

Development of ProCaRS Clinical Nomograms for Biochemical Failure-free Survival Following Either Low-Dose Rate Brachytherapy or Conventionally Fractionated External Beam Radiation Therapy for Localized Prostate Cancer

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Abstract

Purpose: Although several clinical nomograms predictive of biochemical failure-free survival (BFFS) for localized prostate cancer exist in the medical literature, making valid comparisons can be challenging due to variable definitions of biochemical failure, the disparate distribution of prognostic factors, and received treatments in patient populations. The aim of this investigation was to develop and validate clinically-based nomograms for 5-year BFFS using the ASTRO II "Phoenix" definition for two patient cohorts receiving low-dose rate (LDR) brachytherapy or conventionally fractionated external beam radiation therapy (EBRT) from a large Canadian multi-institutional database.

Methods and Materials: Patients were selected from the GUROC (Genitourinary Radiation Oncologists of Canada) Prostate Cancer Risk Stratification (ProCaRS) database if they received (1) LDR brachytherapy ≥ 144 Gy ($n=4208$) or (2) EBRT ≥ 70 Gy ($n=822$). Multivariable Cox regression analysis for BFFS was performed separately for each cohort and used to generate clinical nomograms predictive of 5-year BFFS. Nomograms were validated using calibration plots of nomogram predicted probability versus observed probability via Kaplan-Meier estimates.

Results: Patients receiving LDR brachytherapy had a mean age of 64 ± 7 years, a mean baseline PSA of 6.3 ± 3.0 ng/mL, 75% had a Gleason 6, and 15% had a Gleason 7, whereas patients receiving EBRT had a mean age of 70 ± 6 years, a mean baseline PSA of 11.6 ± 10.7 ng/mL, 30% had a Gleason 6, 55% had a Gleason 7, and 14% had a Gleason 8-10. Nomograms for 5-year BFFS included age, use and duration of androgen deprivation therapy (ADT), baseline PSA, T stage, and Gleason score for LDR brachytherapy and an ADT (months), baseline PSA, Gleason score, and biological effective dose (Gy) for EBRT.

Conclusions: Clinical nomograms examining 5-year BFFS were developed for patients receiving either LDR brachytherapy or conventionally fractionated EBRT and may assist clinicians in predicting an outcome. Future work should be directed at examining the role of additional prognostic factors, comorbidities, and toxicity in predicting survival outcomes.

Categories: Radiation Oncology

Keywords: radiotherapy, prostate cancer, ldr brachytherapy, fractionated external beam radiation therapy, biochemical failure, nomogram

Introduction

The treatment of localized prostate cancer in Canada has been evolving over the past few decades to reflect advances in our understanding of the disease and improvements in technology. Historically, single modality radiotherapy (low-dose rate (LDR) brachytherapy or external beam radiation therapy (EBRT)) has been utilized for patients with low and intermediate risk disease with optional androgen deprivation therapy (ADT) for select cases, whereas high-risk disease has typically been treated with EBRT (or less commonly high-dose-rate (HDR) brachytherapy, plus EBRT as dose escalation) followed by two to three years of adjuvant ADT [1-2]. Radical prostatectomy (RP) has typically been reserved for younger patients with clinically confined low-risk disease, and few or no comorbidities [2]. Minimal disease is increasingly being followed with active surveillance until progression [2].

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Much of the existing literature to improve clinical decision making in prostate cancer management has been directed at the development and refinement of existing prognostic risk stratification systems and nomograms, often based on clinical endpoints (survival or biochemical) [3]. Collectively, risk stratification and nomograms in combination with other predictive modelling techniques, including regression tree analyses and artificial neural networks, assist in determining the appropriate treatment course by providing an assigned risk or survival probability prior to treatment selection [3]. Furthermore, several studies have demonstrated that nomograms can yield accurate models with predictability comparable to risk stratification models [4-8]. Many of the existing risk stratification systems are dominated by a set of three key prognostic factors – pre-treatment PSA, T stage, and Gleason score – each of which has been extensively validated to independently predict for a variety of clinical endpoints across a range of non-metastatic prostate cancer populations [3, 9].

Nomograms addressing biochemical and/or survival outcomes in prostate cancer have been published for patients receiving EBRT alone [4-5, 7, 10-17], one of RP or EBRT [18-20], RP or RP followed by salvage EBRT [21-28], and for LDR brachytherapy or LDR brachytherapy followed by EBRT [29-31], each reporting variable rates of ADT utilization. Similarly, the majority of published nomograms incorporate the same set of three key prognostic factors as reported in risk stratification systems (pre-treatment PSA, T stage and Gleason score), with some exceptions in studies reporting on RP or EBRT alone [10, 18] or RP with EBRT salvage [21, 23-28]. Other nomogram prognostic factors include: age [10, 15-16, 18, 24]; PSA doubling time [19, 27]; Gleason pattern [11, 28]; percentage of positive core biopsies [11, 15]; lymph node invasion [21, 23, 27-28]; ADT use or duration [4-5, 11-13, 15, 27]; EBRT use or dose (Gy) [4-5, 11-13, 15-16, 24-27, 30-31]; EBRT biological effective dose (BED) (Gy) [10]; and other RP-related features (positive surgical margin, RP type, extracapsular extension, and/or seminal vesicle invasion) [21-22, 26-28]. Nomograms have also been developed for similar patient populations examining non-survival-based endpoints such as: fecal incontinence [32-35]; rectal bleeding [34-35]; erectile function [36]; urinary retention [37-38]; and Gleason score upgrade [39-41] (Table 1).

Author(s)	Year	Article Type	N	Primary Treatment	Secondary Treatment	ADT	Nomogram End Point(s)	Landmark Analysis	Landmark Threshold
Sanpaolo, et al.	2014	Observational	670	EBRT	No	Yes (70%)	6-year BFFS ("Phoenix")	No	N/A
Stoyanova, et al.	2013	Observational	2012	EBRT	No	Yes (22%)	8-year BFFS ("Phoenix")	No	N/A
Zelevsky, et al.	2011	Observational	2551	EBRT	No	Yes (49%)	5-, 10-year BFFS ("Phoenix")	No	N/A
Westphalen, et al.	2011	Observational	99	EBRT	No	Yes (N/A)	5-year BFFS ("Phoenix")	No	N/A
Spiess, et al.	2010	Observational	450	EBRT	Cryotherapy	Yes (21%)	BFFS ("PSA > 0.5 ng/mL")	No	N/A
Williams, et al.	2008	Observational	3264	EBRT	No	Yes (30%)	5-, 7-year BFFS ("Phoenix")	No	N/A
Zelevsky, et al.	2007	Observational	2253	EBRT	No	Yes (49%)	5-, 10-year BFFS ("Phoenix")	No	N/A
Williams, et al.	2006	Observational	1458	EBRT	No	No	5-, 7-year BFFS ("Phoenix")	No	N/A
Kattan, et al.	2003	Observational	1677	EBRT	No	Yes (7.6%)	5-year metastatic progression	No	N/A
Parker, et al.	2002	Observational	517	EBRT	No	Yes (100%)	1-year to 5-year BFFS ("2 consecutive PSA > 2 ng/mL")	No	N/A
Kattan, et al.	2000	Observational	1042	EBRT	No	Yes (37%)	5-year BFFS ("3 consecutive PSA rises")	No	N/A
Zelevsky, et al.	2012	Observational	1466	LDR	EBRT (36%)	Yes (31%)	5-year BFFS ("Phoenix")	No	N/A
Potters, et al.	2010	Observational	5931	LDR	EBRT (21%)	Yes (36%)	9-year BFFS ("Phoenix")	No	N/A
Kattan, et al.	2001	Observational	920	LDR	EBRT (18%)	No	5-year BFFS ("3 consecutive PSA rises")	No	N/A

Abdollah, et al.	2014	Observational	1107	Sx	EBRT (35%)	Yes (100%)	10-year CSM	No	N/A
Briganti, et al.	2013	Observational	472	Sx	EBRT	No	5-year BFFS ("2 consecutive PSA values $\geq$ 0.2 ng/mL")	No	N/A
Abdollah, et al.	2013	Observational	336	Sx	EBRT	Yes (42%)	10-year CSM	No	N/A
Porter, et al.	2010	Observational	752	Sx	EBRT (16%)	Yes (15%)	5-, 10-, 15-, 20-year CSM	No	N/A
Porter, et al.	2008	Observational	752	Sx	EBRT (16%)	Yes (6%)	Metastatic progression	No	N/A
Suardi, et al.	2008	Observational	601	Sx	EBRT (16%)	No	5-, 10-, 15-year BFFS ("PSA > 0.1 ng/mL")	No	N/A
Stephenson, et al.	2007	Observational	1540	Sx	EBRT	Yes (14%)	6-year PFS	No	N/A
Stephenson, et al.	2005	Observational	1881	Sx	EBRT (1%)	No	10-year PFS	No	N/A
Walz, et al.	2007	Observational	9131	Sx or EBRT	No	No	10-year OS	No	N/A
Slovin, et al.	2005	Other	148	Sx or EBRT	No	No	1-, 2-year PFS, Median PFS	No	N/A
D'Amico, et al.	1999	Observational	1654	Sx or EBRT	No	No	2-year BFFS ("3 consecutive PSA rises")	No	N/A
Fellin, et al.	2014	Observational	515	EBRT	No	Yes (89%)	Grade 1-3 late fecal incontinence	No	N/A
Chipman, et al.	2014	Observational	1201	Sx, EBRT or LDR	No	Yes (N/A)	2-Year functional erection	No	N/A
Mathieu, et al.	2014	Observational	965	EBRT	No	Yes (23%)	5-year grade 2-4 urinary toxicity	No	N/A
Bowes, et al.	2012	Observational	259	LDR-Brachy	No	No	Gleason score upgrade	No	N/A
Fiorino, et al.	2012	Other	586	EBRT	No	No	Late fecal incontinence	No	N/A
Valdagni, et al.	2012	Other	718	EBRT	No	Yes (78%)	Grade 2-3 late rectal bleeding, fecal incontinence	No	N/A
Roeloffzen, et al.	2011	Observational	714	LDR-Brachy	No	Yes (19%)	Acute urinary retention	Yes	6 months
Budäus, et al.	2010	Observational	414	Sx	No	No	Gleason score upgrade	No	N/A
Valdagni, et al.	2008	Other	1124	EBRT	No	Yes (74%)	Grade 2-3 acute lower GI toxicity, moderate/severe stool frequency, severe incontinence, moderate/severe acute rectal bleeding	No	N/A
Kulkarni, et al.	2007	Observational	175	Sx	No	No	Gleason score upgrade	No	N/A
Kattan, et al.	2003	Observational	409	Sx	No	No	Indolent cancer (< 0.5 cc)	No	N/A

TABLE 1: Published literature for nomograms based on external beam radiation therapy, LDR brachytherapy, and/or radical prostatectomy as primary or secondary treatments.

EBRT – External Beam Radiation Therapy; LDR – Low-Dose Rate Brachytherapy; ADT – Androgen Deprivation Therapy; Sx – Surgery; BFFS – Biochemical Failure-Free Survival; BF – Biochemical Failure; CSM – Cancer-Specific Mortality; PFS – Progression-Free Survival; OS – Overall Survival; PSA – Prostate Specific Antigen

Comparisons between existing nomograms are limited due to heterogeneity in reported clinical endpoints, in the proportion of patients receiving secondary/salvage EBRT, and in the proportion/duration/timing of ADT use. Additionally, variability exists between individual patient populations in terms of the distribution

of known and unknown prognostic factors (confounders) directly impacting the degree of generalizability between patient populations. Specifically, nomograms developed using biochemical failure definitions, which differ from the ASTRO II "Phoenix" biochemical failure-free survival 2006 consensus definition of a PSA increase of 2 ng/mL above the nadir PSA, are further limited in the ability to make direct comparisons [42]. The overall aim of this investigation was to develop and validate clinically-based nomograms for 5-year biochemical failure-free survival using the landmark method separately for two patient cohorts receiving LDR brachytherapy or conventionally fractionated EBRT in the context of a large Canadian multi-institutional prostate radiotherapy database.

Materials And Methods

The GUROC ProCaRS database

The GUROC (Genitourinary Radiation Oncologists of Canada) Prostate Cancer Risk Stratification (ProCaRS) database was created by combining retrospectively collected data from 7,974 patients with localized prostate cancer treated with primary LDR brachytherapy, HDR brachytherapy, or conventionally fractionated EBRT (or combination). Patients receiving RP as the primary treatment were not included in the database. All patients were treated between 1994 and 2010 at one of four participating Canadian institutions (British Columbia Cancer Agency (n=3,771), Princess Margaret Hospital (n=1,752), McGill University Health Centre (n=194), and L'Hotel Dieu de Québec (n=2,257)). Further details pertaining to the assembly and quality assurance procedures for the GUROC ProCaRS database have been described previously [43-44].

Patient selection

Patients receiving LDR brachytherapy ≥ 144 Gy alone (n=4,320) or EBRT (n=832) were eligible for analysis. To address EBRT dose heterogeneity across participating institutions and to ensure the nomograms would be relevant to modern radiotherapy practice, only patients identified as receiving sufficient dose escalation, using either three-dimensional conformal therapy or intensity-modulated radiation therapy (defined as ≥ 70 Gy (GUROC low-risk and high-risk) or ≥ 74 Gy (GUROC intermediate risk)) were considered for this analysis [45]. To reduce the risk of survival bias, landmark analysis techniques were applied by manually excluding patients with follow-up durations below an a priori selected landmark threshold [46-49]. Generally, the use of landmark analysis in the development of nomograms for prostate cancer has been absent with the exception of a study published by Roeloffzen, et al. in 2011 examining acute urinary retention in patients receiving LDR brachytherapy [38]. Six months was selected for the present study in order to maintain sufficient statistical power for analysis relative to the primary endpoint of 5-year biochemical failure-free survival [47-48]. Therefore, patients with follow-up durations less than six months were excluded from analysis (LDR brachytherapy (n=112); EBRT (n=10)). This formed two final analysis cohorts of 4,208 patients receiving LDR brachytherapy and 822 patients receiving EBRT. Details of patient selection are shown in Figure 1.

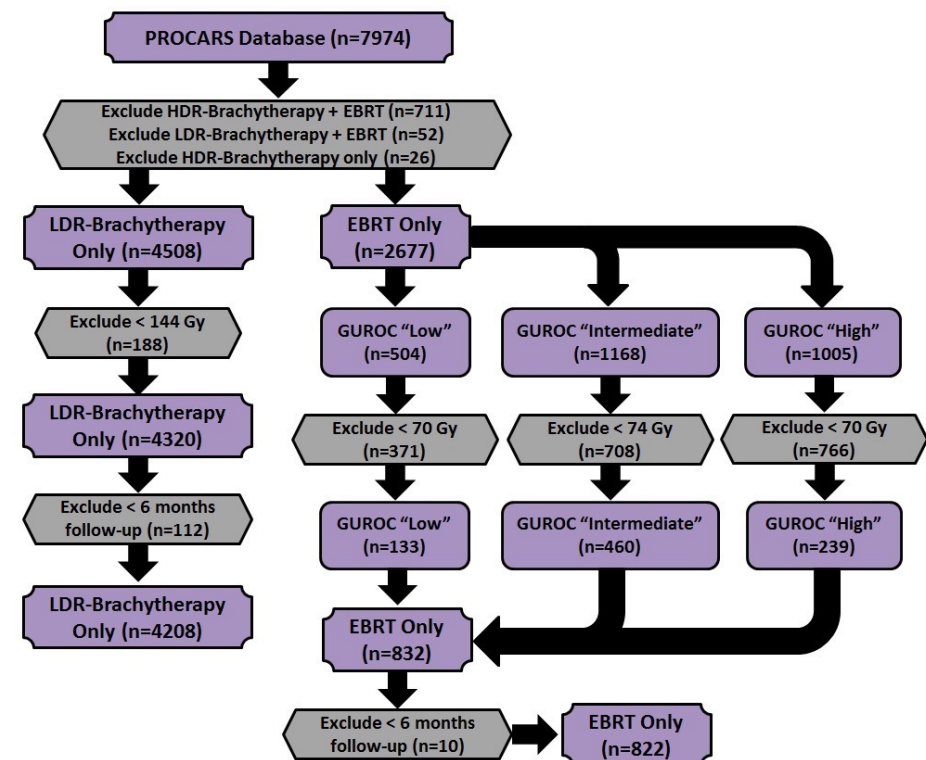


FIGURE 1: Summary of patient selection and creation of final analysis

cohorts (LDR – Low-Dose Rate (Brachytherapy), HDR – High-Dose Rate (Brachytherapy), EBRT – External Beam Radiation Therapy).

Endpoints

The primary endpoint was ASTRO II “Phoenix” biochemical failure-free survival (BFFS) defined as time from initiation of radiotherapy to the date of last follow-up and/or biochemical failure, whichever came first, according to the definition of a PSA increase of 2 ng/mL above the nadir PSA [42]. Technical biochemical failures arising from benign PSA bounces were adjusted using a quality assurance procedure reported previously and applied to both treatment cohorts [43, 45, 50]. Patients with PSA levels that returned to an absolute level of ≤ 0.5 ng/mL without intervention were re-classified as not to have had a biochemical failure, whereas patients with PSA levels > 0.5 ng/mL following biochemical failure were still considered to have biochemically failed [43, 45, 50]. Nomogram predicted individual patient-level probability estimates of 5-year BFFS were also obtained based on multivariable Cox proportional hazards regression for BFFS. Although overall survival (OS) and cancer-specific survival were available in the GUROC ProCaRS database, these were not examined due to an insufficient number of events and/or limited available follow-up required for multivariable regression and nomogram analysis for meaningful nomogram construction.

Statistical analysis

Descriptive statistics were generated for baseline patient, tumour and treatment characteristics for all patients (n=5,030) and stratified by treatment cohort (LDR brachytherapy only (n=4,208), EBRT only (n=822)). Univariable Cox proportional hazards regression analysis was performed on a set of prognostic factors previously shown to be significant predictors of BFFS and/or OS, based on the complete GUROC ProCaRS database, to identify significant predictors of ASTRO II “Phoenix” BFFS separately by treatment cohort. This list included age, ADT (yes/no and duration), baseline PSA (ng/mL), T stage, Gleason score (categorical), and positive core percentage [43-44]. BED defined with a α/β of 2, was additionally examined in the EBRT cohort. Multivariable Cox proportional hazards regression was performed for BFFS separately by treatment cohort using backward elimination techniques, beginning with all eligible factors and sequentially removing factors until all remaining covariates had p-values < 0.20. Given the high degree of missing data for positive core percentage, this specific variable was only reported in univariable procedures.

Nomograms based on the final multivariable Cox proportional hazards regression models for BFFS were generated separately by treatment cohort to calculate individual patient-level probability estimates for 5-year BFFS, according to each patient’s particular combination of baseline characteristics. Nomogram validation was performed via calibration plots of observed probability (calculated using Kaplan-Meier estimates) by nomogram predicted probability for 5-year BFFS for each nomogram separately. All statistical analysis was performed using SAS version 9.3 software (SAS Institute, Cary, NC) and the R language environment for statistical computing version 3.0.3, using two-sided statistical testing at the 0.05 significance level.

Results

Baseline patient characteristics are presented in Table 2. Overall for patients receiving LDR brachytherapy: mean age was 64 ± 7 years; mean baseline PSA was 6.3 ± 3.0 ng/mL; 55% and 45% had T1 and T2 disease, respectively; 75% had Gleason 6 and 15% had Gleason 7; 27% had ≥ 50% positive core biopsies; 38% received ADT (36% for ≥ 6 months; 3.7% for ≥ 1 year); and 75%, 24%, and 1% of patients were classified as GUROC low-, intermediate-, and high-risk, respectively. Biochemical failure was observed in 216 patients (5%), 168 (4%) occurring within five years of radiotherapy, and patient deaths were observed in 239 (6%) (138 (3%) within five years of radiotherapy). The median actuarial follow-up was 5.55 years. For patients receiving EBRT: mean age was 70 ± 6 years; mean baseline PSA was 11.6 ± 10.7 ng/mL; 36% and 50% had T1 and T2 disease, respectively; 30% had Gleason 6, 55% had Gleason 7, and 14% had Gleason 8-10; 50% had ≥ 50% positive core biopsies; 49% received ADT (18% for ≥ 2 years; 8% for ≥ 3 years); and 16%, 55%, and 29% were classified as GUROC low-, intermediate-, and high-risk, respectively. Biochemical failure was observed in 228 patients (28%), 147 (18%) occurring within five years of radiotherapy, and patient deaths were observed in 113 (14%) (49 (6%) occurring within five years of radiotherapy). The median actuarial follow-up was 7.10 years.

Characteristic	N	All Patients (n=5030)	LDR Only (n=4208)	EBRT Only (n=822)
Centre – n(%)				
British Columbia Cancer Agency	5030	2098 (41.7)	1757 (41.8)	341 (41.5)
Princess Margaret Hospital		1399 (27.8)	918 (21.8)	481 (58.5)

L'Hotel Dieu de Québec		1533 (30.5)	1533 (36.4)	--
		65.31 ± 7.20	64.35 ± 7.03	70.23 ± 5.99
Age – mean ± SD, median, (min, max)	5029	66.00	65.00	71.00
		(34.00, 84.00)	(40.00, 83.00)	(34.00, 84.00)
		7.19 ± 5.52	6.31 ± 2.99	11.61 ± 10.74
Baseline PSA (ng/mL) – mean ± SD, median, (min, max)	4958	6.20	5.98	8.47
		(0.10, 130.75)	(0.10, 40.00)	(0.26, 130.75)
T stage – n(%)				
T1	4951	2573 (52.0)	2284 (55.2)	289 (35.5)
T2		2255 (45.6)	1849 (44.7)	406 (49.9)
T3		117 (2.4)	4 (0.1)	113 (13.9)
T4		6 (0.1)	--	6 (0.7)
Gleason score – n(%)				
2-5	4958	400 (8.1)	382 (9.2)	18 (2.2)
6		3362 (67.8)	3119 (75.4)	243 (29.6)
7		1075 (21.7)	627 (15.2)	448 (54.6)
8-10		121 (2.4)	9 (0.2)	112 (13.6)
		37.07 ± 23.02	33.96 ± 20.74	48.10 ± 26.99
Positive vores (%) – mean ± SD, median, (min, max)	3036	33.33	30.00	45.64
		(5.26, 100.00)	(5.26, 100.00)	(5.56, 100.00)
Radiotherapy treatment year – n(%)				
1994-1999	5030	439 (8.7)	396 (9.4)	43 (5.2)
2000-2002		1520 (30.2)	1136 (27.0)	384 (46.7)
2003-2005		1894 (37.7)	1535 (36.5)	359 (43.7)
2006-2010		1177 (23.4)	1141 (27.1)	36 (4.4)
		76.37 ± 3.65	--	76.37 ± 3.65
EBRT: Dose (Gy) – mean ± SD, median, (min, max)	822	75.60	--	75.60
		(70.00, 79.80)	--	(70.00, 79.80)
		39.61 ± 2.89	--	39.61 ± 2.89
EBRT: Number of fractions – mean ± SD, median, (min, max)	822	42	--	42
		(35, 42)	--	(35, 42)
		1.93 ± 0.07	--	1.93 ± 0.07
EBRT: Dose per fraction (Gy) – mean ± SD, median, (min, max)	822	1.90	--	1.90
		(1.80, 2.11)	--	(1.80, 2.11)
		150.08 ± 5.95	--	150.08 ± 5.95
EBRT: Biological effective dose (Gy)– mean ± SD, median, (min, max)	822	148.00	--	148.00
		(136.80, 156.00)	--	(136.80, 156.00)
ADT – n(%)	5030	1995 (39.7)	1589 (37.8)	406 (49.4)
		7.89 ± 8.13	6.08 ± 4.99	13.89 ± 12.52

ADT (months) – mean ± SD, median, (min, max)	1738	5.88 (0.30, 132.67)	5.75 (0.30, 132.67)	9.33 (0.49, 99.68)
Pathologically confirmed local relapse – n(%)	5030	107 (2.1)	31 (0.7)	76 (9.3)
ASTRO II “Phoenix” biochemical failure – n(%)	4850	444 (9.2)	216 (5.3)	228 (28.4)
5-year ASTRO II “Phoenix” biochemical failure – n(%)	4850	315 (6.5)	168 (4.2)	147 (18.3)
Death – n(%)	5030	352 (7.0)	239 (5.7)	113 (13.8)
5-year death – n(%)	5030	187 (3.7)	138 (3.3)	49 (6.0)
Prostate cancer death – n(%)	5030	51 (1.0)	24 (0.6)	27 (3.3)
5-year prostate cancer death – n(%)	5030	30 (0.6)	17 (0.4)	13 (1.6)
Cause of death – n(%)				
Dead of disease	352	51 (14.5)	24 (10.0)	27 (23.9)
Dead (other)		223 (63.4)	160 (67.0)	63 (55.8)
Dead (NOS)		78 (22.2)	55 (23.0)	23 (20.4)
GUROC – n(%)				
Low	4969	3253 (65.5)	3122 (75.3)	131 (15.9)
Intermediate		1451 (29.2)	999 (24.1)	452 (55.0)
High		265 (5.3)	26 (0.6)	239 (29.1)
ProCaRS 5 – n(%)				
Low	4940	3253 (65.9)	3122 (75.8)	131 (16.0)
Low-intermediate		1265 (25.6)	913 (22.2)	352 (42.9)
High-intermediate		162 (3.3)	58 (1.4)	104 (12.7)
High		192 (3.9)	21 (0.5)	171 (20.8)
Very high		68 (1.4)	5 (0.1)	63 (7.7)
Actuarial follow-up (years) (using reverse Kaplan-Meier method) –median (min, max)	5030	5.81 (0.50, 15.15)	5.55 (0.50, 15.15)	7.10 (0.54, 11.45)

TABLE 2: Baseline tumour, patient and treatment characteristics for: (A) all patients (n=5030), (B) LDR Brachytherapy only (n=4208), and (C) EBRT only (n=822).

PSA – Prostate Specific Antigen; LDR – Low-Dose Rate Brachytherapy; EBRT – External Beam Radiation Therapy; ADT – Androgen Deprivation Therapy

Cox proportional hazards regression

Results from univariable Cox proportional hazards regression for BFFS are shown in Table 3. For LDR brachytherapy, only ADT duration (hazard ratio [HR] per one month increase: 1.03; 95% CI: 1.01-1.05, $p=0.008$) and baseline PSA (HR per 1 ng/mL increase: 1.10; 95% CI: 1.07-1.14, $p<0.001$) were significant independent predictors of BFFS. Multivariable modelling also identified ADT duration (HR: 1.03; 95% CI: 1.02-1.05, $p<0.001$) and baseline PSA (HR: 1.11; 95% CI: 1.08-1.15, $p<0.001$) as significant predictors in addition to age (HR per one year increase: 0.98; 95% CI: 0.96-1.00, $p=0.038$) and receiving ADT (HR: 0.53; 95% CI: 0.37-0.76, $p<0.001$). T stage ($p=0.164$) and Gleason score ($p=0.080$) also met the criteria for inclusion in the final multivariable regression model ($p<0.20$) but were not found to be statistically significant. For EBRT, baseline PSA (HR per 1 ng/mL increase: 1.02; 95% CI: 1.01-1.03, $p<0.001$), T stage ($p=0.047$), Gleason score ($p=0.002$), BED (HR per 10 Gy increase: 0.81; 95% CI: 0.66-0.99, $p=0.043$), and positive core percentage (HR per 1 percent increase: 1.01; 95% CI: 1.01-1.02, $p<0.001$) were significant independent predictors of BFFS. From multivariable modelling, only baseline PSA (HR: 1.02; 95% CI: 1.01-1.03, $p<0.001$) and Gleason score ($p=0.005$) remained significant with ADT duration ($p=0.092$) and BED ($p=0.138$) remaining eligible for inclusion in the final model ($p<0.20$) but were not statistically significant.

Dependent Variable:	ASTRO II "Phoenix" Biochemical Failure-Free Survival			
(A) LDR Brachytherapy only (n=4208)	Univariable		Multivariable	
Independent Variables:	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	0.99	0.218	0.98	0.038
Per 1 year increase	(0.97, 1.01)		(0.96, 1.00)	
ADT	0.93	0.581	0.53	< 0.001
Yes vs No	(0.70, 1.22)		(0.37, 0.76)	
ADT duration	1.03	0.008	1.03	< 0.001
Per 1-month increase	(1.01, 1.05)		(1.02, 1.05)	
Baseline PSA	1.10	< 0.001	1.11	< 0.001
Per 1 ng/mL increase	(1.07, 1.14)		(1.08, 1.15)	
T stage	1.25	0.101	1.22	0.164
T2 or T3 vs T1	(0.96, 1.64)		(0.92, 1.62)	
Gleason score		<i>**0.218</i>		<i>**0.080</i>
6 vs 2-5	1.01	0.948	1.11	0.657
	(0.67, 1.54)		(0.71, 1.72)	
7-10 vs 2-5	1.38	0.203	1.68	0.052
	(0.84, 2.28)		(1.00, 2.82)	
Positive cores percentage	1.00	0.467	--	--
Per 1 percent increase	(1.00, 1.01)		--	
(B) EBRT only (n=822)	Univariable		Multivariable	
Independent variables:	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	0.99	0.617	--	--
Per 1 year increase	(0.97, 1.02)		--	
ADT	1.12	0.381	--	--
Yes vs No	(0.87, 1.46)		--	
ADT duration	1.00	0.619	0.99	0.092
Per 1 month increase	(0.99, 1.01)		(0.97, 1.00)	
Baseline PSA	1.02	< 0.001	1.02	< 0.001
Per 1 ng/mL increase	(1.01, 1.03)		(1.01, 1.03)	
T stage		<i>**0.047</i>		--
2 vs 1	1.48	0.010	--	--
	(1.10, 1.99)		--	
3 vs 1	1.53	0.062	--	--
	(0.98, 2.40)		--	
4 vs 1	2.11	0.208	--	--
	(0.66, 6.70)		--	
Gleason score		<i>**0.002</i>		<i>**0.005</i>
7 vs 2-6	1.52	0.011	1.53	0.010

	(1.10, 2.09)		(1.11, 2.10)	
8-10 vs 2-6	2.05	< 0.001	2.01	0.003
	(1.36, 3.11)		(1.28, 3.17)	
EBRT biological effective dose	0.81	0.043	0.98	0.138
Per 10 Gy increase	(0.66, 0.99)		(0.96, 1.01)	
Positive cores percentage	1.01	< 0.001	--	--
Per 1 percent increase	(1.01, 1.02)		--	

TABLE 3: Univariable and multivariable Cox regression models of factors predicting ASTRO II “Phoenix” Biochemical Failure-Free Survival for (A) LDR Brachytherapy only (n=4208) and (B) EBRT only (n=822).

PSA – Prostate Specific Antigen; ADT – Androgen Deprivation Therapy; HR – Hazard Ratio; CI – Confidence Interval; P-values < 0.05 shown as BOLD, * *overall analysis of effects (applicable to categorical variables only).*

Clinical nomograms

Prognostic factors identified from the multivariable Cox regression model for BFFS for the LDR brachytherapy cohort are depicted in a nomogram shown in Figure 2A. Based on the calibration plot shown in Figure 2C, the nomogram showed reasonable calibration with only minimal underestimation of the true BFFS percentages for patients with nomogram-predicted probabilities below approximately 70% and approaching 90%. The deviation in the calibration plot below approximately 70% can be partially attributed to the limited number of patients with observed worse BFFS available for testing. Factors shown to be predictive of BFFS for the EBRT cohort from multivariable Cox regression were entered into the nomogram shown in Figure 2B. The calibration plot shown in Figure 2D demonstrated reasonable calibration for nomogram-predicted probabilities above 70%, whereas, below 70%, a combination of underestimation and overestimation of true BFFS was observed. Similarly, deviation in the calibration plot at the lower extreme can be partially attributed to the limited number of patients with observed worse BFFS available for testing.

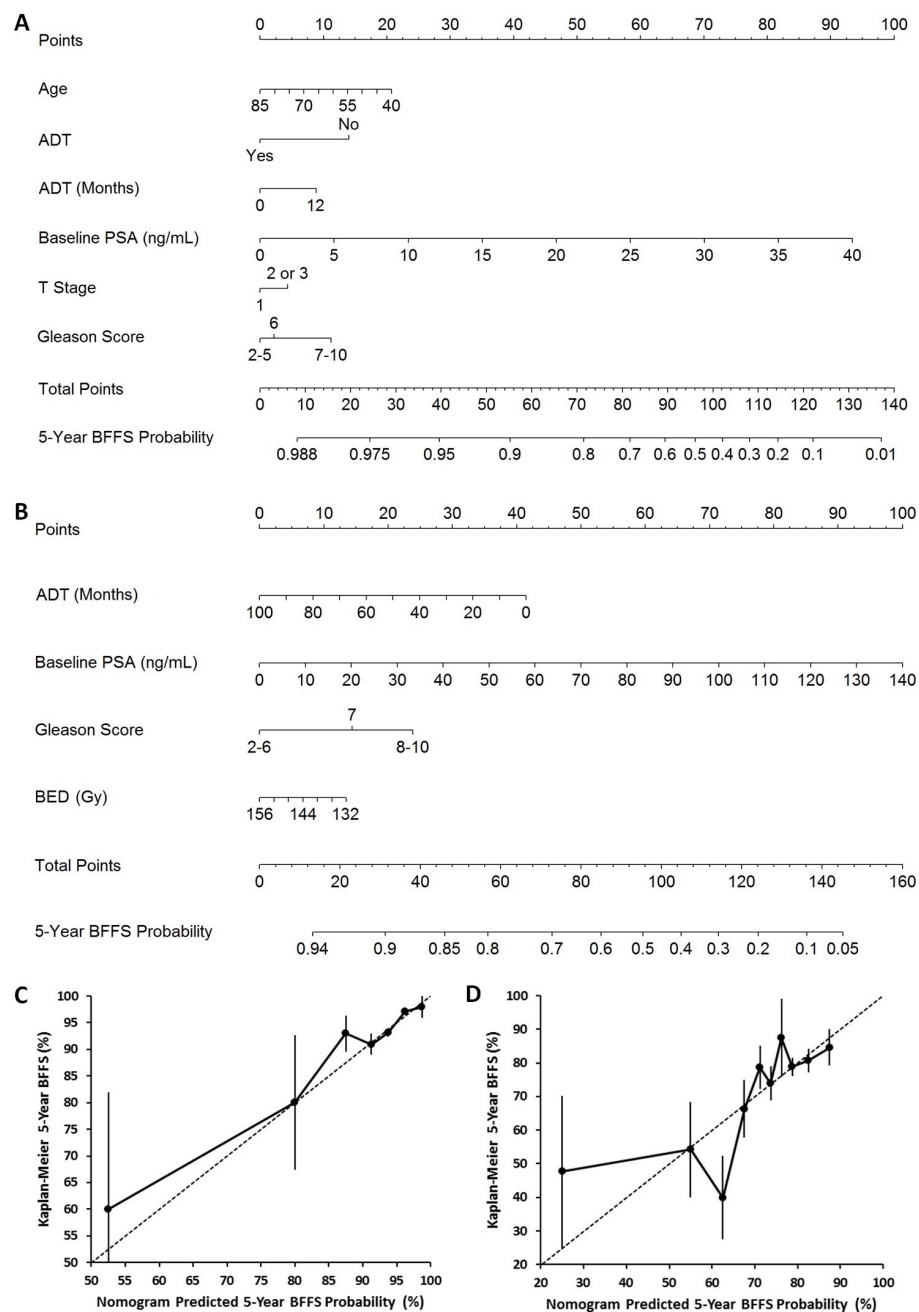


FIGURE 2: Nomograms and corresponding calibration plots predicting 5-year ASTRO II “Phoenix” Biochemical Failure-Free Survival for (A,C) LDR Brachytherapy only (n=4208) and (B,D) EBRT only (n=822).

Discussion

This investigation presented a comprehensive set of clinical nomograms to predict for 5-year BFFS separately for patients receiving LDR brachytherapy and conventionally fractionated EBRT based on a large multi-institutional database. It additionally presented a systematic data-driven approach to the development of each nomogram incorporating only those factors shown to be associated with BFFS in the examined database. For LDR brachytherapy, age, ADT duration, and baseline PSA emerged as important predictors of BFFS from both univariable and multivariable analysis and, to a lesser degree, whether or not patients received ADT and Gleason score. For EBRT, baseline PSA, T stage, Gleason score, BED, and positive core percentage were significant independent predictors of BFFS, with particular importance observed for baseline PSA and Gleason score being significant from multivariable analysis.

The importance of key prognostic factors established in the literature (pre-treatment PSA, T stage, and

Gleason score) was also demonstrated in the current study. However, this effect was prevalent more for pre-treatment PSA and Gleason score, with both variables being represented in each nomogram. T stage was only incorporated into the nomogram for the LDR brachytherapy cohort based on the a priori specified criteria for inclusion in multivariable regression models ($p < 0.20$). Upon further examination, T stage was shown to be an independent significant predictor of BFFS ($p = 0.047$) for the EBRT cohort but was only somewhat associated with BFFS for the LDR brachytherapy cohort ($p = 0.101$). Similar nomograms predictive of either BFFS or OS have also been published omitting T stage [10, 18, 23, 27-28]. In contrast, pre-treatment PSA, T stage, and Gleason score were shown to be predictive of BFFS from multivariable regression reported for the entire GUROC ProCaRS database, which pooled data from patients receiving a variety of radiotherapy approaches [44]. This suggests that the process of creating more homogeneous cohorts of patients by restricting to only one type of radiotherapy and range of delivered dose, in addition to incorporating landmark analysis techniques, may be the primary contributing factor to explaining the observed differences.

Additionally, although the majority of published nomograms incorporate the same set of prognostic factors, it is unclear to what extent each of these factors remained as statistically significant predictors of BFFS across the different patient populations. In cases where only the nomogram is presented without a corresponding multivariable Cox regression model, there is no available mechanism to determine the significance level of a prognostic factor, only the relative importance based on the length of the predictor scales. For instance, with nomograms presented as a series of dichotomous prognostic factors, visual comparisons between adjacent prognostic factors can provide a reliable means to determine the relative importance of each and enable the observer to sort the variables in order of ascending or descending importance.

This analysis demonstrated that the use and duration of ADT administration had impacts on 5-year BFFS for both treatment cohorts. For LDR brachytherapy, the use of ADT (HR: 0.53; 95% CI: 0.37-0.76, $p < 0.001$) was shown to have a protective impact within the first 12 months following treatment, as shown in Figure 2. Given the relatively low number of patients in the LDR brachytherapy cohort receiving ADT for one year or beyond (3.7%), questions still remain regarding the magnitude of benefit of prescribing ADT beyond one year following LDR brachytherapy, which could be addressed in the context of future clinical studies. For EBRT, increasing duration of ADT administration was found to provide a modest protective effect without a time constraint contrary to LDR brachytherapy (HR: 0.99, 95% CI: 0.97-1.00, $p = 0.092$) and is consistent with previously published comparisons of EBRT versus EBRT + ADT [51-52]. Although the nomogram developed for the EBRT cohort incorporates a wide duration for ADT use, this is reflective of a comparatively more heterogeneous patient population with only 18% and 8% receiving ADT for at least two and three years, respectively.

The current study reports on retrospectively collected data from a variety of Canadian institutions, which may not be entirely representative of the greater Canadian population. Although the ProCaRS database underwent extensive quality assurances to improve data quality and accuracy as reported previously [43-44], heterogeneity in data collection procedures across institutions may still be present. Changes in treatment delivery and data entry may have occurred during the data collection period. Additionally, the database contains a wide range of parameters, including prognostic factors, treatment details, and survival-based outcomes; however, toxicity, comorbidity, and other important prognostic factors were not collected and were thus unavailable to assist in explaining the observations reported in the current study. The ability to evaluate long-term outcomes was also limited due to the few numbers of patients with observed follow-up durations in excess of 10 years, which factored into the decision to only report on biochemical outcomes.

Future publications will focus on updates to the proposed nomograms and explore OS outcomes once sufficient follow-up data has been collected. In order to perform extensive multivariable regression analyses required for nomogram development, the final reported nomograms are reflective of only those patients with complete data for all variables under investigation. As a result, positive core biopsy information was only reported in univariable analysis procedures due to elevated rates of missing data. Patients receiving HDR-brachytherapy, plus EBRT, as reported in previous work were not examined due to fewer numbers of eligible patients available for analysis [43-44]. Although clinically useful, patients receiving EBRT were not examined separately according GUROC intermediate- versus high-risk classification given the insufficient statistical power. Future work examining a more extensive range of prognostic factors and comorbidities would provide a useful context for the presented work.

Conclusions

This investigation developed and validated a set of clinical nomograms examining 5-year biochemical failure-free survival for patients with localized prostate cancer receiving either low-dose rate brachytherapy or conventionally fractionated external beam radiation therapy. This work is an extension of a Canadian multi-institutional initiative directed at the improvement of existing risk stratification tools. Future work should be directed at examining the role of additional prognostic factors, comorbidities, and toxicity data in predicting survival-based outcomes.

Additional Information

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue.

Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** Tom Pickles declare(s) personal fees from Abbvie, Amgen, Astellas and Janssen. Advisory board. Himu Lukka declare(s) Clinical trials from Bayer, Janssen, Sanofi and Astra-Zeneca. Juanita Crook declare(s) personal fees from Ferring and Abbvie. Participating in lectures. Charles Catton declare(s) personal fees from Abbvie, Bayer and Paladin. CME program speaker. Charles Catton declare(s) a grant from Abbvie, Bayer and Paladin. Clinical research fellow. Tom Pickles declare(s) personal fees from Abbvie. CME program speaker. Charles Catton declare(s) Clinical trials from NCIC-CTG, OCOG. PR-13 (NCIC-CTG) and PROFIT (OCOG). Himu Lukka declare(s) personal fees from Janssen, Astellas, Amgen, Abbvie, Bayer, Actavis, Sanofi and Astra-Zeneca. Member of advisory boards, speakers bureau. Tom Pickles declare(s) Clinical trials from Sanofi. George Rodrigues declare(s) a grant from Ontario Institute of Cancer Research. High Impact Clinical Trials. George Rodrigues declare(s) a grant from Canadian Association of Radiation Oncology. ACURA. George Rodrigues declare(s) a grant from Janssen Inc. George Rodrigues declare(s) a grant from Motorcycle Ride for Dad (London Chapter). **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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References

1. Lukka H, Warde P, Pickles T, Morton G, Brundage M, Souhami L; Canadian GU Radiation Oncologist Group: Controversies in prostate cancer radiotherapy: consensus development . *Can J Urol*. 2001, 8:1314–1322.
2. Keyes M, Crook J, Morris WJ, Morton G, Pickles T, Usmani N, Vigneault E: Canadian prostate brachytherapy in 2012. *Can Urol Assoc J*. 2013, 7:51–58. [10.5489/cuaj.218](#)
3. Rodrigues G, Warde P, Pickles T, Crook J, Brundage M, Souhami L, Lukka H; Genitourinary Radiation Oncologists of Canada: Pre-treatment risk stratification of prostate cancer patients: A critical review . *Can Urol Assoc J*. 2012, 6:121–127. [10.5489/cuaj.11085](#)
4. Zelefsky MJ, Kattan MW, Fearn P, Fearon BL, Stasi JP, Shippy AM, Scardino PT: Pretreatment nomogram predicting ten-year biochemical outcome of three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for prostate cancer. *Urology*. 2007, 70:283–287. [10.1016/j.urology.2007.03.060](#)
5. Kattan MW, Zelefsky MJ, Kupelian PA, Scardino PT, Fuks Z, Leibel SA: Pretreatment nomogram for predicting the outcome of three-dimensional conformal radiotherapy in prostate cancer. *J Clin Oncol*. 2000, 18:3352–3359.
6. Kattan MW, Leung DH, Brennan MF: Postoperative nomogram for 12-year sarcoma-specific death . *J Clin Oncol*. 2002, 20:791–796. [10.1200/JCO.20.3.791](#)
7. Kattan MW, Zelefsky MJ, Kupelian PA, Cho D, Scardino PT, Fuks Z, Leibel SA: Pretreatment nomogram that predicts 5-year probability of metastasis following three-dimensional conformal radiation therapy for localized prostate cancer. *J Clin Oncol*. 2003, 21:4568–4571. [10.1200/JCO.2003.05.046](#)
8. Mitchell JA, Cooperberg MR, Elkin EP, Lubeck DP, Mehta SS, Kane CJ, Carroll PR: Ability of 2 pretreatment risk assessment methods to predict prostate cancer recurrence after radical prostatectomy: data from CaPSURE. *J Urol*. 2005, 173:1126–1131. [10.1097/01.ju.0000155535.25971.de](#)
9. Sutcliffe P, Hummel S, Simpson E, Young T, Rees A, Wilkinson A, Hamdy F, Clarke N, Staffurth J: Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review. *Health Technol Assess*. 2009, 13:iii, xi–xiii 1–219. [10.3310/hta13050](#)
10. Sanpaolo P, Barbieri V, Genovesi D: Biologically effective dose and definitive radiation treatment for localized prostate cancer: treatment gaps do affect the risk of biochemical failure. *Strahlenther Onkol*. 2014, 190:732–738. [10.1007/s00066-014-0642-0](#)
11. Stoyanova R, Pahlajani NH, Egleston BL, Buyyounouski MK, Chen DY, Horwitz EM, Pollack A: The impact of dose-escalated radiotherapy plus androgen deprivation for prostate cancer using 2 linked nomograms. *Cancer*. 2013, 119:1080–1088. [10.1002/ncr.27857](#)
12. Zelefsky MJ, Pei X, Chou JF, Schechter M, Kollmeier M, Cox B, Yamada Y, Fidaleo A, Sperling D, Happersett L, Zhang Z: Dose escalation for prostate cancer radiotherapy: predictors of long-term biochemical tumor control and distant metastases-free survival outcomes. *Eur Urol*. 2011, 60:1133–1139. [10.1016/j.eururo.2011.08.029](#)
13. Westphalen AC, Koff WJ, Coakley FV, Muglia VF, Neuhaus JM, Marcus RT, Kurhanewicz J, Smith-Bindman R: Prostate cancer: prediction of biochemical failure after external-beam radiation therapy--Kattan nomogram and endorectal MR imaging estimation of tumor volume. *Radiology*. 2011, 261:477–486. [10.1148/radiol.11110457](#)
14. Spiess PE, Katz AE, Chin JL, Bahn D, Cohen JK, Shinohara K, Hernandez M, Bossier J, Kassouf W, Pisters LL: A pretreatment nomogram predicting biochemical failure after salvage cryotherapy for locally recurrent prostate cancer. *BJU Int*. 2010, 106:194–198. [10.1111/j.1464-410X.2009.09078.x](#)
15. Williams SG, Buyyounouski MK, Pickles T, Kestin L, Martinez A, Hanlon AL, Duchesne GM: Percentage of

- biopsy cores positive for malignancy and biochemical failure following prostate cancer radiotherapy in 3,264 men: statistical significance without predictive performance. *Int J Radiat Oncol Biol Phys.* 2008, 70:1169–1175. [10.1016/j.ijrobp.2007.08.021](https://doi.org/10.1016/j.ijrobp.2007.08.021)
16. Williams SG, Duchesne GM, Gogna NK, Millar JL, Pickles T, Pratt GR, Turner S: An international multicenter study evaluating the impact of an alternative biochemical failure definition on the judgment of prostate cancer risk. *Int J Radiat Oncol Biol Phys.* 2006, 65:351–357. [10.1016/j.ijrobp.2005.12.007](https://doi.org/10.1016/j.ijrobp.2005.12.007)
17. Parker CC, Norman AR, Huddart RA, Horwich A, Dearnaley DP: Pre-treatment nomogram for biochemical control after neoadjuvant androgen deprivation and radical radiotherapy for clinically localised prostate cancer. *Br J Cancer.* 2002, 86:686–691. [10.1038/sj.bjc.6600160](https://doi.org/10.1038/sj.bjc.6600160)
18. Walz J, Gallina A, Saad F, Montorsi F, Perrotte P, Shariat SF, Jeldres C, Graefen M, Bénard F, McCormack M, Valiquette L, Karakiewicz PI: A nomogram predicting 10-year life expectancy in candidates for radical prostatectomy or radiotherapy for prostate cancer. *J Clin Oncol.* 2007, 25:3576–3581. [10.1200/JCO.2006.10.3820](https://doi.org/10.1200/JCO.2006.10.3820)
19. Slovin SF, Wilton AS, Heller G, Scher HI: Time to detectable metastatic disease in patients with rising prostate-specific antigen values following surgery or radiation therapy. *Clin Cancer Res.* 2005, 11:8669–8673. [10.1158/1078-0432.CCR-05-1668](https://doi.org/10.1158/1078-0432.CCR-05-1668)
20. D'Amico AV, Whittington R, Malkowicz SB, Fondurulia J, Chen MH, Kaplan I, Beard CJ, Tomaszewski JE, Renshaw AA, Wein A, Coleman CN: Pretreatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. *J Clin Oncol.* 1999, 17:168–172.
21. Abdollah F, Karnes RJ, Suardi N, Cozzarini C, Gandaglia G, Fossati N, Bianchi M, Boorjian SA, Sun M, Karakiewicz PI, Montorsi F, Briganti A: Predicting survival of patients with node-positive prostate cancer following multimodal treatment. *Eur Urol.* 2014, 65:554–562. [10.1016/j.eururo.2013.09.025](https://doi.org/10.1016/j.eururo.2013.09.025)
22. Briganti A, Karnes RJ, Joniau S, Boorjian SA, Cozzarini C, Gandaglia G, Hinkelbein W, Haustermans K, Tombal B, Shariat S, Sun M, Karakiewicz PI, Montorsi F, Van Poppel H, Wiegel T: Prediction of outcome following early salvage radiotherapy among patients with biochemical recurrence after radical prostatectomy. *Eur Urol.* 2014, 66:479–86. [10.1016/j.eururo.2013.11.045](https://doi.org/10.1016/j.eururo.2013.11.045)
23. Abdollah F, Boorjian S, Cozzarini C, Suardi N, Sun M, Fiorino C, di Muzio N, Karakiewicz PI, Montorsi F, Karnes RJ, Briganti A: Survival following biochemical recurrence after radical prostatectomy and adjuvant radiotherapy in patients with prostate cancer: the impact of competing causes of mortality and patient stratification. *Eur Urol.* 2013, 64:557–564. [10.1016/j.eururo.2013.03.006](https://doi.org/10.1016/j.eururo.2013.03.006)
24. Porter CR, Suardi N, Capitanio U, Hutterer GC, Kodama K, Gibbons RP, Correa R Jr, Perrotte P, Montorsi F, Karakiewicz PI: A nomogram predicting prostate cancer-specific mortality after radical prostatectomy. *Urol Int.* 2010, 84:132–140. [10.1159/000277588](https://doi.org/10.1159/000277588)
25. Porter CR, Suardi N, Kodama K, Capitanio U, Gibbons RP, Correa R, Jeldres C, Perrotte P, Montorsi F, Karakiewicz PI: A nomogram predicting metastatic progression after radical prostatectomy. *Int J Urol.* 2008, 15:889–894. [10.1111/j.1442-2042.2008.02105.x](https://doi.org/10.1111/j.1442-2042.2008.02105.x)
26. Suardi N, Porter CR, Reuther AM, Walz J, Kodama K, Gibbons RP, Correa R, Montorsi F, Graefen M, Huland H, Klein EA, Karakiewicz PI: A nomogram predicting long-term biochemical recurrence after radical prostatectomy. *Cancer.* 2008, 112:1254–1263. [10.1002/cncr.23293](https://doi.org/10.1002/cncr.23293)
27. Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, Anscher MS, Michalski JM, Sandler HM, Lin DW, Forman JD, Zelefsky MJ, Kestin LL, Roehrborn CG, Catton CN, DeWeese TL, Liauw SL, Valicenti RK, Kuban DA, Pollack A: Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol.* 2007, 25:2035–2041. [10.1200/JCO.2006.08.9607](https://doi.org/10.1200/JCO.2006.08.9607)
28. Stephenson AJ, Scardino PT, Eastham JA, Bianco FJ Jr, Dotan ZA, DiBlasio CJ, Reuther A, Klein EA, Kattan MW: Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. *J Clin Oncol.* 2005, 23:7005–7012. [10.1200/JCO.2005.01.867](https://doi.org/10.1200/JCO.2005.01.867)
29. Zelefsky MJ, Chou JF, Pei X, Yamada Y, Kollmeier M, Cox B, Zhang Z, Schechter M, Cohen GN, Zaider M: Predicting biochemical tumor control after brachytherapy for clinically localized prostate cancer: The Memorial Sloan-Kettering Cancer Center experience. *Brachytherapy.* 2012, 11:245–249. [10.1016/j.brachy.2011.08.003](https://doi.org/10.1016/j.brachy.2011.08.003)
30. Potters L, Roach M 3rd, Davis BJ, Stock RG, Ciezki JP, Zelefsky MJ, Stone NN, Fearn PA, Yu C, Shinohara K, Kattan MW: Postoperative nomogram predicting the 9-year probability of prostate cancer recurrence after permanent prostate brachytherapy using radiation dose as a prognostic variable. *Int J Radiat Oncol Biol Phys.* 2010, 76:1061–1065. [10.1016/j.ijrobp.2009.03.031](https://doi.org/10.1016/j.ijrobp.2009.03.031)
31. Kattan MW, Potters L, Blasko JC, Beyer DC, Fearn P, Cavanagh W, Leibel S, Scardino PT: Pretreatment nomogram for predicting freedom from recurrence after permanent prostate brachytherapy in prostate cancer. *Urology.* 2001, 58:393–399. [10.1016/S0090-4295\(01\)01233-X](https://doi.org/10.1016/S0090-4295(01)01233-X)
32. Fellin G, Rancati T, Fiorino C, Vavassori V, Antognoni P, Baccolini M, Bianchi C, Cagna E, Borca VC, Girelli G, Iacopino B, Maliverni G, Mauro FA, Menegotti L, Monti AF, Romani F, Stasi M, Valdagni R: Long term rectal function after high-dose prostate cancer radiotherapy: results from a prospective cohort study. *Radiother Oncol.* 2014, 110:272–277. [10.1016/j.radonc.2013.09.028](https://doi.org/10.1016/j.radonc.2013.09.028)
33. Fiorino C, Rancati T, Fellin G, Vavassori V, Cagna E, Casanova Borca V, Girelli G, Menegotti L, Monti AF, Tortoreto F, Delle Canne S, Valdagni R: Late fecal incontinence after high-dose radiotherapy for prostate cancer: better prediction using longitudinal definitions. *Int J Radiat Oncol Biol Phys.* 2012, 83:38–45. [10.1016/j.ijrobp.2011.06.1953](https://doi.org/10.1016/j.ijrobp.2011.06.1953)
34. Valdagni R, Kattan MW, Rancati T, Yu C, Vavassori V, Fellin G, Cagna E, Gabriele P, Mauro FA, Baccolini M, Bianchi C, Menegotti L, Monti AF, Stasi M, Giganti MO, Fiorino C: Is it time to tailor the prediction of radio-induced toxicity in prostate cancer patients? Building the first set of nomograms for late rectal syndrome. *Int J Radiat Oncol Biol Phys.* 2012, 82:1957–1966. [10.1016/j.ijrobp.2011.03.028](https://doi.org/10.1016/j.ijrobp.2011.03.028)
35. Valdagni R, Rancati T, Fiorino C, Fellin G, Magli A, Baccolini M, Bianchi C, Cagna E, Greco C, Mauro FA, Monti AF, Munoz F, Stasi M, Franzoni P, Vavassori V: Development of a set of nomograms to predict acute lower gastrointestinal toxicity for prostate cancer 3D-CRT. *Int J Radiat Oncol Biol Phys.* 2008, 71:1065–1073. [10.1016/j.ijrobp.2007.11.037](https://doi.org/10.1016/j.ijrobp.2007.11.037)

36. Chipman JJ, Sanda MG, Dunn RL, Wei JT, Litwin MS, Crociani CM, Regan MM, Chang P, PROST-QA Consortium: Measuring and predicting prostate cancer related quality of life changes using EPIC for clinical practice. *J Urol*. 2014, 191:638–645. [10.1016/j.juro.2013.09.040](https://doi.org/10.1016/j.juro.2013.09.040)
37. Mathieu R, Arango JD, Beckendorf V, Delobel JB, Messai T, Chira C, Bossi A, Le Pris   E, Guerif S, Simon JM, Dubray B, Zhu J, Lagrange JL, Pommier P, Gnep K, Acosta O, De Crevoisier R: Nomograms to predict late urinary toxicity after prostate cancer radiotherapy. *World J Urol*. 2014, 32:743–751. [10.1007/s00345-013-1146-8](https://doi.org/10.1007/s00345-013-1146-8)
38. Roeloffzen EM, van Vulpen M, Battermann JJ, van Roermund JG, Saibishkumar EP, Monninkhof EM: Pretreatment nomogram to predict the risk of acute urinary retention after I-125 prostate brachytherapy. *Int J Radiat Oncol Biol Phys*. 2011, 81:737–744. [10.1016/j.ijrobp.2010.06.009](https://doi.org/10.1016/j.ijrobp.2010.06.009)
39. Bowes D, Crook JM, Wallace K, Evans A, Toi A, Finelli A, Jewett MA, Fleshner N, Catton C: Results of a surgically derived nomogram to predict Gleason score upgrading applied to a cohort of patients with "favorable-risk" prostate cancer treated with permanent seed brachytherapy. *Urology*. 2012, 80:649–655. [10.1016/j.urology.2012.03.051](https://doi.org/10.1016/j.urology.2012.03.051)
40. Bud  us L, Graefen M, Salomon G, Isbarn H, Lughezzani G, Sun M, Chun FK, Schlomm T, Steuber T, Haese A, Koellermann J, Sauter G, Fisch M, Heinzer H, Huland H, Karakiewicz PI: The novel nomogram of Gleason sum upgrade: possible application for the eligible criteria of low dose rate brachytherapy. *Int J Urol*. 2010, 17:862–868. [10.1111/j.1442-2042.2010.02615.x](https://doi.org/10.1111/j.1442-2042.2010.02615.x)
41. Kulkarni GS, Lockwood G, Evans A, Toi A, Trachtenberg J, Jewett MAS, Finelli A, Fleshner NE: Clinical predictors of Gleason score upgrading: Implications for patients considering watchful waiting, active surveillance, or brachytherapy. *Cancer*. 2007, 109:2432–2438. [10.1002/cncr.22712](https://doi.org/10.1002/cncr.22712)
42. Roach M 3rd, Hanks G, Thames H Jr, Schellhammer P, Shipley WU, Sokol GH, Sandler H: Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys*. 2006, 65:965–974. [10.1016/j.ijrobp.2006.04.029](https://doi.org/10.1016/j.ijrobp.2006.04.029)
43. Rodrigues G, Lukka H, Warde P, Brundage M, Souhami L, Crook J, Cury F, Catton , Mok G, Martin AG, Vigneault E, Morris J, Warner A, Maldonado SG, Pickles T, on behalf of the Genitourinary Radiation Oncologists of Canada (GUROC): The prostate cancer risk stratification (ProCaRS) project: Recursive partitioning risk stratification analysis. *Radiother Oncol*. 2013, 109:204–210. [10.1016/j.radonc.2013.07.020](https://doi.org/10.1016/j.radonc.2013.07.020)
44. Rodrigues G, Lukka H, Warde P, Brundage M, Souhami L, Crook J, Cury F, Catton C, Mok G, Martin AG, Vigneault E, Morris J, Warner A, Maldonado SG, Pickles T, Genitourinary Radiation Oncologists of Canada: The prostate cancer risk stratification project: database construction and risk stratification outcome analysis. *J Natl Compr Canc Netw*. 2014, 12:60–69.
45. Smith GD, Pickles T, Crook J, Martin AG, Vigneault E, Cury FL, Morris J, Catton C, Lukka H, Warner A, Yang Y, Rodrigues G: Brachytherapy improves biochemical failure-free survival in low- and intermediate-risk prostate cancer compared with conventionally fractionated external beam radiation therapy: a propensity score matched analysis. *Int J Radiat Oncol Biol Phys*. 2015, 91:505–516. [10.1016/j.ijrobp.2014.11.018](https://doi.org/10.1016/j.ijrobp.2014.11.018)
46. Park HS, Gross CP, Makarov DV, Yu JB: Immortal time bias: a frequently unrecognized threat to validity in the evaluation of postoperative radiotherapy. *Int J Radiat Oncol Biol Phys*. 2012, 83:1365–1373. [10.1016/j.ijrobp.2011.10.025](https://doi.org/10.1016/j.ijrobp.2011.10.025)
47. Giobbie-Hurder A, Gelber RD, Regan MM: Challenges of guarantee-time bias. *J Clin Oncol*. 2013, 31:2963–2969. [10.1200/JCO.2013.49.5283](https://doi.org/10.1200/JCO.2013.49.5283)
48. Dafni U: Landmark analysis at the 25-year landmark point. *Circ Cardiovasc Qual Outcomes*. 2011, 4:363–371. [10.1161/CIRCOUTCOMES.110.957951](https://doi.org/10.1161/CIRCOUTCOMES.110.957951)
49. Anderson JR, Cain KC, Gelber RD: Analysis of survival by tumor response. *J Clin Oncol*. 1983, 1:710–719.
50. Thompson A, Keyes M, Pickles T, Palma D, Moravan V, Spadinger I, Lapointe V, Morris WJ: Evaluating the Phoenix definition of biochemical failure after (125)I prostate brachytherapy: Can PSA kinetics distinguish PSA failures from PSA bounces?. *Int J Radiat Oncol Biol Phys*. 2010, 78:415–421. [10.1016/j.ijrobp.2009.07.1724](https://doi.org/10.1016/j.ijrobp.2009.07.1724)
51. Schmidt-Hansen M, Hoskin P, Kirkbride P, Hasler E, Bromham N: Hormone and radiotherapy versus hormone or radiotherapy alone for non-metastatic prostate cancer: a systematic review with meta-analyses. *Clin Oncol (R Coll Radiol)*. 2014, 26:e21–46. [10.1016/j.clon.2014.06.016](https://doi.org/10.1016/j.clon.2014.06.016)
52. Williams S, Buyyounouski M, Kestin L, Duchesne G, Pickles T: Predictors of androgen deprivation therapy efficacy combined with prostatic irradiation: the central role of tumor stage and radiation dose. *Int J Radiat Oncol Biol Phys*. 2011, 79:724–731. [10.1016/j.ijrobp.2009.11.044](https://doi.org/10.1016/j.ijrobp.2009.11.044)