Active surveillance: where are we now?

By Kalli Spencer

Active surveillance (AS) is an approach that uses a combination of PSA testing, prostate examinations, and prostate biopsies to monitor prostate cancer. Traditionally its has been advocated for those with localised very low risk and low risk stages of disease, but more recently has included favourable-intermediate risk low volume disease as well. The risk group stratification is determined by what the urologist can feel during a prostate exam, the PSA level and what grade group the patient is designated by the pathologist based on the prostate biopsy results. The benefit of active surveillance is that it avoids radical therapies such as radiation and radical prostatectomies thereby avoiding some of the side effects of those treatments that may hamper quality of life, such as erectile dysfunction and urinary incontinence. This blog will highlight some of the current research findings as presented in a recent review article published this year.

The article reviews 13 different studies from various parts of the world including Australia. The average age range was between 62-68 years, with studies containing over 5000 participants and follow-up periods of up to 10 years. The inclusion criteria for each of the studies varied. PSA levels of up to 20 were acceptable in some studies, the urologist may feel cancer in both lobes of the prostate (clinical stage: T2C) and the pathology report Grade Group 2 was the maximum. Some studies also used 2-3 positive prostate biopsy cores as a limit or the percentage positive cores up to 50%.

Follow up/surveillance protocols were variable:

- PSA monitoring (every 3–6 months)
- Prostate exam (every 6–12 months)
- Follow-up prostate biopsy (at 1–3-year intervals)
- Several studies include regular MRI (every 1–3 years)

Triggers to switch to active/curative treatments (as mentioned above) include:

- Patient anxiety (>20% of patients)
- Repeat biopsies which demonstrate:
    - Grade group >2
    - >2 cores positive
    - >50% cores involved
- Previously PSA kinetics such as PSA velocity and doubling times cut offs were used as triggers for treatments but now, they help guide further investigations.

Across the studies rates of local and distant metastases (disease spread) remained low. About half of patients did not switch to active treatment for 5-10 years after initial diagnosis.

The role of MRI

MRI is often used at the initiation of AS to confirm eligibility, improve diagnostic specificity, to assess for undetected high-grade disease and large tumours that might have been overlooked. It can also be used for monitoring during surveillance to assess for the risk of

progression. It can be used for targeted biopsy planning, reducing the number of systematic cores taken. The most recent research has also looked at MRI replacing the need for ongoing prostate biopsies during the AS protocol thereby reducing potential side effects, discomfort, and anxiety. This however has remained controversial with some studies reporting a very low likelihood of progression on biopsy. The ASIST study found that for this concept to be successful there is a need for high-quality MRI, high quality targeted biopsies and experienced radiologists reporting on the MRI. Some study results show that there may be a small chance of missed cancers and potential risk of disease progression. Therefore, most current guidelines suggests that the greatest utility of MRI and targeted biopsies comes from their combined use rather than a direct replacement and negative MRI should not be used to forgo a scheduled surveillance biopsy.

The use of biomarkers

These are particularly important in those with hereditary cancer with BRCA2 gene mutations. BRCA2 gene mutations have been associated with worse outcomes on AS, prompting the need for closer monitoring. Various biomarkers have been studied such as Prolaris Cell Cycle Progression (CCP) score, ProMark, Oncotype DX Genomic Prostate Score, although long term outcomes in this population have not be investigated. Preliminary research suggests that these tissue-based assays can be utilized in prostate cancer patients with higher volume Grade Group 1 or favourable intermediate risk Grade Group 2 to help guide clinical decision making but at the present they should not be used for routine use and should not be used for patients who have clear clinical indications for either an AS protocol or immediate active treatment. PSA density has proven to be useful, with a higher PSA density associated with an increased risk for biopsy reclassification, allowing it to be used as a threshold for inclusion into AS protocols. Urinary markers such as PCA3 or Select MDx have also been evaluated, but the results are mostly inconclusive across different studies and needs further validation. Both the Prostate Health Index (PHI) and 4Kscore blood biomarkers have been shown to be associated with improved prediction of clinically significant prostate cancer. Certain pathological findings during examination of prostate biopsy cores such as the presence of invasive cribiform and/or intraductal carcinoma have been associated with a poorer prognosis and possible exclusion from AS protocols.

Inclusion of the intermediate risk classification

In the past those with this classification (Gleason Pattern 4 or Grade Group 2/3) were not eligible for AS protocols and would continue directly with active treatments. Many more centres globally are now including favourable intermediate risk patients onto AS protocols if their cancer remains stable. The specific eligibility criteria varies but the following recommendations have been proposed based off two well-known trials (PIVOT and ProtecT):

- Low percentage Gleason pattern 4
- Low PSA density
- Carefully monitoring for signs of progression (particularly after 10 years)
- Negative MRI or positive MRI with favourable targeted biopsy + Grade Group 2, <5-10% Gleason pattern 4

It may be useful to do genetic testing to assess for BRCA 1/2 gene mutations, HOXB13 gene mutation, DNA-gene repair mutations (ATM, CHEK2, MSH2), and single-nucleotide polymorphisms as AS failures may be caused by undetected genetic predispositions that can cause more aggressive disease.

Quality of life during AS protocols

Studies have shown that AS patients asses their own quality of life positively with high ratings across all health state utilities. Despite this some urologists may be reluctant to start AS out of fear of elevating stress and invoking anxiety with effects on mental health. Contrary to this, patients have felt increased control over their cancer rather than uncertainty, helping to minimize cancer-related fears and anxieties.

Often active surveillance is confused with the concept of watchful waiting. Its important to emphasize that the intention of each of these management options are different. For active surveillance the patient is monitored with an intention to treat actively/curatively if there are any signs of disease progression. Watchful waiting is usually used in those with advanced disease where there is no curative intent and any symptoms such as pelvic pain or urination difficulties are treated as they arise.

Active surveillance has many advantages and remains an important option where indicated. With the change in eligibility criteria increasingly more patients will be enrolled onto AS protocols going forward. There is a wealth of research studies investigating whether MRI or biomarkers may eventually completely replace prostate biopsies. Risk calculators such as the Canary Prostate Active Surveillance Study Risk Calculators (PASS-RCs) are being developed to help predict classifications based on biopsies. It is also important to understand factors that influence acceptance, adherence to and discontinuation of active surveillance protocols. This is an established treatment modality but with time we will see revisions to eligibility criteria, monitoring processes and triggers for active treatment.

Reference

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About the Author

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Kalli is an internationally renowned Urological Surgeon, specialising in oncology and robotic surgery. He trained and worked in South Africa, before relocating to Australia where he has worked at Macquarie University Hospital and Westmead Hospital. His passion for what he does extends beyond the operating room, through publichealth advocacy, education and community awareness of men's health, cancer and sexuality.

Kalli has been involved with the Prostate Cancer Foundation of Australia for many years, advocating for improved cancer care and facilitating community prostate cancer support groups.