Active surveillance strategy for patients with localised prostate cancer

Criteria for progression

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This review has been accepted as a thesis together with three previously published papers and one unpublished paper by University of Copenhagen 23 October 2014 and defended on 28 November 2014

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Dan Med J 2015;62(2);B5005

ACKNOWLEDGEMENTS

The thesis was supported by grants from the IMK Almene Fond. The study funders had no role in the design, conduct or interpretation of the studies. The content of the thesis is solely the responsibility of the author.

PUBLICATIONS

I Thomsen FB, Berg KD, Røder MA, Iversen P, Brasso K. Active surveillance for localised prostate cancer – an analysis of patient contacts and utilisation of health care resources. Scan J Urol 2014 [Epub ahead of print]

II Thomsen FB, Christensen IJ, Brasso K, Roder MA, Iversen P. PSA doubling time as a progression criterion in an active surveillance programme for patients with localized prostate cancer. BJU Int 2014;113(5b):E98-E105

III Thomsen FB, Marcussen N, Berg KD, Christensen IJ, Vainer B, Iversen P, Brasso K. Repeated biopsies in prostate cancer patients on active surveillance: clinical implications of interobserver variation in histopathological assessment. BJU Int 2014 [Epub ahead of print]

IV Thomsen FB, Berg KD, Iversen P, Brasso K. Poor association between the progression criteria in active surveillance and subsequent histopathological findings following radical prostatectomy. Submitted 2014

ABBREVIATIONS

AS	active surveillance
CI	confidence intervals
cT	clinical tumour category
DRE	digital rectal examination
€	Euro
GS	Gleason score
ISUP	International Society of Urological Pathology
MRI	magnetic resonance imaging
OR	odds ratio
PCa	adenocarcinoma of the prostate
PSA	prostate-specific antigen
PSAdt	prostate-specific antigen doubling time
RP	radical prostatectomy
WW	watchful waiting

INTRODUCTION

The concept active surveillance (AS) offers a tailored, initially non-curative management for patients with localised adenocarcinoma of the prostate (PCa). The strategy aims at differentiating between cancers with a true indolent course and cancers with the biological potential to progressing to clinically significant disease. If the strategy succeeds, lethal PCa is treated within the "window of curability", while patients with slow growing tumours are spared from an unnecessary curative intervention, with its inherent treatment load, risk of complications, and long-term side-effects associated with a reduced quality of life without compromising PCa-specific survival.

BACKGROUND

THE PROSTATE

The prostate is a male accessory reproductive exocrine gland surrounding the urethra just below the bladder [1]. The prostate requires androgen stimulation for its normal development, growth, and function in reproduction [2]. The prostate gland excretes a complex proteolytic secretion into the ejaculate to liquefy the semen and modify the vaginal environment in order to improve sperm mobility and survival, thereby enhancing the chance of fertilisation [3,4].

ADENOCARCINOMA OF THE PROSTATE

The exact aetiology of PCa has not been established. Besides age, sex, race, and hereditary PCa, no aetiological factors have been identified [5]. As well as the normal development of the prostate relying on androgen stimulation, the development of

PCa requires androgen stimulation [6]. However, the association between androgen serum levels and PCa remains unclear [7].

PCa is remarkable in that it can be found in almost all males late in life. Autopsy studies have demonstrated a prevalence of unrecognised PCa in 30% of men in their forties, increasing to approximately 60% in males aged 80 years or older [8,9]. However, there is a huge discrepancy between PCa as a histopathological entity and the fact that only approximately 5% of Danish men will be diagnosed with clinically significant PCa with symptoms from local tumour mass, metastasis, and/or loss of life years (figure 1) [10].

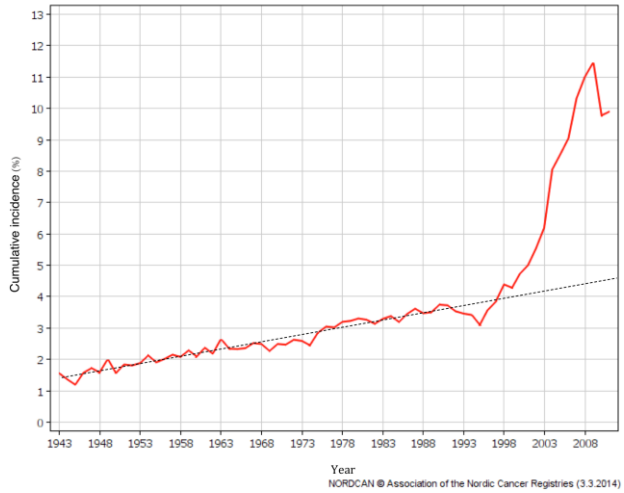

Figure 1
Observed cumulative incidence of prostate cancer diagnosis (red line) and the estimated proportion of patients experiencing clinically significant prostate cancer (dotted line).

The natural history of prostate cancer

The natural history of expectantly managed PCa has been studied in a number of publications. Albertsen et al. reported an estimated 20-year PCa-specific and overall survival of 767 PCa patients with clinical tumour category (cT) 1-3a [11]. The study included a retrospective tissue evaluation by Donald F. Gleason (see below) of the patients' diagnostic specimen. The study demonstrated that the prognosis of PCa is heterogeneous with reported 20-year PCa-specific mortality in the range of 66% in the worst prognostic group to 7% in the best prognostic group. The Örebro study, following 223 patients with clinically localised PCa and a histopathological assessment according to the WHO definition, found an indolent course during the first 15 years in all patients, followed by a steep increase of PCa mortality in patients surviving for 15-20 years [12], which thereafter stabilised [13]. The cumulative PCa-specific survival decreased from 78.7% at 15 years to 54.4% at 20 years. This observation was not confirmed by Albertsen et al. [11]. Of the 148 patients with a WHO grade 1 (i.e. least aggressive tumour characteristics), the PCa-specific mortality in the Örebro study with a 32 year follow-up was 11.5%, while 87.2% died from competing courses [13]. The patients included in both of these studies were diagnosed with clinical symptomatic and non-prostate-specific antigen (PSA)-detected PCa. Recently, Rider et al. have published comparable findings in a registry-based study including more than 75,000 patients managed on watchful waiting (WW) [14]. In the sub-group of patients with the most favourable tumour characteristics, the PCa-specific mortality was 9% after 15 years compared to 50% from non-PCa related causes. The overall survival rate for patients with a Charlson comorbidity index of 0 was identical to a comparable PCa-free cohort.

PROSTATE-SPECIFIC ANTIGEN

Epithelial cells in the prostatic glands produce the protease, PSA [15]. PSA is part of the proteolytic secretion and contributes to the liquefaction of the ejaculate by cleaving semenogelin I and II in the seminal coagulum [15]. In normal men, PSA is found in low concentrations in blood. Any disruption of the basal membrane or of the normal prostatic architecture results in a leakage of PSA into the blood [16,17]. This has led to the use of PSA as a marker for PCa in urological oncology [18]. Unfortunately, other common conditions in the elderly male population, such as benign prostatic hypertrophy, prostatitis, or urinary retention, can affect the PSA level in the blood [17,18]. This implies that PSA is an organ-specific and not a PCa-specific marker.

Despite its shortcomings, PSA has been introduced as a screening instrument for PCa [19]. In 2012, the European Randomized Study of Screening for Prostate Cancer demonstrated that PSA-based screening is able to reduce the rate of death from PCa by 21% with an 13 year follow-up [20]. The absolute risk reduction was only 0.1%. In total, 781 men needed to undergo PSA testing and 27 men needed treatment for PCa in order to prevent one PCa death. Besides this overdiagnosis and treatment, PSA-based screening also resulted in approximately 7 years of lead time – i.e. the period from detection of PCa to clinical diagnosis of PCa [21]. This implies that patients diagnosed by PSA testing often have a clinical asymptomatic presentation at diagnosis and many will remain asymptomatic the rest of their lifetime. Furthermore PSA testing has caused a downward shift in the GS and tumour volume at diagnosis [19]. The survival benefit of PSA-based screening was almost exclusively driven by high-grade cancers [20]. Whether longer follow-up will be able to detect any survival differences also in patients with more favourable tumour characteristics awaits future updates.

Although early diagnosis through systematic PSA testing has never been recommended in Denmark, grey-scale testing has led to an increase in the cumulated incidence of PCa. The PCa incidence for men aged 74 years rose from 3.1% in 1995, the year radical prostatectomy (RP) was introduced in Denmark, to 9.9% in 2011 (figure 1) [10,22]. Currently, more than 4,000 men are diagnosed with PCa annually, making it the second most common cancer among males, surpassed only by non-melanoma skin cancer [10].

DIAGNOSIS AND RISK ASSESSMENT

The diagnosis of PCa is established by a histopathology – most often after a selected-site transrectal ultrasound-guided prostate biopsy or following a transurethral prostatectomy [23,24]. The sampled PCa tissue is most often graded after the Gleason score (GS) system. The GS was introduced in 1966 by Donald F. Gleason, and was refined in 1974 [25,26]. It is the most widely used histopathological grading system in PCa and has been validated as a prognostic marker both in patients after curatively intended treatment and in patients managed expectantly (i.e. WW) [11,27–29]. The Gleason scoring system grades the glandular architecture from 1 through 5. Gleason pattern 1 is the least aggressive, where the PCa closely resembles normal prostatic tissue, and 5 is the most aggressive with single cell infiltration, comedonecrosis, and no glandular formation. Originally, the GS was obtained by adding the most commonly observed pattern and the second most commonly observed pattern together [26]. The International

Society of Urological Pathology (ISUP) updated the grading system in 2005 so that regular cribriform glands, previously considered pattern 3, are now graded as pattern 4 [30]. It was decided that the worst pattern in a biopsy specimen should always be reported and that any lower-grade pattern of less than 5% of the total tumour volume should be ignored. This resulted in an increment of patients diagnosed as GS 7(3+4) [31]. In recent years, molecular and genetic differences have been established between Gleason patterns 3 and 4 [32]. Gleason pattern 3 lacks some of the hallmarks of cancer, i.e. unlimited replicative potential, self-sufficiency in growth signals, sustained angiogenesis, local tissue invasion, and ability to metastasise – all genetic characteristics possessed by Gleason pattern 4. In principle, the Gleason scoring system is therefore able to differentiate between genetically significant PCa and that which others refer to as "pseudo-cancer" [32].

The clinical presentation of PCa is divided into a localised (cT1-2) and a locally advanced (cT3-4) stage based on a digital examination through the rectal wall (DRE) [33]. The localised stage includes patients with a non-palpable tumour (cT1) and a palpable tumour confined within the prostatic capsule (cT2). The cT2 category is further subdivided into cT2a if the tumour involves half of one lobe or less, cT2b if it involves more than half of only one lobe, and cT2c if it involves both lobes.

The initial risk assessment of PCa is based on a combination of PSA, histopathological findings, and clinical characteristics. Different risk assessment tools have been developed to predict the prognosis of localised PCa [34,35]. The D'Amico risk classification system for localised prostate cancer is the most commonly used system and has been externally validated (table 1) [22,34,36].

Table 1 D'Amico risk classification for localised prostate cancer

Risk group	PSA (ng/mL)	Gleason score	Tumour category
Low [a]	≤20	≤6	≤2a
Intermediate [b]	10.1 - 20	7	2b
High [b]	>20	≥8	2c

[a] **Fulfil all three criteria;** [b] **Any one of the criteria**

CURATIVE TREATMENT OPTIONS FOR LOCALISED PROSTATE CANCER

Treatment for localised PCa with curative intent – whether RP alone or external beam radiotherapy – is burdened with treatment load and substantial side-effects, primarily compromised of sexual function and urinary incontinence following RP and bowel dysfunction and urinary urgency after radiotherapy [37–39]. No randomised study has investigated the effect of radiotherapy with an observational strategy. Two randomised trials (PIVOT and SPCG-4) have studied the survival effects of RP compared to an observational strategy (WW) in patients with localised PCa [40,41]. The SPCG-4 study observed an overall survival benefit in favour of RP [41] but neither the SPCG-4 nor the PIVOT study could detect a survival difference in patients with low-risk tumour characteristics (SPCG-4 defined as: GS≤6 or WHO grade 1 and PSA <10 ng/mL, and PIVOT defined as: D'Amico low-risk). The cumulative PCa-specific mortality after 12 (PIVOT) and 18 years (SPCG-4) of observation for low-risk patients randomised to the observational arms of the two studies was 4.1% and 14.0%, respectively [40,41]. These percentages for PCa specific mortality concur with what has been reported from studies of the natural history of PCa (figure 2) [11,12]. The observed difference in PCa mortality between the SPCG-4 and PIVOT studies is to a large extent explained by the difference in follow-up but also differences in the study populations may contribute. Eighty-eight percent of patients included in the SPCG-4 study were cT≥2, while 50% of the patients in the PIVOT study were cT1 PCa. Compared to the SPCG-4 study, the PIVOT study more closely resembles the clinical presentation of a typical PSA detected PCa patient included in a contemporary AS programme.

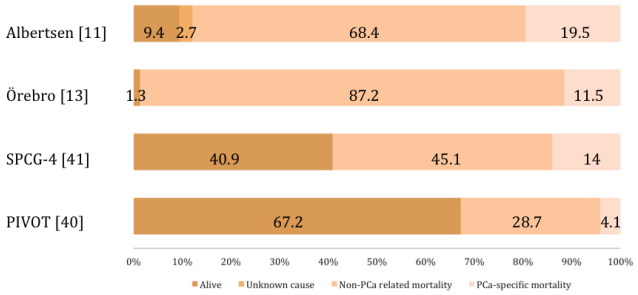

Figure 2
Cumulative incidence of non-prostate cancer (PCa) related mortality and PCa-specific mortality in Albertsen et al. (Gleason score ≤6) [11], Örebro (Low WHO grade) [13], SPCG-4 (PSA<10 ng/mL, Gleason score ≤6 or low WHO grade) [41], PIVOT (PSA≤10 ng/mL, Gleason score ≤6 and cT≤2a) [40] studies with 24, 23, 18 and 12 years follow-up, respectively.

Data from large RP series have found that specimen GS≤6 has very limited if any metastatic potential [28,29], and thereby strongly supports the perception that Gleason pattern 3 lacks the hallmarks of cancer. In one retrospective study including over 14,000 patients presenting with pathological GS≤6 in the RP specimen, not a single patient was diagnosed with lymph node metastasis [29]. In another study including nearly 4,000 patients with specimen GS≤6 and organ confined disease, the PCa-specific mortality at 20 years was 0.2% [28,32]. The 1 patient who died of PCa had GS 7(4+3) at pathological review. In other words, the current literature suggests that men with RP specimen GS≤6 will experience the treatment load and side-effect-induced reduction in quality of life after curative intervention, without obtaining any survival benefit. However, as a consequence of sampling error of transrectal ultrasound-guided biopsies and differences in the histopathological assessment, the diagnostic GS may underestimate the specimen GS [30,42–45]. Surgical series have found that approximately 34.1% of D'Amico low-risk PCa patients will harbour GS≥7(3+4) in the RP specimen [46–61], i.e. men who could potentially obtain a survival gain from curatively intended treatment [11–14].

THE RATIONALE FOR ACTIVE SURVEILLANCE

By combining the information from the PCa natural history studies, the results from the two randomised studies on RP versus WW, the results from the PSA-based screening study, and finally the large surgical series, it becomes obvious that the risk of overtreatment in patients with good prognosis is not purely an academic discussion. It is a fact that cannot be neglected. Still, a subgroup of patients with low-risk features may benefit from curative intent treatment [11–14,46–61].

Traditional WW implies an active decision not to recommend curative intent treatment. Clinical progression of disease will be managed by endocrine therapy and palliation. The concept AS was first formally described in 2002 by Choo et al. [62]. The strategy is an initially non-curative observational strategy in which curative intervention is delayed and only offered to patients thought to benefit from more aggressive treatment either be-

cause they were understaged at diagnosis or because their malignancy developed more rapidly than is acceptable for an observational strategy. In order for the AS strategy to be an effective treatment option, it requires a rigorous follow-up program with reliable, robust and safe criteria, to accurately distinguish between 1) men who will benefit from curative intent treatment in terms of prolongation of life, and 2) men who will not experience a survival gain from such an intervention.

ACTIVE SURVEILLANCE: SELECTION AND PROGRESSION CRITERIA

The majority of the published AS series consider patients defined as low-risk according to the D'Amico risk classification to be candidates for AS. Some AS programmes include PSA density, the number of positive biopsy cores and/or cancer involvement based on the Epstein criteria for insignificant PCa (table 2A) [34,63–74]. D'Amico intermediate-risk patients, primarily GS 7(3+4) and/or PSA <15 ng/mL, are considered candidates for AS in some of the programmes. Others accept well-informed patients with a personal request for AS onto their programmes, even though they do not fulfil all of the selection criteria.

Currently, there is no consensus regarding the optimal timing of curatively intended treatment, and most formalised AS programmes use different criteria for progression (table 2B). However, GS upgrade and/or increased tumour volume in re-biopsies is a cornerstone in all AS programmes. The majority also use the change in PSA over time, i.e. PSA kinetics, calculated as either the years required for PSA to double (PSAdt) or the absolute PSA change per year (PSA velocity), to assess disease development. An increased cT category is used as a progression criterion in some of the programmes.

OBJECTIVES AND HYPOTHESES

The overall objective of the thesis was to investigate AS as a treatment strategy for patients with localised PCa focusing on the follow-up regimen and the progression criteria for recommending curatively intended intervention. The included manuscripts are based on data from a single-institution AS cohort followed prospectively at Rigshospitalet from 2002 to 2013.

HYPOTHESES

AS is economical profitable compared to RP.

The estimated PSAdt is accurate, reflects prostatic histopathology, and may be used as a progression criterion in the follow-up of patients on AS.

Re-biopsies during AS reflect prostatic histopathology, and the interobserver variance between uro-pathologists does not preclude the use of adverse histopathology in re-biopsies as a progression criterion during follow-up of patients on AS.

The objectives of the four publications were:

Study I

To assess the trajectory of AS by a systematic recording of the complete extent of patient follow-up – i.e. tests, procedures, PCa-

Table 2A Selection criteria for active surveillance

Reference	Gleason score	No. positive cores	Percentage cancer involvement	Percentage positive cores	PSA (ng/mL)	PSA density (ng/mL/cc)	Clinical tumour category
[65]	≤6 (no pattern 4 or 5)			<33	<10		≤2a
[66]	≤6	≤2	<50		<10		≤2a
[67]	≤6				≤10		≤2b
[68]	≤6	≤2	≤20		≤10		≤2
[69]	≤6	≤2	<50			<0.15	1c
[70]	≤6				<10		≤2a
[71]	≤7	≤3			≤20		≤2
[72]	≤6				<10		≤2a
[73]	≤6	≤3	<50		≤10		≤2a
[74] [a]	≤6			≤50	<15		≤2

Table 2B Progression criteria used in active surveillance

Reference	Gleason score	No. positive cores	Percentage cancer involvement	Percentage positive cores	PSAdt (years)	PSA velocity (ng/mL/year)	Clinical tumour category
[65]	≥7(3+4)					>0.75	
[66]	≥7(3+4)	>2	>50				Increase
[67]	≥7(4+3)				<3		Increase
[68]	≥7(3+4)	>2					
[69]	≥7(3+4)	>2	>50				
[70]	≥7(3+4)				Significant PSA increase		Increase
[71] [b]							
[72]	≥7(3+4)				Esablished PSA increase		Increase
[73]	≥7(3+4)	>3 or bilateral tumour			<3/5		Increase
[74]	≥7(4+3)			>50		>1	

[a] Men >65 years of age with Gleason score 7(3+4) was considered eligible

[b] No fixed follow-up protocol or progression criteria was adhered to

related treatments, risk of eventual curatively intended treatment – and costs.

Study II

To investigate the reliability, performance, and accuracy of PSAdt as a progression criterion

Study III

To investigate the clinical implications of the interobserver variation in the histopathological assessment of re-biopsies in AS.

Study IV

To investigate the association between the AS progression criteria and the subsequent histopathological findings in RP specimens.

MATERIAL AND METHODS

THE LOCAL ACTIVE SURVEILLANCE PROTOCOL

The selection criteria for AS were: cT≤2a, PSA≤10 ng/ml, GS≤6, ≤3 cores with cancer involvement, and ≤50% tumour in any one core (table 2A) [73]. Well-informed patients with higher risk features and a strong request for initial AS were accepted onto the programme. The AS follow-up regimen consisted of PSA measurements and DRE every three months, and a 10-12 core transrectal ultrasound guided re-biopsy after 12 months (figure 3). Hereafter the risk of progression was evaluated accordingly:

Table 3 Active surveillance risk of progression classification

Risk group	PSAdt (Years)	Progression on re-biopsy	Clinical tumour category
High [a]	<3	GS ≥7(4+3), >3 positive cores and/or bilateral tumour	≥2c
Intermediate [a]	3-5	GS ≥7(3+4)	2b
Low [b]	>5	No progression	No increase

[a] Any one of the three criteria; [b] Fulfil all three criteria

AS high-risk patients were recommended to discontinue AS – i.e. undergo curatively intended treatment. Treatment options either continued AS or curatively intended treatment were discussed with patients in the AS intermediate-risk group. Patients in the AS intermediate-risk group who opted for continued AS had the same follow-up as during the first year of AS, with quarterly DRE and PSA tests and additional re-biopsies following 2 years on AS. Patients categorised as AS low-risk had twice-yearly DRE and PSA tests and additional re-biopsies were only performed if the patients changed risk-category assessed by PSAdt and cT. Following 3-5 years on AS, and without fulfilling any of the progression criteria, patients were followed with annual PSA tests. Change to a WW strategy (i.e. curatively intended treatment was no longer considered an option) was at the individual physician's discretion.

STUDY DESIGNS AND STATISTICS

A short summary of the materials and methods for each publication is presented. A two-sided p-value <0.05 was considered significant in study II, III and IV. For detailed descriptions of each study, please see appendices I-IV.

Study I – Utilisation of health care resources

A complete account was conducted with regards to: patient contact (in the out-patient setting), PSA tests, re-biopsy sessions, change of treatment strategy (i.e. WW or curatively intended treatment) and the reason (i.e. progression criteria or patient preference), treatment for lower urinary tract symptoms, and hospital admission following re-biopsy sessions. Cost estimates were based on the average cost of 10 randomly selected patients.

The cumulative incidence of discontinued AS was analysed using a competing risk model with both WW and death treated as one single competing event. The cost of AS was compared to an estimated cost of curative RP for all patients using a Markov model.

Study II – PSAdt as a progression criterion

The first PSA value used for PSAdt calculation was PSA immediately before diagnostic biopsy, except for patients diagnosed by transurethral prostatectomy, where only post-diagnostic PSA values were included. PSA values during PSA suppressant therapies and all PSA outliers assumed to be falsely evaluated, after patient chart review, were censored. Final histopathological findings following subsequent RP, after programme recommendation, were stratified into three prognostic groups: poor (pT≥3, GS≥8, or N1), intermediate (pT2 and GS≤7 or pT2, GS≤6, and >10% tumour volume), and good (pT2, GS≤6, and ≤10% tumour volume).

PSAdt was calculated according to the Memorial Sloan Cancer Center guideline (http://nomograms.mskcc.org/Prostate/PsaDoublingTime.aspx). All PSA values were used for PSAdt calculation; 95% confidence intervals (CI) were calculated in patients with 4 or more PSA values. The hypothetical probability of being AS high-risk misclassified (table 3) was considered for different scenarios using the median mean root square error and assuming the regression coefficient was Student-t distributed. Chi-squared test was used to assess the association between PSAdt and final histopathological findings.

Study III – Re-biopsy assessment

All study biopsies were primarily evaluated internally by one of three expert uro-pathologists and re-evaluated by an external expert uro-pathologist. The histopathological assessment applied the updated GS system, as published in the ISUP 2005 guidelines [30]. The external uro-pathologist was blinded for any information with regards to initial assessment, patient ID and type of biopsy (diagnostic vs. re-biopsy). Three definitions of re-biopsy progression were investigated: The institutional at Rigshospitalet (GS≥7(3+4), >3 positive biopsy cores and/or cancer in bilateral cores) [73], PRIAS (GS≥7(3+4) and/or >2 positive biopsy cores) [75], and University of Toronto (GS≥7(4+3)) [67].

Unweighted and linear weighted Kappa statistics were used to compare the interobserver agreement. Bhapkar's test was used to test for marginal homogeneity.

Study IV –AS progression criteria and RP findings

The RP findings were dichotomised to stratify between patients with histopathological outcome unacceptable for a continued observational strategy, in this study defined as pT≥3a, GS≥7(3+4), and/or N1 (hereafter adverse histopathology), and patients who may not have achieved survival benefit from RP i.e. pT2, GS≤6, and N0/x (hereafter low-risk histopathology) [28]. Biochemical recurrence was defined as the first PSA measurement ≥0.2 ng/mL following RP. An extended PubMed search was performed for publications evaluating RP findings in patients who were initially

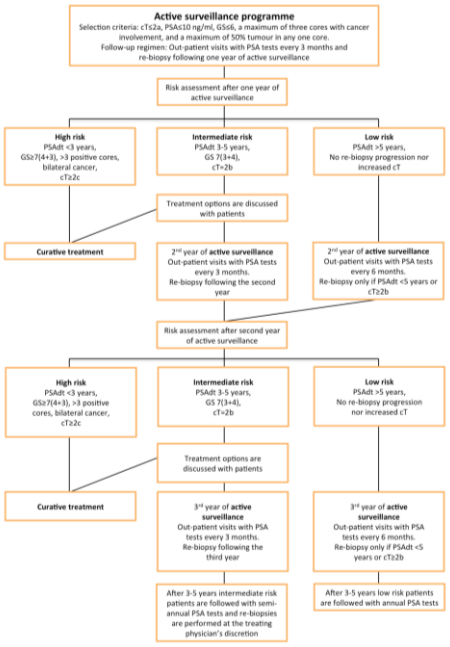

Figure 3 Flow diagram depicting the active surveillance programme at the department of Urology, Rigshospitalet

managed on AS and patients eligible for AS who underwent immediate RP.

Kaplain-Meier estimates were used to analyse the biochemical recurrence-free survival. Univariate and multivariate logistic regression analyses were used to analyse the associations between progression criteria and adverse histopathology. Meta-analyses of RP findings were performed.

Table 4 Patiet characteristics at entry into active surveillance, *study I*

	Median (IQR)	Min-max	No.	%
		Study cohort n = 317		
Age (years)	65 (63-68)	49-73		
PSA (ng/mL)	6.6(5.2-9.1)	0.6-64		
Clinical tumour category				
1			286	90.2
2			31	9.8
Gleason score				
≤6				
7				
No. cores prior to entry	10 (10-18)	6-50		
Number of positive cores				
TURP			36	11.4
1			159	50.2
2			74	23.3
3			26	8.2
≥4			22	6.9
Maximum cancer in one core (%)	10 (5-16.7)	1-90		

IQR: interquartile range; TURP: transurethral prostatectomy

RESULTS

The core results are presented. For detailed descriptions of each study please see appendices I-IV.

Study I – Utilisation of health care resources

The baseline characteristics of the 317 patients included in the study are shown in table 4.

After a median 3.7 year follow-up, 179 patients had left the left the AS protocol, of whom 108 patients had discontinued AS and undergone curatively intended therapy, 68 patients continued on WW, and 3 patients died while on AS (all unrelated to PCa). The 5-year estimated cumulative incidence of discontinued AS in a competing risk model was 39.5% (95% CI:33.4-45.6%) (figure 4). According to the programme progression criteria, the reason for discontinued AS was progression defined by PSAdt for 38 patients, progression on re-biopsy for 53 patients, and progression based on increased cT category for 24 patients, respectively. Overall, 25 patients met more than one progression criterion. Fifteen patients left the AS programme according to their own preference.

During the first 5 years of AS, the number of annual patient contacts and PSA tests was 3-4; within these 5 years, patients had undergone 2-3 re-biopsy sessions. Of the 406 re-biopsy sessions performed, 38 (9.4%) led to subsequent hospital admission owing to infection (n=37) or bleeding (n=1). Finally, 87 patients required at least one form of treatment for lower urinary tract symptoms.

The initial high cost of immediate RP with a less intensive post-surgery follow-up made this strategy more expensive compared to the initial cheaper but more intensive follow-up of the AS programme through-out the study period. The total cost of AS was Euro (€) 1,240,286.

Assuming that all patients had undergone immediate RP, the cost difference with 3.7 year follow-up favoured AS with a net benefit of € 662,661 – representing a net-saving of 34.8%.

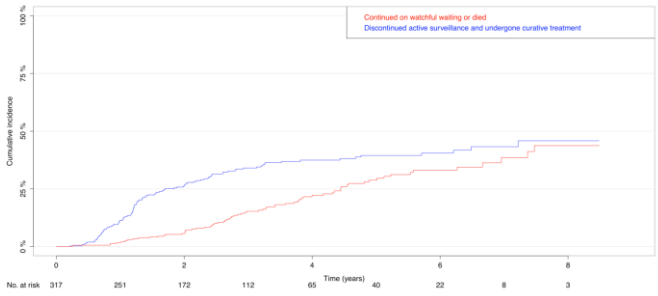

Figure 3
Cumulative incidence of curatively intended treatment after meeting the programme recommendations (progression) or based on own preference (blue line), analysed with both watchful waiting and death as competing events (red line).

Study II – PSAdt as a progression criterion

The analysis was performed with 2,071 PSA measurements in 258 patients who were followed for a median of 3 years. PSAdt with 95% CI was calculated in 221 patients with ≥4 PSA measurements. Figure 5 depicts the estimated PSAdt with 95% CI for the 154 patients with a rise in PSA. Overall, the upper limit of the 95% CI was confined below 3 years in 41% of patients with an estimated PSAdt <3 years, while 60% of patients with an estimated PSAdt >5 years had a lower CI above 5 years.

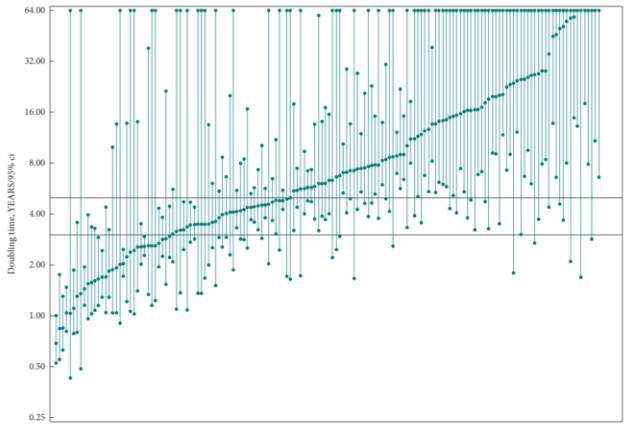

Figure 4
Calculated PSA doubling times (PSAdt) with 95% confidence intervals (CI) in each of the 154 patients with a positive PSAdt. PSAdt 3 and 5 years are marked with horizontal lines. The y-axis is log-scale and truncated at PSAdt 64 years.

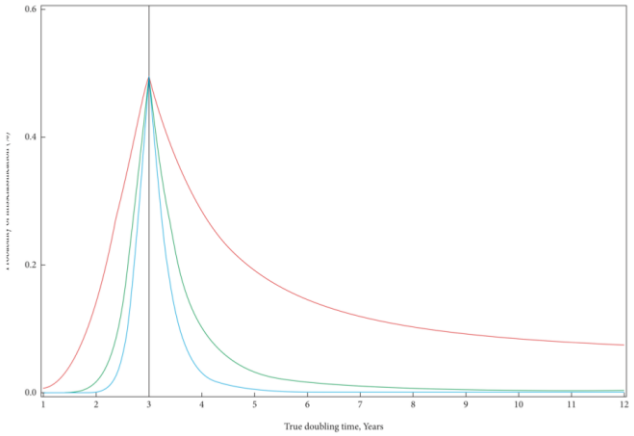

Figure 5
The hypothetical probability of being misclassified i.e. PSAdt <3 years vs. ≥3 years. The x-axis shows the true PSAdt and the y-axis the predicted probability of misclassification. Three patterns are depicted: red line after 1 year follw-up (a total of 5 PSA measurements), green line after 2 years follow-up (a total of 7 PSA measurements), and blue line after 3 years follow-up (a total of 9 PSA measurements).

The probability of a true PSAdt ≥3 years being misclassified as a PSAdt <3 years (false AS high-risk classification) or vice versa is illustrated for three different PSA testing scenarios in figure 6. The figure illustrates that after one year on AS (red line), the risk of being misclassified was substantial. One in 5 patients with a true PSAdt of 5 years and 1 in 10 patients with a true PSAdt of 9 years will incorrectly be recommended curative intent treatment based on a false AS high-risk classification. With more PSA tests taken over a longer period of time, the PSAdt estimate becomes more accurate, with less risk of a misclassification (green and cyan lines).

Finally, there was an almost identical proportion of patients in each of the three AS risk groups defined by PSAdt that was identified with poor (22-27%), intermediate (41-54%), and good prognostic final histopathology (25-37%), respectively (p=0.90).

Study III – Re-biopsy assessment

The study comprised 107 patients with a total of 93 diagnostic and 109 re-biopsy sets. All patients fulfilled the applied selection criteria for AS at Rigshospitalet on the primary institutional evaluation and had undergone at least one re-biopsy.

The interobserver agreement of diagnostic biopsies between the institutional and external evaluation was 79.6% with regard to whether the selection criteria for AS according to the protocol at Rigshospitalet was met (table 5A). Re-evaluation could not confirm a cancer diagnosis in seven patients. Moreover, 12 patients were found to have tumour characteristics that were incompatible with AS enrolment. This included GS 7(3+4) (n=8), GS 7(4+3) (n=1), more than 3 biopsy cores containing cancer (n=1), and more than 50% of cancer tissue in one single core (n=2).

Table 5A Interobserver agreement between primary and re-evaluation of diagnostic biopsies (selection criteria: GS ≤6, ≤3 positive cores, and ≤50% tumour in any one core)

		External evaluation				
		Biopsies	No cancer	Fulfil the selection criteria	Poorer histopathology	Agreement
		93				79.6%
Institutional evaluation	No cancer		-	-	-	(95% CI 69.7-87.0)
	Fulfil the selection criteria		7	74	12	
	Poorer histopathology		-	-	-	

Table 5B Interobserver agreement on re-biopsy progression (progression criteria: GS ≥7(3+4), ≥4 positive cores or bilateral tumour)

		External evaluation						
		Biopsies	No cancer	No progression	Progression	Agreement	Weighted Kappa	Bhapkar's test
		109				80.7%	0.746	0.12
Institutional evaluation	No cancer		52	7	1	(95% CI 71.8-87.4)	(95% CI 0.596-0.896)	
	No progression		3	22	7			
	Progression		0	3	14			

Abbreviation: GS Gleasons score; CI confidence interval

Table 6A Association between progression criteria and adverse histopathology in the radical prostatectomy specimen

	No.	OR (95% CI)	P
PSAdt progression	83		
No (ref)		1	
Yes		0.46 (0.18-1.19)	0.11
Re-biopsy progression	74 [a]		
No (ref)		1	
Yes		4.03 (1.35-12.03)	0.01
Clinical tumour category progression	83		
No (ref)		1	
Yes		0.88 (0.31-2.54)	0.82

Table 6B Adjusted association between progression criteria adverse histopathology in the radical prostatectomy specimen

Model 1	71		
Age [b]		1.08 (0.94-1.24)	0.27
PSA ratio [c]		0.61 (0.19-1.95)	0.41
PSA density [c]		1.63 (0.72-3.71)	0.24
PSAdt progression			
No (ref)		1	
Yes		0.39 (0.14-1.10)	0.08
Model 2	65 [a]		
Age [b]		1.03 (0.87-1.23)	0.72
PPB [c]		1.34 (0.67-2.68)	0.40
Maximum tumour involvement [c]		1.04 (0.61-1.76)	0.89
Re-biopsy progression			
No (ref)		1	
Yes		1.95 (0.54-7.07)	0.31
Model 3	83		
Age [b]		1.07 (0.94-1-21)	0.30
Clinical tumour category			
1 (ref)		1	
2		1.07 (0.24-4.74)	0.93
Clinical tumour category			
Unchaged (ref)		1	
Increased		0.86 (0.29-2.55)	0.79

Abbreviation OR odds ratio; CI confidence interval; PSAdt prostate-specific doubling time; PPS percentage positive biopsies (no. of biopsies with tumour/total no. of biopsies)
[a] only including patients where a re-biopsy was performed; [b] analysed for 1 year change; [c] analysed ofr two-fold change

The median number of re-biopsy cores was 10 (range: 9-13). The GS agreement in the re-biopsies was 68.8% (weighted Kappa 0.670). The institutional assessment found no cancer in 60 of the 109 re-biopsy sets, while the external evaluation found no cancer in 55, with agreement in 52 re-biopsy sets (table 5B). The two evaluations agreed that 14 patients had progression according to the Rigshospitalet progression criteria. The institutional assessment identified 3 additional patients as having progression, while 8 different patients met the definition of progression according to the external evaluation. The overall agreement on progression was 80.7% (weighted Kappa 0.746). The Bhapkar's test found no significant difference between the two assessments (p=0.12).

The interobserver agreement according to the PRIAS (GS≥7(3+4), >2 positive biopsy cores) [75] and University of Toronto (GS≥7(4+3)) [67] definitions of re-biopsy progression was 82.6% and 89.0%, respectively. Using these progression criteria, 27 (24.7%) and two (1.8%) patients were assessed as having progression in at least one of the two evaluations.

Treatment recommendations would have differed in up to 10.1% (95% CI:5.4%-17.7%) of the 109 re-biopsy sets depending upon which histopathological assessment and which definition of progression had been used for therapeutic planning.

Study IV –AS progression criteria and RP findings

The 317 patients comprising the study population were followed for a median of 4.1 years. During the study period, 111 patients discontinued AS. Of the 99 patients who underwent RP, 83 met at least one of the progression criteria and were included in the analysis. According to the AS progression criteria: 34 patients progressed on PSAdt, 49 patients progressed on re-biopsy, and 21 patients had an increase in cT, respectively. Twenty-one patients met two of the progression criteria.

The RP specimen revealed findings perceived incompatible with continued AS (adverse histopathology: GS≥7(3+4), pT≥3 and/or N1) in 57 (68.7%) of the 83 patients, while 26 (31.3%) patients had low-risk histopathology. The 3-year Kaplan-Meier estimated biochemical recurrence-free survival to be 93.7% (95% CI:88.4-99.0%).

Progression on re-biopsy was the only progression criterion significantly associated with adverse histopathology in univariate analysis (odds ratio (OR)=4.03 (95% CI:1.35-12.03)) (table 6A). The association between progression on re-biopsy and adverse histopathology was almost exclusively driven by GS upgrade (OR=31.50 (95% CI:3.91-253.98)). Neither >3 positive biopsy cores (OR=1.78 (95% CI:0.61-5.19)) or bilateral tumour (OR=2.17 (95% CI:0.69-6.86)) were significantly associated with adverse histopathology. Patients meeting two of the three progression criteria had a non-significant higher OR of being characterised with adverse histopathology compared to patients meeting only one progression criterion (OR=3.54 (95% CI:0.94-13.33), p=0.06).

Although the predefined level of significance was not met, a negative association between progression on PSAdt and adverse histopathology was seen in multivariate analysis (OR=0.39 (95% CI:0.14-1.10)) (table 6B – model 1). In multivariate analysis, progression on re-biopsy was no longer significantly associated with adverse histopathology (OR=1.95 (95% CI:0.54-7.07)) (model 2).

No association between increased cT and adverse histopathology was found in multivariate analysis (OR=0.86 (95% CI:0.29-2.55)) (model 3).

In total, 5 publications on RP findings after initial AS [76–80] and 16 publications on RP findings in candidates for AS who underwent RP as primary treatment [46–61] were identified. Tumour characteristics were worse in patients who underwent RP subsequent to AS (55.1% had GS≥7(3+4) and 20.7% had pT≥3a, respectively) compared to patients treated with immediate RP (34.1% had GS≥7(3+4) and 12.4% had pT≥3a, respectively) (table 7).

Table 7 Radical prostatectomy (RP) findings for patients initially managed on active surveillance (AS) and for patients fulfilling the selection criteria for AS but underwent immediate RP.

	Selectio criteria	Patients on AS	RP patients	GS ≥7(3+4)	pT≥3	N1
AS cohorts		No.	No.	%	%	%
[76]	cT1, GS ≤6, ≤2 cores with cancer, PSA density <0.15	470	48	48	35	4
[77]	cT1, GS ≤6, ≤2 cores with cancer, PSA density <0.15,	283	61	56	21	2
[78]	cT2, GS ≤6, ≤2 cores with cancer, PSA ≤10, PSA density <0.15,	2079	167	53	19	0
[79]	cT1, GS ≤6, ≤2 cores with cancer, PSA density <0.15	>800	67	55	24	0
[80]	cT ≤2a, GS ≤6, ≤3 cores with cancer, ≤50% tumour volume, PSA ≤10	681	67	55	18	4
Study IV	cT ≤2a, GS ≤6, ≤3 cores with cancer, ≤50% tumour volume, PSA ≤10	317	99	62	18	5
Meta-analysis (95% CI)			509	55.1 (50.8-59.5)	20.7 (17.2-24.2)	1.6 (0.3-3.0)
Immediate RP						
[46]	cT ≤2a, GS ≤6, PSA ≤10	-	549	23	5	-
[47]	cT ≤2, GS ≤7(3+4), ≤3 cores with cancer, ≤50% tumour volume, PSA ≤15	-	596	31	17	-
[48]	cT ≤2, GS ≤6, ≤33% positive cores, ≤50% tumour volume, PSA <15	-	278	35	10	-
[49]	cT ≤1, GS ≤6, PSA ≤10	-	177	51	19	-
[50]	cT ≤2a, GS ≤6, PSA ≤10	-	771	47	11	-
[51]	cT 1, GS ≤6, PSA <10	-	93	25	8	-
[52]	cT ≤2, GS ≤6, ≤2 cores with cancer, PSA ≤10, PSA density <0.2	-	85	28	6	1.2
[53]	cT ≤2a, GS ≤6, ≤33% positive cores, PSA <10	-	186	33	10	-
[54]	cT ≤1, GS ≤6, <3 mm tumour length, PSA <10	-	919	34	13	-
[55]	cT ≤2a, GS ≤6, PSA <10	-	159	38	30	5.7
[56]	cT ≤2a, GS ≤6, <3 mm tumour length in 2 biopsy cores, PSA <10	-	43	16	5	-
[57]	cT ≤2a, GS ≤6, PSA ≤10	-	1560	30	27	0.6
[58]	cT ≤2, GS ≤6, ≤2 cores with cancer, PSA ≤10, PSA density <0.2	-	626	45	21	-
[59]	GS ≤6	-	295	30	6	0
[60]	cT ≤2, GS ≤6, ≤3 cores with cancer, ≤50% tumour volume, PSA ≤10	-	259	33	7	2.3
[61]	cT ≤2a, GS ≤6, ≤2 cores with cancer, PSA ≤10	-	84	48	10	-
Meta-analysis (95% CI)			6.680	34.1 (29.5-38.6)	12.4 (8.4-16.4)	1.4 (0-2.7)

Abbreviation CI confidence interval; GS: Gleason score; N1: positive lymph node; pT: pathological tumour category

DISCUSSION

The thesis has demonstrated that AS is feasible with regards to reducing the number of patients undergoing curatively intended treatment and that short-term follow-up is cost-effective compared to immediate RP. PSAdt is unreliable as a progression criterion based on a statistical uncertainty of the estimates and the lack of association to final histopathology following subsequent RP. Progression on re-biopsy in part fulfils the requirements for a useful progression criterion. A substantial interobserver agreement between expert uro-pathologists was found and re-biopsy progression was associated with specimen RP findings that were incompatible with a continued observational approach – although the definition of statistical significance at the 0.05% level was only reached in univariate analysis with the available sample size.

GENERAL CONSIDERATIONS

The current AS programme which forms the basis for the present thesis has obvious limitations with regard to re-biopsy complications and imperfect progression criteria. Still, the shortcomings of an initial observational strategy are outweighed by the benefits of such an approach as opposed to initial curative intervention. The natural history of expectantly managed PCa is heterogeneous but patients with low-risk features have a good long-term prognosis [11–14] and RP have, in randomised settings, failed to reduce PCa-specific mortality in these patients [40,41]. Thus, overtreatment is an important consideration when informing and discussing treatment options with these patients. From a patient's perspective, the psychological benefits of being cured without a succeeding survival gain must be held against the treatment load, side-effects and reduction in quality of life associated with curatively intended treatment options. From a socio-economic perspective, study I found AS to be cost-effective compared to immediate RP, a finding that was supported by Keegan et al. with a 10 year estimate [81]. Although a longer follow-up is necessary to fully evaluate the economic consequences, a greater

proportion of the available resources could potentially be redistributed to improve quality of life and survival in patients with a far graver prognosis [11–14,82].

AS for patients with localised PCa is not equal to a total refrain from "treatment". Most patients were seen in the out-patient clinic every three months, underwent 2-3 re-biopsy sessions with the risk of infectious complications, and almost 30% required treatment for lower urinary tract symptoms during the first 5 years. At this point, 39.5% had discontinued AS and underwent curatively intended treatment. As previously mentioned, the PCa-specific mortality for patients who today would be considered candidates for AS in the observational arms of the PIVOT and SPCG-4 studies was 4.1% and 14.0%, respectively [40,41]. In both the observational and active arm of the PIVOT study, 148 D'Amico low-risk patients were included. After 12 years follow-up, the number of patients who developed bone metastasis or died from PCa were 6 and 1, respectively, in each of the two arms (p=0.08) [40]. Thus, the failure rate of RP in D'Amico low-risk patients was 0.7% (1/148). Subtracting the observational arm from the active arm, the cure rate can be estimated to be 3.4% (5/148). This implies that 95.9% (142/148) underwent RP without gaining a substantial benefit from the intervention at 12 years. Combining the number of patients who underwent deferred curative intervention following AS with the survival data in the observational arms of the SPCG-4 and PIVOT studies illustrates that although AS is able to reduce the number of patients requiring curative intervention, overtreatment is not eliminated. When the AS cohorts mature and follow-up reaches that of the observational arms of the SPCG-4 and PIVOT studies, it may be indicated whether AS is able to improve PCa-specific survival compared to a strategy where delayed curative treatment is not an option.

The 3-year biochemical recurrence-free survival for the 83 patients who underwent RP based on the programme recommendations in study IV is comparable to that of the 414 D'Amico low-risk patients who underwent immediate RP at the department of Urology, Rigshospitalet (93.7% versus approximately 90%) [22], indicating that AS does not negatively affect the short-term biochemical prognosis after curatively intended treatment. Although this preliminary conclusion is supported by a recent review addressing the timing of curative treatment [83], to fully answer this question, a prospective, randomised study with long follow-up is needed.

A crucial objective of AS is to identify patients with histopathological characteristics who require more aggressive treatment. Patients primarily managed on AS and who are identified for curatively intended treatment and undergo subsequent RP must logically have worse final histopathological characteristics compared to patients who were considered candidates for AS at the time of RP. However, it is unknown to what extent the currently applied AS programmes are able to identify patients who will benefit from a curative intervention. Subtracting the final histopathological findings in patients considered candidates for AS who have undergone immediate RP from the final histopathological findings in patients initially managed on AS can provide an indirect estimation of the histopathological characteristics of the patients remaining on AS. This requires a number of premises and assumptions: 1) the tumour characteristics in patients who enter AS are similar to those in patients who have undergone immediate RP; 2) histopathology is stable during follow-up; 3) the rate of GS≥7 in patients undergoing RP is 34.1%; and 4) the AS discontinuation rate after 5 years is 39.5% (study I), of which 55.1% is found to have GS≥7 when undergoing RP (study IV). Thus, out of a 1000 patients managed on AS, 605 patients will remain within the programme after 5 years. Of these 605 patients, 123 patients (20.3%) will harbour GS≥7 (34.1%*1000 - 55.1%*395) and 42 patients (6.9%) pT≥3a (12.4%*1000 - 20.7%*395) (figure 7). Acknowledging that this is merely an estimate, it does indicate that the current AS follow-up regimens are only able to reduce the proportion of patients with specimen GS≥7 managed expectantly from 34.1% to 20.3%.

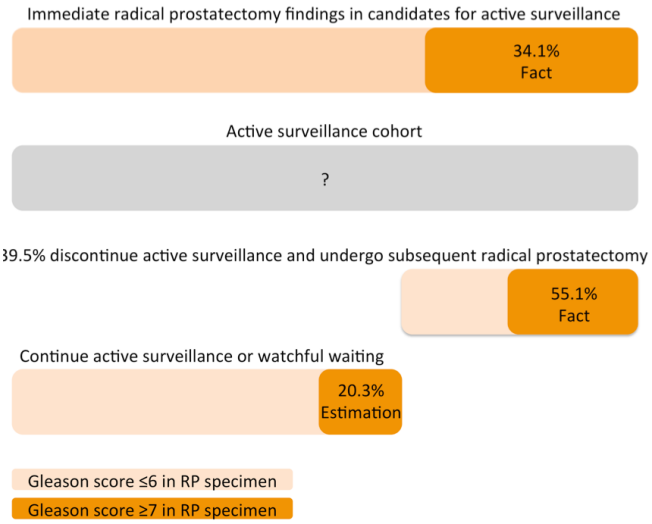

Figure 6
Estimating the histopathological characteristics in patients remaining on active surveillance

THE ACTIVE SURVEILLANCE STRATEGY

The "perfect" AS programme should be able to safely monitor patients with preferably non-invasive parameters or at least invasive parameters with a minimum risk of complications, while at the same time correctly differentiating between patients in whom curatively intended treatment is unnecessary and patients in whom a curative approach provides a significant benefit.

Currently, there is no consensus about the optimal follow-up regimen. The follow-up programmes used in the published AS cohorts have been pragmatic and non-evidence-based defined [63]. Results from the first prospective, randomised trial to study different AS intensity follow-up regimens with a 5-year discontinuation rate as a primary endpoint and quality of life as one of the secondary endpoints are awaited in the not too distant future[84].

The calculation of PSAdt and definition of progression vary between different AS programmes. According to the University of Toronto AS protocol, PSAdt is calculated using a minimum of 3 PSA measurements obtained over a minimum of 6 months [85]. The PRIAS study and the institutional AS protocol at Rigshospitalet calculated the PSAdt after one year of observation based on 5 PSA values [73,75]. Still, the treatment recommendations in all three programmes were based on PSAdt estimates influenced by a significant uncertainty (figure 6). As expected, longer follow-up and more PSA values decrease the uncertainty of the PSAdt estimate (figure 6). However, a dilemma exists, since the longer the follow-up, the bigger the risk that calculated PSAdt may underestimate the current and most recent disease activity. [86].

The definitions of re-biopsy progression used in the three AS programmes (University of Toronto, PRIAS, Rigshospitalet) were all employed in study III [67,73,75]. Interestingly, between 1.8%

and 24.8% of the re-biopsies would result in recommendation of curatively intended treatment depending upon which definition was applied. As expected, GS progression on re-biopsy was associated with a worse histopathology in the RP specimen. However, study IV also demonstated that progression on re-biopsy without GS upgrade was poorly associated with a final histopathology perceived as unacceptable for continued AS (including specimen GS 7(3+4)). This observation is in accordance with a recent AS study [79]. Although GS upgrade appears superior to other re-biopsy definitions of progression, future trials are warranted to establish the optimal re-biopsy progression criterion for identifying patients who will benefit from curative intervention.

PERFORMANCE OF ACTIVE SURVEILLANCE PROGRESSION CRITERIA

The majority of the patients who discontinued AS and underwent curatively intended treatment according to the protocol at Rigshospitalet progressed either based on PSAdt (35.2%) or based on re-biopsy (49.1%).

PSA kinetics

PSA kinetics are used to monitor patients in most AS series and are one of the main parameters used when deciding whether more aggressive treatment is necessary [63]. Study II demonstrates that the calculated PSAdt and subsequent treatment recommendations are associated with significant uncertainties. Study IV found a non-significant association between PSAdt and final histopathology perceived as acceptable for continued AS. Logically, this comparison has significant limitations, since PSAdt was part of the criteria used to select patients for RP. Had the entire cohort undergone RP, an association between rapid PSAdt and poor final histopathology might have been found in studies II and IV.

A number of studies have highlighted the limitations of PSA kinetics in low-risk PCa and when monitoring patients on AS. O'Brien et al. found that pre-RP, PSAdt was incapable of predicting biochemical recurrence or the development of metastatic disease in patients with PSA <10 ng/mL and GS≤6 who underwent immediate RP [87]. Conversely, in two AS cohorts a short PSAdt has been found to be associated with biochemical recurrence following curatively intended treatment in patients who were initially managed on AS [67,88]. Both of these studies had some limitations with incomplete follow-up, definition of PSAdt progression, and unadjusted analysis.

A retrospective analysis of the observational arm of the SPCG-4 study found PSAdt to be associated with lethal PCa after 2 years of observation [89]. However, the authors concludes that their "findings raise the question of whether early PSA characteristics are suitable and safe as decision tools for therapeutic intervention among low-risk patients managed with active monitoring", because there was no clear PSAdt cut-off that could differentiate between patients who would develop lethal PCa and patients who would not. Although the study population was not comparable to a contemporary AS cohort (48.0% had a baseline PSA >10 ng/mL and 6% had a GS≥8), the sensitivity analysis performed included patients with a GS≤7 and yielded similar results. Consistent with this observation, a register-based study, including 2,333 patients treated conservatively, found that PSAdt was not able to predict PCa-specific mortality [90]. Although PSA velocity in the same study showed an association with PCa-specific mortality, the parameter did not improve the accuracy of a single pre-diagnostic PSA alone [90]. PSA velocity has also been shown to enhance the predictive accuracy of worse histopathology following RP [87]. However, the addition of PSA velocity had limited clinical value compared to a single PSA measurement.

PSA kinetics are used for planning re-biopsy during follow-up in some AS programmes [73,75]. However, no clear association between neither short PSAdt nor high PSA velocity and progression on re-biopsy have been established [91–93]. A third PSA kinetic – PSA velocity risk count – has been proposed as a tool to individualise re-biopsy interval in AS [94]. The PSA velocity risk count is calculated as the sum of at least two risk counts based on PSA velocities calculated over a defined period of time, for example following the 1st and 2nd year of AS. If the PSA velocity is >0.4 ng/mL/year following for example 1 year it results in a risk count of 1, while a PSA velocity ≤0.4 ng/mL/year results in a risk count of 0 [94]. Using this definition, a PSA velocity risk count ≥2 has been associated with a 5-fold increased odds for being diagnosed with GS≥8 in a screening cohort and a 4-fold higher risk of progressing on re-biopsy in an AS cohort [95,96]. Although the authors of one of these publications have argued that patients with a PSA velocity risk count ≤1 could safely avoid re-biopsies [96], 38% of the patients diagnosed with GS≥8 and more than 50% of the patients meeting the definition of re-biopsy progression had a risk count ≤1. As such, these publications indicate that although there is an association between PSA velocity risk count and histopathological findings in prostate biopsies, patients with a PSA velocity risk count ≤1 cannot safely avoid re-biopsies in AS programmes.

The PSA level is affected by both benign and malignant changes in the prostate [16–18]. Patients included in AS programmes are likely to have small tumour volumes in prostates affected by varying amounts of benign hyperplastic tissue [97]. A morphometric study has shown that 1 cm3 PCa tissue increases the PSA level by approximately 10-fold compared to 1 cm3 benign prostatic hyperplacia alone [98]. Still, changes in the benign tissue may obscure cancer development and limit the use of PSA kinetics in patients followed on AS.

Progression on re-biopsy

Concurrent with the literature, the overall agreement between expert uro-pathologists of GS assessment was 68.8% in study III [42,44,99]. Previous reports have documented that the distinction between Gleason pattern 3 and 4 is difficult [30,42–44]. The interobserver variation of expert uro-pathologists in boarder line GS 6 and 7 prostate biopsies varies from 47-93% (weighted Kappa value of 0.43) [42]. There is some indication that the risk of assigning a higher GS than the consensus is greater than the risk of assigning a lower GS [42,43]. The interpretation of fusion patterns or small solid strands that can occur with tangential section of a Gleason pattern 3 PCa gland is proposed as a probable explanation for this observation [42].

Even small differences in the assessment of GS can result in major clinical consequences in an AS context. Patients with a diagnostic GS≥7(3+4) are not considered eligible for inclusion in most AS programmes and the presence of Gleason pattern 4 in a re-biopsy would often lead to recommendation of curatively intended treatment [63]. The treatment recommendations would have differed in up to 10% of the re-biopsies re-evaluated in study III depending upon which pathologist's assessment was used for therapeutic planning. Compared to the uncertainty of the calculated PSAdt found in study II, study III indicates that the definition of "progression", when based on the histopathological evaluation, is more reliable than when based on PSA kinetics. Somewhat

logically, patients meeting the definition on re-biopsy progression had an increased OR for final histopathology that was incompatible with continued AS – almost exclusively driven by an increase in GS.

The drawback of using an invasive procedure as a progression criterion is not easily overcome, and less aggressive monitoring tools is needed. An estimated 35% of AS patients would be considered ineligible for entry in AS according to the selection criteria if an immediate re-biopsy was performed [100]. A reported 9-28% have an increase in GS and 2-22% have an increase in the number of positive biopsy cores at their first AS re-biopsy [67,69,73,75]. Hereafter, the annual cumulative risk of progression on re-biopsy has been estimated to be 1% [101]. The high risk of re-biopsy progression following one year of AS is a likely consequence of sampling error [45] and interobserver variation of the histopathological evaluation [42] rather than a biological progression. Different frequencies and intervals between re-biopsies are used in the AS programmes ranging from annual, to every 2-3 years, to depending upon clinical parameters (cT and PSA kinetics) during follow-up [63]. The association between progression on re-biopsy and the final histopathology found in study IV underlines that re-biopsies should be considered a central part of the AS follow-up, as long as the patients remain as candidates for curative treatment. However, concurrent with previous findings, study I underlines that re-biopsies are not without significant risks and side-effects [102–104]. Register-based studies have found an increased incidence of biopsy related complications necessitating in-house admission during the last few decades [102,103]. Both higher comorbidity and the number of previous re-biopsy sessions have been associated with an increased risk of infectious complications [103,104].

The updated GS guidelines from 2005 have led to a significant Gleason inflation with an increase in the proportion of GS 7(3+4) [30,31]. The clinical implications of this development have consequences: 1) a weakened prognostic value of a biopsy GS 7 [31]; 2) the treatment results of diagnostic GS 7 appears to improve because some cases who previously were assigned GS 6 are now assigned GS 7 [105]; 3) the data from the natural history and the randomised RP versus WW studies cannot accurately be employed in a contemporary PCa population [11,12,40,41]; 4) fewer patients will fulfil the selection criteria for AS, table 2A; 5) some patients included on AS before these guidelines were implemented may be identified as having progression on re-biopsy only because of a histopathological evaluation performed in accordance with the updated guidelines, table 2B. In study III, this risk has been accounted for by only including patients diagnosed after implementation of the ISUP 2005 guidelines.

Progression on clinical tumour category

No association between increased cT and final histopathological findings following RP was found in study IV and the ability of this parameter as a sole progression criterion in AS is questionable. Scarification of prostate tissue by repeated transrectal biopsies and differences in the interpretation of DRE is not well investigated, but both may influence the cT assessment. Even though the use of cT in AS is not supported by this thesis, any final conclusion with regards to this parameter cannot be made.

LIMITATIONS

The thesis has focus on follow-up regimen and progression criteria, and therefore lacks data on selection criteria. Also the psychological aspects of harbouring an untreated cancer have not been investigated in this thesis. Other studies have found that D'Amico low-risk PCa patients managed on AS report superior quality of life in specific domains such as voiding, continence, and sexual functioning compared to patients treated with brachytherapy or RP, but a similar overall quality of life [106]. Another study reported that both physical and mental health-related quality of life was stable after one year on AS [107]. Similar to what has been found in other AS cohorts [67,72,74], less than 5% discontinued the programme because of preference, which strongly indicates that the AS strategy is well-accepted by the majority of patients.

The Department of Urology, Rigshospitalet, is a tertiary referral centre for patients diagnosed with PCa, which could result in a selection bias of the patients included in the AS cohort compared to patients managed on AS in other Danish centres. A general limitation shared with many previous reports on AS cohorts is the short follow-up period.

Studies I and III are retrospective in design. Studies II and IV have some limitations in part that are inherent to their observational structure, and the final histopathology in the RP specimen was used as a surrogate for survival endpoints.

In study I, all hospital and out-patient costs of AS were accounted for and compared to the estimated cost of immediate RP, excluding long-term post-surgical complications, treatment for urinary incontinence and erectile dysfunction. Had these costs been included the cost-benefit of AS would increase. Furthermore, longer time on AS may increase the costs associated with follow-up, which may eventually increase beyond the cost of immediate curatively intended treatment.

The PSAdt calculation was performed with PSA values obtained and analysed at different centres. All centres apply the Roche Elecsys® PSA Immunoassay kit and perform the PSA assay with lithium-heparin plasma. The decision to use plasma as opposed to serum for PSA analysis has been based on the practical fact that lithium-heparin plasma is required for other analyses. The PSA values used in the PSAdt calculation are therefore subject to potential both intra- and inter-centre variations. On the other hand, the studies represent clinical practice, where completely standardised measurements are practically impossible.

Interpretation of both studies II and IV is hampered by the fact that progression criteria are evaluated by relating them to final histopathology in patients eventually undergoing RP based on the same progression criteria. This in part leads to self-fulfilling prophecies, i.e. the finding of GS 7 in re-biopsy is logically associated with high frequency of GS 7 in the RP specimen. Also the methodology does only provide specimen based histological information in those patients undergoing RP, while this information naturally is lacking in patients continuing AS.

Study III compares the evaluation of one external expert and the primary evaluation performed as part of the AS follow-up by one of three in-house expert uro-pathologists. Preferentially, one uropathologist from each centre would have evaluated all biopsies, to give exact data on interobserver variations. The result in study III could therefore be seen as inter-institutional observer variation.

The definition of final histopathological outcome in the RP specimen perceived unacceptable for continued AS included GS 7(3+4) and naturally an association between GS progression on re-biopsy and this definition must be expected. Moreover, the definition of final histopathology being unacceptable for continued AS may be considered too wide by some, as patients with diagnostic GS 7(3+4) are considered eligible for AS in a number of

AS programmes (table 2A). Although patients with diagnostic GS 7 had the greatest survival benefit from RP in the SPCG-4 study [41] it is unknown whether this can be directly transferred to patients with RP specimen GS 7(3+4). The definition was chosen because the prognosis of specimen GS 7(3+4) is inferior to that of specimen GS≤6 [28]. The reported 20-year PCa-specific mortality for patients with RP specimen GS 7(3+4) was 9-17% compared to only 0.2-1.2% for patients with RP specimen GS≤6.

CONCLUSION

The trajectory of AS follow-up, as described in study I, resulted in close monitoring during the first 5 years. At this point, an estimated 39.5% will have discontinued AS and undergo curatively intended treatment. Compared to the cost of immediate RP, AS is associated with a net-saving of 34.8%. The re-biopsy sessions were associated with a significant risk of subsequent hospital admission, underlining the need for new techniques and strategies to reduce the number of biopsies.

PSAdt after one year of observation was associated with a considerable uncertainty, which resulted in a significant risk of being misclassified according to the AS risk of progression definition. Combined with the finding that the final histopathology was comparable in all three PSAdt risk assessments groups, study II establishes that PSAdt has significant limitations as a progression criterion in AS.

Kappa statistics demonstrated a substantial agreement between experts' uro-pathologist evaluation of prostate biopsies. Still, the re-evaluation did not consider 20% of the patients eligible for AS and the differences in the evaluations would have resulted in altered treatment recommendations in up to 10.1% of the re-biopsies evaluated in study III.

Study IV found that neither progression defined by PSAdt nor increase cT was associated with final histopathological findings. Although only significant in univariate analysis, progression on re-biopsy was associated with final histopathology that was perceived unacceptable for a continued observational strategy. Study IV empathises the need for more reliable and accurate progression criteria in AS.

PERSPECTIVE FOR FUTURE RESEARCH

New markers and techniques to increase the safety and performance of AS are warranted. The best performing progression criterion (transrectal ultrasound guided re-biopsy) is an uncomfortable procedure with the caveat of sampling error and a significant risk of serious complications [45,102–104]. Future studies should focus on individualising the follow-up regimen, reducing the number of patients who require re-biopsies, and improving the accuracy of tumour sampling. Fortunately, new promising tools for improving AS follow-up have been introduced.

Recent advances in the magnetic resonance imaging (MRI) technology have made it possible to visualise tumours in the prostate. A 1.5 or 3-Tesla MRI evaluated as "low suspicion of tumour presence" prior to a 12 core transrectal ultrasound guided re-biopsy had a negative predictive value of 96-100% for GS upgrade in 388 patients [108]. Another MRI modality with an apparent diffusion coefficient, that was tested in 86 patients, found that none of the patients graded as "favourable" had adverse histopathology at re-biopsy [109]. MRI-ultrasound fusion targeted biopsies can improve the accuracy of detection of significant PCa and can reduce the necessary number of biopsy cores [110]. The combination of a multi-parametric MRI with MRI-guided biopsy in the diagnostic work-up have been found to reduce the number of patients diagnosed with GS≤6 PCa (from 62.7% to 6.1%) compared to the standard transrectal ultrasound guided biopsy [111]. In this study, the MRI had a negative predictive value for GS≥7 of 96.9%. These studies suggest that the issue of sampling error of a standard transrectal ultrasound guided biopsy may be overcome [45] and that patients with favourable/low suspicion MRI could safely avoid AS protocolled re-biopsies.

The gene fusion between TMPRSS2 and ERG has been identified as a genetic alteration in 40–70% of PCa patients [112]. The gene fusion causes the oncogene ERG to become overexpressed by the androgen-regulated TMPRSS2. The gene fusion is associated with an increased risk of PCa-specific mortality in patients managed on WW [113]. Expression of the ERG protein in a diagnostic biopsy has been associated with a 2.5-3-fold higher risk of progressing in an AS programme [114]. TMPRSS2:ERG mRNA is detectable in the urine and increasing levels of mRNA have been shown to correlate positively the diagnosis of clinically significant PCa (in this study defined as: cT≥2, GS≥7, PSA density >0.15, and >33% positive cores) with a specificity of 93.2% [115]. The absence of the TMPRSS2:ERG fusion gene may therefore have implications for the intensity of follow-up in future AS programmes.

SUMMARY

BACKGROUND

Active surveillance – an initial observational strategy – offers a tailored management of patients with localised prostate cancer. The aim of the strategy is to appoint patients with potentially lethal prostate cancer to curatively intended treatment, while patients with slowly evolving tumours are spared from an unnecessary curative intervention.

MATERIAL AND METHODS

All data included were derived from a single-institution active surveillance cohort of 317 patients which was followed prospectively at Rigshospitalet from 2002 until 2013. The patients were managed with serial PSA measurements, repeated biopsies, and regular digital rectal examinations. The programme recommended change of management from active surveillance to curatively intended treatment based on PSA doubling time, deteriorating histopathology in repeated prostatic biopsies, and increased clinical tumour category.

RESULTS

The programme entailed close monitoring during the first 5 years with 3-4 out-patient contacts annually. Altogether, 2-3 biopsy sessions were performed in most patients. Complications necessitating hospital admissions arose in almost 10% of the repeated biopsy sessions. The 5-year cumulative incidence of curatively intended treatment was estimated to be 39.5%. Active surveillance resulted in a 34.8% cost-reduction following 3.7 years compared to the estimated cost of immediate radical prostatectomy. The calculated PSA doubling times were associated with wide 95% confidence intervals, which resulted in a significant risk of being misclassified according to the definition of progression. The interobserver agreement of biopsy histopathology between expert uro-pathologist was substantial. Still, the pathologists' disagreement would have resulted in different treatment recommendations in up to 10% of the re-evaluated biopsies. Neither PSA doubling time nor increased clinical tumour category was associated with final histopathological findings following subsequent radical

prostatectomy. Although the level of significance was only met in univariate analysis, biopsy progression was associated with defined final histopathological findings at radical prostatectomy that was perceived as unacceptable for a continued observational strategy.

CONCLUSION

The thesis has demonstrated that active surveillance is feasible and reduces the number of patients undergoing curative intended treatment. However, active surveillance necessitates close monitoring during the first 5 years. PSA doubling time is unreliable as a progression criterion, while progression on repeated biopsy in part seems to fulfil the requirements of a dependable progression criterion. The need for more accurate progression criteria in the management of prostate cancer patients on active surveillance is emphasised.

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