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Active Surveillance of Prostate Cancer: Use, Outcomes, Imaging, and Diagnostic Tools

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Abstract

Active surveillance (AS) has emerged as a standard management option for men with very low-risk and low-risk prostate cancer, and contemporary data indicate that use of AS is increasing in the United States and abroad. In the favorable-risk population, reports from multiple prospective cohorts indicate a less than 1% likelihood of metastatic disease and prostate cancer-specific mortality over intermediate-term follow-up (median 5 to 6 years). Higher-risk men participating in AS appear to be at increased risk of adverse outcomes, but these populations have not been adequately studied to this point. Although monitoring on AS largely relies on serial prostate biopsy, a procedure associated with significant morbidity, there is a need for improved diagnostic tools for patient selection and monitoring. Revisions from the 2014 International Society of Urologic Pathology consensus conference have yielded a more intuitive reporting system and detailed reporting of low-intermediate grade tumors, which should facilitate the practice of AS. Meanwhile, emerging modalities such as multiparametric magnetic resonance imaging and tissue-based molecular testing have shown prognostic value in some populations. At this time, however, these instruments have not been sufficiently studied to consider their routine, standardized use in the AS setting. Future studies should seek to identify those platforms most informative in the AS

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population and propose a strategy by which promising diagnostic tools can be safely and efficiently incorporated into clinical practice.

Active surveillance (AS) of prostate cancer with curative intent was described in the mid-1990s, and early AS experiences were reported in 2002.[1,2] Under the AS approach, men with favorable-risk cancers are monitored, and curative intervention is pursued upon evidence of higher-risk disease. Over the last 2 decades, AS has emerged as a standard management option for men with very low-risk and low-risk prostate cancer.[3,4] Observations from two large, prospective AS cohorts reach nearly 20 years of follow-up and indicate very low likelihood of metastatic disease or prostate cancer-specific mortality in appropriately selected men.[5,6] Despite its utility in reducing overtreatment, AS is not without morbidity.[7] The contemporary practice of AS remains largely based upon frequent clinical examination, serum prostate-specific antigen (PSA) testing, and prostate biopsy,[8] a procedure associated with patient discomfort and serious complications including infection.[9,10] Furthermore, these methods lack sensitivity for detection of higher-risk disease, as evidenced by the substantial proportion of men meeting AS criteria who demonstrate high-risk features at radical prostatectomy.[11,12]

As such, there is a significant need for more accurate methods of patient selection and monitoring. An ideal diagnostic tool would impart valuable diagnostic and prognostic information with limited associated morbidity at a reasonable cost. While the ideal platform does not currently exist, advances in technology and improved understanding of the molecular basis of prostate cancer have initiated progress toward that goal.[13–16] For example, the use and utility of multiparametric MRI (MRI) of the prostate has increased substantially in recent years.[17] Furthermore, clinically validated molecular tests have established a prognostic role in some clinical contexts.[18] These platforms, along with a recently updated system of pathologic grading, present a unique opportunity to improve the practice of AS.[19,20] This article aims to review the contemporary practice of AS, including trends in use, outcomes, pathologic grading, MRI, and tissue-based molecular testing.

Trends in use of active surveillance

Although the AS approach was previously underutilized,[21,22] recent data from multiple countries have confirmed increasing use, corresponding with its inclusion in multiple national guidelines and the availability of more data on long-term outcomes.[4–6] In the United States, as of 2006, only 10% of low-risk prostate cancer were managed conservatively.[23] Since that time, however, there has been a major expansion in use. By 2011, the New Hampshire State Cancer Registry reported that 42% of low-risk patients there were managed expectantly.[24] In a large registry from Michigan, 49% of low-risk prostate cancers diagnosed in 2012-2013 were managed on AS.[25] Finally, new data from the CaPSURE clinical practice registry reported an increase in conservative management up to 40% of low-risk cases from 2010 to 2013.[26] Similarly, studies from Canada have reported a reduction in the proportion of low-risk cases undergoing radical prostatectomy.[27]

Corroborative findings have been observed in several European studies. In the National Prostate Cancer Register of Sweden, from 2007 to 2011, AS was selected by 59% of very

low-risk patients and 41% of low-risk patients.[28] Meanwhile, data from Germany demonstrated a decline in the proportion of men with Gleason 6 disease at radical prostatectomy from 2000 to 2014.[29] Despite these favorable trends suggesting a reduction in the overtreatment of low-risk prostate cancer, there continues to be substantial variability in management patterns between and within various clinical practice settings.[30,31] Furthermore, in some parts of the world, the use of AS continues to remain more limited.[32] Nevertheless, the indications for AS continue to expand in national guidelines,[33] and it can be expected that this management paradigm will become increasingly offered for favorable-risk disease in the future.

Outcomes of active surveillance

The modern approach to AS was first described in 1995, and numerous programs have now reported follow-up outcomes at 5 years and beyond.[8] In Toronto, Klotz et al.[5] initiated a program of AS aimed at low-risk and select intermediate-risk patients. Their monitoring protocol includes PSA measurements every 3 months for 2 years then every 6 months, with a confirmatory biopsy during the first year and then every 3 to 4 years until age 80. Intervention was initially recommended for histologic upgrading on rebiopsy and/or PSA doubling time less than 3 years, but PSA changes now trigger additional work-up rather than immediate intervention. The most recent update of this cohort was published in 2015, with a median follow-up of 6.4 years, ranging up to 19.8 years. Of the 993 men to enroll in the program since 1995, 28 (2.8%) developed metastases and 15 (1.5%) died from prostate cancer. Meanwhile, treatment rates at 10 and 15 years were 36% and 45%, respectively.

More recently, extended follow-up was reported from the Johns Hopkins AS program, which was also initiated in 1995.[6] This program aims to enroll very low-risk patients with a PSA density <0.15, clinical stage T1c, and Gleason score ≤6 in a maximum of 2 cores with ≤50% cancer involvement in any core. The protocol includes PSA and digital rectal examination (DRE) every 6 months and yearly prostate biopsy. At most recent analysis, the cohort was composed of 71% very low-risk and 29% low-risk men. Triggers for treatment included an increase in grade (Gleason >6) or volume of cancer on biopsy. The 10- and 15-year cumulative incidence of treatment was 50% and 57%, respectively, with a median treatment-free survival of 8.5 years. Meanwhile, 15-year metastasis-free and cancer-specific survival rates were 99.4% and 99.9%, respectively. Table 1 presents published data from these two large prospective cohorts.

Other U.S. centers have similarly reported intermediate-term outcomes from AS. At the University of California San Francisco, 810 men have been managed with AS based on quarterly PSA testing, repeat biopsy within 12 months, and follow-up biopsy every 1 to 2 years depending on medical risk.[34] Of these men, 69% met strict eligibility criteria of PSA ≤10 ng/ml, clinical stage T1/T2, Gleason score ≤6, ≤33% positive biopsy cores, and ≤50% involvement of any core with cancer. The authors reported a 5-year treatment-free survival of 60%, and there were no prostate cancer deaths during a median follow-up of 60 months.

At Royal Marsden in the United Kingdom, the eligibility criteria for AS include age 50-80, clinical stage T1/T2 disease, PSA <15 ng/ml, Gleason score ≤6 (as well as Gleason 3+4 in

men >65), and ≤50% positive biopsy cores.[35] PSA and DRE are performed every 3 months in year 1, every 4 months in year 2, and every 6 months thereafter. A biopsy is performed at 18 to 24 months from diagnosis and then every 2 years. Triggers for treatment are a PSA velocity >1 ng/ml per year, a Gleason score >3+4, and/or >50% positive cores on repeat biopsy. Among 471 men in the program, 323 (68.6%) remained on AS at a median follow-up of 5.7 years, and there were 2 prostate cancer deaths.

Finally, 6-year follow-up data were reported for 439 men from the Göteborg randomized trial of prostate cancer screening who elected AS.[36] The cohort composition was 51% very low risk, 36.7% low risk, 21% intermediate-risk, and 1.4% high risk. The monitoring protocol included PSA testing every 3 to 6 months and rebiopsy at varying intervals, depending on clinical characteristics. Nearly one-half of the cohort remained free from treatment at 10 years, and a single patient died of prostate cancer at 12.7 years from diagnosis. The most common reason for discontinuing AS was an increase in grade or cancer involvement on repeat biopsy, followed by increases in PSA.

In summary, these results demonstrate the durability and safety of AS with careful patient selection and follow-up. At 5 years, the majority of men enrolling in these programs remain free from treatment, allowing preservation of quality of life. Furthermore, the development of metastatic disease or prostate cancer death is rare within the first 10-15 years of AS. Available data suggest that inclusion of higher-risk men and less frequent monitoring biopsy may be associated with increased risk of adverse outcomes. An understanding of these principles is crucial to appropriate patient education and counseling.

Updated International Society of Urologic Pathology grading and implications on active surveillance

In 1966, Donald Gleason[37] developed the classification of prostatic carcinomas using the architectural pattern rather than cytology for assigning the grade. The underlying principles of the Gleason grading system and its contributions to prostate cancer clinical management retain relevance and influence over half a century from the time of its development. However, a number of new clinical and pathological discoveries, changes in prostate cancer screening and detection, and development of new methodologies justified revisions of the original grading system at the 2005 and 2014 International Society of Urologic Pathology (ISUP) consensus conferences.[38,39]

As it relates to AS, there are several major changes to the Gleason grading system. The reporting of Gleason scores 2-5 has virtually disappeared from current clinical practice. In Gleason's original data, Gleason scores 2-5 were seen in 27.9% of patients.[40] Pathologists rendered a diagnosis of Gleason score 2-4 in 22 to 24% of patients in the early 1990s compared with just 1.6 to 2.4% a decade later.[41–43] Helpap et al[44] demonstrated that from 1996-2000 to 2005, reported Gleason scores 2-4 decreased from 2.7% to 0% and reported Gleason score 5 decreased from 12.2% to 0.3%.

Another major divergence from the original Gleason system is in the assignment of grade to cribriform glands. Within Gleason's original illustrations of his cribriform pattern 3, he

depicts large cribriform glands.[45] Cases graded prior to 2005 as Gleason pattern 3 included large cribriform glands that today would uniformly be called Gleason pattern 4.[46,47] Historically, a diagnosis of Gleason score 6 cancer was not as predictive of good behavior, with a higher rate of progression and some men even dying of prostate cancer.[47,48] Currently, it is recommended that all cribriform glands be considered as Gleason pattern 4. Ill-defined glands with poorly formed glandular lumina were not discussed or depicted by Gleason as either Gleason pattern 3 or 4. It was the consensus of the 2005 conference that poorly formed glands should not be considered Gleason pattern 3. Consequently, only individual well-formed glands are currently graded as Gleason pattern 3.

The consequence of the above changes is that contemporaneously graded Gleason score 3+3=6 cancers are incapable of metastatic behavior.[47] Although occasional publications - usually from large prostate cancer databases- infrequently report otherwise, these reports are subjected to incomplete submission of the prostate for histologic examination, errors in data records, use of the older grading system, and lack of recorded tertiary patterns, among other limitations.[49] Gleason pattern 3 in the setting of surrounding Gleason pattern 4 may have metastatic potential as recently shown in a case report supported by molecular evidence of the clonal origin of the lethal cancer from a focus of Gleason pattern 3 in the middle of higher-grade cancer.[50]

There has been a call to change the grading system for prostate cancer, replacing Gleason score 3+3=6 disease (and lower grades) with the term IDLE (Indolent Lesion of Epithelial Origin) to mitigate anxiety and curtail overtreatment of potentially indolent cancers.[51] There exist numerous clinical and morphological reasons why Gleason pattern 3 should be classified as cancer.[52] Rather than changing “Gleason score 6” to a noncancerous diagnosis, there is a need to change the confusing and inconsistent manner in which pathologic grade is reported. One of the major deficiencies of the current Gleason grading system is that the lowest grade assigned in the contemporary setting is 6, despite a scale ranging from 2 to 10; such practice implies that a Gleason score 6 is in the middle of the grading scale in terms of aggressiveness. Similarly, patients with Gleason score 3+4=7 may be overly concerned because a score of 7 is closer to the maximum score of 10 than the lowest score of 2.

To address these deficiencies with the original Gleason grading system, along with other problems not relevant to the practice of AS, a new grading system has been proposed. This system is founded in the original Gleason system, yet is based on extensive subsequent research that has improved the original system in its definition and application. If one were developing a new prostate cancer grading system *de novo*, the goal would be a simple system with the fewest number of distinct grades that can adequately represent established differences in prognosis.

The updated Grade Groups were originally developed in 2013 by Dr. Jonathan Epstein based on data from 7,869 patients who underwent radical prostatectomy at The Johns Hopkins Hospital.[19] This contemporary grading system was subsequently validated in a cohort of 20,845 patients from five academic institutions.[20] Based on these data, the rates of 5-year biochemical recurrence-free survival for grade groups 1-5 based on radical prostatectomy grade were 96%, 88%, 63%, 48%, and 26%, respectively. The grade groups were also

predictive of outcomes based on biopsy grade when biopsy was followed by radical prostatectomy or radiation therapy. These grade groups were recently validated in a population-based setting using data from the National Prostate Cancer Registry of Sweden.[53] With the new grading system, patients can be assured that they have a grade group 1 out of 5, which is the lowest grade, or a grade group 2 out of 5, which is still a relatively low grade. The new grades would, for the foreseeable future, be used in conjunction with the Gleason system. For example, Gleason score 3+3=6 is equivalent to grade group 1. These definitions are listed in Table 2.

Another recommendation of the 2014 ISUP Consensus conference was for pathologists to record the percentage of Gleason pattern 4 present in Gleason score 7 cancers. This recommendation is directly related to the practice of AS. Traditionally, low-volume Gleason score 3+3=6 cancers have been widely considered for a surveillance approach. Depending on patient age, comorbidity, and other clinicopathologic characteristics, however, there may be a proportion of Gleason score 3+4=7 cancers that could be reasonably considered for AS if pattern 4 disease is minimal. Currently, this information is not transparent in pathology reports, in which the percentage pattern 4 in Gleason score 3+4=7 cancers that could range from 1% to close to 50%. Based on these and other improvements, the new grading system has been accepted by the World Health Organizationfor the 2016 edition of Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs.[39,54]

Multiparametric MRI in active surveillance

Multiparametric MRI (mpMRI) offers the ability to detect, measure, and monitor prostate cancers *in viv*o, as well as direct biopsies to a specific target or lesion.[17] Currently, the main role of mpMRI in AS is to determine the appropriateness of patient candidates.[55] For instance, patients with apparently small, low-grade tumors on random biopsy may in fact harbor larger, clinically significant cancers that would render them inappropriate for AS. If concerning lesions are detected on mpMRI, they can be accurately sampled using various image-guided methods such as transrectal ultrasonography (TRUS)/MRI fusion.

Multiparametric MRI has a high negative predictive value for intermediate- and high-risk prostate cancers. Thus, a negative MRI is good evidence that a clinically significant cancer is not present. Furthermore, when a lesion is seen, mpMRI can provide insight regarding tumor behavior.[56,57] For instance, mpMRI has been used to predict Gleason scores mainly through apparent diffusion coefficient (ADC) values derived from diffusion-weighted MRI. Although there are strong inverse correlations between ADC and Gleason grade, mpMRI cannot at this time be considered a replacement for biopsy.[58,59] Nevertheless, ADC values can provide useful information in stratifying patient risk prior to biopsy. For instance, a lesion with very low ADC values that is read as a low-grade tumor on biopsy should be considered for rebiopsy based on the high risk of such a lesion harboring a higher-grade tumor.

Despite its utility in lesion detection and targeting, mpMRI does not routinely appear in decision-making algorithms and clinical nomograms for AS. To date, there are no long-term prospective studies regarding the use of mpMRI in AS. Using a 220 patient cohort, Shukla-

Dave et al[60] developed a nomogram based on clinicopathological data and mpMRI findings; this nomogram demonstrated a high area under the receiver operating characteristic curve (AUC) of 0.854 for selecting patients appropriate for AS. A follow-up study of 181 patients revealed an AUC of only 0.738 for low-risk disease (defined as ≤pT2, Gleason grade<4, and tumor volume ≤ 0.5 cc) for those who underwent radical prostatectomy.[61] The National Cancer Institute nomogram, which uses only mpMRI criteria, generated an AUC of 0.71 for predicting candidates for AS in a cohort of 85 patients, 60 of whom had very low-risk disease (≤cT1c, PSA density <0.15, biopsy Gleason score ≤6, ≤ 2 positive biopsy cores, and ≤50% cancer involvement in any biopsy core).[62] This nomogram was developed with biopsy pathology as an endpoint, which is a method that has not been validated. Thus, while mpMRI appears to provide some incremental value in selecting candidates for AS, it is far from perfect and remains limited by an inability to consistently detect clinically significant lesions, with reported false-negative rates of up to 16%.[63]

The utility of mpMRI in monitoring men on AS has not been well-established. Walton-Diaz et al[64] reported a series of 58 patients on AS with a median follow-up of 16.1 months who underwent serial mpMRI with TRUS/MRI fusion-guided biopsy. Upgrading to Gleason score 3+4=7 was documented for 17 men (29%), and the positive and negative predictive values of mpMRI for Gleason score progression were 53% (95% CI, 28%-77%) and 80% (95% CI, 65%-91%), respectively. One recent retrospective study by Felker et al[65] included 49 consecutive men with Gleason score 6 prostate cancer who underwent mpMRI and targeted prostate biopsy at baseline and again more than 6 months later. Over a mean follow-up of 28.3 months (range, 11-43 months), Gleason score progression occurred for 19 patients (39%). The addition of serial mpMRI improved the detection of Gleason score progression during follow-up.

Preliminary data indicate that mpMRI and targeted biopsy provide incremental value in the selection of candidates for AS. Performing mpMRI prior to entering AS can reduce the number of inappropriate AS candidates by 29% (Figures 1 and 2).[62] Once a patient has initiated AS, mpMRI can be useful in demonstrating lesion stability (Figure 3) but currently lacks the sensitivity to reliably detect higher-risk lesions during follow-up. As such, continued serial biopsies are recommended until mature data indicate that a stable mpMRI may in fact preclude subsequent biopsy. Ultimately, additional studies with longer follow-up are needed to establish the role of mpMRI in the context of monitoring. This practice will continue to evolve as larger studies are published.

Molecular testing in active surveillance

Several molecular profiling tests have been presented for use in the AS setting. Unfortunately, these tools have yet to be prospectively assessed in AS populations or with repeat longitudinal measures. Based on existing data, however, some of which is derived from conservatively managed cohorts, it is both reasonable and biologically plausible to consider some molecular tests in the AS setting.[18] Here we briefly review the molecular tests proposed for use in decisions about AS (Table 3).

Oncotype Dx: Genomic Prostate Score

The Oncotype Dx (Genomic Health, Redwood City, CA) genomic prostate score (GPS) measures expression of a 17-gene panel, including 12 genes from four pathways associated with carcinogenesis and five reference genes. Gene expression levels are incorporated into an algorithm yielding the GPS, which is measured from 0 to 100.[66] GPS is then considered in the setting of traditional clinicopathologic risk categories to determine a predicted likelihood of favorable pathology. In an initial validation study, GPS from 395 men with low- to low intermediate-risk disease was incorporated with preoperative models including the Cancer of the Prostate Risk Assessment (CAPRA) score and National Comprehensive Cancer Network (NCCN) risk categories.[67] In both models, a 20-unit increase in GPS was associated with an approximate twofold increased odds of adverse pathology at prostatectomy (model with CAPRA: odds ratio [OR] 2.1; 95% CI, 1.4-3.2; model with NCCN risk classification: OR, 1.9; 95% CI, 1.3-2.8), defined as primary Gleason pattern 4, any Gleason pattern 5, or non organ-confined disease. In a subsequent study of 402 men with low to intermediate-risk disease,[68] a 20-point increase in GPS similarly conveyed a significant increase in risk of biochemical recurrence after treatment (hazard ratio [HR] 2.93; 95% CI, 2.03-4.15; $p<0.001$) over a median follow-up of 5.2 years; GPS was also an independent predictor of biochemical recurrence (BCR) in multivariable models with baseline clinical factors. While the test is yet to be assessed in an AS cohort, one clinical utility study demonstrated a 10% increased use of AS when GPS scores were incorporated into clinical decision making.[69] However, the long-term impact of these changes in management are unknown.

Prolaris: Cell Cycle Progression

The Prolaris platform (Myriad Genetics, Salt Lake City, UT) is based on tumor cell proliferation as measured by quantitative reverse-transcription polymerase chain reaction of a 46-gene panel, consisting of 31 cell cycle genes and 15 housekeeping genes.[70] The output is reported as a cell cycle progression (CCP) score categorized clinically as <0, 0-1, 1-2, 2-3, and >3. CCP scores were retrospectively assessed for 349 men conservatively managed within the Transatlantic Prostate Group.[71] Ten-year rates of prostate cancer death associated with CCP score groups <0, 0-1, 1-2, 2-3, and >3 were 19.3%, 19.8%, 21.1%, 48.2%, and 74.9%, respectively. In multivariable analysis, the CCP score (HR for one-unit change: 1.65; 95% CI, 1.31-2.09), Gleason score >7 (HR 1.90; 95% CI, 1.18-3.07), and PSA (HR 1.37; 95% CI, 1.05-1.79) significantly predicted prostate cancer death. Perhaps most pertinent to the AS setting, however, the CCP score was not independently predictive of death in men with Gleason score 6 cancers (HR 1.30; 95% CI, 0.61-2.77). Two subsequent analyses have been performed in treated populations. In one multi-institutional study of men treated with radical prostatectomy,[72] a single-unit increase in CCP score on biopsy was associated with increased risk of BCR (HR 1.47; 95% CI, 1.23-1.76) and metastasis (HR 4.19; 95% CI 2.08-8.45) on multivariable analysis. In men treated with radiation therapy, a one-unit increase in the CCP score was similarly associated with a twofold increased risk of BCR (HR 2.11; 95% CI, 1.05-4.25).[73] Based on surveys of ordering physicians, use of CCP score led to a change in management selection in one-third to two-thirds of cases; however, as with the clinical utility studies of OncotypeDx, the long-term impact of these changes in management based on Prolaris results is unknown.[74,75]

ProMark

The ProMark test (Metamark Genetics Inc, Augusta, GA) is based on a quantitative proteomics profile uniquely designed to yield prognostic value regardless of sampling error. To do this, two tissue microarrays (TMAs) were derived from a series of prostatectomy specimens, one using the highest Gleason pattern observed in the specimen, and a second using the lowest.[76,77] Both TMAs were tested using a 12-protein panel that demonstrated similar ability to discriminate tumor aggressiveness (Gleason score ≥7, pT3b, N1, or M1) based on the AUC (using the highest Gleason pattern: AUC, 0.70; 95% CI, 0.62-0.77; using the lowest Gleason pattern: AUC, 0.72; 95% CI 0.64-0.79).[77] This initial panel was reduced to an eight-protein assay and validated for predicting unfavorable pathology (Gleason score ≥4+3 or non organ-confined disease) in a cohort of matched biopsy and prostatectomy specimens.[78] Remarkably, using a threshold score of less than 0.33 the test was 90% sensitive for predicting favorable pathology, and above a score of 0.8 the test was 95% specific for unfavorable pathology. On multivariable analysis, a score increase of 0.25 was associated with 3.1-fold increased odds of unfavorable disease (OR, 3.1; 95% CI, 2.2-4.4).

Phosphatase and Tensin Homolog testing

The PTEN phosphatase and tensin homolog (PTEN) gene is located on chromosome 10q and functions as a tumor suppressor in the PI3K/AKT pathway.[79] PTEN inactivation is an early event in carcinogenesis observed in up to 40% of prostate cancers. Specifically, PTEN loss appears to be associated with increasing likelihood of advanced grade and stage, as well as early recurrence after treatment.[80–82] As such, PTEN loss detected by either fluorescence in situ hybridization or immunohistochemical staining has been proposed for prognostic use. One report from the Transatlantic Prostate Group investigated PTEN in men with conservatively managed prostate cancer with favorable disease characteristics.[83] In the population of men with Gleason score <7, PTEN was highly predictive of prostate cancer death (HR 8.13; 95% CI, 2.8-23.2). Limiting its utility, however, PTEN loss was only present in 3% of this population. Other contemporary studies have described PTEN loss in 11 to 12% of favorable-risk study populations.[84,85] Findings from these studies have consistently supported an association between PTEN loss on biopsy and adverse clinicopathologic outcomes.[84,85] Considering a strong correlation with poor outcomes but its less than 15% prevalence in potential AS candidates, there may be a role for PTEN testing whereby PTEN loss is considered a high-risk feature that may preclude management on AS.

Current status of molecular testing

The true promise of molecular tests lies in their ability to both improve upon and expand beyond biopsy. In addition to practical considerations, the use of biopsy is limited by sampling error and a dependence on subjective grading.[86] Conversely, Long et al[86] have demonstrated consistent gene expression across multiple biopsy cores in a single patient, supporting previous work revealing limited variation in gene expression levels of highly expressed genes across multiple biopsy cores, including both malignant and benign stromal tissue.[88] As others have noted, such consistent gene expression, despite tissue and tumor heterogeneity, supports the notion that one can be confident in the overall prostate biology based on analysis of a limited sample.[89]

Certainly there are many reasons for optimism in exploring molecular tests in the AS setting. Contrary to pathological grading, molecular tests provide an objective result that remains consistent across institutions. Beyond the platforms discussed above, additional tests continue to emerge and may prove useful. For example, the Decipher genomic classifier (GenomeDx Biosciences, Vancouver, BC, Canada), which has been previously validated for predicting metastasis after surgery based on prostatectomy tissue,[90–92] has more recently demonstrated prognostic value in biopsy specimens.[93] At the same time, the majority of current evidence has been gleaned from retrospective analyses of cohorts that were not established with a surveillance approach in mind. Furthermore, these tests remain expensive and their incremental value in the context of other diagnostics such as serum markers and MRI is unknown. For example, the serum Prostate Health Index has demonstrated predictive ability using baseline and longitudinal samples in the AS setting and currently represents a less-invasive, more affordable option.[94,95] Acknowledging the entirety of the data, we lack a definitive answer to the most fundamental questions about molecular testing: does it work, and is it cost-effective? Additional evidence for these important questions is necessary, and will ideally stem from prospectively designed studies.

Active surveillance: present and future

An abundance of data indicate that the use of AS is rising rapidly and that it is a safe option to minimize overtreatment in men with favorable-risk prostate cancer.[8] Nonetheless, based on current methods of patient selection and monitoring, more than one in five men eligible for AS will have evidence of more aggressive disease on prostatectomy.[96] Conversely, some men who fail to meet conventional AS criteria may in fact harbor indolent cancers that will not threaten their quantity or quality of life. Thus, there is substantial need for more accurate diagnostic and prognostic tools to identify both those patients who are appropriate candidates for AS and those who are not.

We have herein outlined the updated grading system for prostate cancer as determined according to the ISUP consensus conference, most recently in 2014. As in the past, prognostic grade groups were determined based on long-term oncological outcomes. Perhaps most clinically important is the conversion from a complex Gleason score scale, traditionally measured from 2 to 10, to a straightforward 1-5 scale. This modification should allow that the information conveyed by pathologic grade is more clearly understood by both patients and physicians. In the realm of AS, the most substantial change in pathologic grading is the recommendation for uniform recording of the percent pattern 4 in Gleason score 7 cancers. Although the safety of AS in higher-risk populations is not well established, the prognostic risk associated with Gleason score 3+4=7 cancer varies substantially between samples with 1% Gleason pattern 4 and 50% Gleason pattern 4.[97,98] Measuring such differences will enable better understanding of these risks, and, when clinically appropriate, consideration of careful expansion of AS to populations with minimal Gleason pattern 4 disease.

We are at a critical point in the evolution of AS. Emerging technologies such as mpMRI and molecular testing undoubtedly add to the bevy of tools available for patient selection and monitoring. These tools, however, currently lack a template for use. Now more than ever,

prostate cancer is diagnosed using TRUS/MRI fusion-guided biopsy, yet there exists no standard by which cancers diagnosed on targeted biopsy can be incorporated into conventional risk classification schemes such as that of the NCCN. Similarly, more complex issues remain unaddressed, such as when and how to incorporate mpMRI and genomic tests into the AS paradigm. A body of retrospective data exists to begin shaping these approaches, but significantly more evidence is needed. With greater experience, the paradigm for incorporating these tests into current management approaches should continue to take shape.

A future in which AS protocols are largely based on mpMRI and molecular testing is easy to envision, but many questions lie between here and there. How soundly these questions are answered will dictate if – and when – we arrive.

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REFERENCES

1. Choo R, Klotz L, Danjoux C, et al. Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. J. Urol. 2002; 167:1664–1669. [PubMed: 11912384]
2. Carter HB, Walsh PC, Landis P, et al. Expectant management of nonpalpable prostate cancer with curative intent: preliminary results. J Urol. 2002; 167:1231–1234. [PubMed: 11832703]
3. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur. Urol. 2014; 65:124–37. [PubMed: 24207135]
4. Mohler, J.; Armstrong, A.; Bahnson, R., et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline): Prostate Cancer. Version 1. 2015.
5. Klotz L, Vesprini D, Sethukavalan P, et al. Long-Term Follow-Up of a Large Active Surveillance Cohort of Patients With Prostate Cancer. J. Clin. Oncol. 2015; 33:272–277. [PubMed: 25512465]
6. Tosoian JJ, Mamawala M, Epstein JI, et al. Intermediate and Longer-Term Outcomes From a Prospective Active-Surveillance Program for Favorable-Risk Prostate Cancer. J. Clin. Oncol. 2015 JCO.2015.62.5764–.
7. Bergman J, Litwin MS. Quality of life in men undergoing active surveillance for localized prostate cancer. J. Natl. Cancer Inst. Monogr. 2012; 2012:242–9. [PubMed: 23271780]
8. Tosoian JJ, Carter HB, Lepor A, et al. Active surveillance for prostate cancer: current evidence and contemporary state of practice. Nat. Rev. Urol. 2016 (In press).
9. Loeb S, Vellekoop A, Ahmed HU, et al. Systematic review of complications of prostate biopsy. Eur. Urol. 2013; 64:876–92. [PubMed: 23787356]
10. Bokhorst LP, Lepistö I, Kakehi Y, et al. Complications after prostate biopsies in men on active surveillance and its effect on receiving further biopsies in the Prostate cancer Research International: Active Surveillance (PRIAS) study. BJU Int. 2016
11. Filippou P, Welty CJ, Cowan JE, et al. Immediate Versus Delayed Radical Prostatectomy: Updated Outcomes Following Active Surveillance of Prostate Cancer. Eur. Urol. 2015; 68:458–463. [PubMed: 26138041]
12. Tosoian JJ, Sundi D, Trock BJ, et al. Pathologic Outcomes in Favorable-risk Prostate Cancer: Comparative Analysis of Men Electing Active Surveillance and Immediate Surgery. Eur. Urol. 2015

13. Stephenson SK, Chang EK, Marks LS. Screening and detection advances in magnetic resonance image-guided prostate biopsy. Urol. Clin. North Am. 2014; 41:315–26. [PubMed: 24725492]
14. Vargas HA, Hötker AM, Goldman DA, et al. Updated prostate imaging reporting and data system (PIRADS v2) recommendations for the detection of clinically significant prostate cancer using multiparametric MRI: critical evaluation using whole-mount pathology as standard of reference. Eur. Radiol. 2015
15. Barbieri CE, Bangma CH, Bjartell A, et al. The mutational landscape of prostate cancer. Eur. Urol. 2013; 64:567–76. [PubMed: 23759327]
16. van den Bergh RCN, Ahmed HU, Bangma CH, et al. Novel tools to improve patient selection and monitoring on active surveillance for low-risk prostate cancer: a systematic review. Eur. Urol. 2014; 65:1023–31. [PubMed: 24491309]
17. Turkbey B, Brown AM, Sankineni S, et al. Multiparametric prostate magnetic resonance imaging in the evaluation of prostate cancer. CA. Cancer J. Clin. 2015
18. Ross AE, D'Amico AV, Freedland SJ. Which, when and why? Rational use of tissue-based molecular testing in localized prostate cancer. Prostate Cancer Prostatic Dis. 2015
19. Pierorazio PM, Walsh PC, Partin AW, et al. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU Int. 2013; 111:753–60. [PubMed: 23464824]
20. Epstein JI, Zelefsky MJ, Sjoberg DD, et al. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. Eur. Urol. 2015
21. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. J. Clin. Oncol. 2010; 28:1117–23. [PubMed: 20124165]
22. Carter HB. Active surveillance for prostate cancer: An underutilized opportunity for reducing harm. J. Natl. Cancer Inst. - Monogr. 2012; 2012:175–183. [PubMed: 23271770]
23. Cooperberg MR, Broering JM, Kantoff PW, et al. Contemporary trends in low risk prostate cancer: risk assessment and treatment. J. Urol. 2007; 178:S14–9. [PubMed: 17644125]
24. Ingimarsson JP, Celaya MO, Laviolette M, et al. Trends in initial management of prostate cancer in New Hampshire. Cancer Causes Control. 2015; 26:923–9. [PubMed: 25840558]
25. Womble PR, Montie JE, Ye Z, et al. Contemporary Use of Initial Active Surveillance Among Men in Michigan with Low-risk Prostate Cancer. Eur. Urol. 2014:1–7.
26. Cooperberg MR, Carroll PR. Trends in Management for Patients With Localized Prostate Cancer, 1990-2013. JAMA. 2015; 314:80–2. [PubMed: 26151271]
27. Louis AS, Kalnin R, Maganti M, et al. Oncologic outcomes following radical prostatectomy in the active surveillance era. Can. Urol. Assoc. J. 7:E475–80. [PubMed: 23914263]
28. Loeb S, Berglund A, Stattin P. Population based study of use and determinants of active surveillance and watchful waiting for low and intermediate risk prostate cancer. J. Urol. 2013; 190:1742–9. [PubMed: 23727309]
29. Huland H, Graefen M. Changing Trends in Surgical Management of Prostate Cancer: The End of Overtreatment? Eur. Urol. 2015; 68:175–8. [PubMed: 25736732]
30. Weerakoon M, Papa N, Lawrentschuk N, et al. The current use of active surveillance in an Australian cohort of men: a pattern of care analysis from the Victorian Prostate Cancer Registry. BJU Int. 2015; 115(Suppl):50–6. [PubMed: 25601201]
31. Filson CP, Schroeck FR, Ye Z, et al. Variation in use of active surveillance among men undergoing expectant treatment for early stage prostate cancer. J. Urol. 2014; 192:75–80. [PubMed: 24518783]
32. Mitsuzuka K, Koga H, Sugimoto M, et al. Current use of active surveillance for localized prostate cancer: A nationwide survey in Japan. Int. J. Urol. 2015; 22:754–9. [PubMed: 25959857]
33. Mohler JL, Armstrong AJ, Bahnson RR, et al. Prostate Cancer, Version 1.2016. J Natl Compr Canc Netw. 2016; 14:19–30. [PubMed: 26733552]
34. Welty CJ, Cowan JE, Nguyen H, et al. Extended Followup and Risk Factors for Disease Reclassification in a Large Active Surveillance Cohort for Localized Prostate Cancer. J. Urol. 2015; 193:807–811. [PubMed: 25261803]
35. Selvadurai ED, Singhera M, Thomas K, et al. Medium-term outcomes of active surveillance for localised prostate cancer. Eur. Urol. 2013; 64:981–987. [PubMed: 23473579]

36. Godtman RA, Holmberg E, Khatami A, et al. Outcome following active surveillance of men with screen-detected prostate cancer. Results from the Göteborg randomised population-based prostate cancer screening trial. Eur. Urol. 2013; 63:101–7. [PubMed: 22980443]
37. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J. Urol. 1974; 111:58–64. [PubMed: 4813554]
38. Epstein JI, Allsbrook WC, Amin MB, et al. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am. J. Surg. Pathol. 2005; 29:1228–42. [PubMed: 16096414]
39. Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am. J. Surg. Pathol. 2016; 40:244–52. [PubMed: 26492179]
40. Gleason, DF. Histological grading and staging of prostatic carcinoma. In: Tannenbaum, M., editor. Urologic pathology. Lea & Feibiger; Philadelphia, PA: 1977.
41. Ghani KR, Grigor K, Tulloch DN, et al. Trends in reporting Gleason score 1991 to 2001: changes in the pathologist's practice. Eur. Urol. 2005; 47:196–201. [PubMed: 15661414]
42. Fine SW, Epstein JI. A contemporary study correlating prostate needle biopsy and radical prostatectomy Gleason score. J. Urol. 2008; 179:1335–8. discussion 1338–9. [PubMed: 18289601]
43. Steinberg DM, Sauvageot J, Piantadosi S, et al. Correlation of prostate needle biopsy and radical prostatectomy Gleason grade in academic and community settings. Am. J. Surg. Pathol. 1997; 21:566–76. [PubMed: 9158682]
44. Helpap B, Egevad L. Correlation of modified Gleason grading of prostate carcinoma with age, serum prostate specific antigen and tumor extent in needle biopsy specimens. Anal. Quant. Cytol. Histol. 2008; 30:133–8. [PubMed: 18630837]
45. Gleason DF. Histologic grading of prostate cancer: a perspective. Hum. Pathol. 1992; 23:273–9. [PubMed: 1555838]
46. McNeal JE, Yemoto CE. Spread of adenocarcinoma within prostatic ducts and acini. Morphologic and clinical correlations. Am. J. Surg. Pathol. 1996; 20:802–14. [PubMed: 8669528]
47. Ross HM, Kryvenko ON, Cowan JE, et al. Do adenocarcinomas of the prostate with Gleason score (GS) ≤6 have the potential to metastasize to lymph nodes? Am. J. Surg. Pathol. 2012; 36:1346–52. [PubMed: 22531173]
48. Nakabayashi M, Hayes J, Taplin M-E, et al. Clinical predictors of survival in men with castration-resistant prostate cancer: evidence that Gleason score 6 cancer can evolve to lethal disease. Cancer. 2013; 119:2990–8. [PubMed: 23719969]
49. Kryvenko ON, Epstein JI. Re: Nationwide prevalence of lymph node metastases in Gleason score 3 + 3 = 6 prostate cancer. Pathology. 2015; 47:394. [PubMed: 25938366]
50. Haffner MC, De Marzo AM, Yegnasubramanian S, et al. Diagnostic Challenges of Clonal Heterogeneity in Prostate Cancer. J. Clin. Oncol. 2014:2013–2015.
51. Esserman LJ, Thompson IM, Reid B, et al. Addressing overdiagnosis and overtreatment in cancer: a prescription for change. Lancet. Oncol. 2014; 15:e234–42. [PubMed: 24807866]
52. Carter HB, Partin AW, Walsh PC, et al. Gleason score 6 adenocarcinoma: should it be labeled as cancer? J. Clin. Oncol. 2012; 30:4294–6. [PubMed: 23032616]
53. Loeb S, Folkvaljon Y, Robinson D, et al. Evaluation of the 2015 Gleason Grade Groups in a Nationwide Population-based Cohort. Eur. Urol. 2015
54. Eble, JN. Cancer IA for R on: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. IARC; 2004.
55. Turkbey B, Mani H, Aras O, et al. Prostate cancer: can multiparametric MR imaging help identify patients who are candidates for active surveillance? Radiology. 2013; 268:144–52. [PubMed: 23468576]
56. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/Ultrasound Fusion–Guided Biopsy With Ultrasound-Guided Biopsy for the Diagnosis of Prostate Cancer. Jama. 2015; 313:390. [PubMed: 25626035]

57. Panebianco V, Barchetti F, Sciarra A, et al. Multiparametric magnetic resonance imaging vs. standard care in men being evaluated for prostate cancer: a randomized study. Urol. Oncol. 2015; 33:17.e1–7. [PubMed: 25443268]
58. Turkbey B, Shah VP, Pang Y, et al. Is apparent diffusion coefficient associated with clinical risk scores for prostate cancers that are visible on 3-T MR images? Radiology. 2011; 258:488–95. [PubMed: 21177390]
59. Vargas HA, Akin O, Franiel T, et al. Diffusion-weighted endorectal MR imaging at 3 T for prostate cancer: tumor detection and assessment of aggressiveness. Radiology. 2011; 259:775–84. [PubMed: 21436085]
60. Shukla-Dave A, Hricak H, Kattan MW, et al. The utility of magnetic resonance imaging and spectroscopy for predicting insignificant prostate cancer: an initial analysis. BJU Int. 2007; 99:786–93. [PubMed: 17223922]
61. Shukla-Dave A, Hricak H, Akin O, et al. Preoperative nomograms incorporating magnetic resonance imaging and spectroscopy for prediction of insignificant prostate cancer. BJU Int. 2012; 109:1315–22. [PubMed: 21933336]
62. Stamatakis L, Siddiqui MM, Nix JW, et al. Accuracy of multiparametric magnetic resonance imaging in confirming eligibility for active surveillance for men with prostate cancer. Cancer. 2013; 119:3359–66. [PubMed: 23821585]
63. Serrao EM, Barrett T, Wadhwa K, et al. Investigating the ability of multiparametric MRI to exclude significant prostate cancer prior to transperineal biopsy. Can. Urol. Assoc. J. 9:E853–8. [PubMed: 26788234]
64. Walton Diaz A, Shakir NA, George AK, et al. Use of serial multiparametric magnetic resonance imaging in the management of patients with prostate cancer on active surveillance. Urol. Oncol. 2015; 33:202.e1–7. [PubMed: 25754621]
65. Felker ER, Wu J, Natarajan S, et al. Serial MRI in Active Surveillance of Prostate Cancer: Incremental Value. J. Urol. 2015
66. Knezevic D, Goddard AD, Natraj N, et al. Analytical validation of the Oncotype DX prostate cancer assay - a clinical RT-PCR assay optimized for prostate needle biopsies. BMC Genomics. 2013; 14:690. [PubMed: 24103217]
67. Klein EA, Cooperberg MR, Magi-Galluzzi C, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. Eur. Urol. 2014; 66:550–60. [PubMed: 24836057]
68. Cullen J, Rosner IL, Brand TC, et al. A Biopsy-based 17-gene Genomic Prostate Score Predicts Recurrence After Radical Prostatectomy and Adverse Surgical Pathology in a Racially Diverse Population of Men with Clinically Low- and Intermediate-risk Prostate Cancer. Eur. Urol. 2014; 68:123–31. [PubMed: 25465337]
69. Badani KK, Kemeter MJ, Febbo PG, et al. The Impact of a Biopsy Based 17-Gene Genomic Prostate Score on Treatment Recommendations in Men with Newly Diagnosed Clinically Prostate Cancer Who are Candidates for Active Surveillance. Urol. Pract. 2015; 2:181–189.
70. Cuzick J, Swanson GP, Fisher G, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. Lancet. Oncol. 2011; 12:245–55. [PubMed: 21310658]
71. Cuzick J, Berney DM, Fisher G, et al. Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. Br. J. Cancer. 2012; 106:1095–9. [PubMed: 22361632]
72. Bishoff JT, Freedland SJ, Gerber L, et al. Prognostic Utility of the Cell Cycle Progression Score Generated from Biopsy in Men Treated with Prostatectomy. J. Urol. 2014; 192:409–414. [PubMed: 24508632]
73. Freedland SJ, Gerber L, Reid J, et al. Prognostic utility of cell cycle progression score in men with prostate cancer after primary external beam radiation therapy. Int. J. Radiat. Oncol. Biol. Phys. 2013; 86:848–53. [PubMed: 23755923]
74. Crawford ED, Scholz MC, Kar AJ, et al. Cell cycle progression score and treatment decisions in prostate cancer: results from an ongoing registry. Curr. Med. Res. Opin. 2014; 30:1025–31. [PubMed: 24576172]

75. Shore N, Concepcion R, Saltzstein D, et al. Clinical utility of a biopsy-based cell cycle gene expression assay in localized prostate cancer. Curr. Med. Res. Opin. 2014; 30:547–53. [PubMed: 24320750]
76. Shipitsin M, Small C, Giladi E, et al. Automated quantitative multiplex immunofluorescence in situ imaging identifies phospho-S6 and phospho-PRAS40 as predictive protein biomarkers for prostate cancer lethality. Proteome Sci. 2014; 12:40. [PubMed: 25075204]
77. Shipitsin M, Small C, Choudhury S, et al. Identification of proteomic biomarkers predicting prostate cancer aggressiveness and lethality despite biopsy-sampling error. Br. J. Cancer. 2014; 111:1201–12. [PubMed: 25032733]
78. Blume-Jensen P, Berman D, Rimm DL, et al. Development and Clinical Validation of an in situ Biopsy Based Multi-Marker Assay for Risk Stratification in Prostate Cancer. Clin. Cancer Res. 2015
79. Leslie NR, Downes CP. PTEN function: how normal cells control it and tumour cells lose it. Biochem. J. 2004; 382:1–11. [PubMed: 15193142]
80. Lotan TL, Gurel B, Sutcliffe S, et al. PTEN protein loss by immunostaining: analytic validation and prognostic indicator for a high risk surgical cohort of prostate cancer patients. Clin. Cancer Res. 2011; 17:6563–73. [PubMed: 21878536]
81. Krohn A, Diedler T, Burkhardt L, et al. Genomic deletion of PTEN is associated with tumor progression and early PSA recurrence in ERG fusion-positive and fusion-negative prostate cancer. Am. J. Pathol. 2012; 181:401–12. [PubMed: 22705054]
82. Liu W, Xie CC, Thomas CY, et al. Genetic markers associated with early cancer-specific mortality following prostatectomy. Cancer. 2013; 119:2405–12. [PubMed: 23609948]
83. Cuzick J, Yang ZH, Fisher G, et al. Prognostic value of PTEN loss in men with conservatively managed localised prostate cancer. Br. J. Cancer. 2013; 108:2582–9. [PubMed: 23695019]
84. Lotan TL, Carvalho FL, Peskoe SB, et al. PTEN loss is associated with upgrading of prostate cancer from biopsy to radical prostatectomy. Mod. Pathol. 2014; 28:1–10.
85. Mithal P, Allott E, Gerber L, et al. PTEN loss in biopsy tissue predicts poor clinical outcomes in prostate cancer. Int. J. Urol. 2014:1209–1214. [PubMed: 25099119]
86. Amin MB, Lin DW, Gore JL, et al. The critical role of the pathologist in determining eligibility for active surveillance as a management option in patients with prostate cancer: consensus statement with recommendations supported by the College of American Pathologists, International Soci. Arch. Pathol. Lab. Med. 2014; 138:1387–405. [PubMed: 25092589]
87. Long Q, Xu J, Osunkoya AO, et al. Global transcriptome analysis of formalin-fixed prostate cancer specimens identifies biomarkers of disease recurrence. Cancer Res. 2014; 74:3228–37. [PubMed: 24713434]
88. Peng Z, Andersson K, Lindholm J, et al. Operator dependent choice of prostate cancer biopsy has limited impact on a gene signature analysis for the highly expressed genes IGFBP3 and F3 in prostate cancer epithelial cells. PLoS One. 2014; 9:e109610. [PubMed: 25296164]
89. Reichard CA, Stephenson AJ, Klein EA. Applying precision medicine to the active surveillance of prostate cancer. Cancer. 2015; 121:3403–11. [PubMed: 26149066]
90. Erho N, Crisan A, Vergara IA, et al. Discovery and Validation of a Prostate Cancer Genomic Classifier that Predicts Early Metastasis Following Radical Prostatectomy. PLoS One. 2013; 8
91. Karnes RJ, Bergstralh EJ, Davicioni E, et al. Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk Patient population. J. Urol. 2013; 190:2047–53. [PubMed: 23770138]
92. Den RB, Feng FY, Showalter TN, et al. Genomic prostate cancer classifier predicts biochemical failure and metastases in patients after postoperative radiation therapy. Int. J. Radiat. Oncol. Biol. Phys. 2014; 89:1038–46. [PubMed: 25035207]
93. Klein EA, Haddad Z, Yousefi K, et al. Decipher Genomic Classifier Measured on Prostate Biopsy Predicts Metastasis Risk. Urology. 2016
94. Tosoian JJ, Loeb S, Feng Z, et al. Association of [−2]proPSA with biopsy reclassification during active surveillance for prostate cancer. J. Urol. 2012; 188:1131–6. [PubMed: 22901577]
95. Hirama H, Sugimoto M, Ito K, et al. The impact of baseline [−2]proPSA-related indices on the prediction of pathological reclassification at 1 year during active surveillance for low-risk prostate

cancer: the Japanese multicenter study cohort. J. Cancer Res. Clin. Oncol. 2013; 140:257–263. [PubMed: 24352745]

96. Tosoian JJ, JohnBull E, Trock BJ, et al. Pathological outcomes in men with low risk and very low risk prostate cancer: implications on the practice of active surveillance. J. Urol. 2013; 190:1218–22. [PubMed: 23643603]
97. Cooperberg MR, Cowan JE, Hilton JF, et al. Outcomes of active surveillance for men with intermediate-risk prostate cancer. J. Clin. Oncol. 2011; 29:228–234. [PubMed: 21115873]
98. Han M, Partin AW, Zahurak M, et al. Biochemical (Prostate Specific Antigen) Recurrence Probability Following Radical Prostatectomy for Clinically Localized Prostate Cancer. J. Urol. 2003; 169:517–523. [PubMed: 12544300]

Key Points

-Active surveillance represents a standard management option for men with very low-risk and low-risk prostate cancer.

-With follow-up extending to 20 years (median 5 to 6 years), multiple AS cohorts report metastasis and prostate cancer mortality in less than 1% of favorable-risk men; these outcomes appear to be more frequent in men who fail to meet low-risk criteria, but higher-risk populations have not been adequately studied.

-Revisions to pathologic grading from the 2014 International Society of Urologic Pathology consensus conference should facilitate a clearer understanding of pathologic data and more accurate assessment of risk in men bordering AS criteria.

-Multiparametric MRI and tissue-based molecular testing may improve extant monitoring protocols but first require additional study and validation.

-As the practice of AS continues to evolve, it is important that modifications of protocols are based on evidence of patient benefit.

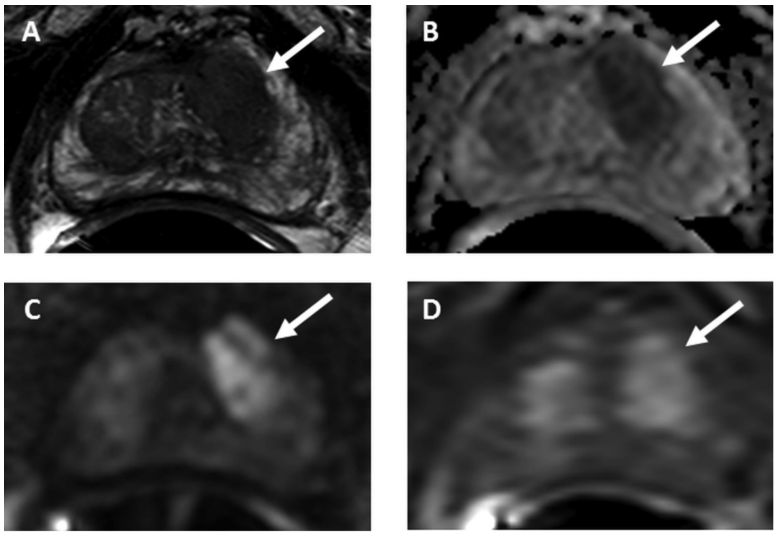

Figure 1.

A 71 year man with serum PSA of 5.47ng/ml was found to have Gleason score 3+3 cancer (5%) on random biopsy. Due to rising PSA levels, he underwent MRI scan prior to enrollment in active surveillance. (A). An axial T2-weighted MRI scan shows a PI-RADS 5 lesion in the left mid-anterior transition zone (arrow). (B-D) The lesion is positive on the apparent diffusion coefficient map (B), diffusion-weighted MRI (b=2000mm/s^2) (C), and dynamic contrast-enhanced MRI (D; arrows). A TRUS/MRI fusion-guided candidate after multiparametric MRI and a TRUS/MRI fusion-guided biopsy approach.

Abbreviations: PI-RADS, Prostate Imaging Reporting and Data System; PSA, prostate-specific antigen; TRUS, transrectal ultrasonography.

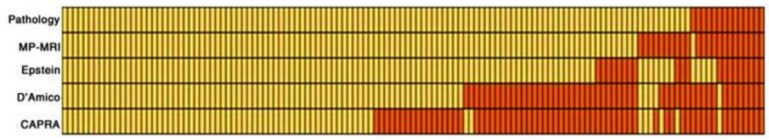

Figure 2.

A comparison of pathology-defined candidates (top row) for active treatment (yellow) and active surveillance (orange) versus definitions based on multiparametric MRI, the Epstein criteria, the D'Amico criteria, and CAPRA score. Each patient is represented by a column of the array. Note that multiparametric MRI results most closely mirrored pathology results with fewest "false-positive" decisions for active treatment in good active surveillance candidates.

Abbreviations: CAPRA, Cancer of the Prostate Risk Assessment; MP, multiparametric.

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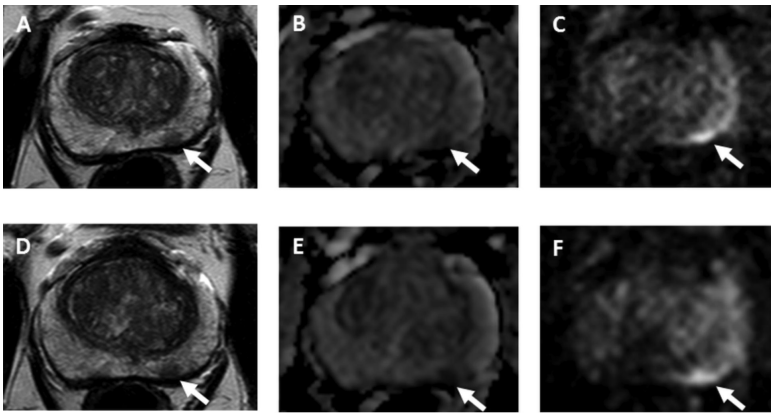

Figure 3.

A 59-year-old man presenting with a serum PSA of 4.68 ng/ml. (A–C) An axial T2-weighted MRI scan (A), apparent diffusion coefficient map (B), and b1500 diffusion-weighted MRI (C) show a lesion in the left mid-peripheral zone (arrows). This lesion was biopsied and found to harbor Gleason 3 + 3 prostate cancer (10%). The patient elected active surveillance. (D–F) A 1-year follow-up MRI scan (serum PSA = 5.10 ng/ml) shows that the lesion is stable in size and MRI signal features. The follow-up biopsy also revealed Gleason 3 + 3 prostate cancer (15%). MRI may become a tool for monitoring patients on active surveillance.

Abbreviation: PSA, prostate-specific antigen.

Table 1

Basic characteristics of two large prospective AS cohorts

	Patient selection		Monitoring	Outcomes			
Cohort	**N**	**GS≥7**	**Frequency of biopsy**	**Median follow-up**	**10-year treated**	**10-year PCSM**	**Metastatic disease†**
Toronto[5]	993	13%	~3-4 yrs.	6.4 yrs.	36%	1.9%	2.8%
JHH[6]	1298	0%	~1 year	5.0 yrs.	50%	0.1%	0.4%

Abbreviations: JHH, Johns Hopkins Hospital; GS, Gleason score; PCSM, prostate cancer-specific mortality.

†Proportion of patients during total follow-up; time-adjusted values not available.

Table 2

Histological definition of the updated grading system

	GS equivalent	Characteristic Features
Grade Group 1	3+3=6	Only individual discrete well-formed glands
Grade Group 2	3+4=7	Predominantly well-formed glands with a lesser component of poorly-formed/fused/cribriform glands
Grade Group 3	4+3=7	Predominantly poorly-formed/fused/cribriform glands with a lesser component of well-formed glands†
Grade Group 4	8	Only poorly-formed/fused/cribriform glands or Predominantly well-formed glands and a lesser component lacking glands†† or Predominantly lacking glands and a lesser component of well-formed glands††
Grade Group 5	9-10	Lack of gland formation (or necrosis) with or without poorly formed/fused/cribriform glands†

Abbreviations: GS, Gleason score

†For patients with greater than 95% poorly-formed/fused/cribriform glands or lack of glands on a core or at RP, the component of less than 5% well-formed glands is not factored into the grade.

††Poorly-formed/fused/cribriform glands can be a more minor component

Table 3

Molecular tests proposed for use in AS

Test	Manufacturer	Platform	Biological Process	Endpoints Assessed
Oncotype DX GPS [a]	Genomic Health (Redwood City, CA)	qRT-PCR	RNA quantification (gene expression)	Likelihood of favorable pathology at RP [†]
Prolaris CCP score [b]	Myriad Genetics (Salt Lake City, UT)	qRT-PCR	RNA quantification (gene expression)	10-year risk of PCSM
ProMark [c]	Metamark Genetics Inc. (Augusta, GA)	QMPI	Protein quantification	Likelihood of unfavorable pathology [††]

Abbreviations: qRT-PCR, quantitative reverse transcriptase polymerase chain reaction; QMPI, quantitative multiplex proteomics imaging; RP, radical prostatectomy; PCSM, prostate cancer-specific mortality

[a] Genomic Health (Redwood City, California);

[b] Myriad Genetics (Salt Lake City, Utah);

[c] Metamark Genetics Inc. (Augusta, Georgia)

[†] Freedom from: primary Gleason pattern 4, any Gleason pattern 5, and non-organ-confined disease.

[††] Gleason score of 4+3 of greater or non-organ-confined disease (≥pT3, N1, or M1)