Treatment for Early Prostate Cancer - Reducing Side Effects Without Jeopardizing Cure

Elin Axén

Department of Urology
Institute of Clinical Sciences
Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

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elin.axen@vgregion.se

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Gotta keep on going

Looking straight out on the road

Can't worry 'bout what's behind you

Or what's coming for you further up the road

Klara and Johanna Söderberg - First Aid Kit

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Sahlgrenska Academy, University of Gothenburg
Gothenburg, Sweden

ABSTRACT

The overall aim of this thesis is to gain further knowledge of how surgical choices affect the outcome for patients undergoing radical prostatectomy for early prostate cancer including preoperative evaluation and long-term prognosis after surgery. Within the non-randomized Laparoscopic Prostatectomy Robot Open trial, comparing the outcomes between open and robot-assisted radical prostatectomy, we evaluated the effect of preservation of the neurovascular bundles on postoperative incontinence (**paper I**), and recurrence of prostate cancer (**paper II**). Findings in Magnetic Resonance Imaging; targeted and systematic prostate biopsies were compared to findings in radical prostatectomy specimens in men diagnosed with prostate cancer within the randomized, controlled GÖTEBORG Prostate Cancer Screening 2 Trial (**paper III**). Long-term risk for recurrence and subsequent treatment after radical prostatectomy was evaluated within the population-based Western Sweden study of Opportunistic Prostate Cancer Screening database (**paper IV**).

Preservation of neurovascular bundles decreases the risk for postoperative incontinence, while increasing positive surgical margins; balancing these outcomes for the individual is essential. Systematic biopsies seldom contribute additional information of importance for surgical decisions and should be avoided if the only purpose is preoperative mapping. After radical prostatectomy, the risk for recurrence remains at 15 years. Length of follow-up should be related to life expectancy, rather than to time since surgery.

Keywords: incontinence, prostate cancer, radical prostatectomy, recurrence

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SAMMANFATTNING PÅ SVENSKA

För att ställa diagnosen prostatacancer tas vävnadsprover. Dessa togs tidigare systematiskt, spridda över hela prostata, men numera används magnetkameraundersökning (MR) i allt högre utsträckning innan vävnadsprovtagning. Prover tas sedan enbart riktat mot områden med misstänkt tumör på MR. Prostata ligger nära urinrörets slutmuskel och de nerver som styr erektionen. Efter en operation för prostatacancer, så kallad radikal prostatektomi, finns risk för bestående urinläckage och impotens. Om erektionsnerverna sparas vet vi att risken för impotens minskar. Inför operationen bedömer kirurgen om nerverna kan sparas eller inte, baserat på tumörens allvarlighetsgrad. När nerverna bevaras går man mycket nära prostatan. Om man opererar för nära ökar risken för att lämna kvar tumörceller. Efter operationen kontrolleras prostataspecifikt antigen (PSA) regelbundet. Ett mätbart värde är en tidig indikation på återfall.

Syftet med den här avhandlingen är att undersöka om systematiska vävnadsprover fortfarande har en plats för att kartlägga tumören inför en operation, eventuella ytterligare effekter av att bevara erektionsnerverna samt utfallet av operationen på lång sikt. De ingående studierna bygger på information från två större studier och en stor databas: Göteborg 2-studien som studerar screening för prostatacancer med en kombination av PSA-test och MR, LAPPRO-studien som jämför öppen och robotassisterad radikal prostatektomi samt WSOP-databasen som skapades för att studera oorganiserad PSA-testning.

Vi har jämfört informationen från riktade och systematiska vävnadsprover hos 160 patienter i G2-studien som opererats för prostatacancer och fann att riktade prover i de allra fall räcker för att kartlägga tumören. Hos 3148 patienter i LAPPRO-studien har vi undersökt hur risken för urinläckage påverkas av att erektionsnerverna sparas. Vi fann att risken minskar när graden av bevarande ökar. Vi har också undersökt hur risken för återfall påverkas av att nerverna sparas. Hos 2401 patienter i LAPPRO som genomgått robotassisterad operation fann vi att risken för att ha kvar tumörceller i kanten av den bortopererade prostatan ökar om mer nerver sparas. Detta ger i sin tur en högre risk för återfall. I WSOP har vi undersökt återfall i form av mätbart PSA hos 6675 patienter. Vi fann att återfall förekommer upp till 15 år efter operationen. Ca hälften av dem som får PSA-återfall får någon typ av behandling inom 15 år efter återfallet. Risken för detta är allra störst för dem som får återfall inom två år efter operationen

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals (I-IV).

I. Steineck G, Bjartell A, Hugosson J, Axén E, Carlsson S, Stranne J, Wallerstedt A, Persson J, Wilderäng U, Thorsteinsdottir T, Gustafsson O, Lagerkvist M, Jiborn T, Haglind E, Wiklund P. Degree of Preservation of the Neurovascular Bundles During Radical Prostatectomy and Urinary Continence 1 Year after Surgery. European Urology 2015; 67: 559-568.

II. Axén E, Arnsrud Godtman R, Bjartell A, Carlsson S, Haglind E, Hugosson J, Lantz A, Steineck G, Wiklund P, Stranne J. Degree of Preservation of Neurovascular Bundles in Radical Prostatectomy and Recurrence of Prostate Cancer. European Urology Open Science 2021; 30: 25-33.

III. Axén E, Arnsrud Godtman R, Hugosson J, Månsson M, Stranne J. Additional value of systematic biopsies for preoperative assessment in MRI-detected prostate cancer. In manuscript.

IV. Axén E, Stranne J, Månsson M, Holmberg E, Arnsrud Godtman R. Biochemical recurrence after radical prostatectomy in a whole-of-population-based setting. Submitted.

CONTENT

ABBREVIATIONS

ADT	Androgen Deprivation Therapy
BCR	Biochemical Recurrence
CI	Confidence Interval
ERSPC	European Randomized Study of Screening for Prostate Cancer
ISUP	International Society of Urological Pathology
LAPPRO	Laparoscopic Prostatectomy Robot Open
MRI	Magnetic Resonance Imaging
NS	Nerve-sparing
PI-RADS	Prostate Imaging–Reporting and Data System
PROM	Patient Reported Outcome Measures
PSA	Prostate Specific Antigen
QoL	Quality of Life
RALP	Robot Assisted Laparoscopic Radical Prostatectomy
SPCG	Scandinavian Prostate Cancer Group
WSOP	Western Sweden study of Opportunistic Prostate Cancer Screening

DEFINITIONS IN SHORT

Positive surgical margin	Tumour cells at the inked margin of the surgically removed prostate (Tan et al. 2011)

1 INTRODUCTION

My great aunt turned one hundred years old this summer. When she learnt that my thesis was about prostate cancer she asked: 'Prostate cancer. It's so common nowadays, but you never used to hear about it before. Why is that?'

1.1 PROSTATE CANCER EPIDEMIOLOGY

In 1960, when my great aunt was 39 years old, 1 565 Swedish men were diagnosed with prostate cancer; in 2016, they were 10 474, almost seven times more. As the population has increased during this time, an increase in number of cases is expected. To take this into account, the incidence, i.e., number of new cases during a specified time period, is often expressed as number of cases per 100 000 inhabitants. In 1960, this number was 41.9; in 2016 it was 207.5, i.e. a net increase of five times. Part of the increase in number of men receiving a prostate cancer diagnosis could thus be explained by an increasing population, but only to a small extent. Prostate cancer, like many other cancers, gets more common with older age; the mean age at prostate cancer diagnosis in Sweden is currently 69 years (Public Health Agency of Sweden 2021). The life expectancy in Sweden has increased during the last sixty years, putting more people at risk for developing cancer; in 1960 life expectancy for men was 71.2 years, in 2019 it was 81.3 years (Statistics Sweden 2021). To account for this, the incidence can be age-standardized, where the number of cases, if the populations had the same age distribution, is estimated by a mathematical formula. If we look at the age-standardized incidence, the increase from 1960 to 2016 is about three-fold, depending on which population is used for standardization (Danckert et al. 2019; Engholm et al. 2010). Looking at crude numbers, we found a seven-fold increase in prostate cancer incidence between 1960 and 2016; when accounting for changes in population size and age the difference diminished to a three-fold increase. An increasing, ageing population is thus part of the explanation why prostate cancer is common nowadays, at least in Sweden, but what accounts for the remaining increase?

The risk of being diagnosed with prostate cancer varies greatly in the world. The incidence in the French Caribbean region of Guadeloupe is highest in the world, more than 500 times higher than in Bhutan, which has the lowest incidence. When adjusted for age, the differences diminish, but there is still a 200-fold difference between the respective countries (fig 1, green bars). In 2018 the average, age-standardised incidence in the world was 29.3 cases per 100 000 individuals, ranging between world regions from 5.0 in South-Central

Asia to 86.4 in Australia and New Zeeland. The second highest incidence, 85.7 was found in Northern Europe (Culp et al. 2020). Within regions there is also great variation between countries. Sweden is on the top ten-list with an incidence of 101.7 cases per 100 000 in 2018, standardised according to the world population (GLOBOCAN 2021; The National Board of Health and Welfare 2021).

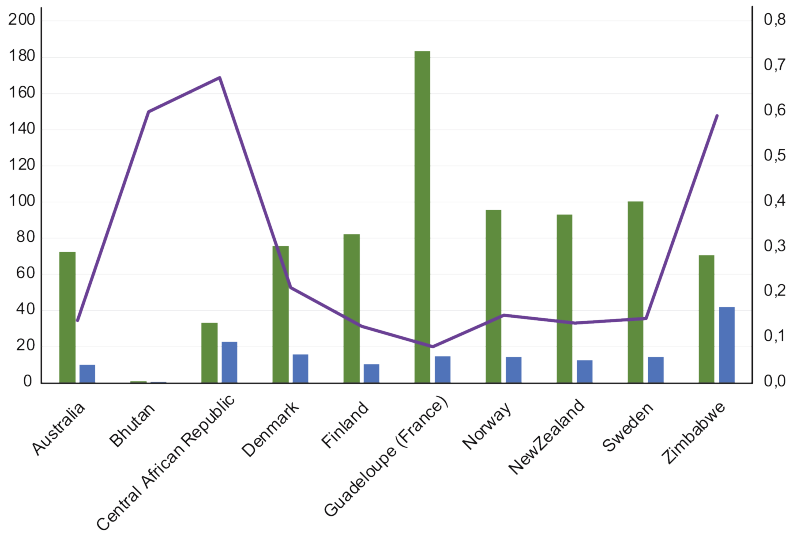

Figure 1. Left y-axis: Age-standardized incidence (green bars) and mortality (blue bars) rates of prostate cancer, cases per 100 000. Right y-axis: Mortality to incidence ratio (purple curve). Data from GLOBOCAN.

When looking at mortality from prostate cancer, the picture changes. Age-adjusted mortality rates range from 0.5 per 100 000 in Bhutan to 41.7 per 100 000 in Zimbabwe (fig 1, blue bars). Despite Bhutan having both the lowest incidence and mortality rates, there is no fixed relationship between the two globally. The so-called mortality-to-incidence ratio has a wide range, from less than 10% to nearly 70% (fig 1, purple line). While prostate cancer incidence in Sweden is among the highest in the world, the Swedish mortality rate on the other hand, is around average. The age-standardized mortality has undergone some changes in the last sixty years, but prostate cancer mortality in Sweden in 1960 and 2016 was the same (figure 2). So, despite the three-fold increase in incidence, mortality has not increased. Cancer treatment, including

treatment for prostate cancer, has improved during this time, but that is not the major explanation.

Figure 2. Prostate cancer mortality in Sweden from 1960 to 2016. Rates are standardized according to the Nordic population. Data from NORDCAN (Danckert et al. 2019; Engholm et al. 2010).

Autopsy studies of the presence of cancer in the prostate among men who have died from other causes show that prostate cancer is even more common than shown in incidence rates. In a review article in 2015, Bell et al. pooled the estimates from 29 autopsy studies, showing the percentage of patients with microscopic prostate cancer according to patient age (figure 3, pink line). This shows an increase with older age, just as in clinical diagnosis, but also that the prevalence of cancer cells in the prostate is high, even in younger men. Compared to the prevalence of having a prostate cancer diagnosis (figure 3, blue line), there is an evident gap. This is sometimes compared to an iceberg, where the blue line (diagnosed prostate cancer) represents the part above water, and the pink line (undiagnosed prostate cancer) is the part hidden under water.

Besides showing that microscopic prostate cancer is far more common than clinical prostate cancer, autopsy studies also show that microscopic prostate cancer is prevalent several decades before it is commonly diagnosed (Bell et al. 2015).

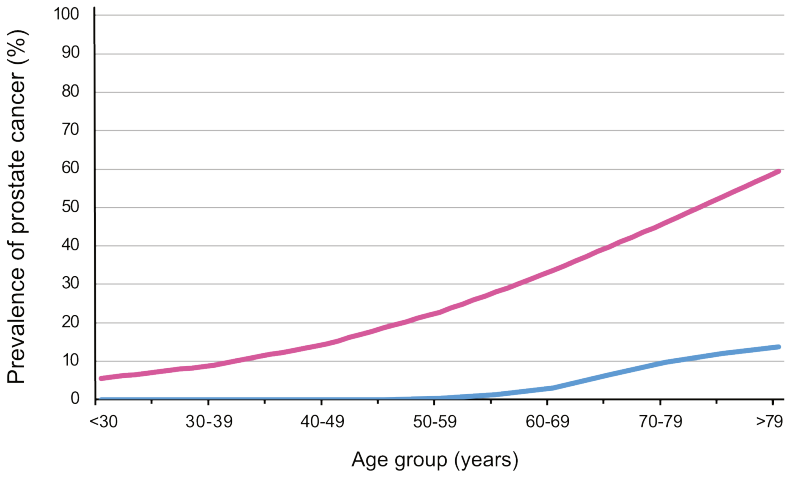

Figure 3. Prevalence of prostate cancer in autopsy studies (pink curve – adapted from Bell, K. J., et al. (2015). "Prevalence of incidental prostate cancer: A systematic review of autopsy studies." Int J Cancer 137(7): 1749-1757.) and among Swedish men in 2016 (blue curve - data from NORDCAN (Danckert et al. 2019; Engholm et al. 2010)

1.2 PROSTATE CANCER DIAGNOSIS

1.2.1 PSA

In the 1950s and 1960s, antibodies were discovered; proteins produced by the immune system and used for detection of objects foreign to the body, each one recognizing a specific object, called an antigen (Kaufmann 2019). This opened a new area of research with numerous applications; including the search for a tumour antigen that could be used for diagnosis and treatment of cancer (Catalona 2014; Flocks et al. 1960). An antigen specific to prostatic tissue was identified in the 1970s (Wang et al. 1979). After a blood test was developed, the antigen, now named Prostate Specific Antigen (PSA), was shown to be elevated in patients with prostate cancer, with higher levels in more advanced disease (Stamey et al. 1987). Initially, PSA was used to monitor response to treatment; in the 1990s, it was shown to be useful for early detection of prostate cancer (Catalona et al. 1991; Catalona et al. 1994).

PSA is an enzyme produced by the prostate gland, excreted as part of the semen where it dissolves the gel surrounding the sperm (Lilja 1985; Balk et al. 2003). Despite its name, PSA has also been found in other organs such as the pancreas and salivary glands, both in men and in woman, but in such low amounts that it is undetectable by our normal tests, and therefore negligible in clinical practice (Pérez-Ibave et al. 2018). The levels of PSA within the prostate are high, and some of it passes to the blood where we can detect it. Since PSA is produced by prostate cells, PSA is found in the blood of every person with a normally functioning prostate; the mere presence of PSA is thus not a sign of prostate cancer. In prostate cancer, more of the PSA produced enters the blood stream, and blood levels are elevated. There are, however, other causes for elevated PSA. Benign prostatic enlargement (BPE) is a common prostatic condition that sometimes causes urinary symptoms. When the prostate is enlarged, more PSA is produced; when more PSA is produced in the gland, more enters the blood stream, and blood levels are elevated. Intermittent elevation can also be seen after febrile urinary infections and in acute urinary retention. This means, that though an elevated PSA could be a sign of prostate cancer, there are many other potential causes.

1.2.2 PROSTATE BIOPSY

An elevated PSA is thus not diagnostic for prostate cancer, neither does it convey the location of the tumour within the prostate. To diagnose prostate cancer, the tissue needs to be examined in a microscope. The sextant biopsy, where six biopsies, i.e. tissue samples, were distributed symmetrically over the prostate under ultrasound guidance via a rectal probe, was first described in

1989 (Hodge et al. 1989); six biopsies were later shown to be insufficient and numbers were increased (Eskew et al. 1997). Symmetric biopsies are also known as systematic biopsies; today, 10-12 biopsies are considered standard. Since the rectum harbours bacteria, the procedure entails a risk for potentially severe infection. To avoid this, prophylactic antibiotics are given, which reduces this risk; despite this, 1% of patients were hospitalized with infection within 30 days after prostate biopsy in a large Swedish study. Infection rates increased significantly with increasing number of biopsies (Lundström et al. 2014). From our experience in the Göteborg 2-trial, which is described below, infection rates are higher in repeated biopsies when the interval between sessions are less than three to four weeks (personal communication, study lead of the Göteborg-2 trial). Increasing antibiotic resistance among common bacteria have prompted the development of new methods where the prostate is accessed through the perineum, the area between the scrotum and anus.

As we know from autopsy studies, microscopic prostate cancer is common and far from all will progress to clinical disease during the lifetime. When prostate biopsies are taken systematically because of elevated PSA, a small, early tumour can be encountered purely by chance, even though the primary reason for elevation of PSA might be BPE rather than prostate cancer. Detection of such tumours is called overdiagnosis. On the other hand, as the whole gland is not examined, more advanced tumours might be missed.

1.2.3 MAGNETIC RESONANCE IMAGING

In an effort to reduce overdiagnosis, prostate magnetic resonance imaging (MRI) has been introduced in recent years. With MRI, lesions in the prostate that indicate potential prostate cancer can be identified, and the level of suspicion can be assessed. The most commonly used system for this assessment is the Prostate Imaging–Reporting and Data System (PI-RADS). It uses defined features in MRI images to score the likelihood of lesions harbouring prostate cancer with Gleason score ≥7 (described below) and/or a volume ≥0.5 cubic centimetres, and/or which extends beyond the prostatic capsule, on a scale 1-5 where 3 is intermediate and 5 is very high risk (Weinreb et al. 2016). Even though a PI-RADS 5 lesion is highly probable to harbour prostate cancer, tissue sampling is still needed for diagnosis. There are currently three main strategies for targeting MRI-lesions: in-bore MRI targeting, where biopsies are performed under real-time MRI guidance, MRI-ultrasound fusion, where MRI images are loaded into the ultrasound software and projected in the real-time ultrasound image, and cognitive fusion, where MRI images are viewed prior to biopsy and cognitively translated to the transrectal ultrasound images during the procedure (Wegelin et al. 2017). The

optimal number of biopsy cores to be taken from each lesion has not been established yet; in the guidelines of the European Association of Urology, 3-5 are recommended (Mottet et al. 2021). This approach has been shown to reduce overdiagnosis, while increasing detection of clinically significant prostate cancer (Ahdoot et al. 2020; Drost et al. 2019; Goldberg et al. 2020; Eklund et al. 2021; Nordström et al. 2021; Kasivisvanathan et al. 2018).

1.2.4 RISK GROUPS

Due to its long clinical course, prostate cancer can be diagnosed anywhere along the line of progression from small cancer foci in the prostate, to metastatic disease. For localized disease, where there is no evidence of spread to distant tissue, the risk for dying from prostate cancer varies greatly. Clinical data is used for prognostication. The risk groups described by D'Amico in 1998 (D'Amico et al. 1998) have been widely adopted; based on PSA value, clinical stage and differentiation, categorization was made in three groups; low, intermediate and high risk. In the most recent version of the Swedish National Prostate Cancer Guidelines (Regional Cancer Centres 2021), information from MRI has been incorporated and the low and high risk groups have been further subdivided into very low, low, intermediate, high, and very high risk respectively (table 1).

Table 1. Prostate cancer risk groups according to the Swedish National Prostate Cancer Guidelines.(Regional Cancer Centres 2021)

	PSA level		Clinical stage		Gleason score		Other requirements
Very low risk	< 10	AND	T1c	AND	6	AND	≤8 mm total cancer length in 1-4 of 8-12 systematic biopsies; PSA density < 0.15 ng/cm^3
Low risk	< 10	AND	T1-T2a	AND	6	AND	Not fulfilling criteria for very low risk
Intermediate risk	10-19	AND/OR	T2b-T2c	AND/OR	7		
High risk	20-49	OR	T3	OR	8 or 4+3 in more than half of systematic biopsies or in targeted biopsies from PI-RADS 5 lesion on MRI		
Very high risk	≥50	AND/OR	T4	AND/OR	9-10	OR	Two or more high risk criteria

1.2.4.1 CLINICAL STAGE

Clinical stage is defined by findings in digital rectal examination (DRE): non-palpable tumours are classified as T1, where T1a and b are tumours diagnosed in tissue from surgery for benign prostatic enlargement, and T1c are tumours diagnosed because of an elevated PSA; palpable tumours within the prostatic capsule are classified as T2, where T2a refers to tumours palpable in less than half of one prostatic lobe (left or right half), T2b in more than half of one lobe and T2c in both lobes; tumours that reach through the prostatic capsule and/or into the seminal vesicles are classified as T3 and tumours invading other organs as T4 (Amin et al. 2017).

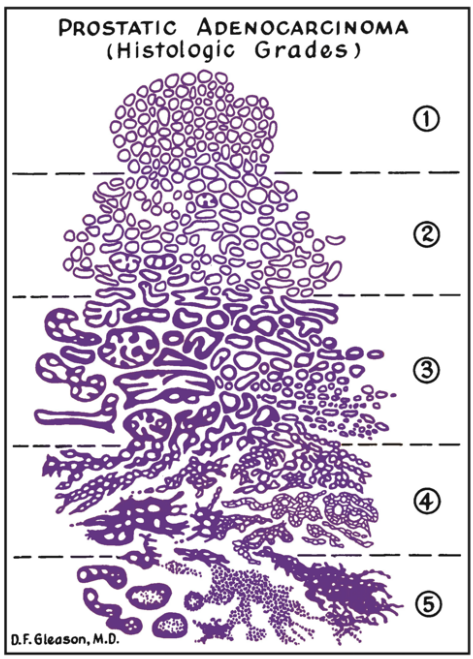

Figure 4. The original drawing of Gleason patterns by Donald F Gleason.

1.2.4.2 GLEASON SCORE

The microscopic appearance of prostate cancer is classified according to the Gleason system, based on the growth pattern of the tumour which often is heterogenous (figure 4). Originally described in 1966 by Donald F Gleason (Gleason 1966), the system has undergone two major revisions in 2005 and 2014 by consensus conferences held by the International Society of Urological Pathology (ISUP). The basis is still the same; five growth patterns from 1-5

with distinct features, where 1 has the least changes compared to normal tissue, and 5 has the greatest changes Initially, the most prominent and second most prominent patters were combined into a score, for example 3+4=7; if there was a tertiary pattern it could be mentioned but was not included in the score. In 2005 the reporting of biopsy specimens was changed to always include the pattern with the highest grade; scores including pattern 2 should be avoided and 1+1=2 should never be diagnosed, neither in biopsies or in prostatectomy specimens. The reasons for advising against the use of pattern 2 in biopsy specimens were poor reproducibility regarding diagnosis of the pattern even among experts, and that in cases diagnosed with pattern 2, radical prostatectomy specimens mostly showed higher grades (Egevad et al. 2019; Epstein 2000; Epstein et al. 2005).

1.2.5 ISUP GRADE

Gleason score has a high prognostic value (Albertsen et al. 2005; Egevad et al. 2002). For Gleason score 7, the prognosis differs between 3+4 and 4+3 (Epstein et al. 2016; Stamey et al. 1999). To take this into account, as well as that the 2005 changes had made 3+3=6 the lowest score diagnosed in prostate biopsies, the 2014 ISUP consensus conference grouped Gleason scores into five categories, referred to as ISUP score or ISUP grade (table 2). The ISUP grading has been criticised for being the product of a rushed decision that causes confusion regarding the nomenclature, and where the broad categorization lacks sufficient detail for prognostication (Egevad et al. 2021). Today, there is no consensus on which system is preferable and both are used in parallel.

Table 2. ISUP grade compared to Gleason score

ISUP grade	Gleason score
1	3+3
2	3+4
3	4+3
4	8
5	9-10

1.3 TREATMENT FOR PROSTATE CANCER

1.3.1 TREATMENT FOR LOCALIZED DISEASE

In early prostate cancer, while the cancer is limited to the prostate gland, there are several treatment options. For low and very low risk cancer, the general recommendation is to abstain from curative treatment to reduce the risk for overtreatment. Analogous to overdiagnosis, overtreatment refers to the treatment of prostate cancer that would not have progressed to cause symptomatic disease or death, if untreated. For patients with a life expectancy of at least ten years, active surveillance is recommended, which means monitoring with repeated PSA-test, clinical check-ups and biopsies and/or MRI in order to initiate curative treatment if there are signs of significant progress of the tumour. For patients with high age or substantial comorbidities, so-called "watchful waiting" is another option. Surveillance is then less intense, without the ambition for curative treatment in case of disease progression; instead hormonal treatment is initiated if needed. In intermediate and high-risk cancer, there are two main options for curative treatment: radiotherapy and surgery, which are two stand-alone treatment modalities, each one used alone. The ProtecT trial is the only randomized trial comparing radical prostatectomy and radiotherapy; all included patients had clinically localized disease, i.e. cancer limited to the prostate (Lane et al. 2014). No significant differences in prostate cancer specific mortality were seen between the treatment modalities after ten years follow-up (Hamdy et al. 2016). In locally advanced disease, i.e. where there is suspicion of the cancer growing through the prostatic capsule, a randomised study conducted by the Scandinavian Prostate Cancer Group is currently evaluating whether surgery improves prostate cancer specific survival compared to radiotherapy and hormonal treatment. In the absence of randomized studies, there is presently more evidence for radiotherapy and hormonal treatment than for radical prostatectomy as a treatment for locally advanced disease, and it is thus considered standard treatment in Sweden. Hormonal treatment, primarily antiandrogen alone, is another treatment option in locally advanced disease.

Radical prostatectomy and recurrence after surgery will be described in more detail below.

1.3.2 TREATMENT FOR METASTATIC DISEASE

When the prostate cancer has spread to other parts of the body, cure is no longer possible. There is, however, effective palliative treatment available. Prostate cancer is dependent of the male sex hormone testosterone and treatment is aimed at reducing the testosterone availability to tumour cells. The primary source for testosterone is the testicles, minor amounts are also produced in the adrenal glands. Hormonal, or endocrine, treatment of prostate cancer was first described in 1941 by Charles B Huggins, who in 1966 was awarded the Nobel Prize in Physiology or Medicine for his discoveries (Huggins & Hodges 1941). Initial treatment consisted of surgical castration, or treatment with the female sex hormone oestrogen which works by interfering with the regulation of testosterone. The levels of testosterone are regulated by a feed-back loop, involving the hypothalamus, the pituitary gland and the testicles (figure 5). Gonadotropin releasing hormone (GnRH), excreted by the hypothalamus acts on the pituitary gland, which excretes Luteinizing hormone (LH), which in turn stimulates testosterone production in the testicles. When the blood levels of testosterone increase, excretion of GnRH decreases, which leads to decreasing levels of LH, less stimulation of the testicles, and subsequently lower testosterone levels. In women, oestrogen is regulated by a similar mechanism, and oestrogen treatment in men works by decreasing GnRH excretion. For forty years, oestrogen treatment was the main treatment option, but cardiovascular side-effects led to a search for alternatives. In 1977, Andrew Schally and Roger Guillemin were awarded the Nobel Prize in Physiology or Medicine for their discoveries regarding the production of peptide hormone in the brain. They had been able to analyse and reproduce the chemical structure of GnRH, and in 1984 the first GnRH-analogues were shown to have equal effect and fewer side-effects than oestrogen (Herbst et al. 1984). GnRH-analogues act by stimulating the pituitary gland, just as natural GnRH does. Initially, this causes an increase in testosterone levels, but with continuous administration which is achieved by injection of slow-release formulas in subcutaneous fat or muscle, the sensitivity for GnRH decreases, resulting in low levels of LH, and subsequently, testosterone (Limonta et al. 2001). Side-effects are related to the desired effect, castration levels of testosterone, and includes hot flushes, decreased libido, erectile dysfunction, decreased muscle mass, weight gain, fatigue, mood disturbance as well as osteoporosis; the individual experience of intensity and frequency of side-effects shows great variation (Nguyen et al. 2015).

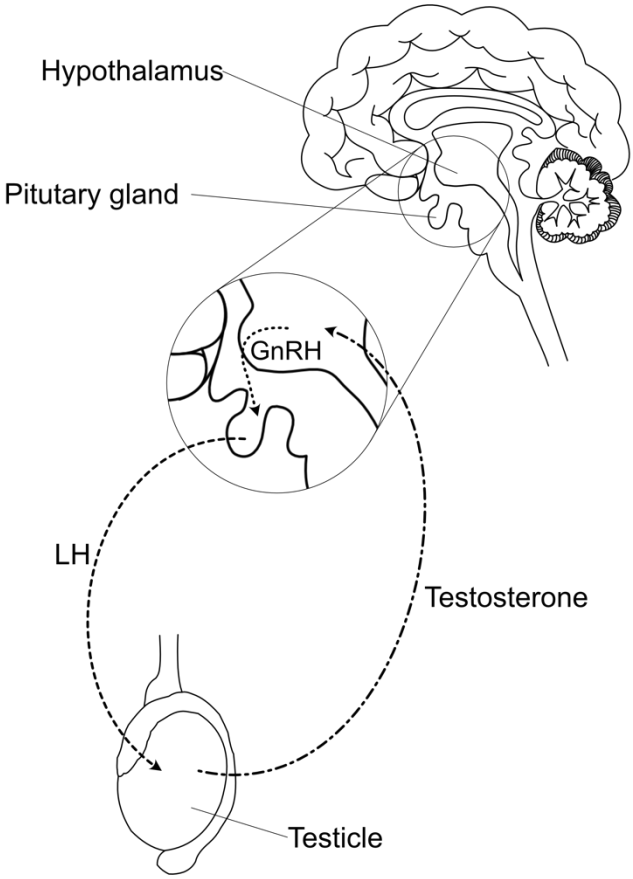

Figure 5. The feed-back loop regulating testosterone levels

Testosterone production in the adrenal glands is not regulated by LH from the pituitary gland, and thus not affected by either surgical or medical castration. Early attempts in blocking testosterone from the adrenal glands to stimulate the tumour included the steroid cytoproterone acetate. Due to the steroidal side-effects, it was eventually replaced by non-steroidal antiandrogens, such as flutamide (Furr & Tucker 1996). Addition of flutamide to medical castration showed benefits over castration alone in advanced prostate cancer (Crawford et al. 1989). However, a frequent side-effect of flutamide is diarrhoea, and in the search for an antiandrogen with better tolerability, bicalutamide was developed (Furr & Tucker 1996). Initially, it was combined with medical castration where it showed benefits compared to flutamide (Schellhammer et

al. 1997); later, it was used alone (Kolvenbag et al. 1998). Bicalutamide in monotherapy has a similar effect on survival as castration in non-metastatic, locally advanced prostate cancer, with less sexual and physical side-effects (Iversen et al. 1998). Treatment with bicalutamide in monotherapy often causes enlargement of the mammary glands, so-called gynecomastia; this can be prevented with a single dose of irradiation to the glands (Tyrrell et al. 2004).

The effect of endocrine treatment is evaluated by monitoring of symptoms and by PSA-tests. Effective treatment is shown by declining levels of PSA. Eventually, the response to hormonal treatment decreases and PSA-levels start to rise, although it might take many years until this happens, and until symptoms occur. In the last ten years, several new drugs with more advanced action on the testosterone metabolism have been developed, providing further treatment options.

1.4 RADICAL PROSTATECTOMY

1.4.1 ANATOMY

The prostate is a fairly concealed organ, situated at the apex of the narrow, male pelvis. Located directly below the urinary bladder, with the urethra passing through it, it is nevertheless accessible via rectum and perineum, as discussed above regarding tissue sampling.

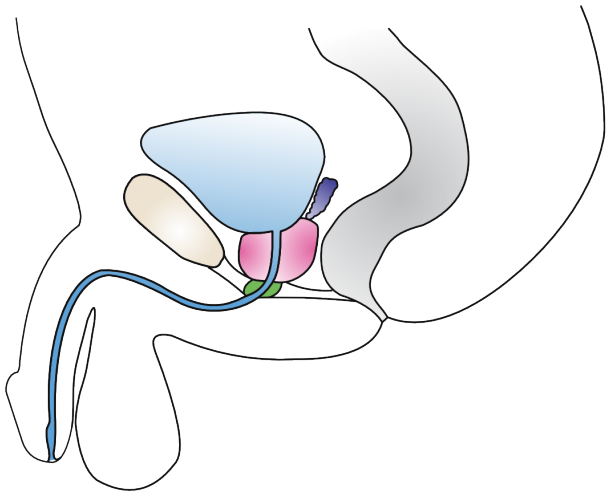

Figure 6. Schematic view of the male pelvis, showing the relationship between the prostate (pink), the seminal vesicles (purple), the urinary bladder and the urethra (both in blue), the pubic bone (beige), and the rectum (grey). The urethral sphincter (green) surrounding the urethra, is in close contact with the apex of the prostate.

The prostate was first mentioned in the 16th century by Niccolò Massa, a Venetian physician, and described in more detail a few years later by Andreas Vesalius, known as the father of modern anatomy. The lack of earlier descriptions has been attributed to anatomical dissections being carried out in animals, where the prostate, if existing, has a considerably different appearance than in humans (Josef Marx & Karenberg 2009). In 1724, Giovanni Domenico Santorini described a plexus of veins, located anteriorly of the prostate, which has been named after him. His descriptions lacked in detail, and severe bleeding was a dreaded complication in surgery in the prostatic region. The first anatomical study of the venous supply from a surgical point of view was conducted by Beneventi and Noback in the late 1940's (Beneventi & Noback 1949); the next major step in understanding prostatic anatomy was taken in

1979, when Reiner and Walsh described the detailed anatomy of the venous complex, and provided a technique for controlling it during surgery (Reiner & Walsh 1979).

Major bleeding had been one of many complications surrounding radical prostatectomy since its first description by Young in 1905 (Young 1905), leading to its relative unpopularity. Another complication was impotence, which had been an inevitable consequence of the procedure. In 1982, Walsh and Donker published the first study of the innervation of the erectile tissue of the penis (corpora cavernosa), and the relation of the nervous supply to the prostate (Walsh & Donker 1982); followed a year later by a description of a new surgical technique, aimed at preservation of the so-called neurovascular bundles, which run bilaterally close to the prostatic surface (Walsh et al. 1983).

Besides severe bleeding and impotence, urinary leakage was the third major complication associated with radical prostatectomy. The muscular anatomy providing the mechanism for male continence was poorly understood, until the extensive anatomical studies performed by Oelrich defined a striated muscle sphincter surrounding the urethra. It develops as a continuous muscle, reaching from the bladder down into the pelvic floor, without connection to the latter; in the adult male, only the part below the prostate remains (Oelrich 1980). The sphincter inserts in the prostatic apex, the anatomy of which is highly variable; thus, the sphincter might be overlapped by the apex in a part of, or the whole circumference (Walz et al. 2010). The part of the urethra surrounded by the sphincter is called the membranous urethra, and extends to the corpora cavernosa.

1.4.2 TECHNIQUE

After the refinements of the surgical technique, presented by Walsh and co-workers, radical prostatectomy gained in popularity. In the 20-year period from 1988 to 2008, the number of radical prostatectomies in Sweden increased 25-fold (Etzioni et al. 2012). In radical prostatectomy, the prostate is separated from the surrounding tissues together with the seminal vesicles. Since the urethra passes through the prostate, the continuity of the urinary tract is restored by an anastomosis between the bladder neck and the remaining urethra. Several variations of technique exist, regarding the direction of the dissection, how to control the surrounding veins and how to reconstruct the urinary tract. A schematic overview of the procedure is found in figure 7. When Young performed his radical prostatectomies, he gained access through the perineum. In 1947, Millin introduced the retropubic radical prostatectomy, performed through a lower midline incision; this remained the common

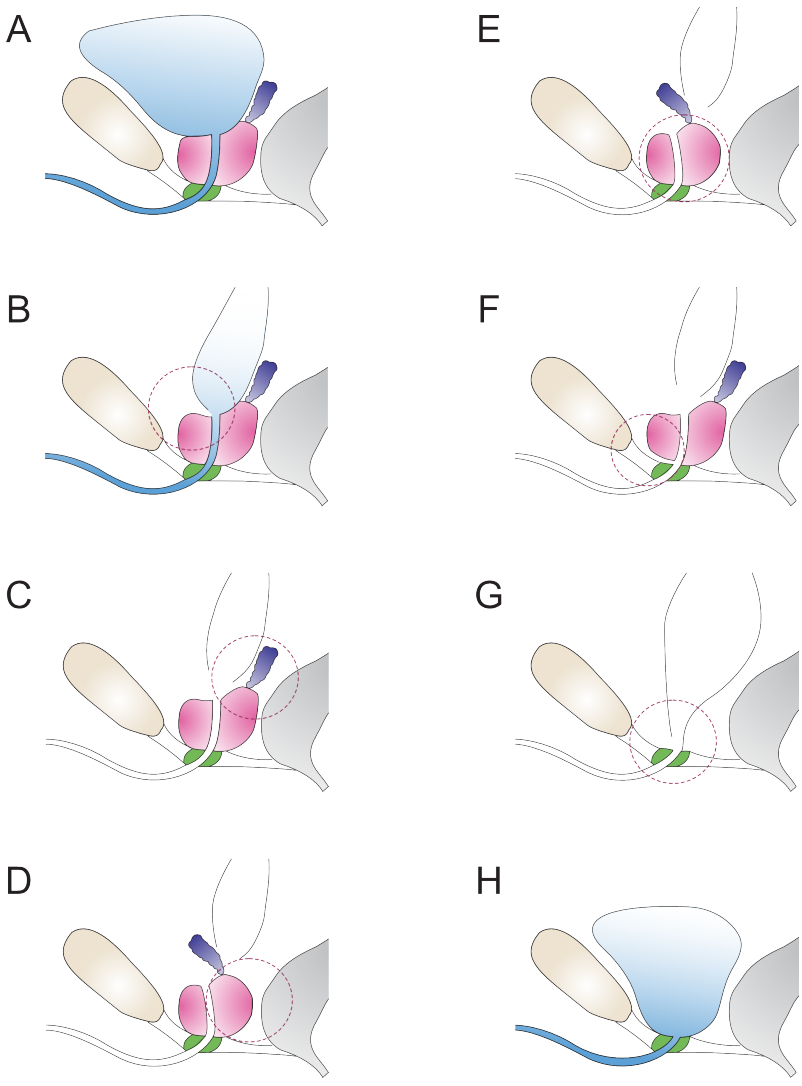

Figure 7. Schematic view of selected surgical steps during radical prostatectomy. A) Before the procedure. B) The bladder has been mobilized to allow access to the prostate, which has been dissected free from the pelvic wall laterally. The bladder neck is incised anteriorly. C) After incision of the posterior bladder neck, the seminal vesicles and the spermatic cords are dissected from the surrounding tissue and the spermatic cords are cut. D) A space between the rectum and prostate is developed. E) The neurovascular bundles are dissected. F) The urethra is divided at the prostatic apex. G) After removal of the prostate, an anastomosis between the remaining urethra and the bladder neck is made. H) After the procedure.

approach for the rest of the 20th century (Millin 1947). The introduction of robot-assisted, laparoscopic technology in the beginning of the 21st century brought hopes that the magnified view and precise dissection now made possible would alleviate long-term side effects. These hopes have so far not been realized, but the technique is associated with other benefits of minimally invasive surgery and has gained wide-spread popularity, despite, or because of, the major investments in technology required (Ilic et al. 2017).

1.4.3 SIDE EFFECTS

Short-term complications include common surgical side-effects; bleeding, infection and venous thrombosis, although all fairly uncommon in modern practice (Ramsay et al. 2012). Stricture of the anastomosis between the bladder and the urethra is a specific complication, with reported rates of 3.6 % and 1.3 % in open and robotic surgery, respectively (Modig et al. 2021). Despite further advances in understanding of the surgical anatomy, impotence and incontinence have remained major long-term side effects. The risk for impotence depends both on patient related factors, such as preoperative erectile function, age and comorbidity, as well as the surgical technique, i.e. to what extent the neurovascular bundles are preserved (Briganti et al. 2009). In a systematic review, potency rates from 63% to 94% two years after surgery were reported in preoperatively potent men; the definition of potency was mostly erection sufficient for intercourse, with or without medication such as Viagra (Ficarra, Novara, Ahlering, et al. 2012). Varying incontinence rates have also been reported in the literature; when continence is defined as no pad use, incontinence rates one year after surgery ranged from 4% to 31% with a mean of 16% in a systematic review (Ficarra, Novara, Rosen, et al. 2012). For severe incontinence after radical prostatectomy, surgery is sometimes an option. The incidence of continence surgery has been evaluated in population-based studies in Austria, Canada and Sweden (Nam et al. 2012; Ventimiglia et al. 2018; Wehrberger et al. 2012); the studied time periods were 1992-2009, 1993-2006 and 1998-2002, respectively. Results were fairly similar; in the Canadian study, 3.9% of radical prostatectomy patients had incontinence surgery at a median of 2.9 years after the primary procedure, in the Swedish study, 3% had surgery at a median of 3 years. In the Austrian study, 2.8% had incontinence surgery, but median time from radical prostatectomy was not reported.

Much effort has gone into understanding and preventing incontinence after radical prostatectomy. Patient-related risk factors include older age, comorbidities such as diabetes mellitus and hypertension have also been proposed, but results are inconsistent between studies (Cakmak et al. 2019;

Wille et al. 2006). Postoperative irradiation is another risk factor (Nilsson et al. 2011).While urinary continence in men relies primarily on the external urethral sphincter described above, there is also an internal sphincter consisting of smooth muscle in the bladder neck, where the bladder passes into the urethra. Preservation of the bladder neck has been evaluated in a randomized trial, showing significantly better continence at long-term follow-up (Nyarangi-Dix et al. 2018). There are, however, concerns about oncological safety if the tumour is located in the prostate base (Bellangino et al. 2017).

The length of the membranous urethra in preoperative imaging has been shown to be a predictor of postoperative continence, where every millimetre in extra length significantly improves the odds (Mungovan et al. 2017). Though urethral length can be measured, the preoperative length can not be influenced by the surgeon; instead techniques to preserve as much of the urethra as possible during surgery have been developed (Schlomm et al. 2011; Hamada et al. 2014), as well as different suturing techniques to reconstruct the urinary tract (Nguyen et al. 2008).

1.4.4 RECURRENCE AFTER RADICAL PROSTATECTOMY

Though radical prostatectomy is a treatment with curative intent, not every patient is cured. The risk for recurrence depends on the biological properties of the tumour. As in newly diagnosed prostate cancer, clinical risk factors are used as proxies in the risk assessment; clinical stage is replaced by pathological stage, i.e. the microscopic spread of the disease, and histologic grade is reviewed from the prostatectomy specimen. Surgical margin status, i.e., whether there are normal cells surrounding the tumour, or cancer cells at the inked margin of the specimen as a sign of cancer cells being left in the surgical field, is another prognostic factor. After surgical removal of the prostate, PSA is supposed to be undetectable. This used to mean a level <0.1 ng/ml; more sensitive methods for analysis can detect PSA at a level of 0.001 ng/ml, but the significance of these levels is disputed (Taylor et al. 2006). Oncological follow-up consists of repeated PSA-test, the first usually undertaken about three months after surgery. There is limited evidence regarding the intensity and length of follow-up. A rising PSA after radical prostatectomy is called biochemical recurrence (BCR); reported rates varies from 15% to 30%. PSA is a very sensitive marker for recurrence, and BCR does not necessarily mean that clinical progression will occur. In a long-term follow-up of a large cohort from the Mayo Clinic, 11.7% of patients with BCR developed metastasis and 5.8% died from prostate cancer at a median follow-up after BCR of 6.6 years (Boorjian et al. 2011).

There is no consensus as to which PSA level should be considered clinically significant; 0.4 ng/ml has been proposed, but ≥0.2 ng/ml is commonly used (Van den Broeck et al. 2019). At these levels, recurrence is not detectable with conventional imaging models, thus, it has not been possible to tell whether the rising PSA is due to local recurrence or distant metastasis. For local recurrences, salvage radiotherapy is an option; assessment of the probability for local recurrence is based on pathological features, when the recurrence occurred and the time in which PSA doubles. Salvage radiotherapy has urinary, bowel and sexual side-effects, including risk for urinary and faecal incontinence, and the risks and benefits must be carefully considered in consultation with the patient (Pinkawa et al. 2008). Positron emission tomography, a relatively new technique in regard to prostate cancer, has been shown to localize recurrences in about one third of cases at PSA levels <0.2 ng/ml, but the clinical utility is not yet evaluated (Crocerossa et al. 2021).

1.5 NATURAL HISTORY OF PROSTATE CANCER

Prostate cancer is, in many cases, a slowly developing disease. From the first malignant cell in the prostate to clinical diagnosis, many years will pass; from diagnosis until metastatic progression and prostate cancer death the development is mostly slow as well (Berges et al. 1995). Prostate cancer can progress locally and cause urinary symptoms; metastasis to regional lymph nodes and distant metastasis can also occur without prominent local progression. The most common site for distant metastasis is bone, accounting for about 90% of distant metastasis, in later stages, lung and liver metastasis can also be found. The exact mechanisms behind bone being the major site for metastasis is not clear (Ye et al. 2007). Before PSA-testing, prostate cancer was mostly diagnosed due to symptoms; predominantly either urinary symptoms and/or hematuria due to local growth of the cancer, or pain from metastasis (Young 1905).

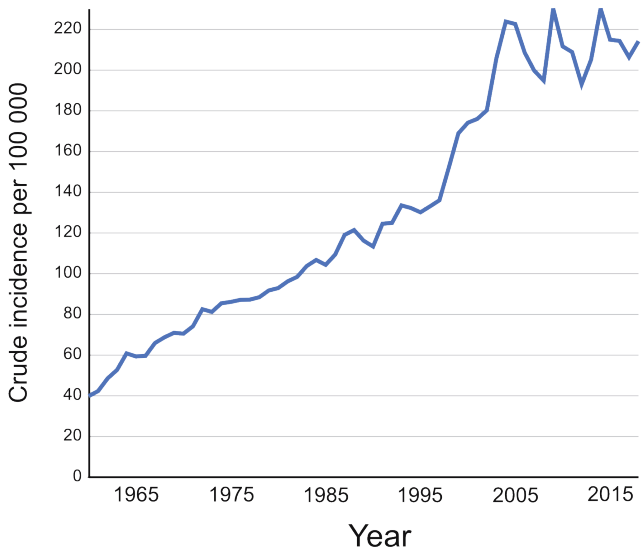

Figure 8. Prostate cancer incidence in Swedish men 1960-2019. Data from GLOBOCAN.

Studies of the development and progression of prostate cancer without treatment other than palliative treatment show that many patients die from other causes than their prostate cancer. Among 767 patients in an American

study, diagnosed between 1971 and 1984 and identified retrospectively, 20 years after the last diagnosis, 29% had died from prostate cancer, 61% from other and 3% from unknown causes; 7% were still alive (Albertsen et al. 2005). In a Swedish, prospective study from the Örebro area, 223 newly diagnosed patients were included between 1977 and 1984; after a follow-up of up to 32 years, 17% had died from prostate cancer and 82% from other causes. (Popiolek et al. 2013). Both of the above-mentioned studies considered patients diagnosed before PSA testing was discovered and adopted. With the introduction of PSA-testing for early detection of prostate cancer came the possibility to diagnose prostate cancer in a preclinical stage.

When PSA testing was introduced in Sweden in the late 1990s, the incidence doubled over a short time (figure 8). Evidently, there were many men with prostate cancer who had not received a diagnosis before this. While PSA-testing enables curative treatment for patients who might have otherwise not been diagnosed until development of symptoms from metastatic disease, it also increases the risk for overdiagnosis.

Prostate cancer can cause significant disease despite not leading to death; in the Örebro study 35% of patients had received treatment for local progression and/or metastatic disease. Nevertheless, the fact that many patients die with, rather than from, their prostate cancer has led to questions whether curative treatment is useful. Curative treatment has been evaluated in randomized studies. Between 1989 and 1999, the Nordic SPCG-4 study by the Scandinavian Prostate Cancer Group (SPCG) included 695 patients with localized prostate cancer, the majority clinically detected, who were randomized between radical prostatectomy and watchful waiting, i.e. no treatment except palliative treatment in case of progression. Data on morbidity and mortality from prostate cancer have been published at different lengths of follow-up. In the most recent update with a mean follow-up of 23.6 years, the relative risk for death from any cause was 0.74, and relative the risk for dying from prostate cancer was 0.55 for patients randomized to radical prostatectomy compared to watchful waiting. Radical prostatectomy gained a mean of 2.9 life years for treated patients, and 8.4 patients needed to be treated to avoid one death (Bill-Axelson et al. 2018). In the US PIVOT study which included 731 patients between 1994 and 2002, the effects were less evident; number needed to treat to prevent one death was 18, and one life-year gained with radical prostatectomy after a follow-up of 22.1 years (Wilt et al. 2020; Wilt et al. 2009). Patients in the PIVOT study were mainly diagnosed because of an elevated PSA, in contrast to in SPCG-4. With PSA-testing, prostate cancer diagnosis is possible before clinical symptoms; the extra time introduced is called lead time, which demands longer chronological follow-up than in

clinically detected cancer for follow-up to be comparable from a disease progression point of view. In the PIVOT trial, a majority of patients were diagnosed with what we call a low risk disease, in which case curative treatment such as radical prostatectomy no longer is the primary recommendation; clinical risk assessment and recommendations regarding treatment will be discussed in more detail below. In the ProtecT trial, 1643 patients were randomized between three treatment strategies; radical prostatectomy and radiotherapy, as mentioned before, and active monitoring, i.e., initial surveillance and curative treatment in case of progression. All included patients were detected by PSA-screening between 1999 and 2009 (Lane et al. 2014). At a median follow-up of ten years, prostate cancer-specific survival was high in all groups, ranging from 98.8% to 99.6%; no significant differences were seen between any of the treatments (Hamdy et al. 2016). Compared to SPCG-4 and PIVOT, follow-up in ProtecT was much shorter, and both prostate cancer-specific and all-cause mortality was low. However, metastasis, an event occurring earlier in progression, was significantly more common in active monitoring. In SPCG-4, the absolute differences in mortality have increased over time; the largest benefits from radical prostatectomy are seen in younger patients. Survival is not only depending on chronological age. The PIVOT trial has been questioned regarding generalizability, since included patients had a high degree of comorbidity. Even though a life expectancy of at least ten years was required for inclusion, 40% of patients had died at the 10-year follow-up (Dalela et al. 2017).

1.6 SCREENING OR NOT?

Screening for disease means applying some diagnostic measure to the whole or a certain part of the population, in absence of symptoms of said disease. In Sweden, all new-born babies are screened for some rare, congenital diseases; screening for breast cancer and cervical cancer is also offered to women in certain age groups, as well as screening for abdominal aortic aneurysms for men (Wanhainen & Björck 2011; Autier et al. 2012; Elfström et al. 2016). Screening for colorectal cancer is recommended by the National Board of Health and Welfare, but not yet implemented all over the country (Thorlacius & Toth 2018).

Due to the overdiagnosis and subsequent overtreatment associated with PSA-screening, and the side effects from treatment, screening for prostate cancer is not recommended in Sweden. In fact, there are only two countries with a national screening programme for prostate cancer, Kazakhstan and Lithuania (Kohestani et al. 2018). Nevertheless, PSA-testing in absence of symptoms is widely adopted; it has been estimated that more than half of Swedish men aged 55-69 years have been PSA-tested at least once (Jonsson et al. 2011). This can be referred to as wild, or opportunistic, screening. General screening for prostate cancer with PSA has been studied in the European Randomized Study of Screening for Prostate Cancer (ERSPC), of which the Göteborg Randomised Prostate Cancer Screening Trial was part. The Göteborg trial started in 1995, when 10 000 men were randomised to PSA-screening every second year from 50 to 70 years of age, and 10 000 men were randomised to a control group, only followed by national registers. After a median follow-up of 14 years, mortality reduction in the screening arm was 44% compared to the control arm (Hugosson et al. 2010). Incidence and mortality rates in the two groups have also been compared to expected rates in absence of PSA-testing, based on historic data, in order to evaluate the effect of opportunistic screening. After 18 years of follow-up, the incidence had increased and the mortality had decreased in both groups. Mortality reduction was largest in the screening group: 42% vs 12% in the control group. The number of patients needing to be diagnosed in order to save one from prostate cancer death can be used to quantify overdiagnosis. In the screening group, 13 men had to be diagnosed with prostate cancer in order to save one man from prostate cancer death; the corresponding number in the control group was 23 (Arnsrud Godtman et al. 2015). In summary, opportunistic screening results in more overdiagnosis than in organised screening, and is less effective in reducing mortality. In a screening programme, start and stop age of screening and the screening interval affect estimates of overdiagnosis. With a screening age of 55-67 years and a screening interval of one year, an overdiagnosis rate of 50% has been

estimated in ERSPC (Draisma et al. 2003). Population studies show that opportunistic screening is common in older age groups, with about 20% of men above 80-85 years having had a PSA-test (Enblad et al. 2020; Nordström et al. 2013).

1.7 QUALITY OF LIFE

While a treatment can have a major effect on the outcome, it can also bring side-effects which impairs the patient's quality of life (QoL). The long natural history of prostate cancer, where survival benefits are evident only after many years, makes this especially important to consider. There is an old saying based on the Roman poet Virgil's words "aegrescitque medendo" from the epic poem Aeneid, translated in English as "the cure is worse than the disease; the Swedish equivalent says that "the cure should not be worse than the disease". Though this principle is appealing, for an individual the right balance can be hard to find. The World Health Organization (WHO), defines quality of life as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (World Health Organization 2012). In order to assess and measure this abstract concept, several questionnaires have been developed and validated; both for general QoL, and for disease-specific as well as symptom-specific QoL.

Quality of life in prostate cancer patients has been investigated for different treatments, both in comparison to each other, or for themselves. Long-term QoL for patients in the SPGC-4 trial were reported in 2011. Even though frequency of symptoms and symptom-related distress in different domains varied between the groups, with distress from urinary leakage and erectile dysfunction being significantly higher in the radical prostatectomy group, QoL was the same; high self-assessed QoL after a median follow-up of 12.2 years was reported by 35% and 34% of patients randomized to radical prostatectomy and watchful waiting, respectively. The corresponding number in a matched control group, randomly recruited from the general population, was 45%. SPCG-4 was conducted before the onset of PSA-testing; 19% of patients in the radical prostatectomy group and 28% in the watchful waiting group had received androgen deprivation therapy (ADT) (Johansson et al. 2011). In a screening-detected cohort of later date, patients in the ProtecT trial were compared regarding treatment related symptoms and QoL at randomization and 6, 12, 24, 36, 48 and 72 months thereafter. As in SPCG-4, symptoms and symptom-related QoL in the respective domains differed between the groups, but no significant differences were seen regarding either health-related, or cancer-related QoL (Donovan et al. 2016). Changes in QoL have been shown to have a significant association with treatment satisfaction in patients treated with radical prostatectomy or radiotherapy (Sanda et al. 2008). Primary ADT is associated with persistent decline in health-related QoL which is more severe than after curative treatment (Sadetsky et al. 2011; Johansson et al. 2009).

Recurrence in other types of cancer has been shown to impair QoL (Bull et al. 1999; Camilleri-Brennan & Steele 2001; Vivar et al. 2009). In a study on breast cancer recurrence, comparing different QoL measures between breast cancer patients with recurrence, and patients who remained free from disease, this effect seemed to be mainly driven by impairment in QoL in patients with metastatic disease, while patients with local recurrences did not significantly differ from disease-free patients (Oh et al. 2004). Biochemical recurrence in prostate cancer is special, since an increasing PSA precedes clinical presentation of a recurrence, often by a very long time, and since a recurrence does not always lead to treatment. Studies on QoL in patients with BCR are scarce. In two studies evaluating QoL with quantitative methodology, using validated questionnaires, QoL in patients with BCR did not significantly differ from prostate cancer patients without recurrence (Ullrich et al. 2003; Pietrow et al. 2001). In a study of 28 patients in 2008, evaluated both with qualitative and quantitative methodology in the form of focus group discussions and administration of validated self-reported measures, Ames et al. found discrepancies regarding reported mood disturbance, where the qualitative measures showed a negative impact from the recurrence, in contrast to quantitative measures where no such effects were seen. In the focus group discussions, coping strategies involving conscious efforts to keep up normal activities without thinking of the recurrence were reported; the authors hypothesize that this may account for the discrepancies (Ames et al. 2008).

1.8 STUDY DESIGN AND STATISTICS

Epidemiological studies are named after the study of epidemics, where the methodology was first applied, but the methods has far wider applications. In epidemiological research, the aim is to assess the effect of an exposure, that for example could be a disease, a genetic predisposition, or the actual exposure of a treatment, or an environmental agent, on an outcome. The outcome could be the development of certain symptoms, a disease, progression of known disease or death, or some other factor of interest. When designing an epidemiological study there are numerous options, each one with its own pros and cons. The choice of design should ideally be dictated only by the possibility to achieve the desired results, but in reality, other factors often have to be considered. If, for example, the long-term outcome for patients receiving a certain kind of treatment is to be studied, one way could be to set up a study where patients with the condition are included before treatment, and specified data on the outcome are subsequently collected at desired time points; a prospective study. In this way it will be possible to get the right kind of data, as it is prespecified according to the requirements of the planned analysis, but it will take long time to achieve long-term results and the studied treatment might already have been modified when the study ends. In a retrospective study, existing data from different sources are used instead. In this way, long-term results can be achieved fast, but the available data might not be optimal for the analysis and the quality of data can not be controlled in the same way as in a prospective study. If the aim is to compare two kinds of treatments in a prospective study, patients already planned for the different treatments could be included, or the allocation to different treatments could be made in the study randomly; the latter will be discussed further below. To make appropriate choices, one has to be clear of one's own aim and know how to compensate for limitations in study design.

1.8.1 CORRELATION AND CAUSATION

By statistical methodology, an association or correlation between the exposure and the outcome can be established. To understand the results obtained, an understanding of the underlying mechanism is needed, otherwise we might draw the wrong conclusions. Stating that an exposure affects the outcome implies causation, i.e. that there is some kind of mechanism by which the exposure acts on the outcome. In epidemiological research, we often deal with observational data, as opposed to in experimental studies where the exposure is introduced by the researcher. To establish a causal relationship, we need either to demonstrate the underlying causal mechanism, or to exclude that the effect is caused by some other mechanism. Without a possible causal

explanation, we are left with only a correlation. Say for example, that to carry a lighter is shown to increase the risk for developing lung cancer. There is no plausible causal mechanism by which a lighter in the pocket in itself affects the lungs; however, smoking is well-known to cause lung cancer, and it is likely that a person carrying a lighter also is a smoker. Carrying a lighter is thus correlated to lung cancer development, but it is not a causal factor.

1.8.1.1 DIRECTED ACYCLIC GRAPHS

Biological processes are often complex and involves multiple exposures besides the one of interest. A theoretical framework is needed to find a way to achieve the desired results. Directed Acyclic Graphs (DAG) is a method to visualize and summarize the relationship between different variables, and thereby structure one's knowledge when planning a study, and when selecting variables for inclusion in statistical models. In a DAG, variables are represented as nodes, with arrows between nodes where there is a causal relationship. The arrows point in the direction of the causal effect; hence, "directed". "Acyclic" means that by following the causal arrows, you can never get back to the starting variable, relationships are not cyclic. In its simplest form, the DAG only involves an exposure and an outcome (figure 9 a); as many variables as needed can then be added.

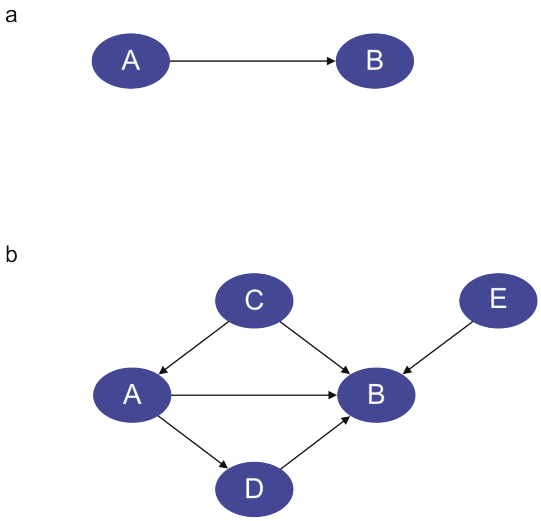

Figure 9. Example of a DAG, A – exposure, B – outcome; b) C – confounder, D – mediator, E – risk factor unrelated to the studied exposure

1.8.2 CONFOUNDING

There can be multiple possible causes for one outcome; some of them might also be correlated to the exposure of interest. In figure 9 b, three additional nodes have been added to the DAG in figure 9 a. Node C represents a factor, associated with both the exposure and the outcome, that is not a part of the causal path between A and B. If we study the effect of smoking (node A) on lung cancer (node B), node C could represent age; age in itself increases the risk for cancer, and smoking status differs between generations. Node D, on the other hand, is part of the causal pathway; it mediates the effect of A on B. If we stick with the lung cancer example, it could be the presence of cigarette smoke in the lungs. Node E represents a risk factor for the outcome B, not related to the studied exposure A; it could for example be a congenital genetic factor increasing the risk for lung cancer where the size of the effect is the same regardless of smoking status.

Factors like C, that are correlated to both exposure and outcome, but are not part of the causal path, are called confounders. Confounders do not have to have a causal effect on the exposure, for example, older age does not cause smoking; an uneven distribution of a risk factor for the outcome between exposed and unexposed groups can cause confounding. When estimating the effect of an exposure on an outcome, confounders have to be controlled for. Mediators, like factor D, should not be controlled for; if we remove the effect of smoke in the lungs in our estimate, we also remove part of the effect we are interested in. Factors like E, that are only associated with the outcome, without any relation to other variables, are not confounders. Inability to identify and control for confounders will result in results that are untrue. The most extreme case is when the real cause is confused with a confounder, which subsequently is thought to be the real cause. A classic example is the effect of birth order on the risk for Down syndrome. In 1966, Stark and Mantel published a study regarding the effects of birth order and maternal age on the risk for leukemia and Down syndrome, prompted by earlier studies that had been inconclusive regarding the effect of birth order on the outcomes (Stark & Mantel 1966). The incidence of Down syndrome increased with increasing birth order, as with increasing maternal age. When the effect of birth order was analysed separately within five-year age groups, there were no longer any differences between children with different birth order; the apparent effect of birth order was caused by the fact that higher birth order implies higher maternal age. In this sense, maternal age can be seen as a confounder for the effect of birth order on the risk for Down syndrome; when maternal age was controlled for, no effect remained.

Apart from causing confusion of causes, confounding could also dilute an effect so it seems less apparent, or even make it seem reverse. If confounders are not handled in one way or another, the effect measure will not show the true effect. Ideally, all possible confounders can be identified and measured, but sometimes what we can measure is only a proxy of the true confounding effect; there is also the possibility for different, completely unknown confounders. For known confounders, there are several different ways of handling them.

1.8.2.1 RESTRICTION

One way to control for a known confounder is to exclude patients with a certain risk factor from the study. Though restriction is very effective in removing a confounding effect, it limits the study population, potentially leading to loss of statistical power. By restriction, the generalizability of the results will also be diminished. If, for example age, is a strong confounder for an outcome, and patients older than a certain age therefore are excluded, the effect of the exposure on younger patients can not automatically be taken for granted in elder patients. Restriction is applied prior to analysis. In the analysis there are other ways of controlling for confounders; some common methods will be presented below.

1.8.2.2 STRATIFICATION

In a stratified analysis, the material is split into groups, strata, based on the value of the stratification variable and the effect measure is calculated separately for each group. The analysis of birth order, maternal age and the risk for Down syndrome is an example of stratification, where the risk according to birth order was calculated separately for children based on maternal age. In this case, the effect of birth order was the same in every stratum, showing that it had no effect on the risk. If the effect differs between strata, there is a confounding effect. Stratification is only possible when there are few possible confounders and sufficient number of cases, otherwise the number of groups will be large, and the number of cases in each group too low for analysis.

1.8.2.3 REGRESSION

When there are many confounders to consider, other methods are needed. In regression analysis, a statistical model for the relationship between one variable, or a number of variables and the outcome is formed; named univariable and multivariable analysis, respectively. In univariable analysis, the effect of one variable on the outcome is estimated. When adding more variables in a multivariable model, the effect of one and each of the other variables are incorporated in the model, providing an estimate of the effect on

the outcome, all variables considered; a separate effect measure is provided for each of the included variables. Estimates in univariable analysis does not consider the effect of any other factor than the one included and is thus called unadjusted analysis; while multivariable analysis is called adjusted analysis. In the presence of confounding, estimates in adjusted analysis differ from the estimates in unadjusted analysis.

Depending on the nature of the outcome, different types of regression based on different mathematic models are used; for binary outcomes, common in epidemiologic studies, *binary logistic regression* can be used. Here, the effect of one or more variables on an outcome that can either occur or not, is estimated; the only information regarding the outcome is whether it has occurred or not. In logistic regression, we typically study an outcome that occurs at a certain point or within a small timeframe. We could for example study the effect of quitting smoking before surgery on the risk a having a wound infection. For events that might occur within a larger time frame, such as mortality in metastatic prostate cancer, this approach entails some limitations. With long enough follow-up, all patients will eventually die, either from prostate cancer or from other causes. If we study the effect of a new drug, it might prolong time to death, but not prevent death from prostate cancer. If we just compare the rate of death from prostate cancer between patients receiving the new drug or not, there might be no differences, despite patients receiving the study drug living longer; in addition, unless the study continues until every patient has died, information from patients still alive at the end of study will be lost. To overcome this, other methods can be used, for example *Cox regression*. Here, the information collected regarding the outcome is not only whether it has occurred or not, but also when it has occurred in relation to when the patient entered the study. For every included individual, the studied time is calculated and used in the analysis; no information will be lost. The starting point is the same for each individual, though inclusion in the study can be on different dates, while the end point differs. For individuals experiencing the studied event, the event itself marks the end of the studied time; for individuals not experiencing the event, their studied time ends when the study ends, or when they leave for some other reason. This is called the censoring point, and cases are said to be censored. The length of studied time, and if the event has occurred or not, forms the basis for the analysis; the estimate of the effect does thus take time as well as the event itself into account. Censoring is supposed to be independent, meaning that censoring and the risk of experiencing the event are not related; individuals leaving the study are supposed to have the same risk for experiencing the event as the remaining individuals. Another assumption in Cox regression is the proportional hazards assumption, meaning that the ratio between the hazards for experiencing the

outcome for any pair of included individuals should be constant over time; if the hazard at different time points should be plotted for both, the curves should have the same relation to each other at every point. Other variables can be included in the Cox model, just as in logistic regression, to provide an adjusted effect measure. Estimates obtained in regression analysis is usually expressed as a ratio between the effects in exposed and unexposed individuals.

1.8.3 RANDOMIZATION

The aim of adjustment is to provide an effect measure that is unbiased, meaning mirroring only the effect of our exposure, if there were no confounding factors. Methods for statistical adjustment do this by producing an artificial situation, where levels of confounders are the same, balanced, between exposed and unexposed groups. Adjustment can only be done for known confounders on which we have information; thus, the effect of any unknown or unmeasured confounders will remain.

Randomization is a way to achieve balance between groups, by randomly assigning individuals to exposure or not. Every included individual thus has the same probability of being exposed, independent from any other factor, including unknown confounders, if such exist. Randomization is typically done in trials of new drugs, but can also be used in other situations, such as the Göteborg Randomised Prostate Cancer Screening Trial referred to above. Randomization often requires a lot of resources, which is one of the factors limiting its use. There are also situations where randomization is hard to achieve; in a drug study, placebo medication that is identical to the study medication, except for not containing any active substance, could be procured. Surgical studies are hard to standardize in the same way; surgeries are complex procedures where outcome depends not only on what procedure is performed, but also on how and by whom it is performed (Nyberg et al. 2020). Randomization can also be impossible due to ethical reasons; patients participating in randomized study can not be put at risk for a worse outcome than with standard treatment.

1.8.4 SURVIVAL ANALYSIS

When analysing time to event data in a regression model as described above, we acquire a measure of the effect on the outcome from our studied exposure, typically presented as a ratio, where the risk (hazard) for experiencing the outcome for the exposed group is divided by the risk for the unexposed group. Often, we are not only interested in the effect size, but also in the differences in time of survival with or without experiencing the event of interest. This can be estimated using Kaplan-Meier survival analysis. In Kaplan-Meier analysis,

the proportion surviving at each time point is calculated as the proportion surviving of individuals still remaining in study at this point, not as the proportion of all patients included; this proportion is then multiplied with the proportion surviving at the preceding time point to provide an estimate of the survival from the studied event. Despite being known as a survival analysis, the Kaplan-Meier method can be used for estimation of time to any binary outcome, for example the development of metastasis or regaining continence after radical prostatectomy. Adjustment for confounders is not possible in Kaplan-Meier analysis; stratification is often used.

Correct estimation by the Kaplan-Meier method relies on the assumption of non-informative censoring, which is similar to independent censoring, as mentioned regarding Cox regression. Essentially, non-informative censoring means that the risk for experiencing the event should be the same for censored cases, as for those remaining in the study. There are situations when this assumption is probable to hold; when patients are censored because they move and are lost to follow-up, for example. For patients censored because of death, on the other hand, the assumption is violated. After death, it is no longer possible to experience a side-effect, get metastasis, die from the studied disease, or any other outcome studied, so the estimates acquired by the Kaplan-Meier method might thus be biased.

1.8.5 COMPETING RISK ANALYSIS

An event, which, if it occurs, makes it impossible for an individual to experience the studied event, is called a competing risk. In the presence of competing risks, Kaplan-Meier and Cox estimates might be biased; instead, a competing risk analysis can be performed. In competing risk analysis, the competing event is included in the model as a separate event, an estimate of survival in the presence of competing risks is obtained. Competing risk analysis can be used by itself, but also as a complement to Kaplan-Meier and Cox regression analysis, where the estimates obtained by each method are compared to assess whether the results where competing risks not are taken into account can be considered as valid.

1.8.6 MISSING DATA

In clinical studies, data can be missing for various reasons. A patient questionnaire or a clinical report form might not be filled out at all, or answers to certain questions might be lacking due to neglect or reluctance, or because of uncertainty about how to answer for example, and in digital forms there is a possibility for technical issues. Missing data can be handled in different ways; the first and most important measure is to take all reasonable steps to avoid it.

If, however, missing data is unavoidable, one must decide on how to handle this in the analysis; this issue should be addressed before the start of the analysis. Depending on the nature of the missing data and the type of missing, i.e. if there is a systematic reason for data being missing or not, and the specific analysis, different strategies can be used. One way is to exclude cases with missing data; either on all or selected variables. This approach can result in a large reduction of the study population. Imputation is another option; in both cases the effect estimates might be distorted if there are systematic reasons for data being missing.

Imputation is the process of replacing missing data with a value, for which different methods that can be categorized as either single or multiple imputation exist. Single imputation can be made by assigning the mean value of a variable to all missing values within that variable; either using the mean for the whole dataset, or by calculating different means for different subsets based on other variables. Other methods of single imputation include using a regression model based on other variables for estimating the value of missing variables. However, regardless of method, the imputed value is treated as the true value for that individual in subsequent analysis, disregarding the fact that it is an estimation with an inherent uncertainty. This can make the estimates of the studied effect seem more certain than they are. Multiple imputation methods account for uncertainty in the estimates by creating multiple datasets where imputed values differ. Separate analyses are made from each one, and estimates from each analysis are then pooled to provide the final estimate (Spratt et al. 2010; Azur et al. 2011; Wulff & Ejlskov 2017).

1.8.7 STATISTICAL SIGNIFICANCE

In statistical analysis, the aim is usually to draw conclusions about an entire population, which could be defined on different grounds: a certain age group, an occupation, pregnant women or patients with early prostate cancer, for example. In most cases, the whole population can not be studied, instead, individuals who are supposed to be representative for the population of interest are selected in one way or another. They can thus be seen as a sample of the true population. The degree of statistical uncertainty in the results is often expressed as a confidence interval (CI) with a specified confidence level; the confidence interval describes a range, and the confidence level the probability with which the interval includes the true value of the studied parameter for the population. The wider the interval, the greater is the uncertainty of the estimate, provided that the confidence level is the same. Confidence intervals can be calculated for estimates of certain parameters, such as mean and median values, but also for effect measures.

Mostly, we do not only want to describe one estimate, but to make comparisons; for example, between treatment groups, or within the same group before and after an intervention. Though the underlying assumption is that the study population is representative, there is a possibility that the results obtained are not, and that the effects seen are only due to chance. Confidence intervals can be used for comparisons, for example between effect measures obtained in regression analysis. As described above, these are often expressed as a ratio between the effects in exposed and unexposed groups, for which a confidence interval can be calculated. The confidence interval describes whether effects differ, i.e., whether the ratio between them differs from one, but also the size of the effect. The p-value describes the probability to achieve the same, or a more extreme result as the one obtained, provided that there is no true difference. To reach statistical significance, the p-value must be below the significance level. The significance level describes the maximal probability for falsely claiming that a difference exists that is accepted in the analysis and is chosen prior to analysis; in epidemiologic studies, a significance level of 5% is often used. Not reaching the level of statistical significance only means that no statistically significant differences were seen; it is not proof that no differences exist.

Statistical significance is not the same as clinical significance. In a large enough study, even a very small difference can reach statistical significance, but the difference also has to be clinically relevant. If, for example, a new medication increased time to distant metastasis in recurrent prostate cancer with two weeks, it would not be considered as clinically significant even though it was statistically significant.

2 AIM

The overall aim of this thesis is to investigate the additional value of systematic biopsies for sufficient preoperative mapping in the light of changing diagnostic pathways for prostate cancer, how surgical choices affects the outcome for patients undergoing radical prostatectomy and the long-term prognosis after surgery.

Objectives of each paper are as follows:

I. To assess whether preservation of the neurovascular bundles during radical prostatectomy affects continence rates one year after surgery.

II. To determine whether the degree of preservation of neurovascular bundles during radical prostatectomy influences oncological outcomes.

III. To evaluate whether the addition of systematic biopsies provides information essential to the planning of surgery for prostate cancer diagnosed by MRI and targeted biopsies.

IV. To estimate long-term risk for biochemical recurrence and subsequent prognosis in a population-based cohort.

3 PATIENTS AND METHODS

The four papers included in this thesis are based on the Laparoscopic Prostatectomy Robot Open (LAPPRO) trial (**paper I-II**), the GÖTEBORG prostate cancer screening 2 trial (**paper III**) and the Western Sweden study of Opportunistic Prostate Cancer Screening (WSOP) database (**paper IV**).

LAPPRO is a prospective, controlled, multicentre study, originally designed to evaluate differences in continence 12 months after surgery between open radical prostatectomy and robot assisted laparoscopic radical prostatectomy (RALP). Patients were included between September 1 2008 and Nov 7 2011 at 14 Swedish urological centres; seven centres performed open and seven performed robotic surgery. Participating centres included both academic, public and private hospitals of different sizes. In total, 4003 patients were included, accounting for about half the number of performed prostatectomies in Sweden during the study period. No randomization was made between methods; patients received open or robotic surgery depending on which method was in use at each site. The inclusion criteria at baseline were age at surgery <75 years, PSA <20 ng/ml, clinical tumour stage <T4, and no clinical signs of distant metastasis. While patients could be included in the study regardless of number of prior surgeries performed by the surgeon, only patients treated by a surgeon who had performed at least 100 prior surgeries with the same technique were included in analysis of the primary endpoint. Methods of data collection are described below. The study was approved by the regional ethical review board in Gothenburg (number 277-07) and registered in the Current Controlled Trials database (ISRCTN06393679). It is described in detail in a previous publication (Thorsteinsdottir et al. 2011).

The Göteborg Prostate Cancer Screening 2 Trial (Göteborg-2 trial) is an ongoing prospective, randomised, population-based study of prostate cancer screening, starting in 2015 and aiming to include 54 000 men. The aim of the study is to evaluate whether screening with PSA and MRI, where biopsies are performed only in case of suspicious lesions on MRI, can reduce the risk of detecting clinically insignificant cancer, primarily defined as Gleason score 3+3 in prostate biopsy, while maintaining detection of clinically significant cancer, defined as Gleason score ≥ 7 in prostate biopsy, compared to screening with PSA alone in patients with PSA ≥ 3 ng/ml. A secondary objective is to evaluate whether detection of clinically significant cancer can be improved if the PSA cut-off is lowered to 1.8 ng/ml in MRI-based screening. A random sample of men 50-60 years residing in the Gothenburg area in Sweden are randomized 2:1 to screening or a control group. The screening group is further

allocated 1:1:1 to one of three study arms and invited to PSA-testing. Men having PSA-levels at or above the threshold (3.0 ng/ml for arm 1 and 2, 1.8 ng/ml for arm 3) are offered MRI. In arm 1, standard, systematic biopsies are performed blinded to MRI results, followed by cognitive targeted biopsies in case of a positive MRI, defined as PI-RADSv2 3-5 (Weinreb et al. 2016). In arm 2 and 3, cognitive targeted biopsies are performed if there is a positive finding at MRI; in case of a negative MRI, no biopsies are performed, unless PSA is ≥ 10 ng/ml, in what case systematic biopsies are recommended. Patients not undergoing biopsies because of PSA below the cut-off or because of a negative MRI, as well as patients with negative biopsies are re-invited for screening at pre-specified intervals, based on: PSA value, previous findings in MRI and whether biopsies have been performed or not. If the patient is diagnosed with prostate cancer and planned for radical prostatectomy, systematic biopsies are performed before surgery. The study is described in detail in a previous publication (Kohestani et al. 2021). The study was approved by the Regional Ethical Review Board in Gothenburg (number 890-14).

WSOP is a database, originally established to describe opportunistic prostate cancer screening using PSA, and to evaluate the effects of opportunistic screening as opposed to organized screening. WSOP is population-based and includes all men from the age of 18, registered as living in the Western Medical Care Region in Sweden on 31 December any year from 1995 to 2014. The database consists of PSA values and pathology data analysed at the hospital laboratories and the largest private laboratory in the region during the same period; availability of data differs between sites. These data are linked to data from several nation-wide and regional registers by means of the Swedish personal identity number. Included registers are: the Swedish Cancer Register, the Total Population Register, the Cause of Death Register, the Multi-generation Register, the National Prostate Cancer Register, the Prescribed Drugs Register, the Longitudinal integrated database for health insurance and labour market studies (LISA), the Patient Register, Region Västra Götaland's database on health care utilization (VEGA) and the database from the Göteborg Randomised Prostate Cancer Screening Trial. Available data includes any cancer diagnoses, inpatient and outpatient encounters, time and cause of death, prescribed drugs, socioeconomic data, data on prostate cancer diagnosis and treatment and identity of father and brother. A detailed description of the database can be found as a supplement to **paper IV**. The study was approved by the Regional Ethical Review Board in Gothenburg (number 467-15).

3.1 STUDY POPULATION

The study population of **paper I** consists of patients included in LAPPRO between September 1, 2008 and November 7, 2011 who were younger than 80 years and without signs of distant metastasis. Patients with any of two known risk factors for postoperative incontinence; preoperative incontinence and postoperative irradiation, were excluded. Of the remaining patients, 3148 (93%) had information on continence 12 months after surgery and were included in the final cohort (figure 10).

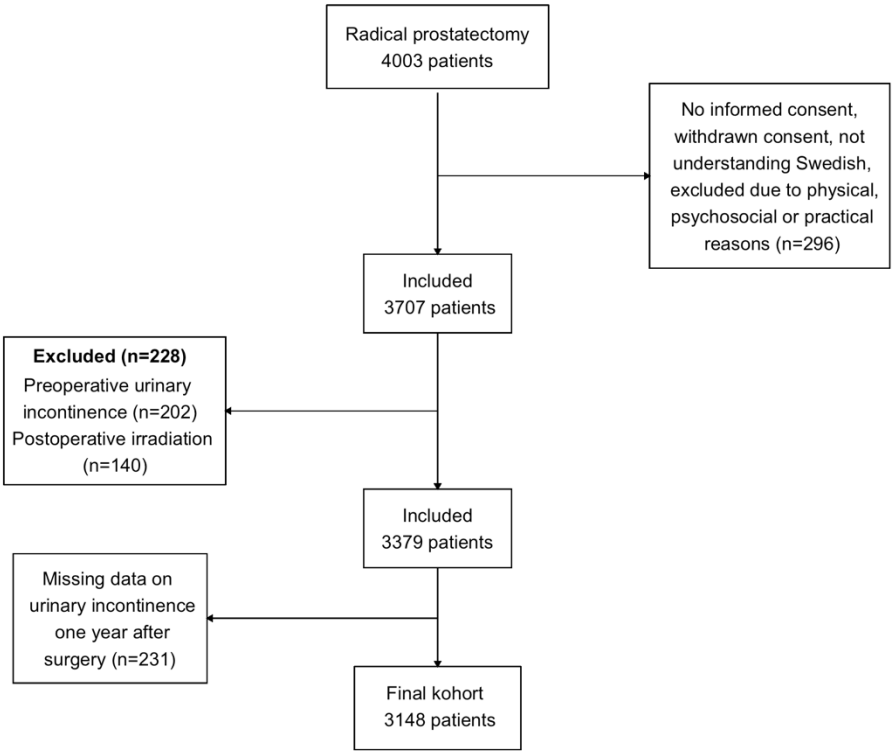

Figure 10. Flow chart, paper 1

The study population of **paper II** consists of patients correctly included in LAPPRO between September 1, 2008 and November 7, 2011, who had robot-assisted surgery. Patients with missing data on possible confounders, as well as patients who still had a PSA above the threshold at the first postoperative measurement or had adjuvant radiotherapy before BCR were excluded, leaving 2401 patients for analysis (figure 11).

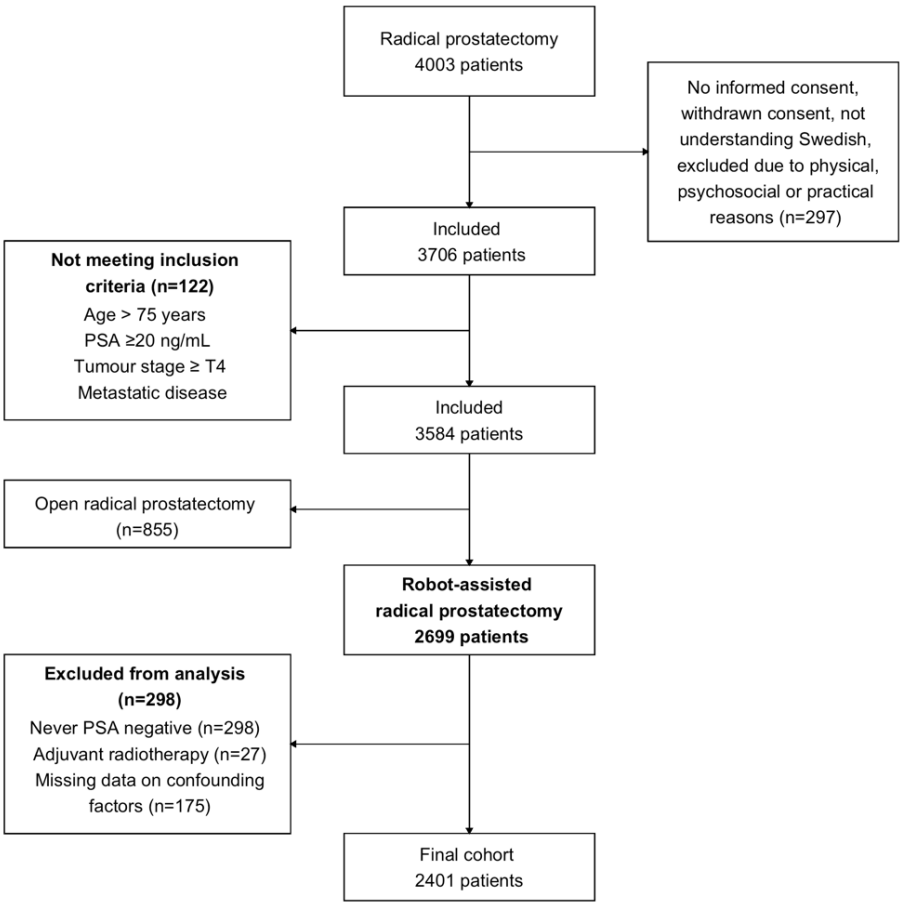

Figure 11. Flow chart, paper II. Axén et al. Published in European Urology Open Science 2021: 25-33.

For **paper III,** we included patients in the Göteborg-2 trial, having radical prostatectomy until March 4, 2021, who had a positive MRI and targeted prostate biopsies performed. Patients not having systematic biopsies, or for whom pathology reports from surgery were unavailable, were excluded. The final population consisted of 160 patients (figure 12).

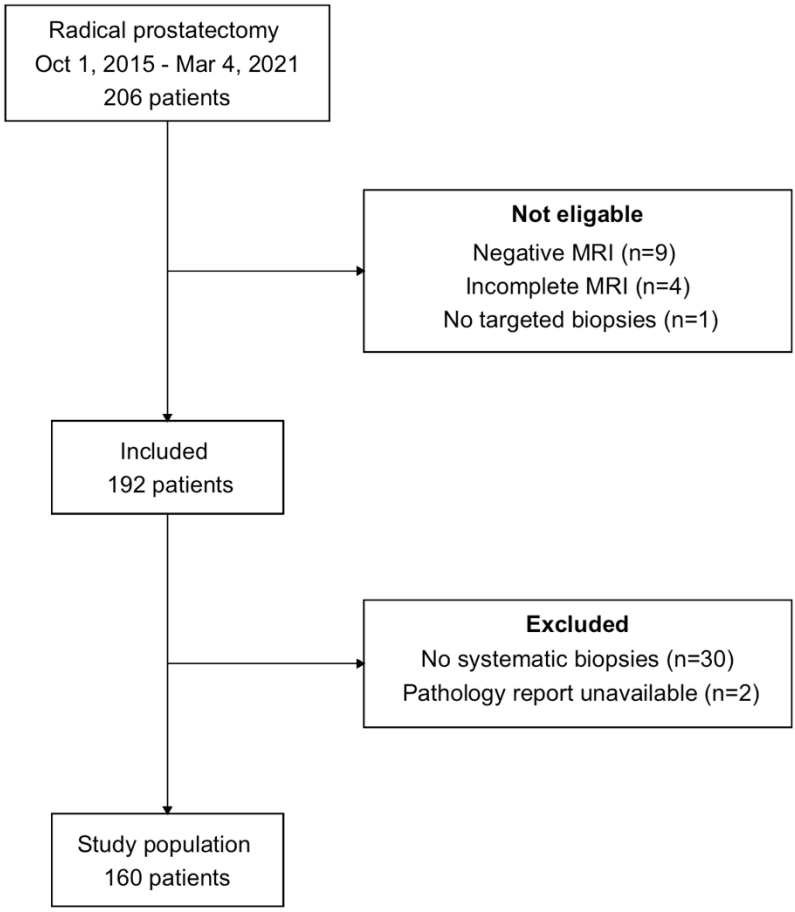

Figure 12. Flow chart, paper III

For **paper IV** we included patients in WSOP, having radical prostatectomy in Region Västra Götaland until December 31, 2014. Patients receiving neoadjuvant treatment, or adjuvant treatment without a recorded PSA value above the threshold, were excluded, as were patients where PSA remained above the threshold after surgery (figure 13).

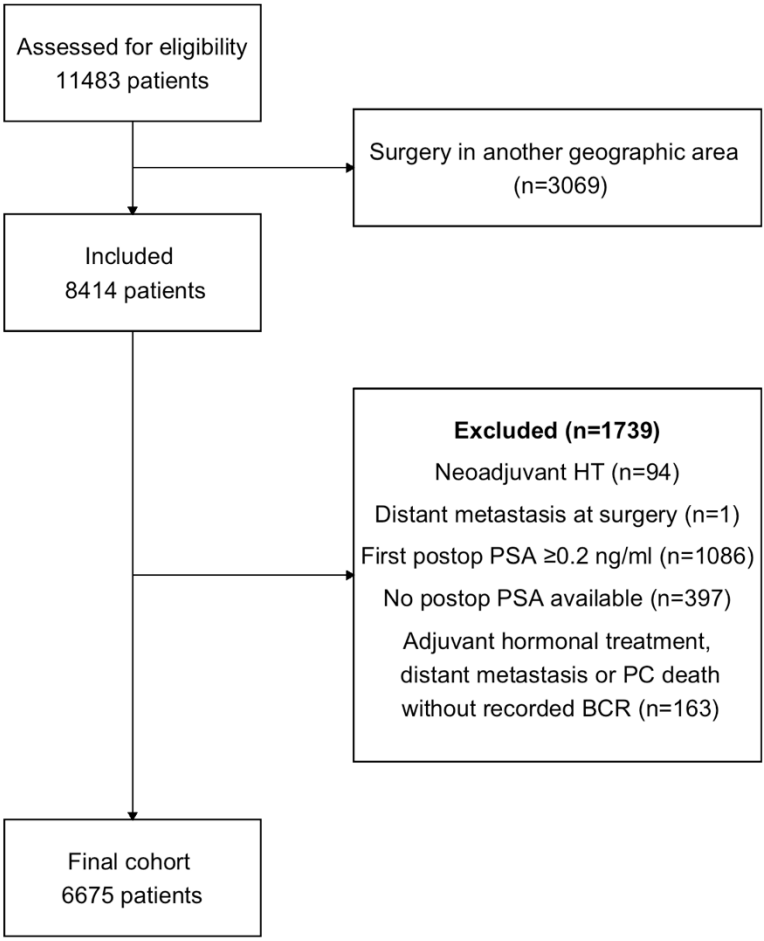

Figure 13. Flow chart, paper IV

3.2 DATA COLLECTION

Several different methods have been used for data collection.

Clinical data from each participating site have been entered prospectively in detailed case report forms (CRF) for the LAPPRO study (Thorsteinsdottir et al. 2011). Data on patient and tumour characteristics were collected before surgery; after surgery the operating surgeons reported on details regarding surgical steps. Clinical data for follow-up were collected at 6-12 weeks and 12 and 24 months after surgery. Pre- and perioperative data were used for **paper I** and **paper II**. In addition, all available follow-up data regarding PSA and secondary treatments were used for **paper II**.

Diagnostic data in the Göteborg-2 trial, entered prospectively into the study database, as well as data from subsequent systematic biopsies and from pathology reports from radical prostatectomy have been used for **paper III**. MRI readings have been performed blinded to study arm, PSA value and clinical data by two out of three experienced radiologists in consensus. Clinical examination and prostate biopsies have been performed by experienced urologists. Pathological review of biopsies has been made by one highly experienced pathologist; external review has been made by two experienced pathologists but results from these reviews were not yet available for **paper III**. Localization of findings on MRI, in clinical examination, in prostate biopsies and in whole-mount pathology specimens have all been recorded according to a common template with 12 dorsal and 12 ventral sectors based on the Swedish National Prostate Cancer Guidelines (Regional Cancer Centres 2021) (figure 14).

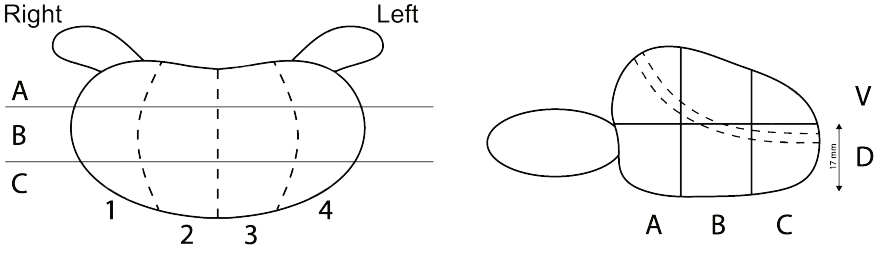

Figure 14. Common prostate template. Left – frontal view; base at the top, right – lateral view; base at the left. V – ventral; D – dorsal. Published in the Swedish National Prostate Cancer Guidelines 2021.

In LAPPRO, validated questionnaires have been used for collection of patient reported outcome measures (PROM) before and at 1, 2 and 8 years after surgery. Data have been collected by a neutral study secretariat, which also conducted a structured telephone interview six years after surgery. Collected data includes patient experience, symptoms, side-effects and further treatments as well as last PSA value. For **paper I**, patient reported erectile function, use of urinary pads as well as data on possible confounders have been used. For **paper II**, all available patient reported data on treatment and PSA values have been used.

Register data from registers on *national* (the National Prostate Cancer Registry (NPCR), the National Patient Registry (PAR), the Cause of Death Registry and the Prescribed Drugs Registry), *regional* (the Regional administrative healthcare database VEGA) and *local* level (radiotherapy departments, clinical chemistry laboratories, pathological laboratories) have been used in **paper IV.**

3.3 STATISTICS

3.3.1 DEFINITIONS

Degree of preservation of neurovascular bundles

As the research question differed between **paper I** and **II**, we used two different definitions of degree of preservation of the neurovascular bundles (NS). Directly after surgery, the surgeon stated degree of NS separately for each lobe in one of four categories; intrafascial NS, interfascial NS, semi-NS, or non-NS) with semi-NS defined as a dissection plane between interfascial and wide excision. For **paper I**, categorization was made in seven levels based on the total amount of preserved tissue (figure 15).

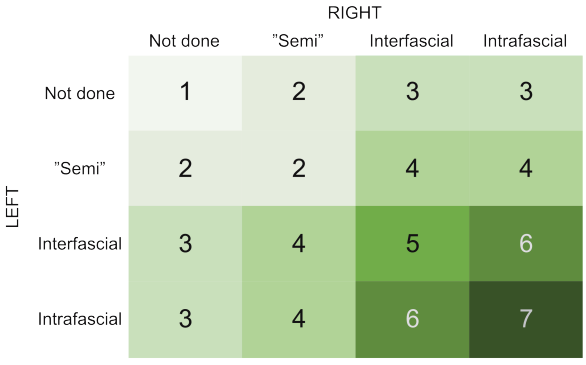

Figure 15. Schematic representation of levels of nerve-sparing in paper I.

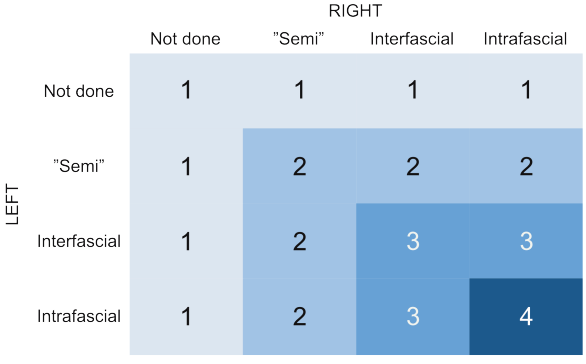

Figure 16. Schematic representation of levels of nerve-sparing in paper II.

For **paper II**, categorization was made in four levels according to the lobe with the lowest degree of NS, assuming that this is the target tumour side and thus reflecting amount of nerve-sparing in relation to the tumour (figure 16).

Substantial findings
Findings in prostatectomy specimens, of which preoperative knowledge has the potential to affect the choice of dissection plane, were named substantial findings. These were defined as extra-prostatic extension of tumour (pT3), or positive surgical margins in organ-confined disease (pT2 m+). A substantial finding was considered as identified by MRI and targeted biopsies if there was a targeted biopsy in the same, or a directly adjacent sector according to figure 14, located in the same lobe (left/right) and the same plane (dorsal/ventral) of the prostate. Systematic biopsies were considered as providing additional information if they either; a) identified a substantial finding not identified by MRI and targeted biopsies, or ; b) showed ISUP 3-5 in an area, identified by targeted biopsies as ISUP 1-2.

Incontinence
Incontinence one year after surgery was assessed based on patient reports. The questionnaire asked "How many times do you change pad, diaper, or other sanitary protection during a typical 24 hours?" with six answering categories;

1. Not applicable, I do not use a pad, diaper, or sanitary protection
2. More seldom than once per 24 h
3. About once per 24 h
4. About two to three times per 24 h
5. About four to five times per 24 h
6. About six times or more per 24 h

Incontinence was defined as changing pad about once per 24 hours or more often; the endpoint was dichotomized between category 2 and 3, changing pads "More seldom than once per 24 h"' and "About once per 24 h", where the two first categories were considered as not being incontinent and the latter four were considered as being incontinent.

Recurrence
For recurrence of prostate cancer after radical prostatectomy we used two different definitions, based on availability of information. In **paper IV** where consecutive PSA measurements were available, we defined biochemical recurrence as at least one PSA measurement ≥0.2 ng/ml after an initial postoperative value of < 0.2 ng/ml. In **paper II**, only the most current PSA

measurement at each follow-up was available. Here we defined biochemical recurrence as a PSA value < 0.25 ng/ml, or treatment for recurrence, after an initial postoperative PSA value of ≤0.25 ng/ml.

Failure

Though BCR after radical prostatectomy means that the curative intention has failed, implications differ. Clinical failure after biochemical recurrence in **paper IV** was defined as hormonal treatment (antiandrogen or androgen deprivation therapy (ADT)), skeletal metastasis or prostate cancer death, whatever occurred first.

3.3.2 HANDLING MISSING DATA

In **paper I**, imputation of missing data on possible confounders was made using multiple imputation by chained equations (MICE). Using information on seventeen possible confounders, identified in consensus among the authors based on current knowledge and a literature search, 50 datasets were imputed. No imputation of tumour or surgical data was made. In **paper II-IV**, analysis was made based on complete cases; cases with missing data were excluded from analysis.

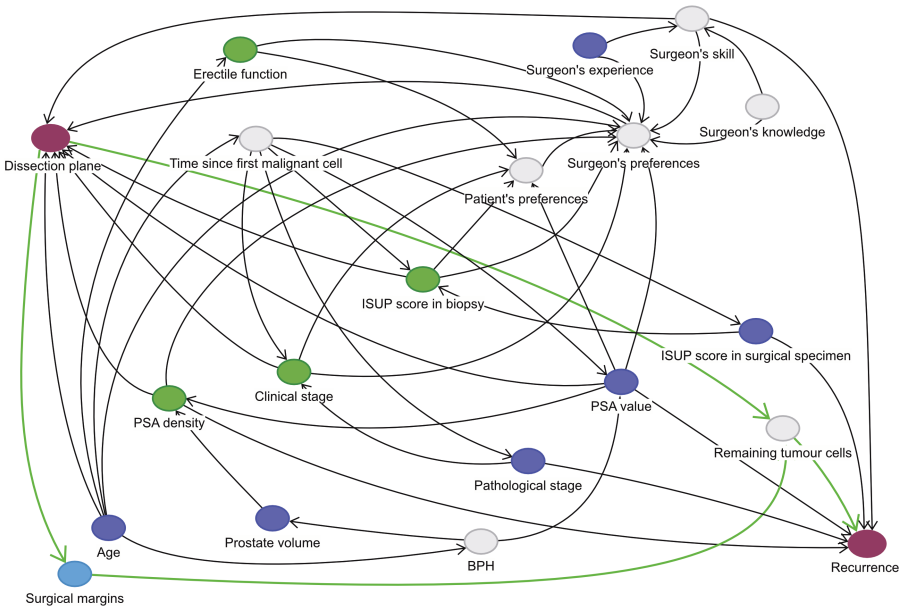

Figure 17. Directed Acyclic Graph for paper II. Purple nodes represent potential confounders included in the analysis; green nodes variables not included; grey nodes represent variables on which we lack information.

3.3.3 HANDLING POSSIBLE CONFOUNDERS

Potential confounders for the association between degree of NS and the respective endpoints incontinence and recurrence were selected based on current knowledge and literature search. For **paper II**, a DAG was constructed (figure 17), visualizing the theoretical relationship between degree of nerve-sparing and recurrence of prostate cancer and possible confounders. Variables were selected based on the DAG; nodes in red represent potential confounders included in the analysis. In **paper I**, 17 probable risk factors for incontinence

were initially identified. From these, final selection of potential confounders was made by successive multivariable modelling on each of the 50 datasets obtained by multiple imputation. The level of statistical significance was set at 0.20; factors reaching this level were included in the final model for each dataset. Possible confounders included in at least 26 of the final models were used as potential confounders in the analysis. In **paper III-IV**, no analyses of potential confounders were made.

3.3.3.1 RESTRICTION

In **paper I**, patients with preoperative urinary incontinence and/or postoperative radiotherapy to the prostatic bed, two known risk factors for postoperative incontinence, were excluded from analysis of the primary endpoint incontinence. In **paper II**, patients receiving adjuvant radiotherapy were excluded since adjuvant radiotherapy is aimed at reducing the risk for recurrence; patients undergoing open radical prostatectomy were excluded due to a different distribution between nerve-sparing degrees and a different pattern regarding positive surgical margins and recurrence compared to RALP in the LAPPRO study.

3.3.3.2 STRATIFICATION

In **paper II**, stratification was used to explore the effect of positive surgical margins on the possible relation between level of nerve-sparing and recurrence. Regression analysis, as described below, was made for patients with and without a positive surgical margin separately. In **paper IV**, time to clinical failure after BCR was analysed stratified on time to BCR.

3.3.3.3 REGRESSION ANALYSIS

Log-binomial regression, a regression model for binary outcomes related to logistic regression, was used in **paper I** to estimate the effect of level of NS on the outcome incontinence without and with adjustment for potential confounders; expressed as relative risks (RR) with 95% CI for incontinence between the highest level of NS and the six lower levels. Reported measures of effect are pooled estimates from the 50 imputed datasets mentioned above. *Logistic regression* was used in **paper II** to estimate the effect of level of nerve-sparing on positive surgical margins.

Cox proportional hazards regression was used to estimate the effect of level of NS on the outcome recurrence without and with adjustment for potential confounders; expressed as hazard ratios (HR) with 95% CI for recurrence between the three NS groups and the non-NS group. Cases were censored at last PSA-measurement.

3.3.4 OTHER METHODS

Kaplan Meier survival analysis was used in **paper IV** to estimate BCR-free survival after radical prostatectomy among all included patients, and failure-free survival after BCR according to time to BCR for patients experiencing BCR. Cases were censored at death of causes other than prostate cancer, or at end of study. For BCR-free survival, an alternative analysis with censoring at last known PSA measurement was also made.

Competing risk analysis, with death from causes other than prostate cancer as the competing event, was used in **paper IV** as a sensitivity analysis for the endpoints BCR-free survival and failure-free survival respectively.

4 RESULTS

Paper I

701 of 3148 patients had urinary incontinence one year after surgery. Preoperative and operative characteristics are found in table 1, **paper I**. The relative risk for urinary incontinence increased with lower degree of nerve-sparing. Adjusted for age, diabetes mellitus, pulmonary disease, mental disorder, prior inguinal hernia, prior abdominal surgery, and employment status one year after surgery, the relative risk for urinary incontinence (RR, 95% confidence interval) was 1.0, 1.07 (0.63-1.83), 1.19 (0.77-1.85), 1.56 (0.99-2.45), 1.78 (1.13-2.81), 2.27 (1.45-3.53) and 2.37 (1.52-3.69) from highest to lowest degree of nerve-sparing (figure 18). When restricting the analysis to preoperatively impotent patients, this gradient persisted; as was the case when open and robotic surgery were analysed separately. The gradient was more pronounced in robotic surgery.

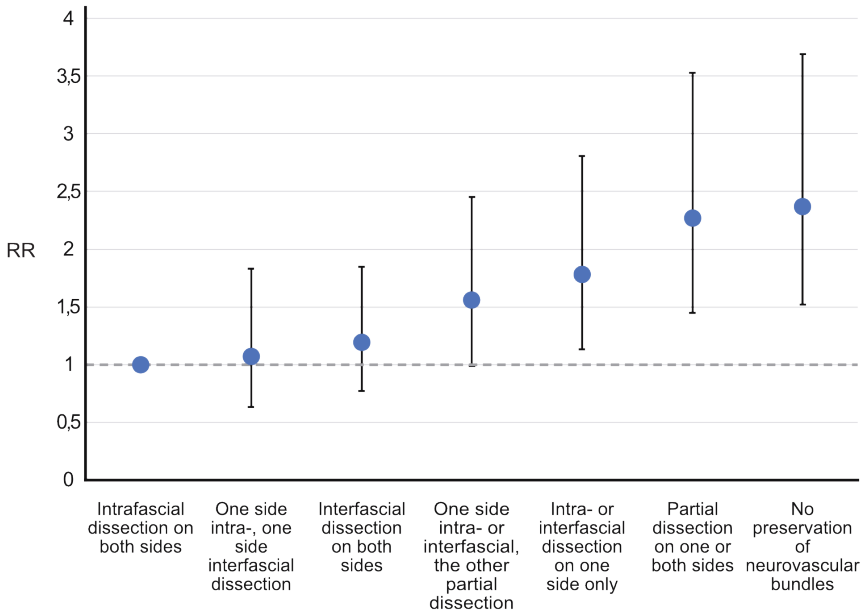

Figure 18. Relative risk with 95% confidence intervals for urinary incontinence one year after surgery according to degree of nerve-sparing

Paper II

Of 2401 included patients, 467 experienced recurrence during the follow-up. The median follow-up for patients without recurrence was 6.6 years (interquartile range 5.7–7.2). Patient and surgeon characteristics are found in table 1, **paper II**. Patients in the non-nerve-sparing group were older and had less favourable tumour characteristics than patients receiving nerve-sparing surgery. Crude recurrence rates were highest for the non-nerve-sparing group; 24.9% vs 15.9, 15.2, 15.2% for semi-, inter- and intrafascial nerve-sparing respectively. In unadjusted analysis, the hazard ratio for recurrence was significantly lower for any degree of nerve-sparing compared to no nerve-sparing; when adjusting for tumour characteristic, these differences did not persist (table 2, **paper II**). When stratified by surgical margin status, point estimates for recurrence for interfascial and intrafascial nerve-sparing differed between the groups with positive and negative surgical margin status. However, the confidence intervals were wide and the effects were not significant (figure 19).

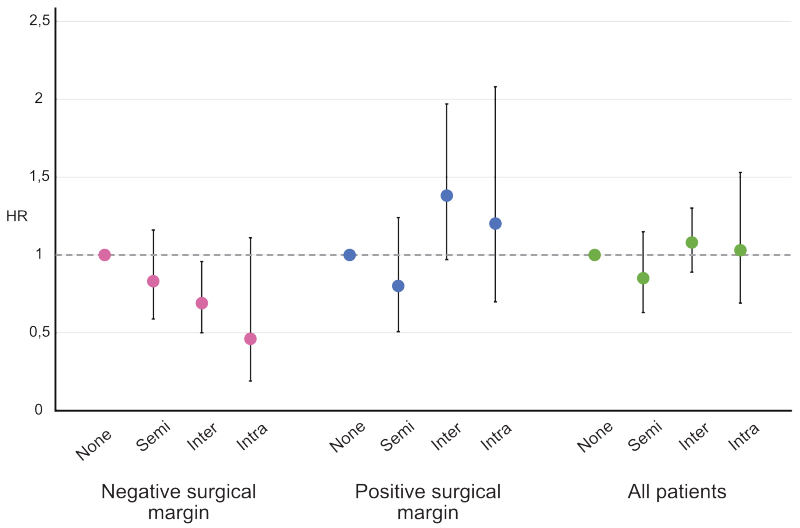

Figure 19. Hazard ratios with 95% confidence intervals for recurrence for different degrees of nerve-sparing for all patients and patients having negative and positive surgical margins respectively, adjusted for tumour characteristics, patient age and surgeon's experience. Axén et al. Published in European Urology Open Science 2021: 25-33.

481 patients (20%) had a positive surgical margin, (pT2 16.5%, pT3/4 29.9%). The frequency increased with higher degree of nerve-sparing and the odds ratios for positive surgical margins were significantly higher for any degree of nerve-sparing vs no nerve-sparing in adjusted analysis. When subdivided by pathological stage, the effect was less pronounced for pT3/4 (figure 20; table 3, **paper II**).

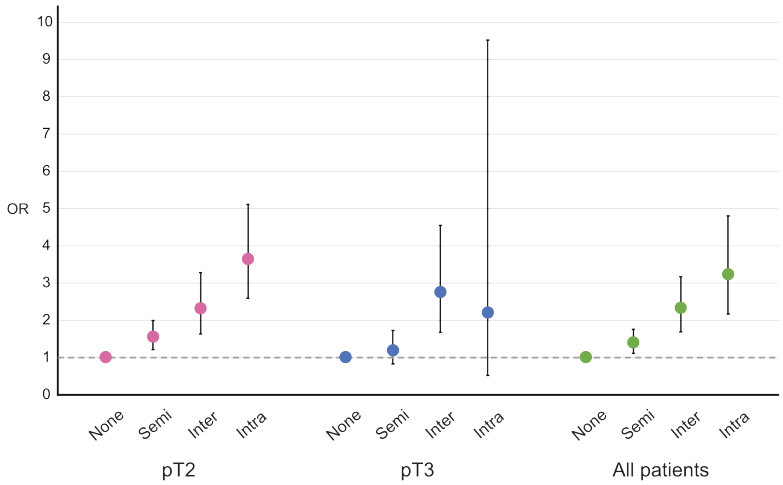

Figure 20. Odds ratio (OR) with 95% confidence intervals for positive surgical margins for different degrees of nerve-sparing according to pathological stage, adjusted for patient age, preoperative PSA, ISUP grading in surgical specimen, prostate weight and surgeon's prior experience and annual volume. Axén et al. Published in European Urology Open Science 2021: 25-33.

Recurrence rates were higher with a positive than negative surgical margins regardless of pathological stage, with the recurrence rate for pT2 with a positive surgical margin exceeding the rate pT3/4 with a negative margin; hazard ratio adjusted for tumour characteristics, patient age and surgeon's experience with 95% confidence intervals 3.32 (2.43-4.53) and 2.08 (1.66-2.62) , respectively (figure 2B, **paper II**).

Paper III

Of 160 patients eligible for analysis, fifty-three patients (33%, 95% confidence interval 26-41%) had at least one area with substantial findings at final pathology; three patients had two areas with substantial findings each. For twelve patients, all substantial findings were located in the ventral part of the prostate, outside the standard, dorsal template for systematic biopsies. One patient was not evaluable due to missing data on localization of SF.

In no area with SF identified by MRI, where targeted biopsies showed ISUP 1-2, did systematic biopsies show ISUP 3 or higher.

In seven cases, the area with SF was not identified by MRI and targeted biopsies. In four cases, systematic biopsies from the area with SF were benign or showed ISUP 1. In the remaining three cases, systematic biopsies provided additional information; in two cases with organ-confined disease, MRI showed ventral lesions, while there were positive margins in the left apical region; in the third case MRI showed an apical lesion while the prostatectomy specimen showed bilateral seminal vesicle invasion and extra-prostatic extension at the prostatic base. Detailed information on these cases is found in figure 21 and in table 2, **paper III**.

Paper IV

1214 of 6675 patients had biochemical recurrence during follow-up, 64 patients died from prostate cancer. Median time from surgery to last PSA for patients without BCR was 4.8 years. The risk for BCR was highest within the first two years after surgery, after which it plateaued and remained constant up to 15 years (figure 3 a, **paper IV**). BCR-free survival at 5, 10 and 15 years was 83% (95% CI 82-84%), 75% (95% CI 74-77%) and 69% (95% CI 67-71%), respectively, estimated by the Kaplan-Meier method. No substantial differences were seen in competing risk analysis.

Cumulative probability of failure for all patients 15 years after BCR was 53% (95% CI 46-60%), vs 50% (95% CI 43-55%) in competing risk analysis. The risk for failure was present in all groups, regardless of time to BCR; albeit highest among patients with BCR within two years after radical prostatectomy. Statistically significant difference was also seen between patients with BCR within 2-5 years and 5-10 years, while the group with BCR after more than ten years only differed from the group with shortest time to BCR; confidence intervals were wide (figure 3 b, paper IV).

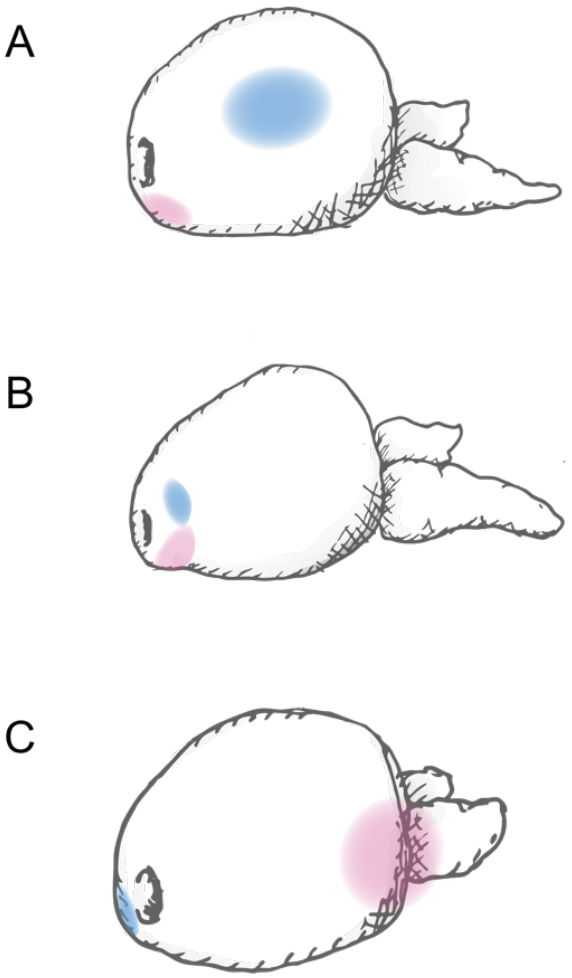

Figure 21. Schematic drawing of the three cases where systematic biopsies provided additional information. MRI findings in blue; substantial findings in surgical specimens in pink. A: MRI lesion, PI-RADS 5, ventral middle, left of the midline; positive surgical margin, dorsal apex, left of the midline. B: MRI-lesion, PI-RADS 4, ventral apex, lateral left; positive surgical margins, dorsal apex, lateral left. C: MRI-lesion, PI-RADS 4, dorsal apex, lateral right; positive surgical margins, extra-prostatic extension and bilateral seminal vesicle invasion, dorsal base. Drawing not to scale.

5 DISCUSSION

We have found that a higher degree of preservation of the neurovascular bundles in radical prostatectomy is associated with better postoperative continence, but also with higher rates of positive surgical margins; however, no association with recurrence of prostate cancer was found. We have also found that the risk for recurrence after radical prostatectomy persists at least 15 years after surgery. When planning the degree of preservation of the neurovascular bundles at radical prostatectomy, we found that, in most cases, systematic biopsies do not add information compared to MRI and targeted biopsies. When evaluating these results, several aspects need to be considered, some of these will be discussed below.

5.1 DEFINITION OF EXPOSURES AND OUTCOMES

Different definitions have been used for the exposure "degree of preservation of neurovascular bundles", as well as the outcome "recurrence", in the different papers. For the exposure "degree of preservation of neurovascular bundles", the different research questions have brought different requirements. When assessing the effect on postoperative incontinence (**paper I**), the total amount of preserved tissue is of interest, prompting the use of a definition taking both neurovascular bundles into account. When assessing the effect on oncological outcomes on the other hand (**paper II**), the degree of preservation in relation to the tumour is the area of interest.

In the LAPPRO trial we have detailed information on the degree of preservation on each side, categorized in four levels (figure 22), but, unfortunately, we lack detailed information of the location of the tumour within each specimen. We therefore made the assumption that the lowest degree of nerve-sparing was performed on the target tumour side, and defined the degree of preservation for the patient as the lowest degree on either side. This assumption relies on correct preoperative identification of the target tumour. Retrospective correlation with pathological specimens might have increased the precision in the categorization, but has not been considered possible to execute due to the multicentre design and large number of patients. Nevertheless, the detailed information on degree of nerve-sparing, recorded by the surgeon directly after surgery, allows for a comparatively high precision.

In 2013, Srivastava et al., in a study of continence 12 weeks after surgery in relation to degree of nerve-sparing (Srivastava et al. 2013), used a definition

of degree of nerve-sparing with four categories, similar to the one used in **paper II**; Kaye et al., in a study of urinary outcomes in relation to nerve-sparing quality (Kaye et al. 2013), categorized the exposure in three groups based on both neurovascular bundles, where quality of nerve-sparing was classified for each bundle separately in five levels. In the majority of other studies concerning the functional and oncological outcomes of nerve-sparing surgery in the literature, categorization of degree of nerve-sparing is less detailed, 'bilateral/unilateral/no' nerve-sparing being a common categorization (Burkhard et al. 2006; Eastham et al. 1996; Kundu et al. 2004; Marien & Lepor 2008; Novara, Ficarra, D'Elia, Secco, Cioffi, et al. 2010; Suardi et al. 2013; Tzou et al. 2009; Ates et al. 2007; Catalona & Bigg 1990; Chun et al. 2006; Coelho et al. 2010; Katz et al. 2003; Moore et al. 2012; Nelles et al. 2009; Tanguturi et al. 2014).

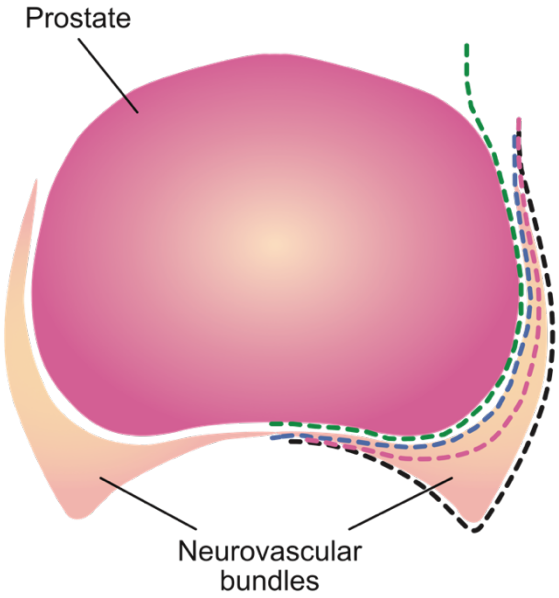

Figure 22. Illustration of four different degrees of nerve-sparing: green - intrafascial; blue – interfascial; pink – semi-nerve-sparing; black – no nerve-sparing

If the exposure "degree of preservation of neurovascular bundles" has been defined differently in different papers out of choice, the definitions of the outcome "recurrence", on the other hand, have primarily been chosen based on availability of data. The different definitions allow for analysis of different endpoints. In LAPPRO (**paper II**), only data from specified time points, the points of follow-up in the trial, are available. It is therefore not possible to base

the definition of recurrence on PSA values without taking possible salvage treatments into account. Consider the case of a patient having PSA levels below the detection threshold at the 2-year follow-up. Half a year later, the PSA starts to increase. Four years after surgery, antiandrogen treatment is initiated, which makes PSA decline to undetectable levels, where it remains at the six- and eight-year follow-up (figure 23). Using only PSA, this patient would have been considered as not having recurrence.

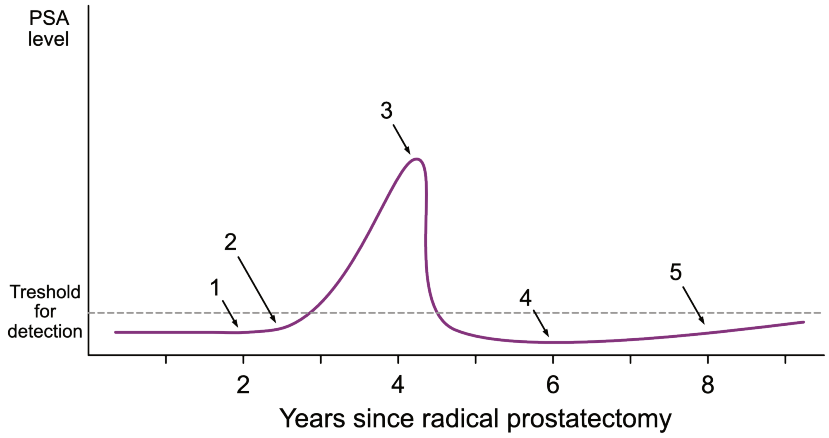

Figure 23. Schematic presentation of a hypothetical patient. 1. 2-year follow-up. 2. PSA starts to rise. 3. Antiandrogen treatment is initiated. 4. 6-year follow-up. 5. 8-year follow-up.

It was therefore essential to include treatment for recurrent disease in the definition. This increases the chance of detecting recurrence, but makes it impossible to investigate prognosis after biochemical recurrence. In WSOP (**paper IV**) on the other hand, we have access to virtually all PSA values for each patient. We therefore defined recurrence based only on PSA, which allowed us to look further into subsequent prognosis. Unlike after curative radiotherapy for prostate cancer, where BCR is defined as increase of PSA with 2 ng/ml compared to the lowest recorded value after radiotherapy (nadir) according to Phoenix criteria (Roach et al. 2006), there is no standard cut-off for defining BCR after radical prostatectomy. As stated in the introduction, a PSA value of ≥0.4 ng/ml has been proposed due to correlation with the development of metastasis (Stephenson, Kattan, et al. 2006), but PSA ≥0.2 ng/ml is commonly used (Van den Broeck et al. 2019). In **paper II**, PSA >0.25

ng/ml was defined as BCR, as in other publications from the LAPPRO study. This, somewhat unusual, cut-off was chosen within the study to account for differences between centres, where some reported PSA with one decimal and some with two (Carlsson et al. 2016). In **paper IV**, BCR was defined as PSA ≥0.2.

What should be considered as failure after radical prostatectomy could be argued. In the SPCG-4 and PIVOT studies, where patients were randomized to radical prostatectomy or watchful waiting, outcomes were all-cause and prostate cancer specific mortality and distant metastasis; in SPCG-4, local progression, defined as clinical stage T3 in watchful waiting and as local recurrence verified in biopsies after radical prostatectomy, was an additional outcome (Holmberg et al. 2002; Wilt et al. 2012). In ProtectT, where patients were randomized between radical prostatectomy, radiotherapy and active monitoring, outcomes were all-cause and prostate cancer specific mortality, as well as primary treatment failure and clinical progression; the latter including distant metastasis, progress to clinical stage ≥T3, urinary catheter because of local progress and long-term ADT (Hamdy et al. 2016). When investigating prognosis after BCR (**paper IV**), we defined failure as either hormonal treatment, bone metastasis or prostate cancer death. In contrast to in SPCG-4 and PIVOT, where patients were randomized between curative and non-curative treatment, this is a study where all patients received curative treatment. Patients later receiving hormonal treatment can not be considered as cured. In ProtecT, where randomization was made between immediate curative treatment and active monitoring, where the aim is to initiate curative therapy in case of progress, ADT was consequently considered as clinical progression. Hormonal treatment is life-long, with potential side-effects affecting the patient in many different ways; both emotionally, psychologically and physiologically (Nguyen et al. 2015). As previously mentioned, the negative impact on QoL is higher for hormonal treatment than for surgery. In our opinion, cure from prostate cancer can not be defined merely as surviving long enough to die from something else, as many patients do even without curative treatment, but as freedom from disease and related treatment.

There is no consensus in the literature regarding the definition of postoperative continence; some authors accept use of a so-called safety-pad (Pompe et al. 2017; Nilsson et al. 2011), while others require no pad use to define the patient as continent (Patel et al. 2009; Srivastava et al. 2013). Incontinence 12 months after radical prostatectomy was the primary endpoint of the LAPPRO study; the definition of incontinence used in **paper I**, changing pads at least once per 24 hours, is the same as in the main study (Thorsteinsdottir et al. 2011). The appropriateness of either definition of continence could be disputed; even

patients reporting no pad use reports urinary leakage to some extent, and urinary bother is significantly higher for patients using less than one pad per 24 hours compared to no pad use (Wallerstedt et al. 2012). Nevertheless, the cut-off in pad use is of less importance in regard to the research question, namely the relationship between degree of nerve-sparing and incontinence; furthermore, additional analyses with varying cut-offs were also performed, showing the same association as in the main analysis.

When evaluating if systematic biopsies could be omitted and replaced by MRI and targeted biopsies, different endpoints have been used in the literature. In the diagnostic setting, the ability to detect high-grade cancer, preferably in conjunction with a low detection rate of low-grade cancer, is desirable. The detection of high-grade cancer is also important when using the results for choice of active treatment or not. Thus, upgrading of histopathological differentiation is often included in the definitions. In **paper III**, we evaluated the role of systematic biopsies in a different context; when diagnosis and subsequent treatment decisions are made based on MRI and targeted biopsies. Therefore, we defined substantial findings from a surgical point of view; as pathological features of which preoperative knowledge would have the potential to affect the surgical approach. A positive surgical margin was included since it is caused by dissecting too close to the tumour. This could however be questioned, as this feature is not pre-existing, but occurs as a consequence of the dissection itself. The preservation of neurovascular bundles is done separately for the left and right side of the prostate, so knowledge of location of the tumour within the prostate is therefore important. A tumour at the base of the prostate demands caution when dissecting the bladder neck, and a tumour at the apex does the same when dissecting the apex and urethra; further emphasising the need for a correct preoperative location. Differentiation on the other hand, is only important to a certain extent. Although the risk for BCR increases with higher ISUP grade (Epstein et al. 2016), a distinct line is seen between ISUP 2 and 3. Therefore, we chose to only consider upgrading from ISUP 1-2 to ISUP 3-5, but not upgrading between ISUP groups.

5.2 DATA COLLECTION – QUALITY OF DATA

As already mentioned, several different methods have been used for data collection. In **paper I-II**, patient reported outcome measures (PROM) have been collected via validated questionnaires. The validation process consisted of face-to-face validation with patients with a recent prostate cancer diagnosis, with subsequent refinements of the questions, and thereafter a pilot study, after which further refinements were made (Thorsteinsdottir et al. 2011). Questionnaires were, with the exception of the preoperative questionnaire, distributed via a neutral, third party secretariate, thus avoiding the potential filtering effect of patients avoiding to report adverse outcomes to please their surgeon.

In **paper I-III**, information has been prospectively collected, specifically for the main studies, LAPPRO and Göteborg 2. This allows for data collection tailored to the specific needs for each research question. The prospective collection of information also ensures that it will not be influenced by knowledge of the outcome for the patient.

In **paper IV,** on the other hand, register data has been used. The quality of register data depends on several factors, such as coverage and accuracy of reported data, both regarding facts per se, and that data are assigned to the right person. For Swedish national registers, the general quality is high (Brooke et al. 2017; Ludvigsson et al. 2011). More specific, the accuracy of death certificates regarding prostate cancer death, and the quality of data in the National Prostate Cancer Register have been shown to be high (Godtman et al. 2011; Tomic et al. 2015). For several registers, registration is mandated by law; coverage is thus high. Data in the Prescribed Drugs Register is to a large extent collected by automated processes; virtually all dispensed medications are included. Whether the patient takes the medication or not can not be assessed by register data; that is, however, of less importance, since we don't investigate the effect of given medication. Regarding data on PSA values, they are collected directly from each laboratory, which allows for highly accurate data.

5.3 STATISTICAL METHODS

5.3.1 CHOICE OF VARIABLES FOR ADJUSTMENT

In **paper I-II**, our aim was to evaluate the effect of degree of nerve-sparing on incontinence and recurrence, respectively. There are many other possible causes for both outcomes, which we attempted to control for by different methods, in order to achieve an unbiased effect measure. In **paper I**, we restricted the analysis to patients who were continent before surgery, since preoperative incontinence is expected to remain after surgery, and patients without postoperative irradiation. Both preoperative incontinence and postoperative irradiation are risk factors for postoperative incontinence. It is improbable that preoperative incontinence is a confounder for the association between degree of nerve-sparing and incontinence; it is associated with the outcome, but hardly with the exposure. Nevertheless, when studying what surgical steps might lead to incontinence, including patients already incontinent does not add anything; there is no reason to believe that the procedure will improve their continence. In the case of irradiation there is a possibility of confounding, since the choice of degree of nerve-sparing is influenced by tumour severity, and more severe tumours are at higher risk for postoperative irradiation. Age is another known risk factor for postoperative incontinence (Wallerstedt et al. 2013), which, without question, could be considered as a confounder since age influences degree of nerve-sparing (Novara, Ficarra, D'Elia, Secco, De Gobbi, et al. 2010). We used log-binomial regression to adjust for the effect of age, as well as for diabetes mellitus, pulmonary disease, mental disorder, prior inguinal hernia, prior abdominal surgery, and employment status one year after surgery. Body mass index, educational level, frequency of physical activity, prior transurethral resection of the prostate, prior coronary arterial bypass grafting surgery, smoking, history of cardiovascular, kidney or neurological disease and prostate weight were all identified as possible confounders in the initial steps of the analysis as well; none of these reached statistical significance in multivariable modelling and were thus not used in the analysis.

In **paper II**, analysis was restricted to patients undergoing robotic surgery. The distribution between nerve-sparing categories was considerably different between robotic and open surgery in the LAPPRO study (Haglind et al. 2015); patterns of BCR and positive surgical margins in regard to pathological stage also differed between the two techniques (Sooriakumaran et al. 2018). As this might induce statistical difficulties, we chose to analyse the largest group, robotic surgery, which is also the most common technique today (National Prostate Cancer Register of Sweden 2020). Patients receiving adjuvant

radiotherapy, defined as radiotherapy within six months from surgery without evidence of BCR, were also excluded; the purpose of adjuvant radiotherapy being to avoid progression.

Possible confounders were identified among the co-authors and visualized in the DAG shown in figure 17. Factors included comprise both variables on which we have information, for example, prostate weight which is measured after surgery; known entities on which we lack information, for example, benign prostatic hyperplasia which is a histological diagnosis; and undefined concepts such as surgeon's knowledge. The relationships visualized are complex, and the DAG might seem almost impossible to decipher at first sight. Even so, it is not in any way a complete representation of reality. The choice to preserve more or less of the neurovascular bundles is based on oncological safety and, preferably also on the patients' preferences. In our model, the patients' preferences are thought to be influenced by pre-operative erectile function, but also by tumour factors (as presented to the patient by the surgeon, not depicted in the DAG), though there is little evidence in the literature on what the actual determinants are (Imbimbo et al. 2011). Erectile function is supposed to influence the dissection plane, both directly via the surgeons' preferences, and indirectly by the patients' preferences, but not to affect the risk for recurrence; hence no adjustment for erectile function was made. Assessment of oncological safety is based on perceived tumour severity, represented by clinical risk factors; the most well-documented being PSA value, tumour stage and histopathological differentiation (Han et al. 2003; Stephenson, Scardino, et al. 2006). Before surgery, tumour stage is assessed by palpation of the prostate, in recent years accompanied by MRI, in an effort to predict pathological tumour stage, which only can be assessed after surgery. In the same way, differentiation in prostate biopsies is thought to mirror the differentiation in the tumour itself. This is represented in the DAG, as clinical tumour stage and ISUP score in biopsies are factors that influence the dissection plane; they are in turn influenced by pathological tumour stage and ISUP score in the surgical specimen, respectively. Pathological tumour stage and ISUP score in the surgical specimen are used for adjustment, but are in reality only proxies for tumour biology, the factor whose influence we wish to eliminate in our analysis. A positive surgical margin is a risk factor for recurrence; as such it is a proxy for remaining tumour cells. It is defined as tumour cells on the inked margin of the surgical specimen, reviewed by the pathologist, and is thus a measure subject to possible error, and considerable variation between pathologists have been shown (Kuroiwa et al. 2010; Netto et al. 2011). Even though there are tumour cells on the inked margin, there are not necessarily any viable tumour cells left; although improbable, the dissection might be done exactly between normal and tumour cells and if

electric cautery has been used, any remaining cells might have been killed by the electric current. Tumour cells could also remain in the body as circulating tumour cells or occult metastasis in lymph nodes or in distant tissue (Freeman et al. 1995; Stott et al. 2010), despite negative surgical margin status. A positive surgical margin is by definition caused by cutting (too) close to the tumour, but, depending on tumour localization, this is not necessarily avoidable by refraining from nerve-sparing. As it is part of, but not the only, causal pathway between degree of nerve-sparing and recurrence, it is not a confounder and should thus not be adjusted for. Nevertheless, we wanted to account for its potential effect on the outcome, which we did by stratifying the analysis on surgical margin status.

The fact that the decision of degree of nerve-sparing is based on risk assessment, where patients at high risk for recurrence receive nerve-sparing surgery to a lesser degree than patients with lower risk, forms a strong confounding mechanism. This is shown by the effect of adjustment; in unadjusted analysis, the risk for recurrence was significantly lower for any higher degree of nerve-sparing compared to no nerve-sparing. When adjusting for tumour characteristics, no significant effects remained. There is, however, reason to believe that there is residual confounding, i.e. that despite adjustment, confounding effects are still present. The notion that our adjustment is insufficient to control for tumour biology is supported by the results in analysis stratified on surgical margin status. When analysing patients with negative surgical margins, point estimates for risk for recurrence decreased with increasing degree of nerve-sparing. Since there is no theoretical ground for higher degrees of nerve-sparing to protect from recurrence, this suggests remaining imbalance in inherent prognosis between the groups. Furthermore, genetic markers have been shown to be independent predictors for prognosis (Karnes et al. 2018). The addition of genetic markers to clinical nomograms predicting recurrence significantly improves their performance, showing that difference in prognosis is not fully captured by clinical risk factors alone (Ross et al. 2016).

In **paper III**, both systematic and targeted biopsies were performed in all patients. We can therefore not exclude the possibility that treatment decisions were made based on information from systematic biopsies; both regarding the choice of performing radical prostatectomy, and regarding the extent of the dissection.

In **paper IV**, no adjustment for confounding was made. This was a deliberate choice, as we wanted to keep it simple in favour of usability; PSA value and time to BCR are fairly robust measures. Other clinical risk factors, such as

tumour stage and differentiation on the other hand, are subject to interpretation. Any estimates based on them would be dependent on that interpretation. Over the study period of twenty years, histopathological grading has changed towards higher grades. This phenomenon, also known as “Gleason inflation”, has been driven by consensus conference decisions, where the effects of the 2005 ISUP revision has been prominent (Danneman et al. 2015; Egevad et al. 2019).

5.3.2 CHOICE OF METHODS FOR ANALYSIS

In **paper I**, the association between degree of nerve-sparing and postoperative incontinence was evaluated in different subgroups, both based on surgical technique, where robotic and open surgery were analysed separately, and in preoperatively impotent men; analyses were also made with varying measures of incontinence and with different cut-offs. Though the gradients were more or less pronounced, the patterns were similar. There is still a possibility for the results to be biased by confounders, for which we lack knowledge and/or information. Functional urethral length is a predictor for postoperative continence (Heesakkers et al. 2017). No examinations have been made to assess this, neither pre- or postoperatively, hence we lack information on this factor; personal communication indicates that the ambition to preserve urethral length in the dissection differs between centres, especially concerning open surgery.

In **paper II**, the applied statistical method, Cox regression, was not sufficient to achieve a true, unbiased measure regarding the effect of degree of nerve-sparing on the risk for recurrence, as stated above. One could argue, that given the baseline differences in risk characteristics between the groups, adding a propensity score weight may improve the analysis further. A propensity score in this case, would, in short, be the probability for a patient to receive a certain degree of nerve-sparing, given the specific characteristics for that patient. To calculate the propensity score, both the identified confounders, and predictors for the exposure such as erectile function can be used. Propensity scores can be used to account for selection regarding the exposure, whether implicit, or explicit as in our case. Traditional multivariable modelling and propensity score methods are different ways of addressing the same issues. Though propensity scores may have theoretical advantages, in practice results are often similar to traditional regression models. In the presence of confounders for which we lack the appropriate measures, as for tumour biology, it is unlikely that choice of methodology will make notable difference (Williamson et al. 2012).

When analysing time to event data, several factors must be taken into account, especially when the time period studied is long. Some subjects are likely to drop out before the end of study from different reasons, depending of methods of data collection. It could, for example, be due to non-response in surveys; relocation abroad where the subject cannot be reached and is no longer included in national registers, or death from related or unrelated causes, depending on the research question and studied outcome. As outlined in the introduction, drop-out (censoring) is assumed to be non-informative, i.e. that

patients who are censored have the same risk for the outcome as patients still in the study, when using Cox regression or the Kaplan-Meier method. Whether this assumption holds must always be considered carefully. In **paper IV**, there are two main factors to consider when studying time to BCR, a) that clinical follow-up with PSA in many cases stopped after a few years for patients without BCR and b) the impact of death from other causes. Point a) is of interest when choosing length of follow-up in the study. To censor observations at last PSA would seemingly fulfil the criteria of non-informative censoring, but entails a risk for overestimation of the cumulative incidence of BCR. Clinical follow-up stopped after median just under five years for patients without BCR. Censoring at last PSA would mean that they no longer were part of the studied population after that time. Patients who later developed symptoms, such as severe back pain, on the other hand, would probably have their PSA checked whether clinical follow-up had been stopped earlier or not.

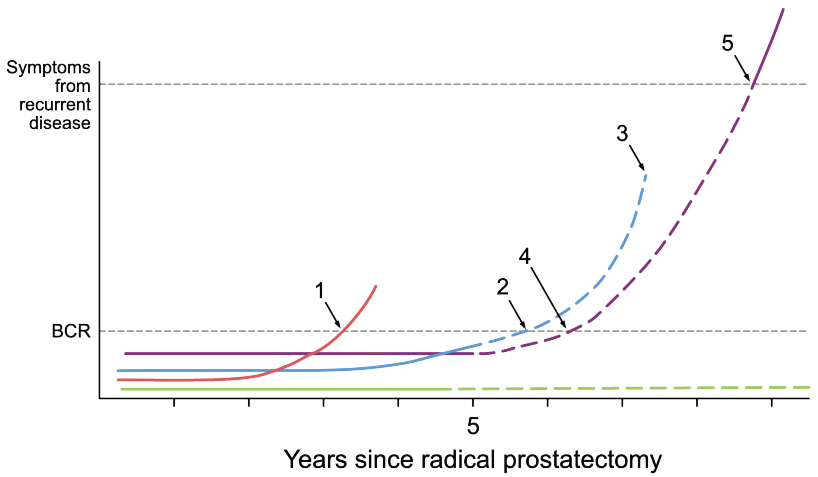

Figure 24. Schematic presentation of four hypothetical patients, red, blue, green and purple curve. Solid line – regular PSA check-ups; dashed line – PSA is no longer checked routinely. The y-axis has no unit, but symbolises the development of recurrent disease. 1. Red develops BCR, detected at routine check-up. 2. Blue develops BCR, which is not detected since PSA is no longer checked. 3. Blue dies from stroke with an undetected, asymptomatic recurrence. 4. Purple develops BCR, which is not detected since PSA is no longer checked. 5. Purple develops clinical symptoms; PSA is checked and recurrence is detected. Green remains asymptomatic and free from BCR throughout the study.

If the probability of having your PSA checked because of symptoms increases with increasing time since surgery, the proportion of patients having BCR among those checking their PSA would be higher than if every patient had their PSA checked. This is illustrated in figure 24.

To avoid this cause for overestimation of the cumulative incidence of recurrence, we chose to censor at end of study or at death from other causes in the main analysis. This still leaves point b), death from other causes. Dying from other causes before developing BCR violates the assumption of non-informative censoring, since it is impossible to develop BCR after death. Ignoring this might also lead to overestimating of the risk for recurrence; however, in our data, the differences was negligible from a clinical point of view, both in the analysis of recurrence and clinical failure after recurrence. When analysing time to clinical failure, we used the Kaplan-Meier method, stratifying the analysis on time to BCR. Intervals were chosen to represent relevant time frames from a clinical point of view. Alternatively, Cox regression analysis could have been used in order to acquire an effect measure for the impact of time to BCR; either as a categorical or a continuous measure. Our interest, however, was not in the effect size, but rather to evaluate whether there were any clinically relevant differences or not. Even though the risk for failure was significantly higher for patients with BCR within two years from surgery from a statistical point of view, the risks for the other groups were still clinically relevant.

The methods in **paper III** differs from the other papers, in that the only statistics used is the calculation of proportions with 95% confidence intervals. Instead, the basis of the analysis is what preoperative information could be considered sufficient for planning whether to do a nerve-sparing procedure or not, and if yes, to which extent nerve-sparing could be done. Even though substantial findings are identified after surgery, in the pathological review, the pathological features (except for positive surgical margins) existed before surgery and could thus be considered as the exposure. The outcome is not only defined as systematic biopsies providing information identifying such findings; this information should also add to the information acquired by MRI and targeted biopsies. In this, we have put much emphasis on the importance of location of findings, and somewhat on differentiation. The ambition was to use a hands-on, clinical approach.

5.4 CHOICE OF STUDY DESIGN

The design of **paper I** provides robust evidence for an effect of nerve-sparing dissection on the risk for incontinence. The mechanism behind this could however be argued. As mentioned above, despite detailed data on degree of nerve-sparing, other details regarding the dissection of the prostatic apex - which is close to the urethral sphincter, have not been collected. That the effect is due to less damage to adjacent structures when dissecting close to the prostate, rather than to amount of remaining neurovascular tissue, can thus not be excluded. Since the publication of **paper I**, some evidence of the former explanation has come forward. In a study in 2016, incontinence rates for patients for whom the neurovascular bundles were initially spared, but removed in a second step after frozen-section had shown suspicion of residual tumour, were compared to patients with intact neurovascular bundles, and patients with an initially non-nerve-sparing dissection, respectively. No significant differences were seen between patients with an initial nerve-sparing dissection, whether the neurovascular bundles were removed later or not. Compared to patients undergoing an initial non-nerve-sparing procedure, on the other hand, patients with a secondary resection of the neurovascular bundles had significantly better continence; suggesting that the effect is related to the dissection itself, rather than to preservation of nervous tissue (Michl et al. 2016).

In **paper II**, despite high quality data regarding degree of nerve-sparing, no significant effects on the risk for recurrence could be demonstrated. Results are most likely encumbered with a high degree of residual confounding; if further attempts to identify and adjust for these confounders would lead to other results or not is impossible to predict. In the presence of unknown confounders, randomization would in theory be a way forward. There are, however, several issues surrounding such an approach. In contrast to a randomised study of new drugs, where the medication and placebo treatment could be made identical except for the substance in question, surgical procedures involve many parameters that are hard to control. Both functional and oncological outcomes have shown large heterogeneity between surgeons (Nyberg et al. 2020). Furthermore, the demonstrated benefits of nerve-sparing surgery, as well as the risk for positive surgical margins associated with nerve-sparing in clinical T3 tumours, make randomization highly questionable from an ethical point of view. Without refined methods for risk assessment, there is little possibility to resolve the issue, since it could not be done in this large study with detailed, prospective data on degree of nerve-sparing. We had access to PSA data from selected time points only, which forced us to included subsequent treatment in our definition of recurrence. Hence, with existing data,

we had no possibility to explore prognosis after BCR in relation to degree of nerve-sparing, which might have given additional insights.

In the literature, there are few other studies concerning the value of systematic biopsies for surgical planning of radical prostatectomy (Gandaglia et al. 2020; Karsiyakali et al. 2021), and to our knowledge, there is none using the same approach as in **paper III**. Our aim was not to determine which methods gives the most information, instead, we based our analysis on what we defined as sufficient information. The design was made possible by the availability of high-quality data, with a common, national prostatic template, used by radiologists, urologists and pathologists alike. Due to the setting, within a large trial conducted at an academic institution, the level of experience among all involved is high. Thus, results might not be valid in a broader population, with less experienced urologists and radiologists.

Paper IV, on the other hand, is population-based. This was made possible by the use of register data, which allowed a broad inclusion, a large study population and long follow-up. As a consequence, clinical follow-up was not standardised as described above. This is a minor issue, considering the benefits.

5.5 ETHICAL CONSIDERATIONS

When participating in screening, i.e. undergoing a test or an examination in order to detect a possible disease, despite not having symptoms, it is possible that one will get a diagnosis one would not have received otherwise. In prostate cancer screening, the clinical significance of the diagnosis might be uncertain, and the person, who has now become a cancer patient, might face regular check-ups, or treatment with associated side-effects. Patients randomized to the screening group in the Göteborg 2-trial are provided with written information on the pros and cons of participating and the possibility to ask questions if needed. By taking a PSA within the study they are considered to leave consent, an approach approved by the Regional Ethical Review Board in Gothenburg. To what extent a person can understand the potential consequences for themselves and foresee their reaction in case of a diagnosis is, however, not obvious. Health literacy, the degree to which individuals have the ability to find, understand, and use information and services to inform health-related decisions and actions for themselves and others, is varied; providing the same information for every individual does not imply the same understanding (Santana et al. 2021; Sørensen et al. 2015). Since prostate cancer is a common disease with a high absolute mortality, these objections are minor compared to the potential scientific gain.

Despite comparing two different techniques for radical prostatectomy, the LAPPRO study was not randomized; patients received the same treatment as they would have received outside the study. Participation entailed collection of sensitive, personal information, both from the hospitals and from patients themselves, who filled out extensive questionnaires including intimate questions, both before and on several occasions after surgery. The protection of personal data is highly important and is achieved by different measures, including assigning a specific study ID to patients, restricting access to the database to only one data manager, and by technical protection of the database. With long-term follow-up within the study, patients might have finished clinical follow-up; being contacted for research purposes might then serve as an unwanted reminder of the disease. Since long-term side-effects, as well as long-term survival, is common among patients treated with radical prostatectomy, the high scientific value can be considered to outweigh this potential risk.

Studies of register data consider only data already collected. In WSOP, data from several registers are combined. In the majority of these registers, participation is mandatory, in other, consent to participation has been given at the inclusion in the register. In no case has the patient consented to our specific

study. All data are kept in unidentified form. This is made possible by a code key, linking the personal identity number for each individual to a study specific serial number, which is held by the state agency Statistics Sweden (SCB). Since data are pseudo anonymized, and analyses are made on group level, there is no threat to the personal integrity of the included individuals. Collecting and managing register data is resource consuming. To gain values from registers, data has to be used; otherwise resources would be wasted.

6 CONCLUSION

In patients diagnosed with prostate cancer by MRI and targeted biopsies within a randomized clinical trial with experienced staff, systematic biopsies provide little additional information regarding tumour extent of value for decisions regarding the extent of nerve-sparing in radical prostatectomy, compared to information from MRI and targeted biopsies. Considering the potential side-effects from prostate biopsies, especially when performed transrectally, to routinely perform a second round of systematic biopsies in patients where surgery already has been decided can not be encouraged. In preoperative evaluation, all information from both MRI and targeted biopsies should be considered.

A higher extent of nerve-sparing in radical prostatectomy is associated with improved postoperative urinary continence, regardless of age or preoperative potency. Whether this is primarily caused by the dissection itself, or by preservation of neurovascular tissue, is not clear. Nerve-sparing should be considered in all patients as a means of improving postoperative continence, not only for preserving erectile function. No direct effect on the risk for recurrence can be seen with higher degree of nerve-sparing when tumour factors are considered in the choice of degree of nerve-sparing. Nevertheless, the risk for positive surgical margins increases irrespective of tumour stage. A positive surgical margin in turn, significantly increases the risk for recurrence. In conclusion, there are functional benefits for all patients with nerve-sparing surgery which has to be weighed against the possible oncological risk. This decision should be made individually in each case, preferably by surgeon and patient in mutual decision-making.

After radical prostatectomy, the risk for BCR with subsequent clinical progression remains at least 15 years. Follow-up with regular PSA-test should be continued until treatment for a possible BCR would no longer be considered due to biological age and/or comorbidity, rather than until a certain time since surgery.

7 FUTURE PERSPECTIVES

Finding the right balance between risk for side effects and risk for recurrence for an individual requires knowledge of these risks, as well as of the patient's preferences. While there are well established clinical risk factors for progression of prostate cancer, there is still large variability in outcome between individuals; existing tools for clinical prognostication do not fully account for tumour biology. In recent years, several tissue-based biomarkers have become commercially available, using genetic testing on tumour tissue from biopsies or radical prostatectomy specimens for prognostication (Basourakos et al. 2021). Although such biomarkers have been shown to be independent predictors of outcome, as well as to impact treatment decisions, the clinical utility is not yet established. An ongoing randomized trial seeks to evaluate the clinical impact of incorporating genetic biomarkers in the care of patients with newly diagnosed prostate cancer (Bishoff et al. 2014; Cuzick et al. 2015; Jairath et al. 2021; Vince et al. 2021). However, considering the demonstrated ability to discriminate between more or less favourable prognosis within the same clinical risk groups, inclusion of such biomarkers in a study of nerve-sparing might be sufficient in reducing confounding to a level where the effect of nerve-sparing on oncological outcome can be further elucidated. Hopefully, in the future, patients and clinicians will be provided with an individualized risk assessment to guide in clinical decision-making.

The causes for postoperative incontinence are not yet fully understood; further studies to clarify the factors behind this common side effect that impairs QoL are needed to increase the possibilities for prevention. One such study is the Incontinence Post robot assisted radical prostatectomy, Anatomical and functional causes (IPA), currently conducted at our institution (ISRCTN67297115). Included patients are evaluated with MRI, dynamic transrectal ultrasound and urodynamics before and three months after surgery, and procedures are filmed with the main objective being to evaluate both patient- and procedure specific factors leading to urinary incontinence after RALP (Stranne 2018). Identifying factors for incontinence is the first step towards creating new methods to avoid, or oppose, the effects of these factors. A better understanding of patient-related risk factors could also provide patients with better estimates of their personal risk for postoperative incontinence.

Specialized methods require specialized professionals. In a recent study from NPCR, a high correlation between surgical volume and outcome was seen, both considering hospital and surgeon volume (Godtman et al. 2021). In a large multicentre study from UK, with dedicated urologic radiologists who received centralized training performing MRI readings, the detection of clinically significant prostate cancer in MRI was high, while in a Western Sweden study of MRI performed outside high-volume centres, detection rates were moderate (Ahmed et al. 2017; Kohestani et al. 2019). In both Swedish studies, variation between individuals was large, both for surgeons and radiologists. This underscores that a high volume does not guarantee high performance; results must be followed continuously to ensure quality, and surgeons and other professionals should stay informed about their own results and how they relate to others. NPCR includes PROM data, but use is still limited; only half of the patients having radical prostatectomy had registered baseline PROM data in 2020 (National Prostate Cancer Register of Sweden 2020). Ideally, internal benchmarking is used to improve all-over performance.

An individualized approach is also needed when dealing with complications and side effects of treatment, as well as in recurrent disease. Quality-of-life aspects of BCR is an understudied subject; more research is needed to increase knowledge of how individuals are affected and what their needs are in terms of support from the health care system. Providing a high quality of care is a team effort, requiring multiple competences and patient involvement.

Our findings regarding information gained in MRI and targeted and systematic biopsies were obtained within a highly specialized environment. Consequently, the conclusion that systematic biopsies seldom contribute additional information of importance for surgical planning needs confirmation in a broader population.

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