Comparison of pathological and oncologic outcomes in "favorable risk" GS 3+4 and low risk GS6 prostate cancer: considerations for active surveillance

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Active surveillance (AS) for prostate cancer has become a mainstay of treatment for men with low risk (LR) disease. More recently, however, AS is increasingly being utilized in select men with intermediate risk (IR) prostate cancer. In Australia, where the practice of AS has been widely embraced, approximately one in four men on AS have IR disease (1). Whilst the pendulum has certainly swung towards AS therefore reducing overtreatment of indolent disease, concerns remain that the pendulum may have swung too far, and we risk undertreatment of more aggressive disease.

The recent NCCN guidelines recommending AS as an option for men with "favourable" IR prostate cancer has prompted several investigators to evaluate the potential harms of including men with higher volume and higher grade disease in AS programs (2). This large retrospective study by Gearman *et al.* of over 8,000 men who underwent radical prostatectomy (RP) for Gleason score ≤3+4 assessed the pathological and survival outcomes of men with LR and IR prostate cancer. The study revealed several notable findings.

Comparing men with Gleason 3+3 and 3+4 at biopsy, the rates of organ-confined disease, extra-prostatic extension and seminal vesicle invasion were 94.1% *vs.* 83.5%, 4.2% *vs.* 11.6%, and 1.7% *vs.* 4.6%, respectively. The rate of Gleason score upgrading was also significant, with 12.3% of men with Gleason 3+4 at biopsy being upgraded to unfavourable risk, compared to 3.2% of men with Gleason 3+3. Multivariate analysis demonstrated that Gleason 3+4 at biopsy was associated with a 3-fold greater risk of non-organ confined disease at RP (OR 3.07, 95% CI: 1.665–5.654, P=0.0003), with a trend towards increased risk of seminal vesicle invasion and positive surgical margins. These findings highlight the significant risk of understaging and undergrading of prostate cancer based on traditional tools such as physical examination (PSA) and transrectal prostate biopsy.

The presence of secondary Gleason pattern 4 disease has been previously shown to be associated with adverse pathology at RP. In the PRIAS Study, among men who underwent RP following reclassification during follow-up, 36% had unfavourable pathologic outcomes, defined as Gleason score ≥4+3 or ≥pT3a. On multivariate analysis, only Gleason score >6 was predictive of unfavourable pathologic outcomes (3). Recently published retrospective studies, have also shown high rates of adverse RP pathology for men with IR disease at biopsy. Aghazadeh *et al.* noted significantly higher rates of pathological upgrading and upstaging for favourable IR *vs.* LR disease (27.4% *vs.* 14.8%). However, unlike the current study, the favourable IR group was restricted to men with <50% positive biopsy cores, which is more consistent with the NCCN criteria for favourable IR prostate cancer (4). Patel *et al.* found rates of adverse pathological findings to be 24.7% *vs.* 5.8% for low volume IR *vs.* LR disease, respectively (5). Similarly, Perlis *et al.* demonstrated 35% of men with Gleason 3+4 at biopsy to have non-organ confined disease compared to 19% in men with Gleason 3+3, although the high incidence in the

latter group suggests the inclusion of a cohort with more aggressive disease than the current study (6). These studies highlight the limitations of our current tools available for accurately grading and staging men with IR prostate cancer.

Refinement of our techniques is required when selecting these men for AS, as Gleason 3+4 is markedly a heterogenous disease. Limiting AS in this subgroup of men to those with small tumour volume, as reflected by fewer positive biopsy cores or lower percentage of core involvement, may be appropriate. A limitation of the current study is that the effect of tumour volume was not assessed.

In men with IR prostate cancer, several investigators have suggested that restricting AS to men with low volume disease may lead to lower rates of adverse pathology at RP. Wong *et al.* compared rates of adverse pathology among men with Gleason 3+3 *vs.* 3+4 disease, who were suitable for AS according to protocols published by Royal Marsden Hospital, University of Toronto and PRIAS. Rates of adverse pathology were significantly higher for men with Gleason 3+4 disease meeting AS criteria as defined by Royal Marsden Hospital and University of Toronto. However, no difference was found between the two groups when restricted to the more stringent PRIAS criteria (PSA <10, PSAD <0.2, ≤2 positive cores, ≤cT2c) (7). Ploussard *et al.* demonstrated that rates of unfavourable pathology in men with Gleason 3+4 at biopsy approached 50%, but could be reduced to <20% if AS was restricted to men with PSA ≤10, PSAD ≤0.15 ng/mL/g, cT1c and ≤2 positive cores (8). As mentioned above, Perlis *et al.* noted a significantly higher rate of adverse pathology for men with Gleason 3+4 at biopsy compared to Gleason 3+3. However, among men with PSA <4, rates of pT3 disease were similar when men with Gleason 3+4 were restricted to low tumour volume (positives cores ≤15%) (6). For men with PSA 4-8, the two groups were similar when restricting to low tumour volume and <10% Gleason pattern 4. In contrast, Patel *et al.* were unable to identify a subgroup of low volume IR men with rates of adverse pathologic findings comparable to LR and very LR cohorts, even after restricting the IR group to pT1c, PSAD <0.15 ng/mL/g, ≤2 positive cores and <50% core involvement (5).

Another potential means of refining patient selection is to specifically limit the amount of Gleason pattern 4 disease, which was not evaluated in the current study. Huang *et al.* demonstrated similar pathological findings at radical prostatectomy in men with Gleason 3+3 and 3+4 disease on biopsy, when the latter group was restricted ≤5% Gleason pattern 4 (9). Similarly, Cole *et al.* showed that percentage of Gleason pattern 4 to be strongly associated with adverse pathology, with odds increasing significantly when reaching >20%. Furthermore, volume of Gleason pattern 4 was shown to be a stronger predictor of biochemical recurrence than Gleason score in men with Gleason 7 disease (10).

In the current study, the authors also assessed the effect of final RP histology on adverse pathological outcomes. Men with Gleason 3+4 on final pathology were more likely to have non-organ confined disease (17.4% *vs.* 6.1%, P<0.0001), positive surgical margins (20.7 *vs.* 15.3%, P<0.0001) and lymph node invasion (1.8% *vs.* 0.3%, P<0.0001). Poorer survival outcomes at 10 years were also observed for men with Gleason 3+4 at biopsy compared to Gleason 3+3, with the former having lower biochemical recurrence free survival (81.2% *vs.* 88.9%, P<0.001), lower systemic progression free survival (96.5% *vs.* 99%, P<0.001) and higher prostate cancer-specific mortality (0.9% *vs.* 0.4%). Rates of adjuvant and salvage radiotherapy were also higher in the Gleason 3+4 group compared to Gleason 3+3. However, prostate cancer survival remained high at 99% and 100% for both groups, respectively.

Prospective trials evaluating survival outcomes of men on AS have also raised concerns about the inclusion of men with Gleason 3+4 disease. In the AS cohort from University of Toronto, which included 13% of men with Gleason 3+4 at diagnosis, survival from prostate cancer was high overall, with 10- and 15-yr cancer-specific survival rates of 98.1% and 94.3%, respectively (11). However, the 15-yr metastasis-free survival in men with Gleason 3+4 disease was significantly lower compared to men with Gleason score ≤6 (84% *vs.* 94%) (12). Outcomes of AS in men diagnosed with prostate cancer in the Goteburg screening study were also assessed by Godtman *et al.* The study comprised of 474 men managed with AS, including 104 men (22%) with IR disease. The authors found that men with IR disease were nearly five times more likely to experience failure of AS compared to men with very LR disease, as defined as death from prostate cancer, development of metastases or biochemical recurrence after curative treatment, or use of salvage radiotherapy or hormone therapy (13).

Given the potential aforementioned risks of AS for IR disease, better tools are still required to avoid understaging and undergrading at diagnosis, and to detect early progression during surveillance. Multiparamentric MRI (mpMRI) in combination with cognitive or fusion targeted

biopsy has been shown to improve detection of clinically significant prostate cancer and reduce detection of clinically insignificant disease (14). In AS, mpMRI is now increasingly being utilized as a surveillance tool in addition to clinical parameters. Frye *et al*. showed that MRI with fusion biopsy outperformed PSA as a predictor of pathological progression in an AS cohort, with 77% sensitivity and 81% negative predictive value (15). Similarly, Nassiri *et al*. demonstrated that serial MRI improved detection of > Gleason 4+3 cancers during follow-up (16). In their AS cohort, 63% of men with Gleason 3+4 tumours were upgraded, with near 100% of all upgrades occurring at an MRI visible or tracked site of tumour. MRI features may also predict likelihood of more favourable pathology at time of radical prostatectomy. In men with Gleason 3+4 disease at diagnosis, Gondo *et al.* found that absence of a dominant nodule on T2 + DWI and low percentage of Gleason pattern 4 predicted pathological downgrading at time of radical prostatectomy (17). Whilst promising, mpMRI is limited by cost, availability, standardization of fusion biopsy techniques and need for expertise.

Adequate prostate sampling at biopsy is critical for estimation of tumour volume and assessment of grade. Saturation biopsies and transperineal approaches using brachytherapy template grids have been shown to improve detection and correlation with radical prostatectomy specimens. In Australia, where transperineal prostate biopsy is being increasingly adopted, this approach has been shown to reduce the odds of Gleason Grade upgrading by 40% compared to the transrectal approach (18). Voss *et al.* found that early confirmatory transperineal biopsy during AS was associated with significant upgrading in one-third of men, who were no longer suitable for AS based on initial transrectal biopsy (19). Other promising tools include genomic tests such as the biopsy-based Oncotype DX Genomic Prostate Score, which has been shown to improve prediction of adverse pathology and outperform tumour volume as a predictor of pathological upgrading at RP (20,21).

Active surveillance for men with IR prostate cancer needs to be used carefully. Prospective cohort data suggests a 15-yr cancer specific survival of 94%, but a lower metastatic free survival (84%). For highly motivated men, parameters such as low PSA, absence of dominant nodule on MRI, low volume disease at biopsy (i.e. ≤2 positive biopsy cores, <50% of single core involved) and small percentage of Gleason pattern 4 disease are suggested to aid selection. Ongoing monitoring of men with IR prostate cancer risks missing the window of curability. Tools such as MRI, transperineal biopsy and genomic tests yield great promise, but are currently limited by expense, required expertise and lack of availability. Further studies are required to ensure that the pendulum does not swing too far away from curative treatment for this group of men.

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Footnote

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