Prostate cancer

Active surveillance as a management option

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Background

Active surveillance, followed by delayed definitive treatment for those who develop evidence of significant cancer progression, is now a recognised management strategy for selected men with low risk prostate cancer.

Objective

This article summarises the role of active surveillance in the management of prostate cancer. It outlines the benefits of active surveillance and the indications for proceeding with curative treatments if required.

Discussion

A considerable proportion of men with low grade prostate cancer on biopsy may never progress to higher stage disease or develop symptoms from their cancers. These patients are suitable for active surveillance under the care of a urologist. Active surveillance involves initial stringent observation of the prostate cancer, with inclusion of monitoring biopsies rather than immediate active treatment in the form of surgery or radiotherapy. With careful selection, about 70% of men will not require any intervention for at least 5 years. Men with low grade disease should be offered active surveillance as a treatment option and provided with information about the risks and benefits of this approach.

Keywords

prostatic neoplasms/management; active surveillance; watchful waiting

The prognosis of prostate cancer has changed dramatically over the past few decades. Recent advances in cancer detection and prostate specific antigen (PSA) screening have diminished the relative incidence of high volume and aggressive tumours, with a stage shift to lower volume, lower grade tumours.[1] The widespread use of PSA has been associated with a substantial decline in prostate cancer mortality.[1,2] Many low grade cancers are unlikely to progress to clinical symptoms, and pose limited risk of death if left untreated.[3] The long term safety of active surveillance depends on the clinician's ability to initiate timely delayed intervention in those who need it, and to avoid overtreatment in those who do not. A range of variables associated with disease progression have been proposed as triggers to proceed with delayed curative therapy.

Prostate cancer is the most frequently diagnosed solid malignant tumour in men.[4] It kills over 3000 Australian men each year, which exceeds the number of women who die from breast cancer.[5] In the past, digital rectal examination (DRE) provided the main approach for suspected prostate cancer, which then mandated use of biopsy for confirmation. Because rectal examination has a low sensitivity and prostate cancer is asymptomatic until the late stages, most men had advanced and incurable disease at presentation. Despite its limitations, the advent of PSA testing has led to a considerably higher number of curable presentations. Nonetheless, mass PSA screening remains controversial. The European Randomised Study of Screening for Prostate Cancer demonstrated a 21% relative risk reduction of death from prostate cancer in the screening group versus patients not offered PSA screening at a median follow up of 11 years.[6] Likewise, a more recent Swedish trial with a longer median follow up of 14 years found the overall rate ratio of prostate cancer mortality for men randomised to PSA screening versus a control group not invited for PSA screening was 44%.[7] The number needed to treat in this study to prevent one death from prostate cancer was 12.

Today, prostate cancers detected by PSA screening increasingly resemble tumours found at autopsy in men who have died of other causes.[1] Findings from a Canadian study of 452 men by Klotz et al[8] suggest that the 10 year survival rate of low grade prostate cancer on an active surveillance protocol was 97.2%. The high prevalence of these small neoplasms relative to the lifetime risk of prostate cancer death raises concerns about cancer overtreatment, compounded by patients' associated morbidities as causes of death.

Many cancers detected by PSA screening are low grade lesions that pose little threat of progression over 15–20 years.[9] The preclinical but potentially detectable phase of prostate cancer can be long in these tumours.[4] A significant portion of these preclinical cancer foci remain asymptomatic and undetected throughout a man's lifetime.[4] In a randomised study of radical prostatectomy versus observation during the early era of PSA testing, radical prostatectomy in the low risk patient cohort did not reduce all cause mortality of prostate cancer during the median follow up of 10 years.[10]

Unfortunately, there is no test which identifies the low grade cancers that are likely to advance to clinically significant disease. The challenge is therefore to identify those patients who are unlikely to experience significant progression while offering radical therapy to those who are at risk.

Defining active surveillance

Active surveillance is a method of delayed curative treatment. The low risk prostate cancer is closely monitored and at the development of significant local progression the patient is treated with curative intent, usually by radical prostatectomy, radiotherapy or brachytherapy. The rationale for an initial observation approach is that prostate cancer often progresses slowly and is often diagnosed in older men who are unlikely to benefit from intervention. Active surveillance limits adverse effects from radical definitive treatments and maintains quality of life.

Only selected patients are suitable for active surveillance protocols (*Table 1*). Characteristically, a regimen requires PSA testing every 3–4 months in the first 2 years after diagnosis, then 6 monthly thereafter. Additionally, repeat biopsies have been incorporated into all protocols. A surveillance prostate biopsy, preferably of a least 12 cores, is performed at 1 year to exclude significant progression of cancer volume or grade, then every 2–3 years beyond this. A trigger for earlier biopsy would be significant change in PSA kinetics or abnormal findings in DRE of the prostate.

Evidence for active surveillance

There is a growing body of evidence to support the safety of active surveillance instead of immediate treatment for low risk cancer. In men with low grade tumours, mortality is unchanged when undergoing active surveillance compared with immediate aggressive interventions.[11] Hayes et al[11] have demonstrated that careful observation as an initial management strategy is associated with the longest quality adjusted life expectancy. Comparison of observational trials with immediate radical prostatectomy by Wilt et al[12] revealed there to be no benefit of radical prostatectomy for men with low risk disease during a median follow up of 10 years. A systematic review of prospective trials by Dall'Era et al[13] demonstrated that the 10 year prostate cancer specific mortality in active surveillance groups is <3%, although median follow up across all studies was <7 years. In this analysis, approximately one-third of patients required definitive delayed treatment within 10 years for significant disease progression, usually by radical prostatectomy.

With careful selection, about 70% of men will not require any intervention for at least 5 years.[8]

Table 1. Patients suitable for active surveillance protocols

Patients with low risk disease: men with low volume malignancy (one of four cores positive or less) of Gleason score 3+3 with a PSA of less than 10 ng/mL on presentation and either a non-palpable tumour on DRE or a small tumour occupying less than half of one lobe (stage T1c–T2a)

Triggers for intervention

The largest problem with the concept of active surveillance is the definition of clinically significant disease. Some men may develop high volume or high grade tumours which will necessitate curative therapy. However, radical therapy for all would result in overtreatment of patients with indolent disease. As such, the decision as to when to instigate definitive treatment remains unclear.

A number of criteria have been proposed for determining when to proceed with curative interventions. These are outlined in *Table 2*. Optimal treatment criteria vary with the age and comorbidity of the patient based on a likelihood of living at least 10 years. That being the case, the art of active surveillance is to identify the most appropriate triggers for intervention in each individual patient.

Prostate specific antigen kinetics are not static, with PSA being an indirect barometer of prostate cancer status in this group, and so a single PSA trigger point should be interpreted cautiously. Klotz et al[8] used a PSA doubling time of <3 years as a suitable trigger to recommend treatment. Recent data from the Royal Marsden cohort in the United Kingdom showed a PSA velocity of >2.0 ng/mL in the year before treatment was linked with significant prostate cancer progression.[14]

Gleason grade on biopsy remains a strong predictor of prostate cancer progression. However, to maximise the value of this operator-dependent parameter, histopathology should be performed and interpreted by somebody with subspecialty expertise. While all low risk prostate cancers will evolve, some do so at a remarkably slow rate. A Gleason score more than 8–10 on surveillance biopsy heralds not only a risk of progression but also a notably higher mortality at 10 years,[7] thus continuing as a persuasive indicator for adjustment to a curative form of treatment when identified on surveillance biopsy.

The future of active surveillance

There are continuing advances in understanding the molecular biology of prostate carcinogenesis and progression. Many groups are conducting studies designed to preferentially detect high grade, and often lethal, prostate cancer, utilising biomarkers such as prostate cancer gene 3 (PCA3). While multiple genes and mechanisms have been discovered in recent times, no single biomarker has been identified that improves current clinical parameters.[4] Although promising, the outcome of

Table 2. Triggers for intervention

Most urologists and oncologists agree that curative treatment is indicated if there is progression to a higher grade tumour or higher volume tumour on surveillance biopsy, there is a PSA doubling time of less than 3 years, or there is a change in patient preference towards definitive treatment

present research into forecasting prostate cancer behaviour remains unclear.

Another area of great promise is multiparametric magnetic resonance imaging (mpMRI). Functional mpMRI techniques have increased accuracy in detecting prostate cancer localisations when compared with standard T2 weighted MRI and transrectal ultrasound (TRUS).[15] Magnetic resonance imaging targeted biopsy techniques can reduce the number of cores required from the prostate and decrease the 20–30% risk of cancer undergrading seen with standard 12 core TRUS biopsies.[16] A 3T mpMRI can detect clinically significant prostate cancer with 90% accuracy.[16] Refinements of this technology may see mpMRI play a bigger role in active surveillance protocols, and perhaps decrease the frequency of repeated biopsies.

Early detection of asymptomatic but high risk prostate tumours followed by curative measures will remain the most efficacious therapy for prostate cancer over the next several years. Investigating the prognostic factors and biomarkers that will reduce the probability of overtreatment, and ways in which active surveillance can be made less intrusive, are both important fields of future research.

Conclusion

Active surveillance is an appropriate option for men with low volume, low risk prostate cancer. This approach maintains quality of life and is associated with excellent cancer specific survival. It is generally well recognised among urology circles that a minority of active surveillance patients will require intervention for significant cancer progression. However, with careful selection, about 70% of men will not require any intervention for at least 5 years.[8]

Limitations of active surveillance methodology include patient anxiety regarding concerns over cancer progression,[17] the need for repeat biopsies and therefore potential infection risk, and the conceivable loss of curability during the active surveillance period, although this is small. Triggers for implementation of curative measures, such as radical prostatectomy and radiation treatments, remain variable and unvalidated. Ongoing long term follow up is necessary to confirm the suitability of active surveillance protocols over the longer term, particularly in men aged less than 65 years at prostate cancer diagnosis. Continued monitoring and assessment of outcome is also mandated for patients who require delayed definitive treatment and thus depart from an active surveillance regimen.

Stringent observation during an active surveillance protocol allows for maintenance of quality of life, yet avoids overtreatment in the majority of patients with low volume, low risk cancer. Men with low grade prostate cancer should be offered active surveillance as a treatment option and educated about the risks and benefits of this approach.

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Competing interests: Robert Gardiner has received payment for consultancy from the Lilly Advisory Board for LUTS.

Provenance and peer review: Not commissioned; externally peer reviewed.

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