests that it is the biologic phenotype of radioresistant prostate cancer that dominates subsequent outcomes, rather than baseline common clinical factors (T-stage or PSA). Other than a higher Gleason score and shorter PSA-DT, the only other independent variable that predicted for time to CRPC from salvage ADT was an increased duration of ADT at time of EBRT ($p=0.007$). Careful interpretation of these findings is paramount to avoid the false conclusion that ADT at time of EBRT is detrimental to all patients and promotes CRPC. This is not supported by our data, and the sound, concise interpretation of our results would be that, despite ADT improving survival amongst the majority of men treated with EBRT for localized prostate cancer,[13, 14] those who fail combined ADT and EBRT are more likely to subsequently fail salvage ADT (also known as CRPC).

Three potential hypotheses may explain why men who fail definitive EBRT and ADT are at increased risk for subsequent failure of ADT. First, patients who progress after combined ADT and EBRT may have developed an acquired resistance to therapy during their initial treatment course. A well-accepted and observed phenomenon with targeted therapy is the development of acquired resistance.[4–7] There are multiple mechanisms of resistance to ADT that lead to CRPC, including production of androgen within the tumor itself, increased expression of AR co-activators, and mutations or splice variants of AR that render it ligand-independent.[8] AR-gene amplification is a common mechanism of resistance found in approximately 25% of CRPC patients, and is felt to develop as a consequence of chronic ADT.[26] Furthermore, it has been demonstrated that in CRPC models, first-generation anti-androgen therapies (i.e., bicalutamide) have AR agonist activity that can promote tumor progression.[27] It is logical to expect that if a man fails prolonged courses of combined EBRT and first-generation ADT, he likely has acquired resistance to therapy and will have an increased likelihood to subsequently fail the reintroduction of first-generation ADT.

A second possibility is that, rather than ADT during definitive therapy leading to acquired resistance, patients that progress following EBRT and ADT may possess tumors with intrinsic resistance to ADT. Although many of the previously mentioned molecular mechanisms of resistance to ADT are thought to be acquired during the course of long-term exposure to this therapy, a recent study from the TransAtlantic Prostate Group found that a subset of tumors possess innate signs of resistance prior to ADT. Merson et al demonstrated in 596 ADT-naïve men that a small subset of patients had pre-existing high-level DNA copy number gain in chromosome X as well as locus-specific AR-gene amplification.[28] The authors concluded that because these amplifications represented a small clonal focal involvement (<1% of tumor specimen), that clonogens containing ADT resistance properties, like AR-amplification, may predate the initiation of ADT. Therefore, it is possible that failing EBRT and prolonged ADT is merely a marker of innate pretreatment biologic aggressiveness.

The third, and most controversial, hypothesis is that ADT promotes a more aggressive phenotype in a genomic subpopulation of prostate cancer tumors. This hypothesis is supported by both preclinical and clinical data.[29–31] Jia et al recently reported in a PTEN-null model of prostate cancer that ADT in fact promotes the progression of high-grade

prostatic intraepithelial neoplasia to invasive CRPC.[29] PTEN is one of the most frequently mutated genes in prostate cancer, and in primary prostate cancers genetic loss or aberration of at least one PTEN allele occurs in 30–70% of cases.[32, 33] Further support for the hypothesis that ADT may in fact promote a more aggressive phenotype can be gained from two large randomized controlled chemoprevention trials using 5-alpha reductase inhibitors (a mild form of ADT): the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial and the Prostate Cancer Prevention Trial (PCPT) with Finasteride.[30, 31] Despite the reduced rate of low-grade cancers, of initial great concern and controversy, there was an increased development of high-grade prostate cancer in both trials. Our data suggests that higher-grade tumors have an increased progression towards CRPC, and when examining the data from the chemoprevention trials it is plausible that a subset of patients may be at increased risk for the acquisition of an aggressive phenotype under the chronic exposure to ADT.

Whether any or all of the herein proposed hypotheses are true, to why men who fail EBRT and ADT have a higher rate of transformation to CRPC from increased duration of ADT, is unknown. Regardless, these men should be identified early after initial failure as having heightened potential for rapid transformation to CRPC if retreated with standard first-generation ADT. For this reason, it is reasonable to suggest more aggressive or alternative forms of salvage systemic therapy for patients who have failed prolonged courses of combined ADT and EBRT. Currently, there are multiple ongoing clinic trials assessing the impact of second-generation anti-androgens in the pre-CRPC setting, including primary prostate cancer at time of definitive therapy, post-prostatectomy during salvage radiotherapy, and pre-CRPC metastatic disease. In contrast to more potent androgen deprivation and receptor inhibition, earlier administration of alternative therapies may prove to be of benefit for patients with resistance to ADT. Investigators have demonstrated that PI3K pathway inhibition amongst PTEN-null studies *in vivo* and in man may improve outcomes.[3, 29] With the surge of novel PI3K pathway inhibitors entering clinical trials, this may provide a novel option for these men.

Limitations of this study warrant further discussion. Most notably, this is a non-randomized retrospective series and therefore is subject to inherent biases. Despite a detailed attempt to correct for a breadth of aggressive clinicopathologic factors commonly reported that may guide the use and duration of ADT, additional variables may exist that were not captured. Finally, as previously stated, duration of salvage ADT was not able to be analyzed as a time-dependent variable, which may have introduce additional bias.

CONCLUSIONS

In summary, in a large cohort of patients treated with modern dose-escalated EBRT, we demonstrate that, amongst patients who failed initial definitive EBRT, those who received prolonged courses of ADT had an increased hazard for development of CRPC. These patients represent a clinically identifiable subgroup who may benefit from more aggressive or alternative forms of therapy. Further efforts to identify the genomic drivers of this phenotype are warranted to intervene at earlier stages of the disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Cumulative incidence rates with competing risk adjustment for the development of CRPC amongst the entire cohort (**A**), and stratified by NCCN risk group (**B**).

Figure 2. Cumulative incidence rates with competing risk adjustment for the development of CRPC for men who failed initial definitive therapy and received salvage ADT (A), and stratified by NCCN risk group (B). Times to CRPC were measured from initiation of salvage ADT until development of CRPC.

Table 1**Baseline Patient and Treatment Characteristics**

Factor	N (%)*
Age	69 (37–90)
NCCN Risk Group	
Low	566 (23)
Intermediate	1144 (46)
High	768 (31)
T-Stage	
1b/1c	1203 (49)
2a	495 (20)
2b/2c	498 (20)
3a	115 (5)
3b/4	167 (7)
Gleason Score	
2–6	1020 (41)
7 (3+4)	682 (28)
7 (4+3)	366 (15)
8–10	410 (17)
PSA	
<10	1558 (63)
10–20	570 (23)
>20	350 (14)
EBRT dose	
7560	443 (18)
>7560, 8100	1027 (41)
>8100	1008 (41)
Use of ADT at time of EBRT	
Yes	1248 (50)
No	1230 (50)
Year of Treatment	
0 (pre-1995)	274 (11)
1 (1995–1999)	558 (23)
2 (1999–2002)	625 (25)
3 (2002–2005)	728 (29)
4 (post-2005)	293 (12)
Biopsy core percent positive	
Low (<50%)	1261 (51)
High (≥ 50)	1217 (49)

Percentages may not sum to 100% secondary to rounding.

Abbreviations: ADT, androgen-deprivation therapy; EBRT, external beam radiotherapy; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen.

Table 2

Univariate Analysis for Predictors of Castration-Resistant Prostate Cancer Amongst Patients on Salvage Androgen-Deprivation Therapy (ADT)

Univariate Analysis		
Factor	Hazard Ratio (95% confidence interval)	* <i>p</i> value
Age (continuous)	0.99 (0.97, 1.01)	0.3
NCCN risk group (intermediate vs. low)	2.36 (1.14, 4.87)	0.021
NCCN risk group (high vs. low)	3.03 (1.49, 6.16)	0.002
T stage (2a vs. 1b/1c)	0.83 (0.52, 1.31)	0.41
T stage (2b/2c vs. 1b/1c)	1.04 (0.72, 1.51)	0.84
T stage (3a vs. 1b/1c)	0.84 (0.47, 1.49)	0.56
T stage (3b/4 vs. 1b/1c)	1.22 (0.80, 1.86)	0.37
Gleason (7 [3+4] vs. 6)	1.06 (0.66, 1.68)	0.82
<i>Gleason (7 [4+3] vs. 6)</i>	<i>1.77 (1.18, 2.67)</i>	<i>0.006</i>
Gleason (8–10 vs. 6)	2.21 (1.52, 3.21)	<0.001
PSA (10–20 vs. <10)	1.03 (0.74, 1.44)	0.85
PSA (>20 vs. <10)	1.25 (0.88, 1.77)	0.21
EBRT dose (75.6, 81.0, 86.4 Gy)	0.93 (0.67, 1.29)	0.66
ADT at time of EBRT (continuous)	1.02 (1.01, 1.03)	<0.001
Year of treatment (1 vs. 0)	1.13 (0.78, 1.64)	0.52
Year of treatment (2 vs. 0)	1.38 (0.92, 2.07)	0.12
Year of treatment (3 vs. 0)	1.72 (1.10, 2.69)	0.018
Year of treatment (4 vs. 0)	1.41 (0.60, 3.31)	0.43
Core percentage positive (<50% vs. 50%)	1.42 (1.01, 2.02)	0.046
PSA-DT (continuous)	0.98 (0.97, 0.99)	< 0.001

* Significance defined as *p* 0.005 for multiple testing corrections.

Bold indicates significant variables. Bold italics indicates trend towards significance.

Abbreviations: EBRT, external beam radiotherapy; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; PSA-DT, prostate-specific antigen doubling time.

Table 3

Multivariable Analysis for Predictors of Castration-Resistant Prostate Cancer Amongst Patients on Salvage ADT

Multivariate Analysis (n=262)		
Factor	Hazard Ratio (95% confidence interval)	*P value
T stage (2a vs. 1b/1c)	0.83 (0.44, 1.53)	0.54
T stage (2b/2c vs. 1b/1c)	1.08 (0.66, 1.75)	0.77
T stage (3a vs. 1b/1c)	0.81 (0.39, 1.68)	0.57
T stage (3b/4 vs. 1b/1c)	0.91 (0.52, 1.61)	0.75
Gleason (7 [3+4] vs. 6)	1.24 (0.67, 2.28)	0.49
Gleason (7 [4+3] vs. 6)	1.85 (1.05, 3.28)	0.034
Gleason (8–10 vs. 6)	1.96 (1.12, 3.43)	0.018
EBRT dose (75.6, 81.0, 86.4 Gy)	0.82 (0.45, 1.50)	0.52
ADT at time of EBRT (continuous)	1.02 (1.01, 1.03)	0.007
Year of treatment (1 vs. 0)	1.31 (0.72, 2.38)	0.38
Year of treatment (2 vs. 0)	1.86 (0.83, 4.16)	0.13
Year of treatment (3 vs. 0)	2.12 (0.82, 5.49)	0.12
Year of treatment (4 vs. 0)	1.19 (0.31, 4.51)	0.8
Core percentage positive (<50% vs. 50%)	1.28 (0.79, 2.10)	0.32
PSA-DT (continuous)	0.98 (0.97, 0.99)	< 0.001

* Significance defined as $p \leq 0.05$ for multivariate analyses.

Bold indicates significant variables.

Abbreviations: EBRT, external beam radiotherapy; PSA, prostate-specific antigen; PSA-DT, prostate-specific antigen doubling time.