Using active surveillance for Gleason 7 (3+4) prostate cancer: A narrative review

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ABSTRACT

The interest in broadening the application of active surveillance (AS) has been increasing, encompassing patients who may not strictly adhere to the conventional criteria for low-risk prostate cancer (PCa), particularly those diagnosed with small-volume Gleason grade group 2 disease. Nonetheless, accurately identifying individuals with low-intermediate risk PCa who can safely undergo AS without facing disease progression remains a challenge.

This review aims to delve into the progression of this evolving trend specifically within this cohort of men, while also examining strategies aimed at minimizing irreversible disease advancement. Additionally, we address the criteria for patient selection, recommended followup schedules, and the indicators prompting intervention.

INTRODUCTION

There has been a growing interest in expanding the use of Active Surveillance (AS) to patients who do not meet the criteria for low-risk Prostate Cancer (PCa), especially those with small volume Grade Group (GG) 2 disease. Historically, only individuals diagnosed with low-risk, clinically localized prostate cancer (PCa), exhibiting attributes like non-palpable disease, prostate-specific antigen (PSA) levels below 10 ng/ml, and Gleason GG1, were deemed suitable candidates for active surveillance (AS). Nevertheless, numerous tumors not fitting within this classification also exhibit low risks of progression. Accordingly, patients with favorable intermediate-risk PCa are being increasingly considered for AS (1). This trend has increased over the last decade.

Intermediate risk PCa is often managed conservatively because the natural history of PCa is long in most patients, not just those with low-risk cancer. PCa is often found during autopsies in older men who died from other causes, and in these cases, the cancer is by definition clinically insignificant. A large study found that over 50% of Asian men who had undiagnosed PCa had evidence of GG2 PCa at autopsy. If these men had been diagnosed earlier, they would have been best managed with surveillance since they died without ever being diagnosed (2) . This highlights the potential for safe conservative management of some GG2 PCa.

Intermediate risk PCa is a diverse disease with significant genetic and clinical variability (3). Although the Gleason scoring system is limited in its ability to accurately classify this type of cancer, AS remains a suitable option for appropriately selected patients. A recent metanalysis of 25 studies published by Baboudjian et al. showed that the difference in oncologic outcomes between intermediate risk disease and low risk disease was not statistically significant in patients with GG 1-2 disease (4). Patients with intermediate risk characteristics did have worse outcomes in terms of metastasis-free survival, cancer-specific survival, and overall survival than those with low risk features. However, some studies included up to 24% of intermediate risk patients with GG 3 disease at initial biopsy, and other unfavorable features were not excluded from the analysis, leading to a comparison of diseases with genuinely different levels of aggressiveness (4). Efforts to identify men with intermediate risk PCa who can benefit from conservative management is a priority.
The objective of this review is to explore how this trend has evolved over time for this specific group of men, offer adjunctive measures to minimize non-salvageable disease progression and also to address the criteria for patient selection, recommended follow-up schedules, and the indicators prompting intervention.

METHODS

Research ethics board approval for this study was waived given the use of publicly available data. A search of EMBASE (OvidSP®), MEDLINE (OvidSP®), and Cochrane CENTRAL (Wiley®) was performed from inception to 1st July 2023. We used the following keywords: “prostate or prostatic” ; “cancer or neoplasm” ; intermediate or medium or moderate; “active surveillance or watchful waiting or deferred treatment”; biomarkers” ; “psychological or psychology”.

Non-human studies, letters, and case reports were excluded. Eligibility was limited to studies written in English. Study selection was performed independently by two authors. Article titles were used as an initial screen, followed by abstract and full-text reviews.

PATIENT SELECTION

Guidelines to assist in the selection of patients for AS are available from different organizations worldwide (Table 1). The inclusion criteria for selecting intermediate risk PCa patients vary between guidelines. Common favorable features include Gleason pattern 4 < 10%, absence of Intraductal PCa (IDC) or cribriform pattern, a low number of positive cores, PSA level below 10ng/ml and negative Magnetic Resonance Imaging (MRI).

Age

Age is a major prognostic factor in decision making among men with localized PCa. Most GG2 disease poses a threat to life 15 to 20 years post-diagnosis, with a mortality rate around 30% at 15 years (5). Recent data from the Protect Trial demonstrates minimal benefit of radical therapy over active monitoring among men under 65 years old (6). The study also revealed that regardless of the treatment group assigned (radical prostatectomy, active monitoring, or radiotherapy), the PCa-specific survival rate was approximately 97% after a 15-year follow-up period. Although radical therapy resulted in a lower rate of disease progression compared to active monitoring, it did not reduce PCa mortality. Radical treatments, such as prostatectomy or radiotherapy, did, however, reduce the rates of metastasis, local progression, and long-term androgen deprivation therapy by half compared to active monitoring. Despite these reductions, there were no differences in mortality at the 15-year mark, a finding that emphasizes the prolonged natural course of this disease (6). With age, the risk of developing high-grade cancer increases due to an accumulation of genetic mutations. In addition, the genetic mutational burden is higher among older patients when grade matched to younger men. Goldberg et al demonstrated that the Decipher determined genetic risk was significantly higher in lower grade tumors among patients older 80 years (7).

However, a strong argument supports the application of AS in younger males, owing to the potential for improved quality of life, including the preservation of sexual and urinary function. An extensive meta-analysis of real-world data gathered from 27 international centers has reached the consensus that men who are diagnosed before the age of 60 and those with intermediate-risk disease should not be categorically disregarded as candidates for AS as their initial therapeutic approach (8). Notably, this is particularly relevant for men under the age of 55, who have a median life expectancy of 25 years or more, and face an increased risk of extended clinical progression. Therefore, continuous and extended monitoring is necessary in these patients (8) .

Histopathological findings at biopsy

Percentage of Gleason pattern 4 disease has important clinical implications. In the literature on radical prostatectomy (RP), minimal Gleason pattern 4 on preoperative biopsy is associated with favourable pathology at the time of RP. Currently, there is no consensus on the maximum GP4 percentage that is acceptable to consider AS in intermediate-risk

patients. Clearly the lower the percentage of pattern 4, the more favorable the outcome (9) . Ordner and colleagues conducted a study involving 488 patients with PCa to investigate the relationship between Gleason scores (GS) and adverse pathology. They found that patients with a GS of 3 + 4 = 7 and a Gleason pattern 4 (GP4) ≤5% on biopsy had no higher rate of adverse pathology than patients with a GS of 3 + 3 = 6 (with 0% GP4) (10). In this study MRI assessment was not performed. Some patients experience a downgrade in their surgical pathology from prostate biopsy to RP. This is likely attributed to the fact that during biopsy, if a core intersects the edge of a Gleason 3 acinus, it may mimic a cluster of cancer cells with no lumen, which is a hallmark of higher grade cancer (11) , resulting in artifactual upgrading. Most clinicians consider GG2 and higher to be 'clinically significant'. This is based on the idea that Gleason pattern 4 carries adverse prognostic implications. However, in the widely used and validated 'CAPRA' risk stratification system, the presence of pattern 4 only adds 1 point, a very modest increment, to the risk score (12).

MRI-targeted biopsies have the potential to reclassify the grade in a significant proportion of men, with a ratio of 1:2-3 (13). According to Ahdoot and colleagues, the utilization of MRI-targeted biopsy, in addition to systematic biopsy, improved the detection of clinically significant prostate cancers (GG≥3) in patients with MRI-visible prostate lesions. Moreover, this approach led to a reduction in the detection of clinically insignificant cancers. Although many of these benefits resulted from MRI-targeted biopsy alone, omission of systematic biopsy would have led to missing the diagnosis of 8.8% of clinically significant cancers (14) . However, the extent of reclassification may vary depending on the initial selection criteria and the criteria used to define reclassification.

Despite efforts to standardize grading of PCa, interobserver variability between pathologists with respect to small foci of Gleason pattern 4 remains a concern. Based on ISUP criteria, Gleason pattern 4 comprises four basic architectural patterns - small poorly-formed glands, glomerulations, fused glands and cribriform proliferations. Small poorly formed glands represent the main source of diagnostic difficulty for pathologists in the setting of AS when compared to other Gleason 4 patterns (15). This may particularly impact MRI targeted biopsies when multiple cores are sampled from the same lesion with a higher chance of finding small areas resembling Gleason 4 pattern composed of poorly formed glands, causing a phenomenon, referred to as MRI-induced grade inflation (16,17)

The utilization of artificial intelligence to establish thresholds in borderline cases can aid in creating more consistent and biologically meaningful distinctions. Over time, it will be crucial to refine AI tools through extensive training on large datasets with known outcomes. Additionally, it's essential to fine-tune AI systems using data from studies that explore how the tumor's appearance reflects its biology. This approach will enable genetic and clinical research results to inform AI, leading to more precise, education-driven decisions (18). Several adverse pathological features may be associated with more rapid disease progression, particularly the presence of Intraductal (IDC) and cribriform architecture. The presence of cribriform morphology has been consistently demonstrated to be associated with adverse oncologic outcomes, including increased risks of biochemical recurrence(19,20), metastasis (21) and cancer-specific mortality (22). There is general consensus that AS is inappropriate

for young men with IDC/Cribriform at biopsy. A significant issue associated with this clinical recommendation is the notable occurrence of false negatives (exceeding 50% in certain studies) in identifying the cribriform pattern as compared to examination of RP specimens (23,24). This gap presents a significant avenue for future research aimed at establishing a dependable biomarker capable of predicting adverse pathology.

There are also 2 considerations regarding the rare instance of IDC with invasive adenocarcinoma showing only GG1 features at biopsy. Firstly, there is a significant difference of opinion between ISUP and the Genitourinary Pathology Society (GUPS) concerning the incorporation of IDC into tumor grade (25,26). ISUP recommends the inclusion of IDC in tumor grade, whereas GUPS does not. As a consequence of the ISUP position, such patients would be considered intermediate risk (at least GG2) with IDC and therefore not be amenable for AS. Secondly, while IDC is encountered infrequently with only GG1 invasive tumor, evidence concerning the adverse prognostic significance of IDC in this scenario is less conclusive compared to GG 2-4 (27). For this reason further diagnostic work-up may be recommended in this particular situation.

Genomic considerations

Certain genetic anomalies, either inherited or acquired, are associated with more aggressive disease. Somatic mutations occur in non-reproductive cells during an individual's lifetime, while germline mutations occur in reproductive cells or early embryos and can be inherited from parents.

Germline anomalies

It has been reported that among men with metastatic PCa approximately 12% (28) possess an inherited germ line gene mutation. These genes include : BRCA2, BRCA1, ATM, HOXB13, CHEK2, mismatch repair genes, PALB2, BRP1, and NBS1 (29). While AS can be a viable treatment option for PC patients with certain inherited genetic mutations, men with BRCA2 mutations who undergo AS have a greater risk of disease progression, with up-grading occurring earlier and more frequently. Carter et al found that mutation status of *BRCA1/2* and *ATM* is associated with more frequent (HR 1.96) grade reclassification among men undergoing AS with 10 years of follow-up (30). Halstuch et al. reported on the short-term outcomes of 18 men with low-grade PCa who had inherited mutations in DNA repair genes, including BRCA2. Among this group, up-staging occurred in 20% of cases, leading to a conversion to treatment, with a median follow-up time of 28 months (31). It is currently unclear if AS is a suitable management strategy for carriers of other genetic variants associated with inherited PCa (32).

Somatic anomalies

Somatic mutations that occur in prostatic tumor tissue can also impact PCa behavior and response to treatment. Sequencing of tumor tissue, such as from a biopsy specimen, can help guide treatment decisions, particularly in cases of advanced disease. Patients who undergo tumor testing should also undergo germline testing when positive to determine whether a germline mutation is present (33).

In a recent study, Gandellini et al. reported that genomic features that are enriched in aggressive tumors can be detected in core biopsies with a Gleason 3+4 from patients on AS. The study concluded that alterations in PTEN and MYC at the time of diagnosis could serve as biomarkers for earlier identification of patients at risk of reclassification/progression, prior to the manifestation of conventional pathological signs (34). Cooperberg et al found that the Decipher biopsy test can accurately identify patients within the GG2 group with higher likelihood of adverse pathology at the time of RP. Men with GG2 and a low or intermediate Decipher score had similar odds of adverse pathology as men with low risk Pca (35) Research is needed to better define germ line and somatic profiles that can reassure patients with GG2 disease to adopt AS or conversely, pursue active therapy.

CRITERIA FOR PROGRESSION/THRESHOLD FOR INTERVENTION

The choice to pursue conservative management in the case of intermediate-risk PCa patients finds support in a body of evidence derived from epidemiological data, randomized trials, and prospective patient cohorts subjected to surveillance. Furthermore, the limitations and risks can also be determined from those studies. The probability of converting to active treatment differs depending on the institution's intervention thresholds, with about half of the patients remaining untreated for 5 to 10 years. The risk of switching to active treatment over time ranged from 24% at 5 years (36) to 52% at 5 years (37) and from 36% at 10 years (36) to 73% at 10 years (37). The cohorts that reported shorter follow-up times saw a probability of active treatment between 11% at 2 years (Royal Marsden) (38) and 29% at 2 years (39). The longest-running cohort at University of Toronto, saw a risk of 45% at 20 years for conversion to active treatment (40) . This has resulted in a range of treatment-free survival times among different AS cohorts, with the majority of patients avoiding any form of active treatment for at least 5 years following the initial diagnosis. These data are largely over-populated with patients who are diagnosed with GG1 disease. In the study by Klotz et al., patients with non GG1 disease had a 2.15 fold higher risk of failing AS (40) .

AS protocols are heterogeneous across different cohorts. Most cohorts utilized regular monitoring with PSA (e.g., every 3–6 months), DRE (e.g., every 6–12 months), confirmatory biopsy (e.g., within 1–1.5 years), and follow-up biopsy (e.g., at 1–3-year intervals). In recent years, several cohorts have included regular MRI (e.g., every 1–3 years). Many protocols employed less intense monitoring (e.g., PSA every 12 months and biopsy every 3–4 years) whereas others used more intense surveillance (e.g., PSA and DRE every 6– 12 months, MRI and re-biopsy every 1–3 years) (36). MRI (associated with favourable PSA kinetics) plays a crucial role in avoiding unnecessary follow-up biopsies and excluding disease progression during AS. The value of MRI is dependent on a high standard of image quality, interpretation, and reporting of serial imaging (41) .

The variety of AS protocols and diverse reasons for switching to radical treatment has been documented previously (42,43) . The main reason for conversion to active treatment is reclassification; upgrading to GG2 or higher, >2 cores or >50% of any core involved are also often utilized triggers. In patients with GG2 at baseline, the trigger for intervention is less obvious. According to Carroll grade progression in GG2 disease is defined as an increase in the biopsy or prostatectomy grade to GG3 or higher (44) .

Initially, PSA velocity or PSA doubling time were used as cut-offs as triggers for intervention. However, this metric lack sufficient specificity. PSA kinetics are currently employed to prompt additional clinical evaluation. Patient preferences or anxiety accounts for 10- 20% of cases where AS is terminated and radical treatment is pursued (43,45) .

OVERALL TREND OF AS FOR FAVORABLE INTERMEDIATE-RISK PCA

There is an increasing trend in the utilization of AS for managing favourable intermediate-risk PCa in studies encompassing men diagnosed with localized intermediate-risk PCa from 2010 to 2022 (46). Four important databases have provided valuable insights into the trends of utilizing AS for intermediate risk PCa: Surveillance, Epidemiology, and End Results Program (SEER), National PCa Register (NPCR) of Sweden and the Michigan Urological Surgery Improvement Collaborative (MUSIC) and Protect Study database. These databases have been utilized in a number of epidemiological studies and quality improvement initiatives to monitor the management trends of localized PCa in men with different risk profiles across the United States and in Europe.

SEER

Mahal et al conducted an epidemiological study using SEER data to investigate the management trends of localized PCa in men with low, intermediate, and high-risk disease in the United States from 2010 to 2015. Among men with intermediate-risk disease, the use of AS/watchful waiting increased from 5.8% to 9.6%, while RP and radiotherapy decreased from 51.8% to 50.6% and 42.4% to 39.8%, respectively. Other investigators, recently also accessed the temporal trends of AS, radiotherapy and RP using newly released national data from SEER data base to 2018. The rate of AS/watchful waiting use increased from 7.8% to 21.8% in patients with intermediate -risk cancers. Income and race and ethnicity continue to play significant roles in PCa treatment delivery (47) .

NPCR of Sweeden

In a study from Sweden that included 98% of newly diagnosed PC from 2009 to 2014, the utilization of AS in the intermediate-risk subgroup, characterized by Gleason score 6 and PSA levels ranging from 10-20 ng/mL, experienced a significant increase from 31% in 2009 to 53% in 2014. In contrast, the employment of AS in individuals with Gleason score 7 (3+4) and PSA levels less than 10 ng/mL, showed a modest but continued growth over the same time period, with figures of 9% and 17%, respectively (48).

MUSIC

The Michigan Urological Surgery Improvement Collaborative (MUSIC) established a quality improvement initiative in June 2014 to increase AS utilization. In this report, they analyzed the rates of AS utilization over time in the state of Michigan (MUSIC) for men with intermediate-risk PCa and they compare these to rates for other men diagnosed with intermediate-risk PCa in the USA outside the state of Michigan. An increase of 366 patients in 2013 to 1076 patients in 2019, which represents a an 193% increase in the overall utilization of AS for favorable intermediate risk group in the State of Michigan (49,50).

Protect trial

During the period of 1999-2009 in the UK, a total of 82,429 men aged between 50 and 69 underwent a prostate-specific antigen (PSA) test, out of which 2664 were diagnosed with localized PCa. Out of these individuals, 1643 men were enrolled in a clinical trial to assess the efficacy of various treatments. The trial randomly assigned 545 patients to undergo active monitoring, 553 to receive prostatectomy, and 545 to undergo radiotherapy .
Contemporary data of risk stratification have shown that 21% (337) of the ProtecT cohort actually had intermediate or high-risk PCa at the time of diagnosis. Furthermore, pathological data from men who had undergone prostatectomy within 12 months after diagnosis revealed that one third went on to have an increase in both the grade and stage of PCa and one half had GG2 disease or higher, which suggests that more intermediate-risk disease was present across the cohort than was previously thought.

By the end of follow-up (15 years), 133 men (24.4%) in the active monitoring group were alive and had neither received radical treatment nor started androgen deprivation therapy. Of these men at the time of diagnosis, 17 (12.8%) were considered to have intermediate or high-risk disease according to the D'Amico criteria and 14 (10.5%) had GG2 disease or higher (6).

FUTURE RESEARCH

Biomarkers

It has been long known that localized PCa has a protracted natural history and that many men are treated unnecessarily. The issue of overtreatment in PCa that has been partially addressed with the implementation of AS. However, accurately identifying patients with low-risk PCa who will not experience disease progression during AS is still a significant challenge for physicians. Misclassifying the risk of PCa is a notable concern and one of the primary reasons for patient anxiety and underuse of AS (51) . To address this issue, considerable efforts have been devoted to identifying novel biomarkers that can differentiate between low-risk and intermediate/high-risk PCa with high sensitivity and specificity (52) . There is also a need for biomarkers that can effectively monitor disease progression during AS. Liquid biopsies, which involve analyzing blood or urine samples, offer the advantage of being easily accessible and capable of providing continuous information during AS management. As a result, there is extensive research into these types of non-invasive or minimally invasive tests, and they are not influenced by tumor sampling, suggesting greater stability in the assays and a more comprehensive evaluation of the disease (53) .

The FDA has approved two blood-based tests, the Prostate Health Index (PHI) and 4Kscore, to predict the risk of PCa in patients with a Gleason score of ≥7 at prostate biopsy. PHI is noninvasive test that has been demonstrated to improve PCa diagnosis and assist in managing PCa patients (54) . It remains unknown how well they perform in the AS setting. To enhance the detection, treatment planning, and prognosis of PCa, the efficacy of PHI and other biomarker tests must be evaluated in conjunction with each other and with MRI (52) . Regarding the urine-based tests commercially available, PCa antigen 3 (PCA3) is a proven urine biomarker that is utilized by several commercially available tests, such as PROGENSA PCA3, Michigan prostate score (MiPS), and ExoDx Prostate (IntelliScore). SelectMDx is

another urinary-based test that measures the mRNA levels of two genes, DLX1 and HOXC6. The test is used to stratify patients with clinically significant PCa disease and to select patients for AS (55)(56) but true validated data in terms of outcome prediction remain aloof. Urinary biomarkers are the ideal sample to reduce morbidity for AS selection and to facilitate compliance in men on AS. In addition, urinary extracellular vesicles (uEV) are a promising noninvasive and easily accessible source of biological material for investigation of biomarkers. Mass-spectometry based proteomics enables large scale and deep profiling of uEV proteomes, which reflect the cellular processes associated with tissue-of-origin, creating new biological insights on agressive PCa (57) .

Several biomarker tissue tests have been shown to predict PCa progression, these include Oncotype DX, Pro-Mark, PTEN/TMPRSS2:ERG, Prolaris, and Decipher. They are different gene expression assays, each evaluating different sets of genes to PCa aggressiveness and guide treatment decisions. Oncotype Dx examines the expression of 17 genes involved in androgen signaling, cellular organization, stromal response, and cellular proliferation (58) . ProMark measures the expression of 8 proteins involved in cell proliferation, stress response, and signaling pathways (54) . In men with atypia or HGPIN, the use of PTEN/TMPRSS2:ERG test might lead to an earlier diagnosis of potentially aggressive PCa. The test predicts PCa aggressiveness by measuring the presence or absence of PTEN and the TMPRSS2:ERG translocation/gene fusion (59) . Prolaris evaluates 46 genes associated with growth rate and potential tumor aggressiveness, with a focus on 31 cell cycle progression genes (60) . Four Decipher analyzes 22 genes involved in cell proliferation, migration, tumor motility, androgen signaling, and immune system evasion (35) . Each test reports a score or score range and has shown utility in predicting PCa aggressiveness and guiding treatment decisions. Although these tests are in use clinically, they have largely been developed in the setting of patients who have had RP, which may have altered the disease natural history itself. They also only predict rates of metastases or PC-related death and have not been approved to predict who will progress on AS. Biopsy sampling of the dominant lesion (more relevant in biopsy versus prostatectomy tissue) also remains a potential for disease biology misclassification.

PET imaging

Prostate-Specific Membrane Antigen (PSMA) is a cell surface transmembrane glycoprotein expressed on most PCa cell surfaces, with increased expression in higher-grade disease. Using a PSMA tagged radioisotope in PET/CT imaging may identify higher risk disease under-graded at diagnosis. Presently used for staging after biochemical recurrence, there is evidence that PSMA PET/CT may identify clinically significant disease prior to any treatment (61) . In a group of 54 men who had ISUP 2-3 disease and underwent RP, PSMA PET outperformed MRI in identifying disease that was clinically significant (ISUP ≥2). Nevertheless, PSMA PET was not very reliable when it came to detecting disease that was considered low-risk (62) . PSMA PET/CT may also play a role in PCa local detection and grading. Maximum standardised uptake value (SUVmax) is a measurement of tracer uptake in tissue for PET imaging. Greater SUVmax on PSMA PET/CT was associated with clinically significant PCa (International Society for Urological Pathology [ISUP] GG3–5) on

biopsy (63) . By adding PSMA PET/CT to mpMRI, the combination of PIRADS score and PSMA PET/CT SUVmax demonstrated higher sensitivity and negative predictive value compared to the two imaging modalities used individually. This suggests that the addition of PSMA PET/CT alongside MRI can enhance the accuracy of detecting significant PCa (63) . In a recent multicenter trial led by Australian researchers, called the PRIMARY trial, the effectiveness of pelvic PSMA PET/CT in detecting intraprostatic malignancy in men with MRI PIRADS 2-5 was evaluated. The trial concluded that the combination of MRI and PSMA PET/CT imaging resulted in an improved negative predictive value (91%) and sensitivity (97%) for detecting clinically significant PCa (64)(65) . Future studies may expand these findings to individuals with AS, opening up the potential for even more precise predictions of disease progression in men with intermediate-risk PCa.

Recent evidence suggests that MRI invisible lesions have favorable genomics and natural history compared to image visible lesions (66). This raises the prospect of image guided therapy. Thus the ideal intermediate risk patient candidate for surveillance would have a non-visible lesion (by MRI and perhaps PSMA). According to this concept, treatment for intermediate risk disease would be offered if the lesion progressed to unequivocal visibility.

Psychological aspects

For individuals with AS, the mental toll of living with untreated cancer can be an added emotional weight to bear. The research evidence regarding the psychological impact of living with AS for PCa is varied in its findings regarding men's emotional well-being. While some studies suggest that men are content with their care, feel supported by their healthcare providers, and are relieved to avoid treatment-related side effects, other research suggests that some men struggle to accept the low-risk nature of their disease. These men may feel unsure about the efficacy of monitoring and the ability of their clinicians and clinical tools to detect disease progression, leading to persistent fears of cancer-related death and a desire to pursue curative treatment, despite the lack of disease progression (67–69) .

Current research on the psychological impact of receiving a diagnosis of lower risk PCa and undergoing AS has yielded mixed results. However, studies focusing on large AS cohorts, conducted in clinical settings with a strong emphasis on understanding and improving the AS process, suggest that men undergoing AS tend to experience less distress than those opting for immediate curative treatments, and that AS is generally well accepted and tolerated. Conversely, studies conducted in institutions with less emphasis on AS have shown less favorable psychological outcomes, acceptance, and tolerance of AS among patients. In light of the importance of disease and treatment information provision, as well as shared and supported decision making, in AS research across different cancers, such as thyroid and breast cancer, it is crucial to shift the focus from determining a 'true reality' of life during AS, to identifying the characteristics of men who may have difficulty tolerating AS programs. This includes examining sociodemographic, disease-related, and clinical variables, and developing strategies to alleviate anxiety and improve compliance among these individuals (70) .

Unique aspects of monitoring GG2 disease is the long term repeated testing (PSA, imaging, biopsy…) that demonstrate worsening disease. This is in contrast to GG1 disease where true radiographic/PSA progression is uncommon (71) . Both patients and clinicians will have to be able to withstand the natural pressure to intervene under these circumstances.

CONCLUSIONS

PCa men with intermediate-risk PCa have a higher risk of disease progression and death compared with those with low-risk disease. However many patients with GG2 may still be appropriate for AS. The presence of IDC or cribriform morphology has been associated with worse disease-specific survival. AS should not be offered to most of these patients. Sampling limitations may result in pathological miss of IDC/cribriform pattern. This emphasizes the need for biomarkers that can categorize low risk versus high risk patients. More validation of biomarkers studies are required .

Men with intermediate-risk PCa may have a harder time tolerating AS than men with low-risk disease, as they may perceive the disease as more threatening and have concerns about the efficacy of monitoring and clinical tools in detecting disease progression. The psychological impact of living with untreated cancer can be a significant emotional burden for those with intermediate-risk disease.

The differences in access to PSMA-PET and MRI in some healthcare jurisdictions represent a significant practical barrier to the expanded use of AS for both low and intermediate risk disease. With the continuous enhancement of patient selection methods, the role of clinical, genomic, and radiological biomarkers is set to become indispensable in effectively stratifying risk and determining optimal approaches for managing PCa. The evolution of more accurate biomarkers holds the promise of transforming the paradigm of PCa monitoring, potentially ushering in less intrusive surveillance for men affected by the condition. Consequently, this shift has the potential to render AS a more enticing choice, especially for individuals contending with intermediate-risk disease.

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FIGURES AND TABLES

Table 1. Risk stratification criteria for localized PCa from different organizations worldwide

Organization	**Very low-risk**	**Low-risk (LR)**	**Intermediate-risk (IR)**		**High-risk (HR)**	**Very high-risk**
			Favorable	Unfavorable		
EAU		Meets all these criteria: - PSA ≤10 ng/mL - ISUP 1 - ≤cT2a	PSA 10–20 ng/mL OR ISUP 2–3 OR cT2b		PSA >20 ng/mL OR ISUP ≥4 OR ≥cT2c	
AUA/Astro/SUO	Meets all these criteria: - PSA <10ng/mL - ISUP 1 - ≤T2a - PSAD <0.15ng/mL/cm^3 - <34% of biopsy cores positive - ≤50% of core involved	Meets these criteria: - PSA ≤10 ng/mL - ISUP 1 - ≤cT2a	PSA 10–20 ng/mL OR ISUP 1 OR PSA <10 ng/mL AND ISUP 2	ISUP 2 AND PSA 10–20 ng/mL OR ISUP 3 OR ISUP 3 OR cT2b–T2	PSA ≥20 ng/mL OR ISUP ≥4 OR ≥cT3a	

NICE		Meets all these criteria: - PSA ≤10 ng/mL - ISUP 1 - ≤cT2a	PSA 10–20 ng/mL or ISUP 2–3 or cT2b		PSA >20 ng/mL OR ISUP ≥4 OR ≥cT2c	
NCCN	Meets all these criteria: -ISUP 1 -cT1c - <3 cores positive - <50% tumor per core - PSAD <0.15 ng/mL/cm^3	Meets all these criteria: -PSA ≤10 ng/mL - ISUP 1 - ≤cT2a	IR factors: -PSA 10–20ng/mL -ISUP 2–3 -cT2b–T2c		HR factors: cT3a OR ISUP 4–5 (excluding primary pattern 5) OR PSA >20 ng/mL	≥ cT3a OR primary pattern 5 OR >4 cores with ISUP ≥ 4 OR ≥2 HR factors
			1 x IR factor AND ISUP ≤2 AND <50% cores positive	≥2x IR factor OR ISUP 3 OR ≥50% cores positive		
D'Amico		Meets all LR criteria: -PSA ≤10 ng/mL -ISUP 1 -≤T2a	PSA 10–20 ng/mL OR ISUP 2–3 OR cT2b		PSA >20 ng/mL OR ISUP ≥4 OR ≥cT2c	