Purpose of review
Active surveillance has become the recommended management strategy for most patients with low-risk prostate cancer (PCA), but whether surveillance criteria can be expanded without compromising oncologic outcomes is a matter of debate. Whereas there is essentially uniform consensus that those with low-risk disease can be safely managed with AS, those with intermediate-risk disease, younger men and African–American men are often excluded.

Recent findings
Outcome data for intermediate-risk patients managed by active surveillance demonstrate acceptable oncologic outcomes, but there is also evidence that such patients have higher rates of progression, adverse disease and metastatic disease. Studies evaluating the utility of quantitative Gleason grade, the use of biomarkers and multiparametric MRI are emerging and are likely to refine risk assessment. Literature describing the effects of young age on outcomes is lacking, but early data appear promising. Data on African–American men show varied results that are sometimes contradictory and further investigation is needed to elucidate the impact of race, independent of socioeconomic status.

Summary
Patients with intermediate-risk PCA should not be excluded from active surveillance based on any single, borderline criterion; rather, treatment decisions should be based on the full clinical picture, and may be further refined by patient characteristics and adjunctive tools.

Keywords
active surveillance, African–American, intermediate-risk, quantitative Gleason, young age
improving the evaluation and diagnosis of clinically significant prostate cancer

key points

- Carefully selected patients with intermediate-risk disease may be candidates for active surveillance, particularly patients with low-volume GS 3 + 4 disease, older age and other comorbidities.

- Quantitative Gleason 4 on biopsy samples may better predict outcomes than the traditional Gleason score, and 20% Gleason 4 of the total tumour length may be a threshold after which definitive therapy should be considered.

- Risk may be refined with biomarkers and imaging (mpMRI).

- Younger patients may have lower rates of progression on active surveillance despite more stringent surveillance, and should not be excluded from active surveillance based on chronological age alone.

- African–American patients should not be excluded from active surveillance based on ethnicity alone as outcome data are conflicting, and may be confounded by socioeconomic status and study design.

patients of whom 810 were consented for research between 1990 and 2013. Strict active surveillance criteria were met by 69% of the patients, with 125 men having features of intermediate-risk disease on diagnosis. With a median follow-up of 60 months, there were no deaths from PCA and one patient developed metastatic disease. Klotz et al. [8**] at Toronto published an update on their active surveillance cohort that included 993 patients. Their heterogeneous cohort was composed of 21% intermediate-risk patients. The 10-year and 15-year PCSS rates were 98 and 94%, respectively, and at 15 years, there were 15 deaths from PCA and an additional 13 patients developed metastatic disease. Despite the heterogeneous composition of these two cohorts with a limited, but still significant number of patients with intermediate-risk clinical features, long-term PCSS rates appear close to those published for immediate definitive treatment [15–17]. Furthermore, randomized trials have not demonstrated a significant long-term survival benefit for immediate radical prostatectomy in low-risk patients [18,19].

Thus, active surveillance has become the recommended treatment for most patients of older age and low-risk disease [20*,21*]; however, there has been significant hesitation to apply this management strategy to younger patients, African–American patients and those with intermediate-risk clinical features. Applying strict definitions of risk allow active surveillance to be offered to fewer than 20% of newly diagnosed patients. Our goal is to review data reported on these distinct patient cohorts, in an effort to help guide management strategies and allow more men to consider this option.

prostate cancer risk stratification systems

The Epstein criteria, defined in 1994, predict low-volume, organ-confined tumours at radical prostatectomy and are the most stringent. Clinically insignificant PCA was defined as cT1c, PSA density (PSAD) less than 0.15 ng/ml/g, Gleason score of 6 or less, less than three positive biopsy cores, presence of less than 50% tumour per core on biopsy [22]. The criteria are still utilized, notably by JHU. The D’Amico staging system was developed in 1998 and stratified patients into three groups on the basis of their risk of BCR after radiation therapy or radical prostatectomy. D’Amico criteria define low-risk as cT1c-T2a, Gleason score of 6 or less and PSA of 10 ng/ml or less, intermediate-risk as cT2b, GS 7 and PSA 10.1–20, and high-risk as cT2c, Gleason score 8–10, PSA more than 20 ng/ml [23]. The American Urological Association (AUA) guidelines for the management of clinically localized PCA follow these criteria. This staging system has since been validated and refined, and because of its simplicity, widely utilized in both clinical and investigative settings. Its simplicity is both a strength and limitation, as it does not account for multiple risk factors.

NCCN guidelines published in 2016 define very low risk as cT1c, Gleason score of six per group I or less, PSA less than 10 ng/ml, less than three positive biopsy cores, 50% or less cancer in each core, PSAD less than 0.15 ng/ml/g, low-risk disease as cT1-T2a, Gleason score of six per group I or less, PSA less than 10 ng/ml, intermediate-risk as cT2b-2c, or Gleason score 3+4/group II, or Gleason score 4+3/group III, or PSA 10–20 ng/ml, and high-risk as cT3a, Gleason score eight per group IV, or Gleason score 9–10/group V, PSA more than 20 ng/ml [24]. The UCSF CAPRA score predicts risk of metastases, PCa-specific mortality (PCSM) and overall mortality by assigning various point values to patient and clinical features, including age, PSA at diagnosis, Gleason score of biopsy, clinical T stage and percentage biopsy cores involved with cancer. A score of 0–2 is considered low-risk, 3–5 intermediate-risk and 6–10 high-risk [25].

For patients with both intermediate and high-risk disease, there is considerable variability in outcomes, suggesting that our stratification systems are not fully accounting for subtle sources of heterogeneity in PCA. Furthermore, most stratification systems classify any secondary Gleason 4 as
intermediate risk except for CAPRA, which adds only a single point for GS 3 + 4 alone. CAPRA score refines risk more precisely than the other risk stratification schemes noted above and should be favoured.

OUTCOMES OF PATIENTS WITH INTERMEDIATE-RISK DISEASE

Whether active surveillance criteria can be expanded to include patients with intermediate-risk clinical features, particularly Gleason 3 + 4 disease, is a topic of growing interest. Data on intermediate-risk patients from several large institutions with heterogeneous active surveillance cohorts have demonstrated acceptable oncologic outcomes to date [8**,26,27,28*]. In 2011, Cooperberg et al. [27] compared patients with low-risk and intermediate-risk tumours by the CAPRA classification system. After a median follow-up of 47 months, they found that patients with intermediate-risk disease were older, had higher PSA values, larger tumour volumes, but were not more likely to have biopsy progression or undergo active treatment while on active surveillance [29]. A recent update of this experience directly comparing outcomes for patients initially diagnosed with Gleason 3 + 3 versus 3 + 4 (not by CAPRA score) shows that those with Gleason score 3 + 4 at diagnosis have higher rates of progression and treatment, although favourable outcomes after radical prostatectomy at progression.

Other studies have endorsed caution with regard to active surveillance for patients with Gleason 3 + 4 diagnoses and other intermediate-risk features. Higher rates of adverse histology on subsequent biopsy [9], biochemical recurrence (BCR) after radical prostatectomy [7] and metastatic disease [30*] have been reported at higher rates in patients with Gleason 3 + 4. In the prospectively followed Toronto active surveillance cohort of 980 patients, 44% of the patients who eventually developed metastatic disease initially presented with Gleason 3 + 4 disease; overall, Gleason 4 was associated with a three to four-fold higher risk of metastatic disease [8**,30*]. Outcomes from the National Prostate Cancer Register of Sweden [31] compared outcomes of 4163 intermediate-risk patients who were managed with active surveillance (23%), radical prostatectomy (52%) and radiation therapy (25%). They found that the cumulative 10-year PCSM was 3.6% in the surveillance group and 2.7% in the curative intent groups. Amongst patients with intermediate-risk disease, the PCSM was 5.2% in the active surveillance group, 3.4% in the radical prostatectomy group and 3.8% in the radiation therapy group. The curative intent PCSM rates are not significantly different from the active surveillance rates reported by Klotz et al. [8**].

The PCSM findings were potentially confounded by selection bias, as the risk of mortality from competing sources was much higher in the active surveillance group (17.6%) than in the radical prostatectomy (6.8%) or radiation therapy (10.9%) groups. The authors accounted for this by adjusting for comorbidities and socioeconomic status, but the adjusted rates were largely unchanged. PCSM rates for intermediate-risk patients treated by active surveillance were higher than the curative intent rates, but the absolute risk difference was relatively modest, 1.4–1.8%. Indeed, competing causes of mortality, particularly in men more than 65 years of age, outweigh the risk of dying from PCa, even in patients with Gleason score 7 disease managed with active surveillance [13,29]. Lu-Yao et al. [13,29] analysed data from the SEER database and reported a 15-year PCSM rate of 5.7% in patients managed with active surveillance who had Gleason 5–7 and age 65–74 years. Approximately half did not require treatment at 15 years, and further analysis confirmed that immediate radical prostatectomy is not associated with improved CSS or overall survival (OS) for men aged at least 65 years with low-risk disease, including for men with Gleason 3 + 4. Thus, many patients with intermediate-risk features may be appropriate candidates for active surveillance, particularly those with low volume disease, older age and other comorbidities in whom competing factors have a greater impact on life expectancy [32*].

THE EFFECTS OF QUANTITATIVE GLEASON 4 DISEASE

Patients with Gleason 3 + 4 have traditionally been excluded from active surveillance due to concern for worse outcomes, but studies have shown that low-volume Gleason 3 + 4 and minimal Gleason 4 pattern on biopsy are associated with favourable disease at radical prostatectomy [33,34*]. Furthermore, evaluation of radical prostatectomy specimens in intermediate-risk patients has shown that approximately 10% of intermediate-risk patients have favourable disease at radical prostatectomy and may, in fact, be appropriate candidates for active surveillance [35*,36]. Gandaglia et al. [35*] evaluated pathologically favourable (low-grade, organ-confined disease) specimens of 3821 intermediate-risk (diagnostic biopsy Gleason 3 + 4 and/or PSA 10–20 ng/ml and/or cT2b-c) patients treated with immediate radical prostatectomy across two academic centres. Overall, 10% of the intermediate-risk patients had favourable disease at
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radical prostatectomy, and 41% were initially diagnosed with Gleason 3+4 disease. These findings further support the notion that a proportion of patients with intermediate-risk features may have indolent tumours. Another study published by Gandaglia et al. [35] evaluating patients eligible for active surveillance and treated with radical prostatectomy found that patients with Gleason score 3+4 PCs did not have worse 5-year BCR-free survival rates compared with those with 3+3 PCs.

Recently, interest in the utility of quantitative Gleason grading in biopsy specimens has grown after demonstration of improved concordance with pathology specimens at radical prostatectomy [37]. Perlis et al. [38] recently published that Gleason score 3+4 on biopsy was associated with significantly higher rates of adverse disease at radical prostatectomy. Similarly, Cole et al. [39] reported that the percentage of Gleason 4 tumour in biopsy specimens was an independent predictor of adverse disease, and on multivariable analysis was associated with adverse disease and shorter time to BCR. They reported that when the amount of Gleason 4 reached 20% of the total tumour length, the risk of adverse disease was significantly higher. The cutoff of 20% may therefore preliminarily represent a potential threshold after which definitive therapy should be considered in patients with Gleason score 3+4 managed with active surveillance.

REFINEMENT WITH CONTEMPORARY ADJUNCTS: PROSTATE-SPECIFIC ANTIGEN DENSITY, MULTIPARAMETRIC MRI, GENOMIC PROFILING

Several factors have been shown to influence disease reclassification and treatment for men managed with active surveillance. A previous study of men initially managed with active surveillance who later underwent prostatectomy found that PSAD was associated with biopsy reclassification and active treatment. A previous study of men managed with active surveillance who later underwent prostatectomy found that PSAD was associated with biopsy reclassification and active treatment, independent of other pathologic characteristics [12*].

The incorporation of multiparametric (mp) MRI in the evaluation of men with PCs may improve disease classification. The PRECISE guidelines were created to standardize reporting of findings in men undergoing mpMRI for active surveillance by outlining key information from each study. For example, identification and characterization of the index lesion is an important measure in men with a visible lesion. Subsequently, routine collection of imaging findings on baseline studies and serial imaging is made easier [40**]. Prior studies have established a role for MRI in the detection of clinically relevant lesions, that abnormal imaging findings may confer an increased risk of upgrading on subsequent biopsy [41]. The negative predictive value of mpMRI for detection of high-grade PCs was 86.6% for men on active surveillance, supporting the notion that there is still a role for systematic biopsy in active surveillance [42]. Those with normal, or not suspicious, mpMRIs have a lower rate of progression and are less likely to harbour clinically significant disease. Using the Prostate Imaging and Data System v.2 (PI-RADSv2) in triaging patients with PCs, the specificity of mpMRI peaks at 92.8% and the negative predictive value reaches 90.8% [43].

Fusion biopsy using mpMRI and transrectal ultrasound has been utilized in an effort to improve the accuracy and efficiency of prostate biopsy, with a significant level of agreement between systematic and MRI-ultrasound fusion biopsy. In addition, MRI-ultrasound fusion biopsy has been shown to detect additional Gleason at least 3+4 cancers not identified with a standard systematic biopsy. On the basis of fusion cores alone, pathologic upgrade was noted in 14% of men biopsied. Among patients with negative MRI-ultrasound fusion biopsies, Gleason score 3+4 or greater was found in 15% [44]. Similarly, in the setting of serial biopsies, fusion biopsies identified 26% additional cases of pathologic progression not identified by systematic 12-core surveillance biopsy, while those with stable mpMRI findings were less likely to have pathologic progression [45].

Genomic profiling using a variety of commercially available, tissue-based assays (Prolaris, Oncotype DX GPS, Decipher and ConfirmMDx) allows better discrimination of PCs aggressiveness and improves risk stratification. Genomic profiling is most strongly indicated for patients with negative biopsies in whom PCs is still suspected, prior to making a treatment decision on initial diagnosis, and after radical prostatectomy to predict outcomes and the potential need for additional treatment.

The Prolaris test detects aberrations in cell cycle progression (CCP) genes as markers of tumour progression and aggressive disease. One study found that in conjunction with the CAPRA-S score, the CCP score generated improved discriminatory ability [46]. It has been validated to predict BCR and metastasis after radical prostatectomy in a subset of patients [47].

A study evaluating the prognostic value of the Genomic Profile Score (GPS) found that when combined with the CAPRA score, GPS improved the area under the curve (AUC) for predicting favourable disease from 0.63 to 0.67. Pertinently, with the incorporation of the GPS score, 18% of patients with intermediate-risk using AUA classification were reclassified into the low-risk GPS group [48].
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Decipher analyses a set of 22 genes, the genomic classifier, involved in a wide range of cellular functions. The genomic classifier score has been found to independently predict metastatic disease after radical prostatectomy, with one study reporting an AUC of 0.79 [49].

The above suggests that mpMRI complemented by fusion biopsy techniques and gene expression profiling, further refines risk and allows some patients with Gleason score 3 + 4 disease to consider active surveillance a well tolerated option.

ACTIVE SURVEILLANCE FOR YOUNGER PATIENTS

Active surveillance for management of younger patients has been questioned given concerns for increased risk of disease progression, need for serial procedures during surveillance, the eventual need for treatment and potential risk of missing the window for cure for patients with longer life expectancies and fewer comorbidities. Conversely, young patients have the most to lose from definitive treatment in terms of reproductive, sexual and urinary function [50], and could potentially benefit the most from delayed treatment. Few studies have evaluated the effects of age on active surveillance outcomes. Recently, Leapman et al. [51] evaluated the association of age with various active surveillance endpoints. They found that patients less than 60 years old received more surveillance biopsies within the same time interval than their older counterparts. Despite more frequent evaluation, the authors reported that younger age was associated with lower risk of biopsy upgrade and progression despite more opportunities for disease reclassification. No significant differences were found with respect to treatment, adverse disease or BCR outcomes. Younger patients considering active surveillance can be counselled that short-term and intermediate-term outcomes are not worse, but that longer-term follow-up is needed. Treatment decisions should ultimately result from a comprehensive clinical assessment and determination of patient preference, rather than chronological age alone.

ACTIVE SURVEILLANCE FOR AFRICAN–AMERICAN MEN

The relationship between race and ethnicity on PCa incidence and mortality remains unclear with several studies reporting an association between black ethnicity and high-risk PCa [52,53]. Concerns about the impact of race on disease progression have led to further investigation of the appropriateness of active surveillance as the initial management in African–American men.

Studies have reported that differences in biological factors may contribute to an increased risk of morbidity and mortality in African–American men. A previous study observed higher serum PSA at diagnosis and increased prevalence of high-risk disease characteristics in African–American men presenting for treatment of PCa [53]. One study using the JHU cohort of African–American men with very low risk disease showed that African–American men not only had higher rates of adverse disease after immediate radical prostatectomy but also higher rates of BCR [52]. A second study demonstrated that the rates of overall reclassification and reclassification by Gleason grade were significantly higher in African–American than in white men, despite all having very low risk disease [54]. Conversely, a study of patients from the UCSF Urologic Oncology Database (UODB) and Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) cohorts showed no significant differences in upstaging or upgrading at radical prostatectomy between ethnicities, although African–American were more likely to have positive surgical margins relative to white men [55].

Interestingly, adjustment for socioeconomic factors has been shown to weaken, and potentially eliminate, the association seen between race and outcomes. Using the CaPSURE cohort, Grossfeld et al. [53] has addressed the potential role of interactions between biological characteristics and socioeconomic factors in the incidence and mortality associated with African–American men with PCa. The authors demonstrated that the association between race and recurrence after radical prostatectomy disappeared after adjustment for household income and education level [53].

The type of treatment also impacts outcomes. The choice of treatment has been shown to differ by ethnicity, even in men with similar risk profiles in the CaPSURE cohort. The association between ethnicity and high risk of overall and cancer-specific mortality is lost after adjusting for socioeconomic factors such as type of insurance and education level. From this study, the authors posit that socioeconomic factors may influence treatment choice more than race [56].

With the SEARCH database, a unique study cohort composed of a large proportion African–American men (39.7%) with clinical low-risk disease and equal access to healthcare, researchers were able to show that despite younger age and higher PSA at diagnosis, no differences were noted in pathologic upstaging or BCR-free survival. From their findings,
the authors supported the continued use of active surveillance in African–American men [57]. Despite the numerous studies focusing on oncologic outcomes in African–American men, the majority of such low numbers, there is insufficient evidence to undoubtedly use race/ethnicity alone to preclude African–American men choosing active surveillance for initial treatment for PCa. To better understand and accurately quantify risk in this patient population, future studies will need to better characterize the relationship between socioeconomic characteristics and oncologic outcomes while also elucidating the impact of race/ethnicity independent from socioeconomic factors.

CONCLUSION

PCa treatment decisions should be based on the full clinical picture, and may be further refined by patient characteristics such as age and race, and adjunctive markers such as PSAD, genomic profiling, mpMRI. Patients should not be included or excluded in/from active surveillance based on a single borderline value alone. Efforts to improve risk assessment for patients considering active surveillance are ongoing, and emerging data will continue to shed light on this topic.

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Conflicts of interest

Research support provided by Genomic Health (Carroll). The remaining authors declare no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as: ■ of special interest □ of outstanding interest


This study reported long-term follow-up on outcomes of a large, heterogeneous cohort of which 21% of the patients were intermediate-risk and 13% had GS 3 < 4 disease.


This study reported long-term follow-up on outcomes of a large selective cohort of very low risk and low-risk patients with excellent oncologic outcomes.


This study reported follow-up outcomes of a large, heterogeneous cohort with low incidence of significant PCa-related events. Further, PSAD was found to be an independent predictor of disease reclassification and recurrence.


The ASCO Endorsement Panel reviewed recommendations made by the Cancer Care Ontario Guidelines. They endorsed the guidelines on active surveillance with modifying statements including that for most patients with low-risk PCa, active surveillance is the recommended treatment, select patients with low-volume, intermediate-risk (GS 7) PCa may be offered active surveillance, ancillary radiologic and genomic tests may have a role in patients with discordant findings.


The Cancer Care Ontario Guidelines reviewed by the ASCO Endorsement Panel.


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