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Conflicts of Interest

None disclosed.

Key words: Prostate cancer, Gleason score, Active Surveillance, Outcomes, Radical Prostatectomy

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Abstract:

Objective:

To examine the feasibility of active surveillance for low volume Gleason sum (GS) 3+4 disease compared to GS 3+3 disease.

Patients and Methods:

Retrospective review of 929 patients, with biopsy proven GS 3+3 and 3+4 PCa, undergoing upfront radical prostatectomy (RP) was performed. Suitability for AS

was adapted from protocols by Royal Marsden Hospital, University of Toronto, and PRIAS by allowing Gleason 3+4 disease.

The outcomes assessed were adverse pathology at RP (upgrading ≥ GS 4+3 and/or upstaging ≥pT3) and biochemical recurrence (BCR) after RP.

Results:

Adverse pathology at RP was compared between GS 3+3 vs 3+4 groups. When selecting patients using Royal Marsden (n=714) or University of Toronto (n=699) protocols, there was statistically significantly more adverse pathology at RP in GS 3+4 group (21% vs 31%, p=0.0028 and 19% vs 33%, p=<0.001 respectively). Using the more stringent PRIAS protocol (n=198), there was no statistical significant difference in groups.

There was no difference in BCR survival between biopsy GS 3+3 and 3+4 groups, regardless of which AS protocol assessed. Pre-operative PSA and clinical staging were the predictors for BCR.

Conclusion:

Presence of Gleason 3+4 at biopsy, when compared to 3+3, increases the risk of adverse pathology being present at radical prostatectomy for less stringent selection criteria. When considering AS, a stricter protocol such as PRIAS, limiting PSA density and number of positive cores to ≤2, appears to decrease the risk of adverse pathology. No differences in BCR were seen between biopsy 3+3 and 3+4 disease, regardless of AS selection criteria.

Introduction:

Active surveillance (AS) is a recognized management for low risk prostate cancer, with the benefit of avoiding side effects of active treatments in men who are thought unlikely to die from prostate cancer. With longer follow-up of this

group of men, the frequency of development of metastases (2.8%) and prostate cancer mortality (1.5%) has been shown to be low(1).

To date, mainstream AS practice has only included men with Gleason 3+3 disease. However, for Gleason 3+4 disease, there are preliminary reports of AS being used in highly motivated men(2), or those with significant comorbidity(1). Data from the Victorian Prostate Cancer Registry showed that 25.6% of men on AS had National Comprehensive Cancer Network (NCCN) intermediate risk (n=251/980)(3). Of these, 53.8% had Gleason 3+4 at biopsy. Additionally, of all men with NCCN intermediate risk category in the database, 8.9% were managed with AS. However, the long-term feasibility and safety of AS in this group of men remains to be elucidated.

For men suitable for AS but undergoing upfront radical prostatectomy, the literature reports the frequency of adverse pathology ranging from 7.1-50.6% (upgrading) and 2.4%-17% (upstaging), depending on the selection criteria used and population studied (4,5). Herein we examine the feasibility for AS for men with biopsy proven Gleason 3+4, in our Australian radical prostatectomy cohort.

Methods:

Respective chart review of the Epworth Prostate Cancer Center database (2005-2013) was performed. Inclusion criteria were men with biopsy Gleason 3+3 and 3+4 disease, with total prostate biopsy cores taken ≥ 10, and undergoing upfront radical prostatectomy (RP). Men were selected as suitable for AS according to recognized protocols utilized by Royal Marsden Hospital (6), University of Toronto (1), and Prostate Cancer Research International Active Surveillance (PRIAS)(7). For the purposes of this study, these protocols were modified to allow biopsy Gleason 3+4, keeping other selection criteria the same (Table 1). RP pathology was obtained, with favorable pathology defined as GS≤ 6 and ≤pT2c, and adverse pathology defined as GS ≥4+3 and/or ≥pT3.

Patients were grouped according to biopsy Gleason score (Gleason 3+3 or Gleason 3+4), and differences between groups determined by Mann-Whitney U or Chi square test as appropriate. The primary endpoint was presence of adverse pathology at RP. The secondary endpoint was biochemical recurrence (BCR), defined as a PSA $\geq$ 0.2 ng/ml. Patients who did not experience a recurrence were censored at the date of their last PSA reading. To assess differences in biochemical recurrence, Kaplan-Meier curves were generated and compared using the log rank test. To determine what variables predicted tumour upgrading/upstaging or biochemical recurrence, binary logistic and Cox proportional hazards regression models were fitted respectively, and odds/hazards ratios (OR/HR) calculated as appropriate. All tests were 2-sided with significance assumed at <0.05. Analyses were performed using SPSS (v18.0, IBM Corporation, Armonk, NY, USA).

Results:

In total, 929 patients were identified with biopsy proven Gleason 3+3 and 3+4 prostate cancer that subsequently underwent upfront RP. Overall, the median age of our cohort was 61.9yrs (IQR 57-66). Comparison of these two groups, demonstrating baseline features at prostate biopsy as well as characteristics at radical prostatectomy, are summarized in Table 2. At prostate biopsy, the Gleason 3+4 group had more positive cores (4 vs 2, p<0.001) and higher proportion of positive cores (33.3% vs 22.2%, p<0.001). Overall, at radical prostatectomy, more patients with Gleason 3+4 at biopsy were upgraded to ≥4+3 (20.2% versus 11.9%, p<0.001), and upstaged to ≥pT3 disease (25.4% versus 16.3%, p=0.001).

The 929 patients were then categorized into suitability for AS, based on their prostate biopsy, according to the modified Royal Marsden (n=714), University of Toronto (n=699) and PRIAS (n=198) protocols. Comparison of subsequent adverse pathology at RP, with AS criteria restrictions, was performed (Table 3). For both Royal Marsden and Toronto AS criteria, there were statistically significant differences in upgrading and upstaging comparing the biopsy 3+4 and 3+3 groups. Both selection criteria had similar proportion of men with

consequent adverse pathology at radical prostatectomy (Royal Marsden 31%, Toronto 33%). The PRIAS criteria, being more stringent, had fewer suitable men in both Gleason 3+3 and 3+4 biopsy groups. However, the difference in adverse pathology at radical prostatectomy was less and not statistically significant (13% versus 19%, p=0.25). Sensitivity analyses examining different combinations of PRIAS inclusion criteria found removing PSA density did not significantly affect adverse pathology (15% versus 23.3%, p=0.81); and similarly allowing 3 positive cores rather than two had minimal effect (15.3% versus 21.1%, p=0.2) (Supplemental Table 1).

To examine biochemical recurrence (BCR) after radical prostatectomy, postoperative PSA data were available in 683 of 714 (95.7%) patients in the Royal Marsden Hospital protocol group, 670 of 699 (95.9%) patients in the Toronto protocol group, and 202 of 211 (95.7%) patients in the PRIAS protocol group. Median follow-up for men without BCR was 26mo (IQR 12-48.5). Kaplan-Meier analysis to compare BCR-free survival after radical prostatectomy is shown in Figure 1 (A,B,C). For all three AS protocols, there were no statistical significant differences between biopsy Gleason 3+3 and Gleason 3+4 disease groups for BCR-free survival (log rank test, p= 0.12, p=0.32 and p=0.72 respectively).

To examine for predictors of adverse pathology, logistic regression analysis was performed on all patients with biopsy proven Gleason 3+3 and 3+4 disease. Age (OR 1.07, 1.04-1.10, p<0.001), number of positive cores (OR 1.11, 1.05-1.17, p<0.001), pre-operative PSA (OR 1.09, 1.05-1.12, p<0.001), clinical stage (OR 1.48, 1.07-2.05, p=0.013) and Gleason sum (3+3 versus 3+4, OR 1.58, 1.15-2.18, p=0.005) were all significant factors on multivariate analysis. However, when a sensitivity analysis was performed, limiting the same logistic regression analysis to men with ≤2 positive cores at biopsy, only age, number of positive cores and PSA remained significant variables. Significant predictors for BCR on cox regression were pre-operative PSA (HR 1.1, 1.06-1.13, p<0.001) and clinical stage (HR 1.91, 1.33-2.73, p<0.001).

Discussion:

In our cohort of men with biopsy proven Gleason 3+3 and 3+4 disease who underwent upfront radical prostatectomy, there were significant differences in adverse pathology found at radical prostatectomy (23.6 vs 36.2%, p<0.001). Modified AS protocols were then used to allow presence of Gleason 3+4 disease at biopsy when selecting patients as suitable for AS. When comparing the biopsy 3+3 and 3+4 groups within the frameworks of these protocols, only the stricter PRIAS criteria was able to reduce the frequency of adverse pathology found at radical prostatectomy (13% versus 19%, p=0.25). Finally, when examining the long-term outcome of biochemical free recurrence, there was no statistical difference between biopsy 3+3 and 3+4 disease, regardless of which modified AS protocol was used.

Across the literature, there have been men with Gleason 3+4 disease, often highly motivated(2) or with some comorbidity(1), managed with AS. Our data suggests, for these men with Gleason 3+4 to be considered for AS, utilization of more stringent criteria such as PRIAS is advisable. PRIAS selection criteria are stricter in that only 2 positive cores at biopsy are allowed, and PSA density must be <0.20ng/ml/cc. Sensitivity analyses of the PRIAS selection criteria suggested dropping PSA density, or allowing 3 positive cores with a PSA density ≤0.20, did not significantly alter the amount of adverse pathology at radical prostatectomy. The allowable number positive cores we found differ to previous findings. Ploussard et al (8) found presence of more than 2 positive cores was significantly associated with higher frequency of Gleason ≥4+3 (27.1% vs 20.9%, p=0.002) and pT3-4 disease (41.1% vs 26.9%, p<0.001). Schiavina et al (9) suggest even stricter interpretation, limiting PRIAS AS criteria to 1 positive core of GS 3+4 disease. They found this selection filter had similar outcomes for adverse pathology and biochemical recurrence when compared to GS 3+3 disease. A percentage amount of Gleason 4 disease ≤5%, relative to the total amount of cancer found at biopsy, has also been proposed as a method for selection with findings that this group of men had similar pathologic stages, total tumor volume, and insignificant tumor rate in RP(10).

Prospective data on AS for men with GS 3+4 disease has been gathered in the University of Toronto, Sunnybrook Hospital single-arm cohort study. Men with Gleason with 3+4 disease were accepted with conditions. Initially (1995-1999), all patients older than 70 years were allowed with PSA ≤15 or Gleason ≤3+4. Subsequently (>Jan 2000), the study was restricted to men with PSA 10-20 and/or Gleason ≤3+4 with significant comorbidities and a life expectancy <10 years (1). In total, 25% of their cohort of 993 patients fulfilled D'Amico criteria for intermediate risk. Overall, only 1.5% of patients died of prostate cancer, and the 10 and 15-year actuarial cancer specific survival (CSS) rates were 98%, and 94% respectively. With so few men dying of prostate cancer, in the context of 25% of the cohort having "intermediate risk", the authors argue that in a screened population, selected men older than age 70 years with intermediate-risk prostate cancer are candidates for surveillance. However, it should be noted that of the 28 men who developed metastases in this cohort, 12 (44%) had Gleason 3+4 at diagnosis.

In a different institution, it was demonstrated that men with intermediate risk (Gleason 3+4 and/or CAPRA 3-5) at baseline were older, had higher PSA values and greater tumour involvement (percentage of core involved) than low-risk men (11). Though follow-up was relatively short, comparison of their intermediate to low-risk group showed similar proportions of progression free survival (61% versus 54%) and progression to active treatment (35% versus 30%)(11). A composite definition of progression was used, including increase in Gleason grade, PSA doubling time ≤2 or 3 years, and progression to treatment. For men enrolled with 3+4 disease, biopsy Gleason 4+3 disease was considered grade progression. It remains to be demonstrated whether an increase in volume of 3+4 disease at biopsy should be used to trigger treatment.

As seen in our series, many men with biopsy Gleason 3+4 disease are offered radical surgery. An alternative is radiotherapy, with the options of external beam radiotherapy (EBRT) or brachytherapy(12). Low dose rate brachytherapy can be used as monotherapy with 3+4 disease, particularly if only low-volume disease (percent cores involved <33%) is present. Long-term biochemical recurrence

free survival for intermediate risk prostate cancer has been reported to be 78% (12 years)(13), similar to the 79.9% reported with combination LDR brachytherapy after 45Gy of EBRT (15 years)(14). These results do appear better than those shown in Figure 1, however there are inherent differences between surgical and brachytherapy patients (such as prostate size) and definitions of intermediate disease making direct comparison difficult.

Advances in imaging and biomarkers may be able to assist with selection of men with 3+4 disease, and deciding if treatment needs to be triggered. The Prostate Health Index (PHI) has been used to successfully predict pathological progression but based on standard Gleason 3+3 criteria(15,16). The Oncotype DX Genomic Prostate Score (GPS) test (Genomic Health, Redwood City, California, USA) is a 17-gene panel that was validated on a cohort of men having National Comprehensive Cancer Network (NCCN) very-low, low and intermediate risk prostate cancer undergoing radical prostatectomy within 6 months(17). The GPS demonstrated ability to predict adverse pathology at radical prostatectomy. Adverse pathology was defined as primary Gleason pattern 4 or any pattern 5 and/or pT3 disease. Cost of the GPS remains a significant barrier for wider uptake. Finally, the ability of multiparametric MRI to grade disease radiologically(18), predict re-classification(19), and guide placement of biopsy needle either in-bore (20)or using ultrasound fusion(21), could assist selecting men with Gleason 3+4 disease for AS.

Patients on AS, whilst avoiding the consequences of radical treatment, are living with untreated cancer. Thus, they may suffer negative psychological effects and anxiety from fear of progression. As men with intermediate risk disease have higher risk of progression, it is possible that they could have more severe psychological effects. Alternatively, as many of these men are often highly motivated, they may be self- selected for calmer personality types. A systematic review suggested that patients undergoing AS reported good quality of life and did not appear to suffer negative psychological impacts(22). In particular, there has been documented low levels of anxiety for men on AS (23,24).

As our data was examined retrospectively, we were limited to the data fields previously collected. Percentage of core involvement with cancer was not collected, hence AS protocols requiring <50% of single core involved could not be tested. Without this variable, analysis to identify a threshold for percentage of core involvement, which might predict lesser risk of progression, could not be performed. In particular, we were unable to test the hypothesis of Huang et al(10) examining a biopsy threshold of <5% containing Gleason 4 having equivalent outcomes at radical prostatectomy to men with only Gleason 3+3 disease. Also, a surgical cohort rather than an active surveillance one will contain unaccounted inherent biases such as age, comorbidities, patient anxiety and institutional factors. We were able to report biochemical recurrence post radical prostatectomy but this is still only a surrogate for longer-term outcomes such as metastasis and cancer specific survival.

In conclusion, appropriately selected biopsy Gleason 3+4 disease may be considered for highly motivated patients. A stricter protocol such as PRIAS should be used with restriction of number of positive cores to ≤2, and consideration of PSA density ≤0.20, as this appears to minimize presence of potential adverse pathology.

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Institution	Clinical Stage	PSA (ng/ml)	Biopsy GS	PSAD (ng/ml/ml)	No of +ve cores
Royal Marsden	T1-T2	≤ 15	≤ 3+4	-	≤ 50% total cores
University of Toronto	T1c/ T2a	≤ 10	≤ 6	-	-
PRIAS	T1c/ T2	≤ 10	≤ 6	< 0.20	≤ 2

	Gleason 3+3	Gleason 3+4
n	399	530
Age (Years)		
Median (IQR)	61 (57-66)	62 (58-66)
PSA (ng/ml)		
Median (IQR)	6.1 (4.8-8.5)	5.9 (4.6-7.9)
Clinical stage		
cT1	323 (80.9%)	373 (70.4%)
cT2a	31 (7.8%)	68 (12.8%)
cT2b	38 (9.5%)	65 (12.3%)
cT2c	6 (1.5%)	21 (4.0%)
≥ cT3	1 (0.3%)	3 (0.6%)
PSA Density		
Median (IQR)	0.2 (0.1-0.2)	0.2 (0.1-0.3)
Biopsy cores taken		
Median (IQR)	12 (10-15)	12 (11-15)
Number of positive cores		
Median (IQR)	2 (2-4)	4 (2-6)
% Positive cores		
Median (IQR)	22.2% (12.5-37.5)	33.3% (18.3-50.0)
Pathological Gleason Score- RRP		
6	138 (34.6%)	28 (5.3%)

3+4	214 (53.6%)	395 (74.5%)
4+3	41 (10.3%)	90 (17.0%)
8	5 (1.3%)	9 (1.7%)
9	1 (0.3%)	8 (1.5%)
pT stage- RRP		
pT2	334 (83.7%)	395 (74.5%)
pT3a	59 (14.8%)	120 (22.6%)
pT3b	6 (1.5%)	15 (2.8%)
Adverse Pathology		
yes	94 (23.6%)	192 (36.2%)
no	305 (76.4%)	192 (63.8%)
Tumour volume (ml)		
Median (IQR)	1.5 (0.6-3.3)	1.9 (1.0-3.5)
Prostate volume (ml)		
Median (IQR)	49 (38.3-63.8)	46 (38.0-58.0)

Biopsy GS	3+3	3+4	p
Royal Marsden Hospital			
n	328	386	
Prostatectomy GS			
≤ 6	123 (37%)	23 (6%)	
3+4	167 (51%)	294 (76%)	<0.001
≥ 4+3	38 (12%)	69 (18%)	
pT Stage			
2	284 (86%)	304 (79%)	0.006
≥ 3	44 (14%)	82 (21%)	
Favourable pathology	259 (79%)	266 (69%)	0.0028
Adverse pathology	69 (21%)	120 (31%)	
Toronto			
n	308	391	
Prostatectomy GS			
≤ 6	118 (38%)	21 (5%)	
3+4	161 (52%)	301 (77%)	<0.001
≥ 4+3	28 (10%)	69 (18%)	
pT Stage			
2	272 (88%)	306 (78%)	<0.001
≥ 3	36 (12%)	85 (22%)	
Favourable pathology	251 (81%)	262 (67%)	<0.001
Adverse pathology	57 (19%)	129 (33%)	
PRIAS			
n	110	88	

Prostatectomy GS			
≤ 6	57 (51.8%)	9 (10%)	<0.001
3+4	45 (40.9%)	69 (79%)	
≥ 4+3	8 (7.3%)	10 (11%)	
pT Stage			
2	102 (92.7%)	78 (87%)	0.32
≥ 3	8 (7.3%)	10 (13%)	
Favourable pathology	97 (88%)	70 (80%)	0.097
Adverse pathology	13 (12%)	18 (20%)	