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Abstract: Although the incidence of prostate cancer is rising due to PSA screening and increased life expectancy, the metastatic potential of low-grade, organ-confined disease remains low. An increasing number of studies suggest that radical treatment in such cases confers little or no survival benefit at a significant cost to morbidity. Active surveillance is a promising management approach of such low-risk cancers: eligible patients are selected based on clinical and pathological findings at diagnosis and are regularly monitored with digital rectal examinations, PSA testing and biopsies. Treatment, however, is deferred until and unless there is evidence of disease progression. This is a key difference from watchful waiting, where treatment is avoided until and unless there are symptoms. The purpose of this work is to review the rationale and evidence behind active surveillance and to offer an overview of current active surveillance strategies and outcomes.

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Thursday, May 11th, 2017

To:
Professor Rolf Stahel, Professor Nicholas Pavlidis,
Editors*, Cancer Treatment Reviews*

Re:
Revision of submitted manuscript CTR-S-17-00042 - "When no treatment is the best treatment: active surveillance strategies for low risk prostate cancers"

Dear Prof Stahel and Prof Pavlidis

Following submission of our manuscript, would like to thank yourselves and the reviewers for carefully reading our work and providing us with very important and useful comments.

We have now revised the manuscript and also prepared a list of changes for your consideration. As corresponding author, I confirm that the revised manuscript has been read and approved for submission by all named authors.

I would very much appreciate it if our revised work was re-considered for publication as an Invited Tumour Review in *Cancer Treatment Reviews*. We look forward to hearing from you.

Yours sincerely,

Vasilis Stavrinides, MSc MRCS

To the Editors, Cancer Treatment Reviews

Author Declaration and Conflict of Interest Statement

Manuscript title: "When no treatment is the best treatment: active surveillance strategies for low-risk prostate cancers"

8th of February 2017

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

We confirm that we have provided a current, correct email address, which is accessible by the Corresponding Author.

Signed by all authors as follows:

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Caroline Moore.

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Chris C Parker

List of changes and responses to reviewers' comments for revised manuscript CTR-S-17-00042 - "When no treatment is the best treatment: active surveillance strategies for low risk prostate cancers"

Reviewer #1:

We would like to thank the reviewer for providing very valuable comments.

This manuscript aims to review the rationale and evidence behind active surveillance and to offer an overview of current active surveillance strategies and outcomes. Below are my comments:

1- Please provide reference(s) for the second sentence of the first paragraph in the introduction.

The sentence has been appropriately amended and referenced.

2- The section on clinically significant disease is well written, please provide a conclusion remark on this concept in this section.

We thank the reviewer for the complimentary remark. A conclusion has now been added.

3- Active surveillance vs. watchful waiting section includes key references and their appropriate discussion. This section is very helpful for reader to better understand these big trials.

We thank the reviewer for the complimentary remark.

4- Very few studies utilized MRI in active surveillance (from NYU, UCLA, NIH), please aim to include this limited experience in the MRI section.

References (and overarching conclusions) from work done at the NYU, UCLA and NIH are included in the third paragraph of section 6.

5- Conclusion (as well as abstract) states that active surveillance is an established approach, however it is relatively new as mentioned in the manuscript. Please reword this.

We have reworded the central message of this remark to reflect the fact that active surveillance is relatively new in certain healthcare systems, but well established in others (e.g. UK, Canada).

6- References and tables are fine.

We thank the reviewer for the comment.

Reviewer #3:

We would like to thank the reviewer for the valuable suggestions.

When no treatment is the best treatment (CTR-D-17) is a review manuscript(invited) to discuss the role of active surveillance(AS) as a standard approach for management of low risk organ confined prostate cancer.
The following comments need to be readdressed :

Abstract:it is informative but we may add the main criteria for active surveillance and to explain that AS is not a watchful and wait strategy

We have now added the criteria for surveillance and mentioned the difference between AS and watchful waiting.

Introduction:the author should replace the phrase, PSA values do not exclude the presence of high grade disease, by PSA value is not the only parameter to judge on the risk of the disease and disease specific mortality but there are other factors including Gleason score, disease volume beside other indicators ,this means that only 30-50% on AS will need active treatment in the future and most of men will never die from active disease.

We thank the reviewer for the comment. This paragraph intends to provide the reader with a starting point for the reasoning behind AS, namely the discrepancy between PSA-detected disease and its malignant potential. For this, it is important to highlight that a significant proportion of cancers now detected through screening are not particularly threatening even in light of a relatively high PSA value. On the other hand, the reader should not equate a low PSA value with negligible risk. We have now slightly changed the wording of this sentence to highlight the fact that risk assessment involves the incorporation of multiple factors described in detail in section 2 (Gleason, volume etc).

The watchful and wait strategy should be restricted to men more than 75y with low volume, low risk disease and life expectancy less than 5y (PIVOT Trial subset).

We thank the reviewer for the comment. We have included this key conclusion from PIVOT in paragraph 3 of section 3.

The author should mention the 3 main active surveillance criteria including PSA testing, Digital Rectal Examination (DRE)and biopsy results (Gleason score) in addition to ancillary tests as multiparametric MRI (mpMRI)and genomic testing

beside disease reclassification depending on PSA density or the combination of race, family history and age (less evident). Also the author should comment on patient heterogeneity in AS group, as young patients with Gleason score 6 but with high volume disease and African American ethnicity whom they may need active treatment.

We have included a sentence in the first paragraph of section 2 to address the comment.

Also the author may include the draw back of AS when the patient will need more intense treatments when cancer progresses with concurrent ADT and radiation therapy or radical prostatectomy with adjuvant radiation therapy.

We thank the reviewer for the comment. We are alluding to those possibilities in the last paragraph of section 4, where we present some of the criticisms AS receives.

The author can explain more how the genomic tests will help to exclude some patients from AS if the test will show a category of patients with high risk of relapse and have higher chances of cancer specific mortality but we need a prospective validation of these tests

We thank the reviewer for the comment. We have included a remark in the first paragraph of section 7.

Conclusion: The author may raise unsolved points : First weather the patients on AS are followed in academic vs community hospitals, by a urologist or oncologist or a multidisciplinary team, second what is the treatment outcome in the presence of heterogeneity of follow-up ,third what about patient's factors as compliance , social factors and socioeconomic factors and fourth the selection of some with intermediate risk for AS and finally do we have to follow one protocol for AS(as NCCN guidelines)or institutional based guidelines and what is the difference.

We thank the reviewer for the comment. We have significantly expanded the conclusion to highlight the unresolved points raised.

Highlights:

- Active surveillance is a standard approach for managing low grade, organ-confined prostate cancers
- Careful selection and close monitoring of eligible patients is necessary
- Magnetic resonance imaging is a useful tool for stratifying risk and for monitoring men on active surveillance

When no treatment is the best treatment: active surveillance strategies for low risk prostate cancers

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Title:

When no treatment is the best treatment: active surveillance strategies for low risk prostate cancers.

Abstract:

Although the incidence of prostate cancer is rising due to PSA screening and increased life expectancy, the metastatic potential of low-grade, organ-confined disease remains low. An increasing number of studies suggest that radical treatment in such cases confers little or no survival benefit at a significant cost to morbidity. Active surveillance is a promising management approach of such low-risk cancers: eligible patients are selected based on clinical and pathological findings at diagnosis and are regularly monitored with digital rectal examinations, PSA testing and biopsies. Treatment, however, is deferred until and unless there is evidence of disease progression. This is a key difference from watchful waiting, where treatment is avoided until and unless there are symptoms. The purpose of this work is to review the rationale and evidence behind active surveillance and to offer an overview of current active surveillance strategies and outcomes.

Keywords:

Prostate cancer, active surveillance, clinically significant cancer, reclassification, magnetic resonance imaging

1. Introduction

Prostate cancer is the most common malignancy in men and the second most common malignancy in the Western world [1]. In the UK alone, more than 46,000 men are diagnosed and over 11,000 die from prostate cancer every year, according to Prostate Cancer UK [2].

The introduction of PSA in the 1990s drastically changed the landscape of prostate cancer diagnosis and management. PSA-related over-detection of prostate cancer and lead-time bias combined with all-cause mortality improvements now pose diagnostic and therapeutic dilemmas. Although low PSA values do not exclude the presence of high-grade disease and accurate assessment of risk requires the integration of multiple clinicopathological variables, the majority of patients are diagnosed as a result of PSA screening and harbor low-grade cancers [3] that have little to no metastatic potential [4]. In recent decades, this has resulted in a discrepancy between prostate cancer incidence and mortality rates. The value of radical prostatectomy and radiotherapy, previously the gold standard, is now increasingly questioned in the setting of low risk cancer as concerns regarding overdiagnosis and overtreatment continue to grow [5]. This is further complicated by the fact that the impact of PSA screening on overall cancer mortality remains unclear [6, 7].

Active surveillance (AS) has emerged as an alternative approach to tackle these conundrums. The key idea is the avoidance of treatment for low-grade-low risk cancers unless there is evidence of disease progression, thus limiting the exposure to radical treatment-related morbidity. However, this poses two important challenges: first, the accurate and early distinction of patients who have low-grade, low-risk cancers from those needing immediate treatment and, second, the accurate recognition of disease

progression such that radical treatment is delivered in a timely manner without compromising oncological outcomes [8]. These hurdles are not trivial and there are substantial efforts to address them in order to facilitate the clinical decision-making process. The concept of "clinically significant" cancer has been developed for this particular purpose and refers to tumours that, based on pre-defined clinicopathologic findings, have greater potential for progression and therefore require treatment. Therefore, a central objective in current AS research is identifying appropriate risk classifiers and optimizing their thresholds so as to minimize overtreatment.

2. Clinically significant cancer

There is a lack of consensus amongst experts in defining "clinical significance" for men on active surveillance. Traditionally, most classification systems have used simple clinicopathological variables, including disease stage on digital rectal examination, tumour grade (Gleason score) or burden on standard biopsy and PSA-related metrics. Factors such as age, race and family history are often taken into account and the efficacy of new genomic classifiers is being investigated (although their prospective validation is incomplete).

The traditional Gleason grading system is based on a 5-point scale of histological features and is expressed as the sum of two scores, the first representing the dominant microscopic pattern and the second the next most frequent pattern. Cancer is deemed Gleason score 3, 4 or 5. The lowest score that can be currently assigned to cancer identified on prostate needle biopsy is 3+3=6. Although Gleason 6 cancer may harbor genetic aberrations such as PTEN inactivation and exhibits some invasive features [9],

it has negligible metastatic potential [4] and carries a very low risk of biochemical recurrence after radical treatment [10].

Some microscopic patterns previously considered Gleason 3 before 2005 are now classified as 4, resulting in a shift in grading with an increase in the proportion of Gleason 7 (3+4 or 4+3) cancers. Gleason 3+3 and 3+4 disease carry a 15-year prostate cancer specific mortality rate of 0.2% and 1.2% respectively following radical treatment [11], reinforcing the view that low-grade, organ confined prostate cancer represents a distinct disease category with good prognosis.

The favorable prognostic features of Gleason 3+3 and 3+4 cancers distinguish them from Gleason 4+3 disease, but their nomenclature can contribute to patient anxiety [12]. As a result, a new grouping system based on 7869 prostatectomy samples was proposed in 2013. This system defines 5 separate grade groups according to prognostic significance (1: Gleason < or = 6; 2: Gleason 3+4; 3: Gleason 4+3; 4: Gleason 8 and 5: Gleason 9 or 10) [13]. It was validated by a multi-institutional study of 20,845 men treated by radical prostatectomy and 5501 men treated by radiotherapy [14]. The 5-year biochemical recurrence-free survival was 96%, 88%, 63%, 48% and 26% for grade groups 1-5 respectively, confirming the grading system's prognostic value and justifying its rapid endorsement by experts and the World Health Organization.

Prostate cancer risk classification systems are currently based on integrating tumour grade with other clinical variables such as stage and PSA level. The D'Amico criteria differentiate between low-risk (stage T1c, T2a and PSA level < or =10 ng/mL and Gleason score < or =6), intermediate-risk (stage T2b or Gleason score of 7 or PSA level >10 and < or =20 ng/mL) and high-risk patients (stage T2c or PSA level >20 ng/mL or Gleason score > or =8) and most classification systems adopt a variation of this scheme [15]. The National Cancer Comprehensive Network (NCCN) includes a

modification of the Epstein criteria (stage T1c or lower, PSA density <0.15 ng/mL, Gleason score 6 or less, 2 positive biopsy cores or less and 50% maximal cancer involvement in any biopsy core) in order to define very-low-risk disease [16].

Tumour volume has been traditionally considered an indicator of clinical significance [17] and it is postulated that the dominant or index lesion drives the natural history of the disease, with satellite lesions playing a secondary role [18]. The most widely used volume threshold for clinical significance is 0.5 mL. It is derived from a classical series of just 139 cystoprostatectomy specimens with incidental prostate cancer [19]. Using epidemiological data, the authors estimated the probability of having a diagnosis of prostate cancer during a man's lifetime to be 8%. They then ranked the specimens by prostate cancer volume. The top 8% had volumes from 0.5-6.1 mL. It was, therefore, extrapolated that a tumour volume of 0.5 mL was likely to represent clinically significant prostate cancer [19]. In another cystoprostatectomy series of 97 specimens, in men in the UK where PSA screening rates are low, the same methodology found a threshold of 1.09 mls, illustrating the arbitrary nature of this volume cut-off [20]. Recent work in screen-detected cancer supports the suitability of the 0.5 mL threshold value for any tumour stage or grade, but for Gleason 3+3, organ-confined disease this value could be as high as 1.3 mL for the index lesion and 2.5 mL for the total tumour volume [21].

In conclusion, although thresholds for clinical significance can differ from one study to the next and depend on the clinical setting, the concept itself is a vital tool that enables clinicians to make the best possible treatment decisions based on the available clinicopathological evidence. The way clinical significance is defined is constantly under revision and it is well possible that more variables (e.g. imaging parameters) are incorporated in its definition in the near future.

3. Active surveillance and watchful waiting

It is important to distinguish between the two main conservative approaches in prostate cancer management, active surveillance and watchful waiting. Active surveillance applies to younger men with low-risk disease and a life expectancy of more than 10 years. Men are followed up according to a pre-defined schedule involving regular clinical examinations, PSA measurements, prostatic biopsies and imaging in an effort to detect progression early and, if necessary, to deliver treatment with curative intent. On the other hand, watchful waiting, usually reserved for patients with a life expectancy less than 10 years, refers to disease monitoring with the purpose of delivering palliative therapy if and when symptoms occur, so as to minimize treatment-related toxicity. This approach is tailored to a specific patient's needs and, as such, there are no specific watchful waiting protocols.

There are three significant randomized controlled trials comparing radical prostatectomy with conservative approaches, based on different populations of men. The Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) randomized 695 patients to radical prostatectomy versus watchful waiting with a median follow up time of 13.4 years [6]. The mean age was 65 years, the mean PSA value was 13 ng/mL and the majority of the participants had locally advanced disease, diagnosed on digital rectal examination and therefore palpable. A reduction of 12.7 percentage points for cumulative incidence of death from any cause and 17.7 percentage points for prostate cancer-related cumulative incidence of death confirmed a substantial reduction in mortality after radical prostatectomy. In addition, it was concluded that prostatectomy

reduced the risk of metastatic disease and the need for androgen deprivation therapy [6].

In the Radical Prostatectomy Versus Observation for Localized Prostate Cancer (PIVOT), 731 men less than 75 years of age with localized prostate cancer (T1-T2NxM0, any grade) were randomized to radical prostatectomy or observation with a median follow up of 10 years [22]. The absolute risk reduction in the intervention group was only 2.9 percentage points for all-cause mortality and 2.6 percentage points for prostate cancer-specific mortality. Nevertheless, RP was associated with reduced all-cause mortality among men with PSA>10 ng/mL and possibly intermediate-risk (stage T2b or Gleason score of 7 or PSA level between 10 and 20 ng/mL) or high-risk (stage T2c or Gleason score > or =8 or PSA level >20 ng/mL) disease, as designated by the D'Amico criteria. PIVOT has been criticized for its low statistical power and low adherence to treatment in the intervention group, but nevertheless indicated a negligible short-term effect of prostatectomy on mortality in older men with low risk disease. It would, therefore, appear reasonable to offer watchful waiting strategies to such men, especially if their life expectancy is low. In SPCG-4 only 12% of men had clinical stage T1c and the mean PSA value was relatively high (13 ng/mL), in contrast with the PIVOT trial where 50% of men had T1c and a lower mean PSA (7.8 ng/mL). It is, therefore, not surprising that the key finding of SPCG-4 (i.e. that radical prostatectomy benefits men with palpable, localized prostate cancer) is not directly comparable with the findings from PIVOT [23].

The UK Prostate Testing for Cancer and Treatment (ProtecT) randomized study compared active monitoring, radical prostatectomy and radical radiotherapy in patients with early, localized prostate cancer diagnosed after screening PSA was

offered via the general practitioner [24]. A total of 1643 patients were randomized to the three groups with a median age of 62 years and median PSA 4.6 ng/mL. The majority of the tumours were low–risk in terms of both grade (Gleason 6 in 77%) and stage (T1c in 76% of patients). The study concluded that death from prostate cancer as well as all-cause mortality in such men remained low at 10 years of follow up (approximately 1% and 10% respectively) regardless of the assigned treatment. Although the rates of clinical progression and metastatic disease were lower in the treatment groups compared to active monitoring ($p<0.001$ and $p=0.004$ respectively), it was not possible to conclude that immediate treatment translates into significant improvements in disease-specific or all-cause mortality. This, however, might be due to the fact that further follow-up is needed to demonstrate a difference. It should be noted that active monitoring in PROTECT was done by regular PSA tests and did not include MRI or planned repeat biopsies. The main trigger for clinical review in order to consider a change in clinical management was a PSA level increase of at least 50% in the previous 12 months. Subsequent possibilities included further monitoring, additional tests and radical or palliative treatment.

The ProtecT group also assessed urinary, bowel and sexual function as well as quality of life and general health of all men enrolled in the study, according to intention to treat [25]. Prostatectomy had the greatest negative effect on sexual function and continence at 6 months and continued to have the greatest effect at 6 years post treatment. In terms of continence, radical prostatectomy was associated with 46% pad use at 6 months, compared to 4% in the active monitoring group and 5% in the radiotherapy group. By 6 years, the rate of pad use in the radical prostatectomy group was 17%, compared to 8% in the active monitoring group and 4% in the radiotherapy group. Of the 545 men randomized to the active monitoring group, approximately 40%

had radical treatment at 6 years according to the latest report [24]. Sexual function was significantly affected across all groups with 67% of men reporting erections sufficient for intercourse at baseline, whilst at 6 months this percentage was 52% for those randomized to monitoring, 22% for those randomized to radiotherapy and 12% for those randomized to radical prostatectomy. Overall quality of life reflected function and there were no differences in anxiety, depression, and general or cancer-related health between the three groups.

In summary, SPCG-4 confirmed that the long-term mortality benefits of radical prostatectomy for palpable prostate cancer are largely seen in men younger than 65 years. PIVOT highlighted that the absolute risk difference between surgery and observation is minimal in men with localized, low-risk prostate cancer and becomes larger in men with greater PSA values and higher risk disease. Finally, for PSA screening-detected, localized low-risk cancers, ProtecT reinforced the notion that surgery and radiotherapy have similar oncological outcomes with active surveillance at 10 years of follow up, albeit at a significant cost on quality of life. Taken together, this evidence suggests that, although radical treatment is most likely beneficial for younger men with intermediate to high risk disease, active surveillance should be seriously considered for men with low-risk prostate cancers, the majority of which are now PSA-detected.

4. Active surveillance strategies

There are currently several AS programs worldwide with significant variation in their inclusion criteria. AS monitoring is based on serial clinical examinations, PSA measurements and prostate biopsies, with MRI being increasingly used. However,

there are varying degrees of flexibility. Unsurprisingly, stringent monitoring and lower disease reclassification thresholds are associated with higher intervention rates [26]. The entry criteria and thresholds for intervention for some of the largest AS cohorts are summarized in **Table 1** and their most recently published oncological outcomes in **Table 2**. It is important to take into account the entry criteria and monitoring protocol when interpreting oncological outcomes for any AS programme.

From the available evidence, it appears that AS has overall favorable oncologic outcomes while reducing the risk of treatment-related complications and maintaining quality of life. AS has, however, attracted criticism from those who see it as doing too little as well as those who see it as doing too much. Some authors have significant concerns about potentially missing the opportunity for cure if progression is undetected. In addition, there is anxiety about worse functional outcomes from radical treatments, either due to disease progression itself (which imposes the need for more complex therapeutic strategies) or the effect of having radical treatment at an older age. Others are concerned about the problems conferred by monitoring such as repeat biopsies and the psychological burden for patients who receive a diagnosis not immediately addressed with curative treatment. However, a recent systematic review of studies measuring health-related quality of life in 966 men on AS concluded that most patients report good quality of life and do not suffer any major negative psychological effects [27].

5. Disease reclassification

Although accurate classification at diagnosis is key, prompt detection of disease progression, sometimes referred to as reclassification, during active surveillance is

equally important. PSA elevation (despite limitations arising from its demonstrated lack of specificity), adverse biopsy features (volume or grade) and clinical upstaging are the most common triggers for intervention, although the use of magnetic resonance imaging and molecular biomarkers is gaining ground [28]. The prognostic value of each of these metrics is being evaluated and there is noticeable variation between different active surveillance cohorts in terms of the different thresholds used.

In a meta-analysis of the factors that trigger change to radical treatment including 7627 men from 26 surveillance cohorts with a median follow up of 3.5 years, 8.8% of patients received radical treatment every year most commonly due to adverse biopsy findings, prostate specific antigen triggers and patient choice driven by anxiety [29]. Unsurprisingly, the rate of change to radical treatment was highest amongst men with higher baseline PSA or disease stage and in programs with scheduled repeat biopsies.

In a systematic review of 61 articles, the extent of cancer at biopsy (number of positive cores or percentage of core involvement) along with PSA density and percentage of free PSA were found to be useful for predicting disease progression [30]. Specifically, the authors reported that greater extent of cancer at initial biopsy as well as on confirmatory biopsies carry prognostic significance for progression. The evidence for the prognostic role of age, race and family history was found to be less robust, but these factors should also be considered. In another large meta-analysis of 32 studies encompassing 24,236 patients on AS for early stage prostate cancer, PSA density, more than one positive core and race were significantly associated with histological progression [31]. Interestingly, age, PSA levels and suspicion on MRI were not. A recent retrospective study also showed that in 102 men on AS with a median follow up of 9.25 years, only PSA density above 0.15 was a significant predictor of

disease reclassification with a mean time to reclassification of 4.7 years (IQR 2.8-7.9) [32]. In this study, there was no significant difference in metastasis-free and overall survival between patients who received treatment and those that continued on AS despite reclassification.

Table 1 summarizes the intervention triggers for some of the largest AS cohorts. Generally, disease reclassification (as defined in each cohort) and patient preference play a major role. In the UCSF cohort, the median time to disease reclassification was 17 months (IQR 10–33 months) and the median time to treatment was 25 months (IQR 15–45). Almost 60% of patients underwent treatment (mostly radical prostatectomy) and their PSA recurrence-free survival at 1 year was 97%. PSA density was positively associated with biopsy reclassification. In the Australian cohort, 38% of men received treatment, 88% of which was due to disease progression (mainly progression on biopsy). The median time to radical treatment was 90 months (IQR 63-146) and a high PSA density or abnormal DRE were the main predictors of significant cancer. In the Royal Marsden cohort, where the 5-year treatment-free probability was 70% (95% CI: 65-75%), the rate of adverse histology at 5 years was 22% (95% CI: 16-29%) and was best predicted by a Gleason score of 3+4, a PSA velocity greater than 1 ng/ml per year and a low free/total PSA ratio. In the Johns Hopkins cohort, the cumulative incidence of curative intervention was 57% and this was mostly associated with PSA density and a greater number of positive cores. Although in the PRIAS cohort 73% of men had discontinued AS at 15 years due to reclassification, the authors pointed out that many had favorable histology after prostatectomy and concluded that only Gleason upgrading and T3 stage were reliable indicators for recommending a transition to radical treatment.

6. MRI in active surveillance

Multiparametric magnetic resonance imaging (mpMRI), which incorporates T2-weighted, dynamic contrast-enhanced, and diffusion-weighted sequences, is being increasingly used in prostate cancer active surveillance. This technique allows the integration of anatomical, biological and functional information. Most studies using histopathology specimens as reference standards have shown that mpMRI outperforms conventional anatomical imaging alone for the detection of prostate cancer [33-36]. There is also evidence that unfavorable findings on mpMRI, especially low ADC values, are associated with adverse histological features [37, 38]. Currently, almost all MRI reporting schemes are structured and use a 5-point scale to quantify the likelihood that clinically significant prostate cancer is present within a radiological region of interest. The PIRADS score introduced in 2012 (and its recently revised PIRADS-2 version) is widely used. This system aims to formalize the scoring based on findings for each of the T2, DCE and diffusion-weighted images and a study has shown a sensitivity, specificity and negative predictive value ranging from 0.70-0.84, 0.68-0.86 and 0.58-0.95, respectively [39]. Another simpler system is the 5-point Likert scale, where the radiologist gives an assessment of the likelihood of clinically significant disease for a given lesion or the whole prostate. Both systems perform well [40], but some studies suggest higher accuracy for the Likert scale approach [41]. There are also concerns regarding the complexity versus clinical utility trade-off in PIRADS-2 as opposed to the less prescriptive Likert scale, although the introduction of PIRADS-2 is recent and further work is needed in this area [42].

In detecting clinically significant prostate cancer in the general diagnostic setting, mpMRI has reported accuracy of 44-87%, sensitivity of 58-97% and specificity of 23-

87% [43]. These values depend heavily on the definition of clinically significant prostate cancer and the mpMRI scoring system or threshold used (i.e. the point on the scale considered positive). There is evidence that the combination of pre-biopsy MRI and MRI-targeted biopsy detects at least an equal number of clinically significant cancer as standard TRUS biopsy, but reduces the number of men biopsied by a third and the men diagnosed with clinically insignificant prostate cancer by 10% [44]. This evidence is further corroborated by the recent results of the PROMIS trial, a prospective study testing mpMRI and TRUS biopsy with respect to 5 mm template mapping biopsy, which is generally considered as the most accurate reference test. In 573 men with elevated PSA (less than 15 ng/mL) who underwent all three tests, MRI outperformed TRUS in both detecting and ruling out clinically significant cancer, with a sensitivity of 93% (95% CI: 88-96) versus 48% (95% CI: 42-55) and a negative predictive value of 89% (95% CI: 83-94) versus 74% (95% CI: 69-78) [45]. Therefore, mpMRI could have a prominent place as a triage test by reducing the need for prostate biopsies without compromising the detection of clinically significant cancer.

The potential value of MRI for monitoring patients already on active surveillance should not be overlooked. Although experience in this area is limited, converging evidence from MRI-based AS cohorts suggests that serial imaging improves the prediction of pathological progression compared to clinicopathological variables alone, whereas stable MRI findings are associated with pathological stability [46, 47, 48]. A meta-analysis of MRI performance involving a total of 1028 surveillance patients demonstrated a low positive predictive value and sensitivity but a high negative predictive value and specificity, suggesting that although a negative MRI is reassuring, men with suspicious MRI lesions should be closely monitored [49].

In summary, mpMRI could be useful in AS through (i) identifying men who would

most benefit from additional biopsy (as presence of suspicious lesions on MRI predicts unfavorable histology [50]), (ii) increasing the diagnostic accuracy of prostate biopsy (as MRI-targeted biopsies in MRI-positive men increase the detection of significant cancers [51], outperform standard biopsies [52, 53] and reduce misclassification [54]), (iii) reducing the number of biopsies needed to diagnose significant cancer [55] and the need for repeat biopsies [56] due to a high negative predictive value and (iv) monitoring diagnosed lesions. The European School of Oncology has recently published the PRECISE guidelines on MRI reporting in AS with the intention of developing a robust data set that will inform the threshold setting for clinical significance and significant change of MRI lesions in men with low and intermediate risk prostate cancer. The key recommendations are to report the size of any lesions in absolute values (diameter on an axial section and volume using 3 parameters or planimetry) at baseline and each subsequent MRI, together with an assessment of the likelihood of clinically significant change for all follow up MRIs on a Likert scale of 1-5 [57].

7. Biomarkers

A growing understanding of the molecular aspects of prostate cancer in recent years has led to the development of predictive or prognostic biomarker assays for the purpose of selecting and monitoring men on active surveillance. Although rigorous studies assessing the validity of these tests are still lacking, preliminary evidence is promising. Genomic tests could be particularly useful for identifying patients with a higher risk of oncological progression and cancer-specific mortality.

The Cell Cycle Progression Score (CCP) is based on measuring gene expression in

paraffin-embedded tumour samples through quantitative RT-PCR. It was first demonstrated to be a robust predictor of prostate cancer-related death in a cohort of patients that had radical prostatectomy or TURP [58]. It is important to note that this cohort was heterogeneous, including patients from different risk strata. The study findings, however, were subsequently extended to tissue obtained through needle biopsies in men managed conservatively [59]. In a similar study on prostatectomy and needle biopsy specimens, the Genomic Prostate Score (GPS) was derived by measuring the expression of genes associated with disease aggressiveness despite tumour heterogeneity or multifocality [60]. Although this study included some patients with intermediate risk Gleason 3+4 tumours (a group not meeting the eligibility criteria of certain AS programmes), GPS was a significant predictor of high-stage and high-grade disease.

Notable efforts to develop similar tests in urine include the PCA3 and TMPRSS2-ERG assays. A study correlating urine PCA3 and TMPRSS2-ERG transcript levels, PSA density, genetic variants and androgenic status with outcome and pathological findings at biopsy found that urine biomarkers were associated with the presence of cancer [61]. Interestingly, PCA3 was also associated with the presence of Gleason 4 and the percentage of positive biopsy cores. It should be again emphasized that the validity of biomarkers should be further confirmed through their serial use in AS cohorts and a significant body of evidence justifying their widespread adoption is still lacking from the literature.

8. Conclusion

Active surveillance is a promising management strategy for low and intermediate

risk prostate cancer. There are some ongoing dilemmas regarding its optimal implementation (e.g. whether flexible local protocols would be preferable to stringent international guidelines or whether academic units are a more suitable environment compared to community hospitals). Despite these and the heterogeneity amongst current AS cohorts that makes direct comparison of outcomes challenging, there is strong converging evidence that cancer-specific outcomes in the surveillance setting are comparable to those of radical treatments without the loss of function commonly associated with surgery or radiotherapy. Therefore, in the era of modern PSA screening, an active surveillance approach should be seriously considered for men with low-grade, low-volume disease. The key to success is appropriate selection of candidates based on clinical, pathological and radiological variables and the continuous assessment of reclassification risk during follow up. Multiparametric MRI appears to be a useful complementary tool for assessing risk and should be considered at baseline and during follow up.

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Cohort	Selection criteria	Current monitoring protocol	Criteria for intervention
UCSF Welty et al. 2015 [62]	PSA < 10 ng/mL T1 or T2 Gleason 3+3 or less <33% positive cores <50% cancer involvement in any core	PSA every 3 months TRUS every 6 months Annual 12-core sextant biopsy (confirmatory biopsy within 12 months of diagnostic biopsy; then biopsies every 12-24 months according to clinical risk)	Biopsy reclassification; change in clinical stage; CAPRA risk reclassification; patient anxiety
Australian Thompson et al. 2014 [63]	PSA < 10 ng/mL Stage < T2b on DRE Gleason 3+3 <20% positive cores <30% or 6 mm cancer in all positive cores	PSA every 3 months for 3 years then 6-monthly DRE every 6 months for 3 years then annually Biopsies at 12 and 24-36 months, then every 3–5 years Watchful waiting once age >75 years or life expectancy <7 years	Adverse PSA kinetics (PSA doubling time <3 years or PSA velocity >0.75 ng/mL), DRE progression (clinical T stage ≥2b), biopsy upgrade (Gleason ≥ 7/ increasing proportion of grade 4), cancer volume progression (>20% of cores positive or >8 mm in any core)
Royal Marsden Selvadurai et al. 2013 [64]	T1 or T2 PSA <15 ng/ml Gleason 3+3, but 3+4 permitted in patients >65 PPC <50% of total number of biopsy cores	DRE and serum PSA levels every 3 months in the first year, every 4 months in the second year and every 6 months thereafter TRUS biopsy after 18–24 months and then every 2 years	PSAV >1 ng/ml per year, adverse histology on repeat biopsy (i.e. primary Gleason > or equal to 4+3, presence of cancer in >50% of cores)
Sunnybrook (Toronto) Klotz L et al. 2015 [65]	1995-1999: Gleason 3+3, PSA < 10 ng/mL (for patients older than 70: PSA < 15 ng/mL, Gleason score < or = to 3+4) January 2000: study restricted to low-risk (Gleason score 6 or less and PSA < 10 ng/mL) or favorable intermediate-risk disease (PSA 10-20 ng/mL and/or Gleason score 3+4 or less)	3-monthly PSA for 2 years, then 6-monthly Confirmatory biopsy within 12 months of initial biopsy, then every 3 to 4 years until age 80	Short PSA doubling time (less than 3 years), histologic upgrade on repeat biopsy, clinical progression (i.e. development of a palpable nodule with histological confirmation)
Johns Hopkins Tosoian et al. 2015 [66]	T1c PSA density < 0.15 ng/mL Gleason 3+3 or less Two or fewer positive cores Maximum 50% involvement in any core	DRE and PSA measurements (total and free) every 6 months Annual 12- to 14-core biopsy	Gleason >6, >2 positive cores, >50% cancer involvement in any core
PRIAS Bokhorst et al. 2016 [67]	Before 2012: Gleason 3+3 or less, T2c stage or lower, PSA<10 ng/ml, two or fewer positive cores, PSA density <0.2 ng/ml/cm^3 2012-2015: criteria adapted to include minimal Gleason 3 + 4 and accommodate changes in number of positive cores obtained by MRI-targeted or saturation biopsies	3-monthly PSA and 6-monthly DRE for the first 2 years, 6-monthly PSA and annual DRE thereafter Standard biopsies at 1, 4, 7, and 10 years after diagnosis, then every 5 years (yearly biopsies if PSA doubling time 0-10 years) Bone scan if PSA >20 ng/ml	Active treatment (recommended until end of 2014): Gleason > 3+3, more than 2 positive cores, stage > cT2, PSA doubling time 0-3 years Criteria adapted for Gleason 3+4 and >2 cores based on MRI or saturation biopsies

Table 1: Summary of selection criteria, monitoring protocol and intervention or disease reclassification criteria for the largest recently published active surveillance cohorts. AS: Active Surveillance. DRE: Digital Rectal Examination. PSA: Prostate Specific Antigen. TRUS: Trans-Rectal Ultrasound.

Cohort	n	Median follow up	Summary of oncological outcomes
UCSF Welty et al. 2015 [62]	810	60 months	5-year overall survival: 98% 5-year treatment-free survival: 60% 5-year biopsy reclassification-free survival: 40% No prostate cancer deaths
Australian Thompson et al. 2014 [63]	650	55 months	Prostate cancer-specific survival 100% Metastasis-free survival 100% Biochemical recurrence-free survival 99% Radical treatment-free survival at 5 and 10 years: 57% and 45 % respectively Median time to treatment 7.5 years
Royal Marsden Selvadurai et al. 2013 [64]	471	5.7 years	5-year rate of adverse histology 22% (95% CI: 16–29%) 5-year treatment-free probability 70% (95% CI: 65–75%) 2 deaths from prostate cancer
Sunnybrook (Toronto) Klotz L et al. 2015 [65]	819	6.4 years	10- and 15-year cause-specific survival rate 98.1% and 94.3% respectively Patients untreated at 5, 10, and 15 years: 75.7%, 63.5%, and 55.0% respectively 149/993 (15%) patients died, 15 deaths (1.5%) from prostate cancer, 13 patients (1.3%) diagnosed with metastatic disease Cumulative hazard mortality ratio (other causes/prostate cancer): 9.2:1
Johns Hopkins Tosoian et al. 2015 [66]	1298	5 years	Overall survival: 93% at 10 years, 69% at 15 years Cancer-specific survival: 99.9% at 10 years, 99.9% at 15 years Metastasis-free survival: 99.4% at 10 years, 99.4% at 15 years Grade reclassification (cumulative incidence): 26% at 10 years, 31% at 15 years Curative intervention (cumulative incidence): 50% at 10 years, 57% at 15 years
PRIAS Bokhorst et al. 2016 [67]	5302	10 years	AS discontinuation (due to protocol-based re-stratification) at 5 and 10 years: 52% and 73% respectively Biopsy reclassification rate (Gleason >3+3 or >2 positive cores on any repeat biopsy): 22-33% 1/3 patients undergoing RP had favorable pathologic features on histology (Gleason 3+3, pT2)

Table 2: Summary of oncological outcomes for the largest recently published active surveillance cohorts. AS: Active Surveillance. PSA: Prostate Specific Antigen.