OPTIMIZING LOCAL THERAPY FOR HIGH-RISK PROSTATE CANCER: EVIDENCE AND EMERGING OPTIONS

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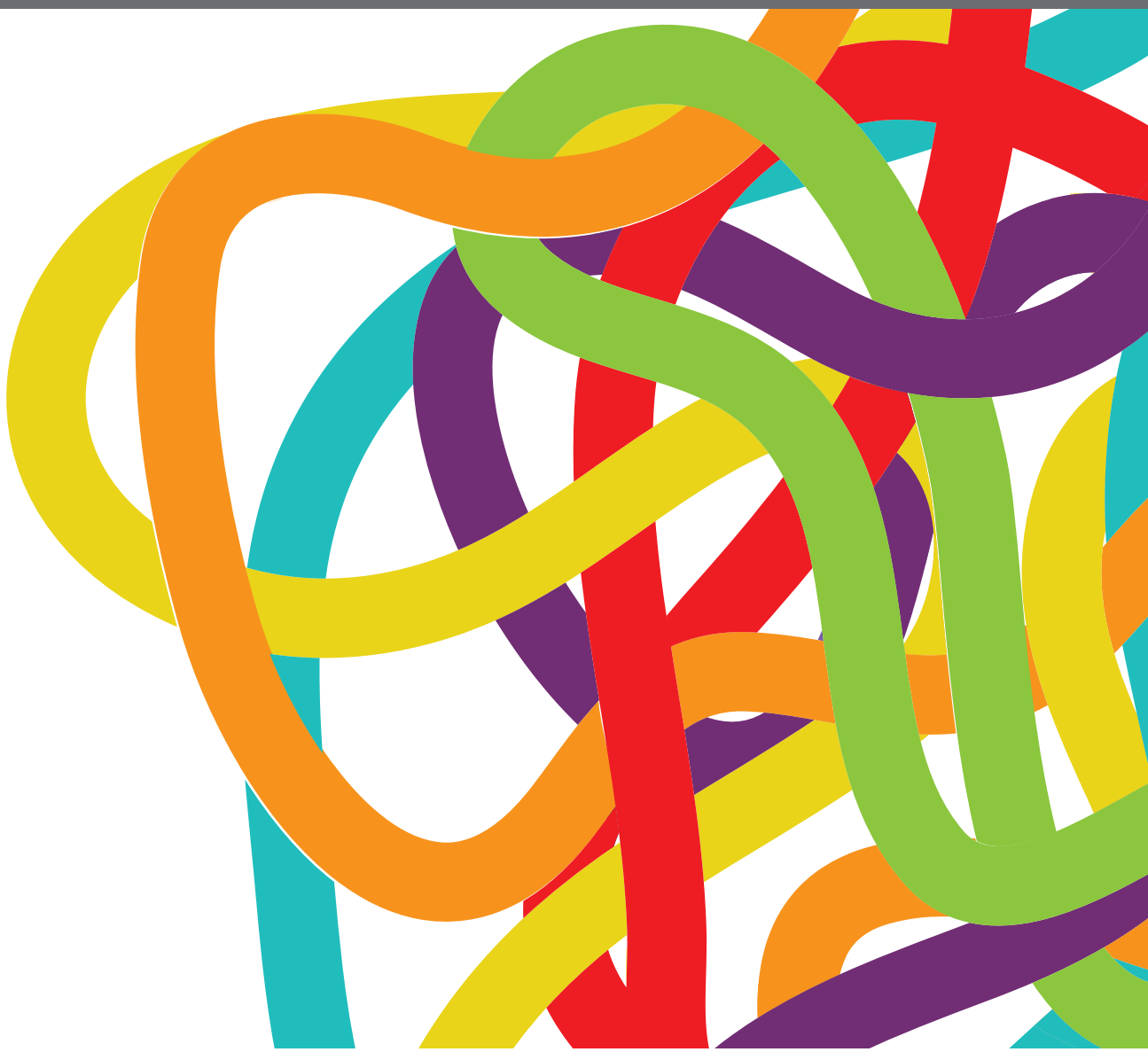

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OPTIMIZING LOCAL THERAPY FOR HIGH-RISK PROSTATE CANCER: EVIDENCE AND EMERGING OPTIONS

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EDITORIAL
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Editorial: Optimizing Local Therapy for High-Risk Prostate Cancer: Evidence and Emerging Options

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Keywords: high risk prostate cancer, androgen deprivation therapy, radical prostatecomy, recurrent prostate cancer, radiation therapy

Editorial on the Research Topic

Optimizing Local Therapy for High-Risk Prostate Cancer: Evidence and Emerging Options

Recent evidence has suggested an important role for local therapy across the spectrum of prostate cancer, including localized and as well as low-volume metastatic prostate cancers, in maximizing cure rates for prostate cancer (1–3). The National Comprehensive Cancer Network (NCCN) guidelines have changed dramatically for these patients in the past several decades. For example, in 2012, for high risk localized disease, the guidelines generally recommended definitive external beam radiation therapy + androgen deprivation therapy (category 1) and radical prostatectomy and appropriate adjuvant or salvage therapy (category 2). In 2017, the guidelines changed so that surgical intervention had a category 1 recommendation; however, in 2019, the guidelines changed again to include external beam radiation therapy + androgen deprivation therapy (category 1) or external beam radiation therapy + brachytherapy boost + androgen deprivation therapy (category 2).

These changes in the guidelines came from newly published studies, and as of 2020, the ideal management of high-risk prostate cancer continues to evolve, mostly because almost all studies have been observational and retrospective (4, 5). A randomized trial of surgery vs. radiation therapy in the setting of high risk disease has only recently gotten underway with the SPCG-15 trial (6), which randomizes between radical prostatectomy vs. androgen deprivation therapy in combination with external beam radiation therapy ± high dose-rate brachytherapy boost.

Further, in patients with low volume metastatic disease, novel therapeutic combination approaches directed toward the primary tumor, and potentially areas of metastasis, are being investigated as strategies to increase cure rates and extend life for men with high risk and metastatic prostate cancers (7–9). Although this is an exciting area for research and contemporary clinical practice for prostate cancer, a range of considerations remain undefined.

This collection features contributions on a range of topics that summarize the best available evidence on this topic and highlight emerging advances that will improve prostate cancer care in the years to come. Several manuscripts focus on the use of laboratory, imaging and pathological information to more accurately predict outcomes after treatment and to tailor therapeutic strategies (Bourbonne et al.; Chys et al.; Guo et al.; Milonas et al.; Venclovas et al.). Motterle et al. review the role of radical prostatectomy for regional risk prostate cancer patients, while Devos et al. investigate the impact of robot-assisted

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prostatectomy in recurrent prostate cancer. Additionally, three manuscripts consider the impact of radiation technical advances on outcomes for high-risk or node-positive prostate cancer (Fischer-Valuck et al.,Greenberger et al.; Koerber et al.). Harat et al. evaluate the comparative effectiveness and cost effectiveness of local therapy options for localized prostate cancer, providing a comprehensive view of treatment options. Finally, Mao et al. provide a peak into the future role of the novel treatment strategy of oncoloytic adenovirus harboring interleukin 24 in combination with radiation therapy to enhance outcomes for advanced prostate cancer (Mao et al.).

Our hope is that this collection of articles contributes to the ongoing interdisciplinary discussions on this topic to continue to improve outcomes for high risk prostate cancer. We believe that tremendous impact can be realized by improving treatment strategies for men with high-risk prostate cancer, as advances in management of locally advanced, node-positive, and low-burden metastatic disease will translate in reduced recurrence risk for men with high risk of metastasis at time of diagnosis.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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frontiers in Oncology

ORIGINAL RESEARCH
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Survival Significance of Patients With Low Prostate-Specific Antigen and High-Grade Prostate Cancer After Radical Prostatectomy, External Beam Radiotherapy, or External Beam Radiotherapy With Brachytherapy

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Objective: This study compared survival of prostate cancer patients with low prostate specific antigen level (PSA $\leq$ 10 ng/ml) and high-grades of Gleason score (GS) of 8–10 with different treatment options (i.e., radical prostatectomy [RP], external beam radiotherapy [EBRT], or external beam radiotherapy with brachytherapy [EBRT+BT]).

Materials and Methods: The Surveillance, Epidemiology and End Results (SEER) database data (2004–2013), and overall survival (OS) and prostate cancer-specific mortality (PCSM), were evaluated using the Cox proportional hazards regression model and Fine and Gray competing risk model.

Results: The SEER data contained 9,114 patients, 4,175 of whom received RP, 4,114 received EBRT, and 825 received EBRT+BT with a median follow-up duration of 47 months. RP patients had significantly better OS than patients with EBRT and EBRT+BT (adjusted HR [AHR]: 3.36, 95% CI: 2.43–4.64, $P < 0.001$; AHR: 2.15, 95% CI: 1.32–3.48, $P = 0.002$; respectively). There was no statistical difference in PCSM between RP and EBRT+BT (AHR: 1.31, 95% CI: 0.61–2.80, $P = 0.485$), while EBRT had worse OS ($P < 0.05$). The subgroup analysis revealed that there was no statistical difference in prognosis of patients with age of >70 years old, or PSA levels of $\leq$ 2.5 ng/ml between RP and EBRT+BT ($P > 0.05$).

Conclusion: RP patients with low PSA levels and high GS had better OS compared to either EBRT or EBRT+BT, while RP and EBRT+BT resulted in significantly lower PCSM, compared to EBRT. Moreover, EBRT+BT and RP were associated with similar survival of patients with age of > 70 years old, or PSA levels of $\leq$ 2.5 ng/ml.

Keywords: prostate cancer, prostate specific antigen, gleason score, radical prostatectomy, radiotherapy, SEER data

INTRODUCTION

In the USA, prostate cancer has an estimated of 164,690 new cases and 29,430 cancer-related deaths in 2018 (1). Clinically, most prostate cancer patients are diagnosed as early staged low or intermediate-risk of disease, and merely one-third of American men are diagnosed with a high-risk disease (2), which has different treatment options, such as radical prostatectomy (RP) and radiation therapy (RT) (3). RT includes external beam radiation therapy (EBRT) and EBRT plus brachytherapy (EBRT + BT), and previous randomized trials have revealed that EBRT + BT have an advantage in the biochemical disease-free survival of patients, when compared with EBRT (4). Furthermore, other retrospective studies have also revealed better survival of patients after EBRT + BT (5). Recently, studies have reported that RP could improve cancer-specific mortality in patients with high-risk prostate cancer (6). However, another retrospective study revealed that there was no statistically significant difference in survival between patients receiving RP and EBRT + BT with or without androgen deprivation therapy (ADT) in high-risk localized prostate cancer patients after adjusting for the prognostic factors of prostate cancer (7). In addition, increased PSA level is an indicator of the poor prognosis (8, 9) and high-grade diseases. However, patients with high-grade and low PSA level had poorer prognosis (10). Furthermore, low PSA level and high-risk of disease may represent a unique entity with potential dedifferentiation biology (11). To date, there is still no uniform treatment standard for this group of patients. The present study selected these patients from the Surveillance, Epidemiology, and End Results (SEER) database, and assessed their survival significance after treatment with RP and RT (EBRT or EBRT + BT).

METHODS

Database and Patient Selections

The US SEER database, a population-based cancer registration system, provides different datasets on cancer incidence and survival by covering ∼28% of US populations (https://seer.cancer.gov/). In the present study, the SEER* Stat 8.3.5 software was utilized to query the data of patients diagnosed with primary prostate adenocarcinoma, had a pre-treatment PSA of ≤10 ng/dL, a GS of 8–10, and a clinical stage of N0 and M0 between 2004 and 2015. GS provided by the SEER program represents the highest GS found during a surgical or non-surgical biopsy. These patients received one of the three treatments (radical prostatectomy [RP], external beam radiotherapy [EBRT], or external beam radiotherapy with brachytherapy [EBRT+BT]), while patients who received prostate procedures and treatment before and after receiving RP were excluded. This dataset included 9,114 patients (**Figure 1**). The primary study endpoint was prostate cancer-specific mortality (PCSM) and overall survival (OS, death of any reason).

Statistical Analysis

All statistical analyses were performed using Stata/MP 14.0 (StataCorp LP 4905 Lakeway Drive College Station, TX, USA) and R Studio v1.1.447 with survival and twang packages at a two-tailed level of significance of 0.05. The differences in categorical variables between groups were analyzed by chi-squared test, while

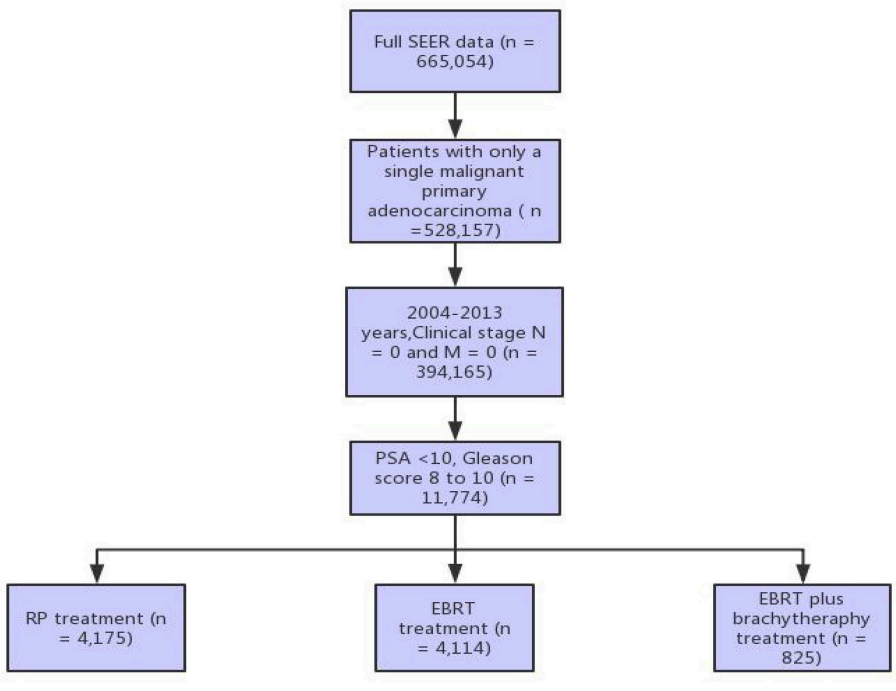

FIGURE 1 | Illustration of the patient selection process.

normally distributed continuous variables were analyzed by one-way analysis of variance (ANOVA) test and the Kruskal-Wallis test for skewed continuous variables. The *P*-value of multiple comparisons was corrected using the Bonferroni method, while the propensity score was estimated by using the generalized boosted model (GBM), which analyzed the involvement of an iterative process with multiple regression trees to capture complex and non-linear relationships between the treatment assignment and pretreatment covariates without over-fitting the data, according to previous studies (12, 13). Moreover, the outcome of this model was a categorical variable, with 1 for RP, 2 for EBRT, and 3 for EBRT+BT. The co-variables of the model included race, marital status, age at diagnosis, years of diagnosis, PSA level, clinical T stage, and GS. Then, the mean and maximum standardized bias stopping rules were used to select the iteration that yielded the optimal balance to fit each GBM. The mnps () function in the twang package automated the propensity score and weight estimation process by running the GBM fitting algorithm for many iterations, and selecting the iteration to minimize the user-specified stopping rule. This produced weights from the selected model, and all the steps for all treatment groups were repeated. Moreover, for the standardized bias (absolute standardized mean difference) of each covariate, <0.20 was considered small, 0.40 was considered moderate, and 0.60 was considered large, according to a previous study (14). The estimated treatment effect on survival was analyzed using the Cox proportional regression model, according to previous studies.

In addition, Kaplan-Meier survival analysis was used to evaluate overall survival at 5 year and 10 year of follow-up and log-rank test generated *P*-values. Multivariate Cox regression was used to estimate the hazard ratios of overall survival between treatment groups with or without inverse propensity score of treatment weights, including the patient marital status, age at diagnosis, year of diagnosis, race, PSA, clinical T stage, and Gleason score in the Cox regression model along with the treatment indicator (therapy). Similarly competing risks regression was used to estimate the hazard ratios of prostate cancer-specific mortality between treatment groups with or without inverse propensity score of treatment weights, including patient marital status, age at diagnosis, year of diagnosis, race, PSA, clinical T stage, and Gleason score in the Fine-Gray model at the same time.

TABLE 1 | Clinicopathological features of prostate cancer patients with low PSA levels and high Gleason scores.

Clinical characteristics	Unweighted, *n* (%)			*P*-value		
	RP (*n* = 4,175)	EBRT (*n* = 4,114)	EBRT+BT (*n* = 825)	EBRT vs. RP	EBRT+BT vs. RP	EBRT+BT vs. EBRT
Age at diagnosis				<0.001	<0.001	<0.001
Mean (median)	63.7 (64.0)	70.6 (71.0)	67.3 (68.0)			
[range], year	[59.0–68.0]	[66.0–76.0]	[62.0–73.0]			
PSA level				<0.001	<0.001	>0.999
Mean (median)	5.9 (5.7)	6.3 (6.3)	6.3 (6.1)			
[range], ng/mL	[4.6–7.2]	[4.8–7.9]	[4.9–7.8]			
Marital status				<0.001	<0.001	0.228
Married	3,176 (76.1)	2,747 (66.8)	577 (70.0)			
Divorced/widowed	405 (9.8)	623 (15.1)	99 (12.0)			
Singled	376 (9.0)	333 (8.1)	74 (9.0)			
Unknown	218 (5.2)	411 (10.0)	75 (9.1)			
Race				<0.001	<0.001	0.001
White	3,298 (79.0)	3,189 (77.5)	595 (72.1)			
Black	524 (12.6)	600 (14.6)	161 (19.5)			
Other	309 (7.4)	233 (5.7)	58 (7.0)			
Unknown	44 (1.1)	92 (2.2)	11 (1.3)			
AJCC T stage				<0.001	<0.001	0.012
T1	19 (0.5)	2,241 (54.5)	500 (60.6)			
T2	2,608 (62.5)	1,612 (39.2)	278 (33.7)			
T3	1,448 (34.7)	228 (5.5)	45 (5.5)			
T4	100 (2.4)	33 (0.8)	2 (0.2)			
Gleason score				<0.001	>0.99	0.003
8	2,998 (71.8)	2,601 (63.2)	573 (69.5)			
9	1,116 (26.7)	1,380 (33.5)	238 (28.8)			
10	61 (1.5)	133 (3.2)	14 (1.7)			

RP, radical prostatectomy; EBRT, external beam radiotherapy; EBRT+BT, external beam radiotherapy with brachytherapy boost; PSA, prostate-specific antigen.

RESULTS

Patients Characteristics

The SEER database had 9,114 prostate cancer patients with a GS of 8–10 and a pre-treatment PSA level of ≤10 ng/dL, among which 4,175 (45.8%) received RP, 4,114 (45.1%) received EBRT, and 825 (9.1%) received EBRT + BT with a median follow-up duration of 47 months (interquartile range [IQR], 34–60), 47 months (IQR, 34–60) for RP, 47 months (IQR, 33–60) for EBRT, and 51 months (IQR, 37–62) for EBRT + BT. Furthermore, the median age of patients was 67 years old (IQR, 62–73), 64 years old (IQR, 59–68) for RP, 71 years old (IQR, 66–76) for EBRT, and 68 years old (IQR, 62–73) for EBRT+BT (**Table 1**; **Supplementary Table 1** and **Supplementary Figure 1**).

Association of Treatment Options With OS and PCSM of Patients

Treatment options were associated with OS and PCSM of patients and the 3-, 5-, and 10-year OS of patients were as follows: 98.4, 96.8, and 67.5% for RP, respectively; 95.1, 87.3, and 58.0% for EBRT, respectively; 96.7, 92.8, and 61.5% for EBRT+BT, respectively. Furthermore, the 3-, 5-, and 10-year PCSM of patients were as follows: 0.5, 1.4, and 16.3% for RP, respectively; 1.4, 4.8, and 23.7% for EBRT, respectively; 0.8, 2.3, and 6.5% for EBRT+BT, respectively (**Figure 2** and **Table 2**). The multivariate Cox regression analysis after adjusting for the patient's marital status, age at diagnosis, race, PSA level, clinical T stage, and GS revealed that RP was associated with better OS, compared to EBRT or EBRT+BT (adjusted HR [AHR]: 3.36, 95% CI: 2.43–4.64, $P < 0.001$; AHR: 2.15, 95% CI: 1.32–3.48, $P = 0.002$; respectively; **Table 3**). However, in the competitive risk model after adjusting for the patient's marital status, age at diagnosis, race, PSA level, clinical T stage, and GS, no significant difference was found in PCSM for patients treated with RP vs. EBRT + BT (AHR: 1.31, 95% CI: 0.61–2.80, $P = 0.485$). Moreover, RP was associated with significantly better PCSM, compared to EBRT (AHR: 2.46, 95% CI: 1.45–4.18, $P = 0.001$; **Table 3**).

Association of Treatment Options With OS and PCSM of Patients Stratified by Age and PSA Level

Treatment options were associated with the OS and PCSM of patients stratified by age and PSA level. The Cox proportional

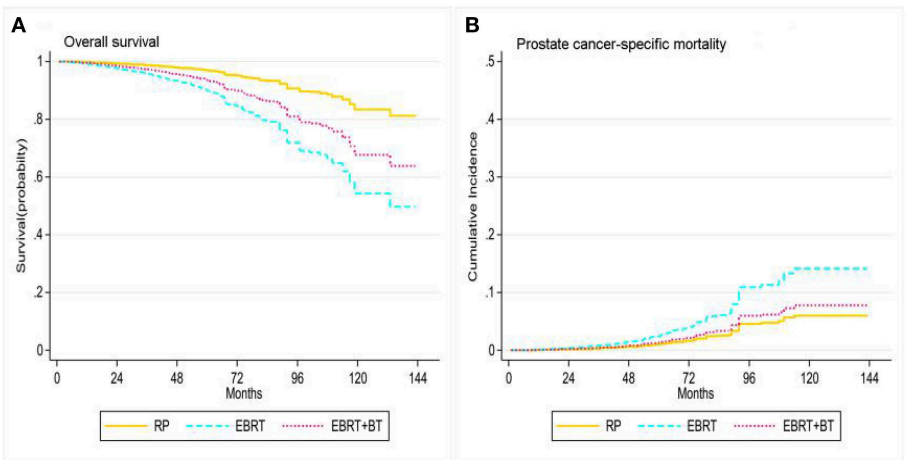

FIGURE 2 | Adjusted survival curves for overall survival **(A)** and prostate cancer-specific mortality **(B)** by RP, EBRT, and EBRT+BT treatment options after weighting (adjusted curves after stratified by RP, EBRT, and EBRT+BT treatment options were generated by adding marital status, race, age at diagnosis, disease stage, PSA level, and GS into the Cox proportional hazards model or competing risks regression model, respectively).

TABLE 2 | The 3-, 5-, and 10-year overall survival and prostate cancer-specific mortality of patients after RP, EBRT, and EBRT+BT.

Therapy	*n* (%)	Unweighted (%)			Weighted (%)		
		3-year (95% CI)	5-year (95% CI)	10-year (95% CI)	3-year (95% CI)	5-year (95% CI)	10-year (95% CI)
OVERALL SURVIVAL USING KAPLAN MEIER ANALYSIS							
RP	4,175 (45.8)	98.3 (97.9–98.7)	96.2 (95.3–96.9)	73.5 (54.8–85.5)	98.4 (98.1–98.7)	96.8 (96.2–97.2)	67.5 (49.3–80.4)
EBRT	4,114 (45.1)	94.0 (93.2–94.6)	86.3 (86.2–87.6)	54.7 (39.0–68.0)	95.1 (94.6–95.6)	87.3 (86.3–88.2)	58.0 (49.4–65.6)
EBRT+BT	825 (9.1)	96.8 (95.3–97.9)	92.5 (0.89.8–94.5)	66.5 (35.5–85.2)	96.7 (96.3–97.1)	92.8 (92.1–93.5)	61.5 (47.3–72.9)
PROSTATE CANCER-SPECIFIC MORTALITY							
RP	4,175 (45.8)	6 (4–9)	16 (12–22)	17.1 (8–34.3)	5 (4–7)	1.4 (1.1–1.7)	16.3 (8.4–30.1)
EBRT	4,114 (45.1)	1.9 (1.5–2.4)	5.3 (4.4–6.4)	20.8 (13–32.4)	1.4 (1.2–1.7)	4.8 (4.2–5.5)	23.7 (18.6–29.9)
EBRT+BT	825 (9.1)	1 (0.5–2)	2.6 (1.5–4.4)	8.4 (3.6–18.8)	0.8 (0.6–1)	2.3 (1.9–2.8)	6.5 (4.8–8.7)

hazards regression and competing risk model after adjusting for the patient's marital status, race, PSA level, clinical T stage, and GS found patients who were ≤70 years old after RP had significantly better OS compared to patients who received EBRT and EBRT+BT ($P < 0.05$). However, there was no statistical difference in PCSM between RP and EBRT+BT (AHR: 1.63, 95% CI: 0.69–3.86; $P = 0.266$), and there was no statistical difference in OS for patients who were >70 years old between RP and EBRT+BT (AHR: 1.84, 95% CI: 0.95–3.57, $P = 0.071$), although patients who were >70 years old and received RP had a significant increase in OS compared with EBRT ($P < 0.001$; **Table 4** and **Figure 3**). Moreover, there was no statistical difference in PCSM occurring among all three-treatment groups ($P > 0.05$; **Table 4** and **Figure 3**).

In addition, the Cox proportional hazards regression and competing risk model, after adjusting for the patient's marital status, age at diagnosis, race, clinical T stage, and GS, found RP and EBRT+BT did not yield any statistical differences in OS and PCSM for patients with PSA levels of ≤2.5 ng/ml ($P > 0.05$), but EBRT contributed to worsen the OS and PCSM of patients with a PSA level of ≤2.5 ng/ml compared to patients who received RP ($P < 0.05$; **Table 4** and **Figure 4**). Furthermore, patients with PSA levels of 2.5–4 ng/ml after RP had significantly better OS compared to patients who received EBRT and EBRT+BT (AHR:

TABLE 3 | Proportional hazards regression model for the association of different treatments with overall survival and prostate cancer-specific mortality.

Covariate[a]	Cox proportional hazards regression overall survival				Competing risk regression prostate cancer-specific mortality			
	Unweighted		Weighted		Unweighted		Weighted	
	Survival, HR (95% CI)	*P*-value	Survival, HR (95% CI)	*P*-value	Survival, SHR (95% CI)	*P*-value	Survival, SHR (95% CI)	*P*-value
RP	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
EBRT	3.29 (2.56–4.19)	<0.001	3.36 (2.43–4.64)	<0.001	2.77 (1.91–3.40)	<0.001	2.46 (1.45–4.18)	0.001
EBRT+BT	2.03 (1.44–2.88)	<0.001	2.15 (1.32–3.48)	0.002	1.76 (0.98–3.14)	0.057	1.31 (0.61–2.80)	0.485

[a] *The multivariate Cox regression and competing risk regression derived-hazard ratios are adjusted for age at diagnosis, marital status, race, Gleason score, disease stage, and PSA level.*

TABLE 4 | Proportional hazards regression model for the association of different treatments with overall survival and prostate cancer-specific mortality stratified by Gleason score, age, and PSA level.

Covariate	Cox proportional hazards regression overall survival				Competing risk regression prostate cancer-specific mortality			
	Unweighted		Weighted		Unweighted		Weighted	
	Survival, HR (95% CI)	*P*-value	Survival, HR (95% CI)	*P*-value	Survival, SHR (95% CI)	*P*-value	Survival, SHR (95% CI)	*P*-value
[a]Age ≤ 70 years old								
RP	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
EBRT	3.10 (2.21–4.34)	<0.001	3.65 (2.58–5.16)	<0.001	3.15 (1.87–5.31)	<0.001	3.12 (1.87–5.18)	<0.001
EBRT+BT	1.90 (1.15–3.14)	0.012	2.35 (1.24–4.45)	0.009	1.65 (0.70–3.90)	0.25	1.63 (0.69–3.86)	0.266
[a]Age > 70 years old								
RP	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
EBRT	3.17 (2.17–4.63)	<0.001	3.07 (1.82–5.17)	<0.001	2.29 (1.31–3.99)	0.004	1.94 (0.87–4.32)	0.105
EBRT+BT	1.86 (1.10–3.13)	0.02	1.84 (0.95–3.57)	0.071	1.04 (0.42–2.59)	0.934	0.98 (0.30–3.15)	0.97
[b]PSA ≤ 2.5 ng/ml								
RP	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
EBRT	2.28 (0.84–6.21)	0.106	4.00 (1.44–11.13)	0.008	2.45 (0.71–8.42)	0.154	5.13 (1.34–19.65)	0.017
EBRT+BT	0.71 (0.76–6.68)	0.765	0.58 (0.09–3.61)	0.556	1.01 (0.18–5.53)	0.993	1.27 (0.25–6.59)	0.774
[b]PSA 2.5–4 ng/ml								
RP	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
EBRT	2.91 (1.46–5.80)	0.002	2.89 (1.50–5.55)	0.001	4.94 (1.76–13.86)	0.002	9.94 (1.51–65.50)	0.017
EBRT+BT	2.49 (0.89–6.96)	0.081	4.33 (1.26–14.8)	0.02	4.56 (0.92–22.58)	0.063	7.29 (0.58–92.03)	0.125
[b]PSA > 4 ng/ml								
RP	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
EBRT	3.70 (2.52–5.43)	<0.001	3.48 (2.40–5.06)	<0.001	2.65 (1.74–4.04)	<0.001	2.19 (1.21–3.97)	0.01
EBRT+BT	2.00 (1.21–3.30)	0.007	2.02 (1.22–3.35)	0.007	1.63 (0.84–3.15)	0.14	1.22 (0.51–2.89)	0.657

[a] *The multivariate Cox regression and competing risk regression derived-hazard ratios are adjusted for marital status, race, Gleason score, disease stage, and PSA level.*
[b] *The multivariate Cox regression and competing risk regression derived-hazard ratios are adjusted for age at diagnosis, marital status, race, Gleason score, and disease stage.*

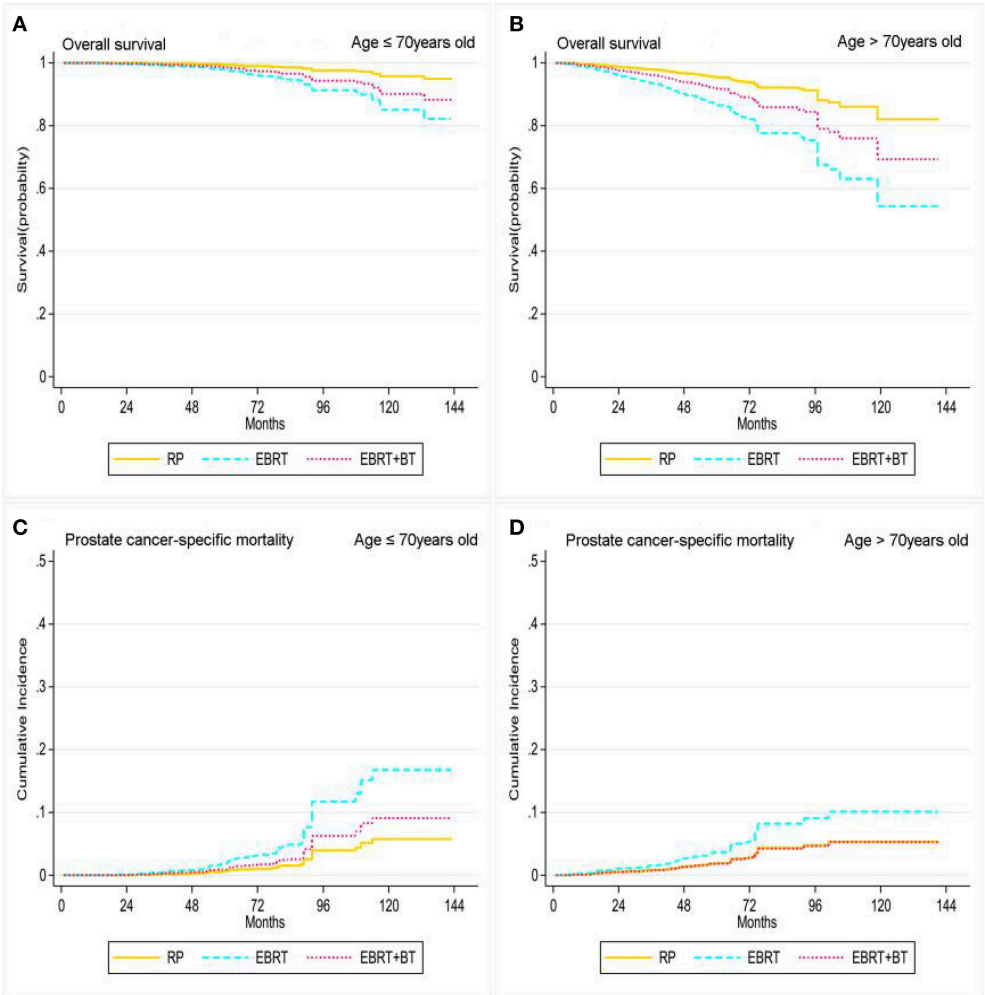

FIGURE 3 | Adjusted survival curves for overall survival (**A**, age ≤ 70 years old; **B**, age > 70 years old) and prostate cancer-specific mortality (**C**, age ≤ 70 years old; **D**, age > 70 years old) by RP, EBRT, and EBRT+BT treatment options after weighting in age subgroups after weighting (adjusted curves after stratified by RP, EBRT, and EBRT+BT treatment options were generated by adding marital status, race, at diagnosis, disease stage, PSA level, and GS into the Cox proportional hazards model or competing risks regression model, respectively).

2.89, 95% CI: 1.50–5.55, $P = 0.001$; AHR: 4.33) 95% CI: 1.26–14.8, $P = 0.02$; **Table 4** and **Figure 4**). Moreover, there was no statistical significance in PCSM for patients with PSA levels of 2.5–4 ng/ml after RP and EBRT + BT ($P > 0.05$), and patients with PSA levels of 2.5–4 ng/ml after EBRT had worse PCSM compared to patients who received RP ($P < 0.05$; **Table 4** and **Figure 4**). Sensitivity analyses showed that prognosis of these three treatments of PSA levels of the 2.5–4 ng/ml group was similar to that of the PSA levels of >4 ng/ml group (**Table 4** and **Figure 4**).

DISCUSSION

Recently, increasing attention has focused on treatment of high-risk localized prostate cancer, especially for the subgroup of high-risk localized prostate cancer (15, 16). Moreover, detection of PSA levels has been widely used to screen prostate cancer and monitor disease progression, although PSA levels may not always represent the degree of prostate cancer malignancy (17). Prostate cancer with low PSA level, but high disease grade, provides a unique and aggressive entity in clinic, and the risk of patient death has more than doubled, when compared to other high-risk diseases, according to the NCCN (11). Although the treatment of these specific high-risk patients with low PSA levels is important, there have been no reports in literature at present. Thus, in the present study, the survival significance of patients with low PSA level, but with high GS for prostate cancer after RP, EBRT, or EBRT plus BT, was assessed for future guidance on the treatment of these kind of patients in clinic. The present data revealed that patients who received RP had significantly better OS, when compared to patients who received EBRT or EBRT+BT. However, EBRT led to worse OS, although there was no statistical difference in PCSM between RP and EBRT+BT. The present subgroup analysis revealed that there was no statistical significance in OS and PCSM between RP and EBRT+BT in patients with age

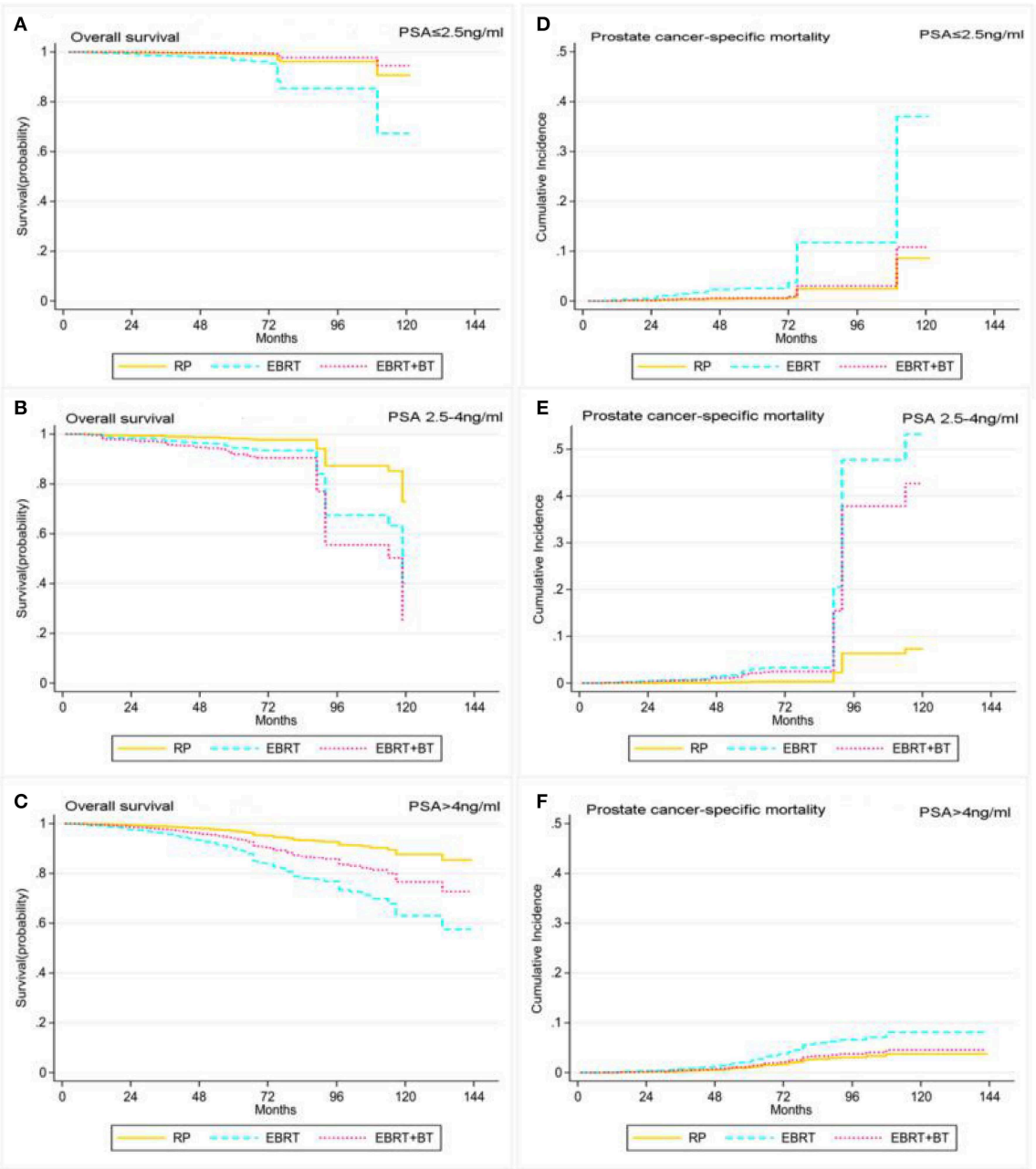

FIGURE 4 | Adjusted survival curves for overall survival (**A**, PSA ≤ 2.5 ng/ml; **B**, PSA 2.5–4 ng/ml; **C**, PSA > 4 ng/ml) and prostate cancer-specific mortality (**D**, PSA ≤ 2.5 ng/ml; **E**, PSA 2.5–4 ng/ml; **F**, PSA > 4 ng/ml) by RP, EBRT, and EBRT+BT treatment options after weighting in PSA level subgroups after weighting (adjusted curves after stratified by RP, EBRT, and EBRT+BT treatment options were generated by adding marital status, race, age at diagnosis, disease stage, and GS into the Cox proportional hazards model or competing risks regression model, respectively).

of >70 years old, or PSA level of ≤2.5 ng/ml. Furthermore, it could be concluded that RP of patients with low PSA level and high GS had better OS, when compared to patients who received either EBRT, or EBRT+BT, and that RP and EBRT+BT led to significantly lower PCSM, when compared to EBRT, suggesting that EBRT+BT might be an alternative option for treating patients with age of >70 years old, or PSA of ≤2.5 ng/ml.

The present data assessed a large cohort of patient samples, and the statistical power was strong, which could minimize significant baseline differences in clinical and demographic variables among these three different treatment options (RP, EBRT, and EBRT+BT) for association with the prognosis. A previous meta-analysis conducted by Wallis et al. revealed that surgery could have reduced the overall and prostate cancer-specific mortality of patients with locally high-risk prostate

cancer (18), while Ennis et al. revealed that there was no survival significance in patients with high-risk localized prostate cancer after treatment with RP or EBRT+BT with or without ADT (7). In the present study, the investigators were able to verify the effectiveness of RP in treating high-risk prostate cancer patients. Other studies have reported that EBRT+BT was better in controlling biochemical recurrence and survival, when compared with EBRT (4, 5), and it was further confirmed by the present data that EBRT+BT was associated with longer 10-year cancer specific survival, when compared to RP and EBRT. Prostate cancer-specific mortality is more frequent than other causes, which may explain the improvement in survival of patients after EBRT + BT. Indeed, randomized trials and retrospective studies have reported similar prostate cancer-specific mortality in EBRT + BT and RP (19, 20). The subgroup analysis of this cohort of patients was also conducted. Since patients in the radiotherapy cohort are usually older and have more comorbidities, a subgroup analysis stratified by the age of patients was thereby performed, while a patient age of 70 years old, as one of the optimal cut-points, was detected using the Optimal Binning procedure that discretizes variable age with respect to the guide variable GS that "supervises" the binning process. In addition, it was found that RP still had a better OS in patients who were $\leq$70 years old, when compared with radiotherapy, while EBRT+BT and RP had the same prognosis in patients with >70 years old. A previous study performed by Huang et al. compared the effects of surgery and radiation therapy on the cancer-specific mortality of locally high-grade prostate cancer patients who were <60 years old, and revealed a significant difference in survival between initial surgery and radiation therapy (16). In addition, patients with high-grade (GS 8–10) localized prostate cancer, a PSA of $\leq$2.5 and 2.5–4 ng/mL was more likely to have cancer-specific death, when compared to PSA levels between 4 and 10 ng/ml (10). In the present study, patients were stratified for PSA levels of 2.5 and 4 as a cutoff value, and it was found that RP and EBRT+BT treatments contributed to the better prognosis of patients with a PSA of $\leq$2.5 ng/mL. However, treated patients with PSA levels of 2.5–4 and 4–10 ng/ml, who had undergone RP, had significantly increased OS, when compared to those who received EBRT and EBRT+BT. Although, patients after RP and EBRT+BT had no significant difference in PCSM. Furthermore, patients with a high-grade, but low-PSA prostate cancer usually have poor prognosis and poorly differentiated tumors, thereby leading to low sensitivity to traditional ADT (11), and making RP a better choice of treatment.

The primary clinical significance of the present data was the discovery showing that RP was the treatment option for patients with high-grade, but low-PSA, prostate cancer, while EBRT+BT is an alternative option for the treatment of patients with an age of >70 years old, or a PSA level of $\leq$2.5 ng/ml. However, in the present study, cases of subsequent treatment with RP were excluded. It is possible that RP shows advantages in treating these kind of patients: (1) simple surgically resected tissue specimens are better for assessing the extent of cancer progression, and the follow-up data will guide further treatments, which is similar to RT in improving the survival of patients (21); (2) surgery could also reduce tumor burden for better local control of the disease and improving systemic treatment response (22); (3) The surgical resection of tissue lesions reduces PSA levels more rapidly, thereby improving physiological conditions for better disease-free survival, when compared with RT; (4) surgery leads to less cytotoxic side effects and comorbidities (23, 24).

However, the present study does have some limitations. For example, it is a retrospective study, and even after adjusting for propensity scores, bias may still exist, when compared to treatment modalities and patient baseline characteristics. Furthermore, the SEER database does not provide data on treatment details, such as ADT, duration, radiation dosage, duration, and comorbidities. In addition, the present study lacked a toxicity data for analysis, which is also a shortfall, because RP and EBRT have different toxicity characteristics (25). Therefore, future prospective studies are needed to determine the long-term outcome of these treatments.

CONCLUSION

The present study demonstrated that the treatment of patients with low PSA, but with high-grade prostate cancer, with radical prostatectomy, contributed to the significant increase in OS, when compared with EBRT and EBRT+BT. Whereas, radical prostatectomy and EBRT+BT were associated with significantly lower PCSM, when compared to EBRT. EBRT+BT could be an alternative option in the treatment of patients with an age >70 years old, or PSA levels of $\leq$2.5 ng/ml.

DATA AVAILABILITY

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

YG and XC: data curation. SM and JZ: formal analysis. BY and XY: funding acquisition and supervision. LW and RW: investigation. AZ and WZ: methodology. XY: project administration and resources. AZ and ZZ: software. YW: validation. BY: visualization. YG: writing—original draft and review and editing.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2019.00638/full#supplementary-material

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Elective Node Irradiation With Integrated Boost to the Prostate Using Helical IMRT–Clinical Outcome of the Prospective PLATIN-1 Trial

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Introduction: This prospective, non-randomized phase II trial aimed to investigate the role of additional irradiation of the pelvic nodes for patients with prostate cancer and a high risk for nodal metastases using helical intensity-modulated radiotherapy with daily image guidance (IMRT/IGRT).

Methods and materials: Between 2009 and 2012, 40 men with treatment-naïve prostate cancer and a risk of lymph node involvement of more than 20% were enrolled in the PLATIN-1 trial. All patients received definitive, helical IMRT of the pelvic nodes (total dose of 51.0 Gy) with a simultaneous integrated boost (SIB) to the prostate (total dose of 76.5 Gy) in 34 fractions. Antihormonal therapy (AHT) was administered for a minimum of 2 months before radiotherapy continuing for at least 24 months.

Results: After a median follow-up of 71 months (range: 5–95 months), pelvic irradiation was associated with a 5-year overall survival (OS) and biochemical progression-free survival (bPFS) of 94.3% and 83.6%, respectively. For our cohort, no grade 4 gastrointestinal (GI) and genitourinary (GU) toxicity was observed. Quality of life (QoL) assessed by EORTC QLQ-C30 questionnaire was comparable to EORTC reference values without significant changes.

Conclusion: The current trial demonstrates that elective IMRT/IGRT of the pelvic nodes with SIB to the prostate for patients with a high-risk of lymphatic spread is safe and shows an excellent clinical outcome without compromising the quality of life. The PLATIN-1 trial delivers eminent baseline data for future studies using modern irradiation techniques.

Keywords: prostate cancer, radiotherapy, pelvic nodes, IMRT, tomotherapy®, simultaneous integrated boost, elective node irradiation

INTRODUCTION

With an estimated incidence of 164,690 new prostate cancer cases in the United States in 2018, carcinoma of the prostate remains the most common malignancy in men (1). For intermediate and high-risk disease according to d'Amico criteria (2), surgery or radiotherapy are available curative, definitive treatment options. Although survival rates are much better compared to other malignant tumors, biochemical relapse occurred in a substantial proportion of patients. For dose-escalated irradiation, prostate-specific antigen (PSA) progression was reported in up to 35% of patients with intermediate or high-risk prostate cancer after 5 years (3). Many patients were diagnosed with lymph node metastases which are usually not included in the initial radiation field. Results from prostate-specific membrane antigen (PSMA) imaging showed positive, pelvic lymph nodes in up to 43.7% (4). Therefore, many studies focused on the role of whole pelvic radiotherapy (WPRT) including pelvic nodes. In 2003, Roach et al. observed a statistically significant improved progression-free survival for patients undergoing WPRT plus neoadjuvant and concurrent hormonal therapy (NCHT) in comparison with prostate-only irradiation (POI) (5). However, the benefit lost the level of significance with longer follow-up (6). This trial and several studies using more conventional radiation techniques reported on acute and/ or late gastrointestinal (GI) and genitourinary (GU) toxicities which occurred more frequently compared to POI (7–9). Moreover, there are some other trials questioning the clinical benefit of WPRT (10, 11).

By integration of modern radiation techniques like intensity-modulated radiotherapy (IMRT), a reduction of acute and late toxicities seems to be possible (12–14). The PLATIN-1 (Prostate and Lymph Node Irradiation with Integrated-Boost-IMRT after neoadjuvant hormonal therapy [NHT]) trial evaluates the role of modern IMRT/ image-guided radiotherapy (IGRT) technique for treatment-naïve prostate cancer patients undergoing optimized WPRT. By using a moderately hypofractionated, simultaneous integrated boost (SIB) to the prostate, the current study also analyzes the influence of moderate hypofractionation on biological effectiveness in a definitive treatment setting after NHT (15). The present article reports on late toxicity and clinical outcome of this cohort.

MATERIALS AND METHODS

Study Participants and Procedures

The present study was approved by the local ethics review board (S-034/2009). In total, 40 men with treatment-naïve and histologically proven prostate cancer were prospectively enrolled in the PLATIN-1 trial between May 2009 and December 2012. All patients had no suspicious lymph node in pelvic computed tomography (CT) or magnetic resonance imaging (MRI) and an estimated risk of pelvic lymph node involvement exceeding 20% according to the Roach formula {2/3 PSA + [(GS−6) × 10]}(16). Antihormonal therapy (AHT) was authorized for all patients and consisted of a minimum of 2 months neoadjuvant treatment and the advice of continuation for at least 24 months after irradiation if tolerated. AHT included luteinizing hormone-releasing hormone (LHRH) agonists or antiandrogen medication.

Treatment planning and radiation were performed as described previously (15). In summary, patients were irradiated once daily and five fractions a week. The prescribed dose of 95% of the planning target volume of the pelvic lymph nodes (PTV-L) was 51.0 Gray (Gy) with a single dose of 1.5 Gy. A simultaneously integrated boost (SIB) of 76.5 Gy was prescribed to 95% of the PTV prostate (PTV-P) with a single dose of 2.25 Gy. Irradiation was performed with helical IMRT/ IGRT using a Tomotherapy® system (Accuray, USA).

Follow-Up and Assessment of Toxicity and Quality of Life (QoL)

Before irradiation, during treatment (weekly) and at the end of the treatment prostate-specific symptoms and treatment toxicity were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Effects (NCI CTCAE) version 3.0. Assessment of QoL using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) was first performed before treatment. The PSA level was assessed every 3 months. The follow-up schedule included visits at 2.5, 6, 12, 18, and 24 months including toxicity records and QoL records (performed only at 6, 12, and 24 months). Patients were regularly followed thereafter based on local standard operating procedures. This included measurement of PSA levels and toxicity assessment. The median follow-up was 71 months.

Statistical Analysis

The primary objective was the examination of biochemical progression-free survival (bPFS), clinical relapse-free survival (cRFS) and overall survival (OS) for patients suffering from non-metastatic prostate cancer undergoing both IGRT/IMRT and AHT. Furthermore, the secondary objectives were to examine late toxicity and prostate specific symptoms. Biochemical failure was defined according to the Phoenix criteria (17), clinical failure was defined as the existence of local recurrence or metastases detected by CT including PET-CT, MRI or bone scan, which were performed after clinical evidence based on symptoms. The Kaplan-Meier method was used for calculating bPFS, cRFS, and OS.

All statistical analyses were performed by using SPSS v.25.0 and a P-Value of <0.05 was defined as significant.

RESULTS

Patients

Due to an increase of PSA levels during NHT, two patients were excluded from the study before radiotherapy. The patient's characteristics of the remaining 38 were previously described by Habl et al. (15). Median age was 70.5 years with a range of 51–75 years. According to the Roach formula, a risk of LNI of more than 40% was calculated for 6 patients (15.8%) of the cohort while 32 patients (84.2%) had a risk of 20–40%. Twenty-seven patients (71.1%) received LHRH agonists, seven patients (18.4%) antiandrogen therapy (bicalutamide) and four patients (10.5%)

TABLE 1 | Patient's characteristics.

Characteristics	Number of patients
Number of patients	38
Age [years], median (range)	70.5 (51–75)
T-Stage, *n* (%)	
T1	21 (55.2%)
T2	8 (21.1 %)
T3	8 (21.1%)
T4	1 (2.6%)
Gleason score, *n* (%)	
≤6	0 (0.0%)
7	18 (47.4%)
≥8	20 (53.6%)
iPSA [ng/ml], median (range)	17.5 (0.5–120.0)
Risk-group according to d'Amico, *n* (%)	
Low	0 (0.0%)
Intermediate	3 (7.9%)
High	35 (92.1%)
Risk of LNI according to Roach formula *n* (%)	
>20–40%	32 (84.2%)
> 40 %	6 (15.8%)
AHT	
<24 months	25 (65.8%)
24–36 months	8 (21.1%)
>36 months	5 (13.2 %)

LNI, lymph node involvement; AHT, antihormonal therapy.

both (complete androgen deprivation). Only 8 patients (21.1%) received AHT for the required period of 24 to 36 months. Twelve patients (31.6%) stopped AHT within 6 to 24 months of follow-up, 13 patients (34.2%) after a maximum period of 5 months (including NHT) due to intolerance or side effects. AHT was continued for five patients (13.2%) until the current evaluation (**Table 1**). For all patients, irradiation was performed as specified in the protocol.

Clinical Outcome

After a median follow-up of 71 months (range: 5–95 months), 34 out of 38 patients (89.5%) were still alive. One patient died almost 7 months after irradiation due to a newly diagnosed, metastasized esophageal cancer. One patient died after 61 months due to cardiac disease, another after 44 months due to acute myeloic leukemia. For one patient, the reason for death is unknown. The 2-year and 5-year overall survival (OS) rates were 97.3% (95% confidence interval [CI] 96.4–98.2%) and 94.3% (95% CI 93.1-95.6%), respectively (**Figure 1**). In 21.5% (8 patients) of the cohort, a biochemical relapse occurred. For four patients with PSA relapse, further imaging with MRI, CT and/ or bone scan was performed. One patient was diagnosed with local recurrence, two patients with bone metastases. No nodal relapse within the pelvis occurred. A biochemical progression-free survival (bPFS) of 89.2% (95% CI 87.6–90.8%) and 83.6% (95% CI 81.6–85.6%) was observed at 2 and 5 years, respectively (**Figure 2**).

Late Toxicity

At the time of last follow-up, toxicity data were available for 29 patients. We observed no grade 3 and 4 late toxicity with regard to gastrointestinal (GI) side effects. Two men (5.3%) reported on grade 1 enteritis, one patient (2.6%) on grade 2 enteritis with pain and moderate bleedings. No proctitis or diarrhea occurred in our cohort at the time of follow-up.

For patients undergoing helical IMRT, there was no grade 4 genitourinary (GU) toxicity. The cumulative incidence of grade 3 urinary side effects was 2.6% including one patient with stress incontinence. Urge incontinence occurred for 9 patients (23.7%; grade 1) and 3 patients (7.9%; grade 2), respectively. Only one patient (2.6%) reported on a light cystitis (grade 1). Without current AHT, five patients (13.1%) reported on grade 2/3 erectile dysfunction, while grade 2/3 loss of libido was found for 16 patients (42.1%). Two patients (5.3%) were identified with grade 1 edema and three patients (7.9%) with grade 2 edema at the time of follow-up. No grade 3 or 4 edema was observed for the entire cohort (**Table 2**).

DISCUSSION

After a median follow-up of 71 months, IMRT/ IGRT of the prostate and pelvic nodes continued to be well-tolerated without excessive side effects. For our cohort of 38 men treated in the present study, no severe (grade 3/4) GI toxicity occurred. The Genitourinary Study Group (GETUG)-1 trial – one of the largest prospective studies investigating the role of pelvic node irradiation–reported on a grade 3/4 toxicity rate for the digestive tract of 10.7% after a median follow-up of 42.1 months. In this trial, irradiation was performed with a four-field box to a total dose of 46 Gy to the pelvis and a maximum of 70 Gy to the prostate (10). Although total dose to the prostate was lower compared to our PLATIN-1 trial according to former guidelines, the reduced number of side effects in the present study can be explained by the use of modern treatment techniques like IMRT in combination with daily imaging (IGRT). This is in accordance with other studies using IMRT: Pervez et al. observed no grade 3/4 late GI toxicity in a group of 60 patients undergoing irradiation of the pelvic nodes and prostate (total dose: 45/68 Gy) in 25 fractions at 5 years follow-up timepoint (18). Similar results were described for GU side effects, however, a direct comparison is difficult due to a lack of detailed data in the majority of other reports and a limited number of feedbacks in our cohort. In the present study, 68.9% of the patients were unwilling or unable to provide any information about their erectile function. Nevertheless, in addition to the reported grade 2/3 erectile dysfunction rate of 14.3% for the current study, a high number of genital constraints might automatically result from AHT and the increasing age of the patients. In the Prostate Testing for Cancer and Treatment (ProtecT) trial, a group of 1,643 men with a median age of 62 years was included. At 72-months follow up, erection not firm enough for intercourse was found for 73% in the radiotherapy compared to 70% in the active surveillance (AS) group (19). Even watchful waiting caused

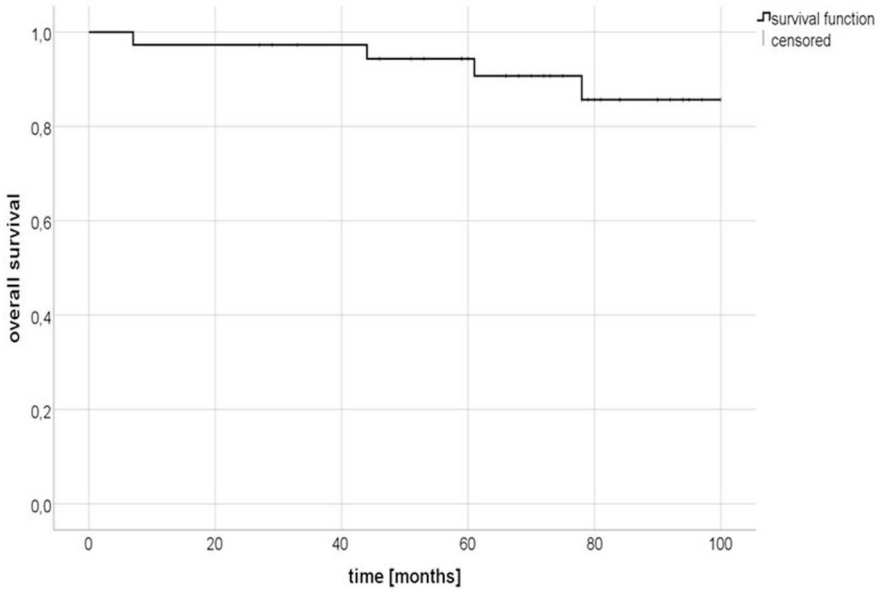

FIGURE 1 | Kaplan-Meier estimates of overall survival (OS).

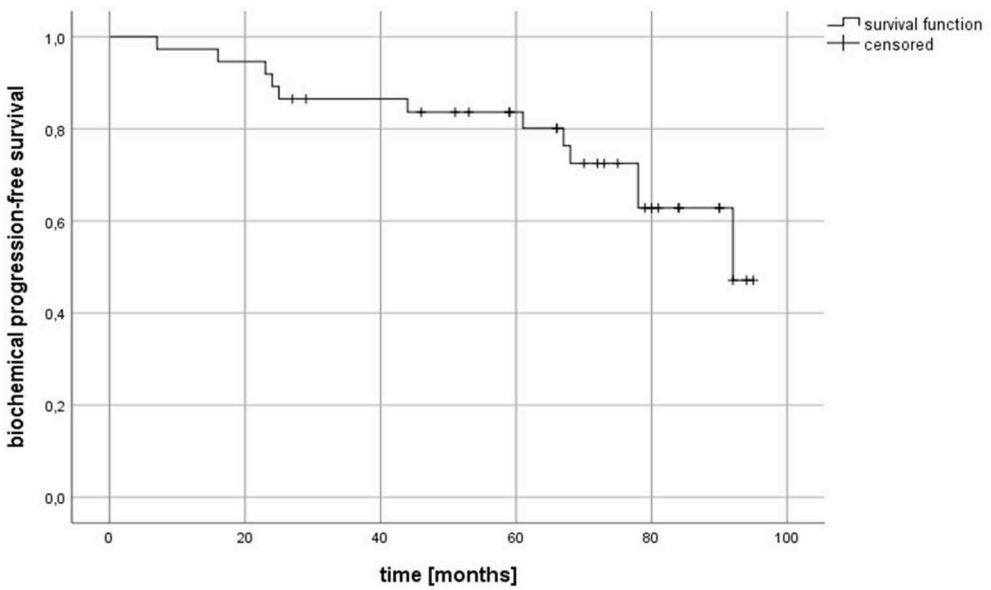

FIGURE 2 | Kaplan-Meier estimates of biochemical progression-free survival (bPFS).

similar limitations in 80% of men in the Scandinavian Prostate Cancer Group-4 at 144-months follow-up, although the median age of this cohort was also younger (64 years) than that of the present PLATIN-1 trial (70.5 years) (20). Age might the relatively high rate of incontinence in our cohort. In total, 21% reported on grade 2/3 stress incontinence while urge incontinence was observed for 7.9% at the time of follow-up. In a phase 1/2 dose-escalation study from UK, the 2-year cumulative rates of grade 2+/grade 3+ bladder toxicity were 4.2%/ 4.2% (cohort 1), respectively. This study investigated the role of IMRT to the prostate (total dose of 70 to 74 Gy) and pelvic lymph nodes (total dose for cohort 1: 50 Gy) including 25 patients with prostate cancer (21). However, our cohort also showed high rates of incontinence before irradiation. Almost 16 % of men included in the PLATIN-1 trial complained about grade 1/2 incontinence at baseline. Overall quality of life assessed by the EORTC QLQ-C30 questionnaire remained largely stable at 71-months follow-up. Global health score was 68.1, which is in accordance

TABLE 2 | Late toxicity (median follow up: 71 months; $n = 38$).

Characteristics	Grade 0	Grade 1	Grade 2	Grade 3	Unknown
Gastrointestinal (GI) side effects					
Enteritis	26 (68.4%)	2 (5.3%)	1 (2.6%)	0 (0.0%)	9 (23.7%)
Proctitis	29 (76.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (23.7%)
Diarrhea	29 (76.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (23.7%)
Genitourinary (GU) side effects					
Cystitis	28 (73.7%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	9 (23.7%)
Urge incontinence	17 (44.7%)	9 (23.7%)	3 (7.9%)	0 (0.0%)	9 (23.7%)
Stress incontinence	22 (57.9%)	0 (0.0%)	6 (18.4%)	1 (2.6%)	9 (23.7%)
Dysuria	16 (42.1%)	1 (2.6%)	1 (2.6%)	0 (0.0%)	20 (52.6%)
Erectile dysfunction					
> Without current AHT	2 (5.3%)	4 (10.5%)	1 (2.6%)	4 (10.5%)	24 (63.2%)
> With current AHT	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	2 (5.3%)
Loss of libido					
> Without current AHT	1 (2.6%)	7 (18.4%)	7 (18.4%)	9 (23.7%)	11 (28.9%)
> With current AHT	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (7.9%)	0 (0.0%)
Edema	22 (57.9%)	2 (5.3%)	3 (7.9%)	0 (0.0%)	11 (28.9%)

AHT, antihormonal therapy.

with EORTC reference values of prostate cancer patients. Compared to month 24, there was a significant improvement of global health status (15). One explanation might be that also protracted, radiotherapy-related symptoms disappeared and AHT was finished for almost all patients. Our observations are at least comparable to a recent report published by Lips et al. comparing QoL in patients with locally advanced prostate cancer after 76 Gy IMRT vs. 70 Gy conformal radiotherapy. The authors concluded that dose-escalated IMRT/ IGRT can be performed without deterioration in QoL (22). The expansion of the target volume by adding pelvic lymph nodes also seems to cause no substantial change, if modern radiation technique is used. At least in our cohort of 38 men undergoing helical IMRT, no significant variations for QoL scores were observed compared to reference values.

However, one crucial question remains: Is there an oncological benefit for pelvic node irradiation in non-metastatic patients with prostate cancer? While several retrospective and small prospective studies report on promising results (9, 18, 21, 23–25), two randomized phase III trials failed to show an improved survival for patients undergoing pelvic irradiation (**Table 3**): The last update of the GETUG-01 randomized study evaluating 446 men with prostate carcinoma summarized, that pelvic nodes irradiation was not able to improve event-free survival (EFS) or OS after a median follow-up of 11.4 years (11). For the RTOG 9413 cohort including 1,322 patients, an improved PFS was observed for NHT plus WPRT compared with NHT plus prostate-only radiotherapy (PORT) and WPRT and adjuvant hormonal therapy after a median follow-up of 8.8 years. Nevertheless, WPRT did not show an improvement in OS compared to PORT while leading to an increased risk of grade 3 or worse GI toxicity with the use of conventional four-field technique (6). In the present trial, IMRT/ IGRT of the pelvic lymph nodes with a simultaneous integrated boost to the prostate achieved no nodal relapse and excellent 5-year bPFS and OS of 83.6% and 94.3% considering the high rate of high-risk patients and short-term (< 24 months) AHT. Although the PLATIN-1 trial was a prospective trial using modern radiation technique, the current study was not powered to provide sufficient data regarding oncological outcome. Due to the small number of patients, the non-randomized setting and a certain number of men with only short-term AHT–major limitations of our study—there is still a lack of evidence regarding prophylactic irradiation of pelvic nodes for patients with prostate cancer. Both, the GETUG-01 and the RTOG 9413 were not able to show a general benefit for WPRT, however, from today's view several parameters could limit the results of them: Besides broad inclusion criteria (GETUG-01) and a low total dose according to former guidelines, the four-field technique without image guidance could have resulted in insufficient doses within some areas like the presacral or external iliac nodes. Therefore, the present PLATIN-1 trial formed a solid basis for ongoing trials using modern photon or proton irradiation and was an important contribution to evaluate prophylactic pelvic node irradiation using IMRT/ IGRT, but more evidence is needed about whether or not an expanded target volume is beneficial to men with non-metastatic, high-risk prostate cancer. With the end of recruitment for one upcoming study, the RTOG 0924 trial, expected by late summer 2019 (6), further information should be available.

In summary, the present PLATIN-1 trial confirms that helical IMRT of the pelvic nodes with a simultaneous integrated boost to the prostate can be performed without severe toxicity and significant deterioration in QoL. Even when our trial achieved excellent oncological outcome, there is still a need for further randomized studies evaluating the role of prophylactic, pelvic irradiation for patients with prostate carcinoma and a high risk for LNI.

TABLE 3 | Overview of prospective trials evaluating the role of WPRT.

References	Trial design/number of patients (*n*)	Radiation technique	Total/single dose pelvic nodes	Total/ single dose prostate	AHT	Follow-up	Results
Adkinson et al. (23)	Prospective, non-randomized phase I trial; $n = 53$	Helical IMRT or step-and-shoot IMRT	56.0/2.0 Gy	70/2.5Gy	88.7% for 6–28 months	25.4 months	Preliminary biochemical control of 81.2% at 3 years; No grade 3+ late GI toxicity, one grade 3 GU toxicity
Di Muzio et al. (26)	Single-center, prospective, non-randomized phase I-II trial; $n = 211$	Helical IMRT	51.8/ 1.85 Gy (for intermediate- and high-risk)	71.4/2.55 Gy or 74.2/ 2.65 Gy	Intermediate risk: 12 months; high-risk 36 months	5 years	5-year bRFS 93.7%, 5-year OS 88.6%; Late grade 3+ toxicity of 5.9% (GU) and 6.3% (GI)
Magli et al. (24)	Single-center, prospective, non-randomized phase II trial; $n = 41$	Step-and-shoot IMRT	50.0/ 2.0 Gy	67.5/ 2.7 Gy	12–24 months	65.4 months	5-year bRFS 95.1%; No grade 3+ late toxicity
Pervez et al. (18, 27)	Single-center, prospective, non-randomized phase II trial; $n = 60$	Helical IMRT	45.0/ 1.8 Gy	68.0/ 2.7 gy	24–36 months (NHT up to 6 months)	63 months	5-years OS 86.7%; 5-year freedom from biochemical failure 91.7%; No grade 3+ GI toxicity; grade 3 GU toxicity 2.4%
Pommier et al. (GETUG-01) (11)	Multicenter, prospective randomized trial; $n = 446$	Conventional four-field technique	46.0/2.0 Gy or 46.8/1.8 Gy or 45.0/ 2.25Gy*	66.0-70.0/2.0 Gy or 68.4–72.0/1.8 Gy or 65.25–69.75/2.25 Gy*	High-risk: NHT for 4-8 months and concomitant (about 60% in each arm)	11.4 years	10-year EFS 57.6% (WPRT) vs. 55.6% (PORT); 10-year OS 74.9% (WPRT) vs. 73.6% (PORT);
Roach et al. (RTOG 9413) (6)	Multicenter, prospective randomized trial (2 × 2 factorial design); $n = 1,323$	Conventional four-field technique	50.4/ 1.8 Gy	70.2/1.8Gy	NHT: 2 months and during RT adHT: start with RT	8.8 years	10y-PFS 28.4% (NHT+WPRT)/ 23.5% (NHT+PORT)/ 19.4% (WPRT+adHT)/30.2% (PORT+adHT); No OS difference (346 patients alive); late grade 3+ GI toxicity of 7% for NHT+WPRT

**only 4 fractions/ week 3D-CRT, 3D-conformal radiotherapy; adHT, adjuvant hormonal therapy; AHT, antihormonal therapy; bRFS, biochemical relapse-free survival; BDFS, biochemical disease-free survival; EFS, event-free survival; NHT, neoadjuvant hormonal therapy; GI, gastrointestinal; GU, genitourinary; IMRT, intensity modulated radiation therapy; OS, overall survival; PORT, prostate-only radiotherapy; WPRT, whole pelvis radiotherapy.*

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript/supplementary files.

AUTHOR CONTRIBUTIONS

SAK and EW were the main investigators who collected and evaluated the clinical information. AS conducted the statistical analysis and critically evaluated the paper. SK, MH, MU, FS, and GH assisted the main author in patient enrollment, data collection and revising the final draft. The paper was wrote by SAK and critically evaluated by KS, KH, and JD. KH and JD designed and supervised the prospective trial. All authors read and approved the final version of the paper.

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MRI-Derived Radiomics to Guide Post-operative Management for High-Risk Prostate Cancer

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Purpose: Prostatectomy is one of the main therapeutic options for prostate cancer (PCa). Studies proved the benefit of adjuvant radiotherapy (aRT) on clinical outcomes, with more toxicities when compared to salvage radiotherapy. A better assessment of the likelihood of biochemical recurrence (BCR) would rationalize performing aRT. Our goal was to assess the prognostic value of MRI-derived radiomics on BCR for PCa with high recurrence risk.

Methods: We retrospectively selected patients with a high recurrence risk (T3a/b or T4 and/or R1 and/or Gleason score>7) and excluded patients with a post-operative PSA > 0.04 ng/mL or a lymph-node involvement. We extracted IBSI-compliant radiomic features (shape and first order intensity metrics, as well as second and third order textural features) from tumors delineated in T2 and ADC sequences. After random division (training and testing sets) and machine learning based feature reduction, a univariate and multivariate Cox regression analysis was performed to identify independent factors. The correlation with BCR was assessed using AUC and prediction of biochemical relapse free survival (bRFS) with a Kaplan-Meier analysis.

Results: One hundred seven patients were included. With a median follow-up of 52.0 months, 17 experienced BCR. In the training set, no clinical feature was correlated with BCR. One feature from ADC (SZE_{GLSZM}) outperformed with an AUC of 0.79 and a HR 17.9 ($p = 0.0001$). Lower values of SZE_{GLSZM} are associated with more heterogeneous tumors. In the testing set, this feature remained predictive of BCR and bRFS (AUC 0.76, $p = 0.0236$).

Conclusion: One radiomic feature was predictive of BCR and bRFS after prostatectomy helping to guide post-operative management.

Keywords: magnetic resonance imaging, prostatic neoplasms, radiomics, machine learning, treatment failure

KEYPOINTS

- Texture analysis, based on prostatic MRI, provides an informative assessment of tumoral heterogeneity which could help to predict biochemical failure risk.
- Management of patients could be performed with a greater confidence.

INTRODUCTION

Prostate cancer (PCa) is the most common cancer among men with ∼165.000 patients diagnosed with the disease in 2017 in the United States, and more than 29.400 annual deaths (1). Radical prostatectomy (RP) is one of the treatments of choice for patients with PCa and is associated with excellent long-term outcomes. Nevertheless, biochemical recurrence (BCR) after RP occurs in 50% of patients, particularly in those who harbor high risk features like locally advanced disease (T3-4), positive margins (R1) or high Gleason score, and is predictive of metastatic relapse and cancer specific death (2). Adjuvant radiotherapy (aRT) of the prostatic bed has been proposed and proven to be effective in 3 randomized controlled trials (EORTC 22911, SWOG 8794, ARO 96-02) comparing aRT versus observation (3–6). All three studies showed a significant benefit for aRT in biochemical relapse-free survival (bRFS), but results were conflicting in terms of metastases-free and overall survival (6). In addition, patients receiving aRT experienced higher rates of grade 2 or higher gastrointestinal and genitourinary toxicities (5). Moreover, based on clinical and histopathological features alone, patient selection remains insufficient. In a multi-institutional study and after a 5-years follow-up (7), ∼50% of the high–risk, operated on patients were still BCR-free and were without the certainty of the benefits from aRT. Therefore, radiation therapy (RT) is often delivered only at the time of BCR as it would then be limited solely to relapsing patients, and would reduce treatment-related side effects. Indeed, some data suggest that early salvage RT (sRT) is as efficient as aRT in this context (8). However, a low pretreatment serum prostate-specific antigen (PSA) level is known to be the strongest predictor of response after sRT, and the question remains as to whether sRT at the first time of recurrence compromises cancer control compared to aRT (9).

The natural history of relapse after radical prostatectomy (RP) is heterogeneous even in patients with high risk features and may reflect a broad range of underlying tumor pathophysiological processes. Recently, in addition to conventional parameters on magnetic resonance imaging (MRI) used to diagnose and stage cancer, there has been a growing interest in the high-throughput extraction of quantitative features from medical images, denoted radiomics. Radiomic features are statistical, geometrical, or textural metrics designed to quantify tumor intensity, shape and heterogeneity, which have been shown to reflect intratumorally histopathological properties and to provide prognostic information in several pathologies including PCa (10–12). For example, the GLSZM is a matrix focusing on the size of areas (or zones) of similar gray-level values. The more heterogeneous the intensities of the voxels in the tumor image are, the smaller the areas (or zones) of similar gray-level become, resulting in lower values of the GLSZM-based features.

An MRI-derived radiomics signature predictive of the outcome of patients after RP has not yet been described. We aimed to develop and validate such a signature with prognostic value in patients with high risk PCa, in order to guide the patients' selection and therapeutic management, especially regarding the use of aRT.

Abbreviations: aRT, Adjuvant radiotherapy; PCa, Prostate cancer; RP, Radical prostatectomy; BCR, Biochemical recurrence; R1, Positive margins; RT, Radiation therapy; sRT, Salvage radiation therapy; PSA, Prostate-specific antigen; bRFS, Biochemical relapse-free survival; MRI, Magnetic resonance imaging; IBSI, Image Biomarker Standardization Initiative; ROC, Receiver operating characteristic; PC, mean absolute Pearson's coefficient; AUC, Area under curve.

METHODS

Patients Selection

All patients with histologically proven PCa patients treated with RP, with or without a lymphadenectomy from 2010 to 2016 at Brest, were retrospectively considered. Among them, those with high-risk features on the pathologic specimen, namely pT3a-b or pT4, and/or R1, and/or Gleason 8-10, and available preoperative pelvic MRI were retrospectively included.

All patients with lymph node involvement after extensive lymphadenectomy were excluded, as were those whose PCa diagnosis was obtained after cystoprostatectomy for bladder carcinoma. Patients who received adjuvant treatment (aRT and/or adjuvant androgen deprivation therapy) or those with post-operative PSA (PSA $>$ 0.04 ng/mL at 3 months following RP) were also excluded.

All patients for which the MRI were not retrievable were excluded.

A follow-up of 24 months was mandatory, except in case of BCR.

Outcome

The primary endpoint was the prediction of BCR, which was defined as a PSA increase above 0.2 ng/mL confirmed on two successive blood samples. The secondary endpoint was the prediction of bRFS.

MRI

The MRI were performed on two different MRI scanners: a Phillips 3T (Philips Healthcare, The Netherlands) and a Siemens 1.5T (Siemens Healthcare, Malvern PA). Both scans were performed using a 6-channel phased-array surface coil. Patients were scanned in supine position. MRI sequences included axial turbo spin echo T2-weighted and axial diffusion sequences using multiple *b*-values (maximal *b*-value: 1,000 s/mm^2), along with a perfusion sequence for Philips 3T and a T1 sequence with gadolinium injection for Siemens 1.5T. ADC maps were calculated using each corresponding manufacturer's software. MRI scans were performed according to ESUR guidelines. Full details about acquisition parameters are provided in the **Table 1**.

TABLE 1 | Summary of MRI scan acquisition parameters.

Acquisition parameters	Siemens 1.5T ($n = 75$)	Philips Achieva 3T ($n = 32$)
Magnetic field strength (Tesla)	1.5T	3T
T2-Weighted		
Matrix (pixels)	192 × 192	268 × 268
Field of view (mm)	250 × 250	320 × 320
ET (ms)	110	90
RT (ms)	2,500	4,500
Slice Thickness (mm)	1.5	1.5
ADC map		
Matrix (pixels)	128 × 128	144 × 144
Field of view (mm)	200 × 200	240 × 240
ET (ms)	80	80
RT (ms)	2,300	2,300
Slice Thickness (mm)	3.5	3.5
Diffusion gradient	B50-400-1000	B100-600-1000

RT, repetition time; ET, echo time.

Clinical Features

The following clinical variables were collected from medical records: size of the delineated tumor, T stage (extra-capsular extension, seminal vesicle invasion), Gleason score, pre- and post-operative PSA, margins status, age at surgery and the CAPRA-S Score (13). All categorical clinical features were remapped to ordinal values.

Tumor Delineation

Prostatic tumors were semi-automatically delineated on all slices using the Fast GrowCut Effect extension available in 3D Slicer® v4.8.0, on both the ADC and T2-sequences using all sequences available on the pre-operative MRI (ADC, T2-weighted, diffusion, perfusion, T1 with gadolinium injection). An example is illustrated in **Supplementary Figure 1**.

Radiomic Features

Prior to extraction of features, wavelet filters were applied to each MRI sequence. The high-pass and low-pass versions of the wavelet (14) basis function coiflet 1 were consecutively applied in the three directions of space, thereby creating eight filtered images: LLL, LLH, LHL, LHH, HLL, HLH, HHL, and HHH. Including the original image, nine images per MRI sequence were thus available for radiomics analysis. One hundred seventy-two radiomic features were extracted, using MathLab®, following the implementation guidelines defined by the Image Biomarker Standardization Initiative (IBSI) (15) workflow (**Supplementary Figure 2**). The textural radiomic features were implemented with different parametrization settings (see **Supplementary Figure 2**). As a result, the total available radiomic variables per MRI sequence per patient was 27,376.

Statistical Analysis

The cohort was first randomly split into two sets, 2/3 for training ($n = 70$) and 1/3 for testing ($n = 37$). A machine learning workflow was subsequently employed to reduce this very large initial number of radiomic features to a relevant subset more suitable for robust statistical analysis. This selection was performed in the training set using an aggressive false discovery reduction procedure relying on stability checks, robustness score, and Pearson's correlation (PC) checks (16). More details about this procedure is provided below: The training set was sub-divided 100 times into different subsets with a 2:1 size ratio using stratified random sub-sampling. The PC of each radiomic feature with BCR was calculated for each of the 100 subsets. A given feature was considered stable if 95% of the absolute PC value were above 0.3. Following stability checks, the optimal extracted parameter was identified for each remaining feature in the set by maximizing the mean absolute PC, such that only one variant per feature was retained. Finally, intra-correlation between features still present in the set was analyzed and features with a coefficient >0.7 were discarded by prioritizing those with the highest PC.

Imbalanced distribution of the clinical outcome (BCR) was adjusted using the SMOTE technique (17) which was applied to the whole teaching set prior to the start of feature set reduction.

The reduced subset of radiomic features identified through the process described above, as well as all clinical variables, were then assessed for their predictive ability with univariate (ROC curves) and multivariate (Cox regression) analyses. Optimal cut-off values for each feature were defined via the Youden Index in the ROC curves. Based on additive combinations between each radiomic and clinical variable, three models were built and evaluated: radiomics-only, clinical-only, and radiomics combined with clinical. The performance of these models was evaluated using Kaplan-Meier curves and the log-rank test in the testing set.

To minimize the effects of variability between different types of scanners (1.5T vs. 3T), radiomics features were separately normalized (using z-score standardization, i.e., mean 0 and standard deviation 1) per scanner type and per training and testing set (16).

Finally, the predictive power of each model was then assessed on the overall population depending on the type of scan (1.5T vs. 3T).

Statistical analysis was performed using MedCalc v13.1.0.

Ethical Considerations

This study was approved by the hospital ethical committee (PREBOP 29DRC18.0108) and all patients gave their consent for the use of their clinical and imaging data.

RESULTS

Patients Characteristics

Between January 2010 and December 2016, 505 patients underwent RP ± extensive pelvic lymphadenectomy. According to pathological analysis, 272 patients (54%) presented high-risk features (T3a/T3b or T4, and/or R1, and/or Gleason 8-10).

Overall, 107 patients were excluded because of positive lymph nodes ($n = 58$), follow up <24 months ($n = 37$) or post-operative PSA >0.04 ng/mL ($n = 40$). Among the remaining patients

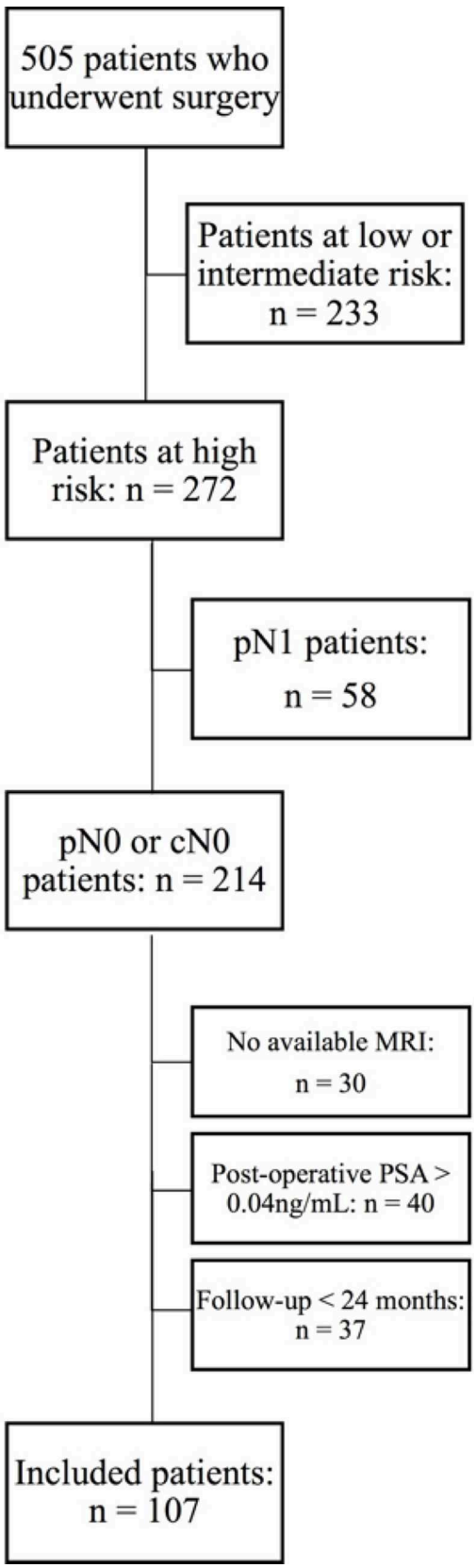

FIGURE 1 | Flowchart of the patients selection.

TABLE 2 | Patients and tumors characteristics in training and testing sets.

Patients characteristics	Training *N* = 70	Testing *N* = 37	*p*-value
Age at diagnosis (mean, y)	65	65	0.81
PSA (mean, ng/mL)	9	9	0.81
MRI characteristics			
Siemens 1.5T (%)	67	73	0.69
Philips 3T (%)	33	27	
Surgical characteristics			
Pathological tumor stage			
pT1-pT2 (%)	33	41	0.57
pT3 (%)	67	60	
pT4 (%)	0	0	
Nodal status			
pN0 (%)	85	78	0.56
cN0 (%)	15	22	
Surgical margins			
R0 (%)	41	41	0.91
R1 (%)	57	60	0.97
Rx (%)	2	0	0.78
Gleason score			
Gleason ≤7 (%)	84	89	0.69
Gleason >7 (%)	16	11	
Capra-S Score (median)	15.7	4	1,00
Post-operative PSA (mean, ng/mL)	0.01	0.01	1,00
bRFS (median, months)	46.3	38.4	0.11
Biochemical recurrence (%)	16	16	0.83
Follow-up (median, months)	56.5	53.6	0.56

PSA, prostate specific antigen, MRI, magnetic resonance imaging; bRFS, biochemical relapse free-survival.

($n = 137$), preoperative MRI was available for 107 (78%). The flowchart of patients' selection is available as **Figure 1**.

Clinical and histopathological characteristics did not significantly differ between the training and testing sets (**Table 2**). A majority of patients had pT3 disease (65%) and microscopic involved margins (67%). No pT4 (0%) patients were finally included. Seventy percent of scans ($n = 75$) were acquired on the Siemens scanner and 30% ($n = 32$) on the Philips scanner (**Table 1**).

Outcome

Median follow-up was 49.9 months (range, 24–100.3). Among the selected 107 patients, BCR occurred in 17 patients (16%) after a median duration of 24 months (4.14–83.1 months). Median bRFS was 42.6 months (4.14–100.3 months).

Within the relapsing population and at last follow-up, 7 (41%) patients experienced a clinical and/or radiological relapse with 3 (18%) having lymph node metastasis and 4 (24%) distant metastasis. All other patients accounted for BCR alone.

Training Set

Using univariate analysis, no clinical feature was significantly correlated with BCR. The most predictive model of survival without BCR was obtained with the combination of pre-operative

PSA and age at surgery. The association between clinical and histopathological features and BCR are shown in the **Table 3**. This clinical model (age >65 y and pre-operative PSA >5.6) resulted in an AUC of 0.76 (sensitivity 82%, specificity 70%, $p = 0.0002$) and was also significantly associated with bRFS with a hazard ratio (HR) of 12.2 ($p = 0.0005$; **Figure 2A**). All individual ROC curves for clinical features are provided in the **Supplementary Figure 3**.

Of note, tumor volume was not associated with BCR (AUC 0.57).

The feature set reduction technique reduced the number of radiomic features to 10 non-redundant, uncorrelated features (**Supplementary Table 1**), which on univariate analysis were all significantly associated with BCR (**Table 4**). On multivariate analysis, three of these 10 radiomic features remained strongly correlated with BCR: SZE_{GLSZM}, $SZLGE_{GLSZM}$, $HGRE_{GLRLM}$ (feature description in **Supplementary Table 1**) with respective Odds-ratio of 16.6 ($p = 0.0266$), 8.8 ($p = 0.0255$), and 15.2 ($p = 0.0111$).

When the selected cut-off was applied (i.e., ≤0.528 for the SZE_{GLSZM} feature), no additive combination of radiomic features outperformed the ADC-based SZE_{GLSZM} feature alone with an AUC of 0.799 (sensitivity 91%, specificity 69%) and was therefore chosen for further evaluation. The model relying on this SZE_{GLSZM} feature alone resulted in strong stratification of patients for bRFS, with a HR of 17.9 ($p = 0.0001$) (**Figure 3A**).

All individual ROC curves for radiomic features are available in the **Supplementary Figure 4**.

The model combining clinical (pre-operative PSA and age at surgery) and radiomic feature (SZE_{GLSZM}) resulted in a high prediction of BCR with an AUC of 0.849, $p < 0.0001$ and a prediction of bRFS with a HR of 23.1, $p < 0.0001$) as shown in **Figure 4**.

Testing Set

When applied to the testing set the clinical model did not hold, with an AUC of 0.57 (sensitivity 67%, specificity 47%), therefore unable to predict bRFS ($p = 0.7$) (**Figure 2B**). On the contrary, the radiomics-only model held well, reaching an AUC of 0.76 (sensitivity 83%, specificity 68%) and predicting rBFS with an HR of 5.1 ($p = 0.0236$) (**Figure 3B**). The combined radiomics-clinical model underperformed with an AUC of 0.52 only.

Analysis According to the Type of MRI Scanner

No demographic differences were found between the two cohorts when focusing on types of MRI (**Supplementary Table 2**).

In the patients acquired with the Siemens 1.5T, the radiomics-only model reached an AUC of 0.76 (sensitivity 87%, specificity 66%, $p < 0.0001$), whereas in these acquired on the Philips 3T, the model had better performance with an AUC of 0.87 (sensitivity 100.00%, specificity 73%, $p < 0.0001$).

TABLE 3 | Correlation between clinical features and biochemical recurrence.

Clinical variable	Univariate analysis			Best cut-off	*p-value*	Odds-ratio
	AUC	Se	Sp			
Age at surgery (y)	0.60	91	51	>65.35	0.2262	10.16
Pre-operative PSA (ng/mL)	0.60	91	39	>5.6	0.2676	6.23
Gleason score	0.65	36	90	>7	0.154	
T stage	0.62	82	34	>T2c	0.1486	
Surgical Margins	0.61	60	61	>0	0.2308	
Post-operative PSA (ng/mL)	0.64	55	71	>0.01	0.1304	
Capra-S Score	0.55	64	53	>3	0.6522	

DISCUSSION

To our knowledge, this work is the first study investigating radiomics as a provider of potential image biomarkers to guide adjuvant treatment decision after RP.

Although none of the clinical variables were significantly predictive of BCR in the training set, combining the pre-operative PSA and age at surgery nonetheless allowed to predict BCR to an extent (AUC of 0.76). These two factors have already been reported to be prognostic for late BCR with 10 years of follow-up (18, 19). However, this clinical-only model demonstrated very low performance in the testing set (AUC 0.57). This could be partly explained by the small cohort, but also emphasizes the need

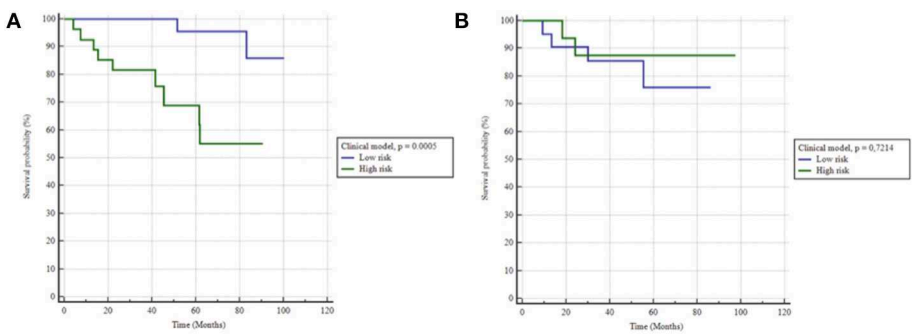

FIGURE 2 | Kaplan-Meier estimates of biochemical relapse free survival using the clinical model for **(A)** training and **(B)** testing set.

TABLE 4 | Correlation between radiomic features and biochemical recurrence.

Radiomic feature	Univariate Analysis					Multivariate Analysis	
	AUC	Se	Sp	Best cut-off	*p-value*	*Odds-ratio*	*p*-value
ADC3	0.84	91	69	≤0.528	<0.0001	16.6	0.0266
ADC6	0.79	73	81	≤0.014	0.0001	8.8	0.0255
ADC10	0.72	64	79	>93.042	0.0155	15.2	0.0111
ADC14	0.75	73	71	≤0.116	0.0005		
ADC18	0.74	82	69	≤0.067	0.0012		
ADC20	0.75	73	78	≤0.058	0.0036		
T1	0.78	91	66	≤324.593	0.0008		
T7	0.76	73	78	≤20.291	0.0009		
T10	0.80	100	59	>348.199	<0.0001		
T17	0.76	55	97	>94.004	0.0066		

ADC, ADC MRI-scan Sequence; T, T2 MRI-scan Sequence; AUC, Area Under the Curve; Se, sensitivity; Sp, specificity.
Each feature description can be found in ***Supplementary Table 1****.*

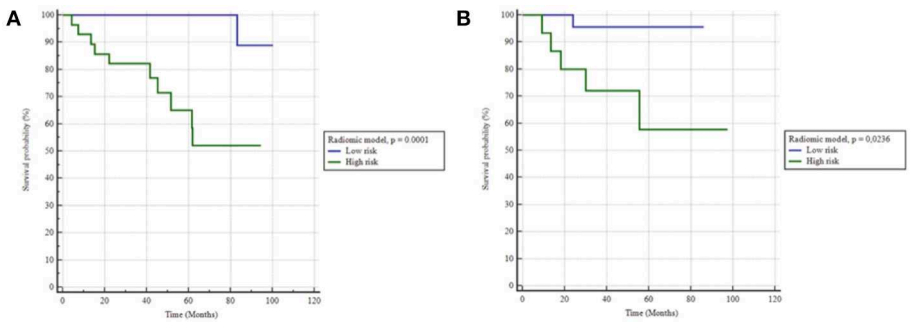

FIGURE 3 | Kaplan-Meier estimates of biochemical relapse free survival using the radiomics model in **(A)** training and **(B)** testing set.

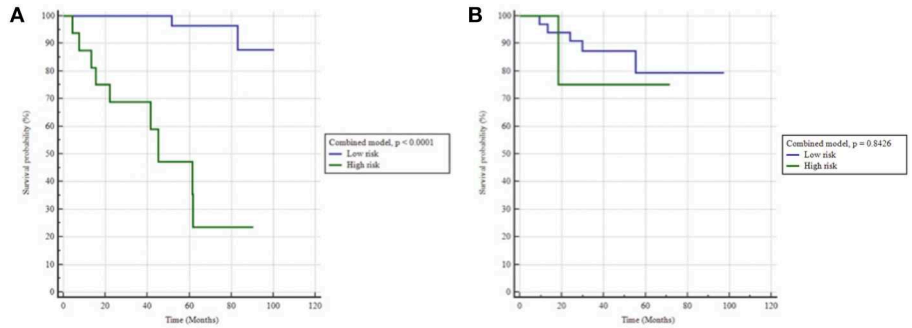

FIGURE 4 | Kaplan-Meier estimates of biochemical relapse free survival using the radiomics + clinical model in **(A)** training and **(B)** testing set.

for more robust predictive markers of BCR to adapt the adjuvant therapeutic strategy.

Radiomic features extracted from pre-therapeutic scans were found to have high predictive ability regarding BCR in PCa. One radiomic feature in particular, small zone emphasis (SZE_{GLSZM}), remained strongly correlated to the risk of BCR, independently from the clinical variables and other radiomic features. SZE is calculated on the Gray-Level Small Zone Matrix (GLSZM). GLSZM quantifies gray level zones, defined as the number of connected voxels sharing the same gray level intensity: a homogeneous tissue will thus have large zones of same gray-level values. On the contrary, a more heterogeneous tissue will exhibit more limited zones with small distances. SZE allows focusing on areas of small zones, particularly adapted to PCa. The lower SZE's value is, the more heterogeneous the intensity distribution in the image is (15).

Recently published EAU guidelines (20) recommend to systematically discuss adjuvant radiotherapy in case of high-risk

prostate cancer. If taken to an extreme, this could result in unnecessary treatment for more than 80% of patients (84% in our cohort), whereas the radiomics-based model, thanks to a predictive negative value of 96%, could allow a reduction of unnecessary treatment to 14/107 (13%) patients. This model could therefore be useful for a better selection of men eligible for aRT.

These findings are in line with several recent studies that investigated radiomics in PCa for diagnosis, prognosis and therapy. Very few studies have been published exploring the possibilities of texture analysis regarding Pca. To our knowledge, most of these studies (21, 22) implied radiomic features extracted from ADC and T2 sequences alone, these sequences being the most useful and robust sequences. Wibmer et al. evaluated MRI-derived radiomics for the detection of PCa in 146 patients (21). Four Gray level co-occurrence matrix (GLCM)-derived textural features (energy, entropy, correlation, and homogeneity) were significantly associated with the presence of PCa. Cameron et al. developed a quantitative radiomics approach for PCa detection combining all imaging sequences and aiming to improve MRI sensitivity and specificity (23). First, tumoral tissues were automatically delineated on a multiparametric MRI. The MAPS (Morphology, Asymmetry, Physiology, and Size) feature model was then used to score the candidate regions. The MAPS model outperformed all other feature sets with a sensitivity of 86%, a specificity of 88% and an accuracy of 87%.

These studies emphasize the recent development of computer-aided diagnosis solutions, waiting for larger datasets and better feature selection to be implemented on a daily basis. Exploring these new developments, a couple of studies were recently published. Based on two institutions (70 and 50 patients) and two different MRI scans, Shiradkar et al. developed a classifier based on radiomics and clinical variables with an AUC of 0.74 in the testing set (24). The main limitation of this work was that the model was trained using a cohort of patients who underwent heterogeneous treatment strategies (surgery, RT or androgen deprivation therapy), but it was then tested only on patients treated with surgery, who underwent a third type of MRI. Focusing on outcomes after RT, Gnep et al. showed the prognostic value of texture analysis after RT with androgen deprivation therapy (25). In their study, Haralick textural features derived from T2-w MRI were able to predict BCR following treatment in 74 patients after a median follow-up of 47 months, with a c-index of 0.90. However, no external validation was performed.

Interestingly, when we evaluated our radiomics model on the entire cohort, its prediction performance was higher on the subset of patients acquired with the 3T scan than the 1.5T scan (AUCs of 0.87 and 0.76, respectively). Numerous retrospective studies support the superiority of 3T over 1.5T scans when using the same type of body phased-array coil. In 2018, Ryznarova et al. showed that the best accuracy for tumor staging was obtained with a 3T MRI with DCE when compared to 3T MRI without DCE and 1.5T MRI with respective accuracy prediction scores of 90, 72, and 66% in a cohort of 103 patients (26).

Furthermore, acquisition parameters differed between the two scans especially the echo-time on T2 acquisitions and B-values on the ADC sequence, differences that we took into account when evenly dispatching patients into the training and testing cohorts.

The type of MRI scan being well-balanced in each cohort, we did not apply any *a posteriori* harmonization such as the Combat method (27), which could however be considered in future works to explore more in depth machine learning methodologies (e.g., 10-fold cross validation and alternate feature selection strategies)

Whether patients at high risk of BCR should receive adjuvant or sRT also remains a matter of debate. At present the choice between postoperative RT and early sRT should be based on a stratified risk approach in the context of a multidisciplinary meeting and according to individual patient preferences. The results of the meta-analysis of the RAVES, GETUG, and RADICALS randomized trials are expected in 2019 and will hopefully answer some of these questions. The availability of highly sensitive imaging modalities such as 68Ga-PSMA-PET will also probably change the therapeutic management of patients with a low PSA ranging between 0.2 and 0.5 ng/mL (28).

The radiomics approach applied to routinely acquired images for diagnosis has the great advantage of being cost-effective and non-invasive. Lately, recent advances in the field of genomics have led to the distribution of several genomic tests such as the Decipher Prostate Cancer test® (29). Among 256 high-risk PCa patients, the c-index of the genomic test was 0.79 (CI 95% 0.68–0.87) (30). Radiogenomics, the integration of quantitative imaging data with genomic signatures could be of interest in the field of PCa, but very few studies are available to this date.

We have to emphasize the short follow-up of our study as a potential limitation, especially in PCa. Selecting a minimal follow-up of 3 years would have resulted in a small cohort prohibiting the data analysis. However, time from RP to BCR is, on average, 3.5 years (31). Furthermore, the BCR rate is low with a rate of 16% after a median follow-up of 48.6 months. This is consistent with previous studies. For example in a cohort of 1997 men who underwent RP, and among which 25.8% had stage $\geq$T2b, and 40% a Gleason score $\geq$7, BCR occurred in 15% of patients (31).

A further analysis with a longer follow-up will definitely be needed to confirm our findings.

Moreover, the addition of other MRI sequences (such as perfusion providing with a dynamic assessment of PCa and diffusion) are currently at work in our center.

CONCLUSION

A radiomics based model was trained and internally validated. It appears to be predictive of BCR and a prognostic factor of bRFS after RP in patients with high risk PCa. With a negative predictive value of 96%, this model could help identifying patients at very low risk of recurrence, allowing for a better guidance of patients eligible for aRT or those who would undergo careful watching, thus reducing the number of unnecessary treatments and associated toxicity. Exploring the correlation between these features and clinical outcome with a longer follow-up is needed and is currently under investigation in our center. In addition, we intend to validate the model in external cohorts.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript/**Supplementary Files**.

ETHICS STATEMENT

This study was approved by the hospital ethical committee (PREBOP 29DRC18.0108) and all patients gave their consent for the use of their clinical and imaging data.

AUTHOR CONTRIBUTIONS

VB is the main investigator. MH and US are the supervisors. Each other author reread and validated the main manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2019.00807/full#supplementary-material

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Comparison of Peri-operative and Early Oncological Outcomes of Robot-Assisted vs. Open Salvage Lymph Node Dissection in Recurrent Prostate Cancer

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Introduction: Salvage lymph node dissection (sLND) has been proposed as a treatment option for prostate cancer patients with lymph node (LN) recurrence following radical prostatectomy to delay or avoid palliative androgen deprivation therapy (ADT). Historically sLND has been performed using an open approach, with its associated morbidity. A limited number of studies have reported peri-operative outcomes following robot-assisted sLND. However, a direct comparison with the open approach has hitherto not yet been reported. This study investigates whether robot-assisted sLND is associated with better peri-operative outcomes compared to the open approach. Early oncological outcomes are also compared.

Patients and methods: In this retrospective study, clinical data were collected from 60 patients undergoing open sLND between 2010–2016 and 30 patients undergoing robot-assisted sLND between 2016 and 2018 at our tertiary referral center. The primary objective of the study was to compare peri-operative outcomes (length of stay, estimated blood loss, operative time, intra-operative, and postoperative complications) and LN yield between both procedures. As secondary objective early oncological outcome [biochemical recurrence-free survival (BRFS) and clinical recurrence-free survival (CRFS)] was compared. Variables of interest were compared using the chi-squared test (categorical variables), two sample *t*-test, and Mann-Whitney *U*-test (continuous variables). To compare BRFS and CRFS, Kaplan-Meier analysis, and log-rank tests were performed.

Results: Robotic sLND was associated with reduced blood loss (median 100 vs. 275cc; $p < 0.0001$) and shorter length of stay (median 2 vs. 7 days; $p < 0.0001$) compared to open sLND. Moreover, postoperative complications within 30 days after surgery were more prevalent in the open sLND group compared to the robotic group (41.6% vs. 20%, $p = 0.04$). No significant differences in LN yield (for each sLND template), BRFS, and CRFS were detected between both groups.

Conclusion: Robot-assisted sLND is associated with significantly reduced peri-operative morbidity compared to open sLND. No difference in LN yield, BRFS and CRFS was seen between both groups. Modern imaging techniques underestimate the tumor burden and therefore, the surgical sLND template should not be limited to the positive spots on pre-operative imaging.

Keywords: prostate cancer, salvage lymph node dissection, lymph node recurrence, robot-assisted approach, open approach

INTRODUCTION

Biochemical recurrence (BCR) after radical prostatectomy (RP) for clinically localized prostate cancer occurs in 15–40% of patients (1, 2). With the emergence of new imaging modalities, such as choline and PSMA PET/CT, more patients are diagnosed with recurrence confined to a limited number of lymph nodes (LN) (3–6). These patients have a better prognosis than those with skeletal or visceral recurrence (1, 7, 8). In clinical practice, these patients are mainly treated with androgen deprivation therapy (ADT) which is a palliative option aimed at delaying symptoms (9). Recently, salvage lymph node dissection (sLND) has been proposed as a therapeutic option in "node-only" recurrence in order to postpone life-long palliative ADT or to possibly improve cancer-specific survival in selected patients (10–12). Historically, this procedure is performed using an open approach, with its associated morbidity (1, 13). Currently, a limited number of studies have reported peri-operative outcomes following robot-assisted sLND (14–17). However, a direct comparison with the open approach has hitherto not yet been published.

In this retrospective study we compared the peri-operative outcomes between open and robot-assisted sLND in patients with node-only recurrence following RP for clinically localized prostate cancer. We also compared early oncological outcomes between both procedures.

MATERIALS AND METHODS

Patient Population

After obtaining approval from the institutional ethical review board (internal number: S61342), we retrospectively collected clinical data from patients undergoing open or robot-assisted sLND between 2010 and 2018 at a single tertiary referral center. Inclusion criteria were biopsy-proven diagnosis of adenocarcinoma of the prostate, BCR following RP (defined as confirmed PSA >0.2 ng/ml), at least one positive LN on imaging at the time of BCR, and open or robot-assisted sLND. Exclusion criteria were external beam radiotherapy (EBRT), brachytherapy, or high intensity focused ultrasound (HIFU) as initial treatment; visible recurrence in the prostatectomy bed; or concomitant skeletal (M1b) or visceral (M1c) recurrence on conventional or molecular-based imaging (as detected by one of the following imaging techniques at time of BCR: bone scan, abdomino-pelvic computerized tomography, MRI, and/or PET/CT).

Patient and Tumor Characteristics

The following data were collected: clinico-pathological disease characteristics at RP, adjuvant/salvage ADT, or radiotherapy (RT) prior to sLND, imaging technique used at time of BCR, site of positive imaging (pelvic, retroperitoneal, or both), number of positive lesions on imaging, PSA at sLND, extent of sLND (pelvic, retroperitoneal, or both), number of LN removed at final pathology, perioperative blood loss (in cc), operative time (in min), and length of hospital stay (in days). Operative time was measured from skin incision to skin closure. Blood loss was estimated by the amount of blood aspirated during the procedure and weighing the surgical gauzes. Pre-operative morbidity of the patients was estimated by the age-adjusted Charlson-comorbidity index (CCI) (18). The BMI and American Society of Anesthesiologists (ASA)-classification at time of sLND was retrieved from the pre-operative anesthesia consultation (19).

Surgical Technique

The pelvic sLND template was defined as the removal of LN distal to the aortic bifurcation (**Figure 1**) (20):

- *External iliac region:* tissue overlying the external iliac vessels. Borders: bifurcation of the common iliac vessels, circumflex iliac vein, psoas muscle, and genitofemoral nerve and medial border of the external iliac vein.
- *Obturator fossa region:* tissue lying below the iliac vessels and above the obturator nerve. Borders: bifurcation of the common iliac vessels, pelvic floor, obturator muscle, obturator nerve, and medial border external iliac vein.
- *Internal iliac region:* tissue lying around the internal iliac vessels. Borders: bifurcation of the common iliac vessels, pelvic floor, bladder wall, and obturator nerve.
- *Common iliac region:* tissue overlying the common iliac vessels. Borders: aortic bifurcation, bifurcation of the common iliac vessels, psoas muscle and genitofemoral nerve, and medial border of the common iliac vein.
- *Presacral region:* tissue overlying the proximal sacral bone. Borders: Triangle between medial borders of common iliac veins and the line connecting the bifurcations of the common iliac vessels; dorsal border: promontory and proximal sacrum (S1–S2).

The retroperitoneal sLND template was defined as the removal of para-aortic and inter-aorto-caval LN above the aortic bifurcation up to the inferior mesenteric artery (or up to the renal hilum in case of nodal recurrence above the inferior mesenteric artery on pre-operative imaging) (**Figure 2**). Paracaval LN were only

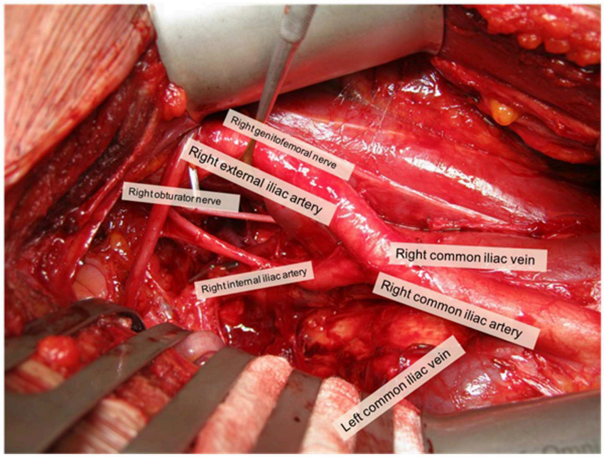

FIGURE 1 | Overview of open pelvic sLND template (right side). Picture was taken with informed consent of the patient.

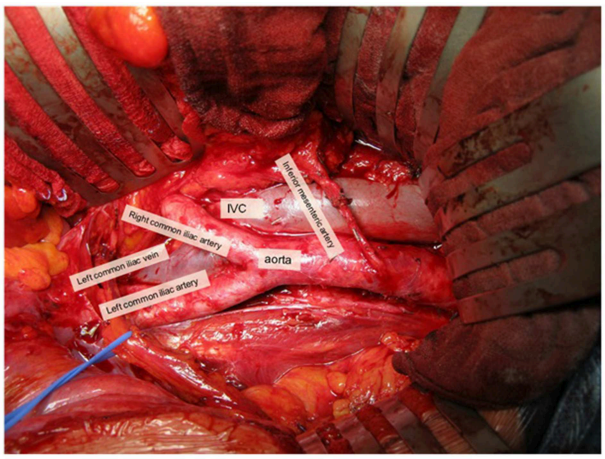

FIGURE 2 | Overview of retroperitoneal sLND. Picture was taken with informed consent of the patient.

removed in case of a positive LN in that area on preoperative imaging. Templates were not limited to the positive spots on imaging and could be modified slightly according to the nodal recurrence site on pre-operative imaging and the extent of the prior pelvic LN dissection during RP.

All procedures were performed by three experienced surgeons (H.V.P., S.J., and W.E.). For the robot-assisted procedures, the Xi Surgical System (Intuitive Surgical, Sunnyvale, CA, USA) was used with a six-port transperitoneal approach. **Supplementary Figure 1** provides an overview of port placement in pelvic sLND and retroperitoneal sLND. In the open sLND group, pelvic LN were approached by extraperitoneal access and retroperitoneal LN by transperitoneal access.

Preoperative bowel preparation was not performed. All patients received postoperative compression stockings and subcutaneous injections with low-molecular weight heparins.

Primary Objective: Comparison of Perioperative Outcome

Intra-operative complications were retrieved from the surgical reports. Postoperative complications up to 30 days after sLND were retrieved by reviewing the electronic medical records and graded using the Clavien-Dindo classification (21). Complications later than 30 days postoperatively were not collected. Intra- and postoperative complications were reported according the recommendations of the European Association of Urology (EAU)-guidelines panel (22).

Lymph node yield for each type of sLND template (pelvic, retroperitoneal, or pelvic + retroperitoneal) was collected and compared between both approaches. Furthermore the proportion of positive LN on preoperative imaging/positive LN at final pathology was calculated and stratified by imaging technique (^{11}C-choline vs. ^{68}Ga PSMA-11 PET/CT) and surgical approach (open vs. robotic approach).

Secondary Objective: Comparison of Early Oncological Outcome

Biochemical recurrence free-survival (BRFS) and clinical recurrence free-survival (CRFS) were compared between both groups. BCR was defined as a PSA-value >0.2 ng/ml post sLND and clinical recurrence was defined as the onset of new lesions on imaging (or if patients became symptomatic). Decisions on performing imaging following sLND was at the discretion of the treating physician and adjuvant/salvage treatments following sLND were decided at the multidisciplinary team meeting. Patients who did not have oncological follow-up data available were excluded from analysis (BRFS and CRFS).

Statistical Analysis

Non-normally distributed continuous variables were reported by medians and interquartile ranges (IQRs) and normally distributed continuous variables by means and standard deviations (SDs). Summary statistics for categorical variables were reported using proportions and frequencies. Categorical variables were compared using the chi-squared test or Fisher's exact test and continuous variables using the two sample *t*-test or Mann-Whitney *U*-test. Kaplan-Meier analysis was performed to assess BRFS and CRFS, and log-rank test to determine a significant difference between both approaches. Statistical analyses were performed using the statistical software Medcalc, Statistical Software version 18.9 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018) with a significance level of $p < 0.05$.

RESULTS

Baseline Patient Characteristics

Table 1 provides an overview of the baseline demographic and tumor characteristics according to surgical technique (open vs. robot-assisted) at time of RP. We identified 60 patients undergoing open sLND between 2010–2016 and 30 patients undergoing robotic sLND between 2016 and 2018. Patients in the open SLND group more often had Gleason score 8–10 prostate cancer compared to the robotic group ($p = 0.03$). No difference in

TABLE 1 | Baseline characteristics at time of RP.

Variable	Open sLND $n = 60$ (66.6%)	Robotic sLND $n = 30$ (33.3%)	p-value (two-tailed)
Mean age at RP, years (SD)	61.2 (6.9)	61.3 (6.4)	0.54
pT-stage			0.37
T2	20 (33.3%)	9 (30%)	
T3a	24 (40%)	8 (26.7%)	
T3b-4	15 (25%)	11 (36.7%)	
Tx	1 (1.6%)	2 (6.7%)	
pN-stage			0.64
N0	38 (63.3%)	16 (53.3%)	
N1	7 (11.6%)	3 (10%)	
Nx	15 (25%)	11 (36.6%)	
Number of LN removed at RP, median (IQR)	9 (5–18.5)	13.5 (5–19)	0.67
pGleason			**0.03**
6	1 (1.7%)	4 (13.4%)	
7	23 (38.3%)	16 (53.3%)	
8–10	31 (51.7%)	8 (26.7%)	
NA	5 (8.3%)	2 (6.7%)	
Positive surgical margin	23 (38.3%)	10 (33.3%)	0.68
Post-RP treatment			0.08
ADT only post-RP	6 (10%)	0	
RT only post-RP	29 (48.3%)	15 (50%)	
ADT + RT post-RP	14 (23.3%)	5 (16.7%)	
No post-RP treatment	9 (15%)	10 (33.3%)	

Patients were stratified according to the surgical technique received (Open vs. robot assisted sLND). Data are presented as n (%) unless otherwise noted. ADT, androgen deprivation therapy; RT, radiation therapy; sLND, salvage lymphadenectomy; RP, radical prostatectomy; IQR, interquartile range; SD, standard deviation; NA, Not available. Bold p-values mean statistical significance.

TABLE 2 | Baseline characteristics at time of sLND.

Variable	Open sLND $n = 60$ (66.6%)	Robotic sLND $n = 30$ (33.3%)	p-value (two-tailed)
PSA (ng/ml) at sLND, median (IQR)	1.6 (0.7–3.4)	1.1 (0.7–2.6)	0.25
Mean age at sLND, years (SD)	67.8 (6)	65.6 (5.5)	0.11
BMI at sLND, median (IQR)	26.3 (24.5–30.8)	26.05 (23.5–28.7)	0.26
ASA classification at sLND			0.65
1	5 (8.3%)	0	
2	39 (65%)	26 (86.7%)	
3	16 (26.7%)	4 (13.3%)	
Age-adjusted CCI			0.92
1	1 (1.7%)	0	
2	4 (6.8%)	3 (10%)	
3	25 (41.7%)	13 (43.3%)	
4	18 (30%)	8 (26.7%)	
5	8 (13.3%)	5 (16.7%)	
6	2 (3.4%)	1 (3.3%)	
7	2 (3.4%)	0	
Type of imaging used			**<0001**
11C-Choline PET/CT	32 (53.3%)	0	
68Ga-PSMA-11 PET/CT	25 (41.7%)	29 (96.7%)	
MRI	2 (3.4%)	1 (3.3%)	
CT	1 (1.7%)	0	
Site of positive imaging			0.36
Pelvic	47 (78.3%)	23 (76.7%)	
Retroperitoneal	8 (13.3%)	2 (6.7%)	
Both	5 (8.3%)	5 (16.7%)	
Median number of positive lesions on imaging, (IQR)	2 (1–3)	2 (1–2)	0.55
Number of positive lesions on imaging			0.81
1–3 lesions	52 (86.7%)	27 (90%)	
>3 lesions	8 (13.3%)	3 (10%)	

Patients were stratified according to the surgical technique received (Open vs. robot assisted sLND). Data are presented as n (%) unless otherwise noted. PSA, prostate specific antigen; sLND, salvage lymphadenectomy; IQR, interquartile range; SD, standard deviation; BMI, body mass index [weight (kg)/length^2 (m)]; ASA, American Society of Anesthesiologists (19); CCI, Charlson-Comorbidity Index. Bold p-values mean statistical significance.

proportion adjuvant/salvage radiotherapy was observed between the open and robotic groups [71.6 vs. 67.7%, respectively ($p = 0.7$)]. The (adjuvant/salvage) radiation field (mostly 66 Gy) was confined to the prostate bed. None of the patients were castration resistant at time of sLND. In total, 45 (75%) and 18 (60%) patients received a concomitant lymphadenectomy at time of RP in the open and robot group, respectively. Of these, information on the number of LN removed during RP was available in 34 (75.6%) and 12 (66.7%) patients in the open and robotic approach, respectively. No difference was observed in median number of LN removed during RP. **Table 2** provides an overview of the baseline characteristics at time of sLND. No difference in preoperative morbidity was observed in terms of BMI, ASA-classification, and age adjusted CCI. In both groups the majority of the patients had oligometastatic recurrence defined as 1–3 lesions. At time of BCR, almost all patients (96.7%) in the robot-assisted group were assessed by ^{68}Ga-PSMA-11 PET/CT compared to only 44% in the open group ($p < 0.0001$). More than half of these patients were evaluated by ^{11}C-choline PET/CT (53.3%).

Perioperative Outcomes

Table 3 provides an overview of the intra-operative and postoperative outcomes and complications. Patients treated with robot-assisted sLND had significantly less estimated blood loss during the procedure compared to open sLND (median 100 vs. 275cc; $p < 0.0001$). However, no intra-operative transfusions were needed in either group. Median operative time between the two procedures was equal (median 150 vs. 150 min; $p = 0.89$). Length of stay was significantly lower in the robot-assisted sLND group compared to the open sLND group (median 2 vs. 7 days; $p < 0.0001$). No difference in intra-operative complications was observed ($p = 0.34$), but postoperative complications within 30 days after surgery were significantly more prevalent in the open group compared to the robotic group (41.7 vs. 20%, $p = 0.04$). Moreover, patients in the open group had more high-grade complications [5 vs. 0 Clavien-Dindo grade III-IV complications; hydronephrosis (double-J stent), arterial bleeding (reoperation), lymphocoele drainage (2x), renal failure (biopsy

was taken to exclude nephrological disease)]. Injury to the iliac veins was the most prevalent was the most prevalent intra-operative complication in both groups. Postoperatively, lymphatic complications were more prevalent in the open group.

Table 4 provides an overview of the pathological outcomes. The number of LN removed for each sLND template (pelvic, retroperitoneal, and pelvic + retroperitoneal) was equal for both groups ($p = 0.88$, $p = 0.24$, and $p = 0.85$, respectively). A total of 477 LN were positive at final pathology, whereas only 200 (41.9%) metastatic LN were detected on imaging. Mean numbers of metastatic LN at final pathology were 4.1 (95%-CI: 2.5–5.7) and 6 (95%-CI: 2.7–9.2) in patients assessed by ^{11}C-choline and ^{68}Ga-PSMA PET/CT, respectively ($p = 0.30$). ^{11}C-Choline PET/CT was able to detect 57 (42.8%) out of the 133 and ^{68}Ga-PSMA PET/CT to detect 134 (41.8%) out of 320 metastatic LN at final pathology. No significantly difference in number of metastatic LN at final pathology was observed between the open and robotic group ($p = 0.11$).

Early Oncological Outcome

Mean follow-up after open and robotic sLND was 53 (median: 53mo., IQR 31.5–75) and 15 (median 15mo., IQR 10.25–21.5) months, respectively ($p < 0.001$). Follow-up data were available for 52 (86.7%) patients in the open group and 28 (93.3%) patients in the robotic group. **Supplementary Table 1** provides information on adjuvant/salvage therapies following sLND. In the open and robotic group, 38.4 and 58% of the patients received adjuvant or salvage treatment, respectively. Median BRFS was similar in both groups (2 months, $p = 0.23$) (**Figure 3**). The majority of patients in both groups experienced BCR (90 and 89%, respectively). No difference was observed in CRFS between both groups [median 25 mo. vs. 32 mo. in the robotic and open group, respectively ($p = 0.87$); **Figure 4**].

To correct for the difference in type of preoperative imaging between both groups, a sub-analysis of patients assessed by only ^{68}Ga-PSMA-11 PET/CT was performed. **Supplementary Table 2** provides an overview of the baseline demographic and tumor characteristics according to surgical technique (open vs. robot-assisted). Baseline tumor characteristics were balanced between both groups. No difference in BRFS (median 2 mo. in both groups, $p = 0.59$) and CRFS (median not attained in the open group and median of 25 months in the robotic group, $p = 0.79$) were observed between the open and robotic approach (**Supplementary Figures 2**, **3**).

TABLE 3 | Peri-operative outcomes of patients treated with sLND according to type of procedure (open vs. robotic).

Variable	Open sLND $n = 60$ (66.6%)	Robotic sLND $n = 30$ (33.3%)	*p*-value (two-tailed)
Area sLND			
Pelvic	37 (61.7%)	20 (66.7%)	0.79
Retroperitoneal	5 (8.3%)	3 (10%)	
Pelvic + retroperitoneal	18 (30%)	7 (23.3%)	
Median operative time, min (IQR)	150 (120–175)	150 (120–180)	0.89
Median blood loss, ml (IQR)	275 (175–675)	100 (25–162.5)	**<0.0001**
Median length of stay, days (IQR)	7 (6–10)	2 (2–3)	**<0.0001**
Intraoperative complications	13 (21.7%)	4 (13.3%)	0.34
Vascular injury (vein)	7	2	
Bladder perforation	2	0	
Ureteral lesion	1	0	
Vascular injury (artery)	1	1	
Nerve injury	1	0	
Chyle leakage	1	0	
Pressure wound left shoulder	0	1	
Postoperative complications <30 days after sLND (Clavien-Dindo classification)	25 (41.7%)	6 (20%)	**0.04**
I-II	20	6	
III-V	5	0	
Type postoperative complication			
Lymphatic:	7	2	
Symptomatic lymphocele	3	0	
Symptomatic scrotal edema	3	0	
Chyle leakage	1	1	
Symptomatic lymph oedema legs	0	1	
Fever/infection	5	0	
Ileus	4	0	
Hydronephrosis	1	0	
Renal failure	1	0	
Stomach bleeding	2	0	
Pulmonary embolism	1	0	
Dyspnea	1	0	
Arterial bleeding	2	0	
Arrhythmia	1	0	
Symptomatic hematoma	0	1	
Pain/stiffness right leg	0	1	
Hyperglycemia	0	1	
Painful left scrotum	0	1	

Data are given as n (%) unless otherwise noted. sLND, salvage lymphadenectomy; SD, standard deviation; IQR, interquartile range; LN, lymph nodes. Bold p-values mean statistical significance.

DISCUSSION

Patients with prostate cancer recurrence confined to a limited number of LN following primary treatment, also called oligometastatic recurrence, are potential candidates for metastasis-directed therapies. The EAU-guidelines introduced sLND as a possible therapeutic option in these patients. Salvage LND is typically performed by an open approach and associated is with substantial morbidity (1, 13). Four studies have so far investigated the feasibility and peri-operative outcomes of robot-assisted sLND, though no direct comparison has been made with the open procedure (14–17). The current study aimed to investigate the peri-operative and early oncological outcomes between open and robot-assisted sLND in patients with LN recurrence after RP.

TABLE 4 | Pathological outcomes of patients treated with sLND according to type of procedure (open vs. robotic).

Variable	Open sLND $n = 60$ (66.6%)	Robotic sLND $n = 30$ (33.3%)	*p*-value (two-tailed)
Number of LN removed at sLND	17 (9–26)	15 (10–27)	0.88
Number of LN removed/sLND template			
Pelvic	16 (6.5–24.75)	15 (8.5–25.5)	0.88
Retroperitoneal	17 (10.75–23)	10.5 (10–11)	0.24
Pelvic + retroperitoneal	20 (10–26)	23 (10.25–33)	0.85
Number of positive LN removed at sLND	3 (1–7)	1 (1–3)	0.11

Data are given as median (IQR) unless otherwise noted. LN, Lymph node; sLND, salvage lymphadenectomy.

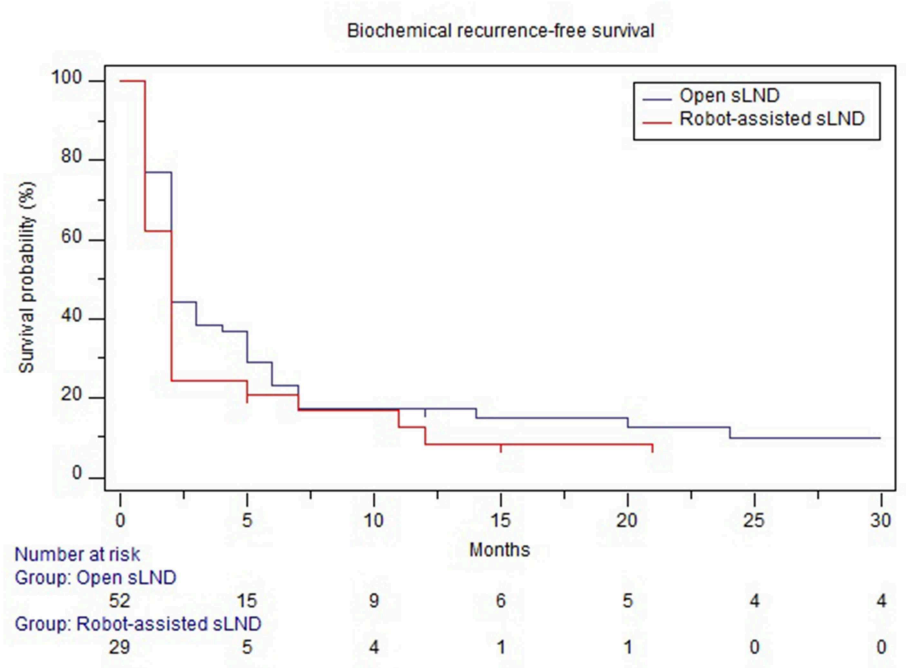

FIGURE 3 | Comparison of biochemical recurrence-free survival between open and robotic sLND. Censored patients are marked with small vertical lines.

Several observations of our study are interesting. First, robot-assisted sLND appears to be a safe alternative with favorable perioperative outcomes compared to the open approach. No high-grade postoperative complications were seen in the robotic group. This is in line with previously published robotic sLND series, where very few high-grade complications were reported (14–17). Only in the series of Linxweiler et al., five patients (13.9%) experienced high-grade (grade III according to Clavien-Dindo) complications (17). Notably, in our study lymphatic complications were more frequent in the open group (28% of all complications). This might be explained by the fact that the pelvic nodes were approached by an extraperitoneal access in the open sLND group (in case of pelvic sLND), while all nodes were removed via a transperitoneal approach in the robot-assisted group (23–25). Moreover, patients in the open group had higher metastatic burden at final pathology compared to the robotic group (median 3 vs. 1 metastatic LN). This might partially explain the higher proportion of intra- and post-operative complications as bulky nodal disease can be associated with increased risk of complications. Further, our results demonstrated significantly less blood loss and a 5-day shorter hospital stay in the robotic group compared to the open group. The higher proportion of postoperative complications with the open approach might explain this difference in hospital stay. Median operation time (150 min) and median blood loss (100 ml) in the robotic cohort were comparable with the previously published robotic sLND series (range 129–228 min and 50–250 ml, respectively) (14–17). Remarkably, the median operation time—generally one of the major drawbacks for robotic procedures—was not different between both groups. Also the number of LN removed for each sLND template (pelvic, retroperitoneal, and pelvic + retroperitoneal) was not different between both groups.

Second, only 200 (41.9%) out of 477 positive LN at final pathology were visible on preoperative imaging. Remarkably,

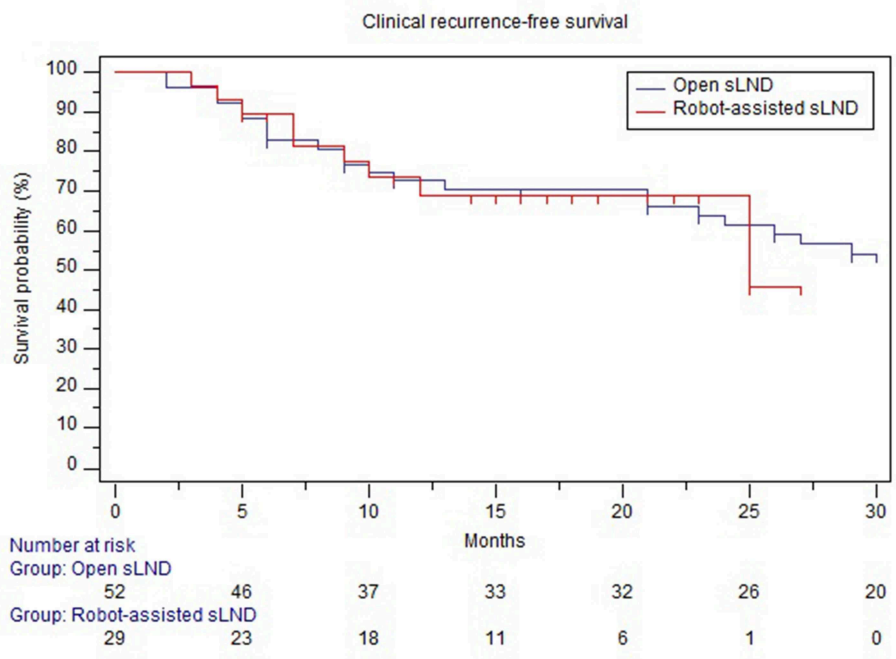

FIGURE 4 | Comparison of clinical recurrence-free survival between open and robotic sLND. Censored patients are marked with small vertical lines.

^{68}Ga-PSMA-11 PET/CT was not superior to ^{11}C-Choline PET/CT to identify metastatic LN. This might partly be explained by the fact that the mean metastatic burden in patients assessed by ^{68}Ga-PSMA-11 PET/CT was higher compared to patients assessed by ^{11}C-Choline PET/CT (although statistically not significant). Some patients who were assessed by ^{68}Ga-PSMA-11 PET/CT had a very high proportion of positive LN at final pathology. For example, one patient had four suspect lesions on ^{68}Ga-PSMA-11 PET/CT and received an open pelvic + retroperitoneal sLND resulting in 70 metastatic LN out of 78 at final pathology. Thus, despite the improved accuracy of novel imaging modalities at low PSA values compared to conventional imaging techniques, sLND should certainly not be limited to the positive spots on pre-operative imaging (26). Today, no consensus exists about the optimal extent of the sLND template. Therefore, radioguided surgery in which metastatic LN are detected intra-operatively with the use of a gamma probe, could provide an interesting alternative to reduce the morbidity of these (extensive) templates (27). Recently, Maurer et al. demonstrated that ^{99}mTc-PSMA-based radioguided surgery had a good accuracy (93%) with promising early oncological outcomes in 31 patients with LN recurrence following RP (28). However, their technique still required an open approach with its associated morbidity (38.7% grade I; 3.2% grade IIIa complications). New promising technologies are currently developed that enable the use of radioguided surgery in combination with robotic surgery, leading to a further decrease in morbidity (29).

Finally, the majority of patients treated with sLND developed BCR independent of the surgical approach and in most cases BCR developed quickly (median time to BCR 2 months). As a consequence, it is important to counsel patients of the non-curative character of the procedure. Probably, CRFS rather than BRFS should be considered as a meaningful endpoint as CRFS in both groups extended 2 years. Patient selection appears to be of utmost importance for sLND. The identification of the "ideal" sLND candidate has already been investigated in a retrospective multi-center study in which our patients were included (30). Gleason grade group 5, a short time from RP to PSA rising, hormonal therapy at the time of sLND, positive retroperitoneal spots on imaging, $\geq$3 positive spots on PET scan and high PSA at time of sLND were significant predictors for early clinical recurrence ($<$1 year following sLND). These patients had a worse cancer-specific survival compared to patients who developed clinical recurrence $>$1 year following sLND. Similar prognostic factors were identified in patients treated by PSMA-based radioguided surgery (22). These findings underline the need for prospective studies to evaluate the oncological usefulness of sLND and to assess the added value of adjuvant treatments. Currently, a prospective phase-2 study (NCT03569241) is investigating the additional value of pelvic RT following sLND.

Our study is not devoid of limitations. First, this is a single center, retrospective case series comparing two techniques and is as such prone to several types of bias (31). Second, patient cohorts were not contemporary: half of the patients in the open group were assessed by ^{11}C-choline PET/CT,

whereas almost all patients in the robotic group were assessed by ^{68}Ga-PSMA-11 PET/CT. This is important as ^{11}C-choline PET/CT is less accurate at low PSA values than ^{68}Ga-PSMA PET/CT (32–34). As a consequence, half of the patients in the open group might have been understaged (occult metastases) compared to their counterparts in the robotic group and more patients with local recurrence might have been missed by choline PET/CT and therefore (falsely) not excluded from the study, both resulting in a worse oncological outcome. Third, patients in the robot-assisted group had less aggressive tumor characteristics (less Gleason score 8–10 at final pathology following RP) and a shorter follow-up compared to their counterparts in the open group. Therefore, we cannot definitively conclude from this data that both sLND approaches provide similar early oncological outcomes. However, a sub-analysis of only those patients who received a PSMA PET/CT at time of BCR showed no difference in BRFS and CRFS.

Notwithstanding these limitations, the extent of surgical templates was identical with both techniques, as was the number of nodes removed within each of the templates (pelvic, retroperitoneal, and pelvic + retroperitoneal). Both groups had comparable baseline patient characteristics (e.g., no difference in post-RP adjuvant/salvage RT proportion between both groups). Moreover, no differences in terms of preoperative co-morbidities (age adjusted CCI, ASA, and BMI) were observed. We therefore believe that the conclusions on surgical feasibility, perioperative, and postoperative complications of this study are reliable. Moreover, this is the first series comparing intra-operative, postoperative and early oncological outcomes between open and robotic sLND.

CONCLUSIONS

Robotic salvage lymph node dissection appears to be a safe alternative for the open procedure with the associated benefits of minimally invasive surgery, including shorter length of stay, lower estimated blood loss, and lower early postoperative complication rates. No difference in early BRFS and CRFS was seen between both groups. Modern imaging techniques underestimate the tumor burden and therefore, the surgical sLND template should not be limited to the positive spots on pre-operative imaging.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethische commissie UZ Leuven. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

GD and SJ: study concept and design. GD, TM, and YR: acquisition of data. GD: analysis and interpretation of data, drafting of the manuscript, and statistical analysis. VC, MA, CB, GM, LM, TV, HV, WE, and SJ: critical revision of the manuscript for important intellectual content. SJ: supervision.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2019.00781/full#supplementary-material

Supplementary Table 1 | Post-sLND treatments according to type of procedure (open vs. robotic).

Supplementary Table 2 | Baseline characteristics of patients with lymph node recurrence after radical prostatectomy treated with open or robot-assisted sLND and who were assessed by PSMA PET/CT.

Supplementary Figure 1 | (A) Overview of port placement in case of pelvic robot-assisted sLND. A six-port transperitoneal approach is used. The camera-port (8 mm) is placed supra-umbilical. The robotic ports are placed at the same height as the camera-port: two on the left and one on the right side (red dots, 8 mm trocars). A 12 mm assistant port is placed on the right side (green dot) and a 5 mm assistant port (blue dot) is placed 5 cm higher between the right robotic port and the camera-port. **(B)** Overview of port placement in case of pelvic+retroperitoneal robot-assisted sLND. Ports are placed 5 cm higher compared to port placement in pelvic sLND. Pictures were taken with informed consent of the patient.

Supplementary Figure 2 | Comparison of biochemical recurrence-free survival between open and robotic sLND for patients who received a PSMA PET/CT. Censored patients are marked with small vertical lines.

Supplementary Figure 3 | Comparison of clinical recurrence-free survival between open and robotic sLND for patients who received a PSMA PET/CT. Censored patients are marked with small vertical lines.

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ORIGINAL RESEARCH
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Impact of the 2014 International Society of Urological Pathology Grading System on Concept of High-Risk Prostate Cancer: Comparison of Long-Term Oncological Outcomes in Patients Undergoing Radical Prostatectomy

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Objective: To investigate the relationship between the new International Society of Urological Pathology (ISUP) grading system, biochemical recurrence (BCR), clinical progression (CP) and cancer related death (CRD) after open radical prostatectomy (RP) and determine whether the 2014 ISUP grading system influences the concept of high-risk prostate cancer (HRPCa).

Patients and Methods: A total of 1,754 men who underwent RP from 2005 to 2017 were identified from a database at a single tertiary institution. Histopathology reports were reassessed according to the 2014 ISUP grading system. All preoperative, pathological, and clinical follow-up data were obtained. Univariable and multivariable Cox regression, Kaplan-Meier and log-rank analyses were performed.

Results: At a median (quartiles) follow-up of 83 (48–123) months, 446 men (25.4%) had BCR, 77 (4.4%) had CP and 39 (2.2%) died from cancer. Grade groups 1, 2, 3, 4, and 5 were detected in 404 (23%), 931 (53.1%), 200 (11.4%), 93 (5.3%), and 126 (7.2%), respectively. 10-year biochemical progression free survival difference between Grade group 3 and 4 was minor but significant (log-rank $p = 0.045$). There was no difference between Grade groups 3 and 4 comparing 10-year clinical progression free and 10-year cancer specific survival: $p = 0.82$ and $p = 0.39$, respectively. Group 5 had the worst survival rates in comparison with other groups (from $p < 0.005$ to $p < 0.0001$) in all survival analyses. Pathological stage (hazard ratio (HR) 2.6, $p < 0.001$), positive surgical margins (HR 2.2, $p < 0.0001$) and Grade group (HR 10.4, $p < 0.0001$) were independent predictors for BCR. Stage and Grade group were detected as independent predictors for CP–HR 6.0,

$p < 0.0001$ and HR 35.6, $p < 0.0001$, respectively. Only Grade group 5 (HR 12.9, $p = 0.001$) and pT3b (HR 5.9, $p = 0.001$) independently predicted CRD.

Conclusions: The new ISUP 2014 grading system is the most significant independent predictor for BCR, CP, and CRD. Grade group 3 and 4 had similar long-term disease progression survival rates and could potentially be stratified in the same risk group. High-risk cancer associated only with group 5.

Keywords: high risk prostate cancer, ISUP 2014 grade groups, radical prostatectomy, clinical progression, survival

INTRODUCTION

The Gleason score (GS) grading system is one of the strongest predictors for prostate cancer (PCa) outcomes and plays a significant role for choosing treatment modality. Since the 1960s when this grading system was developed by Donald Gleason (1), several modifications have been adopted. The International Society of Urological Pathology (ISUP) suggested the currently used GS system in 2005 (2). The division of GS into 6 vs. 7 vs. 8–10 together with corresponding grouping of the prostate specific antigen (PSA) and clinical stages into three groups—low, intermediate and high PCa risk groups,—are known as D'Amico classification (3) that has been adopted in clinical practice and has been widely used for prognostic and therapeutic purposes. The EAU PCa risk group classification, which is based on D'Amico criteria, is used until now (4). Current high-risk PCa definition included PSA >20 ng/ml or GS >7 or clinical stage (cT) ≥2c in localized, or cT3-4 or cN+ with any PSA and any GS for locally advanced PCa (5), and the GS is the most important parameter in these groupings. Recently, some studies have shown that scores 3+4 vs. 4+3, also 8 vs. 9–10 have a different prognosis (6–8). In 2013, based on the data presented by Pierorazio et al. from Johns Hopkins Hospital, a new grading system of five prognostic grade groups (GS ≤6—prognostic grade group 1, 3+4—group 2, 4+3—group 3, 8—group 4 and 9–10—group 5) was proposed (9). Very recently, in a large multi-institutional study, Epstein et al. have confirmed that the five-group ISUP 2014 grading system provides a more accurate grade stratification than the current ISUP 2005 model (10). Biochemical progression free survival (BPFS) was different in all five groups in patients after radical prostatectomy (RP) and radiation therapy (RT). One of the limitations in this study was the use of biochemical recurrence (BCR) as an end-point as opposed to clinical progression (CP) or cancer-related death (CRD). Grogan et al. confirm that the ISUP 2014 grading system is an independent predictor not only for BCR, but also for CP. Harrells' c-index for the ISUP 2014 grading was significantly higher compared to the ISUP 2005 grading system (11). Such recent, new clinical data influenced the addition of ISUP grades 4 and 5 to the definition of high-risk PCa suggested by EAU (12). The aim of the present study was to assess where the ISUP 2014 grading system reflects the recently proposed concept of high-risk PCa in a long-term follow-up cohort of men undergoing RP at a tertiary university hospital. The primary end-point was to assess the association between the ISUP 2014 grading and BPFS; the secondary end-points were to investigate the association between the new grading system and clinical progression free survival (CPFS) and cancer specific survival (CSS).

MATERIALS AND METHODS

Between 2005 and 2017, 2,255 men were treated by RP for clinically localized PCa at a single university hospital centre using similar surgical techniques. We identified 1,754 men with complete pathological and follow-up data. Clinical characteristics, such as PSA level, clinical stage (cT), and biopsy GS were reported before RP. Pathological parameters [pathological stage (pT), GS, surgical margin status (R0 vs. R1) and lymph nodes status N0 vs. N1] were collected after surgery. PSA testing after RP was performed every 3 months in the first year, biannually in the second and third year, and once a year thereafter. BCR was identified as a PSA value of >0.2 ng/ml in two consequent measurements. CP was identified upon skeletal or visceral lesions confirmations by bone scan, CT or MRI using RECIST criteria. Local and loco-regional recurrence was confirmed by histological investigation after surgery or biopsy. Pathological stage was assessed using 2002 TNM system and tumor grading was classified using the revised 2005 ISUP GS grading system (2). Histopathological investigation in the majority of cases was performed by one uropathologist. Adjuvant therapy (RT alone or RT + androgen deprivation therapy) was performed depending on the pathological characteristics of PCa within 6 months after RP and salvage therapy (RT alone or RT + androgen deprivation therapy or salvage lymph node dissection) was applied after detecting BCR. The university's ethical committee approved the prospective collection of the data and all patients signed a consent form provided before RP. According to the pathologist's reports, the 2005 Gleason grading model was reassessed to the five-group system: GS ≤6 (Grade group 1) vs. 3+4 (Grade group 2) vs. 4+3 (Grade group 3) vs. 8 (Grade group 4) vs. 9–10 (Grade group 5) according to the 2014 ISUP Consensus Conference (13). Mortality data were obtained from the National Cancer Registry and reassessed using the department database for clinical progression to ensure the accuracy of the cause of death. Time to BCR, CP, and CRD was defined as the time interval from surgery to the event. BPFS, CPFS and CSS were estimated using Kaplan-Meier analysis. The log-rank test was used to compare differences among groups. The impact of the new 2014 ISUP grouping on BCR, CP, and CRD was analyzed by using univariable and multivariable Cox regression in combination with other factors, such as preoperative PSA,

TABLE 1 | Clinical and pathological characteristics of patients (n = 1,754).

Characteristics	
Age, yr-median (quartiles)	64 (59–68)
PSA, ng/ml-median (quartiles)	6.3 (4.7–9.8)
Clinical stage, *n* (%)	
cT1	481 (27.4)
cT2	995 (56.8)
cT3	278 (15.8)
Biopsy Gleason score, *n* (%)	
6	970 (55.3)
3+4	559 (31.9)
4+3	84 (4.8)
8	93 (5.3)
9–10	48 (2.7)
Pathological stage, *n* (%)	
pT2	1,046 (59.6)
pT3a	555 (31.6)
pT3b	153 (8.8)
Pathological Gleason score, *n* (%)	
6	404 (23.0)
3+4	931 (53.1)
4+3	200 (11.4)
8	93 (5.3)
9-10	126 (7.2)
Positive surgical margins (n = 16,77), *n* (%)	446 (32.5)
Positive lymph nodes (n = 618), *n* (%)	75 (12.1)

PSA, prostate specific antigen.

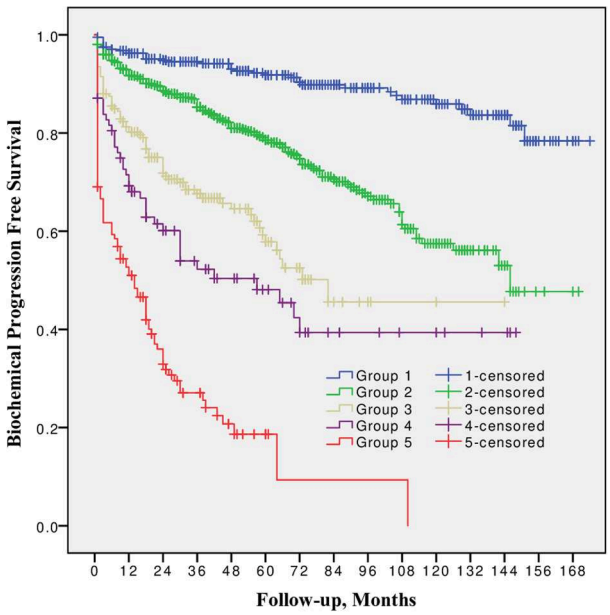

FIGURE 1 | Biochemical progression free survival after radical prostatectomy stratified by 2014 International Society of Urological Pathology suggested Grade Group 1, 2, 3, 4, and 5.

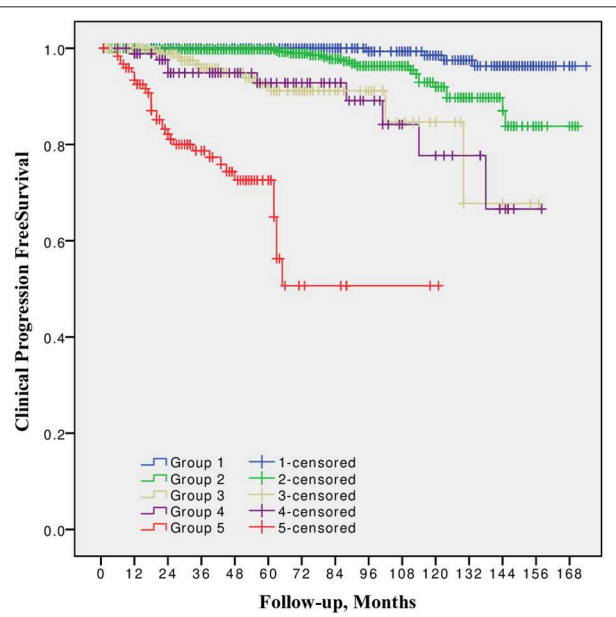

FIGURE 2 | Clinical progression free survival after radical prostatectomy stratified by 2014 International Society of Urological Pathology suggested Grade Group 1, 2, 3, 4, and 5.

pathological stage (pT2 vs. pT3a vs. pT3b and surgical margins status (R0 vs. R1). Variables that had $p < 0.1$ value in univariable analysis were included in the multivariable Cox proportional hazards model. A $p < 0.05$ value was considered as significant and all reported p-values were two-sided. Statistical analysis was performed using SPSS software version 23 (IBM).

RESULTS

The study cohort includes 1,745 men who underwent open RP for clinically localized PCa. Clinical and pathological characteristics of patients are shown in **Table 1**.

The median (quartiles) follow-up was 83 (48–123) months. BCR during the study period was observed in 446 (25.4%) men and CP—in 77 (4.4%) patients: local recurrence was detected in 7 (0.4%), loco-regional in 15 (0.9%) and distant lesions in 55 (3.1%) patients, respectively. There were 216 (12.3%) deaths during follow-up period and 39 (2.2%) documented as CRD.

10-year BPFS for Grade group 1, 2, 3, 4, and 5 was 85.9, 57.5, 45.6, 39.4 and 0.0%, respectively. The difference between all five groups (**Figure 1**) was significant (log-rank p from 0.045 to < 0.0001). The smallest difference was detected between groups 3 and 4 ($p = 0.045$).

10-year CPFS was 98.5, 92.0, 84.7, 77.7, and 50.7% for Group 1, 2, 3, 4, and 5, respectively (**Figure 2**). The difference between all five groups was significant (p from 0.002 to < 0.0001), except between Grade group 3 vs. 4 ($p = 0.8$).

10-year CSS was 98.9, 98.4, 91.7, 87.5, and 79.8% for Group 1, 2, 3, 4, and 5 respectively (**Figure 3**). The difference between Grade group 1 vs. 2, also between 3 vs. 4 was not significant ($p =$

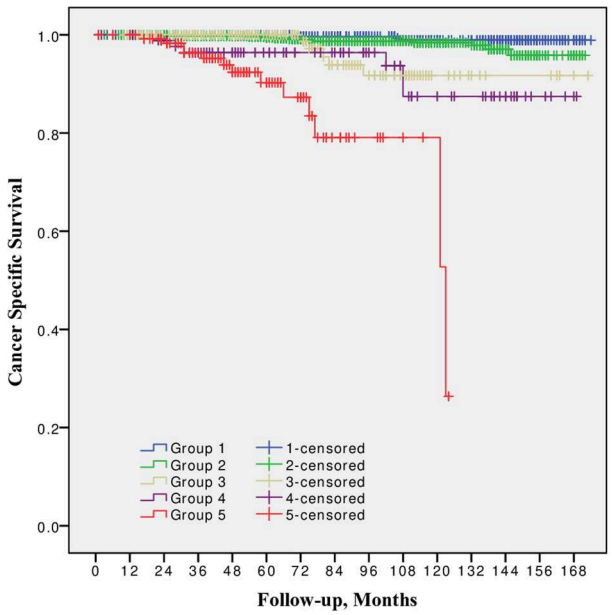

FIGURE 3 | Cancer specific survival after radical prostatectomy stratified by 2014 International Society of Urological Pathology suggested Grade Group 1, 2, 3, 4, and 5.

TABLE 2 | Cox proportional hazards analysis of factors for prediction of biochemical recurrence after radical prostatectomy ($n = 1,745$).

Parameter	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years)	1.0 (0.99–1.02)	0.28	–	–
Preoperative PSA (ng/ml)	1.0 (0.99–1.00)	0.31	–	–
Surgical margins (R0 vs. R1)	3.5 (2.85–4.20)	<0.0001	2.2 (1.77–2.69)	<0.0001
Pathological stage				
pT2				
pT3a	2.6 (2.14–3.29)	<0.0001	1.34 (1.05–1.71)	0.02
pT3b	8.4 (6.53–10.70)	<0.0001	2.2 (1.77–2.69)	<0.0001
Grade group				
1				
2	2.9 (2.09–4.16)	<0.0001	2.2 (1.53–3.16)	<0.0001
3	6.6 (4.43–9.74)	<0.0001	4.4 (2.88–6.76)	<0.0001
4	8.8 (5.73–13.49)	<0.0001	5.2 (3.29–8.35)	<0.0001
5	22.4 (15.21–32.87)	<0.0001	10.4 (6.67–16.15)	<0.0001

PSA, prostate specific antigen.

TABLE 3 | Cox proportional hazards analysis of factors for prediction of clinical progression after radical prostatectomy ($n = 1,745$).

Parameter	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years)	1.0 (0.99–1.07)	0.14	–	–
Preoperative PSA (ng/ml)	1.0 (0.99–1.00)	0.46	–	–
Surgical margins (R0 vs. R1)	3.7 (2.33–6.03)	<0.0001	1.4 (0.85–2.40)	0.11
Pathological stage				
pT2				
pT3a	4.7 (2.47–8.97)	<0.0001	2.3 (1.11–4.61)	0.02
pT3b	22.3 (11.04–41.53)	<0.0001	6.0 (2.91–12.54)	<0.0001
Grade group				
1				
2	4.1 (1.38-12.01)	0.01	2.5 (0.80-7.69)	0.1
3	16.8 (5.3–53.37)	<0.0001	7.1 (2.05–24.32)	0.002
4	16.1 (4.92–52.29)	<0.0001	7.6 (2.17–26.73)	0.002
5	125.3 (41.75–376.23)	<0.0001	35.6 (10.40–121.80)	<0.0001

PSA, prostate specific antigen.

0.09 and $p = 0.4$, respectively). Other pairwise comparison was significant (p from 0.02 to < 0.0001).

In univariable Cox regression analysis risk for BCR increased with a higher Grade group ($p < 0.0001$), a higher pT stage ($p < 0.0001$) and surgical margins status ($p < 0.0001$). Age and PSA were not significant predictors for BCR (**Table 2**). Higher risk of CP was associated with a higher Grade group (p from 0.01 to < 0.0001), a pathological stage ($p < 0.0001$) and positive surgical margins ($p < 0.0001$), but not with age and PSA (**Table 3**). Higher risk of CRD was associated with positive surgical margins ($p < 0.0001$), age ($p = 0.003$), stage after RP ($p = 0.004$ to $p < 0.0001$) and Grade group 3–5 ($p = 0.002$ to <0.0001), but not with preoperative PSA (**Table 4**).

In multivariable analysis surgical margins status, pT and Grade group were detected as independent predictors (all $p < 0.0001$) for BCR (**Table 2**). The Grade group had the highest HR 10.4 compared to other parameters and could be used as the strongest predictor for PSA relapse. Stage and Grade group 3–5 had a significant impact on risk prediction also for CP ($p = 0.02$ to $p < 0.0001$) with the highest HR 35.6 in Grade group 5 (**Table 3**). Only Grade group 5 (HR 12.9, $p = 0.001$) and pT3b stage (HR 5.9, $p = 0.001$) were detected as independent predictors for CRD (**Table 4**).

In all univariable and multivariable Cox regression and log-rank analyses for BCR, CP and CRD Grade group 4 was much closer to Grade group 3 than to group 5. The HR difference between Grade group 4 and group 5 in various analyses was from two- to eight-fold, whereas between Grade group 4 and group 3 it was less than one-fold (**Tables 2–4**). The Kaplan-Meier survival curves were slightly different between Grade groups 3 and 4 ($p = 0.045$) analyzing BPFS and similar analyzing CPFS and CCS. Therefore, the difference between Grade groups 4 and 5 was significant in all survival curves ($p = 0.005$ to $p < 0.0001$), which shows different cancer aggressiveness in these groups (**Figures 1–3**).

DISCUSSION

The GS has been confirmed as one of the most powerful predictors of PCa progression in our previous studies (14, 15).

TABLE 4 | Cox proportional hazards analysis of factors for prediction of cancer related death after radical prostatectomy ($n = 1,745$).

Parameter	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years)	1.1 (1.03–1.14)	0.003	1.1 (1.01–1.13)	0.013
Preoperative PSA (ng/ml)	1.0 (0.99–1.01)	0.8	–	–
Surgical margins (R0 vs. R1)	5.6 (2.69–11.50)	<0.0001	2.2 (0.99–4.95)	0.052
Pathological stage				
pT2				
pT3a	3.8 (1.55–9.3)	0.004	1.7 (0.63–4.76)	0.29
pT3b	24.3 (10.62–55.65)	<0.0001	5.9 (2.09–16.77)	0.001
Grade group				
1				
2	2.9 (0.80–10.19)	0.1	1.4 (0.37–5.57)	0.6
3	9.4 (2.20–40.39)	0.002	3.5 (0.72–16.93)	0.12
4	14.2 (3.54–56.95)	<0.0001	4.4 (0.95–20.26)	0.06
5	65.8 (17.66–245.51)	<0.0001	12.9 (2.78–60.08)	0.001

PSA, prostate specific antigen.

Various GS have been grouped together based on the assumption that they could have a similar impact on cancer behavior (16–18). Therefore, the division of GS into three groups (≤6, 7, and 8–10) becomes most therapeutically relevant and used worldwide in various models (low, intermediate and high-risk D'Amico criteria) for the prognosis of PCa progression (3, 19). Until now, such grouping has been most popular and EAU guidelines recommended it for PCa risk stratification (5). However, recent publications have clearly demonstrated that GS 3+4 vs. 4+3 has different prognosis for biochemical and disease-free survival (6, 7). Also, some studies have shown that GS 9–10 has the worst prognosis and GS 8 is closer to 4+3 than to 9–10 (8). Cases with GS 9 and 10 are quite rare and this has been the main reason for putting them together with GS 8 for more powerful statistical conclusions. However, some very recent studies show different cancer behavior at GS 8 and 9–10 (20). This suggests that the currently used PCa stratification to low, intermediate and high-risk can harbor really very high aggressiveness of cancer with GS 9–10. Moreover, indications for surgical treatment of high-risk PCa has been changed during the last decade and cases with GS 9–10 after RP will becomes more and more often. Understanding about behavior such PCa becomes very relevant.

The new ISUP GS grouping to five groups was proposed in 2013: Grade Group 1 (GS ≤6)—only individual discrete well-formed glands; Grade Group 2 (GS 3+4 = 7)—predominantly well-formed glands with a lesser component of poorly formed/fused/cribriform glands; Grade Group 3 (GS 4+3 = 7)—predominantly poorly-formed/fused/cribriform glands with a lesser component of well-formed glands; Grade Group 4 (GS 8)—only poorly-formed/fused/cribriform glands or predominantly well-formed glands with a lesser component lacking glands or—predominantly lacking glands with a lesser component of well-formed glands; Grade Group 5 (GS 9–10)—lacks gland formation (or with necrosis) with or w/o poorly-formed/fused/cribriform glands (9). The effectiveness of the suggested model was confirmed in a larger than 25,000 men multi-institutional cohort by Epstein et al. The difference for 5-year BPFS varied among all groups and the detected HR was from two- to three-fold higher for each group comparing PSA relapse in patients not only after RP, but also after RT. This study clearly proves that the new GS grouping into five groups is a better prognosticator of BCR than the currently used three group model: Harrell's c-index was higher from 0.02 to 0.05 in biopsy, RP and RT cohorts (10). PSA relapse is not always associated with CP and CRD. Epstein et al. also pointed this out as a limitation of their study (10). Very recently, Grogan et al. have presented the results of patients who underwent RP (1991–1999) with median 15.25 years' follow-up. Histopathology reports were reviewed and assigned to Grade groups in line with the recommendations of the 2014 ISUP Consensus Conference. The authors have concluded that the ISUP 2014 grading system is a significant independent predictor of both BCR and CP, outperforming the 2005 ISUP modified Gleason system (11). The presented results of our study show the same tendencies: Grade group was the strongest independent predictor for BCR, CP and CRD in multivariable Cox analysis. There is no doubt that the ISUP 2014 grading system, referred to as Grade Group in the 2016 WHO Classification (21), will be used in the coming decades in clinical practice. Therefore, there is a need to know how it will influence the worldwide adapted stratification to low, intermediate and high-risk PCa.

The presented study results show some tendencies in cancer behavior, especially in that associated with the high-risk disease. Grade groups had different survival rates when analyzing earlier disease progression—BCR, but Grade group 4 curve was much closer to group 3 (10-year BPFS 39.4% vs. 45.6%, $p = 0.045$) than to group 5 (39.4 vs. 0.0%, $p < 0.0001$, **Figure 1**). In addition to this, clinical disease progression analysis revealed the closer survival rates between Grade groups 4 and 3 (10-year CPFS 77.7 vs. 84.7%, $p = 0.8$) than between groups 4 and 5 (77.7 vs. 50.7%, $p < 0.0001$, **Figure 2**). Finally, the 10-year CSS rates were different between Grade groups 4 and 5 (87.5 vs. 79.8%, $p = 0.005$) and similar between Grade groups 4 and 3 (87.5 vs. 91.7%, $p = 0.4$, **Figure 3**). The Cox regression proportional hazard ratio analysis confirmed such findings: in univariable and multivariable analysis, the HR comparing groups 4 and 3 was much closer than comparing groups 4 and 5 (differences from two- to eight-fold—**Tables 2**–**4**) and only group 5 was associated with CRD. The same tendencies in multivariable Cox regression for Grade groups 3, 4 and 5 have been shown by Grogan et al.: HRs 6.2 vs. 6.5 vs. 12.1 for BCR, and HRs 13.2 vs. 13.9 vs. 34.3 for CP, respectively. The authors did not show survival rate data, but the Kaplan-Meier curves presented by them are similar to those observed in our study (11).

Despite its benefits for better differentiation of PCa aggressiveness it is unclear how the 2014 ISUP suggested five Grade group scheme should be integrated into the currently used PCa risk models. If our findings are considered accurate, D'Amico criteria and other PCa risk stratification nomograms based on the three-grade GS model (GS 6/ISUP

Grade 1—low-risk, GS 7/ISUP Grade 2/3—intermediate-risk and GS 8–10/ISUP Grade 4/5—high-risk PCa) covered very broad groups and should be reassessed and simplified. According to the results of the presented study, Grade group 5 associated with the highest risk for PCa progression and should be split from group 4. Grade groups 4 and 3 could be integrated into the same aggressiveness group because of their similar risk for progression. Grade group 1 and 2 shows very similar risk for disease progression and could be analyzed together. Using Grade groups 4 and 5 together for the definition of high-risk PCa poses a real risk because is masks the biggest aggressiveness of group 5. According to our results, Grade groups 1 and 2 could be integrate into the low-risk, Grade groups 3 and 4—into the intermediate and Grade group 5—into the high risk group.

The present study is not devoid of limitations: these are the relatively short follow-up, the absence of other treatment modality group and direct comparison of results and the relatively small number of cases with CP and CRD. Re-review of the pathology slides also could change the proportion between Grade groups. Relatively high, comparing to single surgeon series, positive surgical margins rate also could impact outcomes. On the other hand positive surgical margin was not confirmed as significant predictor of CP and CRD in multivariable Cox regression analysis. All these above mentioned limitations can influence the results and their interpretation.

The strength of the present study is prospectively collected data, standard evaluation of disease progression and treatment of BCR and pathological investigation by one experienced pathologist in the majority of cases. The end-point of this study was CP and CRD that are most important for cancer behavior analysis.

To our knowledge, there are very few studies that describe CP and CRD as end-point using the 2014 ISUP model after RP and there are no studies addressing high-risk PCa. More studies are needed to confirm our findings.

CONCLUSIONS

The 2014 ISUP Grading model provides very accurate grade stratification and closely reflects cancer behavior and prognosis in patients after radical prostatectomy. Grade group 5 is associated with the highest risk for cancer progression and is significantly different from other groups. Grade group 3 and Grade group 4 have the same risk for PCa progression in long-term follow-up.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Kaunas Regional Biomedical Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DM: study design, statistical analysis, data collection, and manuscript writing. ŽV: statistical analysis, data collection, and manuscript revision. IG: data collection and manuscript writing. SA, KZ, NJ, AB and AP: data collection and manuscript revision. MJ: manuscript revision. SJ: study design and manuscript revision.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Significance of Time Until PSA Recurrence After Radical Prostatectomy Without Neo- or Adjuvant Treatment to Clinical Progression and Cancer-Related Death in High-Risk Prostate Cancer Patients

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Objective: The aim of our study was to evaluate the impact of time until biochemical recurrence (BCR) after radical prostatectomy (RP) without neo- or adjuvant treatment on clinical progression (CP) and cancer-related death (CRD) in high-risk prostate cancer (HRPCa) patients.

Materials and methods: A total of 433 men with clinically HRPCa treated between 2001 and 2017 were identified. HRPCa was defined as clinical stage ≥T2c and/or biopsy Gleason score (GS) ≥8 and/or preoperative prostate specific antigen (PSA) value ≥20 ng/ml. Exclusion criteria were neo- or adjuvant treatment and incomplete pathological or follow-up data. BCR was defined as two consecutive PSA values ≥0.2 ng/ml after RP. CP was identified as skeletal lesions, local or loco-regional recurrence. CRD was defined as death from PCa. All men were divided into two groups according to BCR. The chi-square and *t*-tests were used to compare baseline characteristics between groups. Biochemical progression free survival (BPFS), clinical progression free survival (CPFS), and cancer-specific survival (CSS) rates were estimated using Kaplan–Meier analysis. Patients with detected BCR were analyzed for prediction of CP and CRD with respect to time until BCR. The impact of baseline parameters on BCR, CP, and CRD was assessed by Cox regression analysis.

Results: BCR, CP, and CRD rates were 47.8% (207/433), 11.3% (49/433), and 5.5% (24/433), respectively. Median (quartiles) time of follow-up after RP was 64 (40–110) months. Ten-year BPFS rate was 34.2%; CPFS, 81%; and CSS, 90.1%. Men with detected BCR were analyzed for prediction of CP and CRD with respect to time until BCR. The most informative cutoff for time from RP until CP and CRD was ≤1 year ($p < 0.008$). According to this cutoff, men were divided into two groups: BCR detected within 1 year and after a 1-year period. Ten-year CPFS was 49.8% in men with early BCR vs. 81.1% in men with late BCR; CSS was 70.9 vs. 92.8% ($p = 0.001$). Multivariable analysis confirmed that time until BCR within 1 year predicts CP ($p = 0.005$) and CRD ($p = 0.03$).

Conclusions: Early BCR is associated with poorer oncological outcomes. The presented results may help both to improve follow-up strategy and opt for more aggressive multimodal treatment of HRPCa in men with very early BCR.

Keywords: prostate cancer, high-risk, locally advanced, biochemical recurrence, radical prostatectomy, PSA persistence

INTRODUCTION

Prostate cancer (PCa) remains one of the most often diagnosed cancers among men. There were 1.3 million new cases of cancer in 2018 worldwide (1). According to the D'Amico classification, while the proportion of high-risk prostate cancer (HRPCa) has decreased due to the prostate-specific antigen (PSA) era, 1 out of 3 patients will still be diagnosed as having high-risk disease features (2). The optimal treatment for HRPCa remains debatable because of the lack of randomized clinical trials (3–6). A recently published study showed similar oncological outcomes of RP with external beam radiotherapy and low-dose-rate brachytherapy (7).

Although surgical treatment provides adequate disease control for all risk localized PCa, 1/4 of patients might experience a disease recurrence (2, 8). The most common test used to analyze disease recurrence is a detectable PSA concentration rate in the postoperative period. Although there is an official follow-up strategy after RP, it has its own limitations because it was created for all PCa risk groups. According to the European Association of Urology (EAU) guidelines, biochemical recurrence (BCR) is diagnosed after two consecutive PSA $\geq$ 0.2 ng/ml following RP (9). Special attention should be paid to patients with HRPCa features: they experience BCR more often as the 10-year BCR rate may increase to 85% (6, 10). Furthermore, patients that have a disease recurrence also have an increased risk of developing clinical progression (CP) and of achieving higher cancer-specific and overall mortality rates (11, 12). The timing of BCR is essential; early recurrence is associated with poorer oncological outcomes (11, 13).

Up till now, there have only been a handful of studies where time to BCR and its effect on survival have been analyzed for patients with HRPCa treated with RP without neo- or adjuvant therapy (13–18). In most studies, HRPCa represents only a small number of patients, whereas cases with low and intermediate PCa make up the bulk.

The aim of our study was to evaluate the impact of time until BCR on CP and cancer-related death (CRD) in HRPCa patients that were treated with RP without neo- or adjuvant treatment.

MATERIALS AND METHODS

Patient Population

Between 2001 January and 2017 December, 2387 men with clinically localized PCa underwent open radical prostatectomy at the Department of Urology of Lithuanian University of Health Sciences. Preoperative data included age, clinical stage (cT), preoperative PSA, biopsy Gleason score (GS), and percentage of positive biopsy cores. HRPCa was defined using D'Amico criteria: $\geq$ T2c and/or biopsy GS $\geq$ 8 and/or preoperative PSA value $\geq$ 20 ng/ml (19). Of all the men who underwent RP, 469 met HRPCa criteria and were included into the study. Pathological stage (pT), surgical margins status (R), pathological GS, number of lymph nodes removed, and number of positive lymph nodes were registered after RP. Pathological stage was assessed using the 2002 TNM system, and tumor grading was classified by using the revised 2005 Gleason grading system (20) and 2014 ISUP suggested grade grouping (21).

PSA measurement after surgery was recommended at first, third, and every 3 months of the first year, biannually in the second and third year, and annually thereafter. First PSA value $\geq$0.1 ng/ml after RP within 6 and 8 weeks was defined as persistent. PSA dynamics and additional treatment were registered in these cases. BCR was defined as two consecutive PSA values $\geq$0.2 ng/ml. Adjuvant therapy was defined as androgen deprivation therapy (ADT) or radiation therapy (RT) or both (ADT + RT) within 6 months after RP when post-operative PSA value was <0.2 ng/ml. Salvage therapy was defined as RT or ADT or RT + ADT or salvage lymph nodes dissection (LND) after detected BCR or when persistent PSA was $\geq$0.2 ng/ml. Time from RP to any kind of additional treatment was registered.

CP was identified when skeletal or visceral lesions were confirmed by bone scan, computer tomography (CT), positron emission tomography (PET/CT), or magnetic resonance imaging (MRI); local or loco-regional recurrence was confirmed by biopsy or salvage surgery. Time from BCR to CP was recorded. CRD was defined as death from PCa. Biochemical progression free survival (BPFS) was defined as the time from the operation to the day of BCR, clinical progression free survival (CPFS) was defined as the time from the operation to the day of CP, and cancer-specific survival (CSS) was defined as the time from the operation to the day of death from PCa.

Exclusion criteria were neo- or adjuvant treatment and incomplete pathological or follow-up data. Thirty-seven men were excluded from the study.

Statistics

All men were divided into two groups according to BCR. Medians, interquartile ranges, and frequencies were used for descriptive statistics. The chi-square and *t*-tests were used to compare pre- and postoperative characteristics between the following groups: age, PSA, cT, biopsy GS, percentage of positive cores, number of risk factors according to D'Amico classification, pathological GS, pT, pelvic lymphonodectomy (PLND), lymph node invasion (LNI), and R1.

BPFS, CPFS, and CSS rates were estimated using Kaplan–Meier analysis.

The patients with detected BCR were analyzed for the prediction of CP and CRD with respect to time until BCR (≤1, 1–2, 2–3, 3–4, and 4–5 years). Patients with persistent PSA were not excluded from the initial analysis. Additionally, a sub-analysis was performed to evaluate the impact of persistent PSA on CP and CRD.

Age, preoperative PSA, cT, biopsy GS, percentage of positive cores, number of risk factors according to D'Amico classification, pathological GS, pT, LNI, and R1 were evaluated for BCR, CP, and CRD in the univariable analysis. Only significant covariates were used in the multivariable analysis by using Cox regression backward conditional stepwise method. The number of risk factors by D'Amico classification was excluded from the explanatory variables for correlation in the multivariable analysis because PSA, cT, and pathological GS influence the number of risk factors by D'Amico classification.

All analyses were performed using the SPSS software (version 23.0, SPSS). A p-value of <0.05 was considered statistically significant. The Lithuanian University of Health Sciences Ethical Committee approved prospective collection of the data (BE-2-48). All patients signed a consent form provided before RP.

RESULTS

Baseline Characteristics

The total number of participants included in the final analysis was 433 men. **Table 1** summarizes the characteristics of our study cohort. The median patient age at the time of RP was 65 years old (IQR 60–68). According to the D'Amico risk classification for PCa, 298 men (68.8%) had one risk factor. Most of the patients had ≥ cT2c ($n = 323$, 74.6%) and most common biopsy GS was 6 (3 + 3) ($n = 142$, 32.8%). However, after RP, pathological GS 7 (3 + 4) was the most frequent ($n = 173$, 40%) and almost half of the patients had pT3a ($n = 194$, 44.8%).

Eighty-seven patients (61.27%) with cT1–cT2 were upstaged after the surgery to ≥ pT3. However, 77 patients (27.3%) were downstaged from cT3 to pT2.

Ninety-one (64.1%) tumors graded GS 6 at biopsy were upgraded to GS 7 and 10 patients (7%) were upgraded up to GS ≥ 8 after the surgery. Thirty-seven men (24.7%) with biopsy GS 7 were upgraded to GS ≥ 8; however, 1 patient (0.7%) was downgraded to GS 6. Thirty-seven patients (26.3%) with biopsy GS ≥ 8 were downgraded to GS 7 after RP.

Of 433 men, 323 (74.6%) underwent PLND; median 7 (IQR 5–12) lymph nodes were removed. LNI was found in 56 patients (17.4%) with a median of 2 (IQR 1–3) positive lymph nodes. In 40 cases (71.5%), one or two positive nodes were detected, while in 16 (28.5%) cases, three and more were detected.

When patients were stratified according to the biochemical relapse, there were significant difference between preoperative PSA, biopsy GS, percentage of positive biopsy cores, number of D'Amico risk factors, pathological GS, PLND, LNI and R1 (from $p = 0.006$ to $p < 0.0001$) (**Table 1**).

The Frequency of BCR, CP, CRD, and Rates of BPFS, CPFS, CSS

Median time of follow-up after RP was 64 (IQR 40–110) months. Over this time, 207 men (47.8%) experienced BCR. One hundred twenty-seven men (61.35%) had BCR in the following year after RP, 27 (13.04%) in the second year, 16 (7.73%) in the third, 14 (6.76%) in the fourth, 7 (3.38%) in the fifth, and 16 (7.73%) patients had BCR after 5 years (**Figure 1**). Of 207 men, 181 (87.44%) received salvage radiotherapy (sRT) or hormone therapy (HT) or both sRT + HT due to BCR.

CP was diagnosed in 49 (11.3%) cases. Median time from BCR to CP was 17 (IQR 9.5–35) months. Twelve men (24.5%) had metastases in lymph nodes, 11 (22.4%) had metastases in bones, 19 (36.8%) had metastases in lymph nodes and bones, 1 (2%) had visceral metastases, and 6 (12.2%) had local recurrence in the surgical bed. During the follow-up, 72 patients (16.6%) died. In 24 cases (5.5%) PCa was the cause of death.

According to the D'Amico risk classification, the 5-year BPFS rate after RP of patients with one risk factor was 57.7%, and that with two factors was 34.4%. All patients with three risk factors had BCR in the first 5 years after RP ($p < 0.0001$) (**Supplementary Figure 1**).

In all study cohorts, 5- and 10-year BPFS rate was 49.2 and 34.2%, respectively. CPFS rate was 89.2 and 81% and CSS rate was 95.6 and 90.1%, respectively.

Uni- and Multivariable Regression Analyses Predicting BCR

Preoperative features were analyzed to determine which factors significantly predict BCR after RP. In the univariable analysis, PSA, biopsy GS, percentage of positive biopsy cores, and number of D'Amico risk factors were significant (from $p = 0.007$ to $p < 0.0001$). These factors were used in the multivariable analysis and showed that higher grade of biopsy GS and level of preoperative PSA are the most informative predictors for BCR (from $p = 0.006$ to $p < 0.0001$) (**Table 2**).

In the univariable analysis, all postoperative factors predict BCR after RP ($p < 0.0001$). These factors were used in the multivariable analysis and showed that higher grade of pathological GS, pT, LNI, and R1 are the most informative predictors for BCR (from $p = 0.028$ to $p = 0.005$) (**Table 3**).

Early vs. Late BCR

Patients with detected BCR ($n = 207$) were analyzed for prediction of CP and CRD with respect to time until BCR (≤1, 1–2, 2–3, 3–4, and 4–5 years). The most informative cutoff was BCR in the following year after RP ($p < 0.008$) (**Table 4**).

According to this cutoff, patients were divided into two groups: BCR detected within 1 year (early BCR) ($n = 127$, 61.4%) and after 1 year (late BCR) ($n = 80$, 38.6%). Five-year and 10-year CPFS was 70.7 and 49.8% in men with early

TABLE 1 | Patient characteristics.

Parameter	No BCR (226)	BCR (207)	*p*-value	All ($n = 433$)
Age (years): median (IQR)	65 (60–68)	65 (59–69)	0.68	65 (60–68)
PSA (ng/ml): *n* (%)				
<20	185 (81.86)	146 (70.5)	0.006	331(76.4)
≥20	41 (18.1)	61 (29.5)		102 (23.6)
Clinical stage: *n* (%)				
cT1–cT2a	35 (15.5)	33(15.9)	0.96	68 (15.7)
cT2b	25 (11.1)	17 (8.2)		42 (9.7)
≥cT2c	166 (73.4)	157 (75.8)		323 (74.6)
Biopsy GS: *n* (%)				
6	92 (40.7)	50 (24.2)	<0.0001	142 (32.8)
3 + 4	64 (28.3)	55 (26.6)		119 (27.5)
4 + 3	12 (5.3)	19 (9.2)		31 (7.2)
8	46 (20.4)	49 (23.7)		95 (21.9)
9 – 10	12 (5.3)	34 (16.4)		46 (10.6)
% of positive cores: median (IQR)	38 (25–62)	50 (33–75)	<0.0001	50 (29.25–67)
D'Amico HRPCa: *n* (%)				
1 risk factor	178 (78.8)	120 (58)	<0.0001	298 (68.8)
2 risk factors	47 (20.8)	74 (35.7)		121 (27.9)
3 risk factors	1 (0.4)	13 (6.3)		14 (3.3)
Pathological GS: *n* (%)				
6	33 (14.6)	11 (5.3)	<0.0001	44 (10.2)
3 + 4	122 (54.0)	51 (24.6)		173 (40)
4 + 3	31 (13.7)	36 (17.4)		67 (15.5)
8	24 (10.6)	31 (15)		55 (12.7)
9 – 10	16 (7.1)	78 (37.7)		94 (21.7)
Pathologic stage: *n* (%)				
pT2	104 (46)	34 (16.4)	<0.0001	138 (31.9)
pT3a	110 (48.7)	84 (40.6)		194 (44.8)
≥pT3b	12 (5.3)	89 (43)		101 (23.3)
PLND: *n* (%)	142 (62.8)	181 (87.4)	<0.0001	323 (74.6)
LNI: *n* (%)	1 (0.4)	55 (30.4)	<0.0001	56 (17.4)
R1: *n* (%)	66 (30.6)	122 (58.9)	<0.0001	188 (43.4)
Rx	10(4.4)	10 (4.8)		20 (4.6)

IQR, interquartile range.

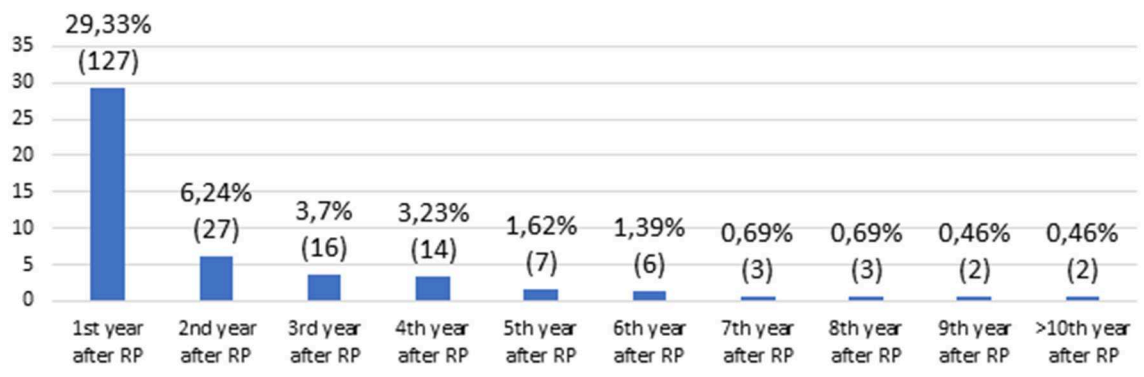

FIGURE 1 | Risk of biochemical recurrence by the following year after radical prostatectomy (%).

TABLE 2 | Univariable and multivariable logistic regression analyses while using preoperative factors for predicting BCR.

	Univariable analysis		Multivariable analysis	
Predictors	**Odds ratio (95% CI)**	***p* value**	**Odds ratio (95% CI)**	***p* value**
Age	0.99 (0.97–1.02)	0.6	–	–
PSA ng/ml				
<10	Reference	0.003	Reference	0.006
10–20	1.65 (1.9–2.28)	<0.0001	1.64 (1.15–2.34)	<0.0001
>20	1.84 (1.31–2.57)		2.02 (1.39–2.95)	
Clinical stage				
T1–T2a	Reference	0.47	–	–
T2b	0.8 (0.45–1.45)	0.66		
≥T2c	1.09 (0.75–1.59)			
Biopsy GS				
6	Reference	0.007	Reference	0.019
3+4	1.7 (1.15–2.5)	<0.0001	1.7 (1.09–2.68)	0.004
4+3	3.03 (1.77–5.18)	0.005	2.42 (1.33–4.41)	0.001
8	1.77 (1.19–2.63)	<0.0001	2.19 (1.38–3.47)	<0.0001
9–10	3.55 (2.28–5.53)		3.84 (2.31–6.38)	
No. of risk factors				
1 risk factor	Reference	<0.0001	–	–
2 risk factors	2.01 (1.5–2.69)	<0.0001		
3 risk factors	3.58 (2.01–6.38)			
% of positive cores	1.01 (1.01–1.02)	<0.0001	1.01 (1–1.02)	0.001

CI, confidence interval.

TABLE 3 | Univariable and multivariable logistic regression analyses, using post-operation features for predicting the presence of BCR.

	Univariable analysis		Multivariable analysis	
Predictors	**Odds ratio (95% CI)**	***p*-value**	**Odds ratio (95% CI)**	***p*-value**
Pathological GS				
6	Reference	0.22	Reference	0.76
3 + 4	1.51 (0.78–2.91)	<0.0001	1.13 (0.51–2.48)	0.072
4 + 3	3.78 (1.9–7.55)	<0.0001	2.13 (0.94–4.84)	0.071
8	3.71 (1.85–7.43)	<0.0001	2.16 (0.94–5.96)	0.005
9 – 10	9.67 (5.01–18.66)		3.15 (1.41–7.0)	
Pathological stage				
T2	Reference	<0.0001	Reference	0.021
T3a	2.17 (1.45–3.24	<0.0001	1.78 (1.09–2.91)	0.007
≥T3b	7.2 (4.81–10.77)		2.16 (1.24–3.75)	
LNI	5.42 (3.85–7.63)	<0.0001	1.61 (1.05–2.47)	0.028
R1	2.48 (1.86–3.32)	<0.0001	1.54 (1.1–2.18)	0.014

BCR vs. 89.9 and 81.1% in men with late BCR ($p = 0.001$) (**Figure 2A**); CSS was 84.8 and 70.9% vs. 98% and 92.8% ($p = 0.001$), respectively (**Figure 2B**).

Sub Analysis of PSA Persistence

A total of 130 patients (30%) had PSA persistence (PSA ≥ 0.1 ng/ml). Seventy-three of them (56.2%) had PSA ≥ 0.2 ng/ml and were assigned to early BCR group. Fifty-seven patients (43.8%) had PSA between 0.1 and 0.2 ng/ml and 44 of them (77.2%) harbored BCR during the study period.

A further analysis was done to evaluate whether PSA persistence could be a predictive factor for CP and CRD. In the univariable analysis, PSA persistence was significant for CP (HR: 7.5; $p < 0.0001$) and CRD (HR: 3.7; $p = 0.004$), but it was not meaningful in the multivariable regression analysis (HR: 1.01; $p = 0.89$ and HR: 1.5; $p = 0.51$) when time to BCR (early BCR vs. late BCR) was added (the data are shown in **Supplementary Table 1**). Therefore, PSA persistence was not included for further CP and CRD analysis as a predictor in order to avoid mismatching PSA follow-up data.

TABLE 4 | CP and CRD rates according to time of BCR.

Time of BCR	CP, $n = 49$ (%)	p	CRD, $n = 24$ (%)	p
≤1 year	38 (77.56)	0.008	21 (87.5)	0.005
1–2 years	5 (10.2)	0.5	2 (8.3)	0.47
2–3 years	2 (4.08)	0.27	–	–
3–4 years	1 (2.04)	0.13	1 (4.2)	0.59
4–5 years	1 (2.04)	0.55	–	–

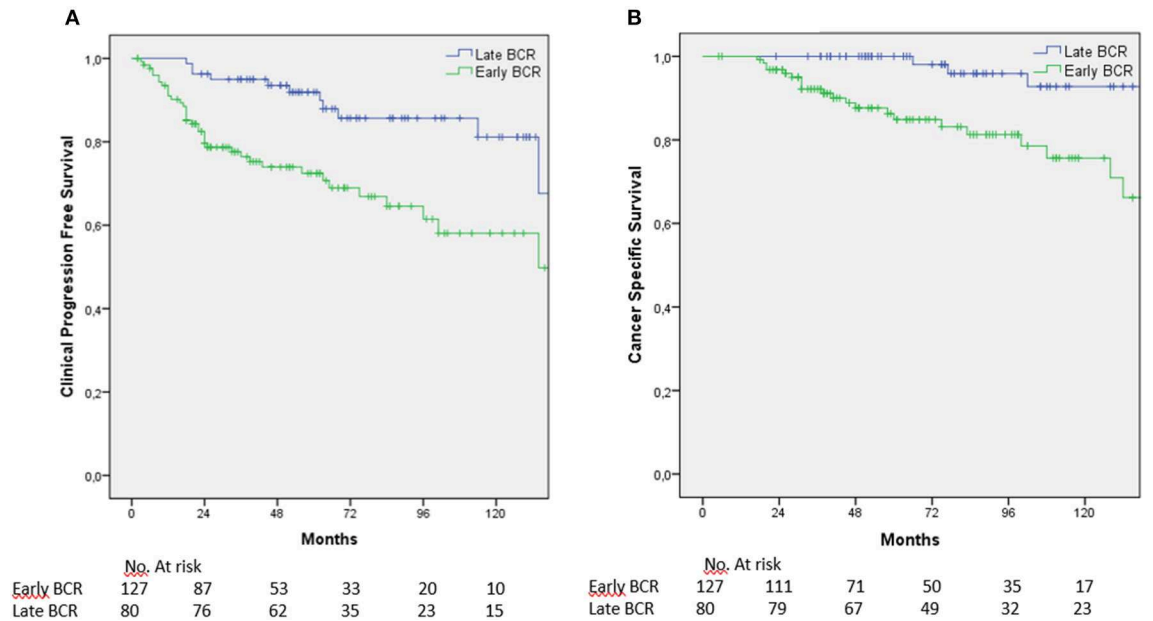

FIGURE 2 | (A) CPFS and **(B)** CSS according to BCR time.

Uni- and Multivariable Regression Analyses Predicting CP and CRD

Patients with BCR were further analyzed. In the univariable analysis for CP, we found that biopsy GS, number of D'Amico risk factors, percentage of positive biopsy cores, pathological GS, pT, LNI, R1, and early BCR were significant and were used in the multivariable analysis. Only stage pT3b and early BCR were detected as significant prognosticators of CP ($p = 0.041$ and $p = 0.005$, respectively).

In the univariable analysis for CRD, only LNI, R1, and early BCR were significant and were used in the multivariable analysis. All of them correlated with CRD (from $p = 0.03$ to $p = 0.002$) (**Table 5**).

DISCUSSION

The oncologic outcomes after RP for patients with HRPCa disease merit specific attention. To date, there have only been a handful of studies where time to BCR and its effect on survival have been analyzed for patients with HRPCa treated with RP without neo- or adjuvant therapy (13–18). Indeed, most studies included mainly patients with favorable disease characteristics; only several of them focused especially on HRPCa. We managed to carry out a study that involved a huge number of 433 patients with HRPCa in comparison with other smaller studies (14–18).

In the presented cohort of men with pre-operative HRPCa features, the 5- and 10-year CPFS were 89.2 and 81%, and 5- and 10-year CSS were 95.6 and 90.1%, respectively. The strongest predictor for CP was time to BCR up to 1 year (HR: 2.7, $p = 0.005$). Early BCR (HR: 4.0, $p = 0.03$) together with LNI (HR: 4.1, $p = 0.002$) and R1 (HR: 4.2, $p = 0.02$) were detected as important predictors for CSS in the multivariate Cox regression analysis.

Several notable points should be mentioned analyzing the role of BCR and time to BCR regarding disease progression in the HRPCa population. To date, PSA remains the most important tool for following patients with PCa after curative treatment. Although surgical treatment provides good control of the disease, some of the patients might experience BCR. During the study period, almost half of men (47.8%) harbored BCR. Previous reports showed that although age was not a significant factor, other preoperative factors such as PSA, cT, biopsy GS, percentage of positive biopsy cores, number of high-risk factors according to

TABLE 5 | Multivariable logistic regression analyses predicting the presence of CP and CRD.

	CP Multivariable analysis		CRD Multivariable analysis	
Predictors	**Odds ratio (95% CI)**	***p*-value**	**Odds ratio (95% CI)**	***p*-value**
After RP GS				
6	Reference		–	–
3 + 4 vs. 6	0.24 (0.04–1.34)	0.1		
4 + 3 vs. 6	0.24 (0.04–1.58)	0.14		
8 vs. 6	0.68 (0.13–3.6)	0.65		
9 – 10 vs. 6	1.99 (0.38–10.43)	0.42		
Pathological stage				
T2	Reference	0.69	–	–
T3a vs. T2	1.29 (0.38–4.4)	0.041		
≥T3b vs. T2	3.44 (1.05–11.24)			
LNI	0.89 (0.79–3.65)	0.73	4.1 (1.66–10.14)	0.002
R1	1.7 (0.79–3.65)	0.18	4.2 (1.23–14.38)	0.02
Early vs. late BCR	2.72 (1.35–5.5)	0.005	3.98 (1.15–13.79)	0.03

D'Amico classification, pathological stage, GS, LNI, and surgical margin (SM) status were predictive factors for BCR (2, 8, 10, 12, 16, 22–27). Our results also proved the strength of all these risk factors for BCR even in the HRPCa population, but the strongest predictors when comparing preoperative factors were GS 8–10 and PSA value $\geq$ 20 ng/ml. Freedland et al. (22) showed that patients having preoperative PSA $\geq$ 20 ng/ml present a more than three times greater chance to have BCR compared to those patients who have preoperative PSA <6 ng/ml. We also managed to find that there is a 2-fold greater chance for BCR if the preoperative PSA is ≥20 ng/ml compared to PSA < 10 ng/ml. Pathological GS 8–10, pT3b, and positive SM have the strongest impact on BCR analyzing post-operative parameters (from $p = 0.014$ to $p = 0.005$, **Table 3**).

Another important finding that should be noted is time to BCR. At the end of the study, 207 men (47.8%) harbored BCR, with the majority of 61% occurring within the first year after RP. These numbers are quite high compared to the recently published Chow et al. (28) study, where they had 44.6% of cases with early BCR. However, the authors presented fewer patients with preoperative high-risk features, which have a significant influence on the rate of BCR. Theoretically, PSA should be undetectable after RP within 21–30 days, considering that PSA's half-life period is 3.15 days (29). Unfortunately, some of the patients have persistent PSA that could have an impact on PCa progression. Lee et al. (17) noticed that if there is still residual prostatic tissue left after RP, which could be the case especially with HRPCa, PSA should be detectable afterwards. The question remains whether it is a residual benign prostatic tissue, extra prostatic tumor sites, or micro metastasis. The role of persistent PSA has been investigated recently by several investigators and ≥0.1 ng/ml PSA value was relied on as definition of PSA persistence (29–33). However, studies of this field are scant or focus on subgroups, such as LNI disease or patients with sRT. Only one very recent study has been aimed at looking for the possible effect of persistent PSA on the long-term oncological outcomes (32), but the real importance of PSA persistence needs to be clarified. Out of 433 men, 130 (30%) had PSA persistence in the cohort presented herein, which is similar to the Bianchi et al. series with LNI patients (32), but higher compared to Preisser or McDonald studies that had more favorable pathological features (31, 33). The population with persistent PSA is heterogeneous. Out of 130 patients, 57 (43.8%) had PSA between 0.1 and 0.2 ng/ml, and 44 of 57 (77.2%) harbored BCR during the study period. Only 11 of 57 (19.3%) had BCR within 1 year, which associates with lower risk for disease progression. Our sub-analysis shows that persistent PSA lost significance for prediction of disease progression in the multivariable regression when analyzed together with early BCR.

In the multivariable analysis, we identified several factors (higher pT and early BCR) that are associated with CP. However, the strongest factor was early BCR ($p = 0.005$). These data coincided with those in the studies of other authors (2, 13, 34, 35). Interestingly, our study identified correlation of LNI, R1, and pathological GS in the univariable, but they were not significant in multivariable analysis. Antonarakis et al. (35) presented a study where patients, after RP, never received adjuvant or salvage therapy before the development of CP. They also did not find correlation in the multivariable analysis between LNI, R1, and CP. However, they found correlation between high grades of pathological GS. Pound et al. (36) emphasize that 1 out of 3 patients with BCR will eventually have CP. In our study, CP was diagnosed in 23.7% (49/207) of cases with BCR, whereas Carver et al. (34) had only 14% of cases. It should be mentioned that Carver et al. included patients with more favorable disease characteristics. In our study, the majority of CP (38/49, 77.56%) appeared for patients having early BCR.

Time to BCR is also crucial for CRD as this has already been demonstrated in our multivariable analysis ($p = 0.03$). Similar results are found in other studies (12, 13, 37). Briganti et al. (13) appropriately point out correlation between early BCR and CRD. It should be mentioned that Briganti et al. defined early BCR as that which occurred in the first 3 years after RP. Pompe et al. (37) demonstrated that CRD correlates with early BCR (≤1 year), pathological GS, and short PSA-DT. We did not calculate

PSA-DT and pathological GS was not a significant factor for CRD in our study. However, we present that LNI and R1 are significant for CRD, which contradicts the arguments found in the Pompe et al. study. Heterogeneous patient cohorts in the aforementioned studies did not allow the identification of a single predictor for PCa progression, but early BCR is one of them, especially in patients with high-risk features.

The limitations of our study include the use of a single institution. According to EAU guidelines (9), PLND should be recommended for all patients having HRPCa features. However, that was not the case in daily practice up to 2010, and in our study, PLND was done not for all HRPCa. We also did not calculate PSA-DT and did not include details of tumor size.

The strengths of our study include a high number of men with HRPCa features. We succeeded in collecting long follow-up data after RP. None of the patients received neo- or adjuvant treatment.

The results presented herein show that HRPCa patients are at high risk for BCR and time to BCR plays a very important role in the prediction of CP and CRD. For these patients, follow-up strategy should be personalized particularly in the first year after RP. Early BCR (up to 1 year) could be useful for counseling and decision making in the additional treatment setting.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

ZV had full access to all the data in the study, takes responsibility for the integrity of the data, the accuracy of the data analysis, participated in data collection, data analysis, and manuscript writing. ZV and DM performed study design, data analysis, and manuscript writing. MJ contributed to manuscript writing.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2019.01286/full#supplementary-material

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REVIEW
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Combined Modality Therapies for High-Risk Prostate Cancer: Narrative Review of Current Understanding and New Directions

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Despite the many prospective randomized trials that have been available in the past decade regarding the optimization of radiation, hormonal, and surgical therapies for high-risk prostate cancer (PCa), many questions remain. There is currently a lack of level I evidence regarding the relative efficacy of radical prostatectomy (RP) followed by adjuvant radiation compared to radiation therapy (RT) combined with androgen deprivation therapy (ADT) for high-risk PCa. Current retrospective series have also described an improvement in biochemical outcomes and PCa-specific mortality through the use of augmented radiation strategies incorporating brachytherapy. The relative efficacy of modern augmented RT compared to RP is still incompletely understood. We present a narrative review regarding recent advances in understanding regarding comparisons of overall and PCa-specific mortality measures among patients with high-risk PCa treated with either an RP/adjuvant RT or an RT/ADT approach. We give special consideration to recent trends toward the assembly of multi-institutional series targeted at providing high-quality data to minimize the effects of residual confounding. We also provide a narrative review of recent studies examining brachytherapy boost and systemic therapies, as well as an overview of currently planned and ongoing studies that will further elucidate strategies for treatment optimization over the next decade.

Keywords: prostate neoplasms, high-risk, clinically localized, prostatectomy, radiotherapy

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INTRODUCTION

Of the cases of newly diagnosed localized prostate cancer (PCa), ∼15% are discovered as high-risk disease (1). There has been clinical equipoise surrounding the issue of selecting optimal definitive therapy, as treatment paradigms have evolved to incorporate both upfront surgery and radiation approaches (2). Definitive therapy for newly diagnosed cases of high-risk disease now routinely includes radical prostatectomy (RP) followed by a consideration of adjuvant radiation (ART) and androgen deprivation therapy (ADT) or a combination of external beam radiation therapy (XRT) with androgen deprivation therapy (ADT) with or without the addition of brachytherapy (BT).

While treatment of favorable-risk localized disease has benefited from the relatively recent publication of randomized controlled data demonstrating no detectable difference in PCa-specific mortality (PCM) between RP- and RT-based approaches (3), there has not been a large-scale randomized clinical trial representing patients with high-risk disease. The available trials in the

setting of high-risk PCa that compare outcomes between RP and RT cohorts are limited by small numbers of high-risk patients (4, 5). Comparing RT and RP over the past several decades has been somewhat of a moving target, as paradigms for treatment of high-risk disease have shifted with steady innovation. Recent practice-shaping trends in RT clinical trials and retrospective investigation have explored optimization of combined modality therapies utilizing radiation, including XRT + BT boost (6), demonstration of efficacy and duration optimization of ADT with and without dose-escalated RT (7–15), incorporation of whole-pelvis XRT for high-risk patients (16–18), assessment of safety of hypofractionation in the setting of high-risk disease (19–22), and exploration of addition of systemic therapies (23–26). Despite the rapid advancement of understanding regarding the optimization of modern therapies, the decision regarding primary intervention with RP vs. RT has remained most elusive. As such, we have sought to provide a narrative review focusing on advancements in the understanding of treatment efficacy of optimized RT- and RP-based approaches to clinically localized high-risk PCa. We have also sought to provide a brief overview of upcoming clinical trials anticipated over the next decade.

METHODS

We aimed to review the available literature regarding the relative efficacy of modern strategies incorporating RP or RT-first techniques targeted at the definitive treatment of high-risk PCa. We constructed search terms corresponding to three separate reference databases: PubMed, Scopus, and Cochrane Central Register of Controlled Trials. Subject headings and MeSH terms were incorporated with text/keyword terms for "radical prostatectomy," "radiotherapy," "outcome," "survival," "mortality, "systemic therapy," and related terms. These were assembled into search strings tailored for each database (**Supplementary Table 1**). Given the heterogeneity in classification schemes of PCa (2), we did not discriminate with regard to the definition of high-risk and aimed to target the common definitions (**Supplementary Table 2**), as well as cohorts constructed to examine subsets of common definitions of high-risk disease, such as Gleason 9–10. Cohorts including, though not exclusively focusing on, locally advanced patients with nodal disease were included, as many investigators did not know nodal status preoperatively. Additional details of the literature search are described in **Supplementary Table 1**. Given changes in practice patterns concerning RT dose-escalation and ADT use in high-risk disease, we drew principally from studies published within the past decade (since 2009). Reference lists of reviews published on clinically localized PCa were also checked for additional relevant publications (26–32). Our primary outcomes of interest were PCM and overall mortality (OM), although a meta-analysis focusing on these outcomes was not the purpose of this review. We excluded studies focusing primarily on surrogate measures of progression or PCM, such as biochemical recurrence/failure (BCR/BF). Studies focusing on toxicity, patient-reported outcomes, and quality of life are beyond the scope of this review.

The United States national online registry of clinical trials located at clinicaltrials.gov, as managed by the National Library of Medicine at the National Institutes of Health, was queried for all current active trials with keyword terms "prostate cancer," "prostate cancer Stage III," and related synonymous terms (**Supplementary Table 3**). The search was limited to exclude trials that had been suspended, terminated, completed, withdrawn, or trials with unknown status. Each clinical trial in the resulting list was individually reviewed for relevance and inclusion in the table of current trials of interest. Furthermore, multiple large, geographically disparate U.S. academic institutions with searchable lists of active clinical trials including University of California San Diego, University of California San Francisco, Thomas Jefferson University, MD Anderson, and Memorial Sloan Kettering Cancer Center were queried for trials investigating PCa therapies to ensure completeness of the initial clinicaltrials.gov search. Ongoing trials that had been previously quoted or otherwise referenced in the other sources surveyed in this review paper were included in **Table 5**.

Lack of Data From Randomized Clinical Trials

Randomized controlled trials (RCTs) providing insight into relative efficacy of upfront RP or RT modalities have remained limited for the past several decades, which has prompted the use of alternative comparison methods to address investigation (**Supplementary Table 4**). There were two early RCTs in PCa, including one performed by the Uro-Oncology research group before routine use of prostate-specific antigen (PSA) and one by the Japanese Study Group for Locally Advanced Prostate Cancer (5, 33). Only the latter provided representation of high-risk disease. Multiple additional studies were initiated and failed to accrue enough patients to investigate mortality endpoints (34–37). These early studies, when reported, demonstrated possibly improved survival outcomes in favor of surgery across localized disease risk groups. However, there were significant concerns regarding stage migration, small sample size, short follow-up, and other methodological limitations of these trials that limited their impact (38). A more recent study of patients with localized or locally advanced PCa undergoing RP or XRT + BT with ADT did not demonstrate a statistically significant difference in OM or PCM. The study was underpowered to assess survival outcomes, though, with only 89 patients (4) (**Table 1**). Although not providing information regarding high-risk disease, the ProtecT study represents a more modern, well-designed, randomized trial in PCa. The comparison of RT- and RP-based modalities contained in this trial did not demonstrate statistically significant differences in PCM ($p = 0.48$), with OM rates also demonstrably comparable between the arms. Interpretation of this trial concerning its RT vs. RP outcomes is limited due to a lack of statistical power, as the observed PCM was lower than anticipated (38, 44). In the setting of high-risk disease, a modern clinical trial targeting a randomization between upfront RT- and RP-based definitive treatment has recently been initiated with the SPCG-15 trial. This trial compares standard (RT + ADT) and

experimental (RP with extended pelvic lymph node dissection and with addition of adjuvant/salvage RT and ADT) treatment at 23 centers in Denmark, Finland, Norway, and Sweden (45) (**Table 5**). As such an effort is just getting underway, it is likely that for the next decade, conclusions regarding the relative efficacy of RP- vs. RT-based approaches for high-risk disease will not be drawn from randomized data.

Limited Ability to Investigate Mortality Endpoints With Limited-Institution Observational Data

Despite the lack of RCTs that provide data regarding high-risk disease, multiple institutions have published retrospective data comparing RP and RT outcomes. Selected studies are presented in **Table 1**, with a more comprehensive list in **Supplementary Table 4**. The largest of these are retrospective studies published by Memorial Sloan Kettering, Mayo Clinic/Fox Chase, and Cleveland Clinic (39–41). The Memorial Sloan Kettering Study described outcomes for cT1c–T3b PCa who underwent either RP with pelvic lymphadenectomy or RT (without coverage of pelvic lymph nodes) to a dose of at least 81 Gy. At a median follow-up time of 5 years, the study reported a 7.8% difference in 8-year metastatic progression in the high-risk subset favoring RP. The hazard ratio (HR) for PCM in RP vs. RT is 0.32 [95% confidence interval (CI), 0.13–0.80; $P = 0.015$] in favor of surgery after adjusting for preoperative Kattan nomogram, age, and treatment year. Adjusted HRs for the high-risk subset were not published. The treatment of high-risk patients in this study was additionally limited by the lack of long-term ADT and possibly the lack of pelvic lymph node irradiation, as has been discussed (2). There is some continuing equipoise regarding the latter issue. The relative benefit of pelvic lymph node irradiation in intermediate- to high-risk PCa is currently undergoing prospective evaluation in RTOG 0924, although the majority of clinical trials publishing outcomes for combination

TABLE 1 | Selected representative institutional studies of comparative effectiveness of radiotherapy and radical prostatectomy in high-risk prostate cancer.

Study type	Representative study	Summary description	Endpoints	Findings related to PCM, OM	Key limitations
Randomized controlled trial	Lennernäs et al. (4) (accrual 1996–2001)	89 patients, T1b–T3a, N0, M0 and PSA ≤50 ng/ml. All underwent total androgen blockade (6 months). RP vs. XRT + BT.	Self-reported HRQoL. Secondary endpoints: OM, PCM	10-year results RP−13.3% PCM, 26.7% OM XRT + BT: 4.5% PCM, 20.5% OM No statistically significant differences	Limited sample size, lack of statistical power
Single or limited multi-institutional observational study	Zelefsky et al. (39) Memorial Sloan Kettering (accrual 1993–2002)	2,380 pts (including 409 NCCN high-risk) with T1c-T3b PCa were treated with intensity-modulated XRT (≥81 Gy) or RP	Primary endpoint: distant metastasis. Secondary endpoint: PCM	5-year results with 95% CI RP: 1.0% (0.1–7.0%) PCM RT: 3.7% (1.8–7.4%) PCM	Hazard ratios not reported for high-risk subset. 3–6 months ADT in 56% of patients. No adjuvant ADT in high-risk patients
	Boorjian et al. (40) Mayo Clinic, Fox Chase (accrual 1988–2004)	1,847 NCCN high-risk patients, treated with RP or XRT with pelvic nodes included	Systemic progression, PCM, OM	10-year PCM 8% (RP), 8% (XRT + ADT), and 12% (XRT alone). Worse HR (1.6) for OM for XRT/ADT compared with RP, though not significant for PCM	56% ADT utilization in XRT cohort, low radiation dose of median 72 Gy XRT
	Ciezki et al. (41) Cleveland Clinic (accrual 1996–2012)	2,557 NCCN high-risk patients, treated with RP or XRT (≥78Gy) or BT (LDR 144 Gy)	PCM, BF, clinical relapse	5-year results PCM was 5.3% XRT, 3.2% LDR, and 2.8% for RP	> 6-months duration of ADT in only 26% of patients with XRT
	Tilki et al. (42) Chicago Prostate Cancer Center, USA and Martini-Klinik Prostate Cancer Center, Germany (accrual 1992–2013)	639 patients with Gleason 9–10 treated with RP ± adjuvant RT ± ADT or XRT + BT + ADT (median 6 months)	OM, PCM	5-year PCM: 21.89% (RP), 3.93% (RP + XRT), 9.83% MaxRP, 27.04% RP + ADT vs. 5-year PCM: 2.22% (MaxRT)	Surgery and RT comparison cohorts at geographically different centers
	Reichard et al. (43) MD Anderson (accrual 2004–2013); comparison with Matched SEER Cohort	304 patients with NCCN high-risk or very-high-risk treated with RP or XRT + ADT	BF, DM, OM, LF	5-year OM RP = 4.3% RT + ADT = 1.5% HR NS	Limited patient number to assess OM or PCM endpoints; only 3.9% of RP patients received adjuvant RT, no PCM reported

BF, biochemical failure; BT, brachytherapy; DM, distant metastases; Gy, gray; HR, hazard ratio; HRQoL, health-related quality of life; LDR, low-dose-rate; MaxRP, RP followed by adjuvant radiation within 1 year; MaxRT, XRT + brachytherapy ± ADT; OM, overall mortality; NS, not significant; PCM, prostate cancer-specific mortality; PSA, prostate-specific antigen; XRT, external beam radiation therapy.

XRT and ADT for high-risk PCa included pelvic lymph node irradiation (7–9, 12).

Large cohorts focusing more on a high-risk group were reported by Mayo Clinic/Fox Chase (40) and Cleveland Clinic (41). The former group focused on RP vs. XRT, with the latter additionally comparing patients who received low-dose-rate (LDR) BT. The Mayo Clinic/Fox Chase group published outcomes for 1,847 National Comprehensive Cancer Network (NCCN) high-risk patients, treated with RP or XRT. Pelvic lymph node coverage was included in the radiation portal. The study principally reported a 10-year cancer-specific survival rate of 92, 92, and 88% after RP, XRT + ADT, and XRT alone, respectively ($P = 0.06$). After adjusting for case mix, there were no significant differences in systemic progression (HR, 0.78; 95% CI, 0.51–1.18; P = 0.23) or PCM (HR, 1.14; 95% CI, 0.68–1.91; $P = 0.61$) between patients who received XRT + ADT and patients who underwent RP. The risk of OM, however, was greater after XRT + ADT than after RP (HR, 1.60; 95% CI, 1.25–2.05; $P = 0.0002$). The study is strengthened by follow-up >10 years for the patients receiving RP and 6 years for patients receiving RT, as well as a median duration of ADT of 22.8 months. It is limited, though, by the low radiation doses used (72 Gy). The Cleveland Clinic cohort published cancer-specific survival outcomes of 2,557 patients with NCCN high-risk PCa treated with XRT ± ADT, LDR ± ADT, or RP ± XRT (41). The PCM at 5 and 10 years, respectively, was 5.3 and 11.2% for XRT, 3.2 and 3.6% for LDR BT, and 2.8 and 6.8% for RP ($P = 0.0004$). Although radiation dose utilized was notably higher than that of the Mayo/Fox Chase Study, with patients receiving at least 78 Gy, the utilization rate of long-course ADT in high-risk patients was low. Only 26% of patients receiving RT had an ADT duration >6 months. This low rate limits the interpretation of the HR from the study in favor of RP when comparing RP vs. XRT.

There have been more recently published single-institution studies demonstrating improved compliance with dose-escalated RT and long-course ADT, though the numbers of patients included have been demonstrably lower (43, 46). A study by Washington University reported outcomes for 62 propensity-score-matched pairs of patients with NCCN high-risk PCa receiving RP or XRT (46). Although not achieving uniform compliance, the study states that 80.6% of the patients receiving XRT received 2 years of total ADT. The median XRT dose was 75.6 Gy. Although PCM was not reported, 5-year rates of metastasis for RP and RT were 33 and 8.9%, respectively ($P = 0.003$), with no difference in overall survival detected. The more recent study was published by MD Anderson, describing a cohort of 304 patients with NCCN high or very high-risk PCa treated from 2004 to 2013 with RP or XRT + ADT (43). The XRT + ADT group included 73 patients, though 100% received ADT with a median duration of 22 months, and all but one patient received ≥75.6 Gy. At 83 months median follow-up, there was no difference in local recurrence (HR, 2.7; 95% CI, 1.0–7.9; P = 0.06), distant metastasis failure (HR, 2.5; 95% CI, 0.8–7.8; $P = 0.1$), or OM (HR, 1.35; 95 CI, 0.4–4.8; $P = 0.6$) between patients undergoing RP vs. RT + ADT, with definition of HR in this study favoring RT at higher values. Although both of these studies demonstrate improved compliance with modern XRT + ADT standard of care compared with previous single-institutional studies, the patient sample size limits statistical power to detect differences in PCM or OM.

Although large single or limited-institutional studies are available comparing RP vs. RT outcomes, the shift that only happened relatively recently to modern ADT and radiation dose regimens continues to limit interpretation of the most extensive studies. Newer single-institutional series will likely provide a more relevant comparison of optimized RT/ADT vs. RP with less confounding as data mature.

Population-Based Databases

With the proliferation of cancer registries, a multitude of PCa outcome studies have been published utilizing large databases to examine late-term OM or PCM (47). Studies using databases with limited reporting of ADT and RT dose compliance include those utilizing PCOS [Surveillance, Epidemiology, and End Results (SEER)], PcBaSe, and other early organized databases. These databases demonstrate a somewhat limited ability to account for adequacy of combined modality therapy in the setting of high-risk treatment due to difficulty accounting for dose-escalation as well as 1.5 months or greater of ADT in the context of XRT/ADT definitive management (**Supplementary Table 5**) (48–51). National Cancer Database (NCDB) studies typically allow for reporting of whether a patient received ADT during or after therapy. The duration of treatment, however, is not reported. NCDB studies are also limited by no report of PCM (52–54). SEER-Medicare studies, on the other hand, have been able to report the median number of days of ADT in some instances, with assessment of both OM and PCM possible (55–57). Virtually all databases have limited difficulty to provide full details regarding the RT plan, including consideration of dose and pelvic nodal treatment. Several representative studies drawn from these databases are shown in **Table 2** and **Supplementary Table 4**. The vast majority of population-based studies point to RT relying solely on external beam without BT as associated with worse OM (49, 51, 52, 56, 57) and PCM (48–51, 55–57) than RP. Ability to eliminate residual confounding, most notably to ensure both adequate RT dose and ADT duration, in any of these studies is limited.

Early Array of Meta-Analyses

To cope with the difficulties presented by the lack of randomized data in the setting of high-risk PCa treated with RT vs. RP, many investigators have sought to pool the above study types to perform meta-analyses comparing outcomes of RT or RP with respect to OM and PCM. Although BCR is commonly used as a metric of clinical relapse in retrospective or observational studies of PCa, there have been arguments against whether this is a clinically meaningful endpoint. For instance, the definition of biochemical recurrence differs depending on whether patients receive upfront surgery or radiation, with the AUA definition used in the former instance and the ASTRO or Phoenix criteria most often used in the latter (58–60). Additionally, surgical data suggest that at 5 years following BCR, ∼10% of men will have developed clinical progression, and ∼5% will have experienced PCM, with no association on multivariate analysis

TABLE 2 | Selected population-based database studies comparing survival endpoints for prostatectomy vs. radiotherapy.

References	Database used/accrual period	Cohort described	Key results	Missing variables of study/ limitations of database used
Hoffman et al. (49)	PCOS/SEER (1994–2010)	1,655, including 437 high-risk (PSA > 10 or Gleason ≥ 8) treated with RP or XRT	High-risk results: RP was associated with statistically significant advantages for OM: HR 0.65 (95% CI 0.48–0.87), and PCM: HR: 0.36 (95% CI 0.20–0.64)	ADT duration RT dose RT modality/plan details Small sample size
Sooriakumaran et al. (50)	PcBaSe Sweden (1996–2010)	32,846 including 7649 modified NCCN high-risk	HR for PCM favors RP over RT: HR = 1.50 (95% CI 1.19–1.88)	ADT use/duration RT dose RT modality/plan details
Ennis et al. (52)	NCDB (2004–2013)	Clinically localized, NCCN high-risk who received RP or XRT + ADT or XRT + BT ± ADT	No difference in OM between RP and XRT + BT, XRT/ADT associated with higher mortality than RP (HR, 1.53; 95% CI, 1.22–1.92).	ADT use/duration RT dose RT modality/plan details PCM
Jang et al. (56)	SEER-Medicare (1992–2009)	T3-T4N0M0 or T3-T4N1M0, age ≥65 treated with RP/adjuvant XRT or XRT/ADT	10-year PCM and OM favored men who underwent RP + XRT over men who underwent XRT + ADT	RT dose; RT modality/plan details; lack of specific information regarding biochemical/clinical recurrence; lack of patient-reported outcomes; data for non-Medicare beneficiaries <65 years
Muralidhar et al. (54)	NCDB and SEER (2004–2012 for NCDB and SEER)	cT1-T3N0M0, Gleason 9–10, PSA 0–40 ng/ml treated with XRT + BT or RP + ART	NCDB: No difference in 5-year OM between RP + ART vs. XRT + BT (HR 1.10, 95% CI 0.95–1.27) SEER: No difference in 5-year PCM (HR 1.22, 95% CI 0.88–1.71)	Limitations as above for SEER and NCDB studies

ADT, androgen deprivation therapy; ART, adjuvant radiation therapy; BT, brachytherapy; HR, hazard ratio; OM, overall mortality; NCCN, National Comprehensive Cancer Network; NCDB, National Cancer Database; PCM, prostate cancer-specific mortality; PSA, prostate-specific antigen; SEER, Surveillance, Epidemiology, and End Results; XRT, external beam radiation therapy.

between time to BCR and risk of systemic progression or PCM (40). The vast majority of meta-analyses have thus focused on OM and PCM, two measures which are difficult for individual observational studies to reliably assess because of an often large sample size and follow-up required (27–30, 32, 61, 62). The most well-known of these meta-analyses utilized pooled results from >90,000 patients for OM and PCM estimates of HRs of RT-based outcomes relative to RP in the setting of all clinically localized PCa (**Table 3**). The study reported that patients treated with RT had a statistically significant higher risk of death (OM, HR, 1.63; 95% CI, 1.54–1.73; PCM, HR, 2.08; 95% CI, 1.76–2.47) (30). These findings were robust to subgroup and sensitivity analysis, as well as covariates tested, including PCa risk group, RT modality, follow-up duration, study accrual period, or geographic region of the study. The authors even detected a survival benefit in favor of RP even in the setting of low-risk disease, an association that was not detected in the UK ProtecT study that was published the same year (3). The authors of this meta-analysis later commented that this result for low-risk patients in the meta-analysis was potentially caused by a statistical anomaly referred to as the Will Rogers phenomenon and, perhaps more importantly, the strong possibility of residual confounding (29, 38, 63, 64).

The findings of this meta-analysis, which has been widely cited as the definitive pooling of observational studies to date examining RP and XRT, have been scrutinized and criticized by some (65–67). Roach et al. (29) attempted to elucidate possible explanations for the magnitude of the HR in favor of surgery. While most studies reporting HRs comparing relative efficacy constructed from observational data utilized validated measures of bias such as the Newcastle-Ottawa Scale or GRADE (68, 69), there is often limited reporting of ADT use, RT modality and dose, or the use of adjuvant radiation in the setting of adverse surgical features. Roach et al. constructed a "reliability score" that incorporated a point-based system favoring studies providing full details of staging with Gleason score, T stage, and PSA. Studies were rewarded for demonstrating high compliance with recommended ADT duration for high-risk disease, whereas studies with limited reporting regarding ADT were penalized. Perhaps more controversially, extensive population-based studies across multiple institutions and those utilizing >12,000 patients were penalized, given a perceived inability to control for residual confounding. Using this somewhat controversial technique, which has been criticized by the authors of the previous meta-analysis (38), Roach et al. demonstrated that the magnitude of the HR estimator in favor of RP decreased for both OM

TABLE 3 | Selected meta-analyses comparing prostate cancer-specific mortality and overall mortality between radical prostatectomy and radiation therapy.

References	Study description	Results	Notable limitations
Wallis et al. (30)	Meta-analysis of 19 studies of low to moderate risk of bias (Newcastle-Ottawa used for assessment), up to 118,830 pooled patients	Worse OM (aHR = 1.63) and PCM (aHR=2.08) with RT compared with RP	Residual confounding, limited quality control regarding adequacy of ADT, RT dose in included studies
Roach et al. (29)	Meta-analysis of 14 studies. Stratified studies by use of "reliability score" incorporating comorbidity adjustment, ADT quality, and study size	10-year OM and PCM favored RP over RT, by 10 and 4%, respectively. Higher "reliability" associated with differences of 5.5 and 1%, respectively.	Residual confounding, use of unvalidated "reliability score" based on somewhat subjective criteria to stratify included studies

ADT, androgen deprivation therapy; OM, overall mortality; PCM, prostate cancer-specific mortality; RP, radical prostatectomy; RT, radiation therapy.

and PCM as the deemed "reliability" of the study increased according to this metric. Although the criticism regarding the use of an unvalidated "reliability score" must be acknowledged, the study did highlight an apparent association between the estimated degree of "surgical superiority" with larger studies that incorporated limited reporting of ADT and RT compliance in the setting of high-risk disease.

The vast majority of population-based studies and meta-analyses pooling these data along with single-institution studies point to superior OM and PCM outcomes with RP over RT. Underlying these studies, however, is valid criticism surrounding the degree to which large-scale studies can account for optimized RT/ADT regimens.

CURRENT QUESTIONS OF INTEREST RELATED TO OBSERVATIONAL DATA REGARDING RP VS. RT

Interpreting Historical Results in Light of Practice-Changing Clinical Trials

Multiple practice-changing clinical trials have been reported in the past two decades that have led to changes in the NCCN recommended standard of care for high-risk PCa, should an upfront RT approach be chosen. Although the studies included heterogeneous inclusion criteria and ADT durations ranging from 4 months to lifelong treatment, multiple studies were published that provided evidence of improved disease-free survival and PCM (7–10). EORTC 22991 additionally provided evidence that disease-free survival remains improved in the setting of intermediate- to high-risk PCa with 6 months of GnRH agonist ADT at 5 years in the context of dose-escalated RT (11). There is continuing uncertainty regarding the optimal duration of ADT in the setting of high-risk disease, though multiple clinical trials have narrowed the typical range recommended by NCCN to 1.5 years or longer when ADT is used in combination with definitive XRT (12–15, 70, 71). Surveys have suggested that since the publication of trials supporting prolonged ADT in the setting of high-risk disease, compliance with longer ADT duration has increased. Notably, however, there are distinct proportions of patients up to ∼50% who continue to receive short-course ADT. Concern regarding comorbidities and uncertainty in the era of dose-escalation are occasionally cited as associated with incomplete compliance (72–75). As such, investigators drawing conclusions from large observational database studies must remain cognizant that there are many reasons why current treatment patterns for high-risk disease remain heterogeneous and not necessarily consistent with level I data provided by these RCTs. Investigators who wish to make such comparisons need to take into account the ADT quality as a potential confounder, along with traditional covariates examined in modern database studies.

Current Questions Related to BT Boost

As discussed in the Introduction, the trend of RT in clinically localized PCa, including high-risk disease, has been to explore safe dose-escalation (76–80). With increasing attention paid to both LDR and high-dose-rate (HDR) BT boost utilized in combination with XRT, observational studies providing comparison of treatment outcomes regarding RP vs. combination XRT + BT ± ADT have been recently published (42, 52–55, 81–83). This treatment regimen has sometimes been referred to as ComboRT (54) or MaxRT (42). There has been increased interest in studying treatment outcomes of this regimen since the publication of the ASCENDE-RT trial that demonstrated improved BF with the addition of I-125 LDR boost to a minimum peripheral dose of 115 Gy. This improved BF came at the cost of a higher risk of genitourinary (GU) toxicity. The ASCENDE-RT study notably included 69% of patients with high-risk disease (6) and reaffirmed earlier retrospective evidence from the Prostate Cancer Results Study Group (84).

There are no randomized data comparing XRT + BT regimens to RP. Many have sought to address this retrospectively with institutional series or multi-institutional registries (42, 81–83). Perhaps most notable among the efforts among limited institutions is a study cohort comprising 639 patients with Gleason 9–10 PCa treated either with RP with pelvic lymph node dissection in the Martini-Klinik Prostate Cancer Center in Germany ($n = 559$) or Max-RT at the Chicago Prostate Cancer Center ($n = 80$) (42). MaxRT was defined as a combination of XRT, BT, and ADT. A strength of this study was the stratification of surgical outcomes by receipt of adjuvant RT and ADT. Fifty patients received MaxRP, defined as RP followed by adjuvant XRT and ADT. The results pointed to significantly reduced PCM for Gleason 9–10 PCa with MaxRT compared to RP, with MaxRT patients receiving a median ADT duration of 6 months. Patients receiving MaxRP, however, did not demonstrate a statistically significant difference in HR for PCM or OM, with the authors computing a plausibility index for equivalence of

treatment of 76.75% between the treatment arms of MaxRP and MaxRT for PCM and 77.97% for OM. One limitation is a source of bias introduced by the geographic separation between the comparator groups.

This paper, along with the Kishan study described below, has drawn the attention of others seeking to utilize large cancer databases and registries to examine the same question. Relatively few studies have been able to draw comparisons in OM (52–55) and even fewer in PCM (54, 55). One study using SEER-Medicare curiously reported a more favorable OM with XRT + BT compared with RP but not PCM (55). Another study utilizing the NCDB in a cohort with NCCN high-risk disease ≤ 65 years of age and with Charlson Comorbidity Index of 0 reported a worse OM with XRT + BT compared with RP (53), a result that was not seen in a larger cohort without age restriction (52). A recent study utilizing both NCDB for comparisons of OM and SEER for comparisons of PCM reaffirmed the apparent lack of statistically significant difference in OM or PCM when comparing MaxRT and MaxRP in patients with Gleason 9–10 disease, not observing any evidence of favorable surgical outcomes in younger patients <65 years (54). Although there is some heterogeneity among the population-based studies when different populations of high-risk disease and age are assembled, the majority of studies seem to suggest a trend toward improved PCM when XRT + BT boost is incorporated alongside ADT. Although associations of improved PCM relative to RP have been contested, there is less evidence suggesting superior surgical outcomes when BT boost is incorporated alongside XRT/ADT. These studies suggest that dose-escalation in the form of BT boost may form a crucial role in achieving superior local control when upfront RT is used.

Multi-Institutional Registries

Many groups have sought to achieve quality control for data collection and reporting with customized multi-institutional registry studies (**Table 4**). Assembling large numbers of patients in a database between institutions does not by itself provide a basis for reducing the potential for residual confounding; the onus remains on participating investigators to thoughtfully survey and record classifiers that ensure quality control and facilitate necessary statistical adjustments. These registries allow improved reporting of ADT regimens and compliance with dose-escalated RT in the setting of high-risk PCa treatment while maintaining the numbers necessary to provide statistical power. Barnes-Jewish Hospital and Cleveland Clinic conducted an early such effort. They published results of 10,429 patients with clinically localized PCa treated with upfront RP, XRT, or BT regimens, including 1,234 patients with D'Amico high-risk disease (85). The authors found XRT associated with increased OM and PCM compared to RP, with BT associated with increased OM but not PCM. Propensity-matched adjusted HRs were reported. This study had the advantage of 82% of high-risk patients receiving XRT or BT receiving ADT. The study is limited by the low radiation dose used and ADT duration delivered for many patients, which are considered insufficient by current standards. A subsequent study conducted by Duke University, Chicago, and twenty-first Century Oncology focused solely on patients <75 years of age with clinically localized Gleason 8–10 disease, treated with either XRT + BT with ADT or RP (81). Patients received ADT for a median of 4.3 months, which started before BT. Their study found that RP was not associated with an increased risk of PCM compared with XRT + BT with ADT, reporting an HR of 1.8 (95% CI, 0.6–5.6).

TABLE 4 | Multi-institutional registry studies.

Author, Institutions	Inclusion criteria	Comparison	Findings
Kibel: Barnes-Jewish Hospital and Cleveland Clinic (1995–2005) (85)	Clinically localized disease; general cohort of 10,429 including 1,234 D'Amico high-risk patients	XRT/ADT or BT vs. RP Note: XRT/ADT—median 74 Gy (Barnes-Jewish) or 78 Gy (Cleveland Clinic) and 82% of high-risk patients received ADT (median 6 months)	Worse OM with XRT/ADT (HR, 1.7; 95% CI, 1.3–2.3) or BT (HR, 3.1; 95% CI, 1.7–5.9) compared with RP, though no detectable difference in PCM in high-risk subset Adjusted 10-year PCM of 1.8% (RP), 2.9% (XRT), or 2.3% (BT)
Westover: 21st Century Oncology, Chicago Prostate Center, Duke University (1988–2008) (81)	Clinically localized, Gleason 8–10, age < 75 657 patients included	XRT + BT vs. RP Note: XRT + BT included 45 Gy + minimum 90–108 Gy BT	No detectable difference in PCM, i.e., PCM for RP not detected as worse than CMT (HR, 1.8; 95% CI, 0.6–5.6)
Kishan: 12 tertiary centers (11 in the United States, 1 in Norway) from 2000 to 2013 (83)	Gleason 9–10, clinically localized disease	XRT + BT (MaxRT) vs. RP Note: XRT- median 74.3 Gy, XRT+BT median 91.5 Gy, pelvic nodes included in 40.7% of XRT patients	Improved OM and PCM with MaxRT compared with RP Adjusted 5-year PCM RP 12% (95% CI, 8–17%); EBRT 13% (95% CI, 8–19%); and EBRT + BT, 3% (95% CI, 1–5%) PCM HR MaxRT vs. RP—0.38 (95% CI, 0.21–0.68) OM HR MaxRT vs. RP—0.66 (95% CI, 0.46–0.96)

ADT, androgen deprivation therapy; BT, brachytherapy; CMT, combined modality therapy; Gy, gray; MaxRT, combination external beam radiation therapy and brachytherapy ± ADT; OM, overall mortality; PCM, prostate cancer-specific mortality; RP, radical prostatectomy; RT, radiation therapy; XRT, external beam RT.

TABLE 5 | Selected clinical trials studying various therapies including systemic, surgical, and radiation interventions in high-risk prostate cancer.

NCT ID #	Phase	Title	Accrual and arms	Treatment arms
Systemic therapy interventions				
NCT03477864	1	Stereotactic body radiation therapy with REGN2810 and/or ipilimumab before surgery in treating participants with progressive advanced or oligometastatic prostate cancer	Active target enrollment: 24 three arms	Anti-PD1 monoclonal antibody (REGN2810) vs. intraprostatic ipilimumab vs. a combination of both, followed by SBRT + RP
NCT02023463	1	Enzalutamide, radiation therapy, and hormone therapy in treating patients with intermediate or high-risk prostate cancer	No longer recruiting actual enrollment: 25 one arm	Enzalutamide + LHRH agonist with goserelin or leuprolide, followed by RT and additional LHRH agonist
NCT03177460	1	Daratumumab or FMS inhibitor JNJ-40346527 before surgery in treating patients with high-risk, resectable localized or locally advanced prostate cancer	Active target enrollment: 30 two arms	Daratumumab (CD38 antagonist) vs. FMS inhibitor JNJ-40346527(CSF-1R tyrosine kinase inhibitor) followed by RP
NCT00099086	1	Docetaxel, radiation therapy, and hormone therapy in treating patients with locally advanced prostate cancer	No longer recruiting actual enrollment: 20 one arm	RT + bicalutamide and GnRH analog prior to, during, and after RT + concurrent docetaxel
NCT03821246	2	Neoadjuvant atezolizumab with or without enzalutamide in localized prostate cancer given before radical prostatectomy	Active target enrollment: 68 three arms	Atezolizumab alone vs. in combination with enzalutamide or in combination with emactuzumab, followed by RP
NCT02506114	2	Neoadjuvant PROSTVAC-VF with or without ipilimumab for prostate cancer	Active target enrollment: 75 two arms	PROSTVAC-VF (PSA-based immunization) ± ipilimumab, followed by RP
NCT02508636	2	Trial of radiotherapy with leuprolide and enzalutamide in high-risk prostate	No longer recruiting actual enrollment: 11 one arm	Definitive RT + Leuprolide + Enzalutamide
NCT02772588	2	AASUR in high-risk prostate cancer	Active target enrollment: 58 one arm	Leuprolide + Abiraterone + apalutamide + SBRT
NCT02903368	2	Neoadjuvant and adjuvant abiraterone acetate + apalutamide prostate cancer undergoing prostatectomy	No longer recruiting actual enrollment: 120 two arms, crossover	Abiraterone, leuprolide, prednisone ± apalutamide, followed by RP. Adjuvant abiraterone, apalutamide, leuprolide, prednisone vs. no adjuvant therapy.
NCT03436654	2	Multi-arm multi-modality therapy for very high-risk localized and low volume metastatic prostatic adenocarcinoma	Active target enrollment: 76 two arms	Apalutamide ± (Abiraterone and prednisone) followed by RP, pelvic lymphadenectomy, GnRH agonist/antagonist
NCT03432780	2	Radiation-hormone and docetaxel vs. radiation-hormone in patients with high-risk localized prostate cancer (QRT-SOGUG)	No longer recruiting actual enrollment: 134 two arms	RT + hormone therapy ± weekly docetaxel
NCT01385059	2	Axitinib before surgery in treating patients with high-risk prostate cancer	No longer recruiting actual enrollment: 60 two arms	Axitinib for 28 days vs. no therapy followed by RP and pelvic lymph node dissection
NCT02849990	2	A phase II neoadjuvant study of apalutamide, abiraterone acetate, prednisone, degarelix and indomethacin in men with localized prostate cancer pre-prostatectomy	No longer recruiting actual enrollment: 22 one arm	Apalutamide, abiraterone, prednisone, degarelix, indomethacin followed by RP
NCT03899987	2	Aspirin and rintatolimod with or without interferon-alpha 2b in treating patients with prostate cancer before surgery	Active target enrollment: 60 two arms	Aspirin + rintatolimod ± recombinant interferon alpha-2b followed by RP vs. RP alone
NCT02949284	2	Androgen receptor antagonist ARN-509 with or without abiraterone acetate, gonadotropin-releasing hormone analog, and prednisone in treating patients with high-risk prostate cancer undergoing surgery	Active target enrollment: 90 two arms	Apalutamide ± (abiraterone acetate, GnRH agonist, prednisone) followed by RP vs. RP alone
NCT01409200	2	Antiandrogen therapy with or without axitinib before surgery in treating patients with previously untreated prostate cancer with known or suspected lymph node metastasis	No longer recruiting actual enrollment: 73 two arms	ADT + axitinib followed by RP and pelvic lymph node dissection vs. ADT alone followed by RP and pelvic lymph node dissection
NCT01546987	3	Hormone therapy, radiation therapy, and steroid 17alpha-monooxygenase TAK-700 in treating patients with high-risk prostate cancer	No longer recruiting actual enrollment: 239 two arms	ADT + GnRH agonist + RT ± TAK-700 (steroid 17alpha-monooxygenase)

(Continued)

TABLE 5 | Continued

NCT ID #	Phase	Title	Accrual and arms	Treatment arms
NCT03767244	3	A study of apalutamide in participants with high-risk, localized or locally advanced prostate cancer who are candidates for radical prostatectomy (PROTEUS)	Active target enrollment: 1,500 two arms	ADT + apalutamide OR placebo, followed by RP, followed by adjuvant ADT + apalutamide OR placebo
NCT00288080	3	Hormone therapy and radiation therapy or hormone therapy and radiation therapy followed by docetaxel and prednisone in treating patients with localized prostate cancer	No longer recruiting actual enrollment: 612 two arms	Androgen suppression with LHRH agonist + oral anti-androgen prior to and concurrent with RT, followed by adjuvant LHRH agonist ± docetaxel x six cycles
NCT00430183	3	Surgery with or without docetaxel and leuprolide or goserelin in treating patients with high-risk localized prostate cancer	No longer recruiting actual enrollment: 788 two arms	Docetaxel + LHRH agonist + surgery vs. surgery alone
Surgical interventions				
NCT00007644	3	Prostate cancer intervention vs. observation trial (PIVOT)	Results published; pending long-term results actual enrollment: 731 two arms	RP vs. observation
N/A	3	Radical prostatectomy or watchful waiting in early prostate cancer (SPCG-4)	Results published; pending long-term results actual enrollment: 695 two arms	Watchful waiting vs. RP
NCT02102477	3	Surgery vs. radiotherapy for locally advanced prostate cancer (SPCG-15)	Active target enrollment: 1,200 two arms	RP ± adjuvant or salvage RT, vs. RT with adjuvant ADT
Radiation therapy interventions				
NCT02830165	1	Stereotactic body radiation therapy in treating patients with high-risk prostate cancer undergoing surgery	Active target enrollment: 12 one arm	SBRT given over three fractions ∼2–4 weeks prior to RP
NCT02346253	1 | 2	High-dose brachytherapy in treating patients with prostate cancer	Active target enrollment: 163 one arm	High-dose brachytherapy over two fractions + ADT
NCT00951535	2	A prospective phase II dose-escalation study using IMRT for high-risk N0 M0 prostate cancer. ICORG 08-17	No longer recruiting actual enrollment: 251	Dose-escalation study from baseline of 75.6 Gy up to a maximum of 81 Gy, depending on volume constraints
NCT01368588	3	Androgen-deprivation therapy and radiation therapy in treating patients with prostate cancer (RTOG 0924)	No longer recruiting actual enrollment: 2,592 two arms	RT to prostate and seminal vesicles alone vs. whole-pelvis RT
NCT00967863	3	Radiation therapy in treating patients receiving hormone therapy for prostate cancer (GETUG-AFU 18)	No longer recruiting actual enrollment: 500 two arms	RT to 80 Gy vs. to 70 Gy given in conjunction with ADT
NCT00667888	3	A phase III intensity radiotherapy dose-escalation for prostate cancer using hypofractionation	No longer recruiting actual enrollment: 225 two arms	RT to 75.6 Gy in 42 fractions vs. RT to 72 Gy in 30 fractions
Other interventions				
NCT03514927	2	High-intensity focused ultrasound in treating participants with intermediate and high-risk prostate cancer	Active target enrollment: 32 one arm	High-intensity focused ultrasound (HIFU) followed by RP

ADT, androgen deprivation therapy; Gy, gray; IMRT, intensity-modulated radiation therapy; LHRH, Luteinizing hormone-releasing hormone; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy; SBRT, stereotactic body radiotherapy.

The most impressive multi-institutional registry endeavor to date was conducted by the University of California, Los Angeles, the California Endocurie Therapy Center, and Fox Chase, broadening to include 12 tertiary centers. These two studies focused on Gleason 9–10 PCa, comparing PCM, OM, and distant metastasis for patients receiving RP, XRT with ADT, or XRT + BT combined with ADT (82, 83). The more extensive publication included 1,809 patients. The authors reported high-quality ADT, including XRT and XRT + BT arms that received 89.5 and 92.4% utilization of ADT as part of the initial treatment strategy, with median durations of 21.9 and 12 months, respectively. After the inverse probability of treatment weighting adjustments, XRT + BT was associated with a significantly longer time until distant metastases (DM) and lower PCM than either XRT or RP. One potential limitation to interpreting the outcomes from the RP arm includes the relatively low utilization of adjuvant RT of 8.7% for Gleason 9–10 disease, with salvage performed in 34.1% of patients. On examination of subgroups by radiation dose, patients receiving <70 Gy had a significantly higher rate of PCM than either those receiving ≥78 Gy, though this relationship did

not hold with DM. The registry did not record and control for comorbidity status, which is a limitation regarding adjustment of HRs between RT and RP. The authors speculated that the lack of this information was unlikely to bias their conclusion in favor of RT, as RT cohorts typically have more comorbidities.

These efforts, conducted by urologists and radiation oncologists alike, have contributed unique opportunities to assemble large cohorts of patients across institutions with a level of quality control regarding recommended treatment compliance, perhaps second only to prospectively organized studies or RCTs. It is likely that these efforts will continue to answer questions too detailed for standard cancer registries, yet impossible to address with currently available RCT data.

Addition of Systemic Therapies; Limited Data Available From Randomized Trials

There has been much interest in both past and current clinical trials to explore the addition of chemotherapy to long-term ADT and dose-escalated RT, with currently available prospective randomized trials demonstrating limited follow-up (23–26). Available data from GETUG 12, RTOG 0521, and the non-metastatic subgroup of STAMPEDE point to an improved relapse-free survival associated with the use of docetaxel in patients treated with XRT + ADT (24, 25, 86), with recently updated data from RTOG 0521 demonstrating an additional improvement in DM (24). Data are still maturing from the majority of available clinical trials, and the decision to use chemotherapy is currently individualized based on patient disease characteristics. There are limited data, especially regarding the interplay between MaxRT incorporating BT and systemic therapy strategies. More extensive recent systematic review and discussion of currently available prospective trials, additionally including consideration of second-generation ADT and adjuvant treatments following surgery, are provided elsewhere (26).

CURRENT PROSPECTIVE TRIALS OF INTEREST

There are multiple active clinical trials currently underway investigating various promising therapeutic interventions for high-risk PCa. The majority of these clinical trials are early-phase (phase I or II). The principal role of these studies is to investigate the role of additional systemic treatment modalities or evaluate the most effective timing of systemic therapy in relation to definitive local treatment modalities such as surgery or radiation. Furthermore, with the surge in interest in immunotherapies for cancer as a whole, high-risk PCa has been seen as a potential area for the integration of further immune treatments into the current standard of care. For example, trial NCT03477864 investigates the safety of injecting intravenous anti-PD1 monoclonal antibody and intraprostatic ipilimumab (either alone or in combination with each other) in the setting of high-risk PCa, to be followed by both SBRT and RP as definitive local modalities. In addition, a phase II trial (NCT02506114) is evaluating the efficacy of a PSA-based form of immunization, with or without additional immunotherapy with ipilimumab, prior to definitive local treatment with RP for high-risk PCa. This is not to say that traditional chemotherapeutic regimens have been overlooked, however; the QRT-SOGUG phase II trial (NCT03432780), of which a preliminary report of results was published in abstract format in 2016, is investigating the safety and efficacy of administering weekly docetaxel concurrently with standard dosing of RT and ADT (87). In addition, there is interest in adapting hormone therapy regimens to incorporate the newest generation of drugs such as apalutamide and abiraterone; the phase II trial NCT02949284 is a trial that is examining the feasibility of performing nerve-sparing RP in the setting of apalutamide given either alone or in combination with abiraterone and prednisone.

There have been relatively fewer phase III trials investigating the role of surgical intervention in high-risk PCa. These include the PIVOT trial, which most recently reported results in 2017 with a median of 12.7 years of follow-up; the PIVOT trial randomly assigned 731 individuals with a diagnosis of localized PCa to observation or RP, and found that the RP arm did not have significantly lower OM or PCM compared to the observation arm (88). Notably, there was a trend toward significance for these metrics in the higher-risk populations–namely, those with a PSA value of >10 and a Gleason score of 7 or higher. In contrast, the SPCG-4 trial, which randomized 695 men with localized PCa to watchful waiting or RP, did demonstrate a benefit to surgery, with a number needed to treat to prevent one death of eight (89). Nevertheless, in the high-risk group of patients in this trial, there was no significant difference in OM, PCM, and risk of metastases, as of the most recent results in 2014 with over 23 years of follow-up. The next generation of trials is found in the phase III SPCG-15 trial, which is currently active and recruiting with a target enrollment of 1,200 patients (45). This trial enrolls patients with locally advanced PCa and randomizes them to either standard of care with radiation and ADT vs. RP (including extended pelvic lymph node dissection) with adjuvant or salvage radiation and hormone therapy if necessary; the primary endpoint is cause-specific survival.

Also, multiple trials are actively investigating variations upon the currently accepted dose, fractionation scheme, and method of delivery of RT for locally advanced high-risk PCa. Phase I trials such as NCT02830165 investigate the safety of adding of hypofractionated stereotactic RT given prior to RP, with the hypothesis that providing patients with two forms of local therapy may aid in increased disease control as well as prompt an immune response in high-risk disease (90). The phase I/II trial NCT02346253, which is not limited to high-risk patients but includes patients up to T3 and a Gleason score of 10, seeks to answer whether HDR-BT delivered over two fractions, in conjunction with ADT and luteinizing hormone-releasing hormone (LHRH) agonist therapy, is safe and efficacious (as assessed by the rates of genitourinary toxicity, PSA nadir, and rates of freedom from biochemical failure). How radiation fields should be defined–that is, in terms of whole-pelvis RT vs. RT to the prostate and seminal vesicles alone–is under active investigation as well in the trial NCT01368588 (RTOG 0924). With an accrual of over 2,500 patients, it is powered to answer

the question of overall survival differential between these two radiation field setups in patients with a moderate or high risk of recurrence. Dose-escalation continues to be actively investigated as well. For example, NCT00967863 (GETUG-AFU 18) examines the impact of dose-escalation to 80 Gy (vs. a standard of 70 Gy) in high-risk PCa patients in a phase III randomized setting; as of November 2015, there was no increased toxicity noted acutely or at 1-year follow-up, but the results for biochemical and clinical control are still pending at this time (91). Other local treatment options have continued to remain of interest. The phase II single-arm trial NCT03514927 seeks to determine whether high-intensity focused ultrasound (HIFU) can be used in conjunction with RP to impact the percent of viable cancer tissue noted on the surgical pathology specimen. Overall, the general thrust of the new emerging data and clinical trials appears to be in adding various systemic therapies, particularly in new hormonal treatments and incorporation of immunotherapies, with some studies also looking at the role of surgery and modifying current radiation techniques and dosages.

CONCLUSIONS

So far, RCTs assessing OM and PCM between RP and RT are limited concerning representation of high-risk, clinically localized disease. Most observational studies and meta-analyses have not historically supported oncologic equivalence between the two modalities. Issues of selection bias, inadequate use of ADT/radiation dose, and residual confounding remain as difficulties in interpreting available retrospective data. Trends have demonstrated more recent curation of multi-institutional registries and databases. These have allowed assessment of outcomes for patients receiving treatment showing improved compliance with modern evidence-based RT/ADT and RP/adjuvant RT regimens. High-dose RT incorporating BT boost has demonstrated evidence of improved PCM. With more recent efforts, estimates of differences in PCM between RT- and RP-based approaches have diminished. There is still a relative lack of prospective randomized trials being organized to provide a comparison between RP and RT strategies, with the majority of trials exploring new hormonal therapies, immunotherapies, and in general augmentation of existing strategies. Likely, retrospective data will still be a significant resource in answering questions regarding the interplay of RP- and RT-based modalities for high-risk PCa.

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BG and RD provided study conception. BG and VC provided initial manuscript preparation, with BG, VC, and RD providing critical revisions and preparation of the final manuscript. RD provided study oversight.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2019.01273/full#supplementary-material

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REVIEW
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The Role of Radical Prostatectomy and Lymph Node Dissection in Clinically Node Positive Patients

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Patients diagnosed with clinically node-positive prostate cancer represent a population that has historically been thought to harbor systemic disease. Increasing evidence supports the role of local therapies in advanced disease, but few studies have focused on this particular population. In this review we discuss the limited role for conventional cross sectional imaging for accurate nodal staging and how molecular imaging, although early results are promising, is still far from widespread clinical utilization. To date, evidence regarding the role of radical prostatectomy and pelvic lymph node dissection in clinically node-positive disease comes from retrospective studies; overall surgery appears to be a reasonable option in selected patients, with improved oncological outcomes that could be attributed to both to its potential curative role in disease localized to the pelvis and to the improved staging to help guide subsequent multimodal treatment. The role of surgery in clinically node-positive disease needs higher-level evidence but meanwhile, radical prostatectomy with extended pelvic lymph-node dissection can be offered as a part of a multimodality approach with the patient.

Keywords: cN1, lymph node dissection, prostate cancer, radical prostatectomy, staging

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INTRODUCTION

In 2018 it was reported that 12–13% of PCa patients presented with regional tumor involvement at the time of diagnosis (1) and this number is likely to increase in the coming years due to novel and more accurate imaging techniques. Following the America Joint Committee on Cancer (AJCC) Staging System, the "N" refers to regional lymph nodes, namely: pelvic, hypogastric, obturator, iliac, and sacral groups. The involvement of distant LNs, namely those outside the true pelvis (for example aortic, common iliac, inguinal, supraclavicular, and retroperitoneal) is considered as M1 disease. Tumor of any "T" stage, negative for distant metastasis but with positive regional nodes involvement is referred as stage IVa (2). This considerable proportion of PCa patients has historically been treated with the assumption that the presence of lymph node metastasis indicates systemic spread of disease, thus guidelines recommend ADT as the gold standard treatment (3, 4). To date no randomized clinical trial exists evaluating the best treatment modality for these patients.

A recent systematic review (5) suggested a potential benefit in CSS and OS for patients receiving local treatment (RP or RT) for cN1 PCa vs. ADT alone. Interestingly, only one of the five studies that met the inclusion criteria included patients treated with radical prostatectomy (6), moreover most of them were redundant and population-based with connected limitations. Thus, while the overall impression is that there is a potential role for local therapy, there is still need to clarify the evidence regarding the role of surgical therapy.

In this review we aim to summarize the evidence reporting the effect of RP in cN1 population, after considering two relevant questions: can we rely on current clinical staging to exclude surgery as a possible primary treatment? Are patients with localized nodal metastasis a unique population?

IDENTIFYING CN1 PATIENTS

As discussed, surgery is not an option considered in current guidelines for cN1 patients, thus the correct clinical diagnosis of nodal involvement is imperative, especially aiming to minimize the rate of false positives where a potential curative intervention could be missed. However, in the following section we will review how such a strong change in treatment indications seems not supported by the performance of current N staging techniques.

CT and MRI

Traditionally, cross sectional conventional imaging techniques such as CT or MRI are used for local and abdominal staging purposes. They assess the presence of LN involvement indirectly, by the evaluation of morphology and size. The most commonly used thresholds are short axis of nodal size of 8 mm in the pelvis and 10 mm outside the pelvis. Predictably, decreasing the threshold size increases sensitivity at the expense of specificity (7).

A meta-analysis in 2008, thus including studies mostly performed in the pre-PSA era, showed that for CT pooled sensitivity was 0.42 (95% CI 0.26–0.56) and pooled specificity was 0.82 (95% CI 0.8–0.83) (8). More contemporary studies including patients showed comparable results. Very high specificity (94–97%) of CT scan was confirmed in a cohort of 1,541 patients treated with eLND, while sensitivity was low and related to tumor characteristics, namely reaching a maximum of 24% in patients with very high risk of nodal invasion calculated with Briganti nomogram (9). The overall discrimination accuracy was low (55%). While focusing on the pN+ patients the PPV of CT scan was only 32.8%, meaning that 67.2% of patients had false positive findings on CT scans (10). Moreover the results showed that the inclusion of the information derived by CT scan did not increase the accuracy of the non-imaging-based Briganti nomogram. Similarly results were reported in another cohort of 1091 CT staged patients with a PPV of 31% (11).

MRI is increasingly used in local staging, particularly with the adoption of multi-parametric MRI in the detection and diagnosis of prostate cancer. In the aforementioned meta-analysis, MRI pooled sensitivity of 0.39 (95% CI 0.22–0.56) and pooled specificity of 0.82 (95% CI 0.79–0.83) was reported. Despite this, the differences in performance of CT and MRI were not statistically significant (8). Other studies performed with modern MRI-techniques and contemporary cohorts of patients confirmed the high specificity of MRI and suggested an improved sensitivity when DWI was incorporated in the scanning technique (12). Considerably higher sensitivity and specificity (1/0.96) were reported in a recent prospective study evaluating the performance of 3.0-T multiparametric whole body MRI in comparison with bone scan and 18F-choline PET/CT for staging purposes. However, these results should be interpreted with caution because the reference standard for true positive was derived from clinical and radiological parameters rather than from pathological evaluation (13).

Molecular Imaging

The role of molecular imaging in the staging of recurrent prostate cancer is promising. With new radiotracers demonstrating impressive results, molecular imaging's role is likely to increase in the future (14). That being said, its role in the primary staging is still under debate and is not yet recommended in current guidelines (3, 4).

A meta-analysis of 10 studies published before 2012 and including 441 intermediate/high-risk PCa patients undergoing 18F-Choline or 11C-Choline PET/CT for nodal staging demonstrated a pooled sensitivity of 0.49 (95% CI 0.39–0.58), pooled specificity of 0.95 (95% CI 0.92–0.97), pooled positive likelihood radio of 8.35 (95% CI 4.5–15.48) and pooled negative likelihood radio 0.55 (95% CI 0.37–0.82) (15). Recently, Schiavina et al. compared the diagnostic performance of 11C-Choline PET/CT and contrast enhanced CT in a population of high risk PCa patients treated with RP +LND and reported sensitivity and specificity of 50 and 76% vs. 21 and 92%, for PET/CT and CT, respectively. Those differences were increased in those patients defined as very high-risk, suggesting this population as a potential target for PET/CT preoperative staging (16).

PSMA is a relatively new radiotracer that has recently been evaluated for promising higher sensitivity in nodal staging (17). A meta-analysis including both patients undergoing 68Ga-PSMA PET/CT for primary staging or after biochemical recurrence showed sensitivity of 0.86 (95% CI 0.37–0.98) and specificity of 0.86 (95% CI 0.03–1.00) for nodal involvement on a "per patient" basis and sensitivity and specificity of 0.8 (95% CI 0.66–0.89) and 0.92 (95% CI 0.92–0.99), respectively, on "per lesion basis" (18). Further studies evaluating the role of PMSA in the specific primary staging setting confirmed the aforementioned results (19, 20). In a prospective study, 30 patients with intermediate-high risk PCa were staged with 68Ga-PSMA PET/CT prior to surgery; on a "per patient" analysis, the sensitivity, specificity, PPV and NPV were 64, 95, 88, and 82%, respectively. On "LN-region-based" analysis, the sensitivity, specificity, PPV and NPV were 54, 99, 92, and 94%, respectively (21). Interestingly, this paper demonstrated that most missed LNs were <5 mm, consistent with one of the main limitations of PET/CT, limited spatial resolution. Considering this limitation, the marginal improvement in sensitivity and higher costs with limited availability, PET/CT is currently not recommended in primary nodal staging setting, where instead PLND remains the gold standard.

Abbreviations: (e)LND, (extended) pelvic lymph node dissection; ADT, androgen deprivation therapy; BRFS, biochemical recurrence free-survival; cN1, clinically node positive; CR, clinical recurrence; CSM, cancer specific mortality; CSS, cancer specific survival; LN, lymph node; OS, overall survival; PCa, prostate cancer; PPV, positive predictive value; RP, radical prostatectomy; RT, external beam radiation therapy.

SURGICAL TREATMENT FOR CN1 PATIENTS

The rationale supporting local treatment in advanced cancers is based on the principle of tumor volume reduction and local control. The benefit of radiation therapy in addition to systemic treatment in cN1 PCa patients has been demonstrated by different studies, both in a subgroup analysis of RCT and in a population based setting (5, 22, 23). In the setting of surgery, a survival benefit of RP in patients with nodal involvement detected during surgery has led to the abandonment of frozen LN section (24, 25).

The first study to specifically analyze the role of prostatectomy in cN1 patients was reported by Moschini et al. (26); oncological outcomes of 50 (17%) cN1 M0 patients undergoing RP + PLND were compared to 252 (83%) patients with cN0, M0 disease. The authors reported no difference between groups in CSS and OS. The only significant predictors of CSM were the number of positive nodes (HR 1.10; $p = 0.02$) and pathologic Gleason score 8–10 vs. <7 (HR 2.37; $p = 0.04$) (26). Both groups were comparable in adjuvant ADT or RT. Although demonstrating promising results, the study lacked of a control group of cN1 patients treated with RT and/or ADT and such comparison is still missing.

Subsequently, a population based study from the National Cancer Database (NCBD) evaluated oncological outcomes of in 2,967 PCa patients with cN1 disease undergoing any local treatment, intended as RP or RT + ADT ($n = 1,987$) vs. ADT alone ($n = 980$). With a median follow-up of 49.7 months, in the multivariable model adjusting for selection bias, local treatment + ADT was associated with a significant overall mortality survival benefit (HR 0.31; 95% CI 0.13–0.74, $p = 0.007$). In a secondary analysis, authors compared RT + ADT and RP + ADT reporting no significant differences in overall survival between the two cohorts. Interestingly, in this population based study 67% of patients received some form of local treatment, despite of guidelines recommendation. Furthermore, 17.8% patients classified as cN1 were pN0 at RP (6).

Another population based study from SEER-Medicare database by Jang et al. evaluated oncologic outcomes between patients older than 65 years with cT3-4N1 disease, treated with RP + adjuvant RT (within 6 months after surgery) compared to RT + ADT (any ADT from 2 months before RT until 3 years after). The two cohorts were propensity matched with respect to clinical and demographic characteristics. The adjusted 10-year CSS rates for cT3N1 disease were 75.7 and 58.6% for those treated with RP + RT and RT + ADT, respectively, with a 95% CI for the difference from −0.8 to 34.2. Similarly, the 10-year OS rates were 44.3 and 40.5% for RP + RT and RT + ADT, respectively, with a 95% for the difference from −10.8 to 22.5 (27).

The aforementioned study by Seisen et al. (6) and Jang et al. (27) also compared RP and RT in cN1 patients and demonstrated contrasting results; overall these results should be interpreted that a main benefit of surgery is the prognostic information, namely the accurate staging. The importance of accurate staging in these patients can't be underestimated. Indeed, false positive rate was reported up to 20% and can be higher as already discussed in the diagnostics section. Correct staging can then guide subsequent adjuvant therapies and, in particular, can limit the adverse events related with ADT if not truly indicated. **Table 1** show an overview of potential advantages and disadvantages on LND in cN1 patients.

To date no other study has directly evaluated the role of surgical treatment in cN1 patients, nor are any current clinical trials registered. Surgical treatment in this subpopulation is made of two components, namely the PLND and the RP, each of them with its own implications. The reported findings are consistent with the increasing evidence supporting local treatment for newly diagnosed metastatic PCa. As we will discuss in the following paragraph, cN1 patients represent a heterogeneous population were surgery plays a role with its cytoreductive effect (28). In particular, cytoreductive prostatectomy in metastatic patients is being evaluated in several RCTs (29, 30), in order to confirm promising results seen in retrospective series (31, 32).

The overall curative impact of LND remains controversial (33); however the interpretation of related studies may be confounded by the heterogeneous LND template employed by surgeons and the inclusion of patients with low risk of CSM. In patients with pN1 disease the removal of more LNs was reported to be associated with lower CSM rates (34) emphasizing the general recommendation of performing an extended LND in all patients with significant preoperative risk of nodal disease. The importance of treating LNs is suggested also from the studies on LND in salvage setting that, although lacking of prospective randomized data, show promising results in selected patients (35).

No definitive paradigm exists for subsequent management of pN1 patients, though early adjuvant ADT ± RT is commonly offered. A recent study demonstrated improved oncologic outcomes in patients treated with surgery and adjuvant ADT + RT compared to surgery alone or surgery and adjuvant ADT (36). These results suggest a potential role of RP as the first step in a multimodal treatment plan.

IDENTIFYING SURGICAL CANDIDATES

Most of the aforementioned studies lacked of information regarding the burden of nodal disease, thus the heterogeneity of

TABLE 1 | Summary of advantages and disadvantages of LND in cN1 patients.

Advantages	Disadvantages
Surgery in cN1 patients	
Gold standard for staging	Morbidity related to surgery
Potentially curative in limited burden	No proven oncological benefit
Cytoreduction	No clear benefit compared to RT
Avoids undertreatment	Technically challenging in advanced cases
Potential sequencing of adjuvant treatments	

the included patients prevented the external validity and further recommendations based on the findings.

In order to define a subgroup of patients with nodal disease who benefit the most form RP, Gandaglia et al. identified 162 patients with cN1 disease detected with conventional cross-sectional imaging and treated with RP at three tertiary centers. They reported that higher Gleason Score and higher number of clinical lymphadenopathies were the only predictors of pathological lymph node involvement in multivariate analysis. Three variables were then identified and used for stratifying patients: number of clinically positive nodes, location of nodes (intended as pelvic vs. retroperitoneal) and biopsy Grade Group. The overall 8-year CR-free and CSM-free survival rates were 59 and 80%, respectively. Differences in 8-year CR-free survival were significant for those with two or fewer lymphadenopathies vs. those with more than two (55 vs. 35%, $p = 0.049$) and in particular retroperitoneal involvement was associated with a 2-fold increase of CR (59 vs. 27% 8-year CR-free survival for pelvic only vs. retroperitoneal involvement, respectively, $p = 0.001$), other factors such as size did not have a significant impact. The multivariate model, adjusting for adjuvant or salvage therapies, showed that the site and the biopsy grade group were predictors of CR and in particular in those patients with pelvic-only LN involvement also the number of nodal stations was significant (37). This attempt to stratify patients suffers of limitations due to its retrospective nature, thus selection bias and the lack of a control group.

Despite the limitations and the need for confirmatory results, this study is interesting since it raises several discussion points. The first comes from the evidence that the size of clinical lymphadenopathies should not be used as a criterion for treatment selection; this finding seems somehow contrasting with those regarding the prognostic values of pathological LN size (38) and again emphasizes the poor accuracy of conventional cross sectional imaging. Overall, the population of cN1 patients is heterogeneous with respect to the burden of nodal involvement, comprising both those with massive lymph node involvement and those with limited nodal disease. While in the former population surgery could be interpreted as a cytoreductive treatment, in the latter it might aim to be a curative intervention. Indeed, there is evidence supporting this hypothesis reporting that patients with less than three LNs involved by PCa had better survival outcomes than those with more extended lymph node involvement, with a reported median CSS at 10-years up to 78.6% (39–41).

M1A DISEASE

Non-regional lymph node metastases are classified as M1a disease (2), in particular common iliac and retroperitoneal nodes are included in this classification. As aforementioned, most of the studies evaluating both primary and salvage treatment for nodal disease suffered from the heterogeneity of the definitions used to describe nodal involvement and LND extension, which sometimes was performed up to the aortic bifurcation (thus including common iliac nodes). The basis of this considerations refers to a pathological mapping study which showed that patients with positive retroperitoneal lymph nodes always had positive lower pelvic lymph nodes, regardless of the location of the nodal area involved, and in particular the common iliac nodes were always involved, suggesting an ascending pathway of metastases starting form lower pelvic nodes to retroperitoneal chains through common iliac nodes (42). While the extension of the disease outside the true regional nodes appears as mirror of systemic disease, there is still debate whether patients classified as M1a are comparable in terms of treatment and outcomes with those with osseous and visceral metastases. In a SEER-based study performed by Culp et al. the subgroup analyses surprisingly showed improved OS in patients treated with RP for M1b ($p < 0.001$) and M1c ($p < 0.001$) disease in comparison with M1a. These results should be however interpreted cautiously because of the lack of information regarding the pelvic node dissection, in addition to the known lack of information regarding ADT typical of SEER studies (31). A study by Moschini et al. evaluated the oncological outcomes of 17 cM1a patients treated with combined pelvic and formal retroperitoneal lymph node dissection up to the renal vessels and a minimum of 6 months of ADT; they found that the CSM-free survival at 5 years was 80.2% in M1a patients compared to 49.0% in M1b but not reaching significant *p*-value (43). While often included in studies evaluating RP in metastatic PCa, stratified outcomes for M1a patients including adequate nodal dissection are missing. Recently, another SEER study test the association of baseline PSA and local treatment within different M1 substages in a propensity matched cohort; M1a patients receiving local treatment (RP or RT) had lower CSM than those not treated with local treatment (HR 0.32 95% CI 0.17–0.60, $p < 0.001$) (44). In the setting of node-only recurrent prostate cancer a prognostic model has been recently developed to predict those who benefit the most from salvage LND, namely those with real oligorecurrent disease: among the others, a number of PET/CT detected nodes > 2 (HR 1.26 95% CI 1.05–1.61, $p = 0.019$) and nodes in the presence of nodes in the retroperitoneum (HR 1.24 95% CI 1.01–1.52, $p = 0.038$) were predictors of worse outcomes (45). To date for newly diagnosed cM1a patients there is insufficient evidence supporting an additional oncological benefit of RP and LND, even though from the experiences in salvage super-extended lymph node dissection could suggest a rationale in supporting lymph node dissection up to the retroperitoneum, in particular when considering also the potential prevention of local complications derived from advanced prostatic and nodal involvement.

DISCUSSION

This review represents the most comprehensive and updated summary of current evidence regarding the oncologic outcomes of radical prostatectomy in cN1 patients to our knowledge. The evidence and rationale provided support an oncological benefit of RP + LND in this setting, consistently with a recent systematic review including studies mainly focused on RT (5). A quick review of the imaging techniques for N staging showed overall poor performance of conventional cross sectional

imaging, this could result potential under/overtreatment of patients. The potential better performance of molecular imaging is still not considered sufficient by guidelines to be implemented in the primary staging (3, 4) and extended LND remains the gold standard for nodal staging and thus guiding subsequent treatments and follow-up.

To the best of our knowledge, all studies evaluating the role of RP in cN1 patients are retrospective and no randomized clinical trial has ever been performed or is currently recruiting cN1 patients in order to evaluate the best treatment options. Additionally most of the retrospective studies lack of adequate assessment of subsequent adjuvant therapies, especially population based ones. These limitations must be taken in consideration while reading these results and this makes the quality of the evidence insufficient for definitive recommendations.

The reported evidence is indeed including great variety of cN1 patients, namely those with false-positive imaging and pN0 disease at surgery, those with minimal nodal involvement and those with massive and sometime extra-pelvic nodal disease. While for pN0 patients the curative role of surgery is clear and treating these patients with primary ADT would result in unacceptable under-treatment, patients with limited nodal involvement could benefit from the curative intent of surgery too. Indeed, patients with pN1 disease after RP + LND without ADT showed 10 year-BRFS of 28% and patients with low nodal burden and GS < 8 represented the most favorable group (41). Furthermore, the rationale of maximizing local control comes from the observation that also both surgical margins and local disease stage represent significant predictors of oncological outcomes (46). Although current classification (2) do not distinguish subcategories of N positive patients, evidence seems to support clear different oncological outcomes between those with low nodal burden of disease (two or less LNs) and those with more extended disease (37, 39–41). The latter are probably the ones in which the old assumption that nodal involvement equals to systemic disease is true, but even in this case it remains questionable whether surgery could play cytoreductive role both on the prostate (47, 48) and the lymph nodes (35).

It is not surprising that the only comparison of surgery and radiation in cN1 patients failed to show any benefit (6); there is however increasing evidence supporting the role of radiation in adjuvant setting after surgery revealing pN1 disease, especially for those patients with low nodal burden of disease and lower tumor grading (49). In light of these considerations, there is strong need of high-quality evidence regarding outcomes of surgery in this particular population; while awaiting results of potential RCTs other retrospective data could be useful too. Indeed data from population databases of the reported studies show that, even if not recommended by guidelines, surgery in cN1 patients is not uncommon in clinical practice.

CONCLUSION

Treatment of clinically diagnosed nodal involvement of PCa remains controversial, with not negligible evidence supporting an oncological benefit derived from radical prostatectomy and pelvic lymph node dissection. This remains a considerable proportion of patients who are not staged properly with conventional imaging techniques and may be undertreated. There is absolute need of prospective randomized data clarifying the role of surgery and its timing in the setting of a multimodal treatment.

AUTHOR CONTRIBUTIONS

GM and RK: conception of the work. GM: acquisition and interpretation of data. GM, JA, and MA: drafting the manuscript. JA, MA, and RK: critical revision for important intellectual content.

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MINI REVIEW
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A Brief Review of Low-Dose Rate (LDR) and High-Dose Rate (HDR) Brachytherapy Boost for High-Risk Prostate

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For patients with unfavorable or high-risk prostate cancer, dose escalated radiation therapy leads to improved progression free survival but attempts to deliver increased dose by external beam radiation therapy (EBRT) alone can be limited by late toxicities to nearby genitourinary and gastrointestinal organs at risk. Brachytherapy is a method to deliver dose escalation in conjunction with EBRT with a potentially improved late toxicity profile and improved prostate cancer related outcomes. At least three randomized controlled trials have demonstrated improved biochemical control with the addition of either low-dose rate (LDR) or high-dose rate (HDR) brachytherapy to EBRT, although only ASCENDE-RT compared brachytherapy to dose-escalated EBRT but did report an over 50% improvement in biochemical failure with a LDR boost. Multiple single institution and comparative research series also support the use of a brachytherapy boost in the DE-EBRT era and demonstrate excellent prostate cancer specific outcomes. Despite improved oncologic outcomes with a brachytherapy boost in the high-risk setting, the utilization of both LDR, and HDR brachytherapy use is declining. The acute genitourinary toxicities when brachytherapy boost is combined with EBRT, particularly a LDR boost, are of concern in comparison to EBRT alone. HDR brachytherapy boost has many physical properties inherent to its rapid delivery of a large dose which may reduce acute toxicities and also appeal to the radiobiology of prostate cancer. We herein review the evidence for use of either LDR or HDR brachytherapy boost for high-risk prostate cancer and summarize comparisons between the two treatment modalities.

Keywords: HDR, LDR, brachytherapy, boost, high risk prostate, cancer

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INTRODUCTION

Nearly 180,000 new cases of prostate cancer are estimated to be diagnosed in 2019 (1, 2). For patients with high-risk prostate cancer, treatment options most often include surgery or a combination of androgen deprivation therapy (ADT) and radiation therapy. External beam radiation therapy (EBRT) is the most common method to deliver radiotherapy for localized prostate cancer.Multiple studies have demonstrated that dose-escalated external beam radiation

therapy (DE-EBRT) improves local control, freedom from biochemical failure, freedom from distance metastases, and decreases the need for salvage therapy (3–6). DE-EBRT, however, has also been associated with increases in late genitourinary (GU) and gastrointestinal (GI) toxicities (3). In the NRG Oncology/RTOG 0126 randomized clinical trial, the 5-years rates of both GI and GU late toxicity were increased with dose escalation (3). Brachytherapy is a method to deliver high-dose radiotherapy and escalate the biologically equivalent dose (BED), either as monotherapy or in tandem with EBRT as a boost, which is highly conformal and can often provide sparing of the surrounding organs at risk that is often not achievable with EBRT. Both permanent seed low dose-rate (LDR) or high dose-rate (HDR) brachytherapy provide a highly conformal escalation of dose to the cancer and allow greater sparing of surrounding normal organs than that possible with any type of EBRT (7). The American Society of Clinical Oncology (ASCO)/Cancer Care Ontario (CCO) Joint Guideline Update published in 2017 explicitly states that for patients with high-risk prostate cancer receiving EBRT and androgen deprivation therapy (ADT), brachytherapy boost (either LDR or HDR) should be offered to eligible patients (8). This recommendation is largely based on the ASCENDE-RT trial which demonstrated a significant improvement in the rates of biochemical relapse for patients treated with a brachytherapy boost (9). In ASCENDE-RT, the brachytherapy boost was delivered using a permanent seed low-dose rate (LDR) implant. LDR brachytherapy is a proven method with decades of follow-up and endorsement by numerous expert consensus groups. Another method of brachytherapy, high-dose rate (HDR) brachytherapy, is an alternative to LDR which has many properties that may make it a superior alternative to LDR. In contrast to LDR, HDR is not a permanent implant and generally allows for more consistent dose coverage and relative lower dose to the rectum, bladder, and urethra (7, 10, 11). Both LDR and HDR boost are recommended in the ASCO/CCO Joint Guideline recommendations and the choice between the two is often determined by physician, hospital, patient, and disease characteristics. We herein report on the importance of the brachytherapy boost as well as compare and contrast the use of both LDR and HDR brachytherapy as a boost in high-risk prostate cancer, and summarize future directions using these treatment modalities.

LDR BRACHYTHERAPY BOOST

LDR brachytherapy, commonly referred to as permanent prostate brachytherapy or seed implant, is a type of procedure in which implanted radioactive sources are permanently placed into the prostate. Defined by the International Commission on Radiologic Units and Measurements, LDR brachytherapy is the utilization of a radiation source with a dose-rate of <2 Gy per hour (12). Brachytherapy boost delivered with LDR has been a well-established treatment modality in the treatment of high-risk prostate cancer with numerous studies supporting its use and efficacy (13–15). Sathya et al. (16) conducted a randomized controlled trial comparing EBRT to 40 Gy in 20 fractions plus a temporary LDR brachytherapy boost with iridium-192–35 Gy vs. EBRT alone to 66 Gy in 33 fractions in patients with high-risk prostate cancer. No androgen deprivation therapy was given neoadjuvantly or concurrently in either arm. The primary outcome was biochemical or clinical failure. With a median follow-up of 8.2 years, 29% of patients in the EBRT plus temporary LDR brachytherapy boost arm failed vs. 61% in the EBRT alone arm (hazard ratio, 0.42; $p = 0.0024$) (16, 17). While the EBRT dose used in this study was low compared to modern standards, this trial laid the groundwork and confirmed the principal that brachytherapy in conjunction with moderate dose EBRT resulted in increased rates of biochemical control than that achieved with EBRT alone.

Recently, the highly anticipated results of a large randomized trial comparing the now standard dose-escalated EBRT to EBRT plus LDR brachytherapy boost were published. The ASCENDE-RT trial was a randomized Phase III study comparing EBRT alone (78 Gy/39 fractions) to EBRT (46 Gy/23 fractions) plus an LDR brachytherapy boost (115 Gy using ^{125}I) in patients with intermediate or high-risk prostate cancer (9). Both arms included 12 months of androgen deprivation therapy. The trial included 398 patients and demonstrated a statistically significant improvement in biochemical progression-free survival (b-PFS) in favor of the brachytherapy boost arm, with 9-years b-PFS of 83 vs. 62% (18). At a median follow-up of 6.5 years, there was no statistical difference in 7-years overall survival although there was a trend toward improvement with the LDR boost (85.7 vs. 81.5%). Longer follow-up of the trial will be necessary to determine if the addition of the LDR-boost correlates to improved metastasis free, cause-specific, and overall survival with these results anticipated with median follow-up of 13 years. With regards to overall survival, Johnson et al. (19) identified patients from the National Cancer Database (NCDB) with unfavorable prostate cancer who were treated with either DE-EBRT or EBRT with a LDR boost. This study attempted to mirror enrollment criteria of ASCENDE-RT but allowed patients to have received ADT up to 8 months prior to definitive radiation therapy. They found that the LDR boost was associated with improved overall survival (7-years OS 82 vs. 73%; $p < 0.001$) (19). The improved survival outcome persisted in multivariable analysis and with propensity score matching, although the study cannot fully account for selection bias in the choice of treatment.

HDR BOOST

HDR differs from LDR in that radiation sources with higher activity are temporarily inserted into the prostate gland using catheter needles and then removed after the prescribed dose has been delivered. The International Commission on Radiologic Units and Measurements defines HDR as a dose delivered at a rate >12 Gy/h, although in actuality this is usually much higher, often in excess of 1 Gy per minute (7, 12). With regards to radiation biology, the degree of dose escalation achievable with HDR brachytherapy, compared to other EBRT techniques and LDR, may be more effective in killing prostate cancer cells (7, 20, 21). The rapid dose delivery seen in

HDR is considered to be selectively more damaging to cells with lower alpha/beta ratios, such as prostate cancer and late responding normal tissues (22–24). Radiobiologic models thus support current clinical evidence for equivalent outcomes with either LDR or HDR, with theoretical advantages to HDR brachytherapy (22).

In terms of HDR brachytherapy boost, there does exist at least one randomized trial although it predates DE-EBRT. Hoskin et al. (25) performed a randomized controlled trial of a HDR boost vs. EBRT alone in patients with mostly intermediate and high-risk disease (25). Patients were randomized to receive either EBRT alone (55 Gy/20 fractions) or EBRT (35.75 Gy/13 fractions) plus an HDR boost (17 Gy/2 fractions). Neoadjuvant androgen deprivation therapy was given in 76% of patients at the discretion of the treating physician. Men in the HDR boost cohort had a 31% decrease in the risk of local recurrence, and late genitourinary toxicities were similar in both arms (7, 25). Despite providing randomized evidence, criticisms of this trial include a low EBRT alone radiation dose (55 Gy/20 fractions) compared to current standards of 60 Gy in 20 fractions or 78–80 Gy in standard fractionation. A randomized feasibility study was conducted by Vigneault et al. to assess the ability to randomize patients between dose escalated image-guided radiation therapy (IGRT) (78 Gy/39 fractions or 60 Gy/20 fractions) and IGRT plus HDR brachytherapy boost (37.5 Gy/15 fractions + 15 Gy HDR boost) with good compliance although small numbers (57 patients randomized) (26). Rates of protocol deviations and acute toxicities were low in both arms, but no biochemical control rates are reported as data matures (26).

While no other prospective, randomized comparisons of DE-EBRT and HDR boost exist, multiple single institution reports have demonstrated favorable biochemical control rates similar to those in ASCENDE-RT with better toxicity profiles. Vigneault et al. (27) reported on a cohort of 832 men with intermediate and high-risk disease treated with a range of doses of HDR brachytherapy boost in combination with EBRT and found biochemical control of 95% with median follow-up of 66 months (27). In this trial, they reported that late grade 3 GU toxicity ranged from ∼2–5% dependent on the dose level the patient was treated on (27). There were no grade 3 GI toxicities reported. Androgen suppression was used in 41.3% of patients in this study (4–6 months in intermediate cases and 18–36 months in high-risk cases). There was significant differences in the median follow-up between the different HDR dose levels which did not allow for valid comparison of biochemical control rates between the different groups. Martinez et al. reported on a dose escalation trial using a HDR brachytherapy boost and found very favorable 10-years PSA control approaching 81% in men receiving the escalated dose treatment (28). Of the over 470 patients treated with EBRT plus HDR, grade 3 genitourinary toxicity was extremely rare at <1% (28). Neoadjuvant and/or concurrent androgen suppression was used in 51.3% of the patients. Additional data is also emerging in support of an HDR boost in the high-risk setting. Kent et al. (29) recently published results of their single institution retrospective review of 46 Gy EBRT plus HDR boost (median boost 18 Gy/3 fractions) compared to EBRT alone (median 70 Gy). The 5, 10, and 15-years overall survival was higher at 92, 81, and 67%, respectively, for the EBRT plus HDR cohort, compared with 88, 71, and 53%, respectively, in the EBRT alone cohort ($p < 0.001$) (29). The 5, 10, and 15-years cause specific survival was also higher in the HDR boost group with survival of 96, 93, and 87% (EBRT plus HDR) and 95, 88, and 79% (EBRT alone), respectively ($p < 0.037$) (29). A limitation of this study is the heterogenous use of androgen suppression at the discretion of the treating physician and specifically an increased use of ADT in the EBRT plus HDR group. Also, a median dose of 70 Gy by standard fractionation in the external beam alone group is again lower than the current standard for dose escalated therapy. Numerous other single institution trials also support the use of HDR brachytherapy boost (11, 30–34) (**Supplemental Methods**).

HDR Vs. LDR BOOST

Multiple studies have suggested that when used in the monotherapy setting for more favorable localized prostate cancer, both HDR and LDR brachytherapy have equivalent biochemical progression-free survival outcomes (35, 36). For high-risk patients, the 2017 American Society of Clinical Oncology (ASCO)/Cancer Care Ontario (CCO) brachytherapy guidelines state that men with high-risk prostate cancer should be offered either an LDR or HDR boost if choosing a definitive radiation management approach (8). The recommendation of a brachytherapy boost was largely based on the previously discussed three randomized controlled trials comparing EBRT alone to EBRT plus a brachytherapy boost and demonstrate improved disease free survival with the boost (**Table 1**). In each of these trials, however, a different modality/type of brachytherapy boost was used. Data comparing LDR and HDR head-to-head are much more limited in the boost setting.

For men with high-risk disease, Kishan et al. (37) reported on the differences in prostate cancer-specific mortality and distant metastasis in prostate cancer patients with high-risk disease treated with either surgery, EBRT with ADT, or EBRT plus either LDR or HDR brachytherapy with ADT in a large multi-institutional cohort (37). Androgen deprivation therapy was given in 89.5% of patients receiving EBRT alone and 92.4% of patients receiving EBRT plus brachytherapy boost (37). The duration of androgen suppression was significantly shorter in the EBRT plus brachytherapy arm (12 vs. 22 months EBRT alone; $p < 0.001$) (37). Despite the difference in androgen suppression duration, this study found that among patients with Gleason 9–10 disease, treatment with EBRT plus brachytherapy and ADT was associated with significantly better prostate cancer-specific mortality and longer time to distant metastases compared to surgery or ADT and EBRT alone (37). They performed a cause-specific regression to determine an effect of LDR vs. HDR on clinical outcomes, including both prostate cancer-specific mortality and distant metastasis, and found no difference between the two techniques (37).

TABLE 1 | Randomized controlled trials comparing external beam radiation therapy (EBRT) vs. EBRT plus brachytherapy boost.

RCT	Year	Treatment	#Patients	Primary outcome	OS	PCSM	MFSR
Sathya[14]	1992–1997	EBRT	53	BCF: 39%	NR	NR	NR
		EBRT + LDR	51	BCF: 71%			
Hoskin[23]	1997–2005	EBRT	111	bDFS: 4.3 y	88%, 7 y	NR	NR
		EBRT + HDR	109	bDFS: 5.1 y	81%, 7 y		
				$p = 0.04$	$p = 0.2$		
Morris[6]	2002–2011	DE-EBRT	200	bDFS: 62%, 9 y	74%, 7 y	5.5%	9%
		EBRT + LDR	198	bDFS: 83%, 9 y	78%, 7 y	3.5%	8.5%
				$p < 0.001$	$p = 0.29$	$p = 0.32$	$p = 0.83$

RCT, randomized controlled trial; OS, overall survival; PCSM, prostate cancer specific mortality; MFSR, metastasis free survival rate; EBRT, external beam radiation therapy; LDR, low dose rate brachytherapy; HDR, high dose rate brachytherapy; BCF, biochemical failure; bDFS, biochemical disease free survival.

King et al. (38) used the National Cancer Database in an attempt to compare LDR vs. HDR boost with regards to overall survival outcomes. In their study, they estimated overall survival in patients with unfavorable prostate cancer treated with dose-escalated EBRT and EBRT followed by LDR boost vs. HDR boost (38). Patients included were diagnosed with NCCN intermediate or high-risk prostate cancer from a time period of 2004–2014. In their analysis of over 120,000 patients, HDR boost was associated with a similar overall survival compared to LDR boost using multivariable analysis [adjusted hazard ratio (AHR), 1.03 (0.96–1.11); $p = 0.38$]. Compared to dose-escalated EBRT, HDR boost was associated with significantly better overall survival [AHR, 1.36 (1.29–1.44); $p < 0.001$] (38). Androgen deprivation therapy was given in 40.4% of patients with the HDR boost, 43.1% of patients with the LDR boost, and 49% of patients with DE-EBRT ($p < 0.001$) (38).

TOXICITY CONCERNS

RTOG P-0019 was a phase II study of EBRT combined with LDR brachytherapy boost (45 Gy/25 fractions + 108 Gy ^{125}I boost) for intermediate risk prostate cancer with the primary goal to estimate the acute and late Grade 3-5 GU and GI toxicity (39). Short-term androgen suppression up to 6 months was allowed and 27% received ADT. A total of 138 patients from 28 institutions were enrolled on the study with acute toxicity evaluable in 131 patients (39). Acute Grade 3 GU toxicity was recorded in 7.6% of patients without any Grade 4 or 5 events (39). Six months after radiation therapy, ∼63% of patients reported a higher International Prostate Symptom Score (IPSS) score compared to baseline (39). The 18-months estimate of both late Grade 3 GU and GI toxicity was 3.3% (39). With longer follow-up, increased rates of Grade 3 or greater GU/GI toxicity were reported, estimated at 15% (95% CI, 8–21%) at 48 months (40). CALGB 99809 was another multi-institutional trial designed to assess the toxicity and feasibility of EBRT plus LDR brachytherapy boost (45 Gy/25 fractions + 100 Gy ^{125}I or 90 Gy ^{103}Pd boost) combined with 6 months of ADT (41). Acute Grade 2 and 3 toxicity occurred in 25 and 7% of men and was most commonly urinary frequency/urgency (41). Late Grade 2 and 3 toxicity was observed in 20% and 2% of men, respectively (41). Differences between these two multi-institutional protocols included an expansion on the LDR boost clinical target volume (CTV) of 5 mm (0 mm posteriorly) in the RTOG trial compared to no expansion in the CALGB trial, which may contribute to the rates of late Grade 3 or greater toxicities.

In the randomized ASCENDE-RT trial, toxicity was increased in the brachytherapy group with the cumulative incidence of grade 3 GU events at 5 years of ∼18% for the brachytherapy boost arm vs. 5% for the EBRT alone arm ($p < 0.001$). There was also a trend toward increased gastrointestinal toxicity with the brachytherapy boost, 8 vs. 3% ($p = 0.12$) (42). However, at the 6-years follow-up time point, health-related quality of life was similar between the two groups in most domains with the exception that physical and urinary function scales were lower in the LDR arm (43). Regardless, the increased toxicity observed in the combined EBRT plus LDR boost arm ASCENDE-RT highlights the importance of careful patient selection and diligent treatment planning as well as early intervention with symptom management as needed for these patients. A detailed analysis of the treatment related morbidity from the trial is available (42).

HDR brachytherapy may be a method to overcome the acute toxicities seen with LDR given the physical properties of this treatment modality. With an LDR implant, the radiation dose is delivered over a time period of months compared to minutes with HDR. For this reason, LDR is associated with a more prolonged recovery period. A prospective non-randomized comparison of quality of life after LDR vs. HDR boost (combined with 4.5 weeks of EBRT) showed a return to baseline IPSS at 6 months with LDR compared to only 12 weeks with HDR (44). Another early analysis of a randomized controlled trial of HDR vs. LDR in the monotherapy setting suggests improved quality of life, shorter return time to baseline urinary function, and lower rates of acute urinary symptoms with HDR monotherapy (45). While the previous studies show very favorable toxicity

profiles with HDR brachytherapy compared to LDR, HDR has been associated with non-insignificant rates of urethral stricture. In a study by Bece et al. reported in 2015, various doses and fractionations of HDR boost (19.5 Gy/3fractions; 17 Gy/2 fractions; 18 Gy/2 fractions; and 19 Gy/2 fractions) in combination with EBRT were used and overall 3 and 6-years stricture incidence were 7.8 and 15.3%, respectively (46). The HDR boost fractionation scheme evolved during their study and the most recent fractionation used (19 Gy/2 fractions) resulted in the lowest three-year stricture rate of 3.0% (46). Yaxley et al. retrospectively analyzed a series of 507 men consecutively treated with EBRT plus HDR brachytherapy with a median follow-up of 10.3 years and found that rates of urethral stricture can be significantly reduced with careful attention to dose heterogeneity constraints, imaging prior to second HDR fraction to control for needle displacement, and tighter apical (inferior) PTV margins during the EBRT (47). Prior to implementation of these "stricture prevention measures," the rate of stricture was 13.6% and this rate dramatically fell to 4.2% using these planning considerations (47).

In terms of long-term toxicity, an investigation using the Surveillance, Epidemiology, and End Results Medicare database (SEER) did not show a statistically significant difference in Grade 3 genitourinary adverse events between LDR and HDR (48). The results of the BrachyQOL randomized controlled trial (NCT01936883) are highly anticipated as they will shed more definitive light on both the acute and late GU/GI side-effect profiles between LDR and HDR in the boost setting (49).

DECLINING USE OF BRACHYTHERAPY BOOST

Despite potential improved outcomes with either LDR or HDR boost, the rates of brachytherapy boost utilization are declining (50, 51). Multiple reasons for the declining use of a boost have been reported including increase of prostatectomies for higher risk patients (52), increases in reimbursement for other EBRT techniques (53), decrease in brachytherapy training (54), and potential perception that brachytherapy is a procedure with excessive liability risk (51). In an analysis by Johnson et al. (19), the utilization of LDR brachytherapy boost dropped from ∼29% in 2004 to 14% in 2012. Previous database-based studies also report the declining use of EBRT plus brachytherapy boost (52). The American Brachytherapy Society (ABS) has started a "300 in 10" initiative to increase the training of brachytherapists by assisting in the training of 30 oncologists per year over a 10-years period. Initiatives such as this are extremely important as a brachytherapy boost has the potential to improve prostate-specific survival outcomes when compared to EBRT alone.

FUTURE DIRECTIONS

While an optimal dose for LDR brachytherapy boost has been established, studies continue to determine the optimal HDR schedule and dose escalation continues to be investigated in the HDR setting. Also, limited data on prostate cancer specific survival outcomes between HDR and LDR exist. The British Columbia Cancer Agency is conducting a Phase III randomized controlled trial in patients with unfavorable intermediate risk and high-risk prostate cancer who will receive 46 Gy in 23 fractions of EBRT and then be randomized to either a LDR boost using ^{125}I (115 Gy) or HDR boost using ^{192}Ir (15Gy x 1). In addition to quality of life measures, a secondary outcome is PSA recurrence-free survival which will provide randomized head-to-head outcomes between LDR and HDR brachytherapy boost. Another unknown for both LDR and HDR boost in the high risk setting is defining the optimal planning target volume (PTV) to balance tumor coverage while minimizing toxicity. The differences in CTV to PTV expansion between RTOG 0019 and CALBG 99809 in the intermediate risk setting were 5 vs. 0 mm, respectively, and may have long term toxicity consequences. In high-risk prostate cancer, while the external beam target volumes should include any extracapsular extension and the at risk proximal seminal vesicles, some intuitions are including both the proximal seminal vesicles and extracapsular extension in the brachytherapy boost volume, but the clinical significance of such inclusion is unknown. Advanced computer planning and CT/MRI/Ultrasound-based planning with HDR brachytherapy may allow better and more reproducible coverage of the seminal vesicles and extracapsular extension compared to LDR given the inherent post-implant treatment planning capabilities with HDR. Additionally, as imaging technology continues to improve, small institutional trials are underway or have completed investigating focal brachytherapy boost to intraprostatic lesions using MRI-transrectal-ultrasound fusion (55). Lastly, SBRT continues to gain popularity given its shorter treatment course and less invasive nature, comparisons between SBRT and brachytherapy are emerging. Preliminary data from a reported literature search of 47 studies on PubMed and Embase (6 SBRT boost and 41 HDR boost), showed that a SBRT boost may be associated with higher acute Grade 2 genitourinary toxicity but lower late Grade 3 GU toxicity, and no difference was seen between the two by quality of life reports. Randomized trials between both LDR and HDR boost and SBRT boost are warranted and underway.

CONCLUSIONS

Both HDR and LDR brachytherapy provide a method of biologically equivalent dose escalation in patients with high-risk prostate cancer who are undergoing definitive intent radiation therapy. In combination with EBRT, brachytherapy is a modality to deliver highly conformal dose escalation while drastically sparing the rectum and bladder compared to EBRT alone. Two randomized controlled trials have shown improved biochemical control with EBRT plus brachytherapy boost but neither demonstrated a statistical difference in overall survival (16, 25). The LDR boost arm in the ASCENDE-RT trial demonstrated a significant

improvement in biochemical progression-free survival and long term survival outcomes are eagerly anticipated (9). Despite the improvements in biochemical control with brachytherapy boost, trends in the use of brachytherapy continue to decline nationally, possibly secondary to concerns of acute genitourinary toxicity with LDR. Initiatives to increase brachytherapy use are currently underway, and HDR brachytherapy may be an opportunity to improve toxicity profiles while exploiting the radiobiology of prostate cancer in the boost setting.

AUTHOR CONTRIBUTIONS

BF-V, HG, SP, BB, and JM: literature search, writing, and final approval.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2019.01378/full#supplementary-material

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A Cost-Effectiveness and Quality of Life Analysis of Different Approaches to the Management and Treatment of Localized Prostate Cancer

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The aim of this study was to compare the cost-effectiveness and quality-adjusted life years (QALYs) of active monitoring (AM), radical prostatectomy (PR), and external-beam radiotherapy with neoadjuvant hormone therapy (RT) for localized prostate cancer. Microsimulations of radical prostatectomy, 3D-conformal radiotherapy, or active monitoring were performed using Medicare reimbursement schedules and clinical trial results for a target population of men aged 50–69 years with newly diagnosed localized prostate cancer (T1-T2, NX, M0) over a time horizon of 10 years. Quality-adjusted life years (QALYs) and costs were assessed and sensitivity analyses performed. Monte Carlo simulations revealed that the mean cost for AM, PR, and RT were $15,654, $18,791, and $30,378, respectively, and QALYs were 6.96, 7.44, and 7.9 years, respectively. The incremental cost-effectiveness ratio (ICER) was $6,548 for PR over AM and $68,339 for RT over PR. Results were sensitive to the number of years of follow-up and procedure cost. With relaxed assumptions for AM, the ICER of PR and RT met the societal willingness to pay (WTP) threshold of $50,000 per QALY. Compared with AM, PR was highly cost-effective. RT and PR for localized prostate cancer can be cost-effective, but RT must offer increased QALYs or decreased procedural costs to be cost-effective compared to PR. Newer and cheaper radiotherapy strategies like stereotactic body radiotherapy may play a crucial role in future early prostate cancer management.

Keywords: active monitoring, cost-effectiveness analysis, prostate cancer, prostatectomy, QALY, radiotherapy

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INTRODUCTION

About 160–240,000 men are diagnosed with prostate cancer in the US each year (1, 2). Prostate cancer has a tremendous and growing economic impact in part due to the costs associated with newer therapies. There is, however, no consensus on the most cost-effective treatment strategy for low- and favorable-risk prostate cancer.

The Prostate Testing for Cancer and Treatment (ProtecT) trial examined the optimal management of men with low-risk, clinically localized prostate cancer detected by prostate serum antigen (PSA) testing by comparing active monitoring (AM), radical prostatectomy (PR), and external-beam radiotherapy with neoadjuvant androgen deprivation therapy (RT). ProtecT

reported no significant differences in prostate cancer-specific mortality or all-cause mortality at a median follow-up of 10 years regardless of strategy. Although the trial revealed worse outcomes for AM in terms of disease progression and metastasis, ProtecT clarified the distinct effects of prostate cancer treatments on urinary, sexual, and bowel function and condition-specific quality of life (QoL) (3, 4).

Differences between treatment modalities in terms of side-effects and costs may translate into more or less cost-effective management. The most recent cost-effectiveness analyses comparing AM with immediate treatment (5) or primary treatments for clinically localized prostate cancer (6) were evaluated before ProtecT reported. The estimates were based on a large systematic review of lower-level evidence and were thus limited by the quality and quantity of data (5).

The aim of this cost-effectiveness study was to estimate the long-term health outcomes and healthcare costs of the three localized prostate cancer treatment strategies used in ProtecT. The study leverages the results of this first multicenter randomized trial and accounts for cost and risk of death, recurrence, salvage therapy, adverse effects, and complications related to treatment.

METHODS

Study Design and Scope

A Markov model of managing newly diagnosed prostate cancer was developed using TreeAge Software (TreeAge Software Inc., Williamstown, MA; **Figure 1**). Monte Carlo simulations were performed to estimate the costs and QALYs of patients with histologically proven, clinically localized prostate cancer (T1-T2, NX, M0) over the 10 years from diagnosis in 6 months increments (stages). Costs of diagnosis were not included because they were treatment-independent. The analysis was conducted from the US healthcare payer perspective, with national-average Medicare reimbursements for year 2008 used as payer costs. In accordance with economic guidelines, the 3% discount rate was used to adjust costs to their net present value.

The analysis included three prostate cancer treatments: active monitoring (AM), prostatectomy (PR), and external beam radiotherapy (RT). Health states for each stage were remission, local progression, metastatic disease, and prostate cancer-related and non-prostate cancer-related deaths. Cost analyses did not include patients that did not start any treatment or started another form of treatment in the ProtecT trial. To exclude protocol-driven costs (7), we verified the protocol according to well-established National Comprehensive Cancer Network (NCCN) recommendations (8).

Simulations of various scenarios to estimate cost of treatment of clinically localized prostate cancer (PSA level <20, Gleason 6–10, stage ≤T2) were conducted. Men entered the model aged 50–69 and exited at the time of death or after 10 years of follow-up.

The decision tree in **Figure 1** shows the microsimulation model used to simulate costs and quality-adjusted life-years (QALYs). According to the study profile, the three groups (AM, PR, and RT) were analyzed, and the decision tree considered

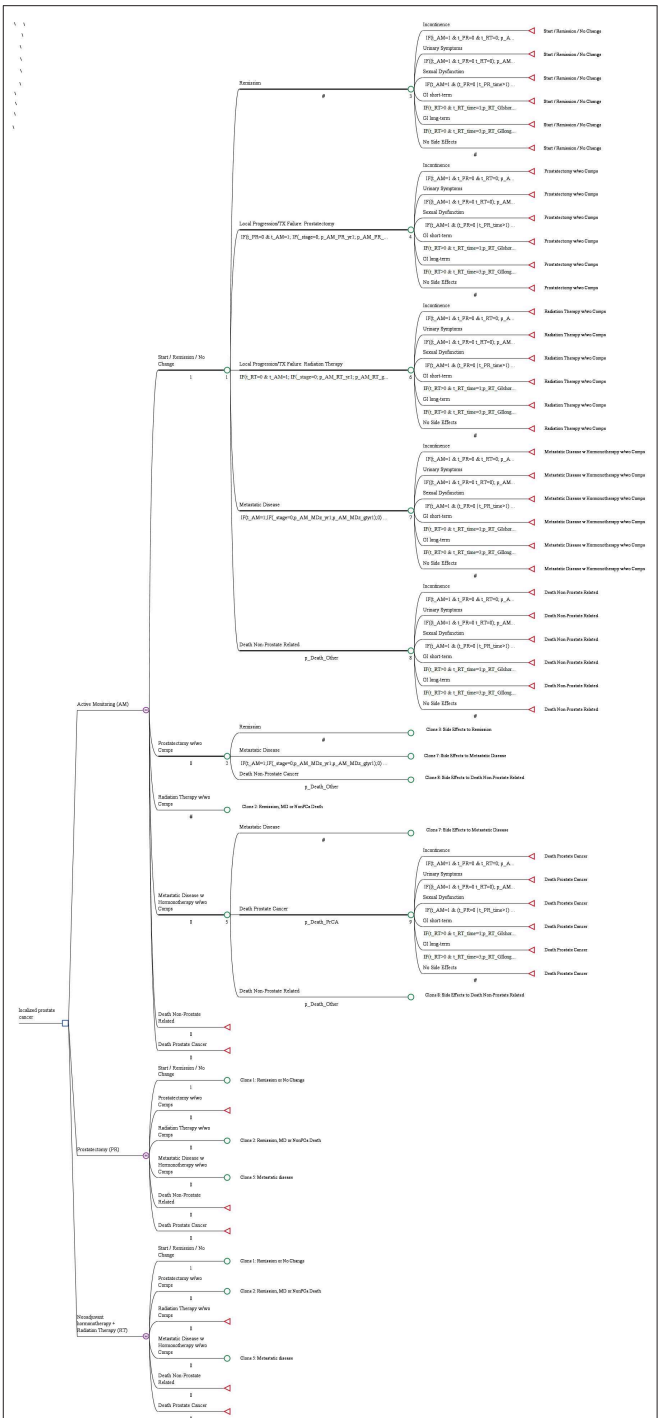

FIGURE 1 | A decision tree for managing newly diagnosed prostate cancer. The blue square indicates a decision node, a point at which a treatment strategy is chosen; the purple encircled letter "M" indicates the Markov node, with branches indicating the health states in transition every 6 months; the green circle indicates the chance node, after which there is a probability of the occurrence of each health state (remission, local progression treated with prostatectomy, local progression treated with radiation therapy, metastatic disease, death not prostate related, death from prostate cancer); and the red triangle indicates the terminal node, the end of a pathway within a 6 months cycle.

three health states (progression-free survival, progressive disease, and death). The target population was a hypothetical cohort of 545 people with the same characteristics as those in ProtecT.

Model Inputs

Treatment scenarios, group sizes, and cost centers were generated based on the original study results (3, 4). Other phase three randomized trials on active surveillance for localized prostate cancer (3, 9–12) were used to predict missing cost centers, incidence of events, and treatment results not reported in Hamdy et al. (3) and validated by expert panels.

A previous decision analysis of the ProtecT trial was used to estimate QALYs (13). Model inputs are described in detail in **Supplementary Table 1**. To standardize costs, we derived unit and resource costs from the Medicare Fee Schedule for the Technical Component of Hospital Outpatient Radiology Procedures (14, 15).

Sensitivity analyses were undertaken to handle parameter uncertainty. Specific analytic assumptions about the variation in costs and outcomes were made in order to obtain confidence intervals on cost effectiveness ratios (16). Sensitive parameters taken into account were number of follow-up years, specific costs, and probabilities.

For the purpose of this study, we assumed that patients underwent prostatectomy via the conventional retropubic approach. The risk of post- or peri-operative complications per model stage was set at 7.5% for urinary symptoms, 22% for incontinence, and 27% for sexual dysfunction for all patients undergoing prostatectomy (3). In our scenario, the frequency of minor vs. major surgical complications was assumed to be 2:1 based on Institute for Clinical and Economic Review (14, 15). The corresponding probabilities in the AM treatment were 2.5, 0.5, and 2.6% and in the RT treatment were 4.6, 0.3, and 20.5%. In addition, patients receiving RT risked short- (2.5%) and long-term (3.6%) gastrointestinal problems.

For each treatment, specific costs and management of treatment-related adverse effects were derived from Institute for Clinical and Economic Review (14, 15) and Hodges et al. (17), and the numbers of patients with treatment-related adverse effects were extracted from patient-reported outcomes (4) and long-term functional outcome data (18). The number of patients that received treatment-related negative effects was calculated based on the following formula: max % of patients that reported negative effect—% of patients with negative effect at baseline x number of patients treated.

We calculated the ICERs expressed as monetary costs per life-years gained (LYG) and per QALYs gained, and compared each to the cost-effectiveness threshold, which represents society's willingness to pay (WTP) for an additional unit of benefit. In the US, the commonly accepted standard threshold is $50,000 per QALY gained.

One-way sensitivity analysis was performed for all parameters to assess the impact that a fixed change in each parameter had on the ICER. A cost-effectiveness acceptability curve was constructed to determine the probability of each strategy of being cost-effective. The multivariate probabilistic analysis was performed running 1,000 patients in 10,000 Monte Carlo iterations. Since this was a secondary analysis of anonymized data, no IRB approval was required.

RESULTS

Model Validation

The difference in survival benefit in ProtecT was not significant between the AM, PR, and RT groups, but the distant metastasis and progression rates were higher in the AM group. The model accurately reproduced the survival outcomes of ProtecT in terms of overall undiscounted survival over a 10 years period: PR average 9.57 life years, RT average 9.57 life years when rounded, but slightly <PR, and AM average 9.53 life years.

Cost and Life Years as an Effectiveness Measure

After applying a 3% annual discount rate, RT was the most expensive at $30,378 over 10 years. Since RT was equally effective as PR but also more expensive than PR at $18,791, PR could be regarded the better choice. Both PR and AM represent rational choices, because AM is less effective and less expensive at $15,654.

However, AM was the best choice by ICER standards, because PR had an estimated ICER of $116,000 per life year gained (**Figure 2**). By US and UK standards, this is very expensive and probably unacceptable to most governments or insurance companies.

Quality-Adjusted Life Years as an Effectiveness Measure

In the base case, RT provided the best quality-adjusted survival with an average of 7.61 QALYs in a 10 years model. PR was second-best at 7.44, and AM was least effective at 6.96. QALY differences were much greater than the life-year differences, to the extent that the ICER for PR vs. AM was only about $6500, making PR a good alternative to AM. PR was no longer the obvious choice over RT when QALYs were used, but the ICER for RT vs. PR was high at about $68,000 and within the threshold of about $50,000 to $100,000/QALY accepted by many US insurers. The results of the base-case analysis comparing AM, PR, and RT are presented in **Tables 1**, **2**. Over 10 years, RT was 53.4% below the WTP threshold compared to AM, while PR was 85.4% below the threshold. AM was cost-effective at a WTP threshold of $1,000, PR at $1,500, and RT at $70,000.

Sensitivity Analysis

In order to test model responsiveness and result robustness, one-way sensitivity analysis was conducted. The variables in the sensitivity analysis varied from −50 to −200% of the base case values. The results are shown in **Figure 3**.

The model was most sensitive to the number of years of follow-up, cost of procedure, and probability of metastatic disease, followed by cost of follow-up after PR and probabilities of death from other causes and salvage treatment. Only number of follow-up years and procedural costs decreased the RT vs. PR ICER below the WTP threshold of $50,000/QALY. Variation of the other values had little effect and resulted in ICERs that

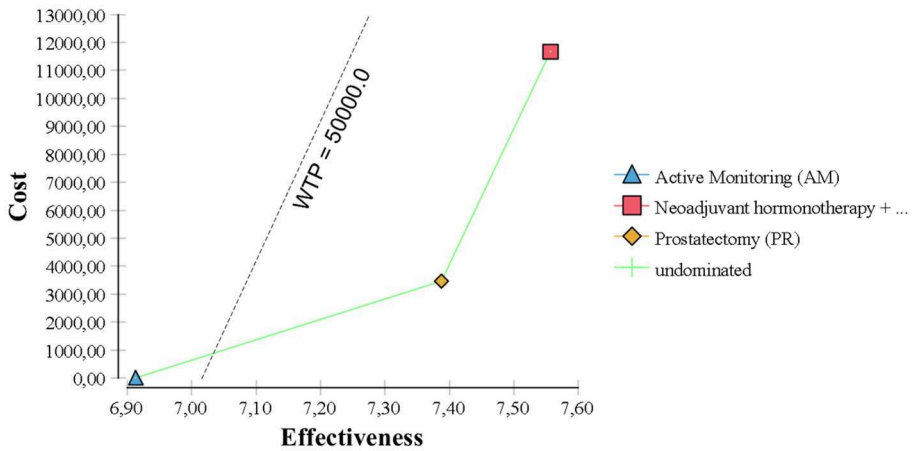

FIGURE 2 | Incremental cost-effectiveness analysis.

TABLE 1 | The results of the base case analysis.

	Costs in $ (discounted 3%/year)			Life years (not discounted)			QALYs (not discounted)		
	Active monitoring	Prostatectomy	Radiotherapy	Active monitoring	Prostatectomy	Radiotherapy	Active monitoring	Prostatectomy	Radiotherapy
Mean	15,654	18,791	30,378	9.54	9.57	9.57	6.96	7.44	7.61
Std Deviation	21,466	12,756	13,990	1.64	1.61	1.62	1.20	1.25	1.29

TABLE 2 | Life years and QALYs as cost-effectiveness measures.

	Active monitoring	Prostatectomy	Radiotherapy
Cost effectiveness ($/LY)	Base	116,488	626,012
Cost effectiveness ($/QALY)	Base	6,548	68,339

differed from the base case by <$10,000 per QALY. For follow-up years, the ICER was maximized in the first 3 years and then decreased up to the end of a trial observation period (**Table 3**). Of note, changes to RT cost had the greatest impact on the results of all the treatment-related costs. The probabilistic sensitivity analysis was considered using a cost-effectiveness acceptability curve and acceptability at WTP thresholds (**Figure 4**). At a threshold of $50,000/QALY, the probability of RT being cost-effective was 26% (**Table 2**). The cost-effectiveness acceptability curve also showed the probability of PR being cost-effective at a threshold limit of $70,000, and, at a threshold limit of $100,000/QALY, the probability of RT being cost-effective was 92.1%.

DISCUSSION

When different treatment methods have similar survival outcomes, health economics may support clinical and administrative decision-making on the most appropriate management. Here we assessed the cost-effectiveness of RT and PR in relation to AM using QALYs as the effectiveness measure. Over 10 years, with relaxed assumptions for AM, the ICER of PR and RT met the societal WTP threshold of $50,000 per QALY.

Prostatectomy and radiotherapy provide similar treatment efficacy at a higher cost during the early phases of treatment. However, these costs were balanced by better QoL than AM over the 10 years perspective. Whilst radical treatments resulted in reduced rates of metastases and disease progression, this was not shown to translate into a late survival benefit at 10 years, notwithstanding that further follow-up might reveal differences in survival benefit.

There are few cost-effectiveness analyses of different treatment modalities for prostate cancer. Earlier economic analyses were from the US (19–21) or Canadian (22) healthcare perspectives, the US cost-based analyses not including treatment of recurrences or side-effects and the other analyses excluding the costs of adverse effects.

Lao et al. (23) recently highlighted the impact of conversion from AM to PR. Approximately 20% of patients over first 2 years and 50% of patients over 10 years will progress to more aggressive cancer and subsequently undergo curative intervention, most commonly with surgery or radiotherapy (3, 4, 10, 23, 24). With this in mind, AM was less likely to be cost-effective compared to radical prostatectomy for younger men diagnosed with low-risk localized prostate cancer, with an estimated 5% conversion rate from AM to PR. With an annual conversion rate of 1.6%, life-time

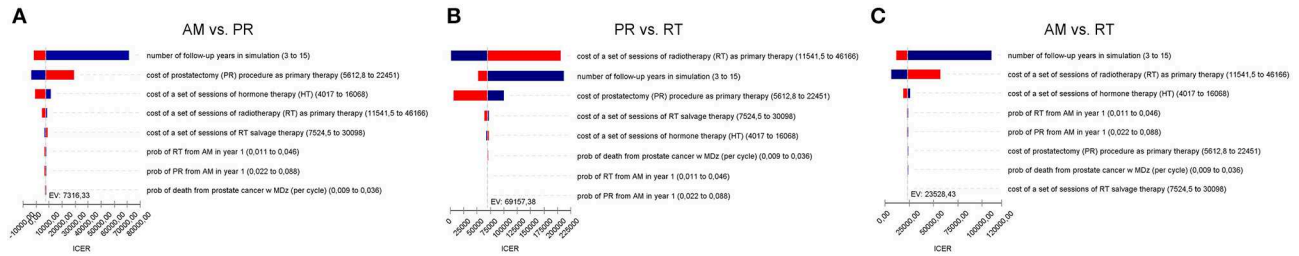

FIGURE 3 | (A) Tornado diagram summarizing the results of one-way sensitivity analysis to identify model variables associated with the AM and PR in the treatment of localized prostate cancer. The influential factors are listed descending with the variation in value. **(B)** As **(A)** but for PR and RT. **(C)** As **(A)** but for AM and RT.

TABLE 3 | One-way sensitivity analysis of years of follow up (costs in $).

No. of years	Strategy	Cost	Incremental cost	Effectiveness	Incremental effectiveness	ICER	NMB	C/E
2.0	AM*	3,848	0	1.45	0	0	−9,415	2,659
2.0	PR**	13,979	10,131	1.54	0.09	10,6332	−35,539	9,063
2.0	RT***	25,498	11,519	1.58	0.04	3,22,400	−65,736	16,158
4.0	AM	5,653	0	2.85	0	0	−21,786	1,981
4.0	PR	14,860	9,207	3.04	0.19	48,992	−60,060	4,885
4.0	RT	26,249	11,389	3.11	0.07	1,61,619	−1,07,945	8,433
6.0	AM	8,426	0	4.22	0	0.0	−44023	1995
6.0	PR	16,032	7,606	4.50	0.28	27,345	−88,222	3,561
6.0	RT	27,310	11,277	4.60	0.10	1,08,114	−1,53,127	5,928
8.0	AM	10,923	0.0	5.57	0.0	0	−71,717	1,962
8.0	PR	16,431	5,509	5.95	0.38	14,420	−1,14,165	2,763
8.0	RT	27,841	11,410	6.09	0.14	82,806	−1,97,276	4,575
10.0	AM	13,297	0.0	6.88	0.0	0.0	−1,04,758	1,933
10.0	PR	16,742	3,445	7.36	0.48	7,117	−1,39,996	2,274
10.0	RT	2,83,560	11,618	7.53	0.17	68,119	−2,41,981	3,765

**Active monitoring, **Prostatectomy, ***Neoadjuvant hormonal therapy + radiotherapy.*

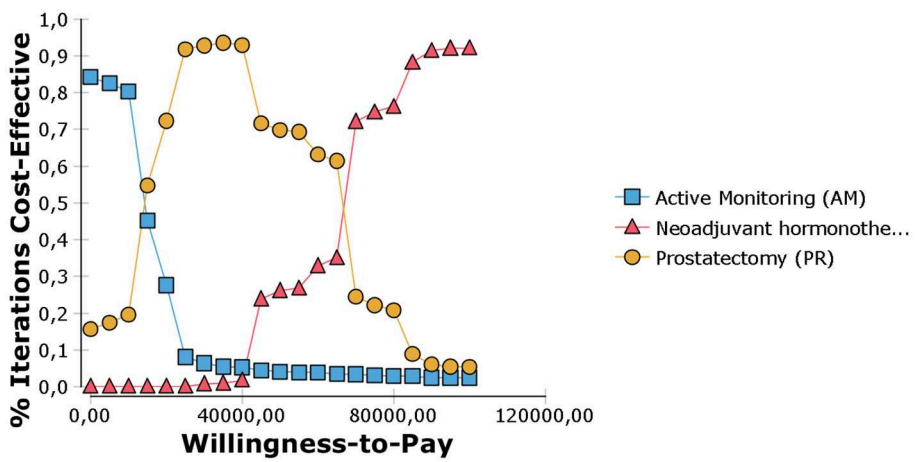

FIGURE 4 | Cost-effectiveness acceptability curve (calculated with discounted incremental cost-effectiveness ratio (ICER) expressed as $/QALY. The WTP threshold corresponds to a given threshold ICER expressed as $/QALY.

costs of AM were lower than the costs of radical prostatectomy for men aged 55–70 (23).

We assumed that the probability of having treatment annually in the AM arm was 13% in the first year and 5% in consecutive years, assuming that the conversion rates reported in the ProtecT trial made our analysis more realistic. Further, in Lao et al.'s study (23), the AM arm only considered radical prostatectomy as a treatment option, which may decrease the real cost of AM. Taking radiation and surgery as definitive treatments into account could be considered a strength of the current analysis.

Similar studies have been affected not only by the possibility of having radical prostatectomy when managed with AM but also uncertainties around good QoL data for men under AM. We used Markov decision analysis modeling of ProtecT trial data to assess QALYs from the 10 years perspective, as it was the first prospective trial with QoL life data on all three management strategies. Earlier studies (5, 25) based on the PIVOT (12) and SPCG (26) trials reported different results. In an analysis by Hayes et al. (5), AM was associated with improved QALYs compared with initial treatment. Further, in a German study (25), AM was superior to initial treatment with higher QALYs. In this case, costs were included from the German health service perspective and substantially differed from US costs. Moreover, probabilities were taken from trials comparing PR with watchful waiting, the latter representing a different strategy to AM in ProtecT, in that watchful waiting tends to be reserved for older men with significant medical comorbidities who are likely to suffer decreased QoL with aggressive treatment. However, in contrast to watchful waiting, an AM protocol advocates a potential intention to treat and therefore imposes often rigorous follow-up with frequent PSA measurements, office visits, and prostate biopsies.

Our model was sensitive to the probability of developing metastases under AM, similar to reported previously (25). At a time horizon of 2.5 years, conservative management was preferable to radical prostatectomy in terms of costs in a claims data analysis (27), consistent with our data showing that cost-effectiveness is very sensitive to follow-up time and was not a cost-effective approach over short periods of observation. Thus, AM should be a reasonable option for patients with shorter life expectancy.

Our AM strategy attempted to reproduce the ProtecT protocol but was modified slightly to reach current NCCN recommendations. According to NCCN, PSA should be assessed every 6 months from the beginning of monitoring, while in ProtecT it was every 3 months in year one and every 6–12 months thereafter (8). Regardless, sensitivity analysis showed little impact of PSA test costs on ICERs. In a recent cost-effectiveness analysis of active surveillance strategies for men with low-risk prostate cancer (28), a similar strategy was compared with MRI incorporation into surveillance protocols, which was found to be cost effective; however, this was not used in ProtecT so was not considered here.

Our results are in line with Cooperberg et al. (6), which showed substantial payer and patient costs when radiotherapy was used. In a recent analyses utilizing time-driven activity-based costing (29, 30) brachytherapy and stereotactic body radiotherapy were notably cheaper radiation modality and alternative to 3D conformal radiotherapy used in ProtecT. However, attending physician may work 1.6–3.4x more time per relative value unit when delivering brachytherapy compared to intensity-modulated radiotherapy (IMRT) (31). This resulted that contemporary practice usually involves the more costly but less intensive and non-invasive IMRT (31). Recent cost-effectiveness studies have shown that SBRT is an attractive alternative to IMRT (32, 33), with SBRT cost savings attributable to shorter procedure times and fewer visits required for treatment. This may be especially attractive in terms of cost-effectiveness, as ICERs could decrease below a critical WTP threshold. If used routinely, SBRT should increase QALYs or decrease costs. Our cost-effectiveness acceptability curve suggested that SBRT (cost $11,665) could be superior to the alternatives, but only if it results in a similar QoL. Precise evaluation of SBRT QoL compared to RT may play a crucial role in future early prostate cancer management.

Based on SEER data, the incidence of prostate cancer in the US is expected to reach 160,000 new cases per year (1). Due to this high incidence, the cost savings for AM would amount to hundreds of billions of dollars per year, so the willingness to pay for a QALY in this large population needs careful assessment.

This analysis was based on effectiveness, risk of complications and adverse events, progression, cancer, and non-cancer related deaths, and QoL data from the first prospective, randomized study of three management alternatives and adhering to cost-effectiveness analysis standards. However, because ProtecT excluded patients >69 years of age or with PSAs >20 ng/ml or PSAs 10–20 ng/ml without a bone scan performed, our results should be interpreted with caution in such groups.

There are several important limitations to this study. According to standard practice guidelines, androgen deprivation therapy or antiandrogen therapy should not be used routinely in low and favorable intermediate risk localized prostate cancer (8). Our cost analysis is based on a model that used published data not source data, so progression rates may reflect deficiencies in the literature used. In this context, men who progressed on AM received either PR or RT based on our assumptions and understanding of the published data, and we deliberately excluded brachytherapy or cryotherapy due to the lower popularity of these therapies and to simplify this model. The procedure costs were from Medicare 2008 and may differ from today's prices; additionally, some model inputs relied on expert opinion and may differ between institutions. However, sensitivity analysis was performed to assure the robustness of the findings. The probabilities were fit to males aged 50–69 with at least 10 years life expectancy and may not be easily generalizable to other populations (34). Further, our study used summary rather than individual patient data from a randomized trial, and summary data limits the unexpected rate of differences. Also, to avoid influence, trials results are never free from factors affecting generalizability, and trial-based cost analyses inherit these limitations (35). However, the strength of modeling through decision is to address the problem of generalizability of clinical trial results to real-world settings and alleviate problems associated with the inclusion of protocol-driven costs (7). In

contrast to cost analyses based on raw data from clinical trials, we focused only on the costs occurring for a clinical reason (7).

The strength of this paper was transferring all outcomes and costs to the US payer perspective independent of the location in which the original trial was undertaken. To our knowledge, this is the first cost-effectiveness evaluation of ProtecT. The model can be considered an abstraction of a trial by synthesizing information from multiple sources to provide decision makers with the best available evidence to reach a decision (36).

In conclusion, prostatectomy or radiotherapy prevented decreased QoL and did so at a cost that was below common willingness-to-pay thresholds. These results were robust to extensive sensitivity analyses.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

AH and MH coordinated and performed data analyses, reported study results, and drafted the manuscript. MM performed analyses. MH was the clinician responsible for the interpretation of clinical data. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.00103/full#supplementary-material

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Preoperative Risk-Stratification of High-Risk Prostate Cancer: A Multicenter Analysis

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Background: Cancer-specific survival (CSS) within high-risk non-metastatic prostate cancer varies dramatically. It is likely that within this heterogenous population there are subgroup(s) at extraordinary risk, burdened with an exaptational poor prognosis. Establishing the characteristics of these group(s) would have significant clinical implications since high quality preoperative risk stratification remains the cornerstone of therapeutic decision making to date.

Objective: To stratify high-risk prostate cancer based on preoperative characteristics and evaluate cancer specific survival after radical prostatectomy.

Method: The EMPaCT multi-center database offers an international population of non-metastatic high-risk prostate cancer. Preoperative characteristics such as age, biopsy Gleason score, PSA and clinical stage were subcategorized. A multivariate analysis was performed using predictors showing significant survival heterogeneity after stratification, as observed by a univariate analysis. Based upon the hazard ratios of this multivariate analysis, a proportional score system was created. The most ideal group distribution was evaluated trough different score cut-off's. The predictive value was tested by the herald C index.

Results: An overall 5-years CSS of 94% was noted within the entire high-risk cohort (n = 4,879). Except for age, all preoperative risk factors showed a significantly differing CSS. Multivariate analysis indicated, T4 stage as being the strongest predictor of CSS (HR: 3.31), followed by ISUP grade 5 group (HR 3,05). A score system was created by doubling the hazard ratios of this multivariate analysis and rounding off to the nearest

complete number. Multivariate analysis suggested 0, 4, 8, and 12 pts as being the most optimal group distribution (*p*-value: 0.0015). Five-years CSS of these groups were 97, 93, 87, and 70%, respectively. The calculated Herald C-index of the model was 0.77.

Conclusion: An easy-to-use pre-operative model for risk stratification of newly diagnosed high-risk prostate cancer is presented. The heterogeneous CSS of high-risk non-metastatic prostate cancer after radical prostatectomy is illustrated. The model is clinically accessible through an online calculator, presenting cancer specific survival based on individualized patient characteristics.

Keywords: prostate, prostate cancer, EMPACT, risk stratification, high risk prostate cancer

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer among men. It represents the 5th most frequent cause of cancer related death (1). According to the WHO cancer report (2014), 1.1 million men received a new diagnosis of prostate cancer in 2012 causing 0.3 million disease related deaths (2). Since the introduction of PSA screening in the beginning of the 80's an impressive incidence rise has been observed. Fortunately, this trend was counterbalanced by a reduction in mortality since the 90's due to earlier detection and improved curative treatments. Nevertheless, mortality attributed to PCa is expected to rise in the following decades implying an expanding burden to society (3).

Non-metastatic PCa is prognostically stratified as low, intermediate or high-risk as suggested by D'Amico in 1998 (4, 5). Currently, management of non-metastatic prostate cancer includes active surveillance, radical prostatectomy (RP) with or without pelvic node dissection and radiotherapy (RT) with or without androgen deprivation therapy (ADT). As illustrated by the PROTECT-Trial, no significant difference in low to intermediate risk Pca specific mortality was observed between RP and RT over a 10-years period (6). However, PCa specific mortality was low. Although low risk prostate cancer is most prevalent and known to have a good prognosis, high risk prostate cancer is less frequent but contributes most to PCa specific death (6).

Depending on fitness, low risk PCa is manageable trough active surveillance or radical prostatectomy (RP) without lymph node dissection (LAD). RP has shown to significantly reduce the overall mortality of Intermediate-risk prostate cancer (IRPCa) (7). If probability of lymph node invasion exceeds 5%, an additional extended LAD is recommended (4). Although general consensus concerning treatment of high-risk PCa is lacking, a multimodal strategy including RP with extended LAD is accepted by our in-house protocol (4).

High-risk PCa, according to the national comprehensive cancer network (NCCN), is defined as Gleason score $\geq$8, PSA $>$ 20 ng/ml or clinical stage $\geq$T3a (8). Interestingly the EAU differs from this as it defines high-risk PCa starting at a T2c clinical stage (4). An overall established definition of high-risk disease is thus lacking. Remarkably, metastasis free survival (MFS) varies from 70 to 95% and 10-years biochemical recurrence (BCR) shows a variability of 50% (5, 9). Efforts to dissect this heterogeneity have been undertaken, as illustrated by Joniau et al. (10).

High quality risk stratification remains the cornerstone of therapeutic decision making. This retrospective study aims to stratify non-metastatic PCa into subgroups showing significantly differing CSS. Through this stratification, we aim to identify and correlate patient and tumor related characteristics so individual patients can be profiled within the heterogeneous group of non-metastatic high-risk PCa.

PATIENTS AND METHODS

Patient Population

The European Multicenter Prostate Cancer Clinical and Translational (EMPaCT) research database served as the source for our patient cohort. This International research database contains 9,167 men from 14 institutions who underwent radical prostatectomy for non-metastatic high-risk PCa between 1986 and 2016. Each institution acted in accordance of their own standards, indications and treatment protocols. Since only patients with complete datasets could be included, the criteria for exclusion were defined as: lacking a preoperative PSA (*n*:121), absent Gleason biopsy score (*n*:1,070), incomplete staging (*n*:1,966) and lost to follow up (*n*:1,014). Staging was in accordance with the 2002 TNM system. All biopsies were evaluated by an experienced pathologist in each respective center. Follow up was defined as an annual clinical control with serum PSA measurement. Cancer related deaths were judged by the treating urologist or oncologist. Adjuvant and salvage therapies were admitted on individual bases and institutional preferences. From this eligible cohort, all high-risk (PSA $\geq$ 20 ng/ml and/or GS $\geq$ 8 and/or cT $\geq$ T2c) patients were identified and included (**Figure 1**).

Statistical Analysis

Preoperative prognostic variables were identified and stratified into subcategories. PSA was subcategorized into a $<$20 ng/ml, a 20 ng/ml$-$50 ng/ml and a $>$50 ng/ml. Clinical stage was divided into T1, T2, T3a, and T3b+T4 categories. Biopsies were categorized by the international Society of Urological Pathology (ISUP) grading. Finally, a primary Gleason grade 5 subcategory was created and age was stratified into $<$60, 60–69, and $\geq$70 years old. A univariate analysis of these preoperative variables was performed to evaluate their impact on CSS. A multivariate

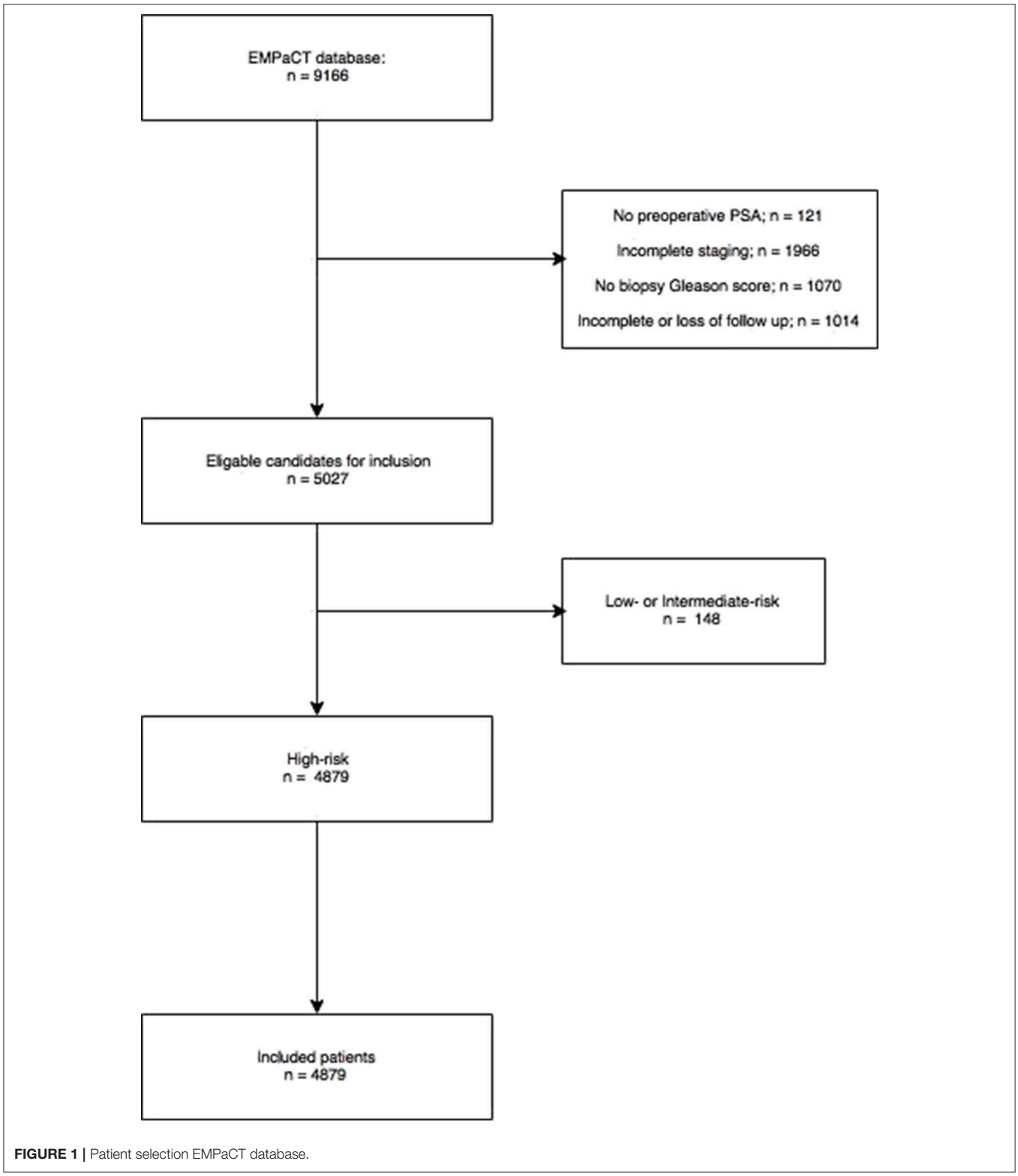

FIGURE 1 | Patient selection EMPaCT database.

cox regression analysis was performed using the significant variables. Based on the hazard ratio's (HR), a proportional score system was created. Multiple cut-off values were tried and different possibilities were compared by multivariate cox regression analysis. The most appropriate model was selected and its prognostic value was calculated using the concordance index (C-index). All univariate and multivariate analyses were performed using MedCalc Statistical Software version 17.9.7

(MedCalc Software bvba, Ostend, Belgium). The C-index was calculated using SAS-software version 9.4 (SAS Institute Inc., Cary, NC, USA). $P < 0.05$ were considered to be significant.

RESULTS

Study Population

Four thousand eight hundred seventy-nine men met the criteria for final inclusion. A mean follow-up of 60.5 months was noted with an interquartile range of 65 months (21–84 months). The mean PSA amounted to 22.7 ng/ml (0–1,710 ng/ml). A biopsy Gleason Score of <7 was most prominent within HRPC. Clinical stage cT3 showed most prevalent, constituting 37.5% of all high-risk cases. An overview of the characteristic of the population is given in **Table 1**. The 5, 10, and 15-years CSS were 94, 89.5, and 84.6%, respectively.

TABLE 1 | Characteristics of study population.

Included patient cohort characteristics *n* = 4,879				
Age		Mean (SD)	64.9 (6.8)	
		Median (IQR)	65 (60–70)	
PSA (ng/ml)		Mean (SD)	22.7 (41.6)	
		Median (IQR)	13 (7–27)	
		<20 μg/l	2,859 (58.6)	
		20–50 μg/l	1,415 (29)	
		>50 μg/l	373 (7.6)	
Clinical stage, *n* (%)		cT1	1,755 (36)	
		cT2	1,245 (25.5)	
	cT3	N.O.S.	1,830 (37.5)	745 (15.3)
		cT3a		948 (19.4)
		cT3b		137 (2.8)
		cT4	49 (1.0)	
biopsy Gleason score, *n* (%)		≤ 7	2,457 (50.4)	
	8	N.O.S	1,466 (30.0)	143 (2.9)
		3 + 5		156 (3.2)
		4 + 4		1,116 (22.9)
		5 + 3		51 (1.0)
	9	N.O.S.	855 (17.5)	60 (1.2)
		4 + 5		608 (12.5)
		5 + 4		187 (3.8)
		10	101 (2.1)	
Follow up (months)		Mean	60.5 (53.8)	
		Median	48 (21–84)	
		min	0	
		max	293	

N.O.S, not otherwise specified.

TABLE 2 | Multivariate analysis of preoperative risk factors.

		***P*-value**	**Exp(b)**	**Points**
PSA	<20 ng/ml	Reference		0
	20–50 ng/ml	**0.03**	1.43	3
	>50 ng/ml	**<0.0001**	2.81	6
Clinical stage	≤T3b	Reference		≤T3b
	T4	**0.01**	2.73	6
ISUP	≤3	Reference		0
	4	**0.0001**	2.21	4
	5	**<0.0001**	3.05	6
	Any ISUP with primary grade 5	**<0.0001**	7.17	14

Bold values statistically significant P < 0.05.

Univariate Analysis

PSA, clinical stage, Gleason biopsy score, age and the presence of a Gleason grade 5 underwent categorization and univariate analysis for cancer specific survival as primary outcome (**Figure 2**). PSA was divided into three groups: <20, 20–50, and more than 50 ng/ml. Gleason score was categorized by the ISUP groups. Clinical stage was divided into four groups: T1, T2, T3a+b, and T4. Three age groups were identified by cut-off values of 60 and 70 years old. Finally, the presence of a primary Gleason grade 5 was dichotomised as present or absent. Except for age, all subdivisions of these preoperative risk factors showed significantly differing CSS.

Multivariate Analysis

The preoperative risk factor groups which showed a significantly differing CSS were included in a multivariate cox regression analysis (**Table 2**). Biopsy characteristics were clearly the strongest CSS predictor. The presence of a primary Gleason grade 5 (HR: 7.17), followed by ISUP grade group 5 (HR: 3.05).

Multiple combinations of clinical staging were tried in the multivariate analysis. However, only T4 showed a significantly different CSS as is illustrated in **Figure 2D**.

Based upon the hazard ratios from the multivariate analysis, a proportional score was determined for each subgroup. This score system was then applied to all patients. Score-based groups were identified who showed significant differing CSS. Different cut-offs were evaluated. After multivariate analysis the 0–4, 5–8, 9–12, and >12 pts was selected as being the optimal distribution due to strongly differing CSS between all groups ($p < 0.0001$) (**Figure 3**, **Table 3**). Five-years CSS of these groups were 97.4, 92.8, 85.2, and 72.2%, respectively.

Score Validation

In order to assess the predictive value of this score system, the concordance index (c-index) was determined. A value of 0.77 was noted, implying a good correlation between the model determined subgroups and the CSS. The model is accessible online through as an easy-to-use clinical tool. (https://app.calculoid.com/?#/calculator/41236).

DISCUSSION

When confronted with a new diagnosis of non-metastatic prostate cancer, it is common to divide patients into low-, intermediate- and high-risk subgroups (4). These groups are known to harbor a significantly differing prognosis. To date, this risk stratification remains the cornerstone of therapeutic decision making. Although there is no discussion concerning the need for surgical treatment in the high risk group, CSS is known to vary strongly thus suggesting this group to be quite

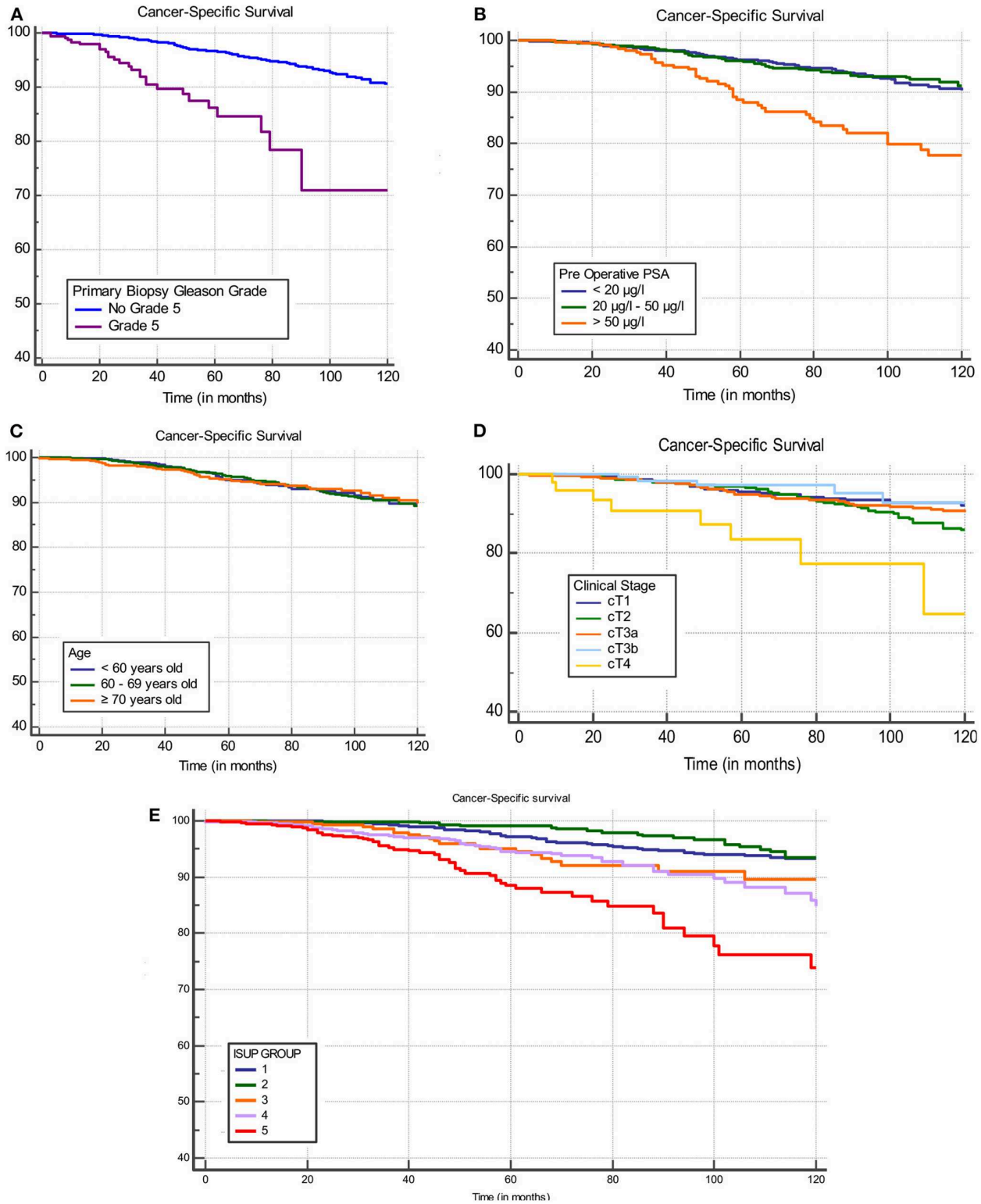

FIGURE 2 | Univariate analysis of stratified preoperative risk factors: presence of a biopsy Gleason grade 5 **(A)**, PSA **(B)**, age **(C)**, clinical stage **(D)**, and ISUP group **(E)**.

TABLE 3 | Ten-years CSS, blue line: 0–4 pts, green line: 5–8 pts, orange line 9–12 pts, red line: >12 pts.

	Number at risk						
	0 months	**20 months**	**40 months**	**60 months**	**80 months**	**100 months**	**120 months**
0–4 pts	3,301	2,646	1,991	1,473	1,059	731	529
5–8 pts	906	644	434	279	189	114	86
9–12 pts	518	345	196	106	59	33	16
>12 pts	104	55	32	15	8	4	4

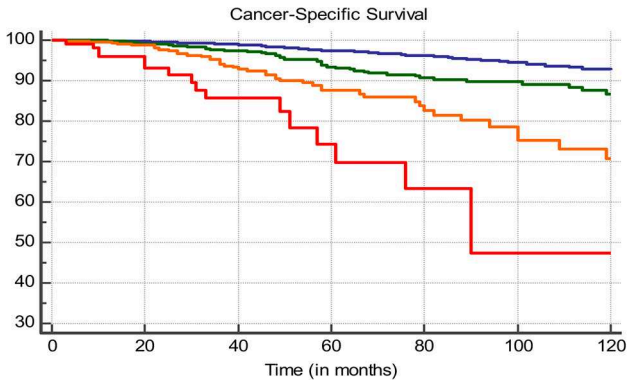

FIGURE 3 | Ten-years CSS, blue line: 0–4 pts, green line: 5–8 pts, orange line 9–12 pts, red line: >12 pts.

heterogeneous (5). This can easily be illustrated by observing CSS after categorization by the number of high-risk factors. Intuitively a poorer prognosis is observed in patients showing multiple high-risk factors (**Figure 4**).

Historically, tumors with unfavorable characteristics (PSA > 100 ng/ml, Gleason Score 9–10, T4 or cN1) were not considered ideal candidates for surgery (8). This is largely due to fear for occult metastasis, which is not yet detectable by conventional staging technology at a given time. However, favorable results have been achieved in surgical treatment for non-metastatic, hormonal sensitive locally advanced prostate cancer (11).

Previous efforts have been undertaken to stratify high-risk PCa (9, 10). The capability to distinguish good from poor surgical candidates remains critical in clinical practice.

Sundi et al. illustrated that the presence of a primary grade 5 on biopsy, or ≥5 cores showing a Gleason score 8–10 were predictive for a significantly increased risk of metastasis and cancer specific mortality (5). Unfortunately, no data concerning number of positive biopsy cores is available in the EMPaCT database. However, univariate analysis of ISUP grading and presence of a primary Gleason grade 5 clearly shows its independent and strong prognostic significance. Thus, our findings are similar to Sundi et al.'s observation.

It has been suggested that PSA is a less valuable predictor (10, 12). Gontero et al. illustrated that, although prognosis diminishes with rising PSA, no absolute upper limit for radical prostatectomy exists (12). This biomarker is susceptible to a couple of difficulties. Firstly, it is a continuous variable. A clear cut-off is lacking. Secondly, our results suggest that PSA harbors the weakest CSS prognostic predictive value (HR 1.48). Only very high PSA values (>50 ng/ml) are good predictors for poor CSS (HR 2.97). These findings thus align with general belief that this biochemical marker should not be decisive in therapeutic decision making, except if extremely elevated.

Although age showed no independent value in the univariate analysis of CSS, it is very important in therapeutic decision making since age is mostly inversely proportional to general fitness. unfortunately, our data and model has no eye for comorbidity such as a Charlson score since this information was only available for a minority of patients.

Further evaluation shows that higher scoring patients were more likely to need adjuvant therapy such as androgen deprivation therapy, radiotherapy or both. Furthermore, we were able to illustrate that this score system proportionately correlates with positive surgical margins and lymph node invasion (**Table 4**).

This model was created as a tool to aid the clinician in estimating the CSS within the heterogeneous high-risk PCa group. It is able to distinguish those who will fare well from those who will benefit poorly from RP, irrespective of future need for adjuvant therapy. It can thus help tilt the scale toward more or less intense treatment based upon more detailed high-risk patient and tumor characteristics.

Remarkably, the lowest score category (0–4 pts) makes up a very significant part of the entire cohort (n = 3,186; 65.3%). This implies that practitioners are already intuitively capable of selecting the best from the worst within the high-risk Pca group. This selection bias is a major explanation for the favorable 5- and 10-years CSS of the general high-risk PCa cohort.

The magnitude of this international multi-center patient cohort is undoubtable the major strength of this study. Compromising more than 20 years of interinstitutional data collection, each center treated patients according to their own protocol and standards. This presents a more realistic

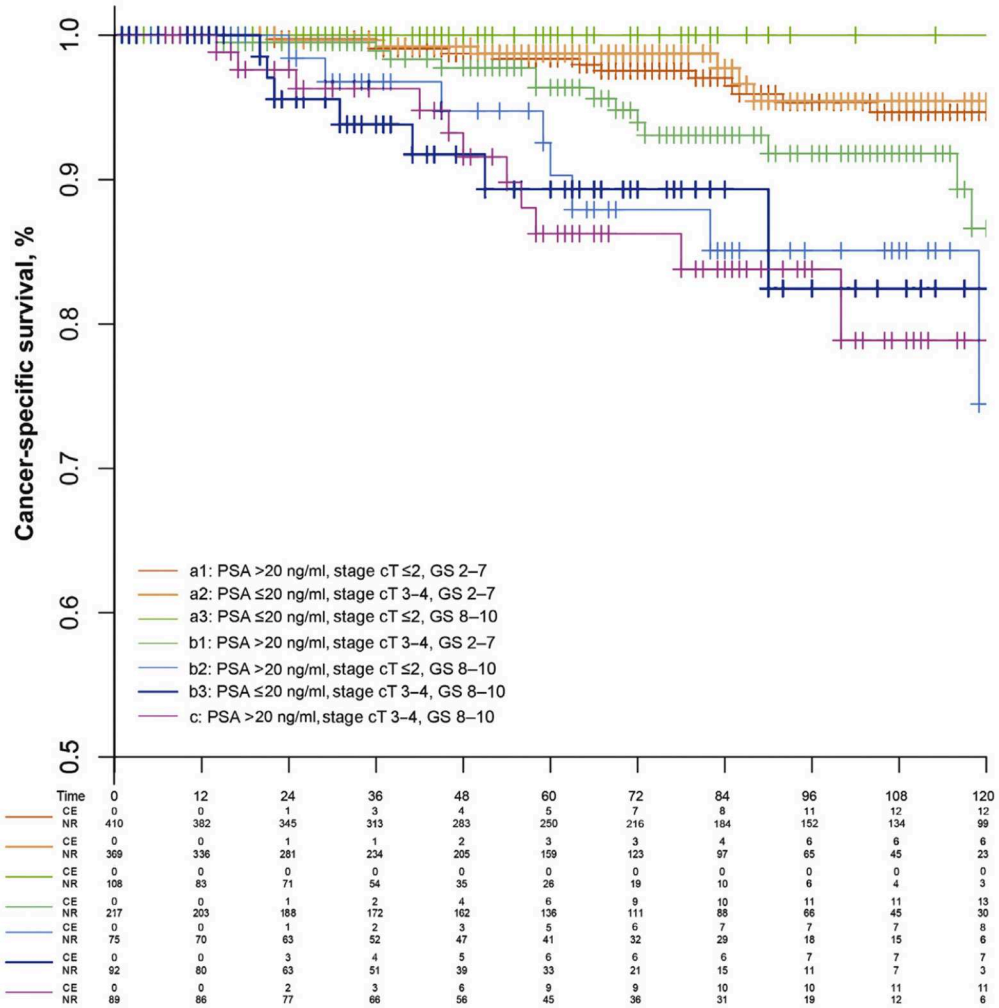

FIGURE 4 | Prostate cancer–specific survival for the extended model with seven subgroups of high-risk prostate cancer patients (10).

TABLE 4 | Need for (neo)adjuvant therapy, positive surgical margins, and lymph node invasion.

	n	Neoadjuvant therapy (ADT)		Adjuvant therapy (ADT/ADT+RT/RT)		surgical margins: R1 +		Positive lymph nodes: N+	
0–4 pts	3,301	454	13.7%	738	22.4%	971	29.4%	744	22.5%
5–8 pts	906	160	17.6%	354	39.1%	424	46.7%	346	38.2%
9–12 pts	518	128	24.7%	253	48.9%	292	56.4%	260	50.2%
>12 pts	104	35	33.6%	62	59.6%	71	68.3%	62	59.6%

Stratified by model subgroups.

reflection of general population and practice. Secondly, this subcategorization of established preoperative high-risk factors enables a more accurate prediction of CSS after RP, thus helping to identify those with good prospects after surgery. Thirdly, by using ISUP grading we follow the new pathological classification. Finally, the model is made clinically accessible through an easy-to-use online calculator.

This study is however not without limitations. Firstly, a retrospective study has inherent limitations due to variable data quality. Secondly, the EMPaCT database consists only of men treated by RP, thus a selection bias of fit men is inevitable. thirdly, no data was available concerning the number of positive cores in biopsy samples, as suggested by Sundi et al. Finally, interinstitutional variability impedes standardization.

CONCLUSION

By subdividing the established preoperative high-risk factors for prostate cancer, a new model is presented. The extended stratification provides a more accurate prediction of CSS after

radical prostatectomy for non-metastatic high-risk prostate cancer. A free online calculator is offered to simplify clinical use.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was approved by the Ethical Committee of the University Hospitals Leuven.

AUTHOR CONTRIBUTIONS

BC conducted the literature research, statistics, data gathering and processing, and writing. SJ, WE, MA, GM, KH, and HVP provided critical feedback. GD data gathering. LM and FC contributed to the data and statistics. PG, RK, CG, PC, MG, BK, GM, RS, BT, HVDP, JW, MS, and AB contributed to the EMPaCT database.

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Combination Therapy of Prostate Cancer by Oncolytic Adenovirus Harboring Interleukin 24 and Ionizing Radiation

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Prostate cancer is a common malignant tumor and the second leading cause of cancer-related death in men. Radiation therapy is a curative treatment for localized prostate cancer and has a limited effect for castration-resistant prostate cancer (CRPC). Interleukin 24 (IL-24) has a radiosensitizing effect in cancer cells. Our previous studies showed that ZD55-IL-24, an oncolytic adenovirus harboring IL-24, had better anti-tumor effect with no toxicity to normal cells. In this study, we evaluated the synergistic anti-tumor effect of oncolytic adenovirus ZD55-IL-24 combined with radiotherapy in prostate cancer. *In Vitro* and *In Vivo* experiments showed that the combined therapy significantly inhibited the growth of prostate cancer and provoked apoptosis of prostate cancer cells. In conclusion, the combination of ionizing radiation and oncolytic adenovirus expressing IL24 could achieve synergistic anti-tumor effect on prostate cancer, and is a promising strategy for prostate cancer therapy.

Keywords: IL-24, oncolytic adenovirus, ionizing radiation, prostate cancer, combined treatment

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INTRODUCTION

Prostate cancer is a common cancer in the male (1). Prostatectomy, radiation therapy, chemotherapy, and androgen deprivation therapy are main methods for the treatment of prostate cancer (2). For early stage prostate cancer, most patients show tumor regression and reduced prostate specific antigen (PSA) level after treatment. However, after long-term androgen deprivation therapy, castration-resistant prostate cancer (CRPC) will develop, leading to poor prognosis (3). In particular, CRPC shows chemoresistance and radioresistance (4, 5). Therefore, novel treatment strategy for CRPC is urgently required.

Interleukin 24 (IL-24) is originally produced in human melanoma tumor cells and exhibits anti-tumor effect by enhancing cancer cell apoptosis, inhibiting cancer metastasis, and improving immune regulation (6). IL-24 can be used to treat various cancers but has no obvious adverse effects on normal cells (7). Oncolytic adenovirus is a natural or genetically modified viral species that selectively infects and kills tumor cells (8). Cancer targeting gene-viral therapy (CTGVT), which has better anti-tumor effects than gene therapy alone or viral therapy alone, was designed by inserting a tumor suppressor gene into an oncolytic viral vector (9). Previous study showed that oncolytic adenovirus ZD55-IL-24 with the deletion of E1B-55 gene and the insertion of IL-24 gene, had a

better anti-tumor effect than ZD55 with no toxicity to normal cells (10). In this study, we evaluated the synergistic anti-tumor effect of oncolytic adenovirus ZD55-IL-24 combined with radiotherapy on prostate cancer. We further explored the underlying mechanisms to provide potential strategies for clinical treatment of prostate cancer.

MATERIALS AND METHODS

Cell Culture

PC-3 cell, DU-145 cell line and HEK-293 cell lines were provided by the Institute of Biochemistry of Chinese Academy of Sciences, cultured in RPMI-1640 or DMEM medium supplemented with 10% fetal bovine serum (Gibco, MA, USA) and 100 U penicillin/streptomycin (Gibco), and maintained at 37°C in a humid incubator with 5% CO_2. Cells were irradiated with different doses of X-ray by Varian Clinac 23EX Linear Accelerator (Varian, USA).

Recombinant Adenovirus

ZD55-IL-24 was provided by the Institute of Biochemistry of the Chinese Academy of Sciences and the construct was described previously (10). Mass production of the virus was performed in HEK293 cells using the Adeno-XTM Maxi Purification Kit (Clontech, USA). Viral titers were determined with the QuickTiterTM Adenovirus Titer Immunoassay Kit (Cell Biolabs, San Diego, CA, USA).

CCK-8 Assay

Cell Counting kit-8 (CCK-8; Dojindo Molecular Technologies, Inc., Japan) was used to evaluate cell proliferation. PC-3 and DU-145 cells were seeded in 96-well plates with 3,000 cells per well. Then cells were exposed in different doses of X-ray (0, 2, 5, 10, 15 GY); or treated with ZD55-IL-24 of different titers (0, 1, 10, 20, 50 MOI); and treated with PBS, 10 GY X-ray, 10 MOI ZD55-IL-24, 5 MOI ZD55-IL-24 plus 5 GY X-ray. The radiation was performed at 12 h after virus injection. After 24, 48, 72 and 96 h incubation, 10 μL CCK-8 solution was added into each well. With 1-4 h incubation, the absorbance of cells at 450 nm was measured by microplate reader.

Hoechst33258 Staining

The apoptosis of cells was assessed by Hoechst33258 staining. PC-3 and DU-145 cells were seeded in 6-well plates. Cells were treated with PBS, 10 GY X-ray, 10 MOI ZD55-IL24, 5 MOI ZD55-IL-24 plus 5 GY X-ray. The radiation was performed at 12 h after virus infection. After 48 h incubation, cells were fixed by 4% paraformaldehyde. Next the cells were stained with Hoechst33258 for 10 min, washed with PBS 3 times, and observed under fluorescence microscope.

TUNEL Assay

In situ apoptosis assay kit (KeyGenBio, Nanjing, China) was used to stain apoptotic cells. The nuclei were counterstained with DAPI. Apoptotic cells were observed under a fluorescence microscope and cells in 6 randomly selected fields were counted.

Western Blot Analysis

Proteins were extracted from cells and tumor tissues using protein extraction kit. Equal amounts of protein were separated by SDS-PAGE and transferred to PVDF membranes. The membranes were then incubated with antibodies for IL-24 (1:1000, Proteintech, USA), Caspase-3 (1:1000, Proteintech, USA), Caspase-8 (1:1000, Proteintech, USA), Bcl-2 (1:1000, Abcam, UK) and β-actin (1:1000, Proteintech, USA). After incubation at 4°C overnight, the membranes were incubated with the secondary antibody for 2 h. Protein bands were then detected using ECL reagents and the gray scale values of the bands were analyzed using Image-J software.

Xenograft Tumor Model

Five-week old male BALB/c nude mice were obtained from Vital River Laboratory Animal Technology (Beijing, China). All animal experiments were approved by Institution Committee on Animal Care and Use. A xenograft model was established by subcutaneous injection of 1×10^6 PC-3 cells into each mouse. Nude mice were divided into 4 groups ($n = 5$): (1) PBS group: mice received intratumoral injection of PBS; (2) Radiation group: mice were exposed by 10 GY X-ray in 10th day; (3) ZD55-IL-24 group: mice received intratumoral injection of ZD55-IL24 (1×10^9 pfu) every 3 days; (4) Combination group: mice received intratumoral injection of ZD55-IL24 (5×10^8 pfu) every 3 days and exposed by 5 GY X-ray in 10th day; Tumor volume was measured on 7 days after subcutaneous injection of cells. Tumor volume was then measured every 3 days. Until the 28th day, all the mice were killed. Tumor volume (TV) was calculated by the following formula: TV (mm^3) = length × width^2 × 0.5.

Hematoxylin-Eosin Staining

Tissues of xenograft tumors were dissected and fixed with 10% formalin. After embedding in paraffin, the tissue sample was cut into a thickness of 5 μm. After deparaffinization, the sections were stained with hematoxylin-eosin and fixed with a neutral resin. The morphology and pathological changes of the samples were observed with an optical microscope (Nikon DS-Ri1, Japan), and 5 randomly selected non-repetitive regions were photographed.

Immunohistochemical Staining

The sample in the paraffin was cut into a thickness of 4 μm. After deparaffinization and hydration, the sections were subjected to antigen retrieval. The endogenous peroxidase activity of the sections was blocked with 3% hydrogen peroxide. After incubation with blocking serum for 30 min, the sections were incubated with antibodies for Caspase-3 (1:500, Proteintech, USA), Caspase-8 (1:500, Proteintech, USA) and Bcl-2 (1:500, Abcam, Uk). After incubation at 4°C overnight, sections were stained with DBA kit (ZSGB-Bio, Beijing, China). The sections were observed under optical microscope (Nikon DS-Ri1, Japan) and analyzed by Image-J software.

Statistical Analysis

The data were analyzed by SPSS 16.0 and plotted by Graphpad Prism 6 software. Data were expressed as mean ± SD. The T test was used for comparison between the two groups. One-way ANOVA was used for comparison among multiple groups. $P < 0.05$ was considered significant.

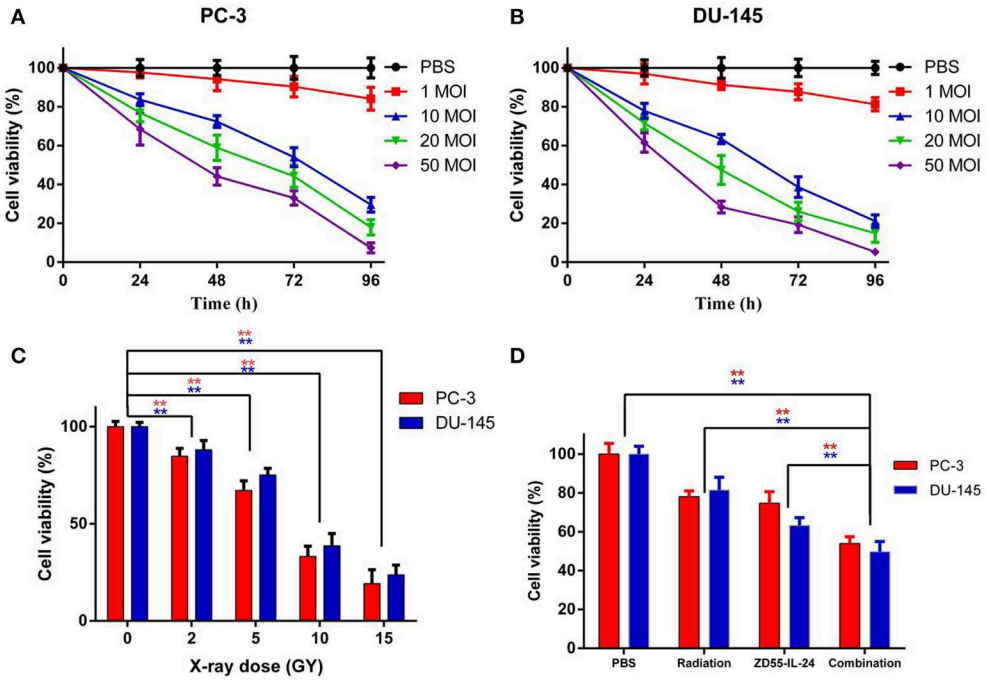

FIGURE 1 | The proliferation of PC-3 and DU-145 cells exposed to ZD55-IL-24 or/and radiation. **(A)** Different titers of ZD55-IL-24 inhibited the proliferation of PC-3 cells. **(B)** Different titers of ZD55-IL-24 inhibited the proliferation of DU-145 cells. **(C)** Different doses of radiation inhibited the proliferation of PC-3 and DU-145 cells. $^{**}P < 0.01$ vs. PBS group. **(D)** The combination of ZD55-IL-24 and radiation inhibited the proliferation of PC-3 and DU-145 cells after 48 h. $^{**}P < 0.01$ vs. combination group.

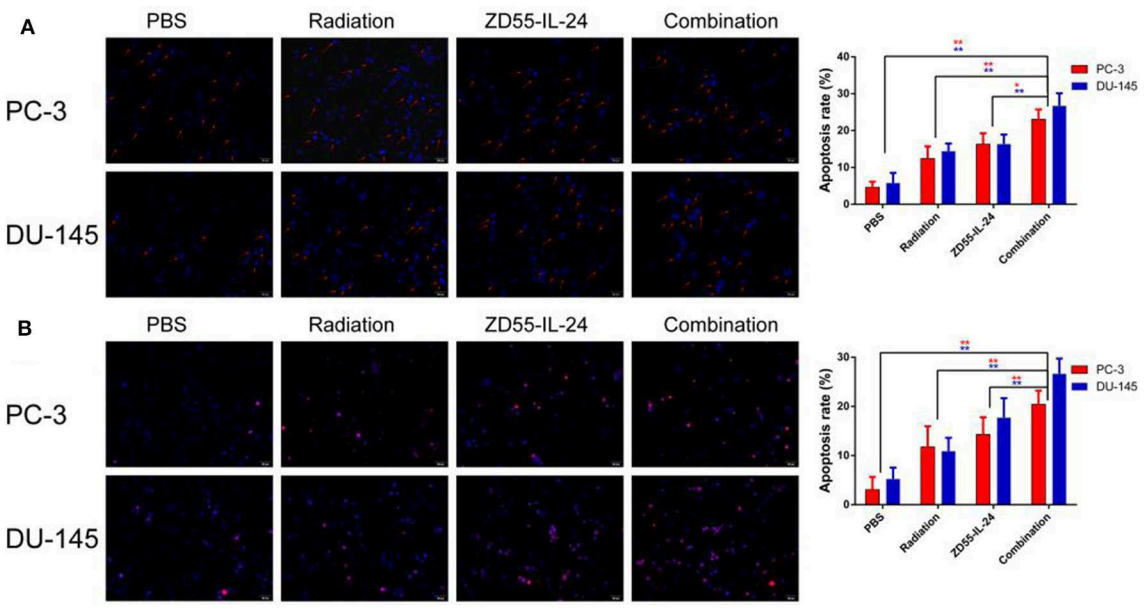

FIGURE 2 | The apoptosis of PC-3 and DU-145 cells exposed to ZD55-IL-24 or/and radiation. **(A)** Hoechst-33258 staining showed the apoptosis rate of PC-3 and DU-145 cells in each group (200×). **(B)** TUNEL assay showed the apoptosis rate of PC-3 and DU-145 cells in each group (200×). $^{**}P < 0.01$ vs. combination group.

RESULTS

Inhibition of Prostate Cancer Cell Proliferation by ZD55-IL24 and Radiation

ZD55-IL-24 inhibited the proliferation of PC-3 and DU-145 cells in a time and dose dependent manner (**Figures 1A,B**, $P < 0.01$). Radiation inhibited the proliferation of PC-3 and DU-145 cells in a dose dependent manner (**Figure 1C**, $P < 0.01$). We chose 5 MOI ZD55-IL-24 plus 5 GY X-ray as combination treatment. After 48 h of treatment, cell proliferation in combination group was significantly lower than that of the ZD55-IL-24 group or radiation group (**Figure 1D**, $P < 0.01$).

Induction of Prostate Cancer Cell Apoptosis by ZD55-IL24 and Radiation

Hoechst-33258 staining showed that the apoptosis rate of combination group, ZD55-IL-24 group, radiation group and PBS group in PC-3 cells was (20.54 ± 3.11)%, (15.52 ± 2.34)%, (13.72 ± 3.65)%, (5.75 ± 1.60)%, respectively, with significant difference between the combination treatment group and the monotherapy group (**Figure 2A**, $P < 0.01$). The apoptosis rate of combination group, ZD55-IL-24 group, radiation group and PBS group in DU-145 cells was (24.92 ± 3.37)%, (17.59 ± 2.26)%, (11.36 ± 3.56)%, (4.81 ± 2.83)%, respectively, with significant difference between the combination treatment group and the monotherapy group (**Figure 2A**, $P < 0.01$).

In addition, TUNEL assay showed that the apoptosis rate of combination group, ZD55-IL-24 group, radiation group and PBS group in PC-3 cells was (20.44 ± 2.57)%, (14.31 ± 3.47)%, (11.76 ± 4.20)%, (3.06 ± 2.57)%, respectively, with significant difference between the combination treatment group and the monotherapy group (**Figure 2B**, $P < 0.01$). The apoptosis rate of combination group, ZD55-IL-24 group, radiation group and PBS group in DU-145 cells was (26.65 ± 3.08)%, (17.71 ± 3.98)%, (10.90 ± 2.71)%, (5.23 ± 2.30)%, respectively, with significant difference between the combination treatment

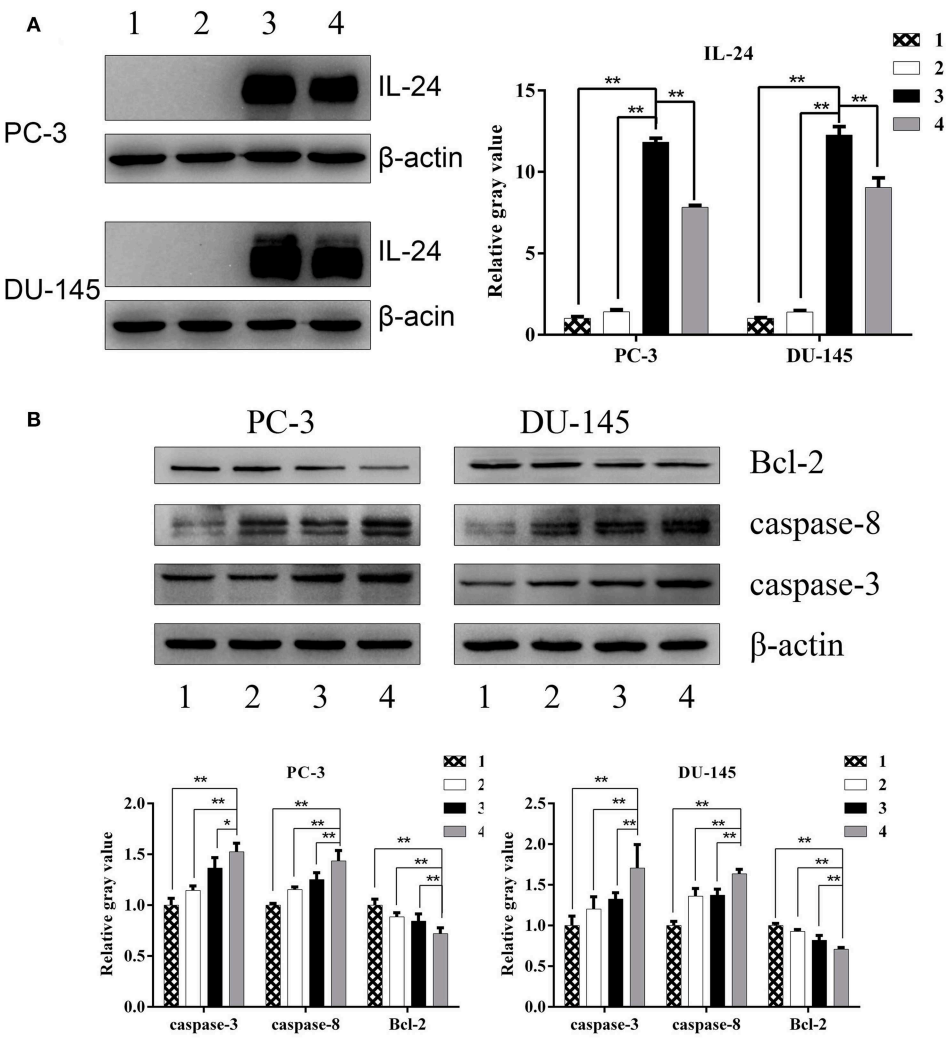

FIGURE 3 | The expression of apoptosis related proteins in PC-3 and DU-145 cells exposed to ZD55-IL-24 or/and radiation. **(A)** Western blot analysis of IL-24 protein levels in PC-3 and DU-145 cells in each group. **(B)** Western blot analysis of Bcl-2, caspase-3, and caspase-8 protein levels in PC-3 and DU-145 cells in each group. 1, PBS; 2, radiation; 3, ZD55-IL-24; 4, combination of ZD55-IL-24 and radiation. *$P < 0.05$, **$P < 0.01$ vs. combination group.

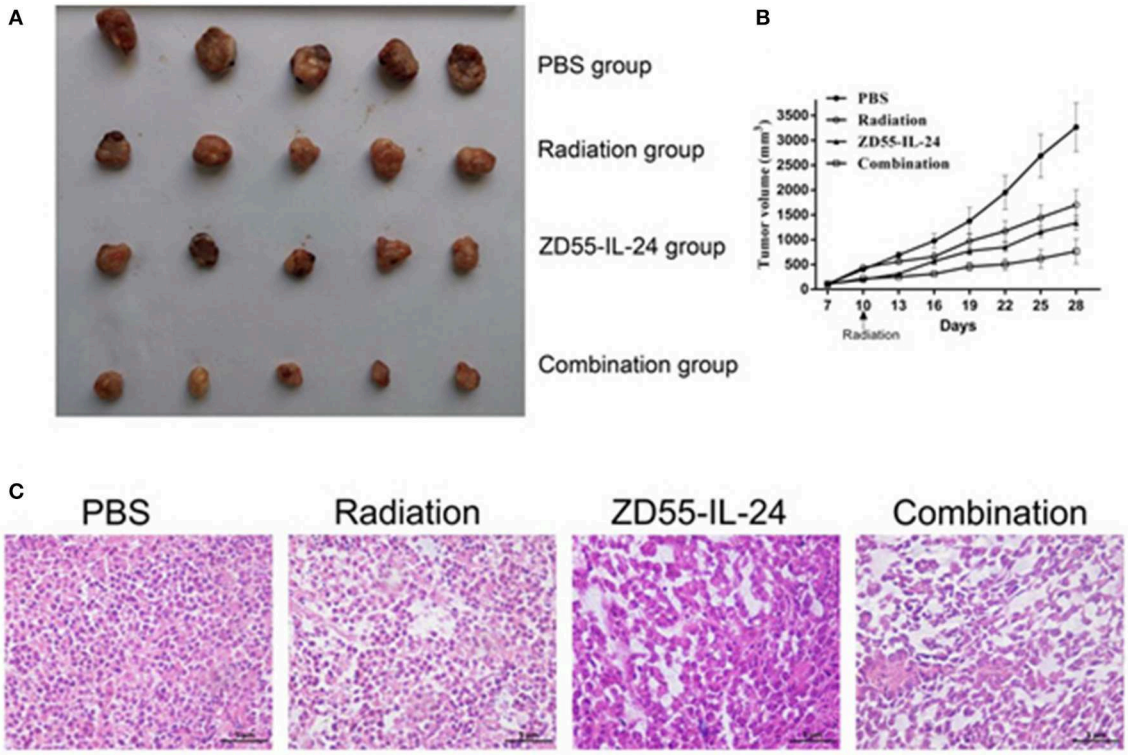

FIGURE 4 | Combination of ZD55-IL-24 and radiation inhibited the growth of xenografts. **(A)** Prostate tumor xenografts were harvested from each group. **(B)** Tumor volume was measured at 3-day intervals. Date were expressed as tumor volume ± SD ($n = 5$). Tumor growth curves were drawn to show the growth of tumors in each group. **(C)** HE staining of xenografts of different groups (400×). 1, PBS; 2, radiation; 3, ZD55-IL-24; 4, combination of ZD55-IL-24 and radiation.

group and the monotherapy group (**Figure 2B**, $P < 0.01$). Taken together, these data indicated that ZD55-IL-24 combined with radiation had better apoptosis-inducing capability than single therapy.

The Expression of Apoptosis Related Proteins in Prostate Cancer Cells Treated by ZD55-IL24 and Radiation

Western blot analysis showed high expression of IL-24 in PCa cells treated by ZD55-IL-24 (**Figure 3A**, $P < 0.01$). The protein levels of Caspase-3 and Caspase-8 in combination group were significantly higher than in monotherapy group (**Figure 3B**, $P < 0.05$), while Bcl-2 protein levels in combination group were significantly lower than in monotherapy group (**Figure 3B**, $P < 0.01$). These results indicated that ZD55-IL-24 and radiation modulated the expression of apoptosis related proteins.

Combination of ZD55-IL24 and Radiation Inhibited Xenograft Tumor Growth in Nude Mice

Next we examined the synergistic anti-tumor effects of ZD55-IL24 and radiation *in vivo*. The time-growth curve of xenografts showed the final volumes of xenografts in each group as follows: combination group: (768.56 ± 251.61) mm^3; ZD55-IL-24 group: (1338.87 ± 143.60) mm^3, radiation group: (1701.68 ± 297.79) mm^3, PBS group (3265.03 ± 489.72) mm^3. Compared with ZD55-IL-24 group, radiation group and PBS group, combination group could significantly inhibit the growth of xenografts (**Figures 4A,B**, $P < 0.01$). Furthermore, HE staining showed that tumor cells in PBS group had different size nuclei, and had irregular shape. In contrast, combination group showed more dead cells that split into pieces with fractured nucleus pyknosis (**Figure 4C**).

Combination of ZD55-IL24 and Radiation Induced Xenograft Tumor Apoptosis

Immunohistochemistry analysis of xenografts showed that the integrated optical density (IOD) of Bcl-2 in combination group, ZD55-IL-24 group, radiation group and PBS group was (56.26 ± 4.46), (69.93 ± 7.33), (81.36 ± 6.18), (96.11 ± 11.56), respectively. Compared with ZD55-IL-24 group, radiation group and PBS group, combination group could significantly downregulate Bcl-2 expression (**Figure 5A**, $P < 0.01$). The IOD of caspase-3 in combination group, ZD55-IL-24 group, radiation group and PBS group was (34.11 ± 4.65), (55.84 ± 5.07), (63.77 ± 6.69), (74.02 ± 6.69), respectively. Compared with ZD55-IL-24 group, radiation group and PBS group, combination group could significantly upregulate caspase-3 expression (**Figure 5A**, $P < 0.01$). The IOD of Caspase-8 in

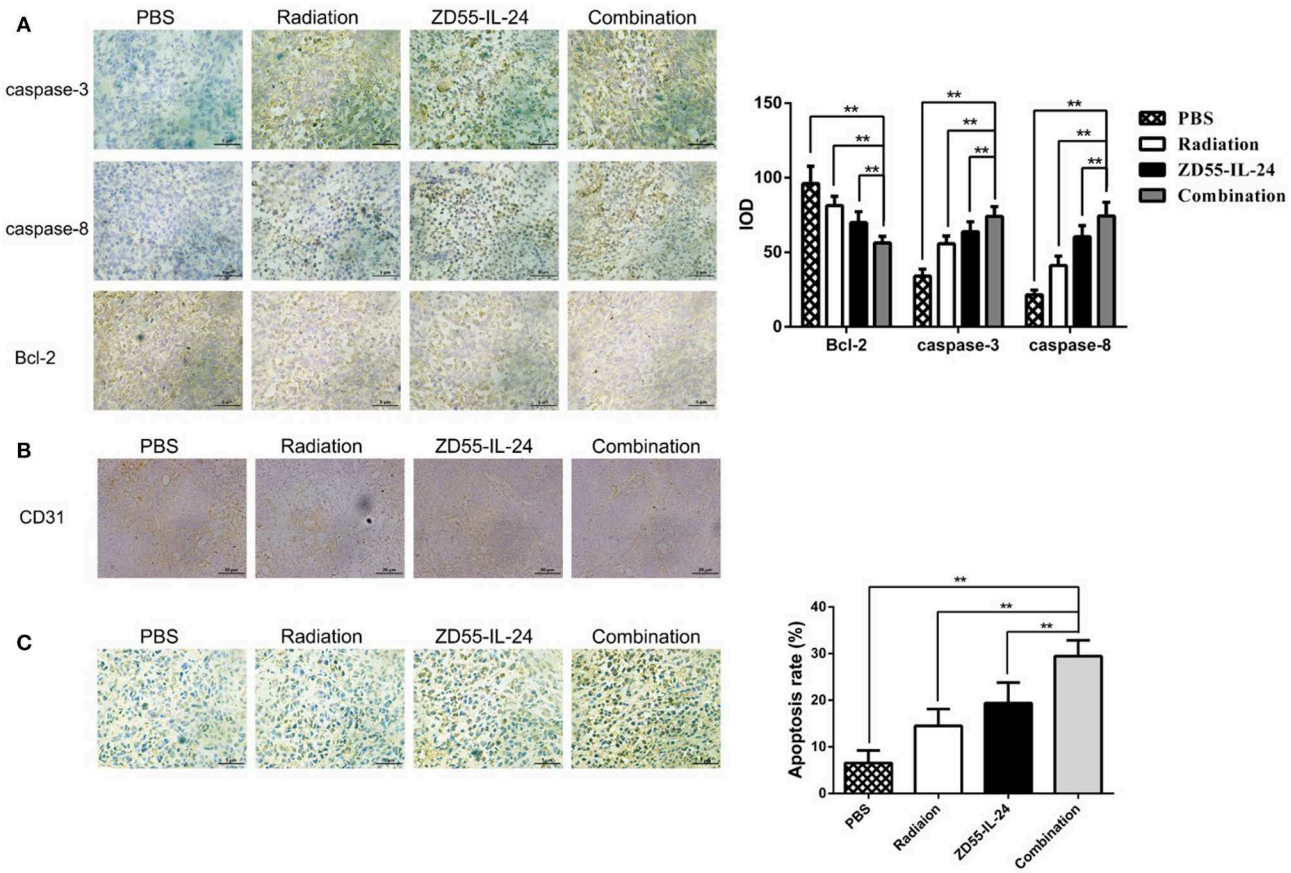

FIGURE 5 | Combination of ZD55-IL-24 and radiation induced the apoptosis of xenografts. **(A)** Immunohistochemistry staining of Bcl-2, caspase-3, and caspase-8 in xenografts of different groups (400×). **(B)** CD31 staining of xenografts in each group of mice. **(C)** TUNEL staining of apoptotic cells in xenografts of different groups (400×). 1, PBS; 2, radiation; 3, ZD55-IL-24; 4, combination of ZD55-IL-24 and radiation. $^{**}P < 0.01$ vs. combination group.

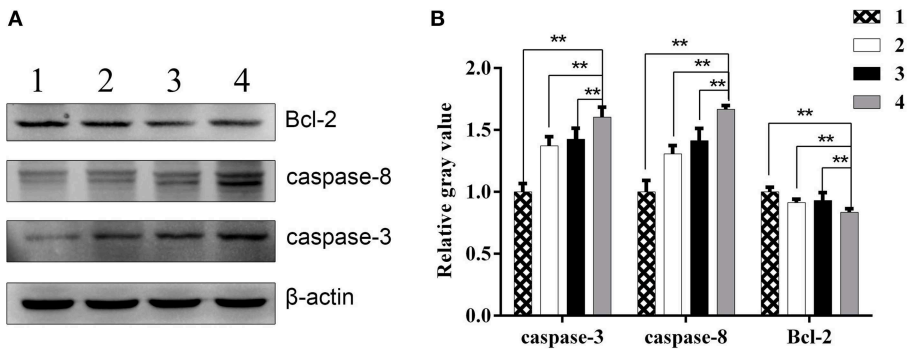

FIGURE 6 | The expression of apoptosis related proteins in xenografts. **(A)** Western blot analysis of Bcl-2, caspase-3, and caspase-8 protein levels in xenografts of different groups. **(B)** Quantitative analysis of relative Bcl-2, caspase-3, and caspase-8 protein levels in xenografts of different groups. 1, PBS; 2, radiation; 3, ZD55-IL-24; 4, combination of ZD55-IL-24 and radiation. $^{**}P < 0.01$ vs. combination group.

combination group, ZD55-IL-24 group, radiation group and PBS group was (21.59 ± 3.08), (41.14 ± 6.27), (60.48 ± 7.51), (74.43 ± 9.17), respectively. Compared with ZD55-IL-24 group, radiation group and PBS group, combination group could significantly upregulate caspase-8 expression (**Figure 5A**, $P <$ 0.01). Furthermore, combination group showed weaker CD31 staining than monotherapy group (**Figure 5B**).

TUNEL assay indicated that the apoptosis rate of combination group, ZD55-IL-24 group, radiation group and PBS group in tumor tissues was (6.56 ± 2.70), (14.53 ± 3.58), (19.38 ± 4.41),

(29.50 ± 3.36)%, respectively, with significant difference between the combination treatment group and the monotherapy group (**Figure 5C**, $P < 0.01$).

Moreover, Western blot analysis showed that relative Bcl-2 protein levels in combination group, ZD55-IL-24 group, radiation group and PBS group were (0.84 ± 0.03), (0.93 ± 0.06), (0.91 ± 0.03), (1.00 ± 0.04), respectively. Compared with ZD55-IL-24 group, radiation group and PBS group, combination group significantly downregulated Bcl-2 expression (**Figure 6**, $P < 0.01$). Relative Caspase-3 protein levels in combination group, ZD55-IL-24 group, radiation group and PBS group were (1.60 ± 0.08), (1.43 ± 0.09), (1.37 ± 0.07), (1.00 ± 0.07), respectively. Compared with ZD55-IL-24 group, radiation group and PBS group, combination group significantly upregulated Caspase-3 expression (**Figure 6**, $P < 0.01$). Relative Caspase-8 protein levels in combination group, ZD55-IL-24 group, radiation group and PBS group were (1.67 ± 0.03), (1.41 ± 0.10), (1.31 ± 0.07), (1.00 ± 0.09), respectively. Compared with ZD55-IL-24 group, radiation group and PBS group, combination group significantly upregulated Caspase-8 expression (**Figure 6**, $P < 0.01$). Collectively, these results demonstrated that combination of ZD55-IL-24 and radiation had better apoptosis-inducing capability *in vivo*.

DISCUSSION

The sensitivity of tumors to ionizing radiation and drugs depends on gene expression in the cells. The abnormal expression of oncogenes and tumor suppressors would influence tumor radiosensitivity. The overexpression of HER-2/neu gene is associated with the resistance of tumor cells to radiation therapy (11). The mutation of p53 gene is also related to tumor resistance to radiotherapy (12, 13). In addition, IL-24 could enhance the sensitivity of tumors to radiotherapy (14, 15). How to enhance the radiosensitivity of tumor cells and the effectiveness of radiotherapy has become a challenge.

Oncolytic virotherapy is a promising treatment for tumors. CTGVT showed better anti-tumor effect. ZD55-IL-24 can inhibit the growth of tumors and express IL-24 in cancer cells. ZD55-IL-24 is better than single oncolytic virotherapy and gene therapy. Therefore, we wondered whether ZD55-IL-24 could further increase radiosensitivity of prostate cancer. In this study, we aimed to investigate the anti-tumor effect of combining ZD55-IL-24 with radiation therapy in prostate cancer. We found that the combination of ZD55-IL-24 and ionizing radiation exhibited better inhibition effect on prostate cancer cell viability and better induction of prostate cancer cell apoptosis *in vitro*. These results suggest that the combined therapy strategy is feasible. To explore the anti-tumor effects of combined therapy *in vivo*, we constructed a xenograft tumor model in nude mouse. Based on this *in vivo* model, we confirmed that the combined therapy had stronger inhibition on the growth of xenograft tumor than single virotherapy and radiation therapy.

The induction of cell apoptosis plays a major role in anti-tumor mechanism. Proteins of cysteine-aspartic acid protease (caspase) family, inhibitor of apoptosis proteins (IAPs) family and B-cell lymphoma-2 (Bcl-2) family are implicated in the regulation of apoptosis (16–18). Caspase-3, caspase-8 and caspase-9 belong to caspase family and participate in the initiation and execution of apoptosis (19). Caspase-9 is involved in mitochondrial mediated endogenous pathway of apoptosis, while Caspase-8 is involved in death receptor mediated exogenous pathway of apoptosis. Caspase-3 is a downstream effector protein that leads a cascade reaction after it is activated (19). In both *in vitro* and *in vivo* experiments, we found that all the therapy increased the levels of caspase-3 and caspase-8 but decreased the level of anti-apoptotic Bcl-2. These changes were more significant in combined therapy than other single therapy. Furthermore, the results of TUNEL assay demonstrated that the combined therapy induced stronger cell apoptosis.

CD31 (platelet endothelial cell adhesion molecule-1, PECAM-1) is expressed in blood vessels and lymphatic endothelial cells and involved in tumor angiogenesis and metastasis (20, 21). The combination group showed weaker CD31 expression compared to single therapy. These results suggest that ZD55-IL-24 combined with radiation could inhibit the angiogenesis of prostate cancer. Further studies are needed to investigate the underlying mechanism.

In conclusion, the combination of ionizing radiation and oncolytic adenovirus expressing IL24 could achieve synergistic anti-tumor effect on prostate cancer, and is a promising strategy for prostate cancer therapy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

LM, YK, BL, SM, YL, and DY performed the experiments. CY designed the study. All authors read and approved the manuscript.

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