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Comment

Increasing trend of utilising active surveillance for Gleason Score 7 (3 + 4) prostate cancer

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Traditionally, only patients with low-risk, clinically localised prostate cancer (PCa), characterised by features such as impalpable disease, PSA levels <10 ng/mL, and Grade Group 1 (GG1), were considered eligible for active surveillance (AS). However, many tumours that fall outside of this category have low risks of progression. There has been a growing interest in expanding the use of AS to patients who do not meet the strict criteria for low-risk PCa, especially those with small volume GG2 disease. However, accurately identifying patients with low–intermediate-risk PCa who will not experience disease progression during AS remains a challenge. The objective of this comment is to explore how this trend has evolved over time for this specific group of men and to discuss adjunctive measures to minimise non-salvageable disease progression.

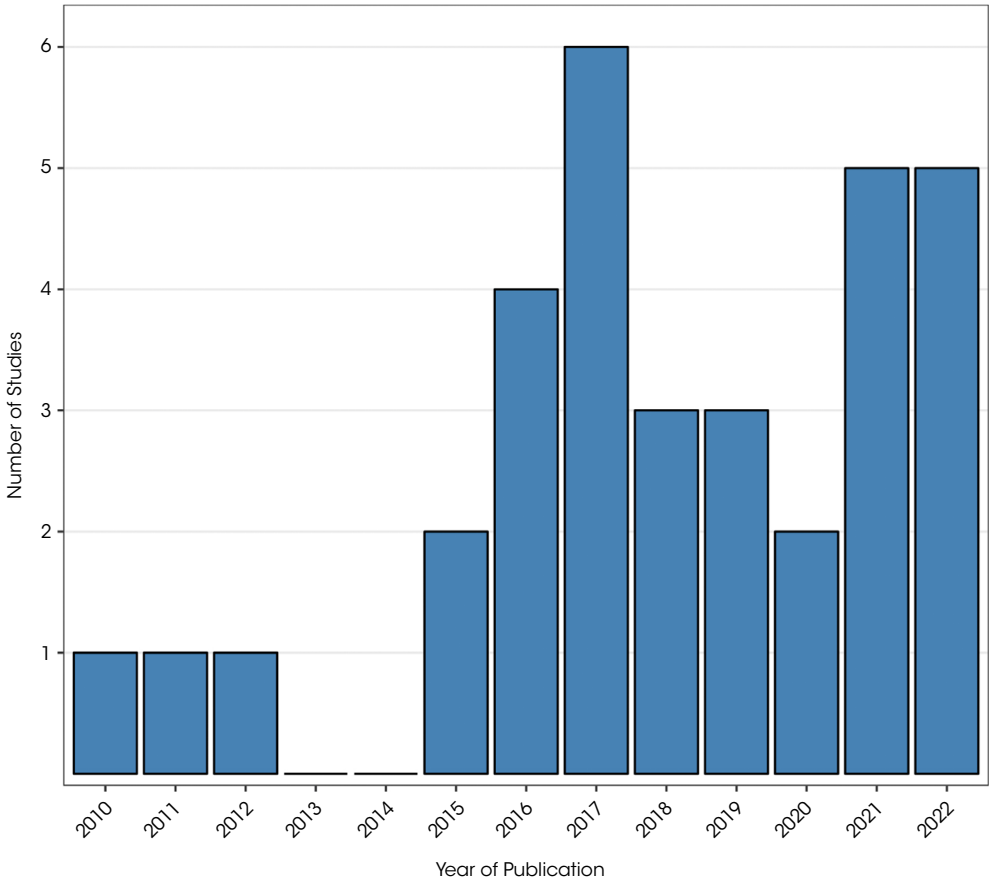
To evaluate the trends of utilising AS for favourable intermediate-risk PCa we performed a MEDLINE search of studies that included men with localised intermediate-risk PCa (patients) managed with AS from 2010 until 2022. Briefly, we used the following keywords: 'prostate or prostatic'; 'cancer or neoplasm'; 'intermediate or medium or moderate'; 'active surveillance'. We excluded watchful-waiting studies, and we included both prospective and retrospective studies. In case of duplicate publications, either the higher-quality or the most recent publication was selected. Reviews, meta-analyses, editorials, commentaries, authors' replies, and case reports were also excluded. Overall, we observed an increase in the number of studies from 2016 to 2022 compared to the period from 2010 to 2015 (Fig. 1). This substantial difference may reflect a growing trend towards the use of AS for favourable intermediate-risk PCa.

The inclusion criteria for selecting patients with intermediate-risk PCa vary between guidelines. Common favourable features include Gleason pattern 4 <10%, absence of intraductal PCa or cribriform pattern, a low number of cores, PSA level <10 ng/mL and negative MRI. Currently, there is no consensus on the maximum Gleason 4 percentage that is acceptable to consider AS in intermediate-risk patients. 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 Cancer of the Prostate Risk Assessment (CAPRA) risk stratification system, the presence of pattern 4 only adds 1 point, a very modest increment, to the risk score [1]. There is general consensus that AS is inappropriate for men with intraductal or cribriform pattern at biopsy. A major concern regarding this clinical recommendation is the high false-negative rate (>50% in some series) for the detection of cribriform pattern when comparing to radical prostatectomy specimens [2]. This unmet need is an important avenue for future research towards developing a reliable biomarker for predicting adverse pathology.

There is also a compelling argument to employ AS among younger men, as they can benefit from the improved quality of life such as preserved sexual and urinary function. A meta-analysis of real-life data from 27 centres located worldwide concluded that, men aged <60 years at time of diagnosis and those with intermediate-risk disease need not be excluded from AS as initial therapy [3]. There is a higher risk of clinical progression over a longer period, especially for men who are aged <55 years with median life expectancies of ≥25 years. Therefore, continuous, and extended monitoring is necessary in these patients.

It has been long known that localised 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 [4]. 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 [5]. There is also a need for biomarkers that can effectively monitor disease progression during AS.

Fig. 1 Number of studies published on AS for favourable intermediate-risk PCa from 2010 to 2022. A Poisson model was fitted to see if the number of studies by year differed from ≤2015 vs >2015. The model models the number of studies as a count and allows for differences in group sizes. The *P* value from this model was 0.001, and the average number of studies per year in >2015 was 4.80-times higher than ≤2015 (95% CI 2.02–14.13). Statistical analysis and graph done by Katherine Lajkosz, Statistical Department, Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada.



Furthermore, certain genetic anomalies, either inherited or acquired, are associated with more aggressive disease. 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.

The decision to opt for conservative management for patients with intermediate-risk PCa is supported by evidence gathered from epidemiological data, randomised trials, and prospective cohorts of patients managed with surveillance. In addition, the limitations and risks of this approach can also be determined from these 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 5–10 years. 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 overpopulated with patients who are diagnosed with GG1 disease.

In conclusion, there is an increasing trend in the utilisation of AS for managing favourable intermediate-risk PCa in studies encompassing men diagnosed with localised intermediate-risk PCa from 2010 to 2022. 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. As patient selection continues to improve, clinical, genomic, and radiological biomarkers will play a crucial role in risk stratification and patient selection for PCa management. The availability of more accurate biomarkers will ultimately lead to less invasive monitoring for men with PCa in the future and make AS more appealing for those with intermediate-risk disease.

Author Contributions

Conceptualisation: Rui Bernardino, Rashid K. Sayyid, Ricardo Leão, Alexandre R. Zlotta; Neil E. Fleshner; Data Curation: Rui Bernardino, Rashid K. Sayyid, Ricardo Leão, Neil E. Fleshner;

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Disclosure of Interests

The authors declare no relevant conflicts of interest.

Ethics Statement

The requirement for ethics approval by research ethics board was waived due to the nature of the study.

Previous Presentations

None.

Data Availability Statement

We have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The data sets generated during and/or analysed during the present study are available from the corresponding author on reasonable request.

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Abbreviations: AS, active surveillance; GG, Grade Group; PCa, prostate cancer.

