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## INTRODUCTION

The incidence of prostate cancer varies by >100-fold in the world, being most common in the so-called Western world and least common in South-east Asia [1]. During recent years the incidence of prostate cancer has increased dramatically in the Western world, and, e.g. in the USA there was a sharp increase from the beginning of the 1990s, peaking in 1993, and then declining to about double the original incidence in 1997 [2]. From then on the incidence has increased again but more slowly. During this period the mortality in prostate cancer has decreased in the USA [2] and in some other Western countries [3], but the underlying reasons for this are obscure. A large difference in the incidence and mortality has raised concerns about over-treatment, and watchful waiting and active surveillance are strategies that have been suggested to decrease any possible over-treatment [4].

The true natural history of prostate cancer that is completely untreated can only be assessed in series of patients before the mid-20th century. Bumpus [5] reported on 1000 cases with almost no 5-year survival. In 1946 Nesbit and Plumb [6] reported on 795 men where 80% were dead from prostate cancer and another 10% had died from treatment at the follow-up. Fortunately, the present survival of patients with prostate cancer has improved considerably, and in low-risk groups, e.g. patients with localized disease and with low PSA levels, the relative survival at 5 years is currently almost 100% [7]. However, for patients with metastatic disease the survival is still dismal, with a median survival of slightly more than 3 years [7].

The present natural history of early prostate cancer can best be described from published series of watchful waiting and active surveillance.

## WATCHFUL WAITING

Watchful waiting, which is also sometimes termed 'deferred treatment' or 'symptom-guided treatment', is an active decision not to treat the patient, who instead is followed closely, and if and when the tumour progresses clinically with or without symptoms, treatment is started. Treatment in this situation has mostly been some kind of hormonal therapy, although in some series also radical treatment has been used. The rationale behind this strategy, which predominantly was used before the advent of PSA testing, was the experience that prostate cancer often had a protracted course and occurred mainly in elderly men with high competing mortality. At that time the incidence-to-mortality ratio was 2-3:1. The outcome studies on watchful waiting usually included what would currently be defined as intermediate-risk tumours, predominantly palpable, and those studies can be followed for up to 25 years. In these studies, 'hard' endpoints, e.g. overall survival and disease-specific survival (DSS), are being used. Watchful waiting is still considered to be an option for elderly patients with less aggressive tumours or for patients with limited life-expectancy [8]. The current use of watchful waiting varies worldwide and, e.g. in the USA only ≈5% of the patients in the CaPSURE database were managed by watchful waiting in 2002 [9], while in Sweden watchful waiting or active surveillance was used in ≈20% of all new cases in 2005 [7].

The outcomes in terms of DSS in various watchful waiting series are shown in Table 1 [10-20]. There is remarkable consistency in the DSS rate at 10 years, at 82-87%. There are

few studies with data beyond 10 years; in three studies, the DSS at 15 years was 80%, 79% and 58%, respectively [13,15,17], and in two of these the 20-year DSS was 57% and 32% [13,15]. The outcome of watchful waiting in conservative management is highly related to the tumour grade, and it has been shown that patients with low-grade tumours seldom die from prostate cancer, while high-grade tumours are more likely to kill the patient in the long term [10,13,18]. Data on the conversion rate from watchful waiting to treatment are sparse, but again the reported rates are quite consistent. The 10-year treatment-free survival in three series was reported to be 40-48% (Table 2) [15,21,22]. In the Surveillance, Epidemiology and End Results (SEER) database Berge *et al.* [23] found that 29% of 3612 patients initially managed with watchful waiting received some kind of treatment within 66 months of follow-up. Most (78%) were treated with some kind of hormonal therapy, while 6% received radiotherapy. Local and other problems during the follow-up of patients managed with watchful waiting are sparsely reported. In 122 patients Adolfsson *et al.* [24] found that 30 patients had had a TURP because of BOO, and seven a repeat TURP, with a median follow-up of 109 months. Johansson *et al.* [25] found six patients with local pain, four with complicated UTI, four with urethral obstruction and 19 having had urinary retention, in their series of 223 patients managed by watchful waiting at 10 years of follow-up. Thirty patients had had a TURP and five a bladder neck incision because of BOO [25]. Borre *et al.* [26] reported a retrospective population-based study with 15 years of follow-up of 719 patients managed conservatively. Altogether 71% had had a TURP during the follow-up. However, the study comprised all patients diagnosed irrespective of tumour stage. Only 65 (6%) had no symptoms at diagnosis, 197 (17%) had urinary retention at diagnosis, 133 (12%) had bone pain, 154 (24%) elevated alkaline

TABLE 1 DSS and overall survival rates reported in studies on watchful waiting and active surveillance

Reference	Stage/grade	No. of patients	DSS, % at n years			Overall survival, %		
			10	15	20	10	15	20
Watchful waiting								
[10]	Clinically localized Grade 1-2	757	87					
[11]	Organ-confined Grade 1-3	19 989	82					
[12]	T1-2 Grade 1-3	813	85					
[13]	T1-2 Grade 1-3	117	87	80	57		23	10
[14]	T0-2 Grade 1-2	348	15*				32*	
[15]	T1-2 Grade 1-2	119	85	58	32	53	24	9
[16]	Organ-confined Grade 1-2, age < 60 Age ≥ 60	1 740 17 191	4* 8*					
[17]	Clinically localized Gleason ≤ 7	104	87	79				
[18]	T 1-3, G1-3 Age < 70 Age ≥ 70	104 274	85 64					
Active surveillance								
[19]		299	99+			85+		
[20]		278	100+			89+		

\*Cumulative incidence of prostate cancer death; †8 years.

There has been a concern that the quality of life of the patients is affected by the knowledge of living with an untreated tumour. However, in the studies published on this topic, the views differ. Schapira *et al.* [28] found no change in the quality of life in patients on watchful waiting, while those treated with radical prostatectomy or radiotherapy had significant symptoms affecting their quality of life. Bacon *et al.* [29] found that patients who had radical surgery had a better generic quality of life than those managed by radiotherapy, watchful waiting or hormonal therapy. Siston *et al.* [30] found that patients on watchful waiting had urinary problems, and those treated with radical prostatectomy or radiotherapy instead had sexual and urinary problems. Steginga *et al.* [31] found no change in overall quality of life for watchful waiting, while those treated actively had problems with sexual, bowel and urinary function. In that study there was basically no change in overall quality of life for either treatment, but a consistent finding was that those who had problems deciding on treatment had a worse quality of life. Hoffman *et al.* [32] found a higher risk of having urinary and sexual problems after aggressive treatment for localized prostate cancer than with conservative management. In the only randomized trial in this field, comparing watchful waiting with radical prostatectomy, there were differences in symptoms such as erectile dysfunction, urinary leakage and weak urinary stream, but there was no difference in overall quality of life [33]. However, anxiety seems to be a predictor for patients on watchful waiting to start treatment [34]. There is no consistent pattern of the affect on quality of life of watchful waiting, and further preferably longitudinal studies in this field are needed.

## ACTIVE SURVEILLANCE

Active surveillance is a new strategy used during the last decade; it includes an active decision not to treat the patient immediately, followed by close surveillance and treating the patient at predefined thresholds that define progression. Treatment in this case is intended to cure the patient. The rationale behind this strategy is again the often protracted course of the disease at present, also often adding an unknown but possibly substantial lead-time due to the use of PSA testing with diagnostic intention. Currently the incidence-to-mortality ratio is greater, at up to 9:1 [2], which raises concerns that

Ref.	No. of patients	Treatment-free survival, %		TABLE 2 Treatment-free survival rate in series on watchful waiting and active surveillance
		5 years	10 years	
Watchful waiting				
[15]	119	72	43	
[22]	1158	58	48	
[21]	88	60	40	
Active surveillance				
[36]	80	79		
[20]	278	71		
[43]	407	70*		*Estimated from fig. 1 in [43].
[38]	99	85		

phosphatase levels, and acid phosphatase levels were elevated in 234 (35%) of the patients. This population was thus quite different, with more advanced tumours than in previous series. Recently Berge *et al.* [27] reported a 10% TURP/bladder-neck incision rate in 3612 patients within 66 months of follow-up in the SEER

register and managed with watchful waiting. In that study the TURP rate after radical surgery and radiotherapy was 3.7% and 6.8%, respectively. Thus, the rate of BOO seems to be somewhat higher after watchful waiting than after radical surgery and radiotherapy, but formal comparisons are lacking.

patients with early prostate cancer are being over-treated [4]. Patients included in the active surveillance series usually have tumours perceived as being at low risk both for progression and causing the death of the patients. Inclusion criteria vary, but usually the patients have T1–T2 tumours, Gleason scores of  $\leq 7$ , and a PSA level of  $<15$ – $20$  ng/mL [20,21,35–38].

The criteria for offering treatment vary to some extent [19,35,39]. Usually the PSA doubling time or some kind of dynamic PSA measure is included. In terms of PSA doubling time, different threshold have been used, from  $\leq 2$  years to  $\leq 4$  years. Sometimes the threshold criteria have also included a histological evaluation of repeat biopsies in the strategy, and progression in Gleason score to  $\geq 7$  has been suggested [19,38,39]. Other measures, such as PSA velocity, 'rolling PSA doubling time', percentage free PSA, etc. have been suggested but not used [19]. The PSA doubling time has been shown to be prognostic for progression [40,41] and for death from prostate cancer [42]. However, in terms of sensitivity and specificity, no specific threshold in the PSA doubling time was apparent in one study using receiver operating characteristic curves for the PSA doubling time [42]. Thus, PSA doubling time seems to be less efficient in predicting death from prostate cancer for individual patients, and possible thresholds for active surveillance must be studied further.

There are few outcome studies of active surveillance; those that have been published include low-risk tumours only and the follow-up is usually  $\leq 10$  years. There are few 'hard' endpoints evaluated and typically progression-free survival or treatment-free survival has been used. However, two studies [19,20] reported an 85% and 89% overall survival rates, and a 99% and 100% DSS, respectively, at 8 years of follow-up (Table 1). In the studies of Soloway *et al.* [38] and Carter *et al.* [43] no patients had died from prostate cancer within a mean follow-up of 45 months and 2.8 years, respectively. The conversion rate to active treatment was 34% in the study of Klotz [19], with a median follow-up of 64 months, and 14% in Hardie *et al.* [36] after a median of 42 months. Treatment-free survival rates at 5 years were reported to be 70–85% [20,36,38,43] (Table 2).

Data on the quality of life of patients on active surveillance are sparse. Burnet *et al.*

[44] reported an equal quality of life in patients receiving active surveillance, radical prostatectomy or radiotherapy, using the Hospital Anxiety and Depression Scale. There might also be different psychosocial barriers that need to be addressed before active surveillance can be fully accepted as a management strategy by the patients [45].

### COMMENT

In the watchful waiting series, the outcome in terms of the DSS rate was remarkably constant at  $\approx 85\%$ . Watchful waiting seems to be an option for patients with low-grade clinically localized prostate cancer and with a life-expectancy of 10–15 years. Very few patients had died from prostate cancer in the active surveillance studies, but the follow-up in these studies is in general shorter than in series of watchful waiting. Treatment-free survival rates at 5 years were lower in the watchful waiting series, but not substantially lower. Currently there are no major differences in comparable outcomes such as rate of conversion to treatment and treatment-free survival of watchful waiting and active surveillance. However, treatment in series of watchful waiting was mostly but not only hormonal treatment. In the series of active surveillance, treatment was mostly radical surgery or radiation therapy.

In general series of watchful waiting are from the era before PSA testing, whereas those of active monitoring are after this era. The use of PSA in the diagnostic evaluation of men with LUTS or as a frank screening test in asymptomatic men has moved the point of diagnosis of prostate cancer to an earlier stage of the disease [7]. A lead time is thus introduced, compared with patients who were diagnosed before PSA was available. The lead time induced by PSA can be as long as 10 years [46,47]. In terms of survival analyses, a lead time inevitable results in an improvement in survival. Such a lead time is likely to result in better survival of current patients than previously.

Active surveillance might be an option for patients with low-grade clinically localized prostate cancer, and the PSA doubling time might be a trigger for treatment. Hopefully this strategy can reduce the over-treatment of men with localized prostate cancer. However, a better understanding of triggers for treatment in the active surveillance strategy is needed. Studies with hard outcome

data, e.g. overall and DSS, are few and it remains to be shown that active surveillance reduces over-treatment in patients with early prostate cancer.

### CONFLICT OF INTEREST

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**Abbreviations:** DSS, disease-specific survival; SEER, Surveillance, Epidemiology and End Results.