Original Article

The Prostate Cancer Risk Stratification Project: Database Construction and Risk Stratification Outcome Analysis

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Abstract

This investigation reports on the biochemical and clinical outcomes of a newly created pan-Canadian Prostate Cancer Risk Stratification (ProCaRS) database developed by the Genitourinary Radiation Oncologists of Canada (GUROC). GUROC ProCaRS template-compliant data on 7974 patients who underwent radiotherapy were received from 7 unique databases. Descriptive analysis, Cox proportional hazards, and Kaplan-Meier analyses were performed using American Society for Radiation Oncology (ASTRO) biochemical failure-free survival (BFFS), prostate cancer–specific survival, and overall survival. Multivariable modeling for the primary ASTRO BFFS end point showed that age, prostate-specific antigen, T stage, and Gleason score and components such as hormonal therapy, and radiation treatment (brachytherapy with better outcome than external-beam) were predictive of outcome. Kaplan-Meier analysis of the existing GUROC and new NCCN classification system both showed good separation of all clinical outcome curves. The construction of a pan-Canadian database has informed important prostate cancer radiotherapy outcomes and risk stratification. (*J Natl Compr Canc Netw* 2014;12:60–69)

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The management of nonmetastatic prostate cancer is complex because of the interplay of multiple considerations, including risk stratification, relative treatment efficacy/toxicity, competing risk of death from cancer versus other causes, and patient preferences.[1] Published randomized controlled trials support the use of radiotherapy in the primary[2] and postoperative[3] settings, with other randomized controlled trials assessing appropriate dosing of external-beam radiotherapy[4] and the concomitant use of hormonal therapy.[5] Alternatives to dose-escalated external-beam radiotherapy include low-dose-rate (LDR)[6] and high-dose-rate (HDR)[7] brachytherapy (with or without integrated external-beam radiation therapy), hypofractionated radiation therapy,[8] stereotactic body radiation therapy,[9] and particle therapy.[10] Various clinical trials have been initiated to further define best practices for the use of radiotherapy either alone or in combination with other treatments.

Multiple pretreatment risk stratification systems have been published to support decision-making, interphysician communication, clinical trial stratification/design, and outcome reporting in nonmetastatic prostate cancer. Five unique commonly used systems (not exhaustive) have been described in the literature, including

- Harvard[11]/American Urological Association[12]/European Association of Urology[13]

- Genitourinary Radiation Oncologists of Cancer (GUROC)[14]/National Institute for Health and Clinical Excellence[15]
- Cancer of the Prostate Strategic Research Endeavour (CaPSURE)[16]
- European Society of Medical Oncology[17]
- NCCN[18,19]

Despite the proliferation of publications on prostate cancer prognostic factors and risk stratification systems, the definition of a universally accepted classification system with superior statistical and clinical decision-making properties is still required.[20] In a recent review of pretreatment prostate cancer risk stratification, 4 specific improvements to risk stratification systems were identified, including 1) the definition of a very-low-risk category that would be appropriate for surveillance strategies, 2) reassessment of the interface between intermediate risk and high risk, 3) the definition of a new extreme-risk category, and 4) division of the intermediate-risk category into 2 subgroups.[21] The latest NCCN risk stratification system has addressed 3 or 4 of these potential improvements (ie, very-low-risk category, change of the intermediate- and high-risk interface, and the definition of a very-high-risk category) with the creation of a 5-group risk stratification system.[18,19] The ability of this new system to categorize patients into distinct clinical outcomes group has not been previously assessed; however, the previous 3-group NCCN system compared favorably with the American Joint Committee on Cancer Staging system in a recent publication.[22]

This investigation reports on the creation and clinical outcomes related to a pan-Canadian Prostate Cancer Risk Stratification (ProCaRS) radiotherapy database, which was constructed to explore various risk stratification issues in prostate cancer. This database will also explore the statistical properties of the 5-group NCCN risk stratification system for the prediction of clinical prostate cancer outcomes.

Materials and Methods

The GUROC ProCaRS Database

A GUROC ProCaRS database template based on the British Columbia Cancer Agency (BCCA) cancer database[23] was created and approved for dissemination to all Canadian investigators with potential databases for inclusion in this national database project. Primary ethics approval was obtained from the Western University Research Ethics Board (London, ON, Canada), with secondary ethics approvals obtained at all participating sites before data exchange. ProCaRS template–compliant data on 7974 patients who underwent radiotherapy were received from 4 institutions (BCCA; n=3771 [47%]), Princess Margaret Hospital (PMH; n=1752 [22%]), McGill (n=194 [3%]), and Laval (n=2257 [28%]), with a total of 7 unique databases, and locked for analysis on October 15, 2011. These 7 databases included a provincial database (BCCA, n=3771 [47%]), 2 LDR brachytherapy databases (PMH, n=1163 [15%] and Laval, n=1630 [20%]), 1 combined HDR plus external-beam radiotherapy database (Laval, n=627 [8%]), and 3 external-beam databases (PMH dose-escalation, n=401 [5%]; PMH neoadjuvant Casodex study #9907, n=188 [2.5%]; and McGill radiotherapy, n=194 [2.5%]).

Database Quality Assurance and Clinical Outcomes

An extensive quality assurance program was initiated to confirm database quality, including various error checking, missing data minimization, and outcome confirmation procedures. Risk stratification categories were calculated from the available information in the ProCaRS database, including GUROC 3-group[14] and NCCN 5-group[18,19] risk stratification. In terms of GUROC risk stratification, the following risk groups have been defined:

- Low-risk: 1997 AJCC T1–T2a, prostate-specific antigen (PSA) ≤10 ng/mL, and Gleason score ≤6
- Intermediate-risk: 1997 AJCC T1–T2, PSA ≤20 ng/mL, and Gleason score ≤7 not otherwise low-risk
- High-risk: 1997 AJCC T3–T4 or PSA >20 ng/mL, or Gleason score 8–10

The current NCCN risk categories[18,19] are defined as:

- Very-low-risk: T1c, Gleason score ≤6, PSA <10, <3 biopsy cores positive, ≤50% cancer in each core, and PSA density <0.15 ng/mL/g
- Low-risk: T1–T2a, Gleason score 2–6, and PSA <10 not very-low-risk
- Intermediate-risk: T2b or T2c, and/or Gleason score 7, and/or PSA 10–20 not low-risk
- High-risk: T3a, or PSA >20, or Gleason score 8–10 not very high risk
- Very-high-risk: T3b–4

Various clinical outcomes were computed from the ProCaRS database using the date of radiotherapy initiation as the starting date for all outcome calculations. The primary outcome for the analysis was defined as the biochemical failure-free survival (BFFS; biochemical failure or initiation of salvage therapy before biochemical failure) as currently defined by the American Society of Radiation Oncology (ASTRO).[24] The secondary end point for this analysis was overall survival. Other end points that have been computed in the ProCaRS database include prostate cancer–specific survival and ASTRO biochemical failure (ie, biochemical failure alone not including initiation of salvage therapy). Additionally, biochemical failure and failure-free survival using the original ASTRO definition (ie, 3 successive increases in PSA, with failure backdated to halfway between 0th and 1st rising PSA) are also available in the database.[25] Technical biochemical failures from brachytherapy bounces were adjusted using a quality assurance procedure whereby patients with PSA levels that decreased to 0.5 ng/mL or less without intervention were considered to not have had a biochemical failure.[26]

Statistical Analyses

Descriptive analysis of all available patient, tumor, and treatment variables was performed. Additionally, a descriptive analysis of various risk stratification categories and available outcomes was also performed. Both univariable and multivariable Cox proportional hazards modeling were performed on the primary (ASTRO BFFS) and secondary (prostate cancer–specific survival, overall survival) outcomes of interest. Kaplan-Meier curves were generated for both the primary and secondary outcomes stratified by GUROC/NCCN risk stratification for all patients, all external-beam–alone patients, all external-beam–alone patients receiving greater than the equivalent of 70 Gy in 35 fractions of radiotherapy in 1.8 to 2.0 Gy/d (70 Gy/35#: 185/904 [20.5%]; 72 Gy/36#: 15/904 [1.7%]; 74 Gy/37#: 211/904 [23.3%]; 75.6 Gy/42#: 82/904 [9.1%]; 76 Gy/38#: 3/904 [0.3%]; 78 Gy/39#: 3/904 [0.3%]; and 79.8 Gy/42#: 405/904 [44.8%]), and all patients treated with brachytherapy (LDR, HDR brachytherapy with or without external-beam). Statistical significance was determined using the log-rank statistic. All statistical analyses were performed using either SAS 9.2 software (SAS institute, Cary NC) or the R software platform (www.r-project.org).

Results

Descriptive Analysis

Mean age was 66.5 years (SD, 7.4). Mean PSA, PSA velocity, and PSA doubling time were 9.19 ng/mL (SD, 11.0), 0.27 ng/mL/y, and 1.17 years, respectively. T-stage distribution was 45.2% for T1, 46.0% for T2, 8.2% for T3, and 0.6% for T4. Gleason grade distribution was 65% for 2 to 6, 30% for 7, and 5% for 8 to 10. Mean percentage core involvement was 43%. GUROC risk stratification was low in 3928 (49.5%), intermediate in 2888 (36.5%), and high in 1097 (14%) patients. NCCN risk stratification was very low in 877 (11%), low in 2776 (35%), intermediate in 3100 (39.5%), high in 800 (10%), and very high in 293 (3.5%) patients. Descriptives broken down according to participating institutional databases are depicted in Table 1.

External-beam radiation therapy was used as monotherapy in 2793 of patients with a median dose fractionation of 68 Gy in 34 fractions (range, 50.0 Gy in 20 fractions to 79.8 Gy in 42 fractions). LDR brachytherapy was used in 4560 (57%) patients with a mean reported dose of 153.9 Gy (SD, 13.2). HDR brachytherapy (in combination with 40–45 Gy in 1.8–2.0 Gy/d external-beam radiation therapy) was used in 737 (9%) patients with a mean reported dose of 17 Gy (SD, 4.0). Collectively, 5297 (66%) patients received some form of brachytherapy as primary treatment of their prostate cancer. Hormonal therapy was used in 2999 patients (38%), with a mean use of 10.4 months. Table 2 depicts hormonal therapy use and duration versus GUROC/NCCN risk stratification grouping.

Table 3 summarizes clinical outcomes for the entire ProCaRS database and its constituent databases. Median follow-up for the entire ProCaRS database was 78.9 months (range, 0–190.7). Median follow-up for the 7 included databases ranged from 28.1 to 94.1 months. A total of 1442 of 7974 patients (19.1%) had ASTRO BFFS, with 1392 (18.5%) having a biochemical failure before any initiation of salvage therapy. A total of 1230 (15.4%) patients died, with 273 of these mortality events (22.0%) confirmed as cancer-related deaths. Additionally, 821 of 1230 patients (67.0%) died of other causes, with another 136 (11.0%) dying without any mortality attribution.

Cox Regression Analyses

Multivariable modeling for both the primary (ASTRO BFFS) and secondary (overall survival) end

Table 1 Baseline Tumor, Patient, and Treatment Characteristics for All Patients and Stratified by Center/Cohort

			Center/Cohort						
Characteristic	**N**	**All Patients (N=7974)**	**BCCA Registry (n=3771)**	**PMH LDR-Brachy (n=1161)**	**PMH EBRT Dose Escalation (n=403)**	**PMH Trial #9907 (n=188)**	**Laval LDR-Brachy (n=1630)**	**Laval HDR-Brachy + EBRT (n=627)**	**McGill EBRT (n=194)**
Age: mean ± SD, median, (min, max)	7970	66.52 ± 7.36 67.00 (34.00, 88.00)	68.29 ± 7.08 69.00 (34.00, 88.00)	63.01 ± 7.11 63.00 (40.00, 83.00)	69.98 ± 5.91 71.00 (45.00, 84.00)	70.86 ± 4.91 71.00 (58.00, 84.00)	63.84 ± 6.90 64.00 (42.00, 86.00)	65.29 ± 7.14 65.50 (40.00, 85.00)	68.35 ± 6.55 70.00 (47.00, 83.00)
Baseline PSA (ng/mL): mean ± SD, median, (min, max)	7844	9.19 ± 11.01 6.80 (0.10, 250.00)	11.57 ± 15.12 7.60 (0.24, 250.00)	5.66 ± 2.54 5.40 (0.15, 26.10)	9.20 ± 6.22 7.51 (0.26, 51.40)	9.32 ± 4.79 8.17 (1.20, 22.30)	6.42 ± 2.97 6.00 (0.10, 35.00)	8.56 ± 5.41 7.19 (0.37, 43.45)	10.27 ± 4.68 10.31 (1.17, 30.44)
T stage: n (%)									
T1	7839	3553 (45.3)	1169 (32.0)	768 (66.2)	176 (43.9)	74 (39.4)	928 (57.4)	337 (54.1)	101 (53.2)
T2		3606 (46.0)	1825 (49.9)	393 (33.9)	223 (55.6)	114 (60.6)	689 (42.6)	273 (43.8)	89 (46.8)
T3		638 (8.1)	622 (17.0)	—	2 (0.5)	—	1 (0.1)	13 (2.1)	—
T4		42 (0.5)	42 (1.2)	—	—	—	—	—	—
Gleason total: n (%)									
2	7839	17 (0.2)	7 (0.2)	—	—	—	10 (0.6)	—	—
3		46 (0.6)	18 (0.5)	9 (0.8)	—	—	19 (1.2)	—	—
4		247 (3.2)	137 (3.8)	—	—	—	107 (6.6)	3 (0.5)	—
5		575 (7.3)	404 (11.1)	6 (0.5)	1 (0.3)	—	152 (9.4)	12 (1.9)	—
6		4267 (54.4)	1619 (44.4)	1025 (88.3)	141 (35.0)	35 (18.6)	1290 (79.6)	99 (15.9)	58 (29.9)
7		2301 (29.4)	1158 (31.7)	120 (10.3)	235 (58.3)	144 (76.6)	38 (2.3)	470 (75.3)	136 (70.1)
8		229 (2.9)	173 (4.7)	1 (0.1)	13 (3.2)	9 (4.8)	3 (0.2)	30 (4.8)	—
9		151 (1.9)	126 (3.5)	—	13 (3.2)	—	2 (0.1)	10 (1.6)	—
10		6 (0.1)	6 (0.2)	—	—	—	—	—	—
Positive cores (%): mean ± SD, median, (min, max)	4475	40.16 ± 24.62 33.33 (0.00, 100.00)	42.68 ± 24.96 33.33 (0.00, 100.00)	29.40 ± 18.89 25.00 (4.76, 100.00)	43.97 ± 25.98 38.46 (5.56, 100.00)	49.58 ± 27.32 50.00 (6.35, 100.00)	— — —	— — —	41.04 ± 23.13 37.50 (10.00, 100.00)
Radiotherapy treatment year: n (%)									
1994–1999	7973	1953 (24.5)	1698 (45.0)	43 (3.7)	2 (0.5)	11 (5.9)	194 (11.9)	5 (0.8)	—
2000–2002		1973 (24.8)	930 (24.7)	328 (28.3)	227 (56.3)	85 (45.2)	306 (18.8)	62 (9.9)	35 (18.1)
2003–2005		2238 (28.1)	878 (23.3)	413 (35.6)	174 (43.2)	70 (37.2)	507 (31.1)	109 (17.4)	87 (45.1)
2006–2010		1809 (22.7)	265 (7.0)	377 (32.5)	—	22 (11.7)	623 (38.2)	451 (71.9)	71 (36.8)
Radiotherapy type: n (%)									
Brachy (HDR) + EBRT	7974	711 (8.9)	—	—	—	—	—	601 (95.9)	110 (56.7)
Brachy (LDR) + EBRT		52 (0.7)	4 (0.1)	48 (4.1)	—	—	—	—	—
Brachy (HDR) only		26 (0.3)	—	—	—	—	—	26 (4.2)	—
Brachy (LDR) only		4508 (56.5)	1765 (46.8)	1113 (95.9)	—	—	1630 (100.0)	—	—
EBRT only		2677 (33.6)	2002 (53.1)	—	403 (100.0)	188 (100.0)	—	—	84 (43.3)

Abbreviations: BCCA, British Columbia Cancer Agency; brachy, brachytherapy; EBRT, external-beam radiation therapy; HDR, high-dose-rate; LDR, low-dose-rate; max, maximum; min, minimum; PMH, Princess Margaret Hospital; PSA, prostate-specific antigen; SD, standard deviation.

points showed that age, PSA, T stage, Gleason score grouping, hormone therapy duration, and type of radiation treatment were predictive of both of these clinical outcomes ($P<.05$; Table 4). Presence or absence of hormonal therapy was found to be significant only on univariable analysis (and not multivariable) for both clinical outcomes.

Kaplan-Meier Analyses

Kaplan-Meier analysis of the existing GUROC and NCCN classification system shows good separation of ASTRO BFFS and overall survival curves for all ProCaRS patients (log-rank $P<.0001$; Figure 1), all external-beam patients (log-rank $P<.0001$, curves not shown), all external-beam patients at 70 Gy in 35 fractions equivalent or greater (log-rank $P<.0001$, curves not shown). GUROC and NCCN classification systems separated groups into distinct ASTRO BFFS groups in the brachytherapy population (log-rank $P<.005$, curves not shown). Additionally, the NCCN classification was able to categorize brachytherapy patients into distinct overall survival groups (log rank $P=.001$), whereas the GUROC classification was not able to resolve these groups to the same extent (log rank $P=.264$).

Discussion

Risk stratification in the management of prostate cancer allows for prediction of the risk associated with various positive or negative clinical outcomes, the directing of appropriate therapy, clinical trial stratification and inclusion/exclusion criteria definition, and a common nomenclature for institutional outcome reporting. No consensus exists for the ideal risk stratification scheme, as evidenced by the multiple different (but related) systems[20] that have been adopted by various organizations interested in the management of prostate cancer.[21] Other risk stratification systems have been proposed in the literature, but these systems have not gained widespread acceptance.[27,28]

In addition to the reporting of important clinical outcomes related to radiotherapy treatment, this newly formed ProCaRS database will allow for the systematic investigation of various aspects of nonmetastatic prostate cancer pretreatment risk stratification/categorization. Other large prostate cancer databases exist in the literature, including CaPSURE,[29] SEER and SEER-Medicare,[30] and the Memorial Sloan-Kettering Cancer Center,[31] which have investigated various research questions, including comparative effectiveness analyses, risk modeling/nomograms, population-based analyses, and treatment use.

This ProCaRS analysis has confirmed previously investigated prognostic factors related to ASTRO BFFS and overall survival, including various patient (age), tumor (PSA, Gleason score, positive core percentage), and treatment (hormonal therapy duration, form of radiation therapy) factors.[20] Missing prediagnostic PSA data within the ProCaRS dataset prevented robust investigation into novel prognostic factors, such as PSA velocity and doubling time, in

Table 2 Summary of Hormone Therapy Use and Hormone Duration Stratified by GUROC and NCCN Risk Classification Systems (N=7974)

	Hormone Therapy		Hormone Therapy Duration (mo)		
Characteristic	Yes n (%)	No n (%)	Mean ± SD	Median	(Min, Max)
GUROC					
Low	911 (23.2)	3017 (76.8)	5.97 ± 7.42	5.29	(0.23, 132.67)
Intermediate	1253 (43.4)	1635 (56.6)	8.01 ± 9.26	5.85	(0.10, 99.68)
High	774 (70.6)	323 (29.4)	18.60 ± 21.54	11.63	(0.23, 143.74)
NCCN					
Very low	201 (22.9)	676 (77.1)	5.49 ± 2.41	5.52	(0.99, 15.21)
Low	641 (23.1)	2135 (76.9)	5.87 ± 6.61	5.03	(0.76, 84.63)
Intermediate	1311 (42.3)	1789 (57.7)	8.00 ± 9.79	5.82	(0.10, 132.67)
High	550 (68.8)	250 (31.3)	17.59 ± 17.55	11.79	(0.23, 133.39)
Very high	224 (76.5)	69 (23.6)	20.99 ± 28.74	9.87	(0.23, 143.74)

Abbreviations: GUROC, Genitourinary Radiation Oncologists of Canada; max, maximum; min, minimum; SD, standard deviation.

Table 3 Risk Stratification and Clinical Outcomes for All Patients and Stratified by Center/Cohort

			Center/Cohort						
Characteristic	N	All Patients (N=7974)	BCCA Registry (n=3771)	PMH LDR-Brachy (n=1161)	PMH EBRT Dose Escalation (n=403)	PMH Trial #9907 (n=188)	Laval LDR-Brachy (n=1630)	Laval HDR-Brachy + EBRT (n=627)	McGill EBRT (n=194)
GUROC: n (%)									
Low	7913	3928 (49.6)	1348 (36.3)	1004 (86.5)	95 (23.6)	10 (5.3)	1421 (87.2)	37 (5.9)	13 (6.7)
Intermediate		2888 (36.5)	1407 (37.9)	155 (13.4)	263 (65.3)	166 (88.3)	195 (12.0)	524 (83.6)	178 (91.8)
High		1097 (13.9)	955 (25.7)	2 (0.2)	45 (11.2)	12 (6.4)	14 (0.9)	66 (10.5)	3 (1.6)
NCCN: n (%)									
Very low	7846	877 (11.2)	397 (10.8)	437 (37.6)	37 (9.2)	4 (2.1)	—	—	2 (1.0)
Low		2776 (35.4)	787 (21.4)	565 (48.7)	52 (12.9)	6 (3.2)	1332 (83.2)	30 (4.8)	4 (2.1)
Intermediate		3100 (39.5)	1540 (41.9)	157 (13.5)	269 (66.8)	166 (88.3)	256 (16.0)	527 (84.6)	185 (95.4)
High		800 (10.2)	663 (18.0)	2 (0.2)	44 (10.9)	12 (6.4)	13 (0.8)	63 (10.1)	3 (1.6)
Very high		293 (3.7)	288 (7.8)	—	1 (0.3)	—	1 (0.1)	3 (0.5)	—
Death (any cause): n (%)	7974	1230 (15.4)	1069 (28.4)	43 (3.7)	37 (9.2)	13 (6.9)	53 (3.3)	8 (1.3)	7 (3.6)
Cause of death: n (%)									
DOD	7974	273 (3.4)	262 (7.0)	1 (0.1)	3 (0.7)	3 (1.6)	2 (0.1)	1 (0.2)	1 (0.5)
Dead (other)		821 (10.3)	736 (19.5)	26 (2.2)	16 (4.0)	7 (3.7)	26 (1.6)	4 (0.6)	6 (3.1)
Dead (NOS)		136 (1.7)	71 (1.9)	16 (1.4)	18 (4.5)	3 (1.6)	25 (1.5)	3 (0.5)	—
Cause of death: n (%)									
DOD	1230	273 (22.2)	262 (24.5)	1 (2.3)	3 (8.1)	3 (23.1)	2 (3.8)	1 (12.5)	1 (14.3)
Dead (other)		821 (66.8)	736 (68.9)	26 (60.5)	16 (43.2)	7 (53.9)	26 (49.1)	4 (50.0)	6 (85.7)
Dead (NOS)		136 (11.1)	71 (6.6)	16 (37.2)	18 (48.7)	3 (23.1)	25 (47.2)	3 (37.5)	—
BF and DOD Status: n (%)									
BF–, DOD–	7550	6108 (80.9)	2653 (74.4)	1022 (88.4)	269 (69.0)	115 (62.5)	1390 (91.0)	524 (91.6)	135 (87.7)
BF+, DOD–		1169 (15.5)	652 (18.3)	133 (11.5)	118 (30.3)	66 (35.9)	135 (8.8)	47 (8.2)	18 (11.7)
BF+, DOD+		273 (3.6)	262 (7.4)	1 (0.1)	3 (0.8)	3 (1.6)	2 (0.1)	1 (0.2)	1 (0.7)
BF to DOD interval (mo):	264								
mean ± SD,		40.55 ± 33.25	39.92 ± 33.46	9.63	51.10 ± 11.32	68.03 ± 25.53	68.45 ± 17.91	—	59.76
median,		37.27	35.37		44.68	59.14	68.45	—	
(min, max)		(0.00, 139.07)	(0.00, 139.07)		(44.45, 64.16)	(48.13, 96.82)	(55.79, 81.12)	—	

Abbreviations: BCCA, British Columbia Cancer Agency; BF, biochemical failure; brachy, brachytherapy; DOD, died of disease; EBRT, external-beam radiation therapy; GUROC, Genitourinary Radiation Oncologists of Canada; HDR, high-dose-rate; LDR, low-dose-rate; max, maximum; min, minimum; NOS, not otherwise specified; PMH, Princess Margaret Hospital; SD, standard deviation.

terms of the univariable and multivariable analyses. This analysis strongly confirms the utility of existing risk stratification schema to categorize different radiotherapy patients (external-beam radiation therapy vs brachytherapy) into different prognostic groups. Furthermore, analysis of the ProCaRS dataset suggested that the implementation of more than 3 risk categories may have important prognostic benefits for overall survival. In particular, inspection of clinical outcomes related to the "very-low-risk" and "low-risk" NCCN categories shows a difference between groups in terms of the BFFS end point but not the prostate cancer–specific survival or overall survival end points (Figure 1). This Kaplan-Meier information confirms the high curability of all forms of low-risk prostate cancer, likely because of the underlying indolent nature.

This investigation has several limitations. The ProCaRS database is a retrospective entity based on data that were made available by various Canadian clinical investigators. The patients contained within the database may not be completely representative of a great patient population. Additionally, increasing levels of hormonal therapy were used with increasing risk stratification, which may impact the interpretation of the Kaplan-Meier curves. Evidence of this phenomenon exists with the observation of the large low-risk and LDR brachytherapy patient populations contained within ProCaRS. Despite the extensive quality assurance procedures used in the creation and curation of this database, it is important to acknowledge that different investigators at different institutions probably collected the constituent datasets during different periods. Despite these potential

Table 4 Multivariable Cox Regression Models of ASTRO BFFS and Overall Survival for the ProCaRS Database (N=7974)

	Multivariable: ASTRO BFFS			Multivariable: OS		
Independent Variables	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Age						
per 1-year increase	0.983	(0.975, 0.991)	<.001	1.054	(1.043, 1.064)	<.001
Hormone therapy						
Yes vs no	—	—	—	—	—	—
Hormone therapy duration						
Per 1-month increase	0.988	(0.983, 0.992)	<.01	0.993	(0.989, 0.998)	.002
Radiation treatment						
Brachy only vs EBRT only	0.301	(0.259, 0.350)	<.001	0.590	(0.494, 0.703)	<.001
Brachy + EBRT vs EBRT only	0.482	(0.373, 0.623)	<.001	0.297	(0.162, 0.543)	<.001
			<.001[a]			<.001[a]
PSA						
per 1-ng/mL increase	1.010	(1.008, 1.013)	<.001	1.004	(1.000, 1.007)	.035
T stage						
2 vs 1	1.221	(1.074, 1.387)	.002	1.192	(1.023, 1.388)	.025
3 vs 1	1.577	(1.319, 1.886)	<.001	1.639	(1.359, 1.978)	<.001
4 vs 1	2.468	(1.567, 3.888)	<.001	3.118	(2.107, 4.614)	<.001
			<.001[a]			<.001[a]
Gleason score						
6 vs 2–5	1.032	(0.872, 1.221)	.712	1.072	(0.905, 1.270)	.421
7 vs 2–5	1.368	(1.158, 1.615)	<.001	1.197	(1.008, 1.421)	.040
8–10 vs 2–5	1.879	(1.497, 2.360)	<.001	1.897	(1.525, 2.358)	<.001
			<.001[a]			<.001[a]
Positive cores percentage						
per 1% increase	—	—	—	—	—	—

Multivariable models omit hormone therapy and positive core percentage.

Abbreviations: ASTRO, American Society of Radiation Oncology; BFFS, biochemical failure-free survival; brachy, brachytherapy; EBRT, external-beam radiation therapy; HR, hazard ratio; OS, overall survival; ProCaRS, pan-Canadian Prostate Cancer Risk Stratification; PSA, prostate-specific antigen.

[a]Overall analysis of effects (applicable to categorical variables only).

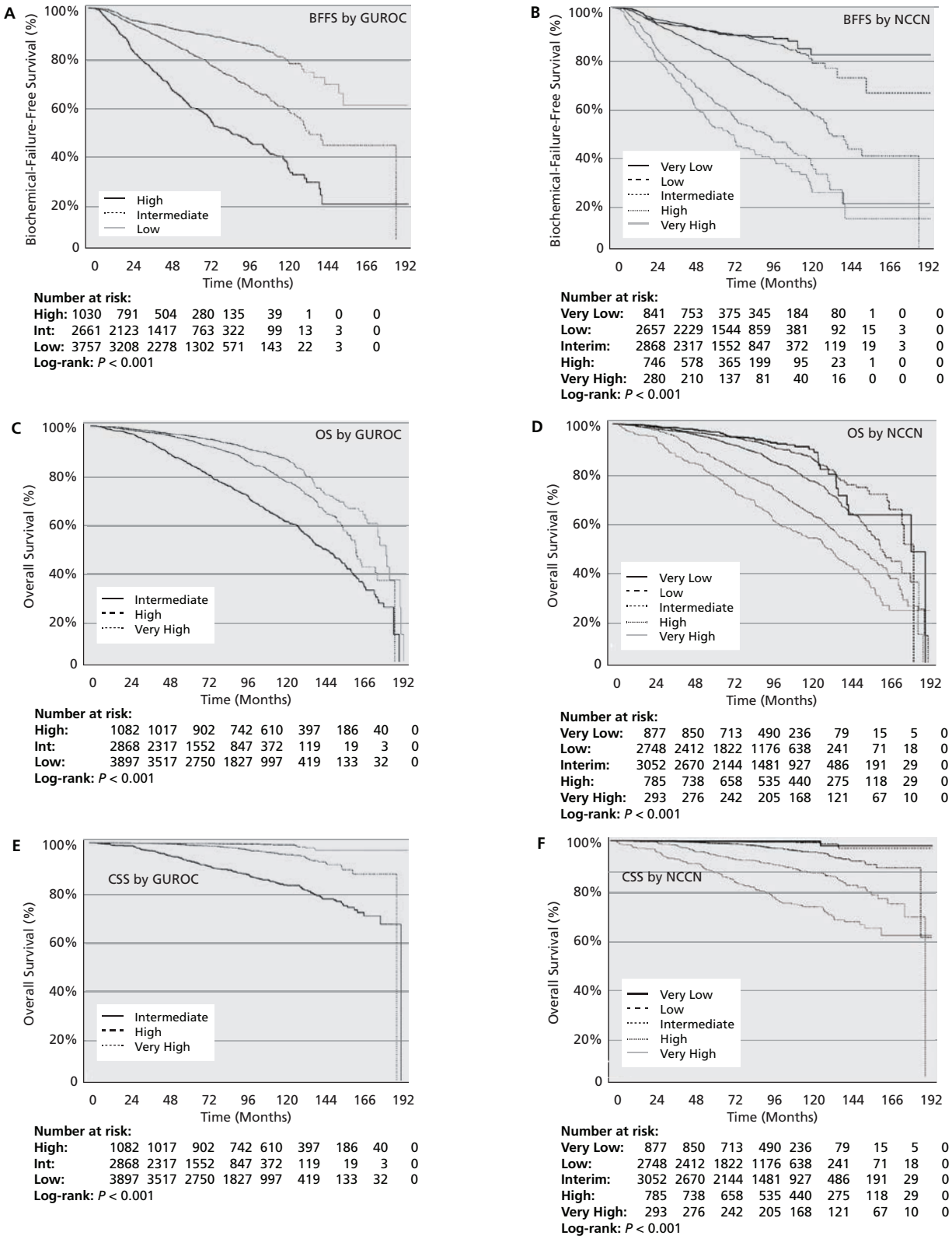

Figure 1 Kaplan-Meier American Society of Radiation Oncology (ASTRO) biochemical failure-free survival (BFFS) and overall survival (OS), and prostate cancer–specific survival (CSS) curves for all pan-Canadian Prostate Cancer Risk Stratification patients. (A) Genitourinary Radiation Oncologists of Cancer (GUROC) ASTRO BFFS. (B) NCCN ASTRO BFFS. (C) GUROC OS. (D) NCCN overall survival. (E) GUROC CSS. (F) NCCN CSS.

issues, the sample size of this dataset allows for high levels of statistical power to test new and novel hypotheses related to risk stratification and/or outcome analyses. Another limitation of this analysis was that it was restricted to common risk stratification systems used in clinical practice; alternative published multivariable systems/models were not considered in this initial investigation.

Subsequent to the establishment of this large prostate cancer radiotherapy database, the GUROC research group initiated several investigations related to the prediction of clinical outcomes. Specifically, they are using recursive partitioning analysis, clinical nomogram creation, and artificial neural network techniques to create de novo risk classification systems for the prediction of ASTRO BFFS and overall survival. Head-to-head comparisons of various alternative multivariable models/systems can also be conducted using the ProCaRS dataset. Additionally, they are investigating the utility of adapting the existing 3-group classification system (ie, the GUROC system) to allow for the splitting of low-, intermediate-, and high-risk categories into clinically relevant subcategories. In this project, up to 6 categories (very-low-risk, low-risk, low-intermediate-risk, high-intermediate-risk, high-risk, and extreme-risk) will be defined and characterized in terms of ASTRO BFFS and overall survival. In addition, the ProCaRS database will be used to perform direct propensity score matched pair analyses of various interventions (eg, brachytherapy vs external-beam radiation therapy).

Conclusions

This investigation has shown that cross-institutional collaboration to obtain robust clinical data to assess prostate cancer radiotherapy outcomes and to explore risk stratification is feasible. This investigation has demonstrated the ability of 2 risk stratification schemes to categorize patients who underwent external-beam radiation therapy or brachytherapy into various risk groups for 2 important clinical outcomes (ASTRO BFFS and overall survival). This work suggests that the definition of additional risk categories (ie, very-low-risk and very-high-risk consistent with the NCCN approach) may further improve patient risk categorization, particularly in brachytherapy patient populations. Further work will assess the importance of novel risk stratification systems, clinical nomograms, artificial neural networks, and direct treatment comparisons.

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