Current evidence for active surveillance for intermediate risk prostate cancer: editorial on comparison of pathological and oncologic outcomes in "favorable risk" GS 3+4 and low risk GS6 prostate cancer by Gearman *et al.*, *Journal of Urology*

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Comment on: Gearman DJ, Morlacco A, Cheville JC, *et al.* Comparison of Pathological and Oncologic Outcomes in Favorable Risk Gleason Score 3 + 4 and Low Risk Gleason Score 6 Prostate Cancer: Considerations for Active Surveillance. J Urol 2017. [Epub ahead of print].

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Active surveillance is now endorsed as the preferred treatment approach for patients with National Comprehensive Cancer Network (NCCN) very-low and low risk prostate cancer. Large prospective series demonstrate rates of progression of ~50% at 10 years, with very low rates of metastatic progression (0.5–2.8%) and prostate-cancer specific mortality (0.1–1.5%) (1,2). The recently published ProtecT randomized controlled trial from the UK has corroborated the low risk of metastatic progression while on active surveillance (6 events per 1,000 person-years) (3). Of note, this study randomized all risk categories of prostate cancer, and although no post-hoc subanalysis was performed, it is very possible that the ~25% of men with intermediate and high risk disease accounted for the higher rate of metastatic disease observed in the entire active surveillance cohort (compared to 2.4 per 1,000 for surgery and 3 per 1,000 for radiotherapy). Improved outcomes have indeed been seen in series that have more restrictive criteria for enrollment [i.e., Johns Hopkins cohort (2), which excludes men with prostate-specific antigen (PSA) density >0.15 ng/mL] compared to the Toronto cohort which allowed men with favorable Gleason 3+4=7 disease (4). Progression while on active surveillance has been linked to increasing number of biopsy cores involved, higher PSA density, and African American race (5,6).

While active surveillance of Gleason 3+4=7 disease may be thought of as a variation of "watchful waiting" for men >70 years old or with limited life expectancy due to comorbidities, the longer term outcome for younger men is an area of much current interest and research. It has been published that men with intermediate risk (IR) prostate cancer have higher rates of prostate-cancer specific mortality compared to low risk men (4). This finding has fueled the controversy as to whether IR men are suitable for any period of active surveillance. Many retrospective series have been published and the prospective evidence is currently growing. Furthermore, metastatic progression may not be the gold-standard outcome measure to gauge safety of active surveillance. Certain adverse pathologic features found at radical prostatectomy have been demonstrated to be independent predictors of biochemical recurrence, which leads to higher rate of metastatic progression and death from prostate cancer. These features include extraprostatic extension (EPE), seminal vesicle invasion (SVI), and positive surgical margins (PSM). So, although men with IR may not progress to metastasis while on active surveillance (AS), they may indeed have higher rates of adverse pathologic features.

Thus, the present study by Gearman *et al.* sought to compare the rates of these adverse pathologic features between Gleason 3+3=6 and 3+4=7 prostate cancer patients who have undergone radical prostatectomy in their institutional prospective database. Gearman *et al.* found significantly higher rates of adverse features (e.g., EPE, SVI, LN positive disease) and consequently higher rates

of biochemical recurrence, systemic progression, prostate-cancer specific, and overall mortality at 10 years (7). It should be noted that they assigned risk according to pathology, PSA, and clinical staging and therefore this cohort of IR patients may not be as "favorable" as would be generally considered for active surveillance. Specifically, they did not use known clinical predictors of disease progression such as PSA density or percentage of positive biopsy cores in their inclusion criteria.

Similar studies have been published. Aghazadeh *et al.* did a similar study comparing pathologic features in men with prostate cancer stratified by NCCN risk category: low risk, favorable IR, and unfavorable IR. The group found rate of adverse pathologic findings in favorable IR was significantly higher than low risk (27.4% *vs.* 14.8%, P<0.001) and significantly lower when compared to unfavorable IR (27.4% *vs.* 48.5%, P<0.001). Time to biochemical recurrence was significantly different between the NCCN assigned risk groups (P<0.001) with unfavorable IR having worse outcomes than low risk (LR) and favorable intermediate risk (FIR) (5 years recurrence free survival rates for LR, FIR, unfavorable IR was 93%, 87%, 79%). When comparing FIR and LR, time to recurrence was not significant (8).

There are limitations to retrospective examination of adverse pathologic features as a surrogate for safety of active surveillance. Indeed, Gearman *et al.* does not exactly address the safety of active surveillance, but rather highlights the established difference in prognosis between low risk and IR disease, which is the very foundation for distinct risk group classification. Given that all patients underwent prostatectomy, there may also be selection bias as to an inherently poorer performing group of patients that were counseled toward surgery, beyond the variables controlled for in the study.

Stronger evidence to examine safety of AS for IR patients comes from a few prospective cohort studies whose experience is gaining maturity. Klotz *et al.* assessed long term outcomes of men with low (n=837) and IR (n=132) prostate cancer, which included 71% favorable risk deemed by D'Amico criteria with remainder who were IR (13%, defined at PSA >15, Gleason 3+4=7, or T3). After median follow-up of 9.6 years, 2.8% of patients developed metastatic disease, (44% of whom were Gleason 3+4=7 at diagnosis). A greater proportion of IR patients therefore developed metastasis (9%) compared to low risk patients (1.9%). A total of 93% of patients were either diagnosed with or upgraded to Gleason ≥7 before developing metastatic disease. Interestingly, 26% of the patients fulfilled Epstein criteria for very low risk (1).

Musunuru *et al.* published data on survival outcomes for IR prostate cancer men on active surveillance. IR was compared to LR and the authors found metastasis-free survival rate to be significantly worse in IR (91% and 82% in IR *vs.* 96% and 95% in LR for 10 and 15 years respectively, HR =3.14; 95% CI, 1.51–6.53, P=0.001). Overall survival (OS) (67% and 51% in IR *vs.* 84% and 67% in LR, HR =2.13; 95% CI, 1.53–2.98, P<0.0001) and cause specific survival (97% and 89% in IR *vs.* 98% and 97% in LR, HR =3.74; 95% CI, 1.32–10.61, P=0.008) were also worse for IR compared to LR at 10 and 15 years. The study found a 3 times higher risk of M1 disease in IR. More specifically, men with Gleason 6 or less and PSA 20 or less benefited from higher metastasis free survival up to 10 and 15 years while men with Gleason 3+4 and PSA 20 or less had favorable metastasis free survival at only 10 years but not at 15 years along with Gleason 4+3 and PSA less than 20 group which saw poor metastasis free rates at both 10 and 15 years. Data from this study supports AS in LR disease and select IR disease (Gleason 6 or less, PSA 10–20) (4). Cooperberg *et al.* from San Francisco looked at outcomes of AS in men with IR using validated Cancer of the Prostate Risk Assessment (CAPRA) scores which is based on PSA, Gleason score, age, clinical T stage, and percent of biopsy cores positive. IR category was assigned to men with Gleason sum of 7 or CAPRA score 3–5 which is associated with higher volume disease and/or higher PSAs. This group found 30% of IR patients (based on PSA) were upgraded (to Gleason ≥7) based on biopsy. Thirty-five percent of intermediate versus 30% of low risk underwent active treatment within the median follow-up of 47 months, and PSA velocity was comparable between the two risk groups. Overall progression free survival (defined as no upgrade, no PSA double time, no active treatment) was higher but not significant in IR group at 61% and 54% in low risk within the median follow-up of ~4 years (9).

Lastly, Bul *et al.* assessed long-term outcomes of men on AS for low and IR PCa who had been enrolled in the Rotterdam and Helsinki arms of the European Randomized Study of Screening for Prostate Cancer (ERSPC). IR was defined as Gleason 6 with PSA 10–20, Gleason 7 (either 3+4 or 4+3), and three or fewer positive biopsy cores. Of note, 3% of the IR group was Gleason 4+3=7. The 10-year active-therapy-free survival rate was 49.7% in the LR group and 30.3% in the IR group, which was significantly different. Distant metastasis was found in one low risk and three IR patients, resulting in 10-year metastasis-

free survival rate of 99.7% for low risk and 96.4% for IR (P=0.03). Although the OS rate was significantly higher for the low risk group (84.3% *vs.* 71.3%), there was no difference in disease specific survival between the two risk groups after median follow-up of 7.4 years (99.1% *vs.* 96.1%). A total of 56.6% of patients were able to avoid active therapy for median of at least 6.8 years. The authors endorse AS for selected men with IR disease, especially for men >70 years old or with significant comorbidities. Although there is higher rate of metastasis (2.3% *vs.* 0.3%), this ~2% rate is still modest and the authors cite the similar rate of prostate-cancer specific death (0.8% *vs.* 1.6%) (10). The higher rate of OS cannot be denied, however, and perhaps this result may be explained by the higher rate of androgen deprivation therapy use for the IR group (23.2% *vs.* 10.5%) and consequent cardiovascular morbidity. The specific cause of mortality was not able to be explored by this study, however.

Future studies should focus on a more standardized approach of prostate cancer risk stratification so as to allow for one to one comparison (i.e., is Gleason 6 with PSA 10–20 ng/mL different than Gleason 3+4=7 with PSA <10 ng/mL?). Additionally, as the prospective trials mature, more robust data will be forthcoming. Until then, utilizing the data available to us, we cannot full assess the safety of AS for men with IR prostate cancer. The selected studies reviewed above give reassurance that selected men that fall in the IR risk can be managed with AS, however the parameters for selecting IR patients most favorable for AS, may not be adequate.

Even if men with IR disease have a higher rate of progression to treatment, it does not automatically mean that they cannot enjoy a treatment-free latency period free of the morbidity of surgery or radiation. However, if these men are truly destined to have worse adverse pathologic features immediately after diagnosis—without any period of active surveillance as the Gearman *et al.* paper suggests—should they be considered at all for active surveillance? This is a difficult question to answer and prompts the follow-up question: are some favorable IR patients are more favorable than others?

Confirmatory genome-based assays may be employed in this realm to elucidate which patients are suitable for AS and which should consider active treatment. Such assays include Oncotype-DX, Decipher, and Prolaris. Similarly to the present study, the Oncotype-DX assay serves to predict risk of adverse pathologic features at radical prostatectomy by employing a 17-gene reverse transcriptase polymerase chain reaction (PCR) assay selected from the domains of cellular proliferation, cellular organization, stromal response, and androgen receptor signaling (11). Furthermore, the growing role of multi-parametric magnetic resonance imaging (MRI) to survey prostate lesions and to assess growth/progression of disease is an active area of research as well. The utility of this technology is still evolving, especially as a stand-alone predictor of disease progression. A recent study by Felker *et al.*, demonstrated limitations in serial lesion characterization to predict disease upgrading on biopsy during active surveillance. Their radiographic criteria for lesion progression included increase in PIRADS score, doubling of lesion volume, and ADC value decrease of ≥150 mm^2/s. Although the specificity was favorable at 90%, the negative predictive value was only fair at 70%. The overall performance of MRI had a relatively unfavorable AUC =0.63. It was only after combining MRI lesion characteristic changes with maximum cancer core length and PSA density >0.15 ng/mL^2 in their predictive model that AUC rose to 0.91 (12). The lack of change in MRI characteristics over time but presence of upgrading on repeat biopsy may not necessarily be a limitation of the imaging modality, but a reflection of the inherent sampling error/potential for under-grading of 12-core systematic biopsy. The Felker *et al.* study, however, specifically included men who underwent MRI-transrectal ultrasound (TRUS) fusion biopsy initially. As more TRUS-MRI fusion biopsies are performed as initial or confirmatory biopsies to enroll/maintain patients on active surveillance, the data on MRI lesion surveillance as a surrogate marker for disease progression will surely be refined, perhaps identifying an earlier threshold for intervention with definitive treatment without the need for invasive biopsy.

As more men are enrolled in active surveillance, there is also a need for defining the optimal treatment modality at the time of progression. Whalen *et al.*, identified low and IR men who did not undergo treatment within 12 months of prostate cancer diagnosis (including those on active surveillance, watchful waiting, and those refusing treatment). The authors concluded that men on AS may be inadequately treated with radiotherapy when compared to other modalities. Furthermore, they found that patients with PSA velocity >2 ng/mL/year had superior 10-year OS after radical prostatectomy when compared to radiotherapy (13). There are a few reasons why treatment after active surveillance may represent a different clinical scenario than treatment early after cancer diagnosis. Under-sampling error from prostate biopsy may fail to identify high-risk

disease that would benefit from neoadjuvant androgen deprivation along with radiotherapy, while the ability of surgery to provide definitive stage and grade diagnosis via the final pathological specimen may improve selection for adjuvant local and systemic treatment. This may be especially pertinent for men who have had a significant period of time without definitive treatment of their active malignancy. Although the conclusions of this study are provocative, further investigation is needed.

Therefore, the controversy continues. As Gearman *et al.* have demonstrated, active surveillance for intermediate-risk disease may indeed be a riskier treatment option compared to low risk patients, but does that mean it should be abandoned completely? Given the protracted natural history of prostate cancer, it is reasonable that some limited period of active surveillance should indeed be safe, but current level one evidence is lacking to support its routine use for IR patients. The ProtecT trial will provide valuable information as the data matures beyond the median 10-year follow-up. Clinicians and patients alike often cite the rationale for definitive treatment when the disease is known to be organ-confined and curable, rather than risking the chance of development of EPE or SVI after a period of surveillance, which portends higher risk of biochemical recurrence, metastasis and overall mortality. The key will be in developing more refined selection criteria within IR patients based on pathologic (i.e., percentage of Gleason 4 at biopsy), genomic (i.e., Oncotype DX), and radiographic criteria (i.e., mp-MRI lesion size and stability).

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Footnote

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