REVIEW
Active surveillance for intermediate-risk prostate cancer
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BACKGROUND: Utilization of active surveillance (AS) for prostate cancer is increasing. Optimal selection criteria for this approach are undefined and questions remain on how best to expand inclusion beyond typical men with very low- or low-risk disease. We sought to review the current experience with AS for men with intermediate-risk features.

METHODS: PubMed was queried for all relevant original publications describing outcomes for men with prostate cancer managed with AS. Outcomes for patients with intermediate-risk features as defined by the primary investigators were studied when available and compared with similar risk men undergoing immediate treatment.

RESULTS: Cancer-specific survival for men managed initially with AS is similar to results published with immediate radical intervention. A total of five published AS series describe some outcomes for men with intermediate-risk features. Definitions of intermediate risk vary between studies. Men with Gleason 7 disease experience higher rates of clinical progression and are more likely to undergo treatment over time. Intermediate-risk men with Gleason 6 disease have similar outcomes to low-risk men. Men with Gleason 7 disease appear at higher risk for metastatic disease. Novel technologies including imaging and biomarkers may assist with patient selection and disease surveillance.

CONCLUSIONS: The contemporary experiences of AS for men with intermediate-risk features suggest that although these men are at higher risk for eventual prostate-directed treatment, some are not significantly compromising chances for longer-term cure. Men with more than minimal Gleason pattern 4, however, must be carefully selected and surveyed for early signs of progression and may be at increased risk of metastases. Incorporating information from advanced imaging and biomarker technology will likely individualize future treatment decisions while improving overall surveillance strategies.

INTRODUCTION
Active surveillance (AS) has gained widespread acceptance as the initial treatment choice for certain patients with prostate cancer. Up to 90% of contemporary low-risk men are initially managed in this manner.¹ Several factors have contributed to increased utilization of AS over the last decade, allowing many men to avoid unnecessary interventions and treatment-related side effects. Multiple ongoing series have collected prospective data on men managed expectantly, utilizing varied selection criteria and surveillance strategies. These series, some with long-term follow-up, have documented that an approach of initial surveillance can be safe and effective. In addition, an emphasis on reducing overtreatment of prostate cancer has increased in response to the United States Preventative Service Task Force’s recommendation against widespread PSA screening in 2009.²

When discussing AS, patients are often placed into risk categories based on known clinical features as defined by D’Amico criteria, the National Comprehensive Cancer Network (NCCN) or Cancer of the Prostate Risk Assessment scoring algorithm.³⁻⁴ Although most published data with AS have focused on men with very low- and low-risk prostate cancer, patients and practitioners continue to question the selection criteria for this approach. Some have advocated expanding these to include men with intermediate-risk features. The purpose of this article is to review the background and rationale for AS, and summarize the experience with this approach for men with intermediate-risk prostate cancer.

MATERIALS AND METHODS
We queried PubMed for all relevant original publications describing outcomes for men with prostate cancer managed with AS. Referenced studies must have defined patient inclusion criteria and surveillance strategies to identify early signs of disease progression when treatment with curative intent may be offered. Outcomes for patients with intermediate-risk features as defined by the primary investigators were studied when available and compared with similar risk men undergoing immediate treatment.

RESULTS
Long-term outcomes of AS for predominantly low-risk prostate cancer

Data from two large prospectively studied AS cohorts have recently been published from distinct North American populations. Klotz et al.⁵ have reported an update on their series from the University of Toronto after a median follow-up of 6.4 years (0.2–19.8) with 206 out of 993 men followed for over 10 years. This included a heterogeneous group of men, 21% of whom were intermediate risk at diagnosis. For surveillance, PSA was monitored every 3 months for 2 years, then every 6 months. Repeat biopsy was performed within the first year and then every 3–4 years. Two hundred and sixty seven (27%) men ultimately received definitive treatment to the prostate. Overall survival at 10 and 15 years was 80% and 62%, respectively with 15 deaths (1.5%) attributed to prostate cancer and 13 men alive with documented metastatic
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Despite 44% of the men who eventually developed metastatic disease presented with Gleason 3+4 disease, 26% presented with clinical features of very low-risk prostate cancer. An update from a separate yet similarly large series from Johns Hopkins University described results utilizing more stringent selection criteria and surveillance strategies. Inclusion criteria for this study included only men with very low-risk disease defined as Gleason 3+3, PSA ≤10, clinical stage T1c and ≤2 positive biopsy cores. Disease monitoring included yearly prostate biopsy for tumor grade or volume increase. With a median follow-up of 5 years, 15-year estimated cancer-specific and metastases-free survival are 99.9% and 99.4%, respectively. These two studies utilizing different inclusion criteria and management strategies demonstrate somewhat varying, yet promising long-term results, even with expanded selection criteria for AS. They also suggest that baseline risk assessment is imperfect, and that certain men outside the confines of traditionally low-risk disease may be safely managed with surveillance and delayed intervention as indicated.

Rationale for expanded patient selection criteria for AS: outcomes from immediate treatment of intermediate-risk disease

Cancer-specific survival (CSS) for the men in the studies above closely mirror results published with immediate radical intervention. Patients and significant others need to understand that risks of cancer progression and mortality with treatment may be low, but are not zero. In a multicenter series of over 12,000 men, estimated prostate cancer mortality 15 years after radical prostatectomy (RP) ranged from 5 to 38% for men with lowest and highest risk of disease. Men with Gleason score 7 disease experienced 10- and 15-year cancer-specific mortality rates of 5% and 17%, respectively after RP. Data from the National Prostate Cancer Register of Sweden on men diagnosed with localized, intermediate-risk disease show the cumulative prostate cancer-specific mortality after 10 years was 3.4% after RP and 3.8% after radiotherapy. These rates, similar to the US cohort at 10 years, likely will increase with longer-term follow-up. They are not significantly different than the outcome described by Klotz et al. with AS.

There is evidence that some prostate tumors with intermediate-risk features may have indolent behaviors and be considered ‘low-intermediate risk’. The highest rates of cancer-related mortality after prostatectomy appear to be from Gleason grade 8 to 10 tumors and from those with seminal vesicle invasion. Therefore, predicting these features based on pretreatment clinical features may be most critical when predicting the long-term outcome. Predicting the presence of low-risk tumors based on clinical features alone is not straightforward. Analyzing men with intermediate-risk features who underwent immediate RP, Gandaglia et al. identified potential predictors of organ confined, low-grade cancer on final pathologic analysis. Men were identified who had preoperative clinical Gleason pattern 3+4 disease and/or PSA 10–20 ng ml−1, and/or clinical stage T2b–c. The primary outcomes were pathologically favorable disease at prostatectomy. Nineteen percent had diagnostic biopsy Gleason 6 tumors, whereas 57% had Gleason 3+4 and 23% Gleason 4+3. Ten percent of the group had favorable pathologic features (organ confined, pathologic Gleason 3+3) at the time of surgery. These men were more likely to be younger at diagnosis with lower PSA densities and biopsy Gleason score of 6. Forty-one percent of the men with favorable RP pathology had biopsy Gleason 7 disease. In addition, the men with favorable pathology had fewer numbers of positive cores at diagnosis and lower percentage of positive biopsy cores. These data suggest that men with some traditionally intermediate-risk features including PSA >10 or Gleason 3+4 tumors at diagnosis may actually harbor indolent tumors. Furthermore, these men may further be stratified by estimates of tumor volume on biopsy such as numbers (or percentage) of positive cores or biopsy core length involved with carcinoma. For AS, therefore, the concept of ‘low-intermediate’ risk may apply to men with small volume, organ confined Gleason 3+4 cancers.

Does immediate treatment differentially impact survival for low- and intermediate-risk prostate cancer? Comparing treatment outcomes between men with low- and intermediate-risk cancer, Arvold et al. showed that intermediate-risk men treated with either RP or brachytherapy had a low (0.9%) cumulative prostate cancer specific mortality (PCSM) after median follow-up of 4.8 years that was not significantly different from men treated with only low-risk disease. The authors noted a positive association with age and PCSM within the intermediate-risk cohort, suggesting older men with intermediate-risk disease experience higher death rates from prostate cancer than younger cohorts. In a larger group of men treated with initial brachytherapy, Raladow et al. compared low-risk men with men defined as having favorable intermediate-risk disease (Gleason pattern 3+4, <50% positive cores, and <2 intermediate-risk factors, stage cT2b/c, PSA 10–20, Gleason score 7). After median duration of 7.7 years, there were no discernable differences in disease-specific survival between the groups, suggesting that some men with low-volume Gleason 3+4 disease have similar outcomes to men with lower-risk features after treatment. This was also observed in a surgical study comparing men having a single biopsy core of 3+4 with men having only 3+3 disease before RP that demonstrated no differences in likelihood of unfavorable pathology in screen-detected men with prostate cancer. Although disease-specific outcomes for intermediate-risk disease after treatment are very good, there is clear heterogeneity within this risk category suggesting that some of these men demonstrate risk profiles similar to men commonly offered AS today. This emphasizes the opportunity to expand AS criteria.

Experiences with AS in patients with expanded selection criteria

The number of men with features of intermediate-risk prostate cancer who are currently offered AS is unknown. Non-curative management is initially recorded for around 14% of men with intermediate-risk disease features within the Surveillance, Epidemiology, and End Results and National Cancer Database, however, these data sets are unable to distinguish AS with defined surveillance strategies from traditional watchful waiting or just deferred treatment to the prostate. Within the Swedish Prostate Cancer Registry, however, AS was recorded as the initial treatment choice for 16% of intermediate-risk men. At this time, most intermediate-risk men in the western world are offered curative therapy at the time of diagnosis. Several investigators have published their experiences of surveillance with delayed intervention for men with intermediate-risk disease. Different patient selection criteria and surveillance strategies are described. The ‘intermediate-risk’ category is defined differently for each of the studies analyzed (Table 1). Another confounder is the modification of the Gleason scoring system over time. The International Society of Urologic Pathology update to prostate cancer grading in 2005 resulted in upgrading of many pattern 3s to pattern 4, or 6 to 7. Certain low-risk patients included in series prior to 2005 without contemporary pathologic review, therefore may actually be similar to contemporary men with Gleason 3+4 tumors. The outcomes from the five identified papers including men with intermediate-risk disease are presented in Table 2. Within the Toronto series of 993 men with prostate cancer managed with AS, a group of men with intermediate-risk features (defined as PSA 10–20 or Gleason score ≤3+4) were included. Tumor histology primarily defined this risk category with 63% of men deemed intermediate risk (13% of entire cohort) by harboring Gleason 7 disease. The remaining intermediate-risk men had PSA levels >10, and 3% of the entire cohort had both Gleason 3+4 disease and PSA >10. With a median follow-up of 6.4 years, 1.5% of the cohort
died from prostate cancer and actuarial CSS at 15 years was 95%. On multivariate analysis, both diagnostic Gleason score and PSA were associated with overall survival, and 44% of the men who progressed to metastatic disease had Gleason 7 at baseline, whereas the rest were Gleason 6. In a subsequent publication specifically describing the men who eventually developed metastatic disease, the authors note that the men considered intermediate risk at baseline owing to PSA over 10 in the setting of Gleason 6 histology were not associated with increased risk for metastatic disease compared with the entire cohort.16 No patients with surgically confirmed Gleason 6 progressed to metastatic disease, and all but 2 patients were upgraded prior to the development of metastases. These two men were both radiated specifically describing the men who eventually developed metastatic disease and offered additional therapy for PSA-doubling time of ≤ 3 years, histologic upgrade on repeat prostate biopsy or clinical evidence of progression. Treatment was also associated with baseline PSA levels and Gleason score at 1 year, suggesting that intermediate-risk men are more likely to receive intervention over time.

Cooperberg et al.17 published early outcomes for men with traditional intermediate-risk features managed with AS at the University of California, San Francisco. Intermediate risk in this study was primarily defined by having Cancer of the Prostate Risk Assessment scores of 3–5. Thirty percent of men in this group had Gleason 3+4 disease, whereas 2% were Gleason 4+3 at diagnosis. These men with intermediate-risk features tended to be older at diagnosis (median age 65) than men with low-risk disease. The median PSA for the overall cohort was 10.3 (range 3.14–37.91), suggesting that PSA levels drove risk category in many men more than histology. Clinical progression for this study was defined as Gleason upgrade to any ≥ 4+3, PSA doubling time ≤ 2 or 3 years, and receipt of treatment. At 4 years, 61% of intermediate-risk men were free from clinical progression, which did not differ significantly from men presenting with only low-risk features and managed with AS at this institution. Furthermore, of 16 men who presented with intermediate-risk disease and eventually were treated with RP, 50% showed evidence of pathologic T3 disease, however, none had positive lymph node metastases. In the short term, AS for men with intermediate-risk features provided similar outcomes compared with lower-risk men with selective delayed intervention for men with evidence of disease reclassification.

Within the ERSPC data set, a cohort of men having intermediate-risk disease features and managed with AS was identified with reported long-term outcomes.18 In this series, low risk was defined by the entry criteria for the Prostate Cancer Research International: Active Surveillance protocol: cT1c/T2, PSA ≤ 10, Gleason score ≤ 6, PSA density ≤ 0.2 and ≤ 2 positive cores. Intermediate risk, therefore, consisted of men with PSA 10–20, and/or Gleason 7, and/or ≥ 3 positive cores. Of 128 men with intermediate-risk features, 28 had Gleason score of 7, whereas 77% percent of men were Gleason 6 disease and considered intermediate risk for ≥ 2 positive cores or higher PSA density. For the intermediate-risk cohort, 10-year estimated disease-specific survival was 96.1%, with 53.9% of the men undergoing deferred therapy. There were five deaths due to prostate cancer during the
study period, only two of which occurred in men presenting in the intermediate-risk category. Although the intermediate-risk men experienced lower treatment-free and overall survival, there were no differences in disease-specific mortality between the groups. Although the absolute numbers are small (1 vs 3), 10-year metastases-free survival was worse in men initially with intermediate-risk disease (96.4% vs 99.7% for low risk, \( P = 0.03 \)). A separate analysis from this cohort of intermediate-risk men all defined by having Gleason 7 disease estimated no disease-specific deaths at 6 years, with 26% of men receiving further treatment.19 Treatment-free survival was substantially higher for men who otherwise would have met clinical criteria for AS under the Prostate Cancer Research International: Active Surveillance protocol except for Gleason score. This demonstrates how measures of disease risk may bear different weights in risk assessment. No men who started with Gleason 4+3 disease remained untreated at 7 years.

Within the series from The Royal Marsden Hospital, 88 (18%) men were included with intermediate-risk disease, 33 of whom had Gleason 3+4 cancer.20 After a median follow-up of 5.7 years, 31% had received prostate-directed treatments. On multivariate analysis, diagnostic Gleason score of 7 was associated with time to adverse histology on repeat prostate biopsy, defined by primary Gleason score \( \geq 4+3 \) or \( \geq 50\% \) total prostate cores with cancer on repeat biopsy. Over this time period, there were only two deaths attributed to prostate cancer, one of which occurred in a patient presenting with intermediate-risk disease.

The Prostate Cancer Active Surveillance Study is a prospective multicenter AS study sponsored by the Canary Foundation.21 This multicenter, prospective AS study includes 115 men with intermediate-risk disease by NCCN criteria (13% of cohort), 56 of which have Gleason 3+4 disease. After a median follow-up period of 28 months, 24% of the entire cohort experienced disease reclassification defined by higher Gleason grade or tumor volume on repeat biopsy. No association was noted with baseline NCCN risk category, and either disease reclassification or adverse pathology after RP for those men treated with surgery. More specifically, 40% of men with intermediate-risk disease at diagnosis had adverse pathology (defined as primary Gleason 4 or 5, extraprostatic extension, seminal vesicle invasion or lymph node metastases) at RP. This did not differ significantly from men with baseline very low- (37%) or low-risk disease (32%).

These studies demonstrate that AS is feasible for selected men with prostate cancer and some intermediate-risk features, and caution must be exercised in men with Gleason pattern 4 disease. These findings are important when making treatment decisions and counseling men with localized prostate cancer on options for therapy including AS.

Overcoming barriers to AS for intermediate-risk disease

Treatment decisions for clinically localized prostate cancer are predominately based on risk estimations of disease progression and cancer-specific mortality over time. Physicians must also consider competing risks of mortality from patient comorbidities when counseling them on treatment options for localized prostate cancer. Patients with limited life expectancies (\(< 10\) years) stand to benefit the least from immediate prostate-directed therapy, however, this is often challenging to estimate. Tools exist to help predict the long-term probability of non-cancer mortality for shared decision-making.22 A number of clinical tools including classification systems, nomograms and risk calculators are available to estimate disease outcomes by considering multiple clinical variables, with disease histology being a predominant predictor. Clinical risk assessment based on a single set of prostate biopsies, however, may be underestimated, with a 23–46% likelihood of missing higher-grade or higher-stage tumors after a single biopsy session.23 These figures are based on multiple surgical series comparing pathologic findings after RP from men who would have been considered candidates for surveillance based on contemporary definitions of very low- and low-risk disease, and may be more pronounced for men with intermediate-risk features.23–26 Pathologic interobserver variability is also well-documented, and may contribute to this histology tumor-grade discrepancy at diagnosis and after repeat prostate biopsy.27 Most changes, however, are fairly minimal. The commonest upgrading is from Gleason 3+3 to Gleason 3+4. Likely much of the short-term data on AS comparing low- and intermediate-risk men reflect this inherent clinical undersampling with standard ultrasound-guided prostate biopsy.

For intermediate-risk men, additional biopsy features may be useful to define a ‘low-intermediate’ risk category. A recent analysis utilizing data from the Surveillance, Epidemiology, and End Results program showed that 27.6% of men with clinical intermediate-risk prostate cancer might actually have pathologic high-risk disease (T3-4 or Gleason 8–10).28 They were able to further stratify the intermediate-risk category into favorable or unfavorable intermediate risk by percentage of biopsy cores involved with carcinoma. Intermediate-risk men with \(< 50\% \) cores positive had 18.2% occult high-risk disease, whereas men with \( \geq 50\% \) positive cores had 34.2% risk. When considering AS, men with intermediate-risk features will likely need to be further stratified and reserved for those with lower-intermediate-risk features (a minority of positive biopsy cores, only Gleason 3+4). Several studies suggest that PSA levels \( > 10 \) as the sole intermediate-risk factor may not correlate with higher risk for adverse pathology or biochemical recurrence after RP in the face of low-grade disease, especially when PSA density is considered.29,30 The latest publication from International Society of Urologic Pathology recommends that pathologists record the percent of Gleason pattern 4 for patients with 3+4 disease, which may help risk-stratify men with intermediate-risk features for AS.31 A further consideration is the significance of very small proportion of Gleason 4 in men with Gleason 7 cancer. A study by Huang et al.32 reported that in those patients with \(< 5\% \) Gleason 4 pattern on biopsy, the distribution of RP grade was identical to the patients with Gleason 3+3. Undoubtedly tangential cut of a Gleason 3 acinus, which misses the lumen, may give the appearance of Gleason 4 pattern, and is responsible for artifactual upgrading in many of these cases, particularly where tumor volume is small. Thus, patients with \(< 5\% \) Gleason 4 should be considered excellent surveillance candidates.32 Intermediate-risk patients with low-PSA density appear to behave like low-risk patients. Advances in risk assessment utilizing molecular testing and innovative imaging to predict and identify cancers with higher grade or volume upfront will help limit risk and expand patient selection criteria for AS.

Novel biomarkers

Novel biomarkers are being developed and evaluated to improve patient selection for AS. Many of these can be incorporated with standard clinical variables. In the setting of clinical intermediate-risk features, these are an attractive tool to disaggregate disease heterogeneity based on clinical features alone. A 31-gene expression assay (Prolaris, Myriad Genetics, Salt Lake City, UT, USA), which generates a cell cycle progression score has been validated to predict PCSM in a heterogeneous group of conservatively, treated men.33 Per unit increase in cell cycle progression, the hazard ratio for prostate cancer mortality for men with Gleason 3+4 cancer was 1.77 (95% confidence interval \( 1.22–2.57 \)) and for men with Gleason 4+3 was 2.16 (95% confidence interval 1.31–3.56). Clinical risk prediction in this cohort utilizing the Cancer of the Prostate Risk Assessment score alone yielded a 10-year prostate cancer mortality estimate of 4% for men with low-risk disease. Forty-four percent of men with intermediate-risk
Germline genetic variants/single-nucleotide polymorphisms

Patient germline and somatic molecular data also may facilitate the identification of the best candidates for this approach. Prostate cancer family history and 39 previously identified prostate cancer single-nucleotide polymorphisms (SNPs) were studied for their association with adverse outcomes (defined as adverse history on repeat biopsy or receipt of treatment) within 471 men enrolled in an AS study at the Royal Marsden Hospital in England.37 There was no association between having a first or second-degree relative with prostate cancer and either time to adverse history or subsequent treatment. The authors also noted no association between the studied SNPs and these outcomes. Kearns et al.38 studied the association of 23 SNPs with Gleason upgrading over time in North American surgical and AS cohorts of men with very low- and low-risk prostate cancer. After adjusting for multiple comparisons, a single SNP on chromosome 11q22 was associated with Gleason upgrading at the time of RP and was also associated with eventual Gleason upgrading for men on AS undergoing repeat prostate biopsies over time. A separate analysis of >242,000 SNPs in primarily low-risk Korean men undergoing prostatectomy also identified 15 alleles associated with higher Gleason grade disease at the time of surgery, one of which on chromosome 3 remained significant after adjusting for multiple testing.39 These three studies from disparate countries and populations demonstrate the complexity of utilizing germline genetic variants to predict higher-grade disease or disease progression over time for surveillance of prostate cancer. Ongoing association studies including men with intermediate-risk features may provide additional tools for expanding patient selection and surveillance strategies.

Novel imaging

Most AS protocols include repeat prostate biopsy over time to limit the risk of disease misclassification and to monitor for disease progression. Transrectal prostate ultrasonography alone, however, is poorly sensitive for detecting early changes in tumor volume or grade when intervention may be recommended.40,41 Multiparametric magnetic resonance imaging has emerged as the modality of choice for prostate cancer imaging. Diffusion-weighted imaging sequences are particularly important and the apparent diffusion coefficient has proved useful for detecting primarily higher-grade prostate tumors. In the prediagnostic setting, multiparametric magnetic resonance imaging with a technique for image fusion targeted biopsy is shown to improve detection of primarily higher-grade (Gleason ≥4+3) tumors and has been corroborated in multiple studies.42 Taken together, these data suggest usefulness in men on AS to reduce undergrading at the time of diagnosis as well as to monitor disease progression with time.
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