Journal of Cancer Clinical Trials

Reekhaye and Madaan, J Cancer Clin Trials 2016, 1:2

Commentary Open Access

Active Surveillance for Prostate Cancer

Reekhaye A and Madaan S*

Department of Urology and Nephrology, Darent Valley Hospital, Dartford, United Kingdom

***Corresponding author:** Sanjeev Madaan, Department of Urology and Nephrology, Darent Valley Hospital, Dartford, United Kingdom, Tel: +441322428612; E-mail: sanjeev.madaan@nhs.net

Received date: March 15, 2016; **Accepted date:** April 06, 2016; **Published date:** April 12, 2016

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 cm^3, 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% involvement; or a PSA density of ≤ 0.15 ng/ml per gram and cancer smaller than 3 mm on only one biopsy core [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).

Study	Clinical Stage	Gleason Score	PSA
Epstein et al. [9]	≤ T1c	No Gleason pattern 4 or 5	PSA density of ≤ 0.15 ng/mL/g
		<3 positive cores (out of 6)	
		<50% single core involvement	
D'Amico et al. [10]	≤ T2a	No Gleason pattern 4 or 5	PSA level ≤ 10 ng/mL
NICE [12]	T1-T2a	Gleason ≤ 6	PSA level <10 ng/mL
EAU [13]	T1-T2a	Gleason<7	PSA level <10 ng/mL
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, co-morbidities 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.

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

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

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

Triggers for Active Treatment

While on active surveillance, nearly a third of patients will be re-staged 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 over-treatment.

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 study of 500 patients at the University of California in San Francisco showed that 24% of men received treatment after a median of 3 years on an active surveillance protocol [16]. 38% had an upgrading of their Gleason score on repeat biopsy, which was the main trigger for treatment.

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 at 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

1. UK CR (2013) Prostate Cancer Incidence Statistics. Cancer Res UK.
2. Prostate cancer statistics (2016) World Cancer Research Fund International.
3. Quinn M, Babb P (2002) Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part I: international comparisons. BJU Int 90: 162-173.
4. Tomaškovic I (2015) Low risk prostate cancer: Active treatment or active surveillance? Acta Clin Croat 54: 337-343.
5. Zlotta AR, Egawa S, Pushkar D, Govorov A, Kimura T, et al. (2013) Prevalence of prostate cancer on autopsy: cross-sectional study on unscreened Caucasian and Asian men. J Natl Cancer Inst 105: 1050-1058.
6. Wu JN, Dall'Era MA (2010) Active surveillance for localized prostate cancer - Current practices and recommendations. Scientific World Journal 10: 2352-2361.
7. McVey GP, McPhail S, Fowler S, McIntosh G, Gillatt D (2010) Initial management of low-risk localized prostate cancer in the UK: Analysis of the British Association of Urological Surgeons Cancer Registry. BJU Int 106: 1161-1164.
8. Lellig K, Beyer B, Graefen M, Zaak D, Stief C (2014) [Active surveillance of low risk prostate cancer]. Urologe A 53: 1031-1039.
9. Epstein JI, Walsh PC, Carmichael M, Brendler CB (1994) Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA 271: 368-374.
10. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K (1998) Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 280: 969-974.
11. Boorjian SA, Karnes RJ, Rangel LJ, Bergstralh EJ, Blute ML (2008) Mayo Clinic validation of the D'amico risk group classification for predicting survival following radical prostatectomy. J Urol 179: 1354-1360.
12. NICE (2014) Prostate cancer: diagnosis and management. Nice Guidel CG175.
13. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, et al. (2014) EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol 65: 124-137.
14. Lawrentschuk N, Klotz L (2010) Active surveillance for favorable-risk prostate cancer: a short review. Korean J Urol 51: 665-670.
15. Mazzucchelli R, Nesseris I, Cheng L, Lopez-Beltran A, Montironi R, et al. (2010) Active surveillance for low-risk prostate cancer. Anticancer Res 30: 3683-3692.
16. Dall'Era MA, Cooperberg MR, Chan JM, Davies BJ, Albertsen PC, et al. (2008) Active surveillance for early-stage prostate cancer: review of the current literature. Cancer 112: 1650-1659.
17. Van Den Bergh RCN, Vasarainen H, Pickles T, Valdagni R, Staerman F, et al. (2009) Prospective protocol based active surveillance for early prostate cancer: Short-term results of 500 patients in the prias study. Eur Urol Suppl 181: 606-607.
18. Soloway MS, Soloway CT, Eldefrawy A, Acosta K, Kava B, et al. (2010) Careful selection and close monitoring of low-risk prostate cancer patients on active surveillance minimizes the need for treatment. Eur Urol 58: 831-835.
19. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, et al. (2010) Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol 28: 126-131.
20. Prostate cancer: diagnosis and management (2015) Guidance and guidelines. NICE.
21. Eggener SE, Scardino PT, Walsh PC, Han M, Partin AW, et al. (2011) Predicting 15-year prostate cancer specific mortality after radical prostatectomy. J Urol 185: 869-875.
22. Hadjipavlou M, Promponas J, Madaan S (2015) Active surveillance for low-risk prostate cancer. J Clin Urol 8: 420-428.
23. NICE. Prostate cancer: protocol for active surveillance (2014) Implementing the NICE guideline on prostate cancer (CG175).
24. D'Amico AV, Chen MH, Roehl KA, Catalona WJ (2004) Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. N Engl J Med 351: 125-135.
25. Ali K, Gunnar A, Jan-Erik D, Hans L, Lodding P, et al. (2007) PSA doubling time predicts the outcome after active surveillance in screening-detected prostate cancer: Results from the European randomized study of screening for prostate cancer, Sweden section. Int J Cancer 120: 170-174.
26. Bul M, Zhu X, Valdagni R, Pickles T, Kakehi Y, et al. (2013) Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. Eur Urol 63: 597-603.
27. Ross AE, Loeb S, Landis P, Partin AW, Epstein JI, et al. (2010) Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. J Clin Oncol 28: 2810-2816.
28. Tosoian JJ, Trock BJ, Landis P, Feng Z, Epstein JI, et al. (2011) Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. J Clin Oncol 29: 2185-2190.
29. Stephenson AJ, Jones JS, Hernandez AV, Ciezki JP, Gong MC, et al. (2009) Analysis of T1c prostate cancers treated at very low prostate-specific antigen levels. Eur Urol 55: 610-616.
30. Lund L, Svolgaard N, Poulsen MH (2014) Prostate cancer: a review of active surveillance. Res Rep Urol 6: 107-112.
31. Thomsen FB, Brasso K, Klotz LH, Røder MA, Berg KD, et al. (2014) Active surveillance for clinically localized prostate cancer--a systematic review. J Surg Oncol 109: 830-835.

32. Klotz L, Vesprini D, Sethukavalan P, Jethava V, Zhang L, et al. (2015) Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol 33: 272-277.

33. Selvadurai ED, Singhera M, Thomas K, Mohammed K, Woode-Amissah R, et al. (2013) Medium-term outcomes of active surveillance for localised prostate cancer. Eur Urol 64: 981-987.

34. Carter HB, Kettermann A, Warlick C, Metter EJ, Landis P, et al. (2007) Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience. J Urol 178: 2359-2364.

35. Johnson LM, Choyke PL, Figg WD, Turkbey B (2014) The role of MRI in prostate cancer active surveillance. Biomed Res Int 2014: 203906.

36. Josson S, Chung LW, Gururajan M (2015) microRNAs and Prostate Cancer. Adv Exp Med Biol 889: 105-118.

37. Jackson BL, Grabowska A, Ratan HL (2014) MicroRNA in prostate cancer: functional importance and potential as circulating biomarkers. BMC Cancer 14: 930.

38. Kim JH, Hong SK (2015) Potential Utility of Novel Biomarkers in Active Surveillance of Low-Risk Prostate Cancer. Biomed Res Int 2015: 475920.