Active Surveillance for Prostate Cancer

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Introduction

Prostate cancer is the most common cancer in men in the United Kingdom (UK), with over 42,000 men being diagnosed with the condition every year [1]. It is the second most common cancer in men worldwide. More than 1.1 million cases of prostate cancer were diagnosed in 2012 [2]. The use of Prostate-Specific Antigen (PSA) testing has led to an overall increase in the incidence of prostate cancer rates [3]. Its use has also resulted in the early detection of a large number of localised prostate cancer cases, which do not pose a threat to patients’ health or lives [4]. Prostate cancer detected by PSA screening tend to be detected at an earlier stage and take longer to progress without any treatment compared to cancers detected because of clinical manifestations. Autopsy studies have shown a high prevalence of asymptomatic localised prostate cancer in men who have died of other causes [5]. The management of localised prostate cancer therefore remains a controversial issue. A significant number of patients are undergoing treatment for clinically insignificant disease, with subsequent decrease in their quality of life due to treatment-related side-effects [6]. Active surveillance (AS) is a reasonable strategy to avoid overtreatment of low-risk localised prostate cancer and has now become a standard approach. Data from the British Association of Urological Surgeons (BAUS) have shown that up to 40% of men with low-risk disease have opted for active surveillance [7].

Defining Low-Risk Prostate Cancer

The basic idea behind active surveillance is that some prostate cancers will not progress to the stage that requires treatment within the lifetime of the patient and therefore treatment can be avoided or delayed [8]. This management strategy relies on careful risk stratification in order to identify patients with cancers at low risk of progression. Categorising patients into the low-risk group remains very challenging. Various clinical parameters such as Gleason score, clinical stage and pre-treatment PSA are used to stratify patients in the different groups and estimate the long-term disease progression.

The Epstein criteria, first described in 1994, are commonly used to describe disease risk [9]. They were developed for men who underwent radical prostatectomy for what was considered insignificant disease: tumour size < 0.5 cm³, organ-confined disease, and no Gleason pattern 4 or 5. The pre-operative predictors associated with these tumours include no Gleason pattern 4 or 5 in the biopsy specimen and either a PSA density of ≤ 0.1 ng/ml per gram, less than three positive biopsy cores out of a minimum of six cores, and no cores with >50% single core involvement [6]. The Epstein criteria are still widely used to define clinically insignificant prostate cancer.

D’Amico et al. described another risk classification for patients with prostate cancer using clinical stage, pre-treatment PSA and Gleason score to place patients in low, intermediate, or high risk of PSA recurrence after radical prostatectomy or radiotherapy [10]. The D’Amico criteria have been shown to predict disease-specific mortality in men undergoing radical prostatectomy [11]. Although both the Epstein and D’Amico criteria were developed to predict the outcomes in men treated for prostate cancer, they are commonly used to identify patients suitable for active surveillance (Table 1).

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical Stage</th>
<th>Gleason Score</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein et al. [9]</td>
<td>≤ T1c</td>
<td>No Gleason pattern 4 or 5 PSA density of ≤ 0.15 ng/mL/g</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;3 positive cores (out of 6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;50% single core involvement</td>
<td></td>
</tr>
<tr>
<td>D’Amico et al. [10]</td>
<td>≤ T2a</td>
<td>No Gleason pattern 4 or 5 PSA level ≤ 10 ng/mL</td>
<td></td>
</tr>
<tr>
<td>NICE [12]</td>
<td>T1-T2a</td>
<td>Gleason ≤ 6 PSA level &lt;10 ng/mL</td>
<td></td>
</tr>
<tr>
<td>EAU [13]</td>
<td>T1-T2a</td>
<td>Gleason&lt;7 PSA level &lt;10 ng/mL</td>
<td></td>
</tr>
</tbody>
</table>

EAU = European Association of Urology; NICE = National Institute for Health and Care Excellence

Table 1: Some of the different criteria used to define low-risk prostate cancer.
Active Surveillance

With the widespread use of PSA testing and new protocols for prostate biopsy, the incidence of low-risk prostate cancer has increased [4]. There is an ongoing debate among clinicians whether to treat prostate cancer early to prevent metastatic disease or to observe and only offer treatment when there is evidence of disease progression. The former is associated with risks of over-treating indolent disease whereas the latter risks missing an opportunity for cure among patients who will progress. Active surveillance (AS) has therefore become a reasonable alternative for patients with clinically insignificant disease. AS refers to a systematic programme where men diagnosed with low-risk prostate cancer are periodically monitored with multiple parameters including PSA, digital rectal examination and repeat prostate biopsies. The aim of such an approach is to identify disease progression in a timely fashion so that curative treatment can be offered promptly with good outcomes. AS may spare patients with early disease the side-effects of radical treatment without compromising their survival. It is a credible solution to the problem of overtreatment of clinically insignificant disease [14].

It is important to distinguish the concept of active surveillance from watchful waiting. Watchful waiting involves lax observation of the selected group of patients with late palliative treatment offered in the event of disease progression. This approach is generally reserved for elderly co-morbid patients. Active surveillance on the other hand involves closer monitoring with early radical treatment offered in those with signs of progression [15].

Patient Selection for Active Surveillance

The most important aspect of a successful active surveillance programme is patient selection. Selection depends on patient and tumour characteristics as well as patient's preferences. Age, comorbidities and life expectancy are also important factors to consider. Prospective studies with adequate follow-up and intervention data are currently lacking when it comes to selecting the ideal patients. There are currently no randomised controlled trials comparing the different selection criteria. The Gleason score, clinical stage and PSA at diagnosis are some of the criteria used for risk stratification. Both the Epstein and D'Amico criteria for defining disease risk are commonly used for selecting candidates for active surveillance. The inclusion criteria used in the various studies are quite different as outlined in Table 2 below.

<table>
<thead>
<tr>
<th>Study</th>
<th>Criteria for Inclusion in Active Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dall’Era et al. [16]</td>
<td>PSA ≤ 10 ng/mL, Gleason score ≤ 6, ≤33% positive cores, ≤50% single core involvement</td>
</tr>
<tr>
<td>PRIAS [17]</td>
<td>T1c-T2, PSA ≤ 10 ng/mL, Gleason score ≤ 6, ≤2 positive cores, PSA density ≤ 0.2 ng/mL</td>
</tr>
<tr>
<td>Soloway et al. [18]</td>
<td>T1a-T2, PSA ≤ 10 ng/mL, Gleason score ≤ 6, ≤2 positive cores, ≤20% single core involvement</td>
</tr>
<tr>
<td>Klotz et al. [19]</td>
<td>No mention of stage, PSA ≤ 10 ng/mL, Gleason score ≤ 6, ≤3 positive cores, ≤50% single core involvement</td>
</tr>
<tr>
<td>NICE [20]</td>
<td>T1-T2a, PSA&lt;10 ng/mL, Gleason score ≤ 6, Consider AS for &lt;T2b and PSA&lt;20 ng/mL and Gleason 7 if active treatment not wanted</td>
</tr>
</tbody>
</table>

PRIAS = Prostate Cancer Research International: Active Surveillance

Table 2: Criteria for Inclusion in Active Surveillance

Active surveillance is offered to men who could have also been offered radical treatment in the form of surgery or radiotherapy. It can also be a suitable alternative for patients with intermediate-risk disease and a life expectancy of less than 10 years. It is however not recommended for patients with high-risk disease or those with primary Gleason pattern 4 or 5 as they have a higher risk of harbouring significant disease at diagnosis and progressing to metastatic disease without treatment [21].

Active Surveillance Protocol

The surveillance schedule for patients on active surveillance varies from centre to centre and there is currently no consensus on the optimal strategy [22]. When counselling patients for AS, they should be informed of the importance of compliance with the strict follow-up schedule. Some of the criteria used as part of the follow-up include digital rectal examination, PSA level, PSA kinetics and prostate biopsy.

There is no consensus on whether repeat biopsies are necessary or when they should be carried out. The NICE guidelines in the UK recommend repeat prostate biopsies 12 months after enrolment on the AS programme [23]. This is to rule out higher grade or volume disease that may have been missed on the initial biopsy. The choice between active treatment and continued surveillance is based on disease progression at repeat biopsy [15]. The upgrading in Gleason score remains the most important predictor of disease progression.

PSA remains a valid marker for the monitoring of patients on active surveillance. According to D’Amico, a rapid rise in pre-treatment PSA is associated with an increased risk of dying from prostate cancer [24]. Another study showed that a PSA doubling time of <2 years in patients undergoin surgical treatment after a period of active surveillance was a strong predictor of biochemical relapse [25]. Patients with PSA doubling-time of less than 3 years were also found to have higher mean PSA levels and more aggressive disease at re-biopsy [26]. However, PSA kinetics should not be used to replace repeat biopsy for men on AS [27].

Digital rectal examination as an independent predictor of disease progression remains questionable. It might be difficult to detect subtle changes on examination at such an early stage as it can be quite subjective. A change in digital rectal examination is often unusual in patients with low-risk disease [28]. One study showed that patients with disease progression detected by DRE were more likely to have a PSA doubling time of <2 years [29]. PSA kinetics therefore remains an important tool for detecting progression (Table 3).

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Table 3: The different surveillance strategies for patients on active surveillance.

<table>
<thead>
<tr>
<th>Study</th>
<th>PSA</th>
<th>DRE</th>
<th>Re-biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dall’Era et al. [16]</td>
<td>Every 3 to 6 months</td>
<td>Every 3 to 6 months</td>
<td>At 12-24 months</td>
</tr>
<tr>
<td>PRIAS [17]</td>
<td>First 2 years: every 3 months</td>
<td>No mention</td>
<td>At 1, 4 and 7 years</td>
</tr>
<tr>
<td></td>
<td>Next 2 years: every 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soloway et al. [18]</td>
<td>First 2 years: every 3-4 months</td>
<td>First 2 years: every 3-4 months</td>
<td>Every 12 months</td>
</tr>
<tr>
<td></td>
<td>Next 2 years: every 6 months</td>
<td>Next 2 years: every 6 months</td>
<td></td>
</tr>
<tr>
<td>Klotz et al. [19]</td>
<td>First 2 years: every 3 months</td>
<td>First 2 years: every 6 months</td>
<td>At 6-12 months</td>
</tr>
<tr>
<td></td>
<td>Next 2 years: every 6 months</td>
<td>Next 2 years: every 6 months</td>
<td></td>
</tr>
<tr>
<td>NICE [20]</td>
<td>First year: every 3-4 months</td>
<td>First 5 years: every 6-12 months</td>
<td>At 12 months</td>
</tr>
<tr>
<td></td>
<td>Year 2 to 4: every 3-6 months</td>
<td>After 5 years: every 12 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 5 years: every 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monitor PSA kinetics</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Triggers for Active Treatment**

While on active surveillance, nearly a third of patients will be restaged at high risk of disease progression and will be offered radical treatment. The most common trigger for intervention is a change from low-risk to intermediate or high-risk disease based on the Gleason score, PSA level or stage [30]. The detection of Gleason pattern 4 or 5 on repeat biopsy will trigger a change from active surveillance to active treatment, although some protocols will continue to keep patients with Gleason 7 on AS if they decline treatment [23]. A PSA doubling time of less than 2-4 years may also cause a shift to definitive therapy. However, specific criteria for active treatment are not well defined [22]. Patient’s choice, largely due to anxiety of untreated cancer, can also play a role [31].

**Outcomes of Active Surveillance**

Multiple studies have published their experience with active surveillance. The largest prospective study on active surveillance is the PRIAS study, which included 2499 patients [26]. The patients were followed for a median of 1.6 years. PSA density and the number of positive cores were found to be the strongest predictors for disease progression. The disease-specific survival rate was 100% and the authors concluded that AS was a feasible approach to reduce overtreatment.

In a large study by Klotz et al. [32], which included 993 patients, more than 200 patients were followed for ≥ 10 years and 50 for more than 15 years. After a median follow-up of 6.4 years, 73% remained on active surveillance. Disease-specific survival was 98.5%.

A single-centre prospective cohort study from the Royal Marsden Hospital included 471 patients with a median age of 66 years and a median PSA of 6.4 ng/mL [33]. At a median follow-up of 5.7 years, the 5-year rate of adverse histology was 22% and the probability of not receiving treatment during that time period was 70%. There were 2 prostate cancer-related deaths.

In another cohort of 407 patients, 59% remained on active surveillance at a median follow-up of 3.4 years [34]. 25% underwent curative treatment at a median of 2.2 years following diagnosis and 16% were either lost to follow-up, withdrew from AS or died of other causes.

Soloway et al. [18] also published their data on 99 patients undergoing active surveillance with a mean follow-up of 45 months and a mean age of 66 years. 5 patients underwent radical treatment with either surgery or radiotherapy and were recurrence-free for up to 83 months. No patients died of prostate cancer in that cohort. PSA doubling time and clinical stage were found to be strong predictors of disease progression.

All these studies suggest that active surveillance can be a suitable alternative to immediate radical treatment provided that patients are carefully selected with a strict surveillance protocol. However, AS is based on the assumptions that the cancer is clinically insignificant and that disease progression can be reliably identified and treated with curative intent without affecting survival. These assumptions are questionable and constitute some of the drawbacks of AS. Longer follow-up data are needed to confirm the safety of this strategy.

**Future of Active Surveillance**

Active surveillance has proven to be a suitable alternative to immediate radical treatment for men with low-risk localised prostate cancer. However, the future of AS and its uptake will depend on improved patient selection and timely identification of disease progression [14]. We are now able to detect low-risk disease with
greater accuracy. In the future, multi-parametric magnetic resonance imaging (MRI) and novel biomarkers will play a major role in patient selection and follow-up [35]. Improvements in prostate imaging as well as the discovery of new serum markers will change the approach to the management of patients with localised prostate cancer by enhancing the current risk stratification systems. This will lead to better selection of ideal candidates for active surveillance and better monitoring. Active surveillance may therefore be offered earlier to more patients. It is also likely that enhanced MRI techniques will reduce the number of prostate re-biopsies. Promising biomarkers such as PCA3 and TMPRSS2:ERG have already shown improved accuracy for predicting biopsy outcomes. MicroRNAs (miRNAs), which as short non-coding RNAs, have also been found to be potential biomarkers in prostate cancer [36]. However, the studies investigating their use so far have only involved small number of patients. Some of the miRNAs involved in prostate cancer development include miR-20a, miR-21, miR-145 and miR-221 [37]. Implementing these markers can help reduce the burden associated with AS monitoring, but further studies are needed to validate their use [38].

Conclusion

Active surveillance for low-risk prostate cancer remains an attractive option for men who want to avoid side-effects associated with treatment. This approach enables them to retain the option of radical treatment if there is evidence of disease progression during follow-up. Active surveillance has been shown to be safe in the medium term. Several published AS series have demonstrated that the disease-specific mortality remains low. Careful selection of patients however is key to a successful AS programme. The inclusion criteria and follow-up protocols to identify disease progression have not yet been standardised and various parameters are taken into account when recruiting or monitoring patients. Risk stratification still remains a significant challenge in active surveillance. The use of multi-parametric MRI and novel biomarkers will certainly significantly change our approach to AS when it comes to selecting patients and surveillance.

References

23. NICE. Prostate cancer: protocol for active surveillance (2014) Implementing the NICE guideline on prostate cancer (CG175).


