

# 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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Disclosures can be found in Additional Information at the end of the article

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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  $\geq 144$  Gy (n=4208) or (2) EBRT  $\geq 70$  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  $64 \pm 7$  years, a mean baseline PSA of  $6.3 \pm 3.0$  ng/mL, 75% had a Gleason 6, and 15% had a Gleason 7, whereas patients receiving EBRT had a mean age of  $70 \pm 6$  years, a mean baseline PSA of  $11.6 \pm 10.7$  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.

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| Author(s)          | Year | Article Type  | N    | Treatment | 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                |
| Spies, 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

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.

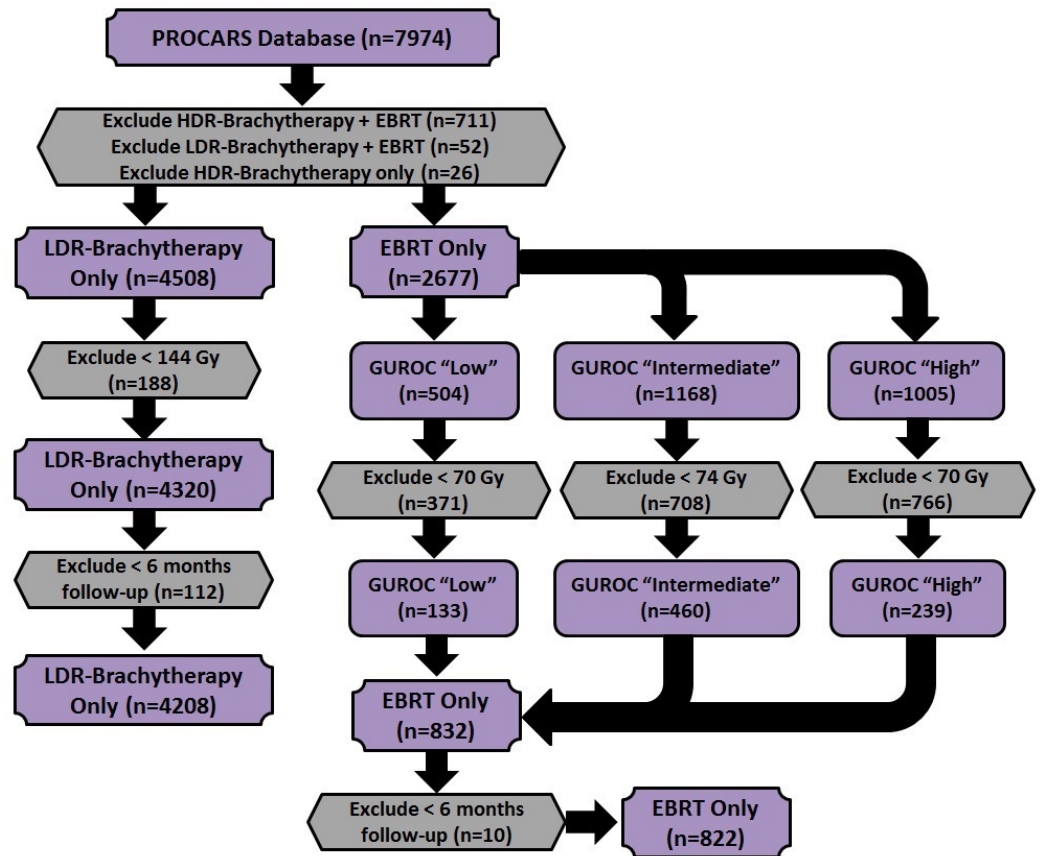
## Materials And Methods

### 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  $\geq 144$  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  $\geq 70$  Gy (GUROC low-risk and high-risk) or  $\geq 74$  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  $\leq 0.5$  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  $\alpha/\beta$  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  $64 \pm 7$  years; mean baseline PSA was  $6.3 \pm 3.0$  ng/mL; 55% and 45% had T1 and T2 disease, respectively; 75% had Gleason 6 and 15% had Gleason 7; 27% had  $\geq 50\%$  positive core biopsies; 38% received ADT (36% for  $\geq 6$  months; 3.7% for  $\geq 1$  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  $70 \pm 6$  years; mean baseline PSA was  $11.6 \pm 10.7$  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  $\geq 50\%$  positive core biopsies; 49% received ADT (18% for  $\geq 2$  years; 8% for  $\geq 3$  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 $\pm$ 7.20      | 64.35 $\pm$ 7.03  | 70.23 $\pm$ 5.99  |
| Age – mean $\pm$ 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)         |
| EBRT: Dose per fraction (Gy) – mean ± SD, median, (min, max)        | 822  | 1.93 ± 0.07      | --             | 1.93 ± 0.07      |
|   |      | 1.90             | --             | 1.90             |
|   |      | (1.80, 2.11)     | --             | (1.80, 2.11)     |
| EBRT: Biological effective dose (Gy)– mean ± SD, median, (min, max) | 822  | 150.08 ± 5.95    | --             | 150.08 ± 5.95    |
|   |      | 148.00           | --             | 148.00           |
|   |      | (136.80, 156.00) | --             | (136.80, 156.00) |
| ADT – n(%)  | 5030 | 1995 (39.7)      | 1589 (37.8)    | 406 (49.4)       |
| ADT (months) – mean ± SD, median, (min, max)                        | 1738 | 7.89 ± 8.13      | 6.08 ± 4.99    | 13.89 ± 12.52    |
|   |      | 5.88             | 5.75           | 9.33             |
|   |      | (0.30, 132.67)   | (0.30, 132.67) | (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<br>(0.50, 15.15) | 5.55<br>(0.50, 15.15) | 7.10<br>(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 |         |               |         |
|-------------------------------------|--|---------|---------------|---------|
|                                     | Univariable  |         | Multivariable |         |
| (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             |              | **0.218 |               | **0.080 |
| 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                   |              | **0.047 |               | --      |
| 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             |              | **0.002 |               | **0.005 |
| 7 vs 2-6                  | 1.52         | 0.011   | 1.53          | 0.010   |
|                           | (1.10, 2.09) |         | (1.11, 2.10)  |         |

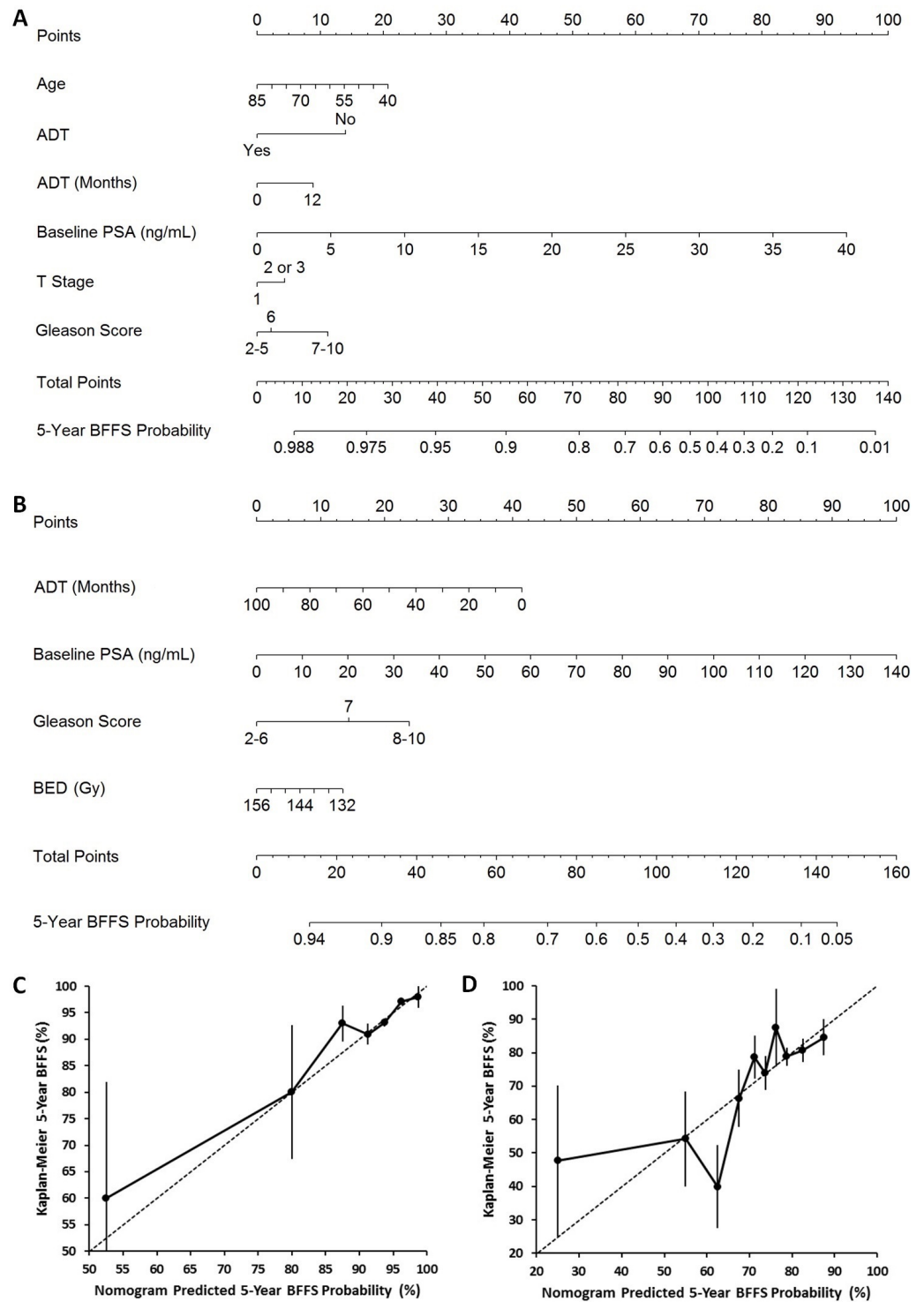
|                                |              |         |              |       |
|--------------------------------|--------------|---------|--------------|-------|
| 8-10 vs 2-6                    | 2.05         | < 0.001 | 2.01         | 0.003 |
|                                | (1.36, 3.11) |         | (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 to 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

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