



ARTICLE



Low-volume grade group 2 prostate cancer candidates for active surveillance: a radical prostatectomy retrospective analysis

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ABSTRACT

Objective: Guidelines support considering selected men with ISUP grade group (GG) 2 prostate cancer for active surveillance (AS). We assessed the association of clinical variables with unfavorable pathology at radical prostatectomy in low-volume GG 2 prostate cancer on biopsy in a retrospective cohort.

Materials and methods: This was a retrospective analysis of 378 men with low-volume (≤ 2 cores) GG 2 localized prostate cancer who underwent prostatectomy at a single tertiary cancer center. Multivariable logistic regression of unfavorable pathology, upgrading to $\geq T3$, or GG ≥ 3 was performed in relation to clinical factors, common variables used in AS in GG 1 and percentage Gleason 4 at biopsy. We compared the performance of potential variables with commonly used combined AS restrictions in GG 1 prostate cancer.

Results: In total, 128/378 (34%) men had unfavorable pathology at radical prostatectomy. On multivariable analysis, $> 5\%$ Gleason pattern 4 was independently associated with an increased risk of GG ≥ 3 . A maximum percentage core involvement $> 50\%$ was independently associated with an increased risk of pT-stage ≥ 3 and unfavorable pathology. Restriction to patients with $\leq 5\%$ Gleason 4 decreased the upgrading of both unfavorable pathology (OR = 0.62, $p=0.041$) and GG ≥ 3 (OR = 0.17, $p=0.0007$) compared to the full cohort, while restriction to those with $\leq 50\%$ of max core involvement did not.

Conclusion: In low-volume GG 2, the percentage of Gleason 4 of $\leq 5\%$ was the strongest predictor in reducing upgrading at final pathology. This easily available pathological descriptor could be used to guide urologists and patients when considering AS in this setting.

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Prostate cancer; active surveillance; ISUP grade group 2; radical prostatectomy; upgrading

Introduction

Active surveillance (AS) for prostate cancer is a well-established treatment alternative for men with localized low risk disease [1–4]. Furthermore, AS is recommended in most guidelines as the primary modality for men with ISUP grade group 1 (GG 1; Gleason 3+3) disease [5,6]. There is increasing interest in AS for select patients with Gleason grade group 2 (GG 2; Gleason 3+4) prostate cancer due to their low risk of metastasis and prostate cancer specific death, though these remain elevated compared to GG 1 disease [7,8]. To date, only a few AS studies have included GG 2 patients. Criteria for selecting appropriate GG 2 patients who can be safely managed by AS remain unclear.

Studies assessing upgrading to unfavorable pathology have found that patients diagnosed with GG 2 disease on biopsy and ≤ 2 positive cores have a lower risk of adverse pathology on radical prostatectomy (RP) compared to those

with > 2 cores [9]. However, there was substantial heterogeneity within groups.

In this study, we aimed to evaluate the association of common clinical variables with the risk of upgrading at RP in patients with low-volume GG 2 prostate cancer (≤ 2 cores on biopsy of GG 2 disease). We hypothesized that there are subgroups of patients with GG 2 prostate cancer who are at lower risk of pathologic upgrading and may be good candidates for AS.

Methods

Patients at our tertiary cancer care center (Princess Margaret Cancer Center, Toronto, Canada) who underwent RP between January 2005 and October 2019, with a prior biopsy of GG 2 were identified and underwent retrospective chart review. Patients with one to two cores of GG 2 disease and any

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number of GG 1 cores were eligible for inclusion. Biopsies were taken with different protocols and templates during the study period, mainly taken transrectally.

The cohort consisted of patients with PSA < 20 ng/ml, clinical stage < T3 and N0/NX, M0/MX. Patients who had surgery performed later than 6 months after their biopsy were excluded to minimize the risk of grade or stage change from diagnosis to treatment [10]. Men who had magnetic resonance imaging (MRI) of the prostate before biopsy were also excluded, as prebiopsy MRI was not standard practice in Canada and these patients might have a higher/different risk of grade inflation [11].

Clinical factors such as age, cT-Stage, PSA, PSA density, percent positive cores, biopsy performed in an academic center, maximum percentage core involvement, as well as percentage Gleason pattern 4 were assessed for their association with the risk of upgrading at radical prostatectomy pathology. A cutoff for percentage Gleason 4 of 5% was selected *a priori* based on existing literature [7]. Upgrading was defined as an upgrade in ISUP Grade group ($GG \geq 3$), pathological stage ($\geq pT3$) or to unfavorable pathology at RP (any of: $GG \geq 3$, $\geq pT3$ and/or N1).

Potential predictors were assessed using multivariable logistic regression analyses. Sensitivity analysis was performed using multiple imputation for missing values (R 'mice' function using the random forest classifier). We also applied commonly-used GG 1 restrictions from the University of Toronto (T1c/T2a, PSA ≤ 10) [4], Royal Marsden Hospital (T1/T2, PSA ≤ 15 , $\leq 50\%$ of total cores positive) [12], Prostate Cancer Research International Active Surveillance (PRIAS) (T1c/T2, PSA ≤ 10 , PSA density < 0.20, ≤ 2 cores positive) [13] and Memorial Sloan Kettering Cancer Center (MSKCC) (T1/T2a, PSA ≤ 10 , ≤ 3 cores positive, $\leq 50\%$ of single core positive) [14] on the cohort. These restrictions, and those generated from our data, were evaluated by comparing the odds of upgrading in each restricted cohort to that of the full baseline cohort using univariable logistic regression.

Results

We identified 1,308 men who were diagnosed with GG 2 prostate cancer on biopsy between 2005–2019 and underwent RP (Figure 1). Of these, 604 patients had a maximum of two GG 2 cores. After including men operated on within 6 months of their biopsy only and applying PSA and cT-stage criteria, 378 patients met the inclusion criteria for analysis.

The clinical and pathological characteristics of the patients are presented in Table 1. Of the 378 men, on final RP pathology, 53 (14%) patients had GG 1, 283 (75%) had GG 2 and 42 (12%) had $\geq GG 3$ disease. One hundred and three (27%) men were upgraded to $\geq pT3$ on RP and two (0.5%) men upgraded to N1. One hundred and twenty-eight (34%) men had unfavorable pathology.

In a complete case multivariable analysis (Table 2), percent Gleason 4 at a threshold greater than 5% was associated with a statistically significant increase in the risk of upgrading at RP to $GG \geq 3$ (Odds Ratio [OR] = 9.26, 95%

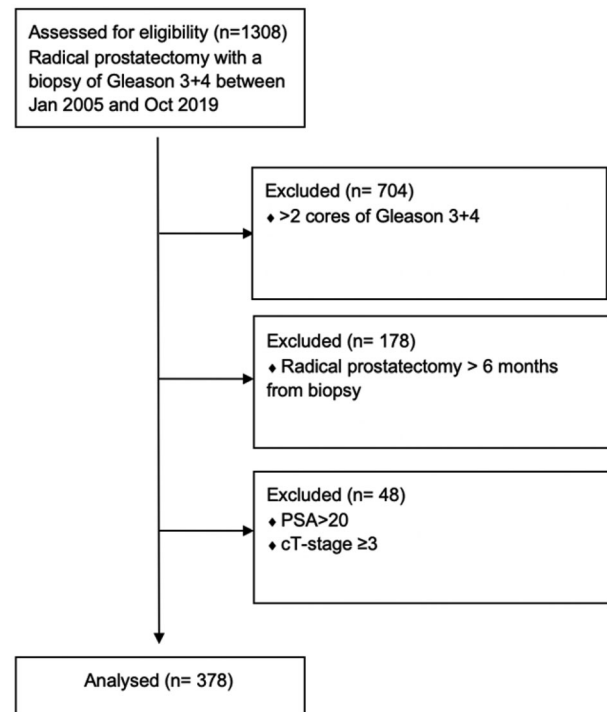


Figure 1. Consort diagram.

Confidence Interval [CI] = 2.58–33.2, $p < 0.001$). A single core with > 50% cancer of any Gleason score increased the risk of pT-stage ≥ 3 (OR = 2.61, 95% CI = 1.46–4.69, $p = 0.0013$) and unfavorable pathology (OR = 1.85, 95% CI = 1.05–3.25, $p = 0.033$).

After multiple imputation of the missing values (Table 1), the association of maximum core percentage > 50% cancer with an increased risk of pT-stage ≥ 3 and unfavorable pathology at radical prostatectomy remained significant (OR = 2.53, 95% CI = 1.52–4.23, $p < 0.001$; and OR = 1.86, 95% CI = 1.14–3.05, $p = 0.014$, respectively). A biopsy with > 5% Gleason 4 also remained significant for predicting an upgrade to $GG \geq 3$ (OR = 4.31, 95% CI = 1.48–12.5, $p = 0.011$).

The variables were applied as restriction criteria to the full cohort to assess their effect on patient selection and risk of early upgrading. Patients eligibility in the cohort for each restriction was 139/301 (46%), 252/305 (72%) and 101/301 (34%) for the $\leq 5\%$ Gleason 4, $\leq 50\%$ maximum percentage core involvement and the two restrictions combined, respectively.

Restricting for $\leq 5\%$ Gleason 4 patients alone led to a decrease in $GG \geq 3$ upgrade from 42/378 (11%) to 3/139 (2%) cases. Restricting for $\leq 50\%$ maximum cancer core involvement, there was a small decrease in pT-stage ≥ 3 upgrade from 103/378 (27%) to 53/252 (21%). The combined restriction of both $\leq 5\%$ Gleason 4 and $\leq 50\%$ cancer maximum core involvement resulted in a decrease in unfavorable pathology from 126/378 (33%) to 20/101 (20%) cases (Figure 2 and Appendix 1).

An analysis of the restricted cohorts versus the baseline cohort are presented in Figure 2, with further details in Appendix 1. Less than or equal to 5% Gleason 4 was associated with a significantly reduced risk of $GG \geq 3$ upgrading on final pathology (OR = 0.17, 95% CI = 0.05–0.55, $p = 0.0007$) and a significantly reduced risk of unfavorable

Table 1. Clinical and pathological characteristics of patients ($n = 378$).

Variable		Missing data
Age at biopsy (years)		0/378
Median (IQR)	62.3 (56.9–66.6)	
< 60	155 (41%)	
60–69	186 (49%)	
≥ 70	37 (10%)	
cT stage		0/378
1	285 (75%)	
2	93 (25%)	
PSA at biopsy (ng/ml)		0/378
Median (IQR)	5.6 (4.2–7.3)	
< 4	79 (21%)	
4–10	262 (69%)	
> 10 to < 20	37 (10%)	
TRUS volume (cm ³)		1/378
Median (IQR)	38 (30–48)	
PSA density at biopsy (ng/ml/cm ³)		1/378
Median (IQR)	0.1 (0.1–0.2)	
≤ 0.15	198 (53%)	
0.15–0.20	82 (22%)	
> 0.20	97 (26%)	
Diagnostic biopsy at academic center		0/378
Yes	210 (56%)	
No	168 (44%)	
Number of cores biopsied		1/378
Median (IQR)	12 (10,13)	
Number of positive cores		1/378
Median (IQR)	3 (2,4)	
% positive cores		1/378
Median (IQR)	25 (16.7–40)	
> 33%	113 (30%)	
Number of GG2 cores		0/378
Median (IQR)	2 (1–2)	
1	160 (42%)	
2	218 (58%)	
Maximum Percentage Core Involvement		28/378 ^a
Median (IQR)	30 (15,60)	
≤ 50%	252 (72%)	
> 50%	98 (28%)	
Percent cancer of total biopsy		72/378 ^a
Median (IQR)	7 (3,11.8)	
Percent Gleason 4 in biopsy		77/378 ^a
Median (IQR)	10 (5,15)	
≤ 5%	139 (46%)	
> 5%	162 (54%)	
pT stage after Radical Prostatectomy		0/378
2	275 (73%)	
3	103 (27%)	
4	0 (0%)	
pN stage after Radical Prostatectomy		0/378
0/X	276 (99.5%)	
1	2 (0.5%)	
ISUP Grade Group after Radical Prostatectomy		0/378
1	53 (14%)	
2	283 (75%)	
3	35 (9%)	
4	4 (1%)	
5	3 (1%)	

^aData primarily missing for patients biopsied outside our center.

pathology (OR = 0.62, 95% CI = 0.40–0.97, $p = 0.041$). Maximal core involvement ≤ 50% cancer was not significant in reducing upgrading for any of the three outcomes.

The combination of ≤ 5% Gleason 4 with ≤ 50% maximal core involvement was significant in reducing pathological upgrading in all the outcomes (OR = 0.24, 95% CI = 0.07–0.81, $p = 0.021$; OR = 0.54, 95% CI = 0.31–0.95, $p = 0.034$; OR = 0.49, 95% CI = 0.29–0.84, $p = 0.0096$). None of the other tested restrictions could significantly reduce pathological upgrading in any of the three outcomes, as described in Figure 2.

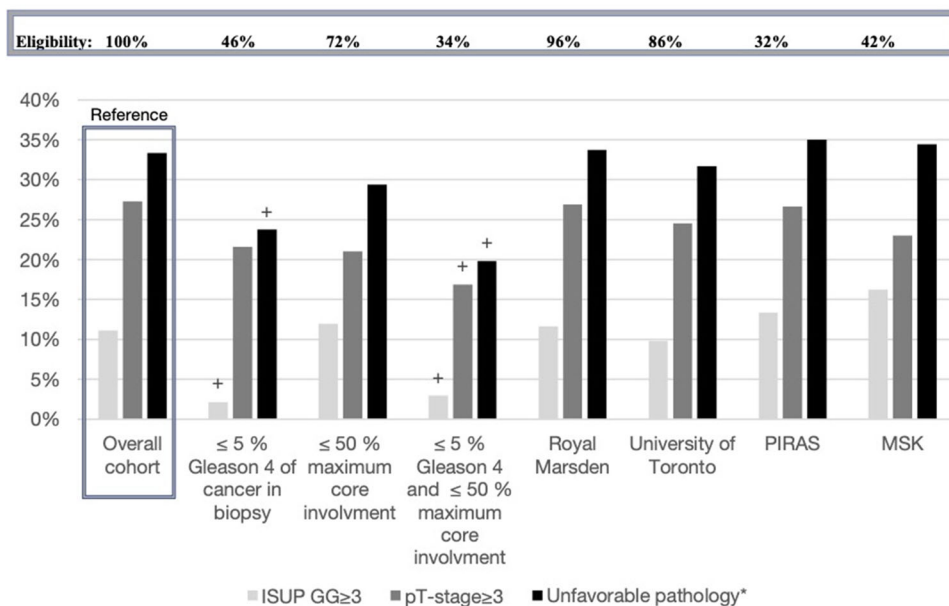
Discussion

This study demonstrated that, in men with low-volume GG 2 disease, ≤ 5% Gleason pattern 4 in the diagnostic biopsy specimen was strongly associated with a reduced risk of GG ≥ 3 disease and unfavorable pathology in the final RP pathology. A single core of ≤ 50% cancer (Gleason score 3 or 4) was initially predictive of a reduced risk of pT-stage upgrade in the multivariate analysis, but this was not maintained in the restricted cohort analyses. The performance of the

Table 2. Complete case multivariable analysis.

	ISUP GG \geq 3 ($n = 42$)		pT-stage \geq 3 ($n = 103$)		Unfavorable pathology ^a ($n = 128$)	
	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
Age at biopsy (years)						
< 60	reference		reference		reference	
60–69	0.91 (0.36–2.27)	0.83	1.64 (0.88–3.05)	0.12	1.39 (0.78–2.46)	0.27
\geq 70	1.02 (0.23–4.53)	0.98	1.45 (0.54–3.86)	0.46	1.18 (0.47–2.98)	0.72
PSA at biopsy (ng/ml)						
< 4	reference		reference		reference	
4–10	1.86 (0.45–7.68)	0.39	1.14 (0.53–2.49)	0.74	1.18 (0.56–2.47)	0.66
\geq 10	2.67 (0.43–16.51)	0.29	1.28 (0.37–4.41)	0.69	1.15 (0.36–3.67)	0.81
PSA density at biopsy (ng/ml/cm ³)						
\leq 0.15	reference		reference		reference	
0.15–0.20	1.56 (0.48–5.09)	0.46	0.66 (0.3–1.46)	0.31	0.94 (0.46–1.93)	0.87
> 0.20	2.72 (0.9–8.2)	0.075	1.31 (0.61–2.82)	0.49	1.8 (0.88–3.68)	0.11
Percent positive cores						
\leq 33%	reference		reference		reference	
> 33%	0.54 (0.16–1.81)	0.32	0.86 (0.45–1.65)	0.65	0.73 (0.39–1.36)	0.32
cT stage						
1	reference		reference		reference	
2	0.44 (0.14–1.4)	0.16	1.23 (0.67–2.28)	0.5	0.95 (0.52–1.72)	0.86
Biopsy at academic center						
Yes	reference		reference		reference	
No	0.98 (0.41–2.33)	0.96	0.76 (0.42–1.38)	0.37	0.71 (0.41–1.24)	0.23
Maximum Percentage Core Involvement						
\leq 50%	reference		reference		reference	
> 50%	0.56 (0.19–1.66)	0.3	2.61 (1.46–4.69)	0.0013	1.85 (1.05–3.25)	0.033
Percent Gleason 4 of cancer in biopsy						
\leq 5%	Reference		reference		reference	
> 5%	9.26 (2.58–33.2)	<0.001	1.2 (0.67–2.17)	0.54	1.66 (0.95–2.88)	0.075

^aDefined as pT \geq 3, ISUP GG \geq 3 and/or pN1.



Note: * \geq ISUP GG 3, \geq pT3 and/or N1. Statistically significant different from the reference.

Figure 2. Rate of upgrading on final pathology in respective cohort.

combination of these two factors was mostly driven by the \leq 5% Gleason 4.

With increasing evidence of the low risk of prostate cancer specific mortality in GG2 patients, as presented in the 29-year follow-up in the SPCG-4 study [15], there is increased interest in expanding AS to these patients, also highlighted by the high prevalence of GG2 in tumors incidentally detected on autopsy [16], suggesting that much of the GG 2

cancer will not present with symptoms increasing the need to select certain GG 2 men for AS.

A recent retrospective study by Carlsson et al. [17] found that deferred treatment for GG 2 was a safe initial management strategy in the short-term. However, the risk of developing metastases is higher for patients with a Gleason 4 component [18], and studies have shown a threefold increase in the risk of adverse pathology in intermediate

compared to low risk prostate cancer [19]. Furthermore, screening trials have shown a lower rate of failure-free survival for intermediate versus low-risk prostate cancer [20]. As a result, GG 2 patients still present a clinical conundrum and most go directly onto treatment in clinical practice.

Our results show that patients in our cohort with low-volume GG 2 cancer at biopsy who exhibit $\leq 5\%$ Gleason 4 have a very low risk of upgrading to GG ≥ 3 at surgical pathology. However, as seen in Table 1 the risk of upgrading to a high risk PCa (GG ≥ 4) was very low (2%) in the entire cohort, indicating that this low volume pre-MRI GG 2 biopsy cohort has a low risk of harboring hidden \geq GG4 disease.

The combination of adding $\leq 50\%$ cancer in any core strengthened the results and reduced the risk of an adverse outcome but came at the cost of reducing potential patient eligibility from 46% to 34% in this cohort. This reduction in risk was driven through a reduction in upstaging to pT-stage ≥ 3 .

Our results are in line with several published studies suggesting the critical impact of the percentage of Gleason pattern 4 on biopsy on the risk of upgrading/upstaging at RP [21]. Cole et al. [22] found that an incremental percentage of Gleason 4 predicted adverse pathology and biochemical recurrence across the entire range of percent Gleason 4 disease. Perlis et al. [23] showed that, for each quantitative percent of Gleason pattern 4 increase, there were 2% higher odds of a pT3 or greater disease.

Our study is the first specifically evaluating men with low-volume GG 2 (one to two GG 2 cores) in order to identify those at low risk of upgrading to GG ≥ 3 at RP who therefore could be safely managed by AS.

Notably, while $\leq 5\%$ Gleason 4 significantly decreased the odds of GG ≥ 3 , no effect on pT-stage ≥ 3 was observed. This suggests that the combination of this criterion with a test or parameter that would reduce the risk of upstaging to pT-stage ≥ 3 might identify the ideal population with low-volume GG 2 disease suitable for AS. Although it could not be directly evaluated in this study, MRI has been shown to reduce extracapsular extension on surgical pathology [24], and combination with MRI would likely reduce the risk of unfavorable pathology at RP substantially. To this end, MRI has been explored in the GG 2 setting with promising results [25], but not in combination with the percentage of Gleason pattern 4.

The major limitation of our study is its retrospective nature with resulting selection, unmeasured confounders, and confounding biases in biopsied patients that went for surgery, radiation, active surveillance, and watchful waiting. However standard of practice during most of the study years have been active treatment in the GG 2 setting which should limit some of the unmeasured selection bias. Furthermore, biopsies and pathology reports were performed at multiple centers, increasing the risk of intra-observer variability and also resulted in some missing covariate data from outside centers.

A second major limitation is the exclusion patients who underwent MRI. MRI was not standard practice in Ontario, Canada, during the years of this study, and a targeted biopsy

with multiple cores taken for a suspicious lesion of the prostate might have interfered with our initial low-volume criteria. Most patients still undergo a first systematic biopsy without the addition of an MRI – although this might be changing in the near future – making our results applicable for most primary diagnosed patients. This study can, therefore, help patients and doctors not routinely choose active treatment in a low-volume GG 2 setting but instead push toward AS, and in most places of the world an MRI would then be the next step.

Thirdly, the lack of long-term follow-up limits the interpretation on definitive correlations between our results and prostate cancer recurrence or prostate cancer specific death. There is also not a definitive correlation between histopathology and disease progression and subsequent treatments, as demonstrated by Kovac et al. [26] in low-risk PCa. We also lack information extent of pT3 disease on final pathology, further limiting the prognostic interpretation.

These results strengthen previous results demonstrating that men with low-volume $\leq 5\%$ Gleason pattern 4 on biopsy prostate cancer are at low risk of adverse pathology on RP. We believe that our results support including the percentage of Gleason 4 when discussing AS with patients with low-volume GG 2 prostate cancer. A combination with MRI will likely strengthen these results but requires further research.

Conclusion

In this retrospective cohort the restrictions of low-volume GG 2 both $\leq 50\%$ any core length and $\leq 5\%$ Gleason 4 in biopsy specimen were the strongest predictors regarding which patients would upgrade at subsequent radical prostatectomy. The restriction of $\leq 5\%$ Gleason 4 providing the largest impact provided through fewer patients upgrading their final ISUP GG score compared to the biopsy.

Ethical approval

Ethical approval was granted from Regional ethics board University of Toronto, RIB number 08-0472.

Author contributions

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Critical review: Johan Björklund, Douglas C. Cheung, Lisa J. Martin, Maria Komisarenko, Robert J. Hamilton, Alexandre R. Zlotta, Antonio Finelli.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Appendix 1. Table of rate of upgrading on final pathology in the respective cohort

	ISUP GG \geq 3	pT-stage \geq 3	Unfavorable pathology ^a	N eligible for restriction (%)
Overall cohort				
Rate of upgrading	11%	27%	33%	100%
\leq 5 % Gleason 4 of cancer in biopsy				
Rate of upgrading	2%	22%	24%	46%
OR (95%CI)	0.17 (0.06–0.55)	0.73 (0.46–1.16)	0.62 (0.40–0.97)	
p-value	0.0007	0.213	0.041	
\leq 50% maximum core involvement				
Rate of upgrading	12%	21%	29%	72%
OR (95% CI)	1.08 (0.66–1.77)	0.72 (0.48–1.04)	0.83 (0.58–1.17)	
p-value	0.799	0.090	0.337	
\leq 5% Gleason 4 and \leq 50% maximum core involvement				
Rate of upgrading	3%	17%	20%	34%
OR (95% CI)	0.24 (0.07–0.81)	0.54 (0.31–0.95)	0.49 (0.29–0.84)	
p-value	0.021	0.034	0.0096	
Royal Marsden				
Rate of upgrading	12%	27%	34%	96%
OR (95% CI)	1.05 (0.67–1.70)	0.98 (0.70–1.36)	1.02 (0.74–1.39)	
p-value	0.906	0.932	0.937	
University of Toronto				
Rate of upgrading	10%	25%	32%	86%
OR (95% CI)	0.87 (0.54–1.41)	0.87 (0.62–1.22)	0.90 (0.65–1.23)	
p-value	0.623	0.437	0.519	
PIRAS				
Rate of upgrading	13%	27%	35%	32%
OR (95% CI)	1.23 (0.67–2.26)	0.97 (0.61–1.54)	1.07 (0.70–1.66)	
p-value	0.515	1.00	0.740	
MSKCC				
Rate of upgrading	16%	23%	34%	42%
OR (95% CI)	1.54 (0.90–2.65)	0.79 (0.51–1.24)	1.05 (0.71–1.56)	
p-value	0.142	0.377	0.838	

^aDefined as \geq ISUP GG 3, \geq pT3 and/or N1