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# Surveillance and follow-up of early prostate cancer

MATS STEINHOLTZ AHLBERG



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### Abstract

Ahlberg, M. S. 2024. Surveillance and follow-up of early prostate cancer. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 2002. 88 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-1990-2.

Active surveillance (AS) for prostate cancer was introduced to address overtreatment resulting from prostate-specific antigen (PSA) testing. Despite advancements such as Magnetic Resonance Imaging (MRI) and targeted biopsies, PSA remains crucial in prostate cancer diagnostics, leading to ongoing challenges of overdiagnosis and overtreatment. This thesis aimed to investigate different aspects of AS and follow-up of early prostate cancer and provide new insights to reduce overtreatment and enhance surveillance and follow-up. In **Paper I**, the rationale and methodology of a randomized controlled trial, the Prostate Cancer Active Surveillance Trigger trial/Scandinavian Prostate Cancer Group study no. 17 (PCASTt/SPCG17), were outlined. This trial's objective is to evaluate the safety of an AS protocol based on MRI and standardized triggers for repeat biopsies and transition to radical treatment. Patient recruitment is anticipated to conclude in 2024. **Paper II** investigated the risks of biochemical recurrence, metastatic disease, and prostate cancer-related death in patients following radical prostatectomy. The analysis was conditioned on time after radical prostatectomy without biochemical recurrence. For patients with favourable histopathology in prostatectomy specimens and no biochemical recurrence five years post-prostatectomy, the probability of developing metastatic disease or dying from prostate cancer within 20 years after surgery was very low. This suggests shorter follow-up for selected patients. **Paper III** compared outcomes of AS for men from different healthcare regions in Sweden with varying traditions of AS. Regions with lower uptake in AS demonstrated a higher probability of transitioning from AS to radical treatment, but no difference in AS failure. The results suggest overtreatment in regions with low uptake in AS. **Paper IV** explored the associations between potential triggers for transitioning from AS to radical treatment and the transition to treatment. We analysed how this association changed with the introduction of prostate MRI. We found an increasingly strong association between triggers, particularly histopathological progression, and transition. However, most treated men had not experienced histopathological progression. The introduction of MRI did not contribute much to the change. **In conclusion**, this thesis outlines an ongoing study on defined triggers for transitioning from AS to radical treatment, suggests shorter follow-up after radical prostatectomy for selected patients, reveals overtreatment in regions with low uptake in AS, and shows an increasing use of histopathological progression as a trigger for transition to radical treatment.

**Keywords:** prostate cancer, active surveillance, follow-up, biochemical recurrence, triggers for transition to radical treatment, overdiagnosis, overtreatment.

*Mats Steinholtz Ahlberg, Department of Surgical Sciences, Urology, Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden.*

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*For every complex problem  
there is an answer that is clear,  
simple, and wrong.  
-H.L. Mencken*



# List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I. Mats Steinholtz Ahlberg, Hans-Olov Adami, Kerri Beckmann, Helena Bertilsson, Ola Bratt, Declan Cahill, Lars Egevad, Hans Garmo, Lars Holmberg, Eva Johansson, Antti Rannikko, Mieke Van Hemelrijck, Fredrik Jäderling, Cecilia Wassberg, Ulrika W N Åberg, Anna Bill-Axelsson. PCASTt/SPCG-17—a randomised trial of active surveillance in prostate cancer: rationale and design. *BMJ J Open* 2019 Aug 22;9(8):e027860. doi:10.1136/bmjopen-2018-027860. PMID: 31444180.
- II. Mats Steinholtz Ahlberg, Hans Garmo, Hans-Olov Adami, Ove Andrén, Jan-Erik Johansson, Gunnar Steineck, Lars Holmberg, Anna Bill-Axelsson. Time without PSA recurrence after radical prostatectomy as a predictor of future biochemical recurrence, metastatic disease and prostate cancer death: a prospective Scandinavian cohort study. *BMJ Open* 2022;12:e057242. doi:10.1136/bmjopen-2021-057242. PMID: 36581423.
- III. Mats Steinholtz Ahlberg, Hans Garmo, Lars Holmberg, Anna Bill-Axelsson. Variations in the Uptake of Active Surveillance for Prostate Cancer and Its Impact on Outcomes. *European Urology Open Science*, Volume 52, 2023, Pages 166-173, ISSN 2666-1683, <https://doi.org/10.1016/j.euros.2023.04.006>.
- IV. Mats Steinholtz Ahlberg, Hans Garmo, Pär Stattin, Rolf Gedeberg, Christer Edlund, Lars Holmberg, Anna Bill-Axelsson. Triggers for transition from active surveillance to radical treatment of prostate cancer 2008-2020 – a case control study. Submitted manuscript.

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# Abbreviations

ADT	Androgen deprivation therapy
ATC	Anatomic Therapeutic Chemical
BCR	Biochemical recurrence
CCI	Charlson comorbidity index
CT	Computed tomography
DCI	Drug comorbidity index
ISUP	International Society of Urological Pathology
MDCI	Multi-dimensional diagnosis based comorbidity index
MICE	Multiple imputation by chained equations
MRI	Magnetic resonance imaging
NPCR	the National Prostate Cancer Register of Sweden
OR	Odds ratio
PCASTt	Prostate Cancer Active Surveillance Trigger trial
PCBaSe	Prostate Cancer data Base Sweden
PET	Positron emission tomography
PI-RADS	Prostate Imaging-Reporting and Data System
PIVOT	Prostate cancer Intervention Versus Observation Trial
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
RCT	Randomized controlled trial
SCB	Statistiska centralbyrån (Statistics Sweden)
SoS	Socialstyrelsen (National Board of Health and Welfare)
SPCG	Scandinavian Prostate Cancer Group
TNM	Tumour Nodes Metastasis



# Introduction

## Incidence, prevalence, and mortality

The incidence of prostate cancer increased following the introduction of prostate-specific antigen (PSA) testing of asymptomatic men in the late 1980s.<sup>1</sup> In Sweden, low- and intermediate-risk cancers account for the majority of this increase, although there has been a slight decline in low-risk cases during recent years.<sup>2</sup> The increased incidence of low- and intermediate-risk prostate cancer, in combination with a longer life expectancy, has led to a dramatic rise in prostate cancer prevalence. As of 2021, close to 130.000 men in Sweden were living with a prostate cancer diagnosis.<sup>3</sup> Although many prostate cancers are indolent and will never cause harm, prostate-cancer is the leading cause of cancer-related death in men in Sweden accounting for approximately five percent of all deaths.<sup>4</sup> Median age of death from prostate cancer in Sweden is 82 years and for the past decade around 2400 deaths each year have been attributed to prostate cancer while the age-standardized mortality rate has experienced a slight decrease.<sup>4</sup> Globally prostate cancer is one of the most common causes of cancer deaths with regional variations.<sup>1</sup>

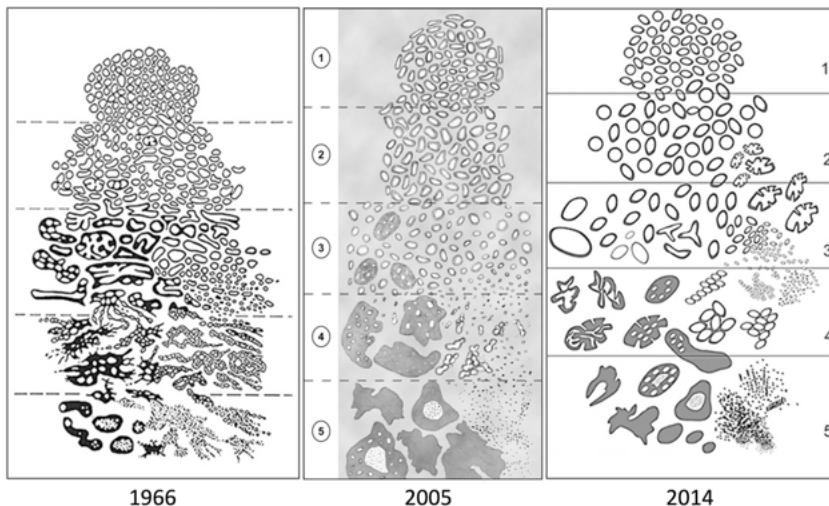
## Diagnosis

A pathological digital rectal exam or an elevated PSA is often the first step in diagnosing prostate cancer. Although PSA is the most frequently used biomarker for prostate cancer it falls short in differentiating between indolent tumours and those with a high risk of progression.<sup>5</sup> PSA levels can increase for various reasons aside from cancer, such as benign prostate hyperplasia (prostate enlargement), a common occurrence that often begins in middle age and continues into later years. To distinguish between prostate cancer and benign prostate hyperplasia as the reason for an elevated PSA, it is essential to consider the PSA value in relation to the prostate size, referred to as PSA density. Low PSA density indicates that the PSA value is normal in relation to the prostate size and the risk of 'clinically significant' prostate cancer is low. Conversely, a high PSA density indicates that the PSA value is high in relation to the prostate size and is more likely explained by a potentially more serious prostate cancer.<sup>6,7</sup>

Today, an elevated PSA or a high PSA density often leads to a magnetic resonance imaging (MRI) of the prostate. If the PSA density is elevated above a certain threshold, or if the MRI reveals lesions suspected to contain prostate cancer according to the Prostate Imaging-Reporting and Data System (PI-RADS) version 2, systematic and/or targeted biopsies from the prostate are recommended.<sup>4,8–12</sup> Briefly, PI-RADS utilizes a 5-point Likert scale, where PI-RADS 1 and 2 are not deemed indicative of prostate cancer, PI-RADS 3 is equivocal, while PI-RADS 4 and 5 are strongly indicative of prostate cancer.<sup>12</sup> MRI followed by targeted biopsies of PI-RADS 3 to 5 lesions detects more intermediate- and high-risk prostate cancers and misses more tumours considered clinically insignificant than do systematic biopsies.<sup>13,14</sup> This approach has been established as the preferred method of further investigation of an elevated PSA, PSA density or pathological digital rectal exam, although additional systematic biopsies are still recommended in certain situations.<sup>4,8–11</sup>

## Grading

The microscopic appearance of cancer tissue forms the cancer grade, and for prostate cancer it is based on the Gleason score.<sup>15</sup> The Gleason grading system is graded from Gleason grade 3 to 5. In biopsies, the Gleason grade of the dominant morphology and the non-dominant morphology with the highest grade are added to form a Gleason score between 6 and 10.<sup>16</sup> In 2005 and 2014, the International Society of Urological Pathology (ISUP) conferences redefined certain Gleason patterns from 3 to 4 (Figure 1).<sup>17,18</sup>



**Figure 1.** Left is Gleason's original drawing from 1966, in the middle is the illustration of the modified version from 2005, and to the right is the 2014 revision illustrated. Reproduced with permission. DOI: 10.1097/01.pas.0000173646.99337.b1; DOI: 10.1097/PAS.0000000000000530

Further, in the ISUP 05 document, calculation of the Gleason score changed from combining the dominant and the second most dominant morphology, to today's dominant morphology and the non-dominant morphology with the highest grade.<sup>17</sup> These redefinitions resulted in many cancers previously classified as Gleason score 3+3=6 changing to Gleason score 3+4=7.<sup>19</sup> In 2014, Gleason score was also translated into a new grading system, Gleason Grade Groups/ISUP-grade, with grades 1 to 5 (Table 1).<sup>18</sup> The predictive value of Gleason score in biopsies originates from systematic biopsies. When grading prostate cancer based on targeted biopsies, or targeted biopsies in combination with systematic biopsies, new challenges arise in definitions of Gleason scores and their predictive value for long-term outcomes.

When discussing long-term outcomes of early prostate cancer, it is crucial to consider a 10-, 15-, or even 20-year time horizon due to the disease's slow progression. Therefore, studies with extensive follow-up that deliver data today include men from before the ISUP redefinitions in 2005 and 2014, and before the era of targeted biopsies.<sup>20-22</sup> Consequently, men classified as having low- and favourable-risk prostate cancer in studies from before the ISUP revisions are not fully comparable to men classified as having low- and favourable-risk prostate cancer diagnosed after the revisions. The earlier diagnosed men with identical Gleason scores represent a less favourable histopathological group.

After surgical removal of the prostate, the histopathological analysis reveals a pathological Gleason score that might differ from the Gleason score in biopsies. The Gleason score after prostatectomy is defined as the sum of the most common and the second most common Gleason pattern.<sup>16</sup> If an increase in Gleason score is revealed after surgery, it is referred to as upgrading, while a decrease is referred to as downgrading.

**Table 1.** Gleason score with corresponding ISUP grade and risk category. For risk group categorization, prostate-specific antigen (PSA) value, PSA density, and clinical T stage are required in addition to the histopathological grading.

Gleason score	ISUP grade	Histopathological risk category
<b>3+3=6</b>	1	Low/Very low
<b>3+4=7</b>	2	Favourable intermediate
<b>4+3=7</b>	3	Unfavourable intermediate
<b>4+4 (and 3+5) = 8</b>	4	High
<b>≥4+5=9</b>	5	High/Very high

ISUP = International Society of Urological Pathology

Another issue concerning histopathological grading involves the interindividual variation in Gleason grading among pathologists, which brings uncertainty into tumour grading.<sup>23</sup> Furthermore, although Gleason 3 morphology patterns exhibit typical histopathological cancer characteristics, it appears that Gleason score 6 tumours may not have the ability to metastasize and could potentially be considered a precancerous lesion rather than true cancer.<sup>24-26</sup>

## Staging

The staging of prostate cancer adheres to the TNM (Tumour Nodes Metastasis) classification system with higher grade representing more advanced tumours.<sup>27</sup> There is a distinction between clinical T stage (cT) and pathological T stage (pT). The cT stage refers to the stage at diagnosis traditionally determined by digital rectal examination before histopathological analysis of the whole gland, today also influenced by radiology (mainly prostate MRI). The pT stage is based on the histopathological analysis following surgical removal of the prostate. The cT stage can be classified as cT1-4, while pT stage is classified as pT2-4. Tumours can be up or down staged after surgery if the pT stage differs from the cT stage.<sup>16,28</sup>

The clinical tumour stage is classified as cT1 (incidentally detected, organ confined), cT2 (palpable, organ confined), cT3 (palpable, growing through the prostate pseudocapsule) or cT4 (palpable, overgrowth on surrounding organs) with additional subcategories.<sup>4</sup> For cT1a and cT1b, tumours are non-palpable, organ confined, and detected by histopathological examination of prostate tissue from transurethral resection of the prostate. A tumour classified as cT1c signifies that the tumour is non-palpable, organ confined, and identified via PSA testing followed by biopsies. A cT2a tumour is an organ-confined tumour palpable in half of one lobe of the prostate; a cT2b tumour is palpable in one entire lobe, while a cT2c tumour is palpable in both prostate lobes. A tumour classified as cT3a is growing through the prostate capsule but not into the seminal vesicles, while a cT3b tumour is growing into the seminal vesicles. A cT4 tumour is invading surrounding organs.

Prostate MRI can aid in staging the primary tumour, particularly cT3 tumours in the prostate's ventral regions that are impalpable, and cT3b tumours invading the seminal vesicles.<sup>12</sup> However, it is not advised to reclassify a cT1 tumour to cT2 based on imaging.<sup>4</sup> The extent of spread to regional lymph nodes (N) and distant metastasis (M) can be evaluated using various imaging techniques, such as computed tomography (CT), MRI, bone scintigraphy and positron emission tomography (PET). PET, particularly prostate-specific membrane antigen (PSMA)-PET, demonstrates higher sensitivity and can detect small metastases that are undetectable using other imaging methods.<sup>29</sup> In studies with long-term follow-up and assessment of progression to metastatic disease, CT and bone scintigraphy were the most employed methods.<sup>20-22</sup>

As a parallel to the discussion on grading prior to the ISUP revisions, men in studies where metastases were detected with less sensitive techniques are not fully comparable to men diagnosed with PSMA-PET. The earlier group rather represents a group of men with a higher probability of having undetected advanced disease, which is essential to remember when interpreting outcomes of studies.

## Risk groups

Based on PSA level, PSA density, Gleason score/ISUP grade, quantity of cancer in biopsies, and TNM classification, tumours can be divided into categories reflecting their risk of progression. A commonly used risk group classification is the National Comprehensive Cancer Network (NCCN) classification system: very low risk, low risk, favourable intermediate risk, unfavourable intermediate risk, high risk, and very high risk (Table 2).<sup>11,30</sup>

**Table 2.** Risk group categorization according to National Comprehensive Cancer Network (NCCN) Guidelines Version 4.2023.

Risk Group	Clinical/pathological features		
Very low	All of the following features: <ul style="list-style-type: none"> <li>• cT1c</li> <li>• ISUP grade 1</li> <li>• PSA &lt; 10 ng/mL</li> <li>• &lt;3 biopsy cores with cancer, ≤50% cancer in each core</li> <li>• PSA density &lt;0.15ng/mL<sup>2</sup></li> </ul>		
Low	All of the following features but not qualified for very low risk: <ul style="list-style-type: none"> <li>• cT1-cT2a</li> <li>• ISUP grade 1</li> <li>• PSA &lt; 10 ng/mL</li> </ul>		
Intermediate	All of the following: <ul style="list-style-type: none"> <li>• No high-risk/very high-risk features</li> <li>• One or more of the following intermediate risk features:               <ol style="list-style-type: none"> <li>1. cT2b-cT2c</li> <li>2. ISUP grade 2 or 3</li> <li>3. PSA 10-20 ng/mL</li> </ol> </li> </ul>	Favourable intermediate	All of the following: <ul style="list-style-type: none"> <li>• 1 intermediate risk feature</li> <li>• ISUP grade 1 or 2</li> <li>• &lt; 50% biopsy cores positive</li> </ul>
		Unfavourable intermediate	One or more of the following: <ul style="list-style-type: none"> <li>• 2 or 3 intermediate risk features</li> <li>• ISUP grade 3</li> <li>• ≥50% biopsy cores positive</li> </ul>
High	No very-high risk features and one high-risk feature: <ul style="list-style-type: none"> <li>• cT3a OR</li> <li>• ISUP grade 4 or 5 OR</li> <li>• PSA &gt;20 ng/mL</li> </ul>		
Very high	At least one of the following: <ul style="list-style-type: none"> <li>• cT3b-cT4</li> <li>• Primary Gleason pattern 5</li> <li>• 2 or 3 high risk features</li> <li>• &gt;4 cores with ISUP grade 4 or 5</li> </ul>		

cT = clinical T stage, PSA = prostate-specific antigen, ISUP = International Society of Urological Pathology

Additionally, more advanced prostate cancer can be categorized as regionally metastatic, oligometastatic (≤4 metastases), distant metastatic, castration sensitive and castration resistant in various combinations based on TNM classification and the response to castration treatment.<sup>4,8–11</sup>

## Overdiagnosis and overtreatment

Many prostate cancers are indolent, allowing men to live with them for a long time, often for the rest of their lives, without experiencing symptoms or progression. The prevalence of prostate cancer increases with age, and autopsy studies have revealed that approximately 60% of men over 80 years have prostate cancer, of which around one third are classified as ISUP Grade Group  $\geq 2$ .<sup>31</sup> The definition of what is a ‘clinically significant’ prostate cancer has evolved over the years, and today Grade Group 2 prostate cancer is in many research studies considered to be clinically significant.<sup>32,33</sup> PSA testing of asymptomatic men increases the incidence of detected prostate cancers, of which many are indolent and will never cause symptoms, a phenomenon referred to as overdiagnosis.<sup>34–36</sup> A corollary of overdiagnosis is that some men will receive unnecessary treatment for their prostate cancer, referred to as overtreatment.<sup>36</sup> The anxiety of bearing a cancer diagnosis and uncertainties about whether the cancer is progressing may be difficult for the patient.<sup>37,38</sup> Besides the mental burden of a cancer diagnosis, side effects from diagnostic procedures and prostate cancer treatment demonstrate that the problem of overdiagnosis and overtreatment needs to be addressed. Some of the main arguments against population-based prostate cancer screening with PSA are overdiagnosis and overtreatment.<sup>39,40</sup> Considerable efforts have been made to reduce overdiagnosis, including using age-standardized PSA levels, PSA density, prostate MRI, and targeted biopsies.<sup>7,13,14,41</sup> Despite this, approximately one fifth of diagnosed prostate cancers in Sweden are low risk.<sup>2</sup> Active surveillance (AS) of low-risk prostate cancer is recommended to reduce overtreatment, but over the past 10 years, approximately 20% of men with low-risk prostate cancers were treated with curative intent as the primary treatment in Sweden.<sup>42</sup>

## Screening

Population-based screening for cancer remains a controversial topic.<sup>43</sup> Three key screening trials based on PSA testing, with long-term follow-up, have shown varied outcomes.<sup>44–46</sup> While two failed to show any statistically significant reduction in prostate cancer mortality during the 10 and 13 years of follow-up, the large European Randomized Study of Screening for Prostate Cancer (ERSPC) trial found a reduction in prostate cancer mortality, but not in overall mortality after 16 years of follow-up.<sup>44</sup> The most optimistic result, in favour of screening, comes from the Gothenburg 1 trial, which is a branch of the ERSPC.<sup>47</sup> After 22 years of follow-up, the relative mortality reduction in the screened arm was 29%, and, when taking competing risk into account, the absolute mortality reduction was 0.5%. Even though there is a prostate cancer-specific survival benefit of screening, the benefits have not been considered



to outweigh the disadvantages of overdiagnosis and overtreatment, and population-based screening is not yet recommended.

With improved diagnostic methods and increased use of AS this might change, and several ongoing studies are evaluating different screening methods, but long-term results on the efficacy of population-based screening are still lacking.<sup>48–50</sup> The European Union Council has recommended improvement of early detection of prostate cancer and encourages member countries to start pilot programmes for prostate cancer screening.<sup>51</sup> In several regions in Sweden, a pilot programme is already in place with the population-based organized prostate cancer testing programme (OPT).<sup>52,53</sup>

Deciding whether avoiding a modest number of prostate cancer deaths outweighs the long-term suffering of many, and determining the appropriate balance between benefit and harm, may be more of an ethical, philosophical, and health policy debate than an epidemiological issue.<sup>54</sup> What we do know is that we live in a world with finite resources and that we cannot possibly cater to everyone's needs. For this reason, it is essential to maintain an open discourse on the advantages and disadvantages of screening.

## Treatment

Radical treatment with curative intent for localized prostate cancer includes radical prostatectomy and radiotherapy. Disease-specific survival after radical treatment varies with stage. For localized prostate cancer, the 10-year relative survival is close to 100%.<sup>55–57</sup> For locally advanced (cT3) and regionally metastasized disease, the 10-year relative survival is around 95%, but for men with distant metastases, the relative 5- and 10-year survival is around 30% and 20% respectively.<sup>56,57</sup> Due to the slow progression of intermediate-risk prostate cancer, a life expectancy of 10 to 15 years is recommended to benefit from radical treatment. For high-risk disease, a life expectancy of five to 10 years is recommended.<sup>4,8–11</sup>

### Radical prostatectomy

Radical prostatectomy can be performed as open retropubic, laparoscopic or robot-assisted laparoscopic. In Sweden today, over 95% of procedures are performed with robot-assisted technique.<sup>42</sup> Oncological results are similar between the different surgical techniques, but laparoscopic techniques show the benefits of minimally invasive techniques, including less blood loss, shorter hospital admission and less postoperative pain.<sup>58–60</sup> The disadvantages of radical prostatectomy are the risks of bothersome side effects, mainly incontinence and impotence, decreasing quality of life. The risk of these side effects varies greatly depending on definitions and patient selection. Generally, older

men with more comorbidities have a higher risk of both incontinence and impotence.<sup>61</sup> Overall, roughly 10-20% will have long-term incontinence after surgery, while approximately 70% will have persistent impotence. Studies have shown that there probably are favourable functional results after robot-assisted laparoscopic surgery compared with open surgery, but the results are conflicting, and the differences small.<sup>58-60,62</sup>

Surgery is recommended for localized disease (cT1-cT2), but not as first-hand treatment for cT3 tumours due to the risk of positive surgical margins.<sup>4</sup> An ongoing randomized controlled trial (RCT) is comparing surgery vs. radiotherapy for cT3 tumours, but awaiting further evidence, radiotherapy is the treatment of choice.<sup>63</sup> Younger men (<60 years) are often recommended surgery in favour of radiotherapy due to better functional outcomes in younger men and the risk of late side effects of radiotherapy arising many years after treatment.<sup>61,64</sup>

## Radiotherapy

Oncological outcomes after radiotherapy and surgery are similar.<sup>21</sup> Radiotherapy is often the preferred treatment for cT3 tumours, men with obesity, advanced comorbidity and in older men (>70 years).<sup>4</sup> However, radiotherapy is less suitable for patients with inflammatory bowel disease, anorectal diseases, a history of previous radiotherapy in the same region, prostate hyperplasia, or bothersome lower urinary tract symptoms, due to associated side effects. Various forms of radiotherapy are employed, including differently fractionated external radiotherapy and brachytherapy.<sup>4</sup> For high-risk tumours, neo-adjuvant and adjuvant hormonal therapy is often recommended to improve oncological outcomes.<sup>4,8-11</sup> The occurrence of side effects is contingent on factors such as radiotherapy technique, radiation field, baseline symptoms, and patient selection. The side effects include urinary symptoms such as urgency and frequency, bowel changes including urgency, frequency, and blood in the stool. Long-term side effects may involve urethral stricture, impotence, bleeding from the bladder and rectum, and secondary malignancies.<sup>64</sup>

## Watchful waiting

Watchful waiting is a strategy of deferred treatment without curative intent. In this approach, follow-up is less intense compared to AS. Treatment is initiated primarily in response to symptoms or a PSA increase signalling locally advanced or metastatic disease. Guidelines recommend watchful waiting for men with low- and intermediate-risk prostate cancer and a life expectancy of less than 10 years, as radical treatment may not provide substantial benefits.<sup>4,8-</sup>

<sup>11</sup> For high-risk disease, a life expectancy of at least more than five years is recommended to benefit from radical treatment.

## Hormone therapy

Metastatic prostate cancer is generally not considered curable. For men needing disease-specific treatment, but where curation, for some reason, is not desirable or possible, androgen deprivation therapy (ADT) and chemotherapy are the most common therapies. ADT includes gonadotropin releasing hormone (GnRH) agonists and antagonists, antiandrogens, androgen synthesis inhibitors and surgical castration. There are several lines of hormonal treatment, and combinations of hormonal treatment and chemotherapy, and during the past 10 years, substantial advances in treatment of metastatic prostate cancer have been made, postponing time to prostate cancer death for metastasized men.<sup>65,66</sup>

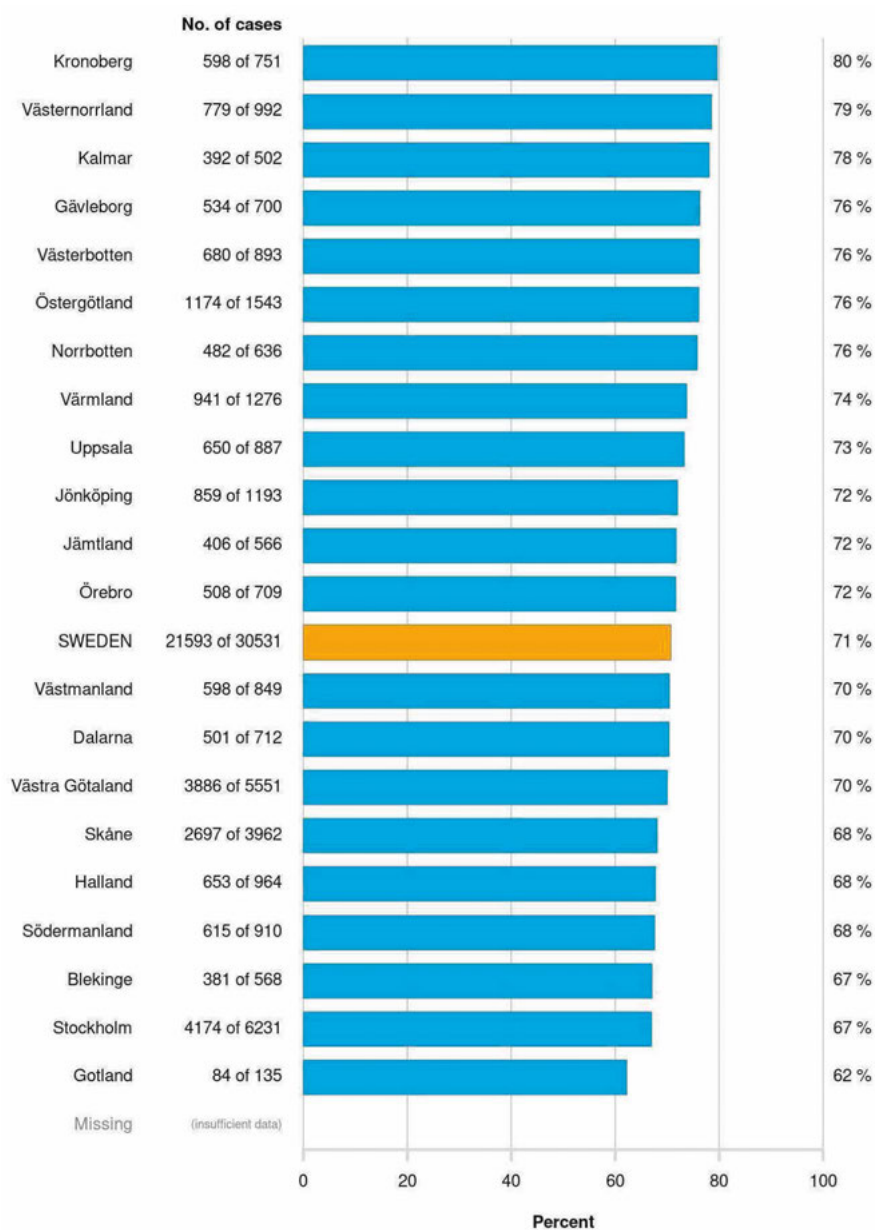
# Active surveillance

## What is active surveillance?

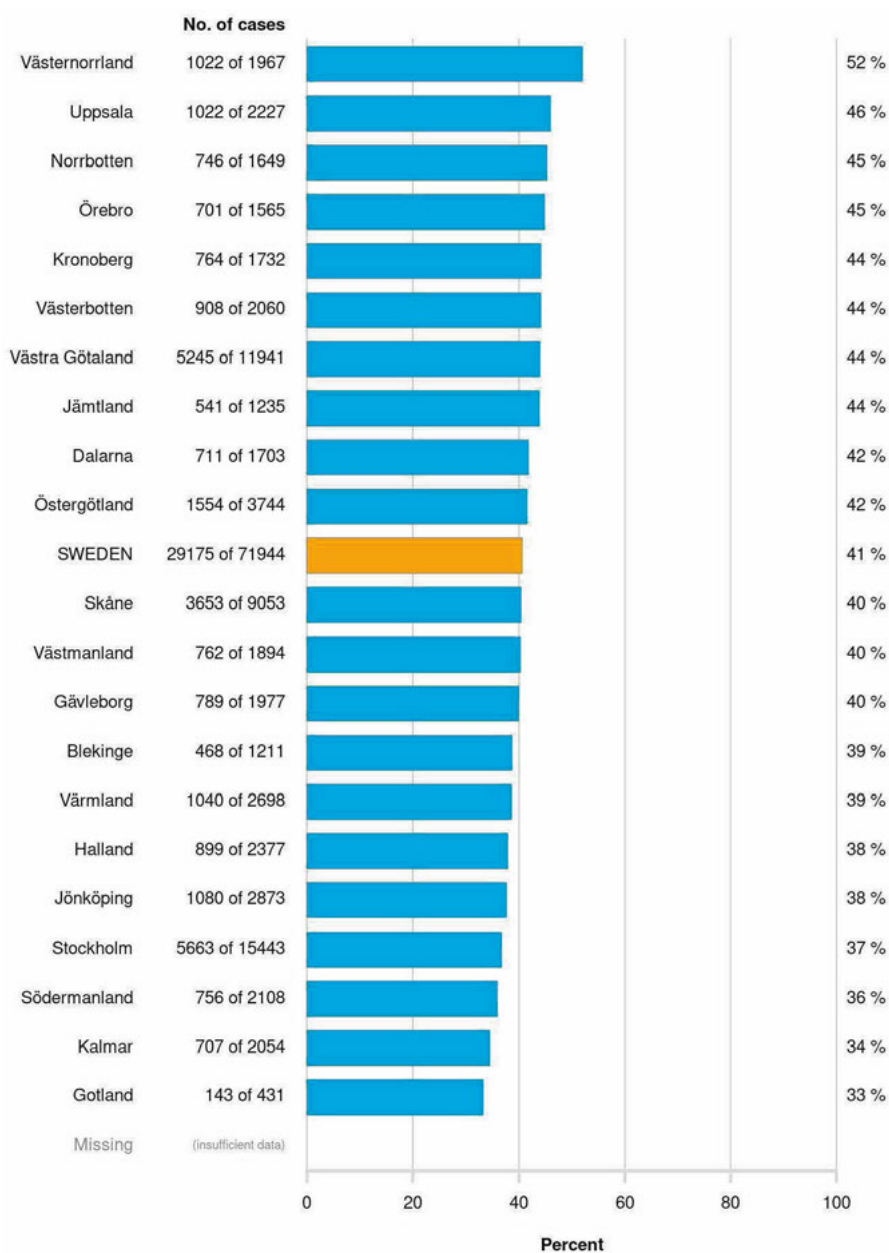
Active surveillance (AS) was introduced during the 1990s to reduce the over-treatment of prostate cancer that followed the introduction of PSA testing.<sup>67</sup> Active surveillance implies monitoring prostate cancer patients with the intention to initiate radical treatment if the tumour shows signs of progression and the patient is deemed likely to benefit from the treatment. For men with low-risk prostate cancer, AS is the first-hand treatment option to avoid over-treatment, and some men with favourable intermediate-risk disease are also often recommended AS.<sup>4,8–11</sup> Due to the low risk of disease progression for men with low- and intermediate-risk disease within 10 years, a life expectancy of at least 10 years is recommended for this strategy. Long-term survival probabilities are similar with immediate radical treatment.<sup>21,22</sup>

Active surveillance has been adopted very differently in the western world.<sup>68,69</sup> The proportion of Swedish men with low-risk prostate cancer who were managed by AS in 2020-2022 was approximately 85% but varied between 67% and 94% in different regions.<sup>42</sup> The regional differences in uptake of AS in Sweden indicate unequal healthcare depending on where you live (Figure 2 and Figure 3).

Repeated biopsies of the prostate have been, and still are, a fundamental part of AS.<sup>4,8–11</sup> Apart from discomfort, bleeding, and lower urinary tract symptoms, infection is a non-negligible risk.<sup>70,71</sup> In Sweden as well as in many other countries, the risk of infections with multiresistant bacteria is increasing.<sup>72,73</sup> Transrectal povidone-iodine swabs and a transperineal biopsy approach may reduce the infection risk after prostate biopsy and are recommended, but the best way to reduce the risk of infection is of course to avoid biopsies when possible.<sup>74–76</sup>



**Figure 2.** Proportion of men, up to 78 years of age, with low-risk prostate cancer given active surveillance as primary treatment. Illustrated by healthcare region in Sweden, 2010-2022. Source: <https://statistik.incanet.se/npcr/>. Reproduced with permission.



**Figure 3.** Proportion of men, up to 78 years of age, with low- and intermediate-risk prostate cancer given active surveillance as primary treatment. Illustrated by healthcare region in Sweden, 2010-2022. Source: <https://statistik.incanet.se/npcr/>. Reproduced with permission.

## Safety of active surveillance

One randomized trial compared active monitoring (similar to AS) with immediate radical treatment.<sup>21,55,77</sup> After 15 years of follow-up, around 60% of the active monitoring patients had undergone radical treatment, and there was great similarity in overall and prostate-cancer-specific survival between the treatment groups and the monitoring group. In the monitoring group, however, there were more men who developed metastases than in the treatment groups. Around 20% of the included men had intermediate- or high-risk prostate cancer, and the active monitoring protocol in the study represents a mixed approach between watchful waiting and AS based almost only on PSA testing, which is not representative of contemporary AS protocols. In a well-known long-term follow-up of a single arm cohort study of AS in almost 1000 low- and intermediate-risk patients, 1.5% died from prostate cancer and another 1.3% developed metastases within 15 years of follow-up, while 55% remained untreated after 15 years.<sup>22</sup> These risks are in line with the expected risks after radical treatment and also with other contemporary AS cohorts with shorter follow-up.<sup>78,79</sup>

Two randomized trials compared radical prostatectomy for localized prostate cancer with watchful waiting. In the American Prostate cancer Intervention Versus Observation Trial (PIVOT), involving men with localized disease primarily detected through PSA testing, there was no statistically significant survival benefit in the treatment group after 12 years.<sup>80</sup> After median follow-up of 19 years, there was a statistically significant association with a small all-cause mortality reduction after surgery in men with intermediate-risk prostate cancer.<sup>81</sup> In the Scandinavian Prostate Cancer Group study no. 4 (SPCG4) of clinically detected localized prostate cancers, there was a statistically significant prostate cancer-specific mortality reduction in the treatment group but no statistically significant overall mortality reduction, after eight years.<sup>82</sup> From 10 years of follow-up and after, a statistically significant overall mortality reduction was seen in the treatment group.<sup>20,83–86</sup> In subgroup analyses of low-risk prostate cancers, and men  $\geq 65$  years of age, there were no statistically significant risk reduction of death from prostate cancer in long term follow-up.<sup>86</sup> These trials were conducted without MRI and targeted biopsies, and before the ISUP revisions in 2005 and 2014, but they nevertheless demonstrate the safety of deferred treatment in men with favourable-risk prostate cancer.

## Who is eligible for active surveillance?

There is no unanimous, evidence-based definition of which men should be recommended AS as a first-hand option. Contemporary AS protocols, guidelines and consensus documents agree that AS is the first-hand option for low-risk prostate cancer, while most also include intermediate-risk disease to some extent.<sup>4,8–11,87,88</sup> Intermediate-risk cancers on AS have a higher risk of

progression to metastatic disease and prostate cancer death compared to low-risk cancers.<sup>89</sup> The diagnostic work-up before AS traditionally included two sessions of systematic biopsies, covering both the peripheral zone and the transition zone of the prostate. Evidence shows that MRI and targeted biopsies before starting AS not only detect more, what are considered to be, ‘clinically significant’ prostate cancers and miss more ‘clinically insignificant’ cancers, but also reduce the number of men who progress in grade during the first years of AS.<sup>13,14,90</sup> At present, a combination of systematic and targeted biopsies is the general recommendation before starting AS.<sup>4,8–11</sup> With the addition of MRI and targeted biopsies of suspected lesions before inclusion in AS, it is reasonable to believe that the long-term oncological results of AS are even better than before (without MRI) and that the AS concept could be broadened to include more intermediate-risk prostate cancers without increased risk of morbidity and mortality due to prostate cancer.

### How should we surveil?

The scarcity of evidence regarding which men to include in AS carries over to the question of how to effectively monitor them during AS. Moreover, adherence to follow-up protocols decreases over time.<sup>91,92</sup> Traditionally, AS protocols included repeated digital rectal exam of the prostate, PSA testing and systematic biopsies. Guidelines today also include repeated MRI with targeted biopsies towards suspected lesions during follow-up.<sup>4,8–11</sup> Biopsies may sometimes be omitted without increased risk of disease progression when utilizing MRI during AS.<sup>93,94</sup> MRI with subsequent targeted biopsies during AS increase detection of Gleason score  $\geq 7$  tumours.<sup>95</sup> Some argue that confirmatory systematic biopsies after one year in AS detect an important number of Gleason score  $\geq 7$  tumours missed by MRI and targeted biopsies alone.<sup>96</sup>

Even though studies indicate benefits of MRI during AS, there are uncertainties, including whether repeated biopsies are necessary when MRI is unchanged and PSA is stable as well as how to combine repeated digital rectal exam, MRI, PSA tests, and biopsies. Further, the long-term benefits of MRI during AS and how it will affect the probability of transition from AS to radical treatment, progression to metastatic disease and prostate cancer death is not known. Active surveillance without MRI and targeted biopsies shows excellent results with low probability of metastatic disease and prostate cancer death, and the room for improvements in these outcomes is small.<sup>21,22</sup> Additionally, some evidence points to increased risk of transition from AS to radical treatment when MRI is added in the algorithm, reasonably due to increased upgrading in targeted biopsies, and there is a concern about increased over-treatment when using MRI in AS.<sup>97,98</sup>

When a patient in AS is no longer considered to benefit from radical treatment, transition to watchful waiting should be discussed. As men with low- or



intermediate-risk prostate cancer are not normally considered to benefit from radical treatment when their life expectancy drops below 10 years, that is the time when the transition to watchful waiting is recommended.<sup>4</sup>

### Triggers for intervention

Around 40% of men transition from AS to radical treatment within five years.<sup>99–101</sup> The differences between regions and countries are substantial and the 5-year treatment-free survival ranges from 48% to 86% in different studies depending on criteria for inclusion in AS, if confirmatory biopsies are mandatory or not, follow-up protocols, and triggers for treatment.<sup>22,100,102–108</sup> The reason for transitioning to treatment varies between cohorts, but most common is clinical, pathological or PSA progression.<sup>99,101,109</sup> Another important reason is anxiety and patient's and/or doctor's preferences, without evidence of progression.<sup>78,99,101</sup>

The appropriate timing and reasons for repeating biopsies and initiating radical treatment remain unclear. Progression on MRI, PSA increase, and progression on digital rectal exam should preferably be followed by a biopsy confirming histopathological progression before transitioning to radical treatment.<sup>88</sup> However, in certain situations, rising PSA and MRI progression alone may be sufficient grounds for recommending radical treatment. Histopathological progression in repeated biopsies serves as the most objective indicator of disease progression and is deemed a reliable basis for transitioning to radical treatment. Furthermore, factors such as anxiety, patient preferences, and challenges in thorough follow-up also contribute to the decision for radical treatment.<sup>88</sup>

# Follow-up after radical prostatectomy

## Why and how to follow-up

PSA is very sensitive for detection of recurrent prostate cancer.<sup>110</sup> Regular PSA testing after radical prostatectomy is the standard follow-up and aims to detect biochemical recurrence (BCR) in order to consider salvage therapies with a curative or palliative intent. The recommended follow-up time after radical prostatectomy is at least 10 years, independent of tumour characteristics.<sup>4,8–11</sup>

## Biochemical and clinical recurrence

Several definitions of BCR after radical prostatectomy have been proposed and investigated over the years.<sup>111–114</sup> American Urological Association (AUA) propose a PSA value  $\geq 0.2$  ng/mL followed by a second rising PSA as the definition of BCR and the European Association of Urology (EAU) recommend imaging for detection of metastases when PSA reaches and remains  $>0.2$  ng/mL.<sup>9,10</sup> Others have proposed lower limits, as early ADT or salvage radiotherapy may increase treatment efficacy, especially when there are unfavourable histopathological features.<sup>115,116</sup> Still others have proposed single higher values of 0.4 ng/mL and 0.6 ng/mL, as many men will not progress further after one or two slightly elevated values, and those thresholds seem to better predict further metastatic disease.<sup>111–114</sup> Biochemical recurrence is a poor proxy for clinical progression, and overly inclusive criteria for BCR could lead to salvage therapy overtreatment.<sup>117</sup>

Depending on tumour stage and grade, definition, and follow-up time, approximately 25–50% of men develop BCR within 10 years after radical prostatectomy, the majority of which occurs within the first three years.<sup>118,119</sup> After a BCR around one third of men develop metastases after a median time of eight years and around 16% die from prostate cancer after a median time of 13 years.<sup>119–121</sup> As the mean age at the time of radical prostatectomy is approximately 65 years in Sweden, if a man develops BCR and later is at risk of dying from prostate cancer, he will probably be old and have many competing risks for death, making the risk of dying from prostate cancer similar to the risk of dying from other causes.<sup>42,121–123</sup>

## Risk factors for biochemical and clinical recurrence

After radical prostatectomy, preoperative PSA, positive surgical margins, high Gleason score from prostatectomy specimen, and high pathological T stage are independently associated with BCR.<sup>124</sup> After identifying a BCR, high Gleason score from prostatectomy specimens and short PSA doubling time are associated with clinical progression and prostate cancer death, while other variables such as surgical margins, pT stage, time from radical prostatectomy to BCR, initial PSA, and Gleason score from prostate biopsy have been investigated but are not as strongly associated with oncological outcomes.<sup>119,121–123,125–127</sup>

## How to handle a biochemical recurrence

There are uncertainties about when to initiate complementary treatment after BCR. Salvage radiotherapy after BCR is an established method that may offer an enduring PSA response and reduced mortality.<sup>128</sup> Salvage radiotherapy is prone with bothersome side effects, primarily from the lower urinary tract, and these problems might worsen over time.<sup>129</sup> The optimal time for salvage radiotherapy is not known, but early treatment is probably favourable for men with unfavourable histopathology (high Gleason score, positive surgical margins, higher pT stage), long life expectancy, and early recurrence.<sup>116,130</sup> For men with longer time to BCR, slow PSA doubling time and favourable histopathology, the benefits of salvage radiotherapy may not overcome the harms.

The timing of androgen deprivation therapy after BCR has been debated. Several studies have failed to show survival benefits for subgroups of men other than those with high-risk disease and early BCR.<sup>131–133</sup> More recent data are contradictory. Some have shown survival benefits after early ADT, while others conclude that early ADT for BCR should primarily be utilized for men with a long life expectancy, adverse histopathology and short PSA doubling time.<sup>115,134</sup> Moreover, long-term hormonal therapy has disadvantages, such as increased risk of cardiovascular morbidity and mortality, and osteoporosis, which can reduce both life expectancy and quality of life.<sup>135</sup>

# Life expectancy

## What is life expectancy?

Life expectancy is an estimation of the mean time a member of a specific cohort is expected to remain alive. The cohort can be defined by sex, country, year of birth, and several other demographic or health-related factors. Life expectancy at birth is heavily influenced by childhood mortality, and it is common to report life expectancy at different ages, given that one has survived to a certain age. However, life expectancy does not consider individual factors and is not particularly informative for individuals with unhealthy or risk-taking lifestyles. Typically presented in life tables, life expectancy is calculated based on age-specific mortality rates: the number of people in a specified age group who die during a specified time period divided by the total person-years of that age group during that time period. For instance, the life expectancy for 77-year-old men in Sweden between 2011-2020 was 10.06 years.<sup>136</sup>

## Implication for prostate cancer

In international guidelines, radical treatment is recommended for intermediate-risk prostate cancer patients with a life expectancy exceeding 10-15 years.<sup>4,8-11</sup> This is based on the low risk of morbidity and mortality from untreated intermediate-risk prostate cancer within that timeframe.<sup>137</sup> To benefit from radical treatment, a man with intermediate-risk prostate cancer must avoid death from competing risks during this period. Clinicians' life expectancy estimations are subjective and often inaccurate, leading to overestimation in those with short remaining lifetimes and underestimation in those with longer life expectancies.<sup>138</sup> Recommending radical treatment, AS, and watchful waiting involves estimating life expectancy, considering age, comorbidities, socioeconomic status, social context, hereditary factors, and other risk factors, and it is important to try to narrow down the range of the estimation to avoid both over- and under-treatment. While statistical methods exist, their reliability compared to freely available life tables is unclear.<sup>139</sup>

## Charlson Comorbidity Index

In 1987, Charlson proposed an index for classifying comorbidities that might change the mortality risk.<sup>140</sup> The Charlson Comorbidity Index (CCI) considers age and several medical conditions and provides a score associated with increased risk of death. The different conditions contribute to the score according to their 1-year risk ratio of death. The index was developed empirically based on the 1-year mortality of 604 internal medicine patients admitted to a hospital in New York in 1984 and validated by its ability to predict 10-year survival in a cohort of 588 breast cancer patients. Already in the original publication, Charlson acknowledged the limitations of the index due to the relatively small size of the cohort, with few patients suffering from the contributing conditions, and stated that the method should be viewed as preliminary. Despite these limitations and the fact that the index was developed in a cohort of hospitalized medical patients almost 40 years ago, it is still widely used in studies, and to some extent to assess the mortality risk in outpatient cancer patients today, not considering advances in medicine.

## DCI and MDCI

There are concerns that CCI is not good enough at discriminating patients with few comorbidities. In the CCI validation cohort, 86% of patients had a comorbidity index score of zero.<sup>140</sup> Moreover, in the earlier-mentioned PIVOT trial, criticized for its high 10-year mortality from other causes than prostate cancer, the majority of patients had a CCI score of zero.<sup>80</sup> To improve life expectancy estimations, Gedeberg et al. developed and validated a Drug Comorbidity Index (DCI) based on the Swedish Prescribed Drug Register.<sup>141</sup> They showed a better prediction of survival in two large populations in Sweden with 11 years of follow-up when combining DCI, CCI and age, compared with CCI and age alone. The DCI, in contrast to other prediction models from pharmacological data, does not rely on drugs prescribed for specific conditions.<sup>142,143</sup> Instead it utilizes the Anatomical Therapeutic Chemical (ATC) codes of 106 drugs available in the Swedish Prescribed Drug Register, accessible through computerized medical charts, and weighted according to their association with survival probability. For example, the prescription of several vitamins was strongly associated with mortality not due to its association with any specific comorbidities, but rather as an indication of bad nutritional status due to a general frailty.<sup>141</sup> Garmo et al. has shown that simulated and observed life expectancy, based on changes in CCI, DCI and age, were similar in a cohort of Swedish males with up to 11 years of follow-up.<sup>144</sup> This model provides a statistical approach to estimate life expectancy based on information available in national healthcare registers of prescribed drugs and medical diagnoses.

To further improve mortality prediction in register-based studies, Westerberg et al. developed and validated a multidimensional diagnosis-based comorbidity index (MDCI).<sup>145</sup> Based on all ICD-10 codes (International statistical Classification of Diseases and health-related problems) in the National Patient Register, frequency of code occurrence, recency, and duration of related hospital admissions were used to create a model that predicts the risk of death within 10 years. The validation indicated that MDCI clearly outperformed CCI as a prediction model for death for men with and without prostate cancer, and when replacing CCI with MDCI, the life expectancy prediction model performed even better and might be used in register-based studies.<sup>145</sup>

# Aims of the studies

## Overall aim

Overtreatment for prostate cancer is a problem regarding immediate radical treatment, transition from AS to radical treatment, and for treating BCR after prostatectomy. The overall aim of this thesis was to study different aspects of AS and follow-up after radical prostatectomy in early prostate cancer to provide evidence for how to reduce overtreatment and improve surveillance and follow-up without increased risk of morbidity and mortality.

## Aim – Paper I

The first paper in this thesis is a methodology manuscript of a randomized multicentre study in which standardized triggers for repeated biopsies and radical treatment during AS are compared with current practice. The aim of the Prostate Cancer Active Surveillance Trigger trial (PCASTt/SPCG17) study is to evaluate the safety of a proposed protocol for AS with standardized triggers for repeated biopsies and radical treatment. MRI is used as a follow-up tool. The hypothesis is that standardized triggers will reduce the number of biopsies during AS, reduce overtreatment, and increase quality of life without increasing the risk of disease progression or mortality due to prostate cancer. The aim of Paper I was to describe the rationale and design of PCASTt/SPCG17.

## Aim – Paper II

For the second study, the aim was to analyse the long-term probabilities of BCR, metastatic disease, and death from prostate cancer after radical prostatectomy conditioned on time after radical prostatectomy without BCR. The hypothesis was that it could be possible to shorten follow-up for men with favourable histopathology in prostatectomy specimens, compared to current recommendations of 10 years, without increasing the risk of metastatic disease and death from prostate cancer.

## Aim – Paper III

There are regional differences in uptake of AS indicating unequal healthcare depending on residential region.<sup>42</sup> In the third paper, we investigated the outcomes of AS, defined as transition to radical treatment, start of ADT, transition to watchful waiting, and death from causes other than prostate cancer, in the different healthcare regions in Sweden. The aim was to analyse the association between different regional traditions of uptake in AS and the outcomes of AS. We hypothesized that men in regions with high uptake in AS would have higher risk of transition to radical treatment and start of ADT compared with men in regions with low uptake in AS.

## Aim – Paper IV

The aim of fourth paper was to analyse the associations between the probabilities of experiencing potential triggers for transition from AS to radical treatment and transition to radical treatment. Further, we wanted to analyse how this had changed over time with the introduction of prostate MRI. We also wanted to describe the probabilities of experiencing potential triggers for men in AS. Our hypothesis was that there would be a stronger association between triggers and transition to radical treatment after the introduction of prostate MRI.



# Patients and Methods

## Data acquisition

For PCASt/SPCG17, the collected data are stored through an electronic case report form (eCRF) in Dynareg, a system used to build complete web-based data registers on clinical data.<sup>146</sup> Access to the database is restricted to the database manager and the trial statistician. The principal investigators will not have access to the results during accrual but can authorize release from the database.

For SPCG4, data were stored in a database at Örebro University Hospital and subsequently made available to the study statistician upon request. For Paper II, which is based on data from SPCG4 trial participants, an anonymized dataset containing only relevant variables was prepared for the researcher's use by the study statistician.

For Paper III and Paper IV, we used data from the National Prostate Cancer Register (NPCR) in Sweden and the Prostate Cancer data Base Sweden (PCBaSe).<sup>42</sup> NPCR has collected data on men diagnosed with prostate cancer since 1998. Compared with the Swedish Cancer Register, where all diagnosed cancers are registered by law, NPCR has a capture rate of 98%, making it a close to complete register over all men diagnosed with prostate cancer.<sup>147</sup> As in other national healthcare registers, men are informed about data collection and registration at the time of diagnosis, and they have the option to opt out at any time. The collected data include PSA at diagnosis, number of biopsies with cancer, millimetre cancer in biopsies, tumour grade and stage, information about performed prostate MRI, primary treatment, waiting times, etc. As new diagnostic methods have been developed and new treatments have been introduced, additional data have been added to the register over the years. For example, prior to 2007, AS and watchful waiting were collectively registered as 'deferred treatment', after when they have been registered as distinct categories. NPCR is linked to several other national registers including the Swedish National Cancer Register, the Cause of Death register, the Prescribed Drug Register, the Multi-Generation Register, the longitudinal integrated database for health insurance and labour market studies (LISA), and the National Patient Register, using the individually unique Swedish personal identity number creating PCBaSe intended for registry research.<sup>148</sup> The completeness

and validity of the register have been shown to be high.<sup>149</sup> Additional information is from time to time included in PCBaSe, creating updated versions. Each update is first approved by the Swedish Ethical Review Authority and then by the National Board of Health and Welfare (Socialstyrelsen, SoS). Cross-linking of the approved amendments based on the unique personal identity number is performed at SoS and Statistics Sweden (Statistiska Centralbyrån, SCB) and stored anonymized at Regional Cancer Centre (RCC) Mel-lansverige, with the code key held at SoS.

## Paper I

### Study design

PCAST/SPCG-17 is a multicentre randomized clinical trial that compares current practice with standardized triggers for men suitable for AS. The study began inclusion in October 2016 in Uppsala, Sweden, and 22 centres in Sweden, Norway, Denmark, Finland, and United Kingdom participate. Men with low- and favourable intermediate-risk prostate cancer eligible for AS are consecutively invited to participate in the study. Inclusion criteria are outlined in Table 3. Included men are randomized in a 1:1 ratio either to the control arm that follows the current practice of the urological centre in question, or to the experimental arm with standardized triggers for repeated biopsies and initiation of radical treatment (Table 4). Randomization is computerized and stratified according to centre and Gleason score. Basic follow-up is identical in the two study arms with a PSA test every six months, yearly clinical check-up, and MRI and quality-of-life questionnaires every two years. We estimate that all 2000 patients will be included before summer 2024.

The primary endpoint is disease progression (PSA relapse in curatively treated men and ADT in untreated men still in AS) with secondary endpoints cumulative incidence of radical treatment, pT3-tumours after radical prostatectomy, distant metastases, transition to watchful waiting, and death from prostate cancer.

**Table 3.** Inclusion criteria in PCASTt/SPCG17.

- Adenocarcinoma of the prostate diagnosed within the past 12 months.
- Tumour stage  $\leq$ cT2a, NX, MX.
- PSA  $<15$  ng/mL and PSA density  $\leq 0.2$  ng/mL<sup>2</sup>.
- Systematic biopsies with  $\geq 10$  cores (optional if the diagnosis is based on MRI with targeted biopsies).
- MRI with targeted biopsies towards PI-RADS 3, 4 and 5 lesions (according to PI-RADS v.2).
- ISUP grade 1 (any number of cores, any involvement).
- ISUP grade 2 in  $<3$  cores (or  $<30\%$  of cores if  $>10$  systematic cores were taken) and  $<10$  mm cancer in one core (systematic or targeted).
- Life expectancy  $\geq 10$  years (no upper age limit).
- Candidate for curative treatment (surgery or radiotherapy) if progression occurs.
- Signed written informed consent.

cT = clinical T stage, NX = not evaluated regional lymph nodes, MX = not evaluated distant metastases, PSA = prostate-specific antigen, MRI = magnetic resonance imaging, PI-RADS = Prostate Imaging-Reporting and Data System, ISUP = International Society of Urological Pathology.

**Table 4.** Triggers for re-biopsies and radical treatment in the experimental arm.

Triggers for re-biopsies		Triggers for radical treatment	
I	PSA density increase to $>0.2 \text{ ng/mL}^2$ , and then at every $0.1 \text{ ng/mL}^2$ increase (systematic biopsies)	I	MRI progression in lesions with Gleason pattern 4 <ul style="list-style-type: none"> <li>• Increase in PI-RADS score to 4 or 5</li> <li>• High suspicion of extra-capsular extension or seminal vesicle invasion (level of suspicion to be 4 or 5 on the Likert scale)</li> </ul>
II	MRI progression in men with ISUP grade 1 cancer (targeted biopsies) <ul style="list-style-type: none"> <li>• <math>\geq 5 \text{ mm}</math> or more increase in size in any dimension of a measurable lesion (defined as <math>\geq 6 \text{ mm}</math> in longest diameter in any dimension in best depicted MRI sequence)</li> <li>• Increase in PI-RADS score to 3, 4 or 5</li> <li>• High suspicion of extra-capsular extension or seminal vesicle invasion (level of suspicion to be 4 or 5 on Likert scale)</li> <li>• A new lesion with PI-RADS score 3-5</li> </ul>	II	Pathological progression <ul style="list-style-type: none"> <li>• Any Gleason pattern 5</li> <li>• Primary Gleason pattern 4 in any core with <math>\geq 5 \text{ mm}</math> cancer</li> <li>• ISUP grade 2 in <math>\geq 3</math> cores (or <math>\geq 30\%</math> of cores if <math>&gt;10</math> systematic cores), or <math>\geq 10 \text{ mm}</math> cancer in one core (systematic or targeted)</li> </ul>
III	MRI progression in men with ISUP grade 2 cancer (targeted biopsies) <ul style="list-style-type: none"> <li>• <math>\geq 5 \text{ mm}</math> or more increase in size in any dimension of a measurable lesion (defined as <math>\geq 6 \text{ mm}</math> in longest diameter in any dimension in best depicted MR sequence)</li> <li>• A new lesion with PI-RADS score 3-5</li> </ul>		

PSA = prostate-specific antigen, PI-RADS = Prostate Imaging-Reporting and Data System, MRI = magnetic resonance imaging, ISUP = International Society of Urological Pathology.

## Statistical analysis

The power calculation was based on previous knowledge of assumed 5-year progression-free survival of 98% in the current practice group.<sup>22</sup> The assumed adherence to randomization was 90%. To achieve a risk of type 1 error of 5% with a two-sided test and ensure the ability to detect an absolute difference of 1.3% in disease progression between the two study arms, along with 85% power (corresponding to a risk of type 2 error of 15%), a total of 2000 patients

was required. Analysis will be carried out according to the intention-to-treat principle.

## Paper II

### Study design

In the second paper, we included men from SPCG4.<sup>82</sup> Shortly, SPCG4 was a multicentre randomized clinical trial comparing prostate cancer mortality between men who underwent radical prostatectomy or watchful waiting. SPCG4 included men between 1989 and 1998 in 14 urological centres in Scandinavia, before the PSA era and thus, most tumours were palpable at diagnosis and not detected after merely an elevated PSA. In the prostatectomy arm, 46% were pT3. In Paper II we included all men in SPCG4 who had undergone radical prostatectomy within one year from randomization.

The study was a prospective cohort study with complete follow-up. Patients were stratified according to Gleason score ( $\leq 3+4=7$  vs.  $\geq 4+3=7$ ), pT stage ( $\leq$ pT2 vs.  $\geq$ pT3), and positive vs. negative surgical margins. We analysed the probabilities of BCR, metastatic disease, and prostate cancer death, conditioned on time after radical prostatectomy without BCR.

### Statistical analysis

The probabilities of BCR, metastatic disease and prostate cancer death were analysed as cumulative incidences with competing risk analysis. Death from other causes was considered a competing risk. We analysed the probabilities and absolute differences at 10, 15 and 20 years after radical prostatectomy for men without BCR five and 10 years after radical prostatectomy.

# Paper III

## Study design

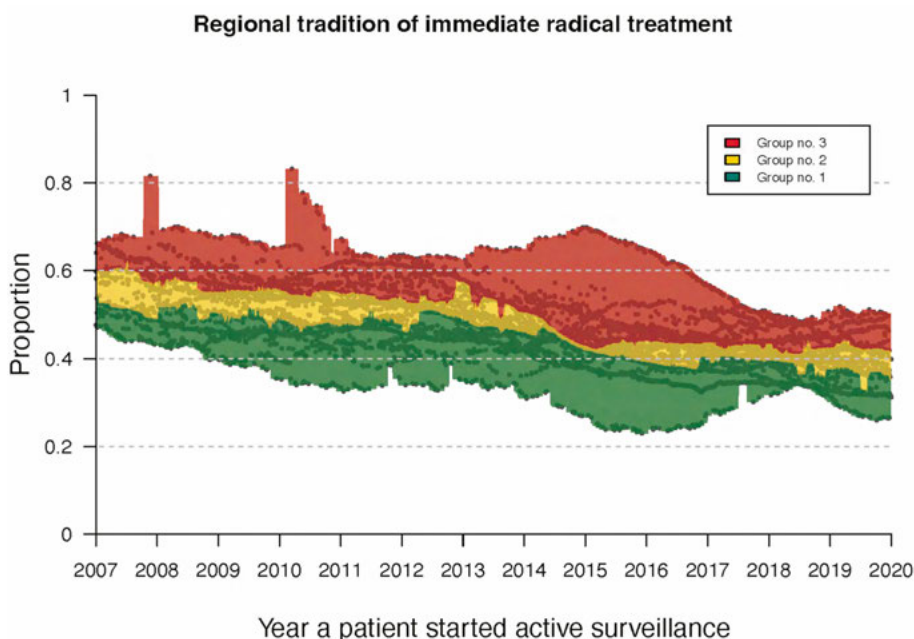
In PCBaSe version 5.0, men who were registered as starting AS, from January 1, 2007, to December 31, 2019, were considered for inclusion in the study. If they also fulfilled similar criteria as in SPCT17/PCASTt, shown in Table 5, they were included and form the cohort.

**Table 5.** Inclusion criteria in studies in Paper III and Paper IV. For cT1a and cT1b tumours diagnosed by transurethral resection of the prostate, additional biopsies were mandatory. For cT2 tumours, no sub-classification was available in the register, and all cT2 tumours were included if they met the other criteria.

Stage	cT1 or cT2
PSA	< 15 ng/mL
PSA density	$\leq 0.2 \text{ ng/mL}^2$
Gleason score	3+3=6 (any number of cores) or 3+4=7 (<30% of cores)

PSA = prostate-specific antigen, cT = clinical T stage.

The study was a population-based cohort study. The exposure was the regional tradition of immediate radical treatment assessed for each man who began AS. This was determined as the percentage of men eligible for AS, in the healthcare region in question, who had undergone immediate radical treatment within the previous three years. The distributions of these regional traditions of immediate radical treatment were then categorized, based on tertiles, into groups with low proportion immediate radical treatment (Group 1), intermediate proportion immediate radical treatment (Group 2), and high proportion immediate radical treatment (Group 3), corresponding to high, intermediate, and low uptake in AS, respectively (Figure 4). We prioritized comparing the group with low proportion immediate radical treatment (Group 1) with the group with high proportion immediate radical treatment (Group 3). Outcomes of AS were defined as transition to radical treatment, start of ADT, transition to watchful waiting and death from causes other than prostate cancer. Transition to watchful waiting was defined as when life expectancy dropped below 10 years, according to the earlier described model for estimating life expectancy based on CCI, DCI and age.<sup>141</sup>



**Figure 4.** Regional tradition of immediate radical treatment computed for each patient in the study cohort at start of active surveillance and categorized into three groups with low proportion immediate radical treatment (Group 1), intermediate proportion immediate radical treatment (Group 2) and high proportion immediate radical treatment (Group 3).

## Statistical analysis

We analysed the association between the three groups with low, intermediate, and high proportion immediate radical treatment, and the outcomes of AS. Probabilities for the different outcomes were estimated as cumulative incidence proportions. For comparison between groups, we analysed both absolute differences and hazard ratios using Cox regression of proportional hazards in both an adjusted and an unadjusted model.

## Paper IV

### Study design

In April 2023, additional data from the healthcare region Halland was cross-linked with NPCR at SoS, including information on PSA tests, prostate MRIs, and prostate biopsies for men after prostate cancer diagnosis. The fourth paper is based on this updated PCBaSe data, including men starting AS from January 1, 2008, to June 30, 2020, with the same inclusion criteria as in Paper III (Table 5). The study was designed as a case-control study and men who met the

inclusion criteria and transitioned from AS to radical treatment were selected as cases. For each case, 10 controls who were still in AS at the time of treatment for their corresponding case were randomly selected without further matching.

We defined three triggers for the transition from AS to radical treatment as exposures: 1) *histopathological trigger*, defined as progression in Gleason score on repeated biopsies, with or without any other trigger, 2) *MRI trigger*, without histopathological trigger, defined according to the criteria for MRI progression in PCASTt/SPCG17 (Table 4), and 3) *PSA trigger*, without any other progression, defined as present if PSA doubling time was less than 3 years, PSA velocity was  $\geq 2\text{ng/mL}$  in two years or PSA density increased  $\geq 0.5\text{ ng/mL}^2$  in two years.<sup>150</sup>

We analysed the probabilities of having experienced a trigger within one year before date of treatment for cases and corresponding controls, and in a sensitivity analysis of the 2- and 3-year periods preceding treatment. We also analysed the probabilities of not having experienced any trigger. We separately analysed two different time periods based on the date of curative treatment: one early period 2008 to 2014, before prostate MRI was incorporated in Swedish guidelines, and one late period 2015 to 2020, after MRI was incorporated in Swedish guidelines. The trigger including MRI was exclusively analysed in the late period as no MRI triggers were identified in the early period.

## Statistical analysis

Employing logistic regression, we analysed the associations between the defined triggers and transition from AS to radical treatment. The analysis included an unadjusted model and two models adjusted for relevant covariates. Results are presented as probabilities for experiencing triggers in cases and controls and as odds ratios (OR) with 95% confidence intervals (CI). To illustrate the continuous changes and the non-linear relationships in trigger probabilities, we used natural cubic splines in an unadjusted logistic regression model.



## Ethical considerations

PCASTt/SPCG17 follow ICH-GCP and the Helsinki declaration.<sup>151,152</sup> All included men are given verbal and written information about all aspects of their participation, including the possibility to leave the study. All patients must give their written informed consent before inclusion. The study has ethical approval from all the participating sites. The basic follow-up protocol including patients in both the control arm and the experimental arm of the trial is very similar to current guidelines. For patients in the control arm, which follows current practice, it is unlikely that they face an increased risk of deteriorated outcomes compared with patients outside the study. For patients in the experimental arm, there is a potential risk of missing the window of cure, but this risk is considered very low and minimized given the thorough follow-up in the study. Additionally, the potential benefits of the experimental arm, including less biopsies and reduced risk of overtreatment, are considered to outweigh the risk.

For Paper II, based on SPCG4 data, men were included in the study between 1989-1998. The current study was based on already collected data and required no further intervention or contact with patients or relatives, and thus there was no risk of physical harm. No personal identification numbers were available for the researcher, and the risk of identifying individuals through this study is considered negligible.

Paper III and IV are register studies based on the previously described NPCR and PCBaSe.<sup>147,148</sup> The registers are approved by the Regional Ethical Review Board, the Swedish Ethical Review Authority, and by the SoS. The data in the registers are regulated by the Patient Data Act. Both studies were individually approved by the Swedish Ethical Review Authority and by the PCBaSe reference group. No contact was taken with individual participants in these studies. Instead, at the time of their prostate cancer diagnosis, they were informed about their participation in the NPCR and the possibility to opt out. Beyond the register data, no additional information was gathered directly from patients, and they were under no risk of physical harm. The register data are kept in an institution with a high level of data security, and all data analyses are conducted on the remote server of that institution, to which only users approved by the PCBaSe reference group are granted access. To further minimise the risk of identification, personal identity numbers are replaced, and only necessary variables are included in the study files. Although there is

always a risk of violating personal integrity in registry studies, with the described actions to prevent identification, the risks are very small, and we consider that the scientific value of the research justifies these minimal risks.

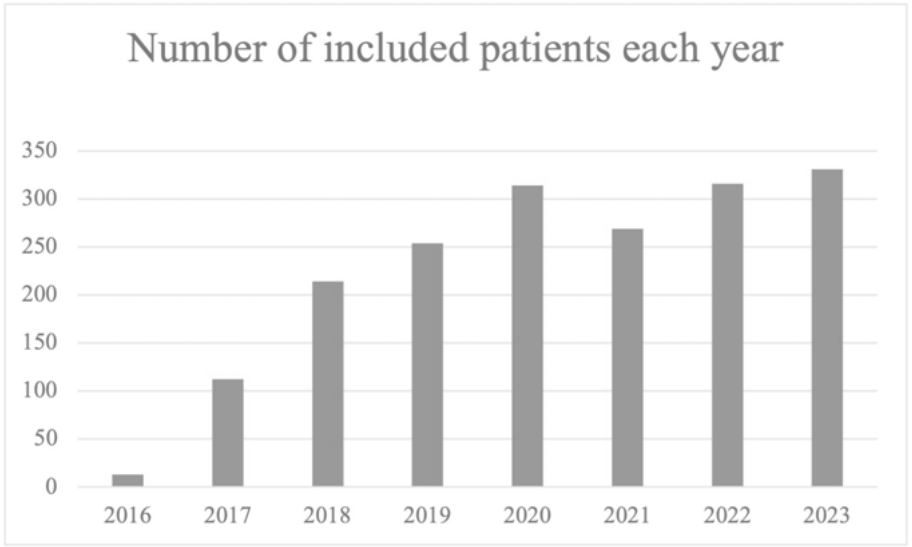
## Ethical approvals

Paper I, based on the PCASTt/SPCG17 trial, was approved in Sweden by the Regional Ethical Review Board in Uppsala (Dnr 2016/204) and in the other participating countries by their respective ethical review committees. For Paper II on SPCG4-data, the study was approved by the Regional Ethical Review Board in Örebro (Dnr 251/89). For the third and the fourth papers, based on PCBaSe data, the studies were approved by the Swedish Ethical Review Authority (Dnr 2021-07051-02 and Dnr 2023-02166-02) as an amendment to the general PCBaSe approval (Dnr 2020-03437).

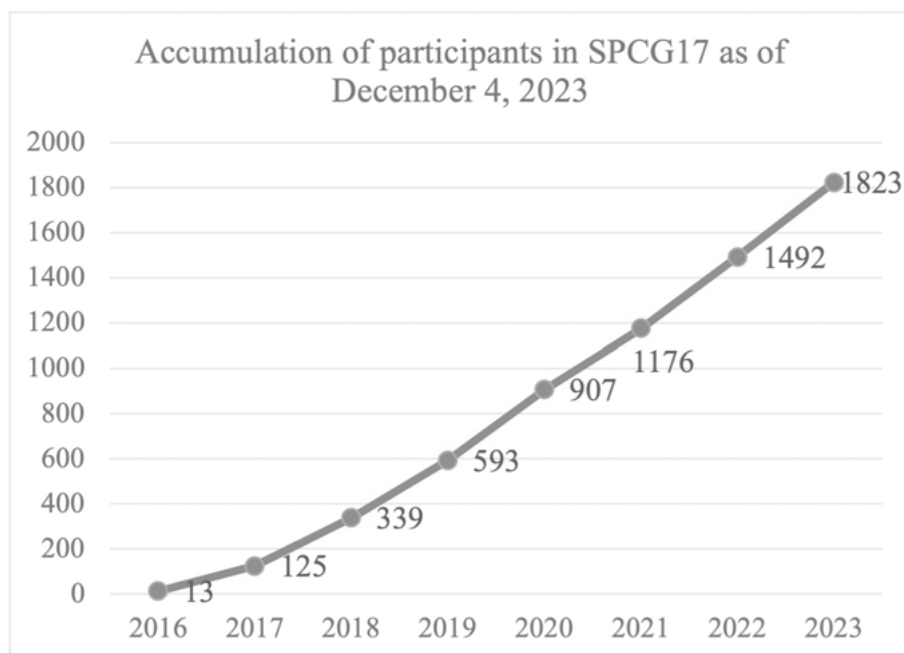
# Results

## Paper I

Enrolment in PCASTt/SPCG17 is ongoing. As of December 4, 2023, more than 1800 men have been randomized in the study. The number of participating centres has increased annually since 2016, and the inclusion rate has risen (Figure 5). During the COVID-19 pandemic, there was a reduced number of detected prostate cancers and inclusion dropped in 2021 but recovered the following year.<sup>153</sup> We aim to complete randomization before summer 2024 (Figure 6).

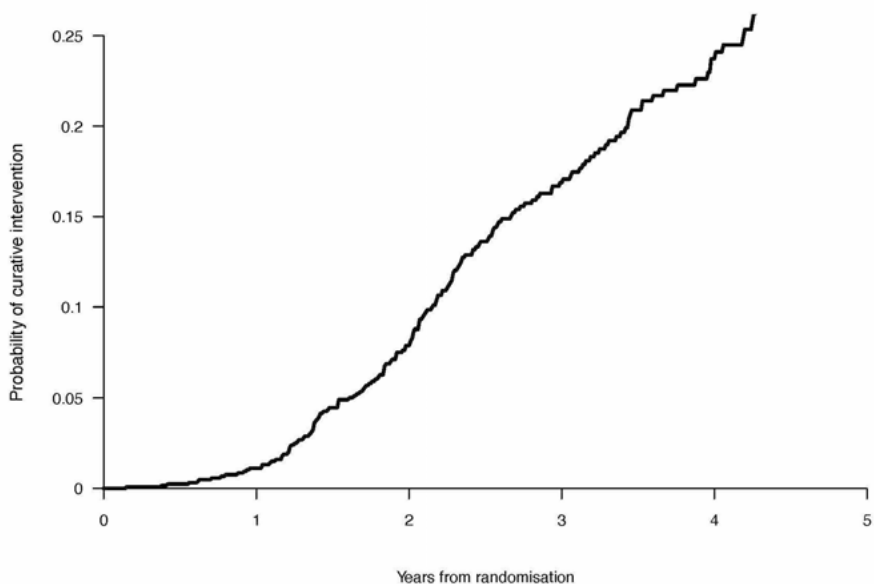


**Figure 5.** Number of included patients in PCASTt/SPCG17 each year as of December 4, 2023.

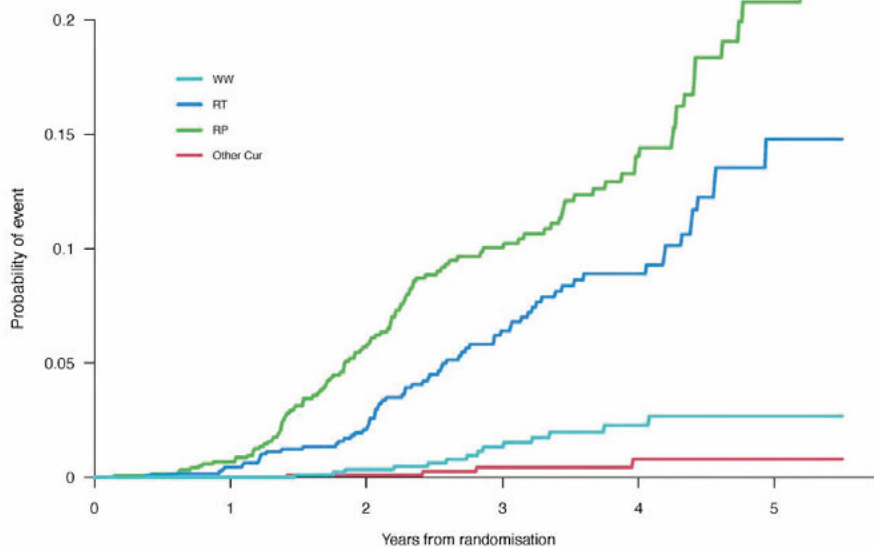


**Figure 6.** Accumulation of patients from the start of the trial.

Because the study has not completed randomization, comparative analyses have not been conducted, and endpoints cannot be assessed. However, some preliminary analyses for the entire cohort, regarding transition from AS to radical treatment and watchful waiting, have been performed. The cumulative incidence of transition to radical treatment is approximately 25% after four years and 35% after five years (Figures 7 and 8). The distribution of treatments with curative intent after five years are roughly as follows: 20% transition to radical prostatectomy, 15% to radiotherapy, and 1% to other treatments with curative intent. Approximately, 2% have transitioned to watchful waiting after 5 years. It is important to emphasize, however, that no information is yet available regarding any difference between the current practice arm and the experimental arm.



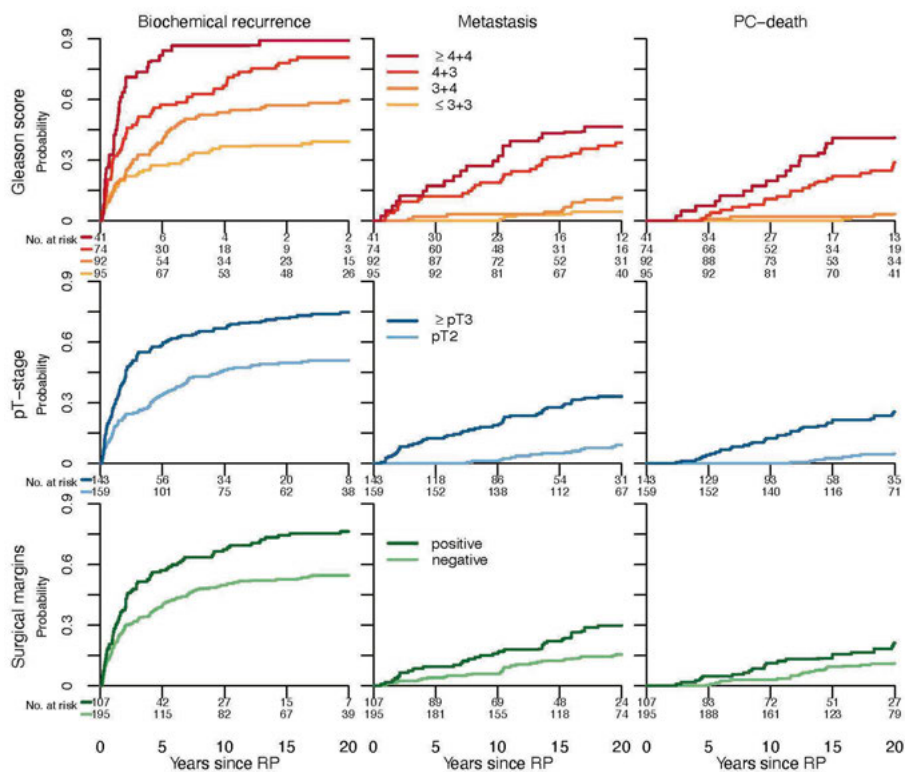
**Figure 7.** Cumulative incidence of transition from active surveillance to radical treatment in both arms of PCASTt/SPCG17.



**Figure 8.** Cumulative incidence of radical prostatectomy, radiotherapy, watchful waiting, and other radical treatment in both arms of PCASTt/SPCG17. WW = watchful waiting, RT = radiotherapy, RP = radical prostatectomy.

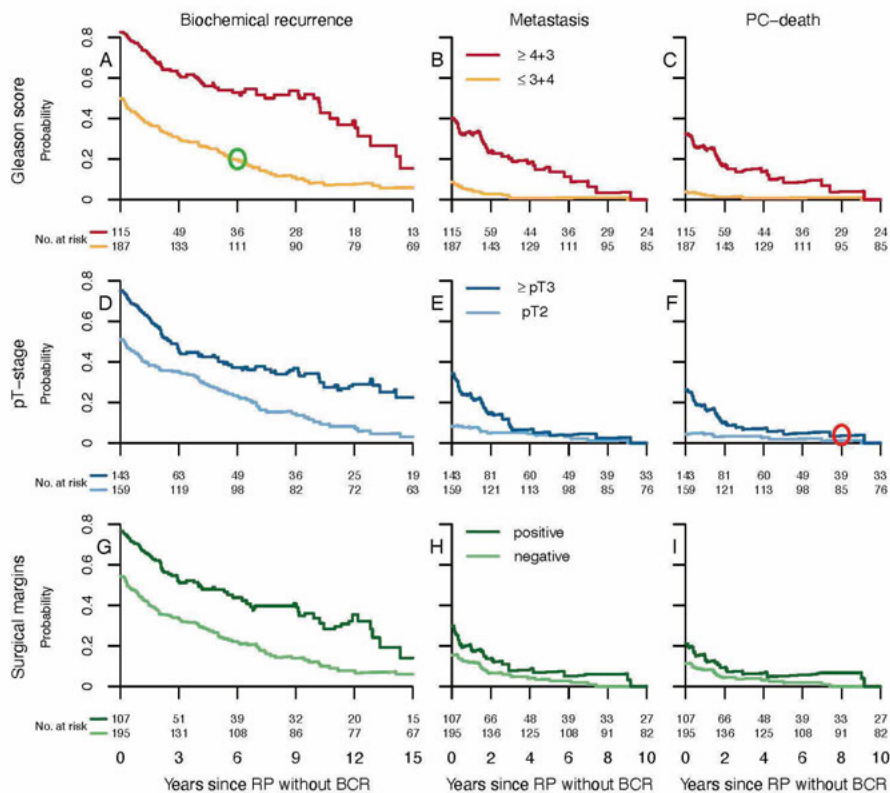
Paper II

We included 302 men who had undergone radical prostatectomy within a year from randomization in SPCG4, 17 of whom had crossed over from the watchful waiting arm. Median follow-up was 24 years, median age at randomization was 65 years, median preoperative PSA 9.8 ng/mL, 35% were Gleason score  $\geq 4+3=7$ , 45% were  $\geq pT3$  and 32% had positive surgical margins. The cumulative incidences of BCR, metastatic disease, and prostate cancer death for men with Gleason score  $\leq 3+3=6$ ,  $3+4=7$ ,  $4+3=7$  and  $\geq 4+4=8$ ,  $pT2$  and  $\geq pT3$ , and negative and positive surgical margins are shown in Figure 9.



**Figure 9.** Cumulative incidence of biochemical recurrence, metastasis, and death from prostate cancer, after radical prostatectomy. PC = prostate cancer, pT = pathological T stage, RP = radical prostatectomy.

Figure 10 shows the 20-year probabilities of BCR, metastatic disease, and death from prostate cancer (y-axis) conditioned on time after radical prostatectomy without BCR (x-axis).

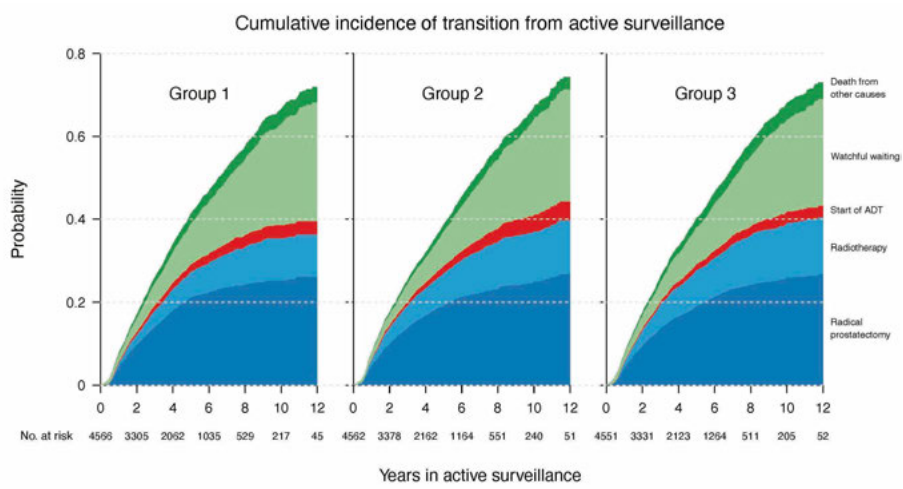


**Figure 10.** The y-axis represents the probability of an event (biochemical recurrence, metastasis, prostate cancer death) for the different strata within 20 years after radical prostatectomy. The x-axis represents time after radical prostatectomy without biochemical recurrence. For example, the green circle in panel A represents probability for a patient with Gleason score  $\leq 3+4=7$ , who was free from biochemical recurrence six years after surgery, to experience a biochemical recurrence within 20 years after radical prostatectomy. The red circle in panel F represents the probability for a man with  $\geq pT3$ , who was free from biochemical recurrence eight years after radical prostatectomy, to die from prostate cancer within 20 years after radical prostatectomy. PC = prostate cancer, pT = pathological T stage, RP = radical prostatectomy, BCR = biochemical recurrence.

We found a rapid decline in probabilities in most strata during the first three years after radical prostatectomy without BCR, after which the decline flattened out. After five years without BCR, the probability for men with Gleason score  $\leq 3+4=7$  to be diagnosed with metastases or die from prostate cancer within 20 years from radical prostatectomy was 0.8%. For men with Gleason score  $\geq 4+3=7$ , the corresponding probability was 17% for metastatic disease and 12% for prostate cancer death. For men without BCR after 10 years, no one was diagnosed with metastatic disease or died from prostate cancer within 20 years after radical prostatectomy.

# Paper III

For the study in Paper III, we included 13.679 men. The tradition of immediate radical treatment varied in the different regions and the proportions were between 43% and 82% in 2007 and declined over the study period to between 26% and 52% in 2019, as is shown in Figure 4 in the methodology section of the thesis (page 41). For the entire cohort, the median age at start of AS was 66 years, median PSA was 5.1 ng/mL, median PSA density was 0.12 ng/mL<sup>2</sup>. Approximately 85% exhibited cT1 tumours, low-risk tumours, and 90% had tumours with Gleason score  $\leq 3+3=6$ . Median time in AS was almost 6 years. The three groups were very similar, displaying almost identical patient and tumour characteristics. The probabilities for transition from AS to radical treatment were 36%, 40% and 40% in Group 1, Group 2, and Group 3, respectively. The absolute difference between Group 1 and Group 3 was 4.1% (95% CI 1.0-7.2) with a hazard ratio of 1.09 (95% CI 1.0-1.2) in the adjusted analysis. The difference was mainly based on differences in transition to radiotherapy, where the absolute difference between Group 1 and Group 3 was 3.4% (95% CI 1.5-5.4) with a hazard ratio of 1.37 (95% CI 1.2-1.6) in the adjusted analysis. There were no other relevant differences between the groups (Figure 11, Tables 6 and 7).



**Figure 11.** Cumulative incidence of transition from active surveillance to the outcomes of active surveillance defined for the study in Paper III. Group 1 – low proportion immediate radical treatment. Group 2 – intermediate proportion immediate radical treatment. Group 3 – high proportion immediate radical treatment. ADT = androgen deprivation therapy.



**Table 6.** Probability of transition from active surveillance to radical treatment (and presented as radical prostatectomy and radiotherapy separately), start of androgen deprivation therapy, transition to watchful waiting, and death from causes other than prostate cancer after 12 years of follow-up, separately for Group 1, Group 2, and Group 3, and for all patients. Absolute differences between groups are presented with 95% confidence interval.

Proportion immediate radical treatment:	Probability of transition to:					
	All radical treatment		Radical prostatectomy		Radiotherapy	
	%	95% CI	%	95% CI	%	95% CI
Low ( <i>Group 1</i> )	36.2	34.2-38.3	26.1	24.3-27.9	10.1	8.9-11.4
Intermediate ( <i>Group 2</i> )	39.7	37.3-42.0	26.8	24.8-28.8	12.9	11.4-14.4
High ( <i>Group 3</i> )	40.4	38.0-42.7	26.8	24.8-28.8	13.6	12.1-15.1
All patients	38.8	37.5-40.2	26.6	25.5-27.7	12.2	11.4-13.1
Absolute differences:						
Low vs. intermediate	3.4	0.3-6.6	0.7	-2.1 to 3.4	2.8	0.8-4.7
Low vs. high	4.1	1.0-7.2	0.7	-2.0 to 3.4	3.4	1.5-5.4
Intermediate vs. high	0.7	-2.6 to 4.0	0.03	-2.8 to 2.9	0.7	-1.5 to 2.8
Proportion immediate radical treatment:	Probability of transition to:					
	ADT		Watchful waiting		Death from other causes	
	%	95% CI	%	95% CI	%	95% CI
Low ( <i>Group 1</i> )	3.2	2.5-3.9	28.7	25.9-31.6	3.8	3.0-4.6
Intermediate ( <i>Group 2</i> )	4.6	3.5-5.6	27.1	24.5-29.7	3.0	2.3-3.7
High ( <i>Group 3</i> )	2.8	2.1-3.6	25.8	23.2-28.4	4.1	3.2-5.0
All patients	3.6	3.1-4.1	27.2	25.7-28.7	3.6	3.2-4.1
Absolute differences:						
Low vs. intermediate	1.4	0.1-2.6	1.7	-2.2 to 5.5	0.8	-0.3 to 1.8
Low vs. high	0.4	-0.7 to 1.4	3.0	-0.9 to 6.8	0.3	-0.8 to 1.5
Intermediate vs. high	1.7	0.5-3.0	1.3	-2.4 to 5.0	1.1	0.0-2.2

ADT = androgen deprivation therapy, CI = confidence interval.

**Table 7.** Unadjusted and adjusted hazard ratios for transition from active surveillance to radical treatment (and presented as radical prostatectomy and radiotherapy separately), start of androgen deprivation therapy, transition to watchful waiting, and death from other causes until 12 years of follow-up. Group 1, with regional tradition of low proportion immediate radical treatment is index group.

Proportion immediate radical treatment:	Transition to all radical treatment				Transition to radical prostatectomy				Transition to radiotherapy			
	HR	95%CI	aHR	95%CI	HR	95%CI	aHR	95%CI	HR	95%CI	aHR	95%CI
Low ( <i>Group 1</i> )	1		1		1		1		1		1	
Intermediate ( <i>Group 2</i> )	1.03	0.95-1.12	1.08	0.99-1.18	0.96	0.87-1.05	0.99	0.90-1.10	1.26	1.08-1.46	1.34	1.14-1.58
High ( <i>Group 3</i> )	1.07	0.98-1.15	1.09	1.00-1.19	0.97	0.88-1.07	1.00	0.90-1.10	1.34	1.16-1.56	1.37	1.17-1.61
Proportion immediate radical treatment:	Start of ADT				Transition to watchful waiting				Death from other causes			
	HR	95%CI	aHR	95%CI	HR	95%CI	aHR	95%CI	HR	95%CI	aHR	95%CI
Low ( <i>Group 1</i> )	1		1		1		1		1		1	
Intermediate ( <i>Group 2</i> )	1.10	0.84-1.46	1.17	0.86-1.60	0.88	0.79-0.99	0.91	0.79-1.04	0.77	0.58-1.02	0.75	0.56-1.01
High ( <i>Group 3</i> )	0.81	0.60-1.10	0.82	0.59-1.16	0.91	0.81-1.02	0.91	0.80-1.04	1.02	0.79-1.32	1.06	0.81-1.39

HR = hazard ratio, aHR = adjusted hazard ratio, ADT = androgen deprivation therapy, CI = confidence interval.

## Paper IV

For the fourth paper, we included 846 men in our study base. In total they underwent 1073 biopsy rounds, 687 MRIs and 8947 PSA tests (Table 8). From 2008 to 2014, we identified 98 cases with a mean age at treatment of 66 years for cases and 68 years for controls. The mean time in AS was 1.6 years for cases and 1.9 years for controls. From 2015 to 2020, we identified 172 cases with a mean age of 68 years for cases and 70 years for controls, and mean time in AS was 3.0 years for cases and 3.5 years for controls. The longer time in AS in the late period is because AS could start in 2008 for both periods.

The probability of experiencing a histopathological trigger was 30% for cases in the early period and 48% in the late period, and for controls 5% and 2% in the early and late period, respectively (Table 9). There was an association between histopathological trigger and treatment in both the early period (adjusted OR 6.88, 95% CI 3.69-12.80), and in the late period (adjusted OR 75.29, 95% CI 39.60-143.17). The probability of experiencing an MRI trigger without histopathological trigger was 6% in cases and 1% in controls, and MRI trigger was also associated with treatment (adjusted OR 6.38, 95% CI 2.70-15.06). The probability of experiencing PSA increase only as a trigger was 34% for cases in the early period and 19% in the late period, and for controls approximately 19% in both periods. There was a weak association between PSA increase only as a trigger and treatment in the early period but not in the late period.

The probability of not having experienced any trigger was 37% for cases in the early period and 27% in the late period, and for controls 75% in the early period and 79% in the late period. Not experiencing any trigger was associated with no transition to radical treatment in the early period (adjusted OR 0.24, 95% CI 0.15-0.40), and in the late period (adjusted OR 0.09, 95% CI 0.06-0.14). In a subgroup analysis, the probability was 4.8% for cases having experienced both a histopathological trigger within one year preceding treatment and an MRI trigger within three years preceding treatment (Table 9). The sensitivity analysis did not change the main outcomes.

**Table 8.** Baseline characteristics of men who started active surveillance January 1, 2008, to June 30, 2020. All covariates are from time of diagnosis except age and time in active surveillance which are from time of treatment.

Characteristics	2008-2014		2015-2020	
	Cases (n=98)	Controls (n=980)	Cases (n=172)	Controls (n=1720)
Age at treatment (yr), mean (95% CI)	65.8 (64.8-66.8)	68.3 (67.9-68.7)	67.8 (66.8-68.7)	69.8 (69.5-70.2)
Time in AS (yr), median (IQR)	1.6 (1.0-2.4)	1.9 (1.2-3.0)	3.0 (1.5-4.7)	3.5 (1.9-5.8)
PSA (ng/mL), median (IQR)	5.4 (4.3-7.2)	5.2 (4.2-6.8)	5.4 (4.4-6.9)	5.2 (4.2-6.9)
PSA density (ng/mL <sup>2</sup> ), median (IQR)	0.14 (0.10-0.21)	0.12 (0.09-0.17)	0.15 (0.11-0.19)	0.13 (0.10-0.17)
Missing, n (%)	4 (4)	48 (5)	5 (3)	57 (3)
Gleason score, n (%)				
Gleason score 3+3=6	81 (83)	885 (90)	146 (85)	1516 (88)
Gleason score 3+4=7	17 (17)	95 (10)	26 (15)	204 (12)
Clinical T stage, n (%)				
I	82 (84)	875 (89)	146 (85)	1537 (89)
2	16 (16)	105 (11)	26 (15)	183 (11)
Risk group, n (%)				
Low risk	76 (78)	827 (84)	138 (80)	1430 (83)
Intermediate risk	22 (22)	153 (16)	34 (20)	290 (17)
Biopsy with cancer, n (%)				
I	52 (53)	562 (57)	72 (42)	917 (53)
2	28 (29)	233 (24)	50 (29)	387 (23)
≥3	18 (18)	106 (11)	38 (22)	256 (15)
Missing, n (%)	0 (0)	79 (8)	12 (7)	160 (9)
mm cancer in biopsy, median (IQR)				
≤2	35 (36)	408 (42)	53 (31)	753 (44)
>2 - 4	14 (14)	110 (11)	37 (22)	323 (19)
>4	32 (33)	157 (16)	63 (37)	377 (22)
Missing, n (%)	17 (17)	299 (31)	19 (11)	267 (15)

Charlson comorbidity index (CCI), n (%)					
0	82 (84)	821 (84)	137 (80)	1412 (82)	
1	11 (11)	82 (8)	21 (12)	196 (11)	
≥2	5 (5)	77 (8)	14 (8)	112 (7)	
Marital status, n (%)					
Married/cohabitant	79 (81)	710 (72)	128 (74)	1256 (73)	
Unmarried	12 (12)	87 (9)	12 (7)	166 (10)	
Single/separated	6 (6)	155 (16)	28 (16)	234 (14)	
Widower	1 (1)	28 (3)	4 (2)	64 (4)	
Educational level, n (%)					
≤ 9 years	26 (27)	310 (32)	49 (28)	450 (26)	
10-12 years	36 (37)	414 (42)	74 (43)	735 (43)	
> 12 years	36 (37)	256 (26)	47 (27)	529 (31)	
Missing, n (%)	0 (0)	0 (0)	2 (1)	6 (0.3)	
Income level, n (%)					
Quartile 1	6 (6)	128 (13)	24 (14)	267 (16)	
Quartile 2	14 (14)	201 (21)	32 (19)	390 (23)	
Quartile 3	31 (32)	249 (25)	55 (32)	466 (27)	
Quartile 4	47 (48)	402 (41)	61 (35)	597 (35)	
Missing, n (%)	0 (0)	0 (0)	0 (0)	3 (0.2)	

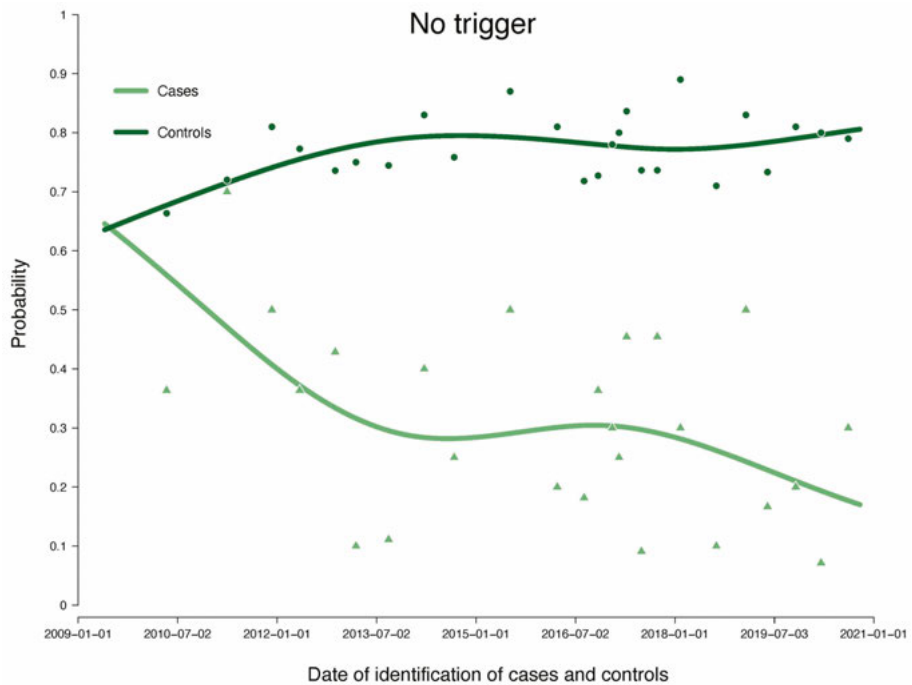
IQR = interquartile range, AS = active surveillance, PSA = prostate-specific antigen, mm = millimetre.

**Table 9.** Probabilities and odds ratios for patients with triggers, and without any trigger, within one year before treatment.

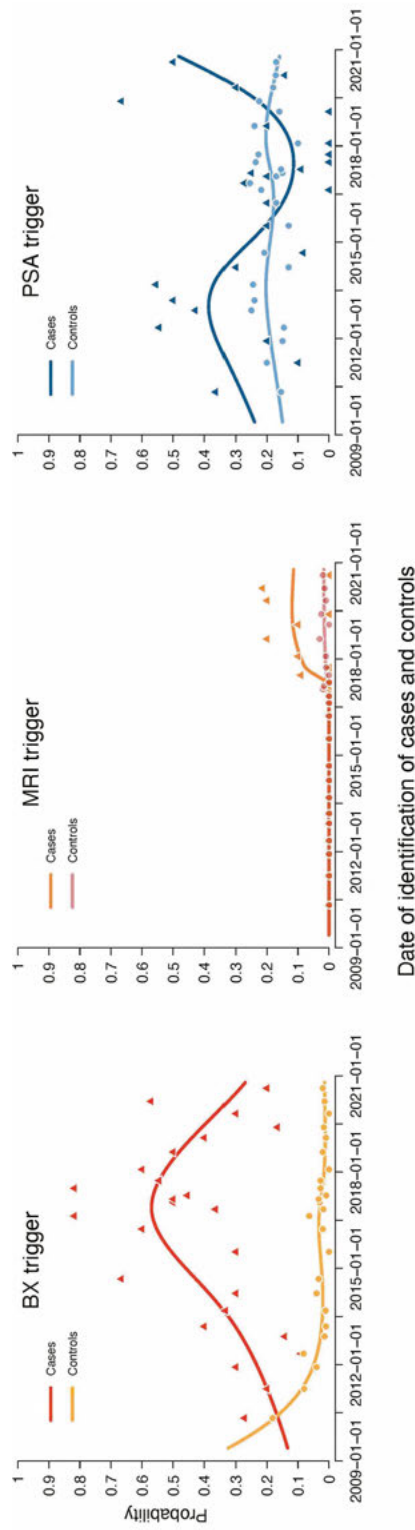
<b>2008-2014</b>					
Trigger	<b>Cases n=98</b>	<b>Controls n = 980</b>	<b>Odds ratios (95% CI)</b>		
	Probability (%)	Probability (%)	Unadjusted model	Patient & tumour characteristics	Adjusted for: + socioeconomic factors
Histopathology	29.6	5.4	7.66 (4.49-13.06)	7.54 (4.15-13.70)	6.88 (3.69-12.80)
PSA increase only	33.7	19.3	2.21 (1.39-3.50)	1.67 (1.03-2.71)	1.55 (0.94-2.56)
No trigger	36.7	75.3	0.19 (0.12-0.29)	0.23 (0.14-0.36)	0.24 (0.15-0.40)
<b>2015-2020</b>					
Trigger	<b>Cases n=172</b>	<b>Controls n = 1720</b>	<b>Odds ratios (95% CI)</b>		
	Probability (%)	Probability (%)	Unadjusted model	Patient & tumour characteristics	Adjusted for: + socioeconomic factors
Histopathology	48.3	2.0	53.01 (30.02-93.62)	67.28 (36.16-125.18)	75.29 (39.60-143.17)
MRI but no histopathology	5.8	1.0	6.32 (2.82-14.17)	5.85 (2.52-13.57)	6.38 (2.70-15.06)
PSA increase only	19.2	18.5	1.04 (0.70-1.55)	0.90 (0.60-1.36)	0.92 (0.61-1.40)
No trigger	26.7	78.5	0.10 (0.07-0.15)	0.09 (0.06-0.14)	0.09 (0.06-0.14)
<b>Subgroup with histopathological trigger within one year and MRI trigger within three years before treatment</b>					
Probability of histopathology and MRI trigger	4.8	0.04			

PSA = prostate-specific antigen, MRI = magnetic resonance imaging, CI = confidence interval.

Over the entire study period, there was a continuous decrease in probability for cases not having experienced any trigger and a simultaneous increase for controls (Figure 12). The changes in probabilities from the continuous unadjusted logistic regression model for all triggers are displayed in Figure 13. It shows that the probability of experiencing a histopathological trigger in cases increased before 2016. The occurrence of MRI trigger emerged in 2017, and PSA trigger in cases varied substantially throughout the whole period.



**Figure 12.** Probabilities for cases and controls of not having experienced any trigger the year before date of treatment. Illustrated by an unadjusted logistic regression model and with point estimates of means of 11 consecutive observations. Natural cubic splines were used to smoothen the non-linear relationship and fit it to a linear curve, illustrating the probabilities continuously over the entire study period.



**Figure 13.** Probabilities for cases and controls having experienced triggers the year before date of treatment. Illustrated by an unadjusted logistic regression model and with point estimates of means of 11 consecutive observations. Natural cubic splines were used to smoothen the non-linear relationship and fit it to a linear curve, illustrating the probabilities continuously over the entire study period. BX = histopathological, MRI = magnetic resonance imaging, PSA = prostate-specific antigen.



# Discussion

## Paper I

Overdiagnosis of prostate cancer has been reduced after advancement in the diagnostic algorithm, including increased use of age-standardized PSA levels, PSA density, and prostate MRI with targeted biopsies.<sup>7,41,154</sup> Overtreatment of prostate cancer has decreased with the introduction of AS.<sup>36,42</sup> However, many diagnosed and treated prostate cancers are indolent, and both overdiagnosis and overtreatment persist.<sup>155</sup> It is obvious that more men should start, and stay longer in AS to reduce harm and healthcare costs.

The Gleason score inflation derives from the ISUP revisions in 2005 and 2014 discussed earlier.<sup>17–19</sup> Most long-term follow-up studies of deferred treatment were undertaken before these revisions and showed excellent survival without immediate radical treatment.<sup>20–22,80</sup> The survival benefits of radical treatment compared with watchful waiting for localized prostate cancer arise after many years of follow-up and for certain groups of men. Altogether this strongly suggests that AS is a good option for many men with intermediate risk prostate cancer. The concern that MRI and targeted biopsies potentially lead to a new era of overdiagnosis of intermediate-risk prostate cancers supports the idea that more men with such cancers should consider AS to prevent further overtreatment.<sup>98,156</sup> Fortunately, guidelines now recommend AS for selected intermediate-risk prostate cancers.<sup>4,8–11</sup>

Repeated biopsies are still recommended in AS. Biopsies are uncomfortable and carry the risk of side effects and complications, of which infections are the most serious.<sup>70,71</sup> The perineal biopsy approach and iodine rectal swabs may reduce, but not eliminate, the risk of infection, but the discomfort and use of resources will remain, and a safe follow-up protocol without mandatory repeated biopsies would be beneficial.<sup>74–76</sup> The follow-up of PCASTt/SPCG17 is based on repeated MRI and PSA testing without mandatory biopsies. The control arm follows current practice, which often includes scheduled repeated biopsies. In the experimental arm, biopsies are triggered by predefined progression on MRI and PSA density and will hopefully reduce the number of biopsies. Transition from AS to radical treatment is triggered by a predefined increase in grade on biopsies, or MRI progression in known Gleason score 3+4=7 lesions. Hopefully, this will reduce the proportion of men who leave AS for radical treatment.

Thus far, the preliminary results show approximately 35% probability of transition to radical treatment after five years in both study arms together, which is comparable to what has previously been reported.<sup>99–101</sup> However, these data are preliminary, and we cannot draw any conclusions at this time. Additionally, we lack information about potential differences between study arms, and none of the study endpoints have been assessed yet. Nevertheless, we eagerly look forward to examining the trial outcomes.

## Strengths and limitations

The randomized design is the main strength of PCASTt/SPCG17. An optimal randomization ensures an equal probability for all trial participants to be allocated to any of the treatment groups, regardless of their individual characteristics, aiming for control against selection bias. Thorough follow-up and adherence to study protocol are necessary to avoid confounding and information bias. Despite aiming to study causal associations between exposure and outcome in a randomized trial, the provided data are associations. Flawed randomization, inadequate adherence to protocol and data collection may introduce selection bias, information bias, and confounding.

Randomization does not protect from any imbalance between study groups, but rather implies that there will most certainly be some imbalance, by chance, regarding patient characteristics. In PCASTt/SPCG17, the randomization is stratified on participating centre and Gleason score. The rationale behind the stratification is to balance centre and Gleason score across the two arms and protect against possible imbalance, even though serious imbalance is rare in a large trial. In theory, a carefully conducted randomized trial can be analysed without bias and confounding using straightforward statistical methods. Statistical tests with corresponding p-values can then allow quantitative statements to be made about the probability that the difference between the study arms can be explained by the random imbalances rather than the intervention itself. Most randomized trials, however, are prone to some bias, as PCASTt/SPCG17 probably will be.

Further limitations of PCASTt/SPCG17 primarily concern the control arm. First, the control arm is an undefined current practice that varies between participating centres and over time. This means that it is unclear what the experimental arm is being compared with. Although this issue might pose a challenge when interpreting potential differences between the study arms, it was a prerequisite to be able to include all necessary patients in the trial. It would have been very difficult to gain acceptance for a coordinated current practice control arm without any evidence to support it.

Second, there has been some criticism that the control arm might deviate towards the experimental arm's practice, essentially resulting in one large cohort study. If this proves to be true, it will still be possible to compare results against other AS cohorts and evaluate the safety of the standardized follow-

up protocol and the defined triggers. Moreover, the trial will generate prospective data on serial prostate MRI in AS, which is a key in modern AS. The highly subjective experience of the author, who has met with and taken care of study patients in clinical practice since the onset of inclusion, is that they tend to be handled differently in the two arms of the trial. This is supported by the findings in Paper IV, examining similar triggers as in the experimental arm of PCASTt/SPCG17, in current practice.

Lastly, the slow inclusion of participants over several years can create problems in clinical trials. For example, if new diagnostic methods or treatment strategies emerge, that impair patient acceptance, make the study question irrelevant, or the follow-up protocol unethical, completion of a study may be difficult. However, the common follow-up protocol for the both study arms in PCASTt/SPCG17 is highly acceptable in a contemporary context, and the inclusion rate has not declined over the years (except during the Covid-19 season), which indicates that this is not a problem for this trial (Figures 5 and 6).

## Paper II

In Paper II, men with Gleason score  $\leq 3+4=7$  in prostatectomy specimens, who remained free from BCR five years post-radical prostatectomy, had less than one percent probability of progressing to metastatic disease or prostate cancer death, regardless of pT stage and surgical margins. Most of the decrease in the probability of clinical progression occurred within the first three years after surgery. For men without BCR 10 years after radical prostatectomy, no metastatic disease or prostate cancer-related deaths were detected.

Earlier studies have presented similar results, with low risk of metastatic disease and prostate cancer death, for men diagnosed with Gleason score 6 tumours if no BCR was detected within five- and 10-years post-prostatectomy.<sup>157,158</sup> In Paper II, we present data with 24 years median follow-up, which is a longer follow-up than found in previous studies. There was a high probability of BCR following radical prostatectomy within the SPCG4 cohort, even in men with favourable histopathology in their prostatectomy specimens. Those men also had a high probability of late BCR, even if they had no BCR five years after treatment. The probabilities of future metastatic disease and prostate cancer death were, however, very low. Regarding tumour characteristics, Gleason score served as the strongest predictor of metastatic disease and death with 20 times higher probability for metastatic disease for Gleason score  $\geq 3+4=7$  compared with Gleason score  $\leq 3+4=7$ , and 15 times higher probability for prostate cancer death. In total, 157 of 302 men were diagnosed with a BCR after more than 5 years post-prostatectomy, seven of whom were diagnosed with metastases. Six of them died from prostate cancer, one of whom was in the Gleason score  $\leq 3+4=7$  group.

The association between time to BCR after radical prostatectomy and long-term oncological outcomes has been assessed in other studies. Some have shown an association between time to BCR and prostate cancer mortality in all risk groups, while others have found that association for intermediate- and high- risk patients only, or for metastatic disease but not for mortality.<sup>119,122,126,159</sup> Other studies have failed to show this association when adjusting for clinical and pathological characteristics.<sup>118,121,123,125,127</sup> None of these studies had the same long-term follow-up as in Paper II where we clearly found support for an association between time to BCR after radical prostatectomy and metastatic disease and prostate cancer death.

To appropriately select men who are likely to benefit from salvage therapy after a BCR, it is crucial to understand the natural progression of metastatic recurrence and mortality following radical prostatectomy. Pound et al. described the natural course of prostate cancer progression after BCR post-radical prostatectomy.<sup>119</sup> In their cohort of men with BCR, 30% had Gleason score 8-10, 90% exhibited  $\geq$ pT3 and 75% experienced BCR within five years after radical prostatectomy. These were unfavourable tumours with a high risk of progression. The median time from BCR to progression to metastatic disease (without any hormone or radiotherapy) was eight years, with an additional five years from the onset of metastatic disease to prostate cancer death. In Paper II, 10% (n=11) of men with Gleason score  $\leq$ 3+4=7 and no BCR within five years after surgery received hormonal therapy. Two of them underwent salvage radiotherapy, and one man developed metastases and died from prostate cancer. Compared with the men in Pound's study, these men had more favourable prostate cancers with reasonably longer time to clinical progression, and a benefit from hormonal treatment or salvage radiotherapy for them is unlikely, as previously discussed.<sup>116,130-132,160,161</sup>

In our analysis of the association between Gleason score and outcomes, we did not adjust for other histopathological features. This means that men with pT3 and positive surgical margins were also included in the favourable Gleason score group. Both of these characteristics independently predicted a lower probability of metastatic disease and prostate cancer death, supporting a very low risk in men with all these favourable histopathological features and no BCR five years post-prostatectomy. For men without BCR 10 years post-prostatectomy, there were no metastatic disease or prostate cancer deaths, which is in line with previous findings.<sup>126,159,162</sup>

According to Swedish and international guidelines, patients should undergo regular PSA testing for at least 10 years after radical prostatectomy, regardless of the tumour's histopathological features.<sup>4,8-11</sup> The aim of this follow-up is early detection of BCR, enabling timely intervention with salvage radiotherapy or hormonal therapy to prevent disease progression, morbidity, and mortality from prostate cancer. The results in Paper II indicate that the benefit of extended follow-up beyond five years in men with favourable

histopathology is questionable and that they could be considered for shorter follow-up than today's standard of 10 years. However, men with a life expectancy over 20 years or those with unfavourable histopathological features in the prostatectomy specimen should continue follow-up until 10 years, as recommended at present.

There is always a risk-benefit balance in healthcare actions. A prostate cancer diagnosis and repeated follow-up bring distress and anxiety in many men.<sup>37</sup> Early initiation of salvage radiotherapy or ADT might postpone time to metastatic disease and prostate cancer death for individual men, but will impair quality of life in many, and increase the risk of death from other causes in some.<sup>64,115,116,128,132,133,135</sup> Ceasing follow-up and declaring a patient cured when there is a very low risk of metastatic disease and death from prostate cancer could be beneficial for patients and the healthcare system.

## Strengths and limitations

Paper II describes a prospective cohort study, i.e., an observational trial. The complete and long-term follow-up are the main strengths. The small size of the cohort is a limitation, making it difficult to perform multivariable analysis with reasonable statistical precision. Generalizability might be impaired due to inclusion of a healthier cohort in a clinical trial compared with the general population, decreasing the risk of death from other causes. The more advanced tumours in SPCG4 (45% pT3) compared with a more modern cohort might impair generalizability further but would make the results a 'worst case scenario', further emphasizing the relevance of the findings.

While the goal of an observational trial is basically the same as that of a randomized trial, i.e., to interpret associations and gain knowledge about causative mechanisms, observational studies are much more prone to selection bias and confounding. Missing data is one mechanism by which selection bias might be introduced, and imputation of missing data is one way to reduce this bias.<sup>163–165</sup> Around 7% of outcomes in Paper II were missing, and we used multiple imputation by chained equations (MICE) to impute missing data for PSA values at diagnosis, Gleason score, pT stage, and surgical margins.<sup>165</sup> After employing MICE, we could generate a dataset with less bias and more accurate measures of uncertainty, compared with a complete case analysis.

## Paper III

In Paper III, we found a slightly lower probability of transitioning to radical treatment in regions with a tradition of high uptake in AS, compared with regions with a low uptake in AS, but not a higher probability of AS failure. We found no association between tradition of uptake in AS and transition to watchful waiting or death.

In our hypothesis, we suggested that a high uptake in AS, representing a low proportion of immediate radical treatment, is indicative of a permissive attitude towards AS and would be associated with higher probability of transition to radical treatment and start of ADT. Conversely, a low uptake in AS, representing a high proportion of immediate radical treatment, would imply a restrictive attitude towards AS including only the most suitable and eager men in AS, with low probability of transition to radical treatment and AS failure. The findings in Paper III were in contrast with our hypothesis. Our interpretation of the findings is that the regional attitude among treating urologists to resort to radical treatment, or resort to deferred treatment, persists from time of diagnosis to time of AS. Although the differences between the groups were small and not clinically relevant, the results suggest that a tradition of high AS uptake is a safe approach, while a lower uptake in AS implies overtreatment, both at the time of diagnosis and during AS.

In previous studies, 35%-40% transition from AS to radical treatment after five years and less than 5% transition to watchful waiting.<sup>99-101,166</sup> In our results, the probability of transitioning to radical treatment was lower while the probability of transitioning to watchful waiting was higher. Local traditions might influence these differences, as the guidelines are not very specific regarding triggers for treatment. Additionally, our theoretical model of transitioning to watchful waiting likely influences these variations.

The transition to watchful waiting is recommended when life expectancy drops below 10 years, that is, when it is considered that the patient will no longer benefit from radical treatment.<sup>4,8-11</sup> The transition from AS to watchful waiting is not a failure of AS, but a sign of correct inclusion of the patient in AS. The high probability of transition to watchful waiting in the present study, similar between groups, indicates that the surveillance strategy was equally successful in all three groups. Assessing life expectancy is difficult, and the transition to watchful waiting is not available in registers and rarely documented in medical charts.<sup>138</sup> We used the previously described statistical model based on prescribed drugs to assess life expectancy and defined the transition to watchful waiting when life expectancy dropped below 10 years.<sup>141,144</sup> The higher probability of transition to watchful waiting in the current study compared with other AS cohorts indicates that the model might underestimate life expectancy compared with the clinical evaluation of patients. The clinical evaluation, however, is prone to subjectivity, and it is possible that our findings of probability of transition to watchful waiting, based on an objective statistical model, are more adequate.

In our study, transition from AS to death from other causes was, as expected, low (3.6% in 12 years). Men who start AS are supposed to have a life expectancy of at least 10-15 years, and the probability of dying during follow-up in our cohort was comparable to what is expected in a corresponding cohort in the general population.<sup>136</sup> We did not evaluate the transition from AS to prostate cancer-related death, as it is highly unlikely that someone in AS will

die from prostate cancer without first transitioning to ADT or watchful waiting.

The persistence of overdiagnosis and the variability in urologists' acceptance of and compliance with AS underscores the need for a comprehensive, efficient, and safe AS protocol. High-level evidence is required to establish clear inclusion criteria, follow-up methods and intervals, and criteria for transitioning out of AS. With clear evidence, urologists and patients can hopefully gain confidence in AS, reducing uncertainty, regional disparities, and overtreatment.

## Strengths and limitations

The strengths of Paper III are the large study cohort, which provides statistical precision, and the high validity of the NPCR and PCBaSe registers.<sup>147–149</sup> Limitations include that the follow-up was too short to catch late signs of AS failure. However, it is unlikely that relevant differences between the groups would emerge, given their similarity in baseline characteristics. Furthermore, other AS cohorts exhibiting low probability of late failures shared similar characteristics, making it unlikely that our cohort would differ substantially.<sup>21,22</sup> Another limitation is the definition of transition to watchful waiting, which is based on the statistical model discussed earlier. The model estimates life expectancy and is validated as highly correct, but differs from the clinical evaluations of the patients and represents a theoretical model of when transition to watchful waiting occurred.<sup>141,144</sup> The study in Paper III is an observational trial with inherent risks of confounding and bias. As the three groups had similar baseline characteristics, serious selection bias is unlikely. Further, in the analysis of group differences, we adjusted for relevant covariates to reduce confounding.

The probabilities of the different outcomes were analysed with a cumulative incidence function considering competing risks.<sup>167–171</sup> This approach enables analysis of the probability of each of the multiple competing events, considering that one event prevents the occurrence of another. Cumulative incidence with competing risk analysis may be preferred, instead of Kaplan-Meier analysis, when focusing on predicting outcomes of clinical value in a population. In Paper III (and in Paper II), we used this approach, as competing events were present, and the focus of the studies was on predicting outcomes rather than aetiology.

## Paper IV

In Paper IV, the results indicate increasing reliance on objective triggers before transitioning to treatment over time, in adherence with current guidelines, but the direct influence of introduction of MRI on these improvements were

small. The probability of experiencing a histopathological trigger within one year before treatment increased over time, establishing a strong association between trigger and treatment. The probability of experiencing an MRI trigger before treatment was low but associated with transitioning to radical treatment in the late period. The absence of any trigger was increasingly strongly associated with no transition to radical treatment. However, even in the late period, a large proportion of men transitioned to treatment without triggers.

Histopathological progression in prostate biopsies serves as the strongest objective trigger for transitioning from AS to radical treatment.<sup>4,8–11,88</sup> Additionally, patient preference is important to consider, while disease progression based on PSA increase or progression on MRI should preferably be verified by biopsies.<sup>88</sup> In a study on NPCR data from 2008 to 2013, 24% transitioned to treatment after five years in AS due to biopsy progression.<sup>99</sup> In the large GAP3 and in PRIAS studies, 28% and 34%, respectively, transitioned from AS to treatment after five years prompted by changes seen as indications of disease progression.<sup>100,101</sup> While direct comparison with results in Paper IV cannot be made due to different definitions of disease progression and different study designs, histopathological progression is an important reason for transition to treatment in all these studies. In Paper IV, there was an increasingly strong association between histopathological progression and transition to radical treatment over time, in line with current recommendations. Nevertheless, in the late period, the probability of not having experienced a histopathological trigger exceeded 50%, indicating that there is room for further improvement and adherence to guidelines.

The exact role of MRI in AS is unclear. It is incorporated into AS protocols, both at initial assessment and for ongoing monitoring, but there are no long-term results on AS based on MRI.<sup>4,8–11,88</sup> Previous studies have shown prostate MRI's negative predictive value during AS being nearly 100%, but a recent review indicates that relying solely on prostate MRI for disease progression lacks accuracy in detecting and ruling out histopathological progression.<sup>98,156,172</sup> In the PRIAS study, MRI findings of PI-RADS  $\geq 3$  statistically significantly predicted histopathological progression on targeted biopsies and showed higher probability of transitioning from AS to radical treatment with MRI usage.<sup>97,173</sup> Considering that AS without MRI has shown excellent outcomes, these findings raise concerns about whether prostate MRI during AS might lead to more aggressive treatment decisions and a new era of overtreatment. This underscores the need for clear guidelines regarding prostate MRI in AS.

Prostate MRI has been gradually introduced in Sweden over the past 15 years and was included in the Swedish guidelines in 2014. In Paper IV, there were no MRI triggers 2008-2014. While the probability of experiencing an MRI trigger before treatment was low 2015-2020, it was strongly associated with transitioning to radical treatment. The continuous analysis revealed the emergence of MRI triggers in 2017, indicating an incipient reliance on MRI



as a true indicator of disease progression after a few years of increased use of this technique. In the subgroup analysis, only 5% of cases had experienced both a histopathological trigger within one year and an MRI trigger within three years before treatment. This suggests that the introduction of prostate MRI did not contribute much to the increased use of histopathological trigger.

PSA progression is known to have low specificity for detection of prostate cancer progression in AS due to multiple non-malignant factors increasing PSA levels.<sup>174</sup> In the NPCR study of AS from 2008 to 2013 mentioned earlier, around half of men who transitioned to radical treatment within five years did so due to PSA progression.<sup>99</sup> In the 5-year follow-up of the PRIAS study, 46% of men who transitioned to radical prostatectomy due to a PSA doubling time less than three years had favourable final histopathology, indicating overtreatment.<sup>100</sup>

In Paper IV, PSA increase only as a trigger was weakly associated with treatment in the early period but not in the late period. While we cannot draw any conclusions due to low statistical precision it might be indicative of reduced reliance of PSA increase only as a trigger for transition in line with current recommendation.<sup>88</sup> This is supported by findings of slightly lower ORs for PSA increase as a trigger in the late period in the sensitivity analysis. Further studies are needed to confirm this.

According to previous studies, approximately 13-30% of men who transition to radical treatment do so without evidence of disease progression.<sup>99-101</sup> For men transitioning to radical treatment due to the patient's or doctor's preference without signs of disease progression, close to 60% had favourable histopathology in prostatectomy specimens, indicating overtreatment.<sup>100</sup> In the present study, the probability of cases of not experiencing any trigger consistently decreased throughout the study period and was clearly associated with no transition to radical treatment. This trend may be attributed to an increased awareness of the safety of AS. However, in the late period, over 25% of treated men had not experienced any trigger the year before treatment, indicating that current practice, at least until 2020, clearly differs from the PCASTt/SPCG17 experimental arm.

Doctor's recommendations strongly affect treatment choices among men with low-risk prostate cancer.<sup>175</sup> To reduce overtreatment in the form of transition from AS to radical treatment based on anxiety or patient's own preference, urologists must first feel secure with the AS concept. To accomplish this, creating useful guidelines based on high-level evidence is essential.

## Strengths and limitations

As in Paper III, the validity and completeness of NPCR and PCBaSe registers are strengths of the study in Paper IV, which to our knowledge is the first registry-based study assessing triggers from AS to radical treatment.<sup>147-149</sup> The size of the cohort is the main limitation, which might impair generalizability.

The studied region, however, is not far from the ‘Swedish average’ regarding uptake in AS, and the results are probably generalizable to regions with similar healthcare organizations and prostate cancer incidence.<sup>42</sup> In Paper IV, we have used a development of the statistical model that was employed to estimate life expectancy in Paper III and described in the previous section.<sup>145</sup> The updated model performs better but has similar advantages and limitations as the earlier version.

Further, the study in Paper IV is a case-control study, i.e., an observational trial like the studies in Paper II and III, with similar risks for confounding and bias. In a case-control study, selection bias might be introduced by the matching of controls. When selecting controls, we have only matched on date of transition to treatment to reduce the risk of introducing this bias. To reduce confounding and evaluate how covariates affected the associations, we used adjusted logistic regression models with covariates relevant to the outcome. Nonetheless, some confounding might still influence the results due to unknown covariates. The continuous analysis of trigger probabilities was unadjusted and susceptible to confounding. Due to limited events for the individual triggers, the statistical precision was low. Consequently, the model primarily serves as a rough visualization of the continuous changes over time.

# Conclusions

- I. PCASTt/SPCG17 is a RCT aimed at evaluating an MRI-based active surveillance protocol with predefined triggers for intervention. Recruitment and randomization of patients have been slower than anticipated but will conclude in 2024. First results from the trial will be published one year after final inclusion.
- II. After radical prostatectomy for localized prostate cancer, men with favourable histopathology in prostatectomy specimens, and no biochemical recurrence after five years, had a very low risk of metastatic disease and prostate cancer death within 20 years from surgery. The benefit of follow-up beyond five years for these men is questionable, while extended follow-up until 10 years is reasonable for men with a very long life expectancy or adverse histopathology.
- III. In regions with a tradition of low uptake in active surveillance, there was a higher probability of transition from active surveillance to radical treatment compared with regions with a tradition of high uptake of active surveillance, but no indications of difference in active surveillance failure. This suggests overtreatment in regions with low uptake in active surveillance.
- IV. Over time there was an increasing probability of triggers before treatment indicating better quality of AS. The introduction of MRI had little influence on that improvement. The association between histopathological progression and transition to radical treatment was strong, especially in the late period. MRI trigger was associated with transition to radical treatment in the late period. The probability of not experiencing triggers before transition declined over time, but many men still transitioned from active surveillance to radical treatment without any identifiable trigger, indicating overtreatment.

## Future perspectives

For PCASTt/SPCG17, the journey has just begun. Inclusion will be completed in 2024. One year after final randomization, the first analysis is planned, with subsequent analyses every three years. There are multiple possibilities for further studies from this trial. Beyond the analyses of the predefined endpoints, evaluation of changes in prostate MRI during AS is one potential subject. Quality-of-life aspects of AS and analyses of biomarkers are other planned studies based on PCASTt/SPCG17, and surely additional ideas will come to mind as time goes by.

The second study questions the need for extended follow-up for all men after radical prostatectomy. Hopefully, discussions about individual follow-up based on tumour characteristics, life expectancy, etc., can take place, and Paper II can serve as a source of evidence in that discussion.

The third study sheds light on the regional variation in uptake of AS and the need for more equal healthcare. This topic is always important, and with the NPCR, we have great possibilities to follow up and try to find ways to decrease regional differences. Paper III contributes to illustrating regional differences and their consequences, a topic that should be further addressed in the future.

In the fourth study we address the question of what current practice in AS actually means. In the ongoing PCASTt/SPCG17, the experimental arm will be compared with an unknown current practice and the findings in Paper IV will probably be valuable when interpreting the results. If similar data on PSA, MRI, and biopsies, from more healthcare regions in Sweden, will be included in PCBaSe, larger studies from that register, with follow-up of men with prostate cancer may be performed in the future.

# Summary in Swedish

## Populärvetenskaplig sammanfattning

En majoritet av de män som får en prostatacancerdiagnos har en lång förväntad tid till symtom även om de inte får behandling. Det betyder att många män aldrig kommer utveckla symtom av sin cancersjukdom, utan kommer i stället dö av andra orsaker. Om dessa män behandlas i kurativt syfte för sin cancersjukdom innebär det onödig behandling med stor risk för onödiga biverkningar. Samtidigt är prostatacancer den cancersjukdom som tillskrivs flest dödsfall i Sverige, ca 2400 per år. Medelåldern att dö i prostatacancer är ca 82 år.

Behandling av lokaliserad prostatacancer innebär i första hand strålbehandling eller kirurgi och är behäftad med relativt stora risker för biverkningar, som impotens, inkontinens och urinträngningsbesvär. Biverkningarna kan drabba vem som helst, oavsett om man har nytta av behandlingen eller inte. Eftersom prostatacancer är en mycket vanlig sjukdom (ca. 10 000 nya fall per år i Sverige) handlar det om många hundra patienter varje år som riskerar att drabbas av besvärliga biverkningar helt i onödan. Hittills finns det inte tillräckligt bra diagnostiska metoder för säkert att avgöra vilka män som kommer att ha nytta av behandlingen och vilka som inte kommer ha nytta av den.

Aktiv monitorering infördes för att minska överbehandlingen av män med låg-risk prostatacancer. Aktiv monitorering innebär att skjuta botande behandling på framtiden och i stället följa patienterna med mål att behandla om sjukdomen utvecklas. Sedan införandet har aktiv monitorering ökat i omfattning och rekommenderas nu för fler patientgrupper med lokaliserad prostatacancer. Hur stor andel av patienterna som rekommenderas aktiv monitorering skiljer sig åt mellan olika sjukvårdsregioner. Vi vet att det är mycket liten risk att en låg- eller mellan-risk prostatacancer leder till spridd sjukdom eller död de närmaste 10 åren och enligt riktlinjer bör aktiv monitorering övergå till symtomstyrd behandling när en patients förväntade återstående livslängd understiger 10 år. Det finns fortfarande många oklara detaljer gällande aktiv monitorering så som: vilka patientgrupper som bör erbjudas aktiv monitorering, hur utredningen inför aktiv monitorering bör ske, hur aktiv monitorering ska bedrivas och vad som ska föranleda att man går vidare till aktiv behandling.

Efter operation för prostatacancer förväntar man sig att PSA värdet ska vara omätbart. Det är ganska stor risk att patienter några år efter behandling får tillbaka mätbart PSA-värde, ett biokemiskt återfall. Denna risk är olika stor

för olika riskgrupper. I riktlinjer rekommenderas minst 10 års uppföljning för alla prostatacancerpatienter med syfte att tidigt hitta ett biokemiskt återfall och ha möjlighet att sätta in ytterligare behandling för att minska risken för symptomgivande sjukdom och död. Vi vet dock att det i många fall dröjer minst 10–15 år innan ett biokemiskt återfall leder till symptomgivande sjukdom. För patienter med ett sent biokemiskt återfall och en relativt snäll prostatacancer kan det röra sig om betydligt längre tid.

## Delarbete I

I den första studien i avhandlingen beskrivs bakgrunden och metodologin för den kliniska studie av män i aktiv monitorering som startade i Uppsala 2016 och som fortsatt rekryterar patienter. Studien är en randomiserad multicenterstudie som inkluderar män med låg- och gynnsam mellan-risk prostatacancer. Flera sjukhus i Sverige, Norge, Finland, Danmark och England deltar i studien. I studien följs alla patienter på samma sätt, med regelbundna PSA-kontroller, kliniska kontroller och magnetkameraundersökningar av prostata. I studien slumpas deltagande patienterna mellan två grupper. Den grupp som utgör kontrollarmen, följs enligt dagens praxis. I experimentarmen finns det tydligt fastställda kriterier för vilka förändringar i PSA värden, magnetkamerafynd, och biopsifynd som ska föranleda vidare utredning med upprepade prostatabiopsier eller övergång till behandling. Syftet med studien är att utvärdera om det föreslagna uppföljningsprotokollet i experimentarmen är säkert jämfört med dagens praxis. Totalt ska 2000 patienter vara med i studien och vi räknar med att ha inkluderat alla under första halvan av 2024.

## Delarbete II

I den andra studien undersökte vi långtidsrisker för biokemiskt återfall, metastatisk sjukdom och prostatacancerdöd efter operation på grund av prostatacancer. Vi ville ta reda på om det kan vara ett säkert alternativ att förkorta uppföljningstiden efter operation för en del män med en snällare form av prostatacancer. Vi identifierade 302 män som opererades för prostatacancer mellan 1989 och 1998. Vi analyserade sannolikheten att drabbas av biokemiskt återfall, spridd prostatacancer, eller död på grund av prostatacancer inom 20 efter prostatacanceroperation för patienter utan biokemiskt återfall 5 och 10 år efter operationen. Vi analyserade skillnader mellan patienter med prostatacancer med olika riskfaktorer för återfall. Våra resultat visade att patienter med prostatacancer där den mikroskopiska undersökningen av prostatan efter operation visade mindre aggressiv prostatacancer, och som inte fick ett biokemiskt återfall inom fem år efter operationen, hade mindre än 1% risk att drabbas av spridd sjukdom eller prostatacancerdöd inom 20 år från

kirurgi. Ingen patient utan biokemiskt återfall efter 10 år diagnosticerades med spridd sjukdom eller dog av prostatacancer inom 20 år från operationen. Slutsatsen av studien var att patienter med en mindre aggressiv prostatacancer utan specifika riskfaktorer, som inte har biokemiskt återfall efter 5 år, kan övervägas för kortare uppföljning än dagens rekommenderade 10 år. Patienter med mycket lång förväntad återstående livslängd eller en mer aggressiv prostatacancer bör följas minst 10 år.

## Delarbete III

Delarbete III baserades på vetenskapen om att det finns stora regionala skillnader i utnyttjande av aktiv monitorering, vilket innebär ojämlik vård beroende på bostadsort. Vi ville undersöka om det fanns något samband mellan den regionala traditionen i utnyttjande av aktiv monitorering och hur det gick för patienterna under aktiv monitorering. Studien baseras på registerdata från det nationella prostatacancerregistret av patienter med låg- och gynnsam mellanrisk prostatacancer som påbörjade aktiv monitorering från 2007 till 2019. Vi delade in samtliga sjukvårdsregioner i Sverige i tre grupper baserat på den regionala traditionen av direkt botande behandling. Vi analyserade om det fanns något samband mellan den regionala traditionen av direkt behandling och sannolikheten till övergång från aktiv monitorering till botande behandling med kirurgi eller strålning, start av hormonell behandling, övergång till symptomstyrd behandling (watchful waiting) eller död. Den enda säkra skillnaden mellan grupperna var att det i gruppen med tradition av hög andel direkt behandling, vilket också innebär en låg andel aktiv monitorering, var en högre sannolikhet att övergå till botande behandling än i övriga grupper. Vi tolkade resultaten som att i regioner med en tradition av låg andel aktiv monitorering fanns det en tradition av att vara mer aktiv i övergång från aktiv monitorering till behandling, talande för mer överbehandling av patienterna i de regionerna.

## Delarbete IV

I den fjärde studien undersökte vi sambandet mellan förekomst av olika 'triggers' för övergång från aktiv monitorering till botande behandling, och sannolikheten för att en övergång till behandling skett, samt hur det sambandet hade förändrats över tid. Vi definierade tre olika 'triggers' baserade på prostatabiopsier, MR undersökning och PSA ökning, och analyserade sambandet mellan förekomst av dessa och övergång från aktiv monitorering till botande behandling. Patienter i nationella prostatacancerregistret med låg- och gynnsam mellanrisk prostatacancer som startade aktiv monitorering 2008 till 2020 inkluderades i studien. Vi analyserade och jämförde två tidsperioder, 2008–2014 och 2015–2020. Resultaten visade ett starkt samband mellan 'triggers'

baserad på prostatabiopsier och behandling, ett samband vars styrka ökande över tid. Även 'triggers' baserad på MR visade ett samband med behandling. Många män blev dock behandlade utan förekomst av någon säker 'trigger'.



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