Association of extended core sampling with delayed intervention and pathologic outcomes for active surveillance patients

A population-based analysis

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ABSTRACT

INTRODUCTION: Combined systematic plus targeted biopsy sampling improves detection of clinically significant prostate cancer (PCa). Our objective was to evaluate whether extended core sampling at initial biopsy in active surveillance (AS) patients is associated with subsequent AS discontinuation and pathologic outcomes.

METHODS: National Comprehensive Cancer Network (NCCN) low- and favorable-intermediate-risk (FIR) AS patients diagnosed between 2010 and 2015 were identified from the Surveillance, Epidemiology, and End Results (SEER) Prostate with Watchful Waiting database. Prostate biopsy sampling was operationalized as: standard (10–12 cores), extended (13–20 cores), or super-extended (21+ cores). Sensitivity analyses using differing cutoffs was performed. Outcomes included delayed definitive intervention (radical prostatectomy [RP]/radiotherapy) and pathologic upgrading and/or downgrading in delayed RP patients. Multivariable logistic regression modelling adjusted for sociodemographic/oncologic variables was performed.

RESULTS: This cohort included 42 459 patients (low-risk: 28 411; FIR:14 048); 25–29% and 3–5% of patients underwent extended and super-extended core sampling, respectively, at diagnosis. Extended core sampling was associated with decreased odds of definitive intervention in low (odds ratio [OR] 0.89, p=0.003) and grade group 2 (GG2) FIR (OR 0.83, p=0.002) patients. Super-extended sampling was associated with decreased odds of definitive intervention in prostate-specific antigen (PSA) 10–20 FIR patients (OR 0.65, p=0.02). Super-extended sampling was associated with decreased odds of upgrading to ≥GG2 disease in low-risk (OR 0.45, p=0.032) and to ≥GG3 disease in GG2 FIR patients (OR 0.67, p=0.044).

CONCLUSIONS: This population-based analysis demonstrates that extended/super-extended sampling at diagnosis is associated with significantly decreased odds of AS discontinuation and pathologic upgrading in low/FIR AS patients. This highlights the significance of extended tissue sampling at initial biopsy to appropriately risk-stratify AS patients and minimize AS discontinuation rates.

INTRODUCTION

Active surveillance (AS) is guideline-recommended for low-risk and select favorable-intermediate-risk (FIR) prostate cancer (PCa) patients.[1,2] A nuanced approach to the selection of appropriate candidates is key to minimizing the potential risk of distant disease spread, while maintaining the 'window of cure' with definitive, local therapy at disease progression. The success of surveillance regimens is thus strongly dependent on appropriate risk stratification. This is of particular significance for the FIR subgroup undergoing AS, with long-term data from the Sunnybrook series demonstrating that such patients have 3.7-fold increased odds of 15-year metastases compared to low-risk patients.[3]

Currently available tools for risk-stratifying patients include clinicopathologic variables,[4-6] genomic markers,[7-9] and various imaging modalities, including magnetic resonance imaging (MRI). MRI with targeted biopsy core sampling has demonstrated significant benefits for the detection of clinically significant PCa in both the biopsy-naive and confirmatory settings, compared to standard biopsy sampling.[10-12] Accordingly, MRI with targeted sampling of concerning lesions has emerged as an essential component of AS regimens to decrease the likelihood of disease undersampling and misattributing high-grade disease.

To date, however, the prognostic significance of extended core sampling, with potential image-guidance,

KEY MESSAGES

- Medicaid/uninsured and lower socioeconomic patients have lower odds of extended core sampling.
- Extended sampling is associated with decreased odds of subsequent active surveillance discontinuation.
- Super-extended sampling is associated with decreased odds of pathologic upgrading on radical prostatectomy specimen.
- We saw no difference in prostate cancer mortality by initial biopsy core sampling volume.

in the initial biopsy setting for AS patients remains unclear, particularly at the population level. The objective of this study was thus to evaluate whether the number of prostate biopsy cores sampled at initial biopsy in low and FIR AS patients is associated with delayed intervention, pathologic, and short-term mortality outcomes in a population-based setting. We hypothesized that increased biopsy core sampling at diagnosis would be associated with enhanced risk stratification and, subsequently, improved PCa-related outcomes.

METHODS

Study design, setting, and participants

We identified all men with National Cancer Comprehensive Network (NCCN) low and FIR PCa from the Surveillance, Epidemiology, and End Results (SEER) Prostate with Watchful Waiting (WW) database. This database captures men with incident PCa from 18 population-based registries, accounting for nearly 30% of the current U.S. census. Patients were diagnosed between 2010 and 2015. All patients were initially managed with AS/WW and did not receive definitive therapy within one year of diagnosis, as per treating institution records.[13] Patients ≥80 years of age were excluded to minimize the proportion of WW patients. To reflect potential AS candidates in contemporary practice, the FIR cohort included men with either grade group (GG)2 disease or a prostate-specific antigen (PSA) level of 10–20 ng/ml.[1,2] All men in the FIR cohort fulfilled the NCCN FIR criteria of only one intermediate risk factor, with percentage of positive biopsy cores <50%.[1] Patients with cT2b-c NCCN FIR PCa were not included in this analysis.

The requirement for research ethics board approval was waived, given the use of publicly available data. The study was performed in accordance with the Declaration of Helsinki.

Study outcomes

The primary outcome was undergoing delayed definitive intervention (i.e., AS discontinuation), defined as either radical prostatectomy (RP) or pelvic radiotherapy (XRT). Secondary outcomes included: 1) pathologic upgrading on prostatectomy specimens of patients undergoing an RP, defined as pathologic ≥GG2 disease in low-risk and PSA 10–20 FIR patients, and pathologic ≥GG3 disease in those with GG2 FIR PCa on initial biopsy; 2) pathologic downgrading to GG1 disease in those with GG2 FIR disease; and 3) PCa-specific mortality.

Study variables

The primary exposure of interest was the number of prostate biopsy cores sampled at the time of the initial diagnostic biopsy, operationalized as follows: standard: 10–12 cores; extended: 13–20 cores; and super-extended: 21+ cores. These cutoffs were chosen in accordance with current guidelines recommendations for 3–5 targeted cores per concerning lesion,[14] with this definition allowing for two targetable lesions per patient. We evaluated different cutoffs for defining extended and super-extended core sampling: 13–18 and 19+ cores; and 15–22 and 23+ cores, respectively. MRI results were unavailable from this database, and we could not ascertain whether targeted sampling was performed. In lieu of MRI data availability, extended and super-extended core sampling was used as proxies for additional MRI-targeted sampling.

The following oncologic variables were only available at baseline (i.e., at time of diagnostic biopsy): prostate biopsy GG score, serum PSA level, clinical stage, and percentage of positive cores, calculated from the number of positive and examined prostate biopsy cores. Prostatic volume and, thus, PSA density were not available. Followup serum PSA, rectal exam, and repeat biopsy findings were unavailable.

Pathologic GG score on prostatectomy specimens of patients undergoing an RP was available; however, other pathologic variables, including the presence/absence of extraprostatic extension and lymph node involvement, were not evaluable due to the large

Table 1. Baseline patient demographics

Variable	Low-risk (n=28 411)	GG2 FIR (n=10 314)	PSA 10–20 FIR (n=3734)
Year of diagnosis, n (%)			
2010	4771 (16.8%)	1547 (15.0%)	615 (16.5%)
2011	4965 (17.5%)	1557 (15.1%)	602 (16.1%)
2012	4971 (17.5%)	1825 (17.7%)	621 (16.6%)
2013	4976 (17.5%)	1783 (17.3%)	672 (18.0%)
2014	4175 (14.7%)	1669 (16.2%)	608 (16.3%)
2015	4553 (16.0%)	1933 (18.7%)	616 (16.5%)
Age at diagnosis in years, median (IQR)	64.0 (59.0–69.0)	66.0 (61.0–71.0)	67.0 (61.0–72.0)
Race, n (%)			
Caucasian	19 569 (68.9%)	7045 (68.3%)	2367 (63.4%)
African American	4258 (15.0%)	1965 (19.1%)	651 (17.4%)
Hispanic	2454 (8.6%)	665 (6.4%)	359 (9.6%)
Asia/Pacific Islander	1276 (4.5%)	414 (4.0%)	256 (6.9%)
American Indian/Alaska Native	107 (0.38%)	39 (0.38%)	16 (0.43%)
Unknown	747 (2.63%)	186 (1.8%)	85 (2.3%)
Marital status, n (%)			
Married	18 280 (64.3%)	6731 (65.3%)	2266 (60.7%)
Not married	5816 (20.5%)	2392 (23.2%)	921 (24.7%)
Unknown	4315 (15.2%)	1191 (11.5%)	547 (14.6%)
Insurance status, n (%)			
Insured	20 828 (73.3%)	7333 (71.1%)	2648 (70.9%)
Medicaid	930 (3.3%)	356 (3.5%)	199 (5.3%)
Uninsured	420 (1.5%)	1821 (17.7%)	600 (16.1%)
Unknown	2413 (8.5%)	804 (7.8%)	287 (7.7%)
Socioeconomic status, n (%)			
1 (lowest)	7199 (25.3%)	2402 (23.3%)	991 (26.5%)
2	6570 (23.1%)	2356 (22.8%)	908 (24.3%)
3	7686 (27.1%)	2686 (26.0%)	1007 (27.0%)
4 (highest)	6956 (24.5%)	2870 (27.8%)	828 (22.2%)
PSA at diagnosis in ng/ml, median (IQR)	5.4 (4.4–6.9)	5.6 (4.5–7.1)	12.1 (10.8–14.4)
Percent positive core involvement, median (IQR)	16.7% (8.3–28.6%)	25.0% (15.4–33.3%)	14.3% (8.3–25.0%)

FIR: favorable-intermediate risk; GG2: grade group 2; IQR: interquartile range; PSA: prostate-specific antigen.

amount of missing data (up to 86%) reported for those variables in previous validation studies.[15,16]

PCa mortality was defined using the SEER variables: "Vital Status Recode," "SEER cause-specific death classification," and "COD to site recode." Patients with discordant values from these three variables were excluded to maintain internal validity. Other oncologic outcomes, including systemic chemohormonal therapy use, progression to castration resistance, and development of metastases, were not available.

Evaluable baseline sociodemographic variables included: year of diagnosis, age, race, marital status, and county-level socioeconomic status (SES), derived from the percentage of individuals in each county who were unemployed, below the poverty line, foreign-born, had less than a high school education, and the median household income.[17,18] Patient-level comorbidity data (e.g., Charlson Comorbidity Index scores) was not available.

Statistical analysis

Descriptive statistics were summarized for baseline patient variables across the cohort. Univariable comparisons of categorical variables were performed using the Chi-squared test. The associations between the number of sampled cores and binary outcomes (delayed definitive intervention, pathologic upgrading, and pathologic downgrading on RP) were evaluated using multivariable logistic regression analyses. We used the a priori approach to multivariable modeling,[19,20] adjusting for sociodemographic (age at diagnosis, race, marital status, insurance status, SES) and oncologic variables (PSA at diagnosis, clinical stage, and percent positive core involvement).

Multivariable modeling was performed separately for each subgroup: NCCN low-risk, GG2 FIR, PSA 10–20 FIR. Date of definitive intervention was not available, precluding time-to-event analyses with Cox regression modeling. To account for patients diagnosed in earlier years (e.g., 2010 or 2011) having an increased exposure time in the cohort, the multivariable model evaluating the association of number of cores sampled and delayed definitive intervention included year of diagnosis as an additional covariate.

We evaluated sociodemographic and oncologic predictors of undergoing extended/super-extended vs. standard core sampling. Variable collinearity was assessed using the variance inflation factor test, with a cutoff value of five used to exclude colinear variables. Sensitivity analyses to evaluate the consistency/internal validity of the study results using the alternate biopsy core sampling cutoffs were performed.

PCa-specific mortality stratified by number of cores sampled was evaluated in each of the three risk subgroups using competing risks analyses, adjusting for other-cause death as the competing event. Cumulative probabilities were estimated using cumulative incidence functions. Univariable comparisons were performed using the Wald test. Statistical significance was set at a two-sided p-value of 0.05. Statistical analyses were performed using R version 4.3.0 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

This cohort included a total of 42 459 patients, of whom 28 411 (66.9%) were NCCN low-risk, 10 314 (24.3%) GG2 FIR, and 3734 (8.8%) PSA 10–20 FIR (Supplementary Figure 1; available at *cuaj.ca*). Median baseline patient age ranged from 64–67 years. African Americans accounted for 15–19% of study patients. Median serum PSA at diagnosis was 5.4 (interquartile range [IQR] 4.4–6.9) and 5.6 ng/ml (4.5–7.1) in the low- and GG2 FIR subgroups, respectively, and 12.1 ng/ml (10.8–14.4) in the PSA 10–20 FIR subgroup.

Predictors of undergoing extended/super-extended core sampling

Extended core (i.e., 13–20) and super-extended core (i.e., 20+) sampling was performed in 25–29% and 3–5% of patients, respectively (Table 1). The proportion of patients undergoing extended or super-extended core sampling increased from 26% in 2010 to 33% in 2015 (Table 2). Sociodemographic predictors of undergoing extended/super-extended core sampling across all three risk groups included higher SES (odds ratios [OR] 1.14–1.43), whereas Medicaid (OR 0.64–0.67) and uninsured patients (OR 0.84–0.85) had significantly decreased odds of undergoing extended/super-extended core sampling. Patients with PSA 4–10 ng/ml, vs. 0–3.9 ng/ml, had significantly increased odds of extended/super-extended core sampling among GG2 FIR patients (OR 1.05, 95% confidence interval [CI] 1.0–1.08, p<0.001) (Table 3).

Delayed definitive therapy

Of the 28 411 low-risk patients, 12 362 (43.5%) underwent delayed definitive intervention compared to 7133 (69.2%) and 1518 (40.7%) of GG2 FIR and PSA 10–20 FIR patients, respectively (p<0.001) (Supplementary Table 1; available at *cuaj.ca*). Compared to standard core sampling, patients undergoing extended sampling had significantly decreased odds of definitive therapy in the low (OR 0.89, p=0.003) and GG2 FIR (OR 0.83, p=0.002) subgroups. In the PSA 10–20 FIR subgroup, patients undergoing super-extended core sampling had significantly decreased odds of definitive intervention (OR 0.65, p=0.02) (Table 4).

Sensitivity analyses using alternate core sampling cut-offs similarly demonstrated that extended core sampling was associated with decreased odds of delayed definitive intervention in low-risk and GG2 FIR patients (Supplementary Table 2; available at *cuaj.ca*).

Upgrading and downgrading on radical prostatectomy

Upgrading to ≥GG2 disease occurred in 410/1968 (20.9%) low-risk and 60/238 (25.2%) PSA 10–20 FIR patients undergoing an RP. Upgrading to ≥GG3 disease occurred in 138/1042 (13.2%) GG2 FIR patients undergoing an RP (Supplementary Table 3; available at *cuaj.ca*). Among low-risk patients, those undergoing super-extended sampling had significantly decreased odds of upgrading to ≥GG2

Table 1 (cont'd). Baseline patient demographics

Variable	Low-risk (n=28 411)	GG2 FIR (n=10 314)	PSA 10–20 FIR (n=3734)
Clinical stage, n (%)			
cT1-2a	24 801 (87.3%)	10 314 (100%)	3734 (100%)
T2b-c	3610 (12.7%)	–	–
Number of biopsy cores sampled			
Standard (10–12 cores)	20 266 (71.3%)	7351 (71.3%)	2487 (66.6%)
Extended (13–20 cores)	7122 (25.1%)	2609 (25.3%)	1075 (28.8%)
Super-extended (20+ cores)	1023 (3.6%)	354 (3.4%)	172 (4.6%)

FIR: favorable-intermediate risk; GG2: grade group 2; IQR: interquartile range; PSA: prostate-specific antigen.

Table 2. Proportion of patients undergoing extended or super-extended core sampling

Year	Number of patients diagnosed	Number of patients diagnosed via extended or super-extended core sampling (%)
2010	6933	1805 (26.0%)
2011	7124	1888 (26.5%)
2012	7417	2106 (28.4%)
2013	7431	2177 (29.3%)
2014	6452	2032 (31.5%)
2015	7102	2347 (33.0%)

Table 3. Predictors of undergoing extended core biopsies (≥13 vs. 10–12 cores) on multivariable logistic regression analyses

	Low-risk		GG2 FIR		PSA 10–20 FIR	
Variable	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Sociodemographic						
Year of diagnosis (reference: 2010–2011)						
2012–2013	1.04 (0.96–1.11)	0.34	0.95 (0.84–1.07)	0.39	1.05 (0.86–1.28)	0.07
2014–2015	1.05 (0.97–1.13)	0.22	1.03 (0.91–1.16)	0.63	1.19 (0.97–1.45)	0.66
Age at diagnosis (reference: <50)						
50–59	1.31 (1.08–1.58)	**0.006**	1.15 (0.78–1.71)	0.49	1.06 (0.48–2.53)	0.09
60–69	1.39 (1.16–1.58)	**<0.001**	1.31 (0.90–1.94)	0.17	1.09 (0.50–2.56)	0.88
70–79	1.41 (1.16–1.71)	**<0.001**	1.19 (0.82–1.78)	0.37	1.05 (0.48–2.47)	0.83
Race (reference: Caucasian)						
African American	1.02 (0.94–1.11)	0.62	1.09 (0.96–1.23)	0.20	0.88 (0.70–1.11)	0.91
Hispanic	1.00 (0.89–1.11)	0.95	0.95 (0.77–1.16)	0.61	0.90 (0.68–1.19)	0.28
Asian/Pacific Islander/American Indian/Alaska Native	1.08 (0.94–1.24)	0.29	1.11 (0.88–1.40)	0.37	0.93 (0.67–1.27)	0.46
Marital status (reference: married)						
Not married	0.93 (0.87–0.99)	**0.046**	0.93 (0.83–1.05)	0.23	0.92 (0.77–1.11)	0.64
Insurance status (reference: insured)						
Medicaid	0.66 (0.52–0.85)	**<0.001**	0.67 (0.50–0.88)	**0.005**	0.64 (0.43–0.92)	**0.02**
Uninsured	0.85 (0.78–0.92)		0.84 (0.74–0.96)	**0.008**	0.85 (0.69–1.06)	0.15
Socioeconomic status (reference: lowest)						
2	1.22 (1.11–1.33)	**<0.001**	1.21 (1.04–1.37)	**0.009**	1.28 (1.03–1.61)	**0.03**
3	1.27 (1.17–1.38)	**<0.001**	1.32 (1.14–1.51)	**<0.001**	1.14 (0.92–1.43)	0.24
4 (highest)	1.33 (1.22–1.46)	**<0.001**	1.36 (1.19–1.56)	**<0.001**	1.43 (1.14–1.82)	**0.003**
Oncologic						
PSA at diagnosis						
4–10 ng/ml (vs. 0–3.9 ng/ml)	1.01 (0.94–1.10)	0.71	1.05 (1.02-1.08)	**<0.001**	–	–
15–20 ng/ml (vs. 10–14.9 ng/ml)	–	–	–	–	1.03 (0.99–1.06)	0.16
Clinical stage (reference: cT1)						
cT2a	1.03 (0.89–1.16)	0.82	1.05 (0.90–1.22)	0.68	0.98 (0.76–1.28)	0.71

Bolding indicates statistical significance. CI: confidence interval; FIR: favorable-intermediate risk; GG2: grade group 2; OR: odds ratio; PSA: prostate-specific antigen.

disease on RP (OR 0.45, 95% CI 0.18–0.94, p=0.032). Similarly, among GG2 FIR patients undergoing an RP, super-extended sampling was associated with significantly decreased odds of upgrading to ≥GG3 disease (OR 0.67, 95% CI 0.46–0.98, p=0.044) (Table 5).

Sensitivity analyses using the alternate cutoffs demonstrated that super-extended sampling was associated with significantly decreased odds of upgrading on RP specimens in low-risk (OR 0.49, p=0.036) and GG2 FIR patients (OR 0.73, p=0.044) (Supplementary Table 4; available at *cuaj.ca*).

Downgrading to pathologic GG1 disease on RP occurred in 227 (21.8%) GG2 FIR patients. Non-significantly decreased odds of pathologic downgrading

Table 4. Predictors of definitive intervention (radical prostatectomy or radiotherapy) in active surveillance patients on multivariable logistic regression analyses

	Low-risk		GG2 FIR		PSA 10-20 FIR	
Variable	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Number of biopsy cores examined at diagnosis (reference: 10–12 cores)						
13–20 cores	0.89 (0.85–0.97)	**0.003**	0.83 (0.74–0.93)	**0.002**	0.86 (0.72–1.02)	0.09
21+ cores	1.00 (0.86–1.17)	0.97	0.85 (0.65–1.11)	0.22	0.65 (0.45–0.93)	**0.02**
Year of diagnosis (reference: 2010–2011)						
2012–2013	0.51 (0.48–0.55)	**<0.001**	0.73 (0.64–0.83)	**<0.001**	0.55 (0.45–0.66)	**<0.001**
2014–2015	0.33 (0.31–0.36)	**<0.001**	0.66 (0.57–0.75)	**<0.001**	0.45 (0.37–0.54)	**<0.001**
Sociodemographic						
Age at diagnosis (reference: 50–59)						
<50	1.05 (0.89–1.23)	0.57	0.99 (0.66–1.47)	0.97	1.41 (0.64–3.17)	0.40
60–69	1.01 (0.86–1.18)	0.94	0.95 (0.63–1.39)	0.80	1.19 (0.55–2.65)	0.66
70–79	1.01 (0.86–1.19)	0.88	0.84 (0.55–1.23)	0.38	1.02 (0.47–2.27)	0.97
Race (Reference: Caucasian)						
African American	1.11 (1.02–1.2)	**0.014**	0.85 (0.74–0.98)	**0.021**	1.00 (0.80 – 1.25)	0.99
Hispanic	1.02 (0.92–1.13)	0.75	0.85 (0.69–1.06)	0.16	0.93 (0.70 – 1.22)	0.58
Asian/Pacific Islander/American Indian/Alaska Native	0.88 (0.77–0.99)	**0.049**	0.84 (0.66–1.09)	0.18	0.92 (0.67–1.25)	0.59
Marital status (reference: married)						
Not married	0.79 (0.74–0.85)	**<0.001**	0.71 (0.63–0.79)	**<0.001**	0.86 (0.72–1.03)	0.096
Insurance status (reference: insured)						
Medicaid	1.09 (0.94–1.26)	0.26	0.94 (0.72–1.24)	0.68	1.05 (0.74–1.50)	0.77
Uninsured	0.98 (0.91–1.06)	0.61	0.98 (0.86–1.12)	0.73	1.06 (0.86–1.31)	0.58
Socioeconomic status (reference: lowest)						
2	1.23 (1.14–1.34)	**<0.001**	1.23 (1.06–1.44)	**0.007**	1.35 (1.08–1.68)	**0.009**
3	1.01 (0.93–1.09)	0.88	103 (0.89–1.19)	0.73	0.84 (0.67–1.05)	0.12
4 (highest)	1.32 (1.22–1.43)	**<0.001**	1.46 (1.26–1.70)	**<0.001**	1.22 (0.97–1.54)	0.096
Oncologic						
PSA at diagnosis						
4–10 ng/ml (vs. 0–3.9 ng/ml)	1.11 (0.93–0.97)	**0.005**	0.97 (0.94–0.99)	**0.023**		
15–20 ng/ml (vs. 10–14.9 ng/ml)	–	–	–	–	1.01 (0.98–1.05)	0.36
Clinical stage (reference: cT1)						
cT2a	1.03 (0.87–1.34)	0.41	1.11 (0.90–1.23)	0.48	1.05 (0.80–1.25)	0.66
Percent positive core involvement	1.03 (1.03–1.03)	**<0.001**	1.03 (1.02–1.03)	**<0.001**	1.03 (1.03–1.04)	**<0.001**

Bolding indicates statistical significance. CI: confidence interval; FIR: favorable-intermediate risk; GG2: grade group 2; OR: odds ratio; PSA: prostate-specific antigen.

Table 5. Predictors of upgrading on radical prostatectomy specimens among active surveillance patients opting for radical prostatectomy on multivariable analysis

	Low-risk (410 upgrading events)		GG2 FIR (138 upgrading events)		PSA 10–20 FIR (60 upgrading events)*	
Variable	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Number of biopsy cores examined at diagnosis (reference:10–12 cores)						
13–20 cores	0.97 (0.72–1.28)	0.81	1.16 (0.74–1.78)	0.50	0.65 (0.26–1.52)	0.33
21+ cores	0.45 (0.18–0.94)	**0.032**	0.67 (0.46– 0.98)	**0.044**	0.56 (0.14–2.24)	0.42
Sociodemographic						
Age at diagnosis (reference: 50–59)						
<50	1.36 (0.81–2.39)	0.26	1.89 (0.70–6.48)	0.26	1.08 (0.29–11.1)	0.94
60–69	1.71 (1.02–3.00)	**0.049**	2.39 (0.92–8.2)	0.11	1.21 (0.34–12.2)	0.87
70–79	1.44 (0.70–3.00)	0.32	3.70 (1.26–13.6)	**0.028**	2.40 (0.58–25.6)	0.47
Race (reference: Caucasian)						
African American	1.21 (0.78–1.86)	0.38	0.98 (0.49–1.85)	0.96	0.37 (0.07–1.38)	0.17
Hispanic	0.97 (0.63–1.47)	0.90	0.87 (0.40–1.75)	0.71	1.69 (0.59–4.71)	0.32
Asian/Pacific Islander/American Indian/Alaska Native	1.13 (0.62–1.96)	0.67	0.98 (0.36–2.26)	0.96	0.92 (0.13–4.20)	0.93
Marital status (reference: married)						
Not married	0.92 (0.65–1.29)	0.64	1.56 (0.97–2.51)	0.059	–	–
Insurance status (reference: insured)						
Medicaid	1.05 (0.49–2.10)	0.89	1.04 (0.23–3.41)	0.96	–	–
Uninsured	1.00 (0.69–1.44)	0.98	1.06 (0.61–1.77)	0.82	–	–
Socioeconomic status (reference: lowest)						
2	0.96 (0.67–1.36)		0.93 (0.51–1.71)	0.83	1.47 (0.58–3.79)	0.41
3	0.85 (0.60–1.20)		0.94 (0.54–1.67)	0.84	0.93 (0.34–2.55)	0.90
4 (highest)	0.77 (0.55–1.09)		0.69 (0.39–1.21)	0.19	0.45 (0.16–1.26)	0.14
Oncologic						
PSA at diagnosis						
4–10 ng/ml (vs. 0–3.99 ng/ml)	1.27 (0.96–1.69)	0.10	1.22 (0.90–1.63)	0.07	–	–
15–20 ng/ml (vs. 10–14.99 ng/ml)	–	–	–	–	1.12 (0.90–1.39)	0.12
Clinical stage (reference: cT1)						
cT2a	1.16 (0.84–1.45)	0.28	1.10 (0.69–1.59)	0.40	–	–
Percent positive core involvement	1.02 (1.00–1.03)	**0.03**	1.04 (0.98–1.10)	**0.07**	1.08 (1.03–1.13)	**<0.001**

*Given the limited number of upgrading events in the PSA 10–20 FIR subgroup (n=60), multivariable modelling with only 6 predictors was performed to avoid model 'overfitting' (i.e., ≥10:1 event to variable ratio). Bolding indicates statistical significance. CI: confidence interval; FIR: favorable-intermediate risk; GG2: grade group 2; OR: odds ratio; PSA: prostate-specific antigen.

were observed in patients undergoing extended (OR 0.72, p=0.11) and super-extended (OR 0.47, p=0.24) sampling (Supplementary Table 5; available at *cuaj.ca*).

Prostate cancer mortality

After a median followup of 43–46 months, PCa-related deaths occurred in 60 (0.2%), 26 (0.3%), and 21 (0.6%) of low-risk, GG2 FIR, and PSA 10–20 FIR patients, respectively. No significant differences were observed in PCa-specific mortality rates among patients undergoing standard, extended, or super-extended core sampling at initial biopsy in low (p=0.52), GG2 FIR (p=0.72), or PSA 10–20 FIR subgroups (p=0.49) (Figure 1).

DISCUSSION

In this population-based analysis of 42 459 low-risk and FIR AS patients, we determined that patients undergoing extended or super-extended core sampling at the time of the initial diagnostic prostate biopsy had significantly decreased odds of AS discontinuation, with extended core sampling in low-risk and GG2 FIR patients associated with 11–17% decreased odds of subsequent definitive therapy and super-extended core sampling associated with 35% decreased odds in the PSA 10–20 FIR subgroup. Furthermore, among AS patients undergoing subsequent RP, extended/super-extended core sampling at initial biopsy was associated with significantly decreased odds of pathologic upgrading (OR 0.45 and 0.67 for super-extended core sampling in low-risk and GG2 FIR patients, respectively). Significantly, consistent results were observed irrespective of the sampling volume cutoff definition used. We note that the percentage of patients diagnosed via extended/super-extended core sampling increased annually between 2010 and 2015 from 26% to 33%, which is potentially a reflection of the underlying increased adoption of MRI use in the population.

This is the first population-based analysis demonstrating that extended/super-extended core sampling at initial biopsy is associated with decreased odds of AS discontinuation and pathologic upgrading among those undergoing a subsequent RP. Furthermore, we demonstrate that this association holds true in a heterogenous cohort of AS patients, including NCCN low-risk and FIR PCa. These results suggest that the use of extended biopsy core sampling, preferentially with MRI guidance, helps better define a cohort of AS patients with "true" underlying low-risk or FIR features that are less likely to have missed or under-sampled higher-grade/volume disease, and thus less likely to discontinue AS in favor of radical therapy.

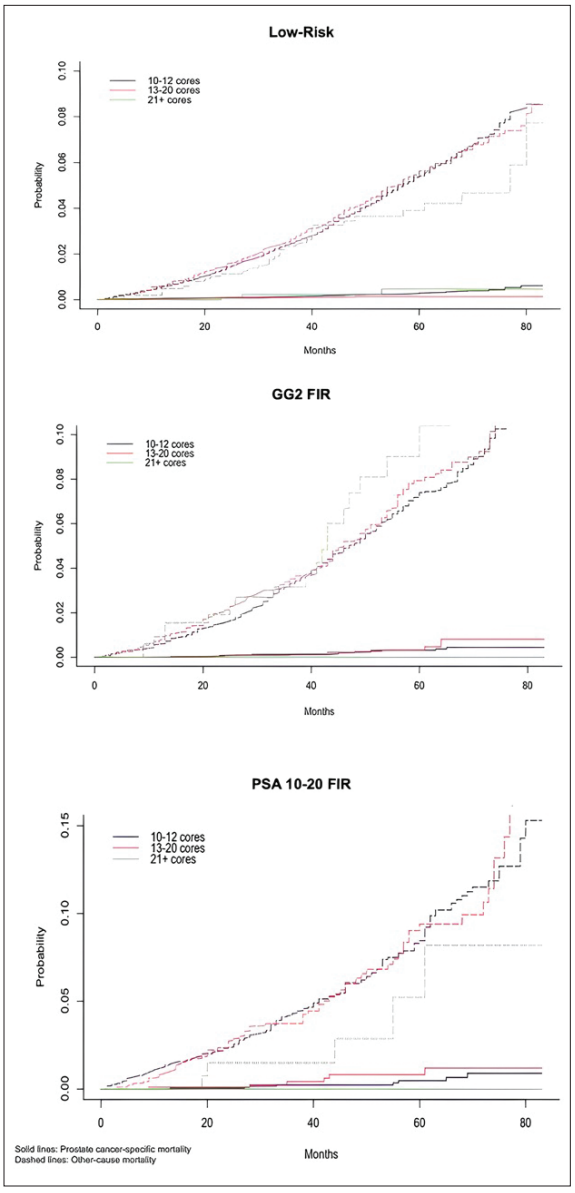

Figure 1. Cumulative incidence function curves of prostate cancer and other-cause mortalities rates stratified by number of biopsy cores sampled in low-risk, grade group 2 (GG2) favorable-intermediate-risk (FIR), and prostate-specific antigen (PSA) 10–20 ng/ml FIR subgroup.

Results of this analysis provide further support to those from Ahdoot et al, who demonstrated that MRI-guided combined biopsies (i.e., targeted + systematic) detected ≥GG2 disease in 43.6% of patients compared to 31% of patients undergoing a systematic biopsy only. Furthermore, among men undergoing an RP, combined biopsy was associated with the fewest upgrades to ≥GG3 on the prostatectomy specimens (3.5%), as compared with MRI-targeted (8.7%) and systematic biopsies (16.8%).[21] Thus, by performing extended core sampling with MRI

guidance, the odds of misattributing higher-grade disease, when present, is decreased, leading to fewer surveillance failures in better-selected AS candidates.

Limitations

The main limitation of this analysis is the lack of available MRI data. We could not discern patients that had MRI-targeted core sampling. Patients in the extended or super-extended sampling groups could have simply had additional systematic cores taken without MRI guidance. Conversely, patients in the standard group of 10–12 cores may have had MRI-targeted cores only; however, considering the study inclusion period of 2010–2015, it is unlikely that this occurred, given the later publication of phase 3 trials in this setting.[21,22]

Followup clinical/oncologic parameters, including repeat biopsy results were not available. Accordingly, we could not ascertain re-classification rates on confirmatory biopsies or identify triggers for intervention in our cohort.

Time-to-event analyses were not possible, given that definitive intervention dates were unavailable. In an attempt to address this limitation, we adjusted for year of diagnosis in our multivariable model to account for variable lengths in potential followup.

Definitive therapy in this analysis was restricted to RP/XRT and does not account for potential subsequent focal therapy treatments (data unavailable). Definitive intervention rates in this cohort (41–69%) are higher than those reported from tertiary centers,[3,23,24] but in keeping with those reported from the ProtecT trial (61%).[25]

The percent of Gleason pattern 4 disease was unavailable, and thus, study inclusion of GG2 FIR patients could not be restricted to those with low-volume pattern 4 disease (e.g., <10%). This may partly explain the high AS discontinuation rates in this risk subgroup (69%). It is also possible that select patients in this cohort underwent WW, as opposed to AS. We attempted to minimize the proportion of WW patients by excluding those >80 years of age. Furthermore, the observed delayed definitive therapy rates suggest that this proportion was low.

Mortality outcomes were limited to the short-/medium-term, with longer-term outcomes pending extended followup of this cohort. Potential complications of increased core sampling, such as higher infection, bleeding, and urinary retention rates, were not evaluable in this cohort.

Finally, this study suffers from limitations inherent to the use of population-based health administrative databases, including its retrospective nature.

CONCLUSIONS

This population-based analysis demonstrates that extended/super-extended core sampling at initial biopsy is associated with significantly decreased odds of AS discontinuation and pathologic upgrading in low-risk/FIR AS patients. This highlights the significance of extended tissue sampling at initial biopsy to appropriately risk-stratify AS patients and minimize AS discontinuation rates.

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