Metastatic progression following multimodal therapy for unfavorable-risk prostate cancer

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Abstract

Introduction: Identifying the optimal management of unfavorable-risk (Prostate Cancer Risk Stratification [ProCaRS] high intermediate-, high-, and very high-risk categories) non-metastatic prostate cancer is an important public health concern given the large burden of this disease. We compared the rate of metastatic progression-free survival among men diagnosed with unfavorable-risk non-metastatic prostate cancer who were initially treated with radiation therapy or radical prostatectomy.

Methods: Information was obtained from medical records at two academic centers in Canada from 333 men diagnosed with unfavorable-risk non-metastatic prostate cancer between 2007 and 2012. Median followup was 90.4 months. Men were eligible for the study if they received either primary radiation therapy (n=164) or radical prostatectomy (n=169), in addition to various adjuvant and salvage therapies when deemed clinically appropriate. Patients were matched on prognostic covariates using two matching techniques. Multivariable Cox proportional hazards models were used to estimate the hazard ratios (HR) and confidence intervals (CI) for metastatic progression-free survival between groups.

Results: After matching, treatment groups were balanced on prognostic variables except for percent core positivity. Hazard ratios from all Cox proportional hazards models (i.e., before and after matching, and with and without multivariable adjustment) showed no difference in the rate of metastatic progression-free survival between groups (adjusted unmatched HR 1.16, 95% CI 0.63, 2.13, p=0.64).

Conclusions: Metastatic progression-free survival did not differ between men diagnosed with unfavorable risk non-metastatic prostate cancer who were treated with either radiation therapy or radical prostatectomy.

Introduction

Prostate cancer (PCa) is a leading cause of cancer morbidity and mortality.[1] Unfavorable-risk non-metastatic disease, including unfavorable intermediate-, high- and extremely high-risk disease,[2] accounts for approximately one-third of all PCa diagnoses, but a disproportionate amount of morbidity and mortality.[3] Optimizing the safety and efficacy of treatments for this disease is thus a major public health concern. Common definitive management options include radical prostatectomy (RP) and prostate radiotherapy (RT). Compared to watchful waiting and active surveillance, definitive management with RT and androgen deprivation therapy (ADT) or RP among men diagnosed with localized PCa has been shown in randomized controlled trails (RCTs) to improve oncological outcomes and survival.[4-6]

The selective use of adjuvant and salvage therapies alongside definitive management has also been shown to further improve outcomes. The use of adjuvant RT for adverse pathological findings post-RP has been found to decrease biochemical recurrence.[7] The addition of ADT to RT post-RP has been shown to further reduce rates of metastatic progression and PCa-specific mortality among those with adverse pathological features. The addition of adjuvant ADT alongside RT for patients with unfavorable-risk PCa has demonstrated decreased PCa-specific mortality.[8] Results from the ASCENDE-RT trial have also shown improvements in biochemical control from combination external beam RT (EBRT) with BT compared to EBRT alone.[9] Finally, RT dose-escalation protocols have demonstrated improvements in biochemical control.[10]

Despite the progress made in the selection and sequencing of adjuvant and salvage therapies and refinements in RT approaches, optimal initial treatment between RP and RT has not been adequately evaluated through a RCT for this population of unfavorable-risk patients. In turn, in the absence of specific patient- or tumor-factors influencing treatment decisions, clinicians and patients rely on evidence generated from observational data, which have limitations

Table 1. Descriptive patient and treatment characteristics

Treatment group	RT n=164	RP n=169	SMD	Variance ratio	GGWPC RP n=75	LHSC RP n=94
Followup time (months), median (Q1, Q3)	83.9 (58.8, 106.3)	96.9 (67.8, 118.4)			98.8 (69.3, 124.0)	94.5 (65.2, 113.1)
Metastatic events, n (%)	20 (12.2)	33 (19.5)	0.20		11 (14.7)	22 (23.4)
Age at diagnosis, mean (SD)	72.5 (7.5)	62.6 (6.4)	1.42	0.74	62.1 (6.7)	63.6 (5.9)
Missing n (%)	3 (1.8)	0 (0)			0 (0)	0 (0)
Baseline PSA (ng/ml), mean (SD)	19.7 (21.9)	16.4 (15.3)	0.18	0.49	14.4 (10.9)	17.9 (18.0)
Missing, n (%)	1 (0.6)	0 (0)			0 (0)	0 (0)
Clinical T stage						
1	75 (48.4)	65 (40.1)	0.17		43 (62.3)	22 (23.7)
2	67 (43.2)	57 (35.2)	0.17		20 (29.0)	37 (39.8)
3	13 (8.4)	37 (22.8)	0.41		6 (8.7)	31 (33.3)
4	0 (0)	3 (1.9)	0.19		0 (0)	3 (3.2)
Missing, n (%)	9 (5.5)	7 (4.1)			6 (8.0)	1 (1.1)
Gleason score						
≤6	4 (2.4)	5 (3.0)	0.03		2 (2.9)	3 (3.2)
7	108 (65.9)	103 (61.0)	0.10		46 (66.7)	55 (58.5)
8	20 (12.2)	31 (18.3)	0.17		7 (10.1)	22 (23.4)
9	32 (19.5)	28 (16.6)	0.08		14 (20.3)	13 (13.8)
10	0 (0)	2 (1.2)	0.15		0 (0)	1 (1.1)
Missing, n (%)	0 (0)	0 (0)			0 (0)	0 (0)
(%) core positivity, mean (SD)	56.4 (27.8)	51.0 (25)	0.20	0.81	50.5 (24.2)	51.7 (25.6)
≥50%	97 (59.2)	93 (59.2)	0.00		39 (56.5)	48 (63.2)
Missing, n (%)	0 (0)	12 (7.1)			0 (0)	12 (12.8)
ProCaRS risk groups						
High-intermediate	72 (47.4)	58 (40.6)	0.14		29 (45.7)	29 (38.7)
High	48 (31.6)	59 (41.3)	0.20		27 (39.7)	32 (42.7)
Extremely high	32 (21.1)	26 (18.2)	0.07		12 (17.7)	14 (18.7)
Missing*, n (%)	12 (7.3)	26 (18.4)			7 (10.4)	19 (20.2)

*Patients with insufficient information to classify risk group were either high- or extremely high-risk. ADT: androgen deprivation therapy; EQD2: equivalent dose in 2-Gy fractions; GGWPC: Gale and Graham Wright Prostate Center; LHSC: London Health Sciences Centre; RP: radical prostatectomy; ProCaRS: Prostate Cancer Risk Stratification; RT: radiation therapy; SMD: absolute standardized mean difference.

due to confounding and comparisons involving outdated treatment regimens. For example, RP compared to RT candidates generally have less aggressive tumor characteristics, are younger, and have fewer comorbidities.[11] Such disparities make statistical assumptions of positivity required for valid estimation of treatment effects questionable.[12] As such, identifying patients treated with RP and RT who have similar baseline characteristics and who have undergone more contemporary forms of treatment is necessary to improve the internal and external validity of evidence in this area.

Herein, we compared the rate of metastatic progression between men diagnosed with unfavorable-risk non-metastatic PCa and initially treated with RT and RP. Data were obtained from a multidisciplinary clinic wherein RT patients were also eligible for RP during the same clinical encounter to mitigate violations of positivity. Furthermore, we took advantage of novel matching strategies to improve the degree of comparability between treatment groups.[13,14]

Methods

Data

Both institutional review boards at Sunnybrook Health Sciences Centre and London Health Science Centre (LHSC) provided ethics approval. We identified men diagnosed from 2007–2012 with unfavorable-risk non-metastatic PCa in the multidisciplinary diagnostic assessment program in the Gale and Graham Wright Prostate Centre (GGWPC) in Canada. Patients in the RT group included those who had undergone EBRT with or without brachytherapy boost (BT) and with or without ADT. Patients in the RP group included those who had undergone RP as their primary treatment modality. Due to limited RP observations from the GGWPC, we also included men diagnosed from 2007–2012 with unfavorable-risk non-metastatic PCa who were treated with primary RP at LHSC in Canada.

Table 2. Treatment characteristics

			GGWPC	LHSC
Radiotherapy patients				
EQD2 for EBRT, median (range)	78 (70, 108.5)			
EQD2 for EBRT+BT, median (range)	113.57 (113.1, 116.7)			
ADT n (%)	95 (57.9)			
Initial ADT, n (%)	67 (40.9)			
Duration ADT, median (range)	22.1 (2.5, 43.3)			
Brachytherapy boost type				
Low-dose rate	1 (0.6)			
High-dose rate	18 (10.6)			
Prostatectomy patients				
Neoadjuvant systemic therapy		40 (23.7)	2 (2.7)	38 (40.4)
Adjuvant radiotherapy		57 (33.7)	9 (12)	48 (51.1)
Adjuvant systemic		32 (18.9)	8 (10.7)	24 (25.5)
All patients				
Local salvage	0 (0)	52 (30.8)	36 (48.0)	16 (17.0)
Salvage RT	14 (8.5)	48 (28.4)	20 (26.7)	28 (29.8)

ADT: androgen deprivation therapy; BT: brachytherapy; EBRT: external beam radiation therapy; EQD2: Equivalent dose in 2-Gy fractions; GGWPC: Gale and Graham Wright Prostate Center; LHSC: London Health Sciences Centre; RT: radiation therapy.

Data collection

We reviewed electronic medical records from identified patients. Patient age at diagnosis, biopsy date, prognostic factors at diagnosis (prebiopsy prostate-specific antigen [PSA] level, TNM stage, Gleason score (GS), and biopsy core involvement), initial treatment decision, treatment date, and treatment details were obtained. Patients were eligible for the study if they met the following criteria:

1. Diagnosed with Prostate Cancer Risk Stratification (ProCaRS) unfavorable intermediate-, high- or extremely high-risk PCa[2]
2. No evidence of regional or metastatic disease
3. Consulting radiation oncologist offered RT
4. Consulting urologist offered RP
5. Diagnosed between July 2007 and December 2012
6. Had ≥1 year of followup

ProCaRS unfavorable intermediaterisk disease entails a GS 7 and one or both of PSA 10–20 ng/mL and/or bilateral clinical disease. High-risk disease entails a PSA>20 ng/mL, cT stage 3–4, or GS 8–10, while extremely high-risk disease entails a PSA >30 ng/mL or high-volume disease, defined as >87.5% biopsy core involvement. Information on patient comorbidities, socioeconomic and demographic characteristics were not available for the majority of patients so were not collected. RT following RP was categorized as salvage if it was administered >6 months after RP or in response to a rising PSA; otherwise, it was categorized as adjuvant.

Outcomes

We analyzed the rate of metastatic progression-free survival between treatment groups. Metastatic progression was confirmed through imaging reports. Survival time was defined as the interval between the date of PCa treatment and the

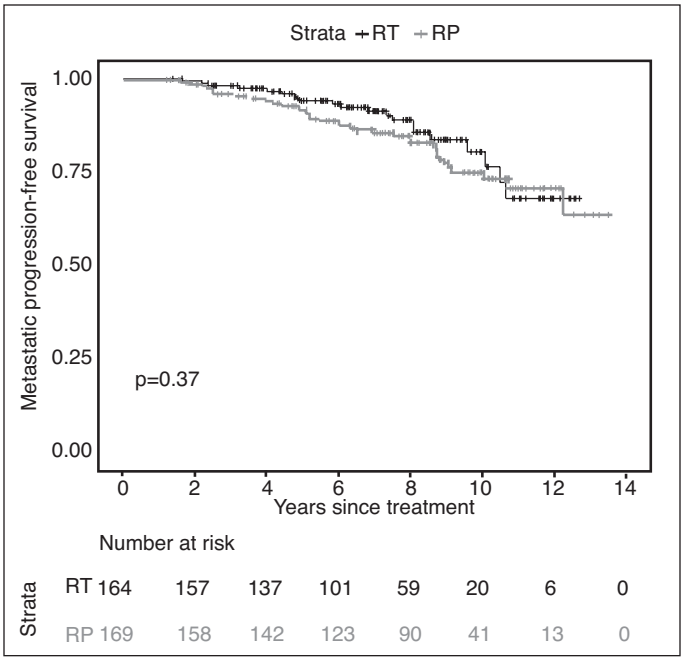

Fig. 1. Kaplan-Meier curve showing the probability of metastatic progression-free survival over time stratified by treatment group. RP: radical prostatectomy; RT: radiation therapy.

date of metastatic progression or last followup. Patients who were event-free at the end of the study period were censored and contributed the time interval from treatment date to the end of the study for the survival analysis.

Covariate selection

We explored the potential for confounding through examining differences between treatment groups in distributions of baseline covariates that have demonstrated a prognostic role in relation to the rate of treatment failure in previous literature.[2] Covariates included tumor characteristics (i.e., prebiopsy PSA level, clinical T (cT) stage, and GS). Age was not included as a covariate since it did not demonstrate a notable association with the outcome examined. Further, age was strongly associated with treatment choice, which would bias effect estimates if adjusted for.[15] An insufficient number of patients had information on biopsy core involvement, so this variable is only reported in the descriptive statistics and not used for adjustment. However, point estimates of the hazard ratios did not notably differ when this variable was included.

Propensity score matching

The propensity score model was a logistic model, with prognostic characteristics as independent variables and treatment received as a binary dependent variable.[15] We explored interactions and non-linearity for baseline covariates when developing the propensity score model.[16] Locally weighted scatterplot smoothers were used to assess for departures from linearity in the relationship between baseline PSA and the log odds of the probability for receiving RP. Improvements in the model fit were assessed using the likelihood-ratio test and pseudo-R^2. DFBETA statistics did not reveal any outliers. Model 1 involved baseline PSA as a linear term and cT-stage and GS as categorical variables. A restricted cubic spline with four knots was found to improve model fit for baseline PSA, and thus was included in model 2. Participants were matched in a 1:1 ratio between treatment groups.[17] We explored a range of caliper widths between 1.0 and 0.01 standard deviations of the logit of the propensity score. Nearest-neighbor matching was used without replacement.

Coarsened exact matching

Patients were matched on progressively coarsened covariates. GS was first dichotomized into ≤7 or 8–10 and then using each category. Clinical T-stage was first dichotomized into ≤2 and 3–4 and then using each category. Progressive coarsening for PSA involved cutpoints from 0 ng/ml to 300 ng/ml first at 20 and 100 ng/ml, with additional cutpoints at 30 and 50 ng/ml and further at 6 and 10 ng/ml. Coarsening ranges are presented in Supplementary Table (available at *cuaj.ca*).

Balance diagnostics

We chose four balance measures that considered different data characteristics in order to monitor improvements in balance when further restricting matching strategies. This enabled systematic identification of matching strategies that optimized balance in the distribution of baseline covariates as a function of data retention. This process is shown in Supplementary Figs. 1, 2 (available at *cuaj.ca*).

Descriptive statistics and multivariable regression analysis

All statistical analyses were performed using RStudio version 3.6.0.[18] Descriptive statistics were calculated for each treatment group before and after matching. Cox proportional hazards regression analyses for estimating the effect of treatment group on the hazard of metastatic progression were performed using the Survival package.[19] The proportional hazards assumption was confirmed using log-minus-log survival plots and scaled Schoenfeld residuals. Improvements in model fit were examined through informally comparing the model log likelihoods after incorporating interaction terms and higher order terms and transformations for continuous covariates. Examination of a plot of DBETA statistics did not identify any influential observations. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated from unmatched data both without and with adjustment for baseline PSA, cT stage, and GS, as well as interactions between baseline PSA and GS and baseline PSA and cT stage. For matched data, we employed Cox models clustered by the matched sets with associated weights to account for variable matching ratios, using robust variance estimators to generate CIs.[19,20]

Results

Descriptive characteristics are displayed in Table 1. At diagnosis, men treated with RT relative to RP were older, had higher PSA levels, a greater percentage of tumor-containing biopsy cores, less advanced tumor staging, and comparable GS. A greater proportion of men treated with RT presented with high intermediate-risk, and a smaller proportion of high-risk disease than those treated with RP, while similar proportions of each treatment group were considered extremely high-risk disease. Some RP patients met risk criteria but were unable to be categorized more specifically as either high- or extremely high-risk.

Treatment characteristics are displayed in Table 2. Among men treated with RT relative to RP, a greater proportion received neoadjuvant ADT and a smaller proportion received adjuvant ADT. Approximately one-third of men in the RP group

Table 3. Hazards ratios and confidence intervals for metastatic progression in RP relative to RT

	Unadjusted			Adjusted*		
	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p
Unmatched	1.29	0.74, 2.26	0.37	1.16	0.63, 2.13	0.64
PSM	1.01	0.50, 2.05	0.64	1.06	0.50, 2.26	0.87
CEM	1.32	0.62, 2.82	0.47	1.55	0.60, 3.98	0.37

*Adjusted model includes baseline prostate-specific antigen (PSA), clinical T stage, and Gleason score as continuous linear variables with interactions between baseline PSA and clinical T stage and baseline PSA and Gleason score. CEM: coarsened exact matched; CI: confidence interval; PSM: propensity score matched; RP: radical prostatectomy; RT: radiation therapy.

received local and systemic salvage therapy, while less than 10% of men treated with RP received systemic salvage therapy aside from adjuvant ADT. The most common form of RT was EBRT without BT boost, with a median dose of 78 Gy. Of those who received BT boost, the vast majority received high-dose rate (HDR), while only one man received low-dose rate (LDR). Finally, two men treated with RT received stereotactic body radiation therapy (SBRT) boost. The median dose for patients treated with either a BT or SBRT boost was 113.57 Gy.

After propensity score matching, 117 subjects were retained in each group, while coarsened exact matching led to retention of 138 and 141 patients from the RT and RP groups, respectively. Both matching strategies led to balance in the multivariable covariate structure according to conventional thresholds for balance (i.e., standardized mean difference [SMD]<0.1 and variance ratio 0.92–1.08).[16] Age and mean percent of tumor-containing biopsy cores remained imbalanced.

Kaplan-Meier curves showing the probability of metastatic progression-free survival over time stratified by treatment group are shown in Fig. 1. Median followup time for censored patients was approximately 93.6 months. Overall, both groups demonstrated similar rates of metastatic progression-free survival and unadjusted and adjusted HRs and 95% CIs before and after matching demonstrated no significant difference (Table 3).

Discussion

We compared the rate of metastatic progression between men diagnosed with unfavorable-risk non-metastatic PCa who were treated with RT or RP. No significant difference was observed in the rate of metastatic progression between treatment groups. Previous reports have demonstrated reduced rates of metastatic progression among men diagnosed with unfavorable-risk non-metastatic PCa who were treated with RT compared to RP.[21-23] This includes a study of men diagnosed with National Comprehensive Cancer Network high- and very high-risk PCa in a multidisciplinary clinic and treated with RT or RP wherein rates of distant metastasis were insignificantly elevated among those treated with RP relative to those treated with RT (HR 2.5, 95% CI 0.8, 7.8, p=0.11).[23] These findings are consistent with another comparison of metastatic progression between men diagnosed with unfavorable-risk PCa and treated with EBRT+ADT relative to RP.[22] The null finding in our study might be attributable to the low rate of ADT administration (57.9%) compared to the much higher rate used in other studies (approximately 100%).

Substantial variation in oncological outcomes has also been observed with the use of combination EBRT+BT relative to EBRT alone. For instance, lower rates of metastatic progression have been found among men diagnosed with unfavorable-risk non-metastatic PCa and treated with combination EBRT+BT relative to RP (HR 0.27, 95% CI 0.17, 0.43).[21] This finding is consistent with other reports demonstrating improved PCa-specific survival among combination EBRT+BT relative to EBRT alone.[24,25] In the current study, few men (11.2%) received combination EBRT+BT, preventing subgroup comparisons.

The rate of salvage therapy post-RP was much higher than that post-RT. Local and systemic salvage therapy were administered to approximately 30% of men post-RP, while only about 8% treated with RT received salvage therapy. These observations are consistent with previous investigations by Kishan et al, who found similar rates of local and systemic salvage therapy post-RP,[21] and Markovina et al, who found salvage much more common post-RP than post-RT.[22] This can, in part, be explained by the increased rates of biochemical failure among men diagnosed with unfavorable-risk non-metastatic PCa who undergo RP relative to RT. Administration of salvage therapy is also less standardized among men with biochemical failure post-RT. Since men who undergo RT are generally older, with poorer health and lower life expectancies, the options and potential benefits of salvage therapy may be limited, with potential for adverse impact on quality of life from associated side effects. Moreover, the rate of salvage local therapy post-RT might be hampered due to limited availability and awareness of modalities, such as cryotherapy and high-intensity focused ultrasound, although the number of patients with local failure only post-RT is not known for this cohort.

The median followup time was 13 months shorter in the RT relative to the RP group. This might be explained by increased rates of competing events that would increase losses to followup. To explain, those receiving RT were also approximately 10 years older than those receiving RP and likely had increased comorbidities. During later phases of PCa management, competing illnesses that decrease

life expectancy may take priority and patients might stop attending followup appointments for their PCa if it poses less threat to their survival. Unfortunately, data from other clinics indicating development of metastasis was not available, preventing competing risks analyses. This missing data issue can bias effect estimates either through limiting the contribution of event-free followup time or limiting the identification of metastatic progression.

Other missing data involved 17 subjects for clinical tumor stage and 23 subjects for percent core positivity, which prevented these observations from contributing to regression and post-matching effect estimation. However, due to the limited number of subjects missing information on these variables, inferences regarding the distribution of missing data are limited and data imputation methods, such as multiple imputation, are unlikely to lead to notably different effect estimates or provide additional information.

The strengths of our study include the comparison of men treated with RT who were also eligible for RP, thereby mitigating violations of positivity required for the conduct of regression analysis.[12] Moreover, systematic identification of comparable treatment groups through propensity score matching and coarsened exact matching has potential to reduce reliance on model specification,[13] thereby improving the robustness of confounding control. Furthermore, since men were diagnosed between 2007 and 2012 from two large academic centers, treatment approaches are expected to be more consistent with contemporary treatment approaches. Finally, the endpoint employed in this study, metastatic progression-free survival, is a clinically meaningful endpoint, and the only validated surrogate endpoint for overall survival to date in prostate cancer.[26]

The findings of this study are subject to limitations. First, the proportion of men treated with RT who received ADT was much lower than other similar investigations. Since ADT has been shown to decrease the rate of metastatic progression, the rates observed among men treated with RT in our cohort may exceed those achievable through the current standard of care, which recommends RT and ADT for men diagnosed with unfavorable-risk PCa.[27] In addition, the series of men treated at LHSC may not have been comparable to men treated at GGWPC so there is potential for confounding of effect estimates by treatment center. Finally, due to data limitations, percent of tumor-containing biopsy cores, comorbidities, and socioeconomic and demographic characteristics could not be controlled for, potentially biasing effect estimates.

Conclusions

The results from our study support findings from previous analyses that more contemporary forms of treatment involving RT as an initial strategy may be, at least, comparable to those involving initial RP for men diagnosed with unfavorable-risk PCa. Furthermore, the decreased use of salvage therapies among men treated with RT relative to RP may have benefits with regard to fewer side effects in the long-term management of this patient population. Given the limitations of observational data, the results from this study must be interpreted with caution.

Competing interests: This research was supported by the Ontario Graduate Scholarship program. Some of the work herein originated from the corresponding author's graduate thesis. Dr. Buckley has been an advisor for Abbvie, Astellas, Ferring, IBCG, TerSera, and Verity. Dr. Cheung has received investigator-initiated research grants from Abbvie, Pfizer, and Sanofi, and speaker honoraria from TerSera. Dr. Chung has receved honoraia from Abbvie. Dr. Loblaw has participated in advisory boards for and received honoraria from Abbvie, Sanofi, and TerSera; has received a research grant from TerSera; has participated in several investigator-initiated studies or CCTG; and is the founder/chair of the Prostate Cure Foundation. The remaining authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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