Active surveillance can reduce overtreatment in patients with low-risk prostate cancer

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ABSTRACT

INTRODUCTION: The incidence of prostate cancer in Denmark rose approximately 50% from 2000 to 2009 in parallel with the introduction of prostate-specific antigen (PSA)-testing. Available evidence indicates a significant overtreatment of patients with low-risk prostate cancer. Active surveillance has been proposed as an observation strategy to reduce overtreatment and limit curatively intended therapy to those patients who need it. We report the first Danish results from an active surveillance cohort.

MATERIAL AND METHODS: A total of 167 patients were prospectively followed in an active surveillance programme.

RESULTS: The median follow-up was 3.4 years (1.1-9.5). At entry the median age was 65 years (51-73), 94% had a Gleason score ≤ 6, 87.4%, a PSA ≤ 10 ng/ml and 99% ≤ cT2a. Ten patients progressed on digital rectal examination, 40 patients progressed due to a short PSA doubling time, and 34 patients progressed on re-biopsy. A total of 59 patients discontinued active surveillance. The estimated five-year probability of remaining on active surveillance was 60.0% (95% confidence interval 50.9-69.1%).

CONCLUSION: Active surveillance as a management strategy for patients with clinically localized, low-risk prostate cancer is accepted by patients, seems feasible and can reduce overtreatment. However, long-term follow-up data are lacking and considerable uncertainties about optimal selection and progression criteria remain.

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Prostate cancer is the most common cancer among men in Denmark excluding non-melanoma skin cancer [1]. From 2000 to 2009, the age-standardised incidence of prostate cancer increased by approximately 50%, which is most likely due to the introduction of prostate-specific antigen (PSA)-testing [2].

Treatment of patients with low-risk prostate cancer remains controversial. Patients diagnosed in the pre PSA-era and managed conservatively have a cancer specific survival of 79% after 20 years [3]. However, in a randomized study by the Scandinavian Prostatic Cancer Group (SPCG-4) which included patients with well or moderately well-differentiated localized prostate cancer from 1989 to 1999, and where 88% of the patients were diagnosed with palpable tumours, radical prostatectomy reduced the risk of prostate cancer-specific mortality by 38% (absolute reduction 6.1%) compared with conservative treatment [4]. Additionally, the European Randomized Study on Prostate Cancer screening demonstrated an absolute reduction of prostate cancer-specific mortality ranging from 2% to 8% (95% confidence interval (CI)) using PSA-based screening [5]. However, overdiagnosis has been estimated to be as high as 66% in PSA-screened patients compared with controls [6] and another recently published study found no benefit from radical prostatectomy after a median of ten years of follow-up in PSA-detected patients [7]. Thus, although radical prostatectomy in both non-screened and screened populations has been proven to reduce prostate cancer-specific mortality, the absolute benefit of this approach is limited and over-diagnosis and subsequent overtreatment remain a major concern.

Active surveillance of patients with clinically localized, low-risk prostate cancer has been proposed as an observation strategy to reduce overtreatment. The aim of active surveillance is to achieve the same cancer-specific survival as if all patients underwent immediate curative therapy, and a crucial element in active surveillance is the ability to identify patients with more aggressive tumours while they are still within curative reach [8, 9]. In this article, we report the first Danish experience with active surveillance in patients with low-risk prostate cancer.

MATERIAL AND METHODS

Active surveillance has been offered at our institution since 2002. Patient data have been prospectively registered in a database approved by the Danish Data Protection Agency (file#2006-41-6256). Patients have been followed from entry in the programme until death or 1st of June 2012, whichever came first.

Inclusion criteria, follow-up programme and progression risk criteria are outlined in **Table 1**. Active surveillance was primarily offered to patients aged 65 years or above, but younger patients were also allowed according to patient preference.

All biopsies were re-evaluated by an in-house uropathologist. Pre-diagnostic PSA was used as entry PSA in patients diagnosed by trans-rectal biopsies. Patients

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TABLE 1

Patient selection, follow-up, and classification of risk of progression.

Inclusion criteria[a]
PSA ≤ 10 ng/ml
Gleason score ≤ 6
cT1-2a
Number of positive cores ≤ 3
Maximum tumour in any one core < 50%
Active surveillance program
PSA and DRE every 3 months
10-12 core re-biopsy performed within 15 months
Active surveillance progression risk criteria[b]
Low
Criteria:
PSA doubling time > 5 years
No progression on re-biopsy or digital rectal examination
Program recommendations:
Continued on active surveillance
Intermediate
Criteria:
PSA doubling time 3-5 years
Increase in Gleason score to 3 + 4
Digital rectal examination = cT2b
Program recommendations:
Curatively intended treatment or continued active surveillance are discussed with patient
High
Criteria:
PSA doubling time < 3 years
Increase in Gleason score to ≥ 4 + 3 or > 3 positive cores or multifocal/bilateral tumour
Digital rectal examination ≥ cT2c
Program recommendations:
Curatively intended treatment

cT = clinical tumour category; DRE = digital rectal examination; PSA = prostate-specific antigen.
a) Patients who did not fulfill all inclusion criteria were only included in the active surveillance if there was a strong patient request
b) Modified progression risk criteria according to [10].

TABLE 2

Clinical characteristics at entry (n = 167).

		n	%
Age, median (range), years	65 (51-73)		
Diagnostic PSA-value, median (range), ng/ml	6.50 (0.60-20.00)		
Primary biopsy cores, median (range), n (N = 143[a])	10 (6-46)		
cT category			
≤ 1b		24	14.4
1c		125	74.9
≥ 2a		18	10.8
Histopathology in primary biopsy			
Gleason score < 6[b]		52	31.1
Gleason score 6		105	62.9
Gleason score 7		10	6.0
Positive biopsy cores, n (N = 143[a])			
1		92	64.3
2		35	24.5
3		9	6.3
> 3		7	4.9

cT = clinical tumour category; PSA = prostate-specific antigen.
a) 24 patients diagnosed after transurethral prostatectomy; b) Including biopsies with insufficient tumour content to obtain Gleason score.

diagnosed after transurethral prostatectomy were included following re-biopsy, and the post-transurethral prostatectomy PSA-value was used as entry PSA.

Patients were followed with digital rectal examination and PSA-tests every three months; and re-biopsies were offered after one year on active surveillance. The risk of progression was hereafter classified according to a modification of criteria originally proposed by Choo et al [10] and patients were managed as outlined in Table 1.

The PSA doubling time was calculated according to the Memorial Sloan-Kettering Cancer Center guidelines including all available PSA-values.

Kaplan-Meier survival analysis was used to estimate the probability of remaining on active surveillance. Data are presented as median and range unless otherwise indicated. Statistical analysis was performed with SPSS version 19.

Trial registration: not relevant.

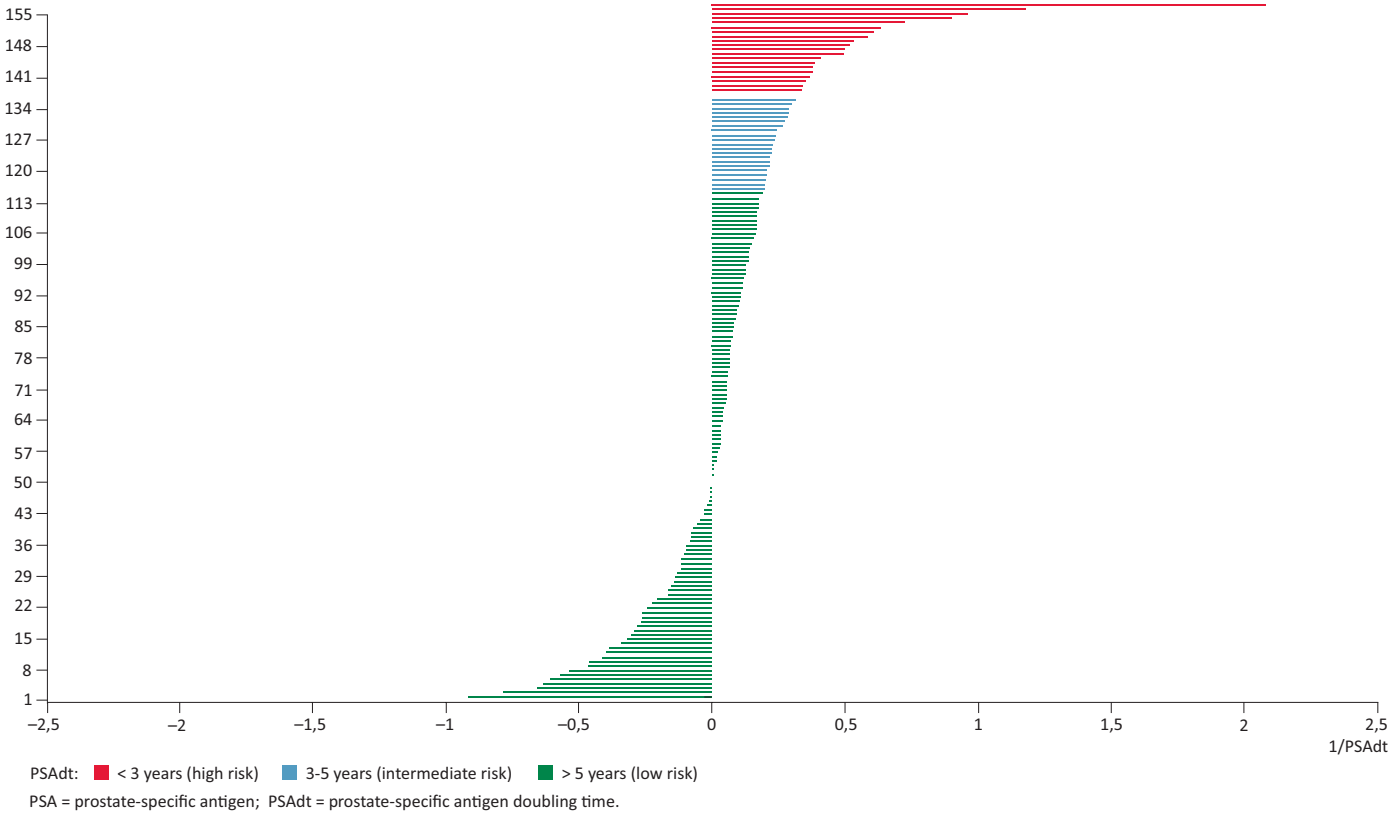
RESULTS

From 2002 to May 2011, a total of 167 patients were included. Their median age at entry was 65 years (51-73). The median follow-up period was 3.4 years (1.1-9.5). Histopathology, PSA and clinical tumour category (cT) category prior to entry are summarized in **Table 2**. Overall, 94% had a Gleason score ≤ 6, and 87.4% had a PSA ≤ 10 ng/ml. Two patients had clinical cT2b and cT2c disease, respectively.

In 11 patients, PSA doubling time calculation was invalid because the patients underwent a transurethral prostatectomy or commenced 5-alpha-reductase inhibitor therapy during follow-up. Of the remaining 156 patients, 73.7% had a PSA doubling time > 5 years, 13.4% had a PSA doubling time of 3-5 years and 12.6% a PSA doubling time < 3 years, **Figure 1**. Of the 167 patients entering the study, 143 (85.6%) had re-biopsies performed. The median time to first re-biopsy was 12.7 months (interquartile range 11.4 and 14.9). Histopathological progression was found in a total of 34 patients on re-biopsy (increase in Gleason score to at least ≥ 7 and/or > 3 positive cores); in 28 of the patients within two years. Ten patients had progression on digital rectal examination, all within three years.

FIGURE 1

1/PSAdt depicted for each of the 156 patients with valid PSAdt calculations.



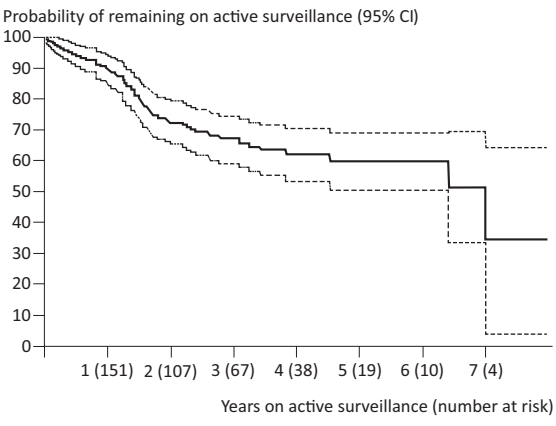
PSA = prostate-specific antigen; PSAdt = prostate-specific antigen doubling time.

During follow-up, a total of 29 patients were classified as having a high risk of progression and another 37 patients had an intermediate risk according to our risk of progression criteria, Table 1. The majority of patients (n = 101; 60%) remained in the low-risk group, **Table 3**.

A total of 59 patients (35.3%) discontinued active surveillance. Of the 47 patients who left the programme after fulfilling our criteria for intermediate or high risk of progression (Table 1), 37 (79%) were within two years from entry. The reasons for their discontinuation of surveillance are listed in Table 3. Ten patients progressed on more than one criterion. Twelve patients (7.2%) left active surveillance according to their own preference without progression. The estimated five-year probability of remaining on active surveillance was 60.0% (95% confidence interval 50.9-69.1), **Figure 2**.

FIGURE 2

B: The Kaplan-Meier estimated probability of remaining on active surveillance (n = 156).



CI = confidence interval.

DISCUSSION

The past decade has seen a dramatic increase in the incidence of prostate cancer in Denmark. The majority of diagnosed tumours are clinically localized [2]. Parallel to this, the number of radical prostatectomies has increased almost tenfold and the expensive robot-assisted laparoscopic technique has been introduced [11, 12].

TABLE 3

Active surveillance follow-up (n = 167).

		n	%
Follow-up, median (range), years	3.4 (1.1-9.5)		
PSA-values, median (range), n	9 (3-29)		
PSAdt, years (N = 156)			
< 3		20	12.8
3-5		21	13.4
> 5		66	42.3
< 0[a]		49	31.4
Re-biopsy, n			
0		24	14.4
1		91	54.5
2-3		52	31.1
Progression		34	20.4
Risk of progression according to criteria			
High		29	17.4
Intermediate		37	22.2
Low		101	60.5
Reason for discontinuing active surveillance[b]			
PSAdt		22	13.2
Re-biopsy progression		30	18.0
Digital rectal examination progression		10	6.0
Own preference		12	7.2
Total		59	35.3

PSA = prostate-specific antigen; PSAdt = prostate-specific antigen doubling time.
a) PSA declined during follow-up.
b) 10 patients progressed on more than one criterion.

Newly published results from the randomized Radical Prostatectomy versus Observation for Localized Prostate Cancer Study strengthen the arguments in support of a conservative strategy in patients with clinically localized, low-risk prostate cancer. The study found no statistically significant survival benefit in favour of radical prostatectomy in a population of patients with PSA-detected tumours [7]. Combined with the results from the SPCG-4 study [4], the available randomised evidence points to an effect of radical prostatectomy on cancer-specific survival in some patients with intermediate and high-risk disease [13], while a significant survival benefit of radical prostatectomy in contemporary patients with PSA-detected, low-risk tumours seems more and more unlikely. In these patients, active surveillance may constitute a more appealing strategy.

During the first nine years we have practised active surveillance, a total of 167 patients have entered the programme. This represents only a small proportion of patients with clinically localized prostate cancer treated at our institution. In the same period, over 1,300 patients underwent radical prostatectomy [11]. Unfortunately, we do not have data on how many eligible patients declined when offered active surveillance and opted for curatively intended therapy instead. However, compliance among patients who did enter active surveillance was high. Only 7.2% chose to discontinue active surveillance without fulfilling the risk of progression criteria. Our programme did not include a validated questionnaire assessing their quality of life, including psychological domains like anxiety and uncertainty about cancer control. However, a Finnish study reported only minor psychological problems in active surveillance patients [14], and the relatively high compliance rate in our series may well reflect a high degree of patient satisfaction with the strategy.

Klotz et al reported the most mature follow-up data available on active surveillance [15]. A total of 450 patients entered their programme and after a median follow-up of 6.8 years, 135 (30%) patients had discontinued active surveillance: 14% due to a short PSA doubling time, 8% with histopathological progression, 1.2% with progression on digital rectal examination, 3.1% due to patient preference and 3.1% due to other causes. In the present study, a comparable number of patients discontinued active surveillance due to a short PSA doubling time (13.2%). However, more patients in our series left the programme due to histopathological progression and progression on digital rectal examination (18% and 6%, respectively). The difference in the percentage of histopathological progression can be explained by the 18 patients progressing from a Gleason score 6 to a Gleason score 7 (3 + 4), and the six patients who progressed due to an increased number of positive cores; progression criteria different from those used by Klotz et al (definition of histopathological progression: Gleason score ≥ 7 (4 + 3)). Only six patients (3.6%) in our cohort had a Gleason score ≥ 7 (4 + 3) on re-biopsy. Of the 6% in our cohort who had progressed based on digital rectal examination findings, two patients (1.2%) had progressed only on digital rectal examination, which is identical to the percentage reported by Klotz et al.

Differences in progression criteria may also explain why the five-year probability of remaining on active surveillance in the series reported by Klotz et al was 72% compared with 60% in our series. Although long-term follow-up is necessary, the finding that the majority of patients are still on active surveillance after five years combined with the observation that 79% of the patients who progressed in our series did so within the first two years on active surveillance indicates that a substantial percentage of low-risk patients are well managed by active surveillance, thereby avoiding more aggressive therapy. The majority of the patients remaining on active surveillance after five years have a PSA doubling time of more than five years, which, combined with a median PSA at entry into the active surveillance programme of 6.5 ng/ml, means that PSA levels where M1 disease is likely (PSA ≥ 50 ng/ml) will not be reached until after 15-20 years.

In total, 19% of the patients did not fulfil all the inclusion criteria used in our active surveillance programme (Table 1) and one third of the patients were younger than 65 years of age at entry. During the study period, data from other active surveillance series [10, 16] suggested that active surveillance is a safe procedure, and patients younger than 65 years of age and patients otherwise deviating from the "inclusion criteria" outlined were therefore accepted within the programme if they had a strong request for active surveillance as opposed to immediate curative therapy.

A median follow-up of 3.4 years in our series does not allow for any meaningful analysis of the long-term efficacy of active surveillance; nor does it allow for comparison of clinical outcome with similar patients receiving curatively intended therapy immediately. An important part of active surveillance as a concept is that patients who progress while being observed are offered curatively intended therapy, either radical prostatectomy or radiotherapy. A major concern is whether active surveillance patients eventually undergoing curatively intended therapy due to progression fare worse than similar patients who are treated immediately following diagnosis of localised prostate cancer. While this naturally must depend upon the tumour progression rate and the length of "delay", it is disturbing that Klotz et al reported a five-year biochemical recurrence-free survival of only 47% in patients undergoing radical prostatectomy after initial active surveillance. Our data are still too immature to confirm this finding, but the significant risk of biochemical recurrence reported by Klotz et al seriously questions the currently employed selection criteria and their ability to select the optimal candidates for active surveillance, as well as the ability of the used progression criteria to identify progressive disease at a point in time when cure is still possible.

Active surveillance is a relatively newly introduced strategy for management of patients with low-risk prostate cancer, and a number of criteria for entering patients as well as a number of different ways of assessing progression and follow-up schedules have been published [17]. Selection as well as progression criteria have been based pragmatically on traditional parameters like PSA, PSA doubling time, Gleason score and cT category. However, these criteria are poorly investigated and are most likely suboptimal. The reliability of PSA doubling time as a predictor for progression has recently been questioned [18]. In future, development of new markers may refine both selection and monitoring of active surveillance patients [19]. The final evaluation of the role of active surveillance in the management of patients with presumed low-risk prostate cancer compared with immediate curative therapy may be answered by international databases prospectively gathering information on patients in active surveillance programmes [16]. Ultimately, results from a large ongoing randomized trial are awaited [20].

Both curative and surveillance strategies exist for management of localized, low-risk prostate cancer and patients often find themselves in a difficult dilemma despite well-intended efforts to provide relevant information.

CONCLUSION

Even though active surveillance as a management strategy for patients with clinically localized, low-risk prostate cancer seems feasible and reduces overtreatment, long-term efficacy is still lacking, and considerable uncertainty about selection and progression criteria needs to be addressed. Hopefully, the combination of new markers to identify prostate cancer with a true, low biological potential and the results of ongoing randomized studies will improve our ability to select and monitor candidates for active surveillance.

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