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Impact of surgical technique and surgeon variability on functional and oncologic outcomes

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Radical prostatectomy - impact of surgical technique and surgeon variability on functional and oncologic outcomes

Abstract

Prostate cancer is the most common cancer in Swedish men and a major health problem. The most common treatment for localized prostate cancer is surgery with radical prostatectomy (RP). In recent decades the technical development has been fast and today, robot-assisted radical prostatectomy (RALP) has almost completely replaced convectional open retropubic radical prostatectomy (RRP) in many countries. This technical shift has occurred without conclusive evidence of superiority in both oncologic and long-term functional outcomes. Furthermore, differences between individual surgeons, so called surgeon heterogeneity, has been shown to be significant in RP, but little is known about what underlying factors related with the surgeons are of importance or how surgeon heterogeneity affects the comparison between surgical techniques.

In this thesis, outcomes after RALP and RRP were evaluated in the large, prospective LAPPRO trial. In total 4 003 men who underwent RP at 14 Swedish centers were enrolled between 2008 and 2011. Data for the assessment of urinary incontinence, erectile dysfunction and cancer recurrence were collected from validated patient questionnaires, telephone interviews and by health care personnel in case record forms at different time points up to 8 years after surgery.

Throughout the follow-up a small and statistically significant benefit was seen for robotic surgery regarding erectile dysfunction, while the rates of urinary incontinence and cancer recurrence were comparable between RALP and RRP. In patients with high-risk tumors the results at 6 and 8 years after surgery indicated that there might also be an advantage for RALP for the oncologic outcome, but due to the low number of events this finding should be interpreted with caution. However, the small differences between techniques were outperformed by the large differences between individual surgeons. A large, statistically significant, surgeon heterogeneity was observed for both functional and oncologic outcomes and remained when only very experienced surgeons were analyzed. To some extent the large heterogeneity was explained by differences in the surgeon's prior experience and annual caseload of the procedure, but the larger part was still unexplained even after these factors were accounted for.

Key words: Prostate cancer; robot-assisted radical prostatectomy; biochemical recurrence; urinary incontinence; erectile dysfunction; surgeon heterogeneity

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Radical prostatectomy

Impact of surgical technique and surgeon variability on functional and oncologic outcomes

Martin Nyberg

LUND UNIVERSITY

Coverphoto by Katarina Ivarsson and Anders Hellberg

To my family

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Abbreviations

AS	Active Surveillance
BCR	Biochemical Recurrence
BPH	Benign Prostatic Hyperplasia
CI	Confidence Interval
CRF	Case Record Form
DRE	Digital Rectal Examination
EBRT	External Beam Radiation Therapy
ED	Erectile Dysfunction
HDR	High-Dose Rate
HR	Hazard Ratio
LAPPRO	LAParoscopic Prostatectomy Robot Open
LDR	Low-Dose Rate
LRP	Laparoscopic Radical Prostatectomy
LUTS	Lower Urinary Tract Symptoms
MRI	Magnetic Resonance Imaging
OR	Odds Ratio
PC	Prostate Cancer
PLND	Pelvic Lymph Node Dissection
PSA	Prostate-Specific Antigen
RALP	Robot-Assisted Radical Prostatectomy
RP	Radical Prostatectomy
RR	Relative Risk
RRP	Retropubic Radical Prostatectomy

Introduction

In the treatment of localized prostate cancer, surgery with radical prostatectomy (RP) has been shown to provide a survival benefit compared to an expectant treatment approach. These proofs rely on the conventional open surgical approach, which has been the surgical gold standard since its introduction in the 1980s. However, in recent decades surgical practice patterns have changed rapidly and robotic-assisted radical prostatectomy (RALP) has challenged the traditional open technique and is today the most common surgical approach in many countries. This shift, with large investments from hospitals, has occurred despite the lack of conclusive evidence of the superiority of robotic surgery regarding both long-term functional and oncologic outcomes.

The present thesis investigates the potential differences in outcomes after RALP and open retropubic radical prostatectomy (RRP) in the large Swedish LAPPRO trial, including more than four thousand men. The two major long-term complications, urinary incontinence and erectile dysfunction (ED), as well as cancer recurrence and mortality were assessed at different follow-up times ranging from 2 to 8 years after surgery.

Radical prostatectomy is a challenging procedure for surgeons, who need to balance the preservation of functional outcomes without compromising with radical removal of the tumor. However, little is known about the effects of the performance of individual surgeons on long-term urinary incontinence, ED and cancer recurrence after surgery. This will be assessed throughout the papers constituting this thesis.

Prostate cancer

PC is one of the most common malignancies in men worldwide and a major health problem. The incidence and mortality vary greatly in different parts of the world, being highest in developed countries in North America and in Europe. In Sweden, PC is the most common cancer, accounting for almost one-third of all newly diagnosed cancers in men (1).

The British surgeon Adams, one of the first to describe PC in the middle of the 19th century, described it as a very rare disease (2). This was the case until at least the middle of the 20th century and PC, as we know it today, is a rather "modern" disease. The main reasons are that men did not live long enough to acquire the disease and that the discrepancy of obstructive urinary symptoms between benign and malignant tumors was poorly defined. In the second half of the 20th century, interest in and knowledge of PC increased with a true paradigm shift in the 1990s with the introduction of the prostate-specific antigen (PSA) test.

Natural history

The natural history of PC is heterogeneous. Often, the tumors progress slowly and remain localized to the prostate gland with a low risk of morbidity and mortality. In other cases, the cancer progresses more rapidly, resulting in a spread beyond the prostate and a considerable effect on long-term survival. Some decades ago, before the PSA test was established, PC was a disease with a poor prognosis. Approximately half of the men with newly diagnosed PC had an incurable form of the disease, and 25-30% presented with metastasized cancer (3). At the time, the diagnostic tools for detecting early stages of PC were limited, and patients were usually diagnosed when symptoms of locally advanced or metastatic disease occurred. The introduction of the PSA test in the 1990s revolutionized the diagnostic pathway for PC, and it is now possible to identify the disease at an early stage without symptoms or palpable tumors.

For ethical reasons, it has been a problem to investigate the true natural history of PC, i.e., the disease progression without any treatment, and it is consequently not fully known. However, it is known from observational studies that many localized tumors grow slowly and have a low risk of causing symptoms or mortality (4-6).

These tumors are referred to as indolent PC. In autopsy studies, it has been shown that from the age of seventy, the majority of men have indolent PC (7-9).

Incidence and mortality

Since the 1990s the incidence of PC in Sweden and other developed countries has increased dramatically. The main reason is that the introduction and wide use of PSA testing has resulted in an increased detection of early-stage tumors, including indolent cancers. In Sweden the incidence peaked in 2005, decreasing somewhat in the following years and thereafter being relatively stable (Figure 1). Sweden has one of the highest incidences of PC, with 10 947 new cases in 2018, making PC the most common cancer among Swedish men (10).

The incidence of PC varies around the world, being the highest among men of African descent in the USA and in the Caribbean, followed by Caucasians in the USA and in Scandinavian countries, while the disease is rather uncommon in South East Asia.

PC was the most common cancer-related cause of death among Swedish men in 2018. In total, 5.3% of Swedish men died as a direct cause of PC. The total number of men dying of the disease has been relatively constant during the last decade, but since beginning of the 20th century the age-standardized mortality has decreased, especially for men under the age of 75 years (Figures 1 and 2) (1, 11).
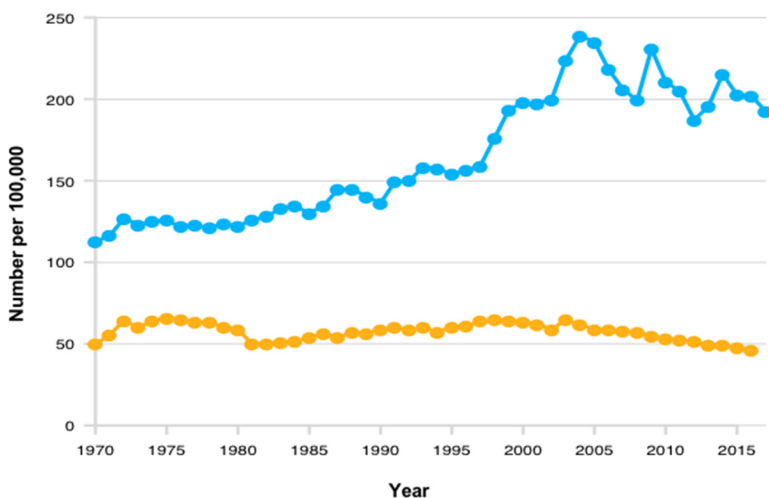
Figure 1. Age-standardized PC incidence (blue line) and mortality (yellow line) in Sweden between 1970 and 2018, shown as the number of cases and deaths per 100,000. Adapted from the National Prostate Cancer Registry (10).
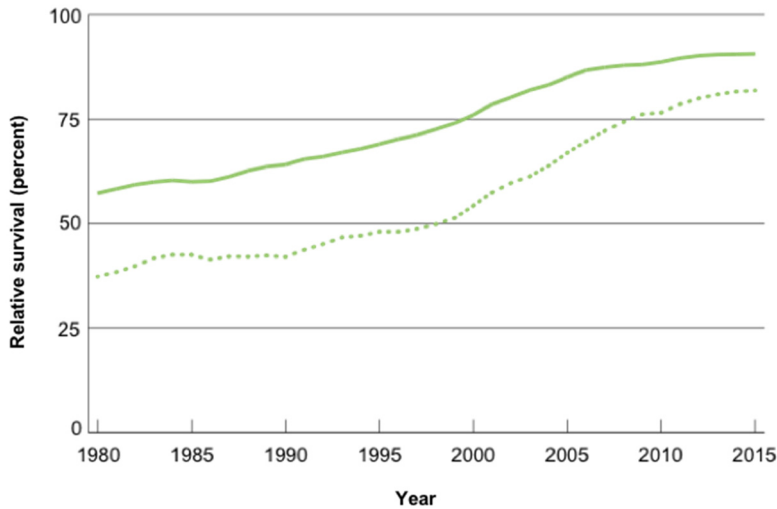
Figure 2. Age-standardized relative 5-year (solid line) and 10-year (dotted line) survival in Swedish men with PC between 1980 and 2015. Adapted from The National Board of Health and Welfare, Cancer incidence in Sweden 2018 (11).

Clinical presentation

Early-stage PC is a silent disease. Symptoms include lower urinary tract symptoms (LUTS) related to obstruction of the urethra such as hesitancy, poor stream, nocturia, frequency and urgency. However, PC tumors most frequently grow in the peripheral zone of the prostate, which is distant from the urethra, and bladder outflow obstruction is a late event (12). Benign prostate hyperplasia (BPH), in contrast to PC, most often originates from the transitional zone of the prostate adjacent to the urethra and thus causes LUTS when the gland becomes enlarged. Only approximately 13% of patients with acute urinary retention have underlying PC (13). Advanced PC can invade the urinary bladder, seminal vesicles and rectum surrounding the prostate and cause symptoms such as hematuria, hematospermia, perineal pain and rectal bleeding.

PC most frequently metastasizes to lymph nodes and to the bone, with other localizations including the liver and lungs. Metastasized disease is associated with severe morbidity often related to pain from bone metastases. A feared condition requiring acute intervention is when metastases in the spinal cord give rise to paralysis of the legs and/or urine bladder. Earlier detection of PC with PSA testing has made symptoms from an undiagnosed metastasized disease uncommon, but unexplained malaise and bone pain in elderly men should raise the suspicion of an underlying PC.

Diagnosis

Since the PSA test was established in the 1990s, one of the major challenges in PC diagnosis has been the differentiation between early stage tumors as indolent or with the potential for aggressive growth. PSA, clinical tumor stage and histological grading are all of prognostic value, but some patients are in a gray area where the balance between under- and overtreatment could be difficult. In recent decades, the diagnostic pathway in PC diagnosis has consisted of PSA, digital rectal examination (DRE), transrectal ultrasound (TRUS) and systemic needle-core biopsy. However, at present a paradigm shift is occurring including prebiopsy magnetic resonance imaging (MRI) in the standard diagnostic pathway (14).

Prostate-specific antigen test

PSA is a glycoprotein that is produced by the prostatic epithelium and was first isolated in the 1970s (15). It is transported with the seminal fluid, and its biological function is to regulate the liquidity of the seminal fluid, thereby influencing the motility of the sperm (16). A small portion of PSA leaks into the systemic blood circulation, where the majority binds to form complexes with larger proteins. In the case of prostatic disease or mechanical manipulation, the natural barrier between the prostatic tissue and capillaries may be affected, resulting in an increased leakage and an elevated PSA level in peripheral blood. This is the case for PC cells in which the normal cell architecture is disrupted, allowing a greater part of the produced PSA to leak into the systemic circulation. Since the prostate is the only significant source of PSA, this makes PSA a marker for PC (16, 17). However, PC is not the only condition that affects the level of PSA. BPH, urinary tract infection, acute urine retention, hypogonadism, chronic renal failure and treatment with 5-alpha-reductase inhibitors are all well-known factors influencing the PSA level in peripheral blood.

Ever since the introduction of PSA testing, the optimal PSA-threshold for recommending further examination with prostate biopsy has been debated. Using a low cutoff value results in a high sensitivity but a low specificity and vice versa. In the present Swedish national guidelines for PC, the recommended cutoffs are age dependent. For men under 70 years, the PSA threshold is ≥3.0 ng/mL, for men 70-80 years, ≥5 ng/mL, and for men over 80 years, ≥7 ng/mL (18). Several PSA-related

factors, such as the ratio between free and total PSA in serum (19, 20), PSA velocity (rate of change in PSA over time) (21-23) and PSA density (serum PSA divided by prostate volume) (24, 25), have been shown to be associated with PC aggressiveness.

Digital rectal examination

A DRE should always be included in the investigation following an elevated PSA test and in men with LUTS to identify palpable tumors. In the combination with an elevated PSA test, an abnormal DRE has been demonstrated to be associated with an increased risk of clinically significant tumors (26, 27). However, in a primary care setting, DRE has been shown to have a sensitivity and specificity below 60% in detecting PC on needle core biopsy (28). A substantial proportion of early stage tumors are missed with DRE because some tumors are located in an anatomical position (ventrally in the prostate) where they are not detectable by DRE, and many cancers are too small to be felt by the physician's finger. Furthermore, the interexaminer variation in detecting PC by DRE has been shown to be substantial (29).

Transrectal ultrasound and needle-core biopsy

TRUS is routinely used in the investigation of prostatic disease. It is performed to measure the size of the prostate and, to some extent, evaluate the prostatic anatomy and detect suspicious tumor areas. If the initial PC investigation (PSA, DRE and MRI) raises suspicion of PC, needle-core biopsies are performed with TRUS after local anesthesia. In the traditional diagnostic pathway, when PC is suspected based on PSA and DRE, systematic biopsies from 10-12 standardized locations in the prostate are performed. However, this pathway is currently changing, and guidelines from the European Association of Urology (EAU) and the Swedish national guidelines for PC now recommend that a prebiopsy MRI is performed (14, 18). Based on the MRI result (and that of PSA and DRE), targeted and/or systemic biopsies are performed.

Magnetic resonance imaging

During the last decade, MRI has come to play an important role in the diagnosis of PC, initially as a second-line diagnostic tool for men with continued suspicion of PC when systematic biopsies were negative, and currently as the recommended

first-line diagnostic tool before biopsy (14, 18). Compared with initial systematic biopsy, prebiopsy MRI has been shown to have higher sensitivity in detecting clinically significant tumors and, at the same time, to decrease the detection of indolent tumors in men with an elevated PSA, reducing the number of unnecessary biopsies and overdiagnosis (30, 31). In a systemic review from 2020, the negative predictive value for multiparametric MRI in detecting clinically significant tumors was 87-97%, depending on the thresholds used for defining a nonsuspicious tumor on MRI and clinically significant cancer (32). However, the heterogeneity between the included studies was large and negative predictive values as low as 63% were reported. Furthermore, the interpretation of MRI has also been shown to differ significantly across independent radiologists (33).

In the diagnosis of PC, multiparametric MRI includes a combination of T2-weighted images, dynamic contrast-enhanced MRI and diffusion-weighted images (34, 35). Suspicious tumors on MRI are classified according to the PI-RADS system, a structured reporting scheme categorizing the suspicious area from 1 to 5. PI-RADS 5 corresponds to the highest degree of suspicion for a significant cancer, while PI-RADS 1 and 2 correspond to changes with a very low and low suspicion and rarely lead to needle-core biopsies.

Risk classification of localized prostate cancer

Staging

The staging of PC is based on the Tumor, Node, Metastasis (TNM) classification (Table 1) (36). The clinical tumor stage (cT-stage) is based on DRE findings and describes the extent of the primary cancer. MRI or other imaging techniques are not considered in the TNM classification. The pathologic tumor stage (pT-stage) is based on the pathology report after RP and is similar to the cT-stage except that all PCs found on pathology examination are at least stage T2 and that no substages for T2 tumors are recognized. Node-stage (N) and metastasis-stage (M) describes whether and to what extent the disease has spread to the lymph nodes (N) and other parts of the body (M). N- and M-stages are based on imaging such as bone scintigraphy, computer tomography and positron emission tomography (PET).

Table 1. TNM classification for prostate cancer. Table adapted from European Association of Urology Guidelines (14).

T	Primary Tumor stage
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
T1a	Tumor incidental histological finding in 5% or less of tissue resected
T1b	Tumor incidental histological finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy (e.g. because of elevated PSA)
T2	Tumor that is palpable and confined within the prostate
T2a	Tumor involves one half of one lobe or less
T2b	Tumor involves more than half of one lobe, but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostatic capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles, external sphincter, rectum, levator muscles, and/or pelvic wall
N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

Histologic grading

The Gleason grading system was developed by Donald F. Gleason in 1966 (37) and, in a modified form, is still used by pathologists worldwide for the histologic grading of prostatic adenocarcinomas (38). Gleason identified five different basic histological patterns (Gleason grades) based on the degree of tissue abnormality, scoring the growth pattern from one to five (well to poorly differentiated) (Figure 3). In the original system, the two most present patterns were added to a Gleason score ranging from 2 to 10. However, following a major revision in 2005, Gleason

scores lower than 6 have not been used in practice, and after another modification in 2014, the histologic grading system, still based on the Gleason grades, has also been reported as 5 prognostic grade groups (ISUP grade 1 to 5) (39, 40).

An important limitation in the histological grading of PC is the interobserver variability among pathologists. Especially when comparing general pathologists and experts in uropathology, the heterogeneity has been shown to be significant (41-45), with an observed coherence in the reported Gleason grade of 78% (46). This is important since the histological grade is a strong prognostic factor and an important when urologists are deciding on the most suitable treatment.
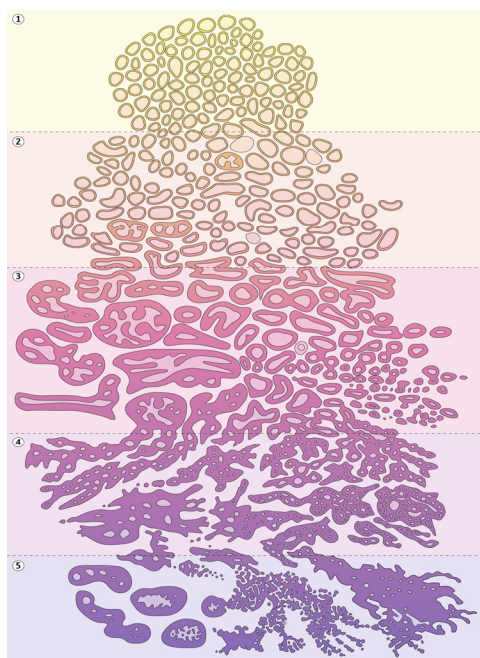
Figure 4. The original Gleason grading system from 1966. Reprinted from (47), with permission from Springer Nature.

Risk groups

Untreated PC without signs of metastasis is categorized into different prognostic risk groups based on the PSA level, cT-stage and Gleason score on systematic biopsy. The definitions originate from the D'Amico risk classification system developed in 1998 and divide the tumors into low, intermediate and high risk (48). The risk classification system has been modified since its introduction, and in the present Swedish national guidelines for PC, the low-risk group is subdivided into very low and low risk groups (**Table 2**) (18, 49).

Table 2. Risk classification groups for localized prostate cancer. Table adapted from the Swedish National Guidelines for PC (18).

Risk group	cT-stage	Gleason score	PSA (ng/mL)	
Very low risk	T1c	≤6	<10	In total ≤ 8 mm of cancer in ≤ 4 out of 8-12 biopsy cores. PSA density < 0.15 μg/cm³
Low risk	T1-T2a	≤6	<10	
Intermediate risk	T2b	7	10-19.9	
High risk	T2c-T3	8-10	≥20	GS 8-10, or widespread growth of GS 4+3=7 in more than half of the biopsy cores

Several factors are associated with the aggressiveness and prognosis of the tumor. The strongest predictive factor is the histologic pattern. Higher Gleason grades are strongly correlated with a more aggressive tumor and a worse prognosis (50-53). In addition to the grade, the extent of a certain grade is also associated with the prognosis (54-56). For example, it may be worse to have an extensive Gleason grade 3+4 than a small focus of Gleason grade 4+4. In concordance with this, the number and percent of positive needle biopsy cores has been shown to be a predictive factor (57). Other factors related to the histologic growth pattern, such as perineural space invasion, lymphovascular invasion, and ductal or neuroendocrine differentiation, are also important for prognosis (58, 59). Furthermore, as previously mentioned, PSA, including the total PSA level, the ratio of free and total PSA and PSA velocity, are predictors of PC aggressiveness.

As a prognostic tool, nomograms have been developed for patients at different stages of the disease. For instance, a nomogram developed at Memorial Sloan Kettering Cancer Center can be used as a support for patients and clinicians in the pre-radical prostatectomy setting. Based on age, prebiopsy PSA level, cT-stage, Gleason grade and number of positive biopsy cores, the nomogram calculates the probabilities for cancer-specific survival, biochemical recurrence (BCR), organ-confined disease, extracapsular extension, lymph node involvement and seminal vesicle invasion (60).

The risk group classification and its prognostic value is based on systematic biopsies. New diagnostic strategies with MRI followed by targeted biopsies probably have a somewhat different prognostic relevance in regard to the number of positive biopsy cores and extent of cancer growth in the biopsies. For instance, a small tumor with Gleason grade 4+3 on targeted biopsy would be classified as high risk because more than half of the biopsy cores are positive but could have been classified as intermediate risk if systematic biopsy had been performed. This problem will have to be addressed in future guidelines with a corresponding upgrade to the risk classification system, but at present, urologists have to individualize treatment recommendations.

Treatment for localized prostate cancer

The choice of treatment for PC is dependent on risk group, the patient's general health and remaining life expectancy, as well as patient preference. The disease is considered to be potentially curable if it is localized to the prostatic gland. Patients with distant metastasis, a PSA level above 100 ng/mL, signs of widespread regional lymph node metastasis and with cT-stage 4 are considered to have an incurable disease, and treatments are administered with a palliative intent. In the primary diagnostic assessment, a metastasis investigation is routinely performed only for patients with high-risk tumors. In the low- and intermediate-risk groups, metastasis is uncommon, and treatment is often planned without further investigation. If incurable, treatment options include expectance, hormonal treatment (androgen deprivation therapy), chemotherapy and symptomatic treatments such as radiotherapy (locally at the prostate or at the bone metastasis) and transurethral resection (in case of urinary obstruction). The most suitable treatment strategy is based on the disease stage, progression rate and symptoms. Recently, novel antiandrogens have been introduced for the treatment of metastatic castration-resistant PC. These drugs can increase the survival patients with a late-stage disease.

Because of the natural history of localized PC with slowly progressing tumors, the patients' remaining life expectancy is of great importance for the choice of treatment. For men with a high age or high degree of comorbidity and a remaining life expectancy of less than 10-15 years, it is considered very unlikely that the tumor will develop into a life-threatening disease. For these patients, the preferred treatment strategy is watchful waiting. Traditionally, this meant that treatment was deferred until symptoms occurred, but today, evidence exists demonstrating that early hormonal treatment can increase survival if the disease progresses to a locally advanced stage (61, 62). For men with initially locally advanced tumors, curative treatment can be an option even with a life expectancy of less than 10 years.

For men with localized disease and a remaining life expectancy of more than 10-15 years, the treatment options are active surveillance, radiotherapy or surgery with RP.

Active surveillance

During the last decade, active surveillance (AS) has been established as a treatment option for low-risk tumors. The rationale is that most low-risk tumors are slowly progressing and will never affect the patient's health or survival. With modern diagnostic tools, the probability of a low-risk tumor progressing to metastatic disease has been shown to be less than 1% during 10 years of follow-up (63, 64). By actively monitoring these patients, overtreatment is reduced (65), and side effects related to active treatment are spared or postponed. Patients suitable for AS are actively monitored with PSA, DRE, repeated biopsies and MRI according to a predefined schedule. If signs of disease progression occur according to predefined thresholds, patients are offered active treatment with radiotherapy or RP (14, 18, 66). Active surveillance is different from watchful waiting, the latter not having a curative intent.

It is clear that the long-term cancer-specific survival for patients on AS is very good. However, approximately one-third of patients are reclassified during follow-up because of upgrading or progression, and most of these patients undergo active curative treatment (67). Moreover, prior AS studies are heterogeneous regarding criteria for inclusion, how patients should be followed or what thresholds trigger intervention (66). A large multinational study including more than 15 000 patients on AS worldwide has been initiated with the goal of creating a global consensus (68), but at present, no international guidelines on how to select and monitor patients exist.

Radiotherapy

Radiotherapy can be administered in the form of external beam radiotherapy (EBRT) or brachytherapy. In EBRT, beams of gamma radiation (usually photons) are directed to the prostate and surrounding organs. The technique has been developed further since its introduction in the 1960s, making it possible to give radiation with higher precision and thereby higher doses without risking more severe side effects (69, 70). In brachytherapy, radioactive sources are planted into the prostate. In low-dose rate (LDR) brachytherapy, iodine or palladium seeds with a half-life of 60 days are permanently deposited into the prostate through the perineum. In high-dose rate (HDR) brachytherapy, hollow needles with iridium are placed, almost in the same manner as for LDR brachytherapy, temporarily in the prostate for 10-20 minutes.

EBRT, in combination with hormonal treatment, has in randomized trials been shown to give superior long-term cancer control over hormonal treatment alone for high-risk PC (71-73). The standard dose for EBRT in Sweden today is 78 Gray in

39 fractions. However, several recent studies have shown that a hypo- or ultrahypofractionated regime (fewer, larger doses of radiation) has the same oncologic effect for intermediate-risk PC but reduces treatment length (74, 75). LDR brachytherapy as monotherapy has in observational studies been shown to be comparable to EBRT for low-risk PC and certain cases of intermediate-risk PC (low cancer volume and small extent of Gleason grade 4) (76). HDR brachytherapy is not recommended as monotherapy, but observational studies have shown an advantage for a combination of HDR brachytherapy and EBRT over EBRT alone, especially for high-risk tumors (77, 78).

Several studies, including the Swedish SPCG-7 trial, have shown that radiotherapy in combination with hormonal treatment is superior to radiotherapy alone for intermediate and high-risk PC (79, 80).

Side effects after radiation therapy are related to damage to the surrounding tissue in the bladder, rectum, striated sphincter and urethra. Short-term side effects, such as irritative urinary symptoms, flatulence, loose stool and rectal bleeding, most often occur in the latter part of the treatment and are often transient. Long-term side effects occur more than six months after radiotherapy and include erectile dysfunction (ED), rectal disorders, hematuria, urinary frequency, urinary urgency and reduced bladder capacity. After EBRT, moderate rectal disorders and moderate urinary symptoms both occur in approximately 10-20% of cases. The probability of ED gradually increases after EBRT and has been reported in 20-80% of cases (81, 82). In general, LDR brachytherapy is related to fewer long-term side effects (besides urinary frequency) than EBRT (76).

Surgery

Radical prostatectomy (RP) is the surgical removal of the prostatic gland and the surrounding tissue. After removal, urinary continuity is recreated by an anastomosis between the bladder neck and urethra. Today, the vast majority of the procedures are performed with robotic-assisted (RALP) or by conventional open (RRP) techniques.

A landmark study showing the advantage of RP over watchful waiting is the Scandinavian SPCG-4 trial (6). In SPCG-4, 695 men with clinically detected T1-2 tumors and a long remaining life expectancy were randomized either to radical prostatectomy or watchful waiting between 1989 and 1999. Patients in the watchful waiting group received no immediate treatment but underwent symptomatic treatment such as transurethral resection in case of urethral obstruction. Both groups received hormonal treatment with surgical castration or gonadotropin-releasing hormone (GnRH) if metastases were confirmed. After a median follow-up time of 23.6 years, the cumulative risk of dying from PC was 19.6% after RP and 31.3%

after watchful waiting. Men gained an average of 2.9 years of life after RP. Distant metastasis was confirmed in 26.6% of patients in the RP group and in 43.3% of patients in the watchful waiting group. For men under the age of 65 years at inclusion, the difference in cancer-specific survival and prevalence of distant metastasis was even greater. In the randomized PIVOT trial, a similar comparison was made but found no significant difference between RP and watchful waiting in terms of overall or cancer-specific survival (83). However, for patients with high-risk tumors or a PSA value > 10 ng/mL, an advantage for RP was seen regarding overall survival and the prevalence of bone metastasis. Compared to the SPCG-4 trial, the PIVOT trial had a shorter follow-up time (12.7 years), and the included men had a higher degree nonpalpable (T1) tumors.

The most prominent long-term side effects from RP are urinary incontinence and ED (84). Most patients suffer from urinary leakage during the first month after surgery. The leakage decreases substantially during the following months, but in some cases, the leakage becomes permanent. To some extent, all men undergoing RP have impaired erectile function postoperatively. The function can improve up to a couple of years after surgery, but the majority will suffer from ED for their remaining life.

Androgen deprivation therapies in conjunction with RP has not been shown to have any benefit and is not recommended.

Active surveillance, surgery or radiotherapy?

The most suitable treatment (AS, RP or different types of radiotherapy) depends on tumor characteristics (risk group), patient characteristics and patient preference. The only randomized trial directly comparing EBRT, RP and AS in localized PC did not show any significant difference between the treatments in overall or cancer-specific survival after 10 years of follow-up (85). However, compared to AS, EBRT and RP was associated with lower rates of disease progression and metastases. A retrospective study comparing RP, EBRT combined with adjuvant androgen deprivation therapy and a combination of EBRT and HDR brachytherapy for high-risk PC (Gleason score 9 or 10) showed a significantly lower mortality with the third treatment (86). Other observational studies have observed an advantage in the survival and prevalence of metastases for RP over EBRT (4, 87, 88). However, none of these studies is randomized, and at present, conclusive evidence favoring radiotherapy or surgery is lacking.

In the present Swedish national guidelines for PC, EBRT and RP are considered equivalent for intermediate-risk PC. EBRT is the preferred treatment for high-risk PC except for clinical stage T1-2 tumors, where the treatments are considered comparable. For low-risk PC, active surveillance is the preferred treatment strategy,

and EBRT and RP are only relevant in special cases (patient preference). The same is true for very low-risk PC, except that monotherapy with LDR brachytherapy is considered equal to EBRT and RP (18).

Since EBRT and RP are considered comparable but have different potential side effects, patient preference is of great importance when choosing the most suitable approach. For EBRT, this includes side effects related to hormonal treatment. However, some tumor- and patient-related factors speak for either treatment. Factors favoring surgery are rectal disorders such as ulcerative colitis or Crohn's disease, urinary obstruction, proximal urethral stricture, neurogenic bladder disorders, and a very large prostate volume. A younger age can also suggest surgery because of the potential risk of a secondary malignancy related to radiation (89). Factors in favor of radiotherapy are a high risk of extraprostatic cancer growth, considerable growth of Gleason 5, high risk of thromboembolism, and risks related to anesthesia.

Pelvic lymph node dissection

It is generally accepted that pelvic lymph node dissection (PLND) provides important information about the correct staging and prognosis of prostate cancer (90). However, it has not been shown that PLND decreases the risk of cancer recurrence or improves survival. The decision to perform PLND is based on preoperative tumor characteristics and the probability of lymph node involvement can be calculated by nomograms. If the risk is appreciated to be more than 5%, it is often considered to be an indication to perform PLND. With extended PLND, which includes the removal of nodes overlying the external iliac artery and vein, nodes within the obturator fossa located cranially and caudally to the obturator nerve, and nodes medial and lateral to the internal iliac artery, 94% of patients have been shown to be correctly staged (91).

Radical Prostatectomy

The German surgeon Theodor Billroth was the first to describe prostatectomy on a patient in the 1860s (92). Later, Young published data from the first series of prostatectomies in the treatment of prostate cancer in John Hopkins Hospital in 1905 (93). These initial series were performed with a perineal approach, and the mortality and morbidity were high. The first to describe the procedure with a retropubic approach was Terence Millin in 1945 (94). The mortality and morbidity rates were still high, with complications such as large blood loss, urinary incontinence, erectile dysfunction and stricture of the vesicourethral anastomosis. The indication for surgery was thus far not curative but rather palliative for treating urinary obstruction since, at time, PC was most often diagnosed in a late stage and not considered curable.

With general medical development and especially with the discovery of PSA, PC began to be diagnosed in earlier stages, and the need for better treatment options with fewer peri- and postoperative complications increased. The major surgical development stage came in the 1980s when the knowledge about the surgical periprostatic anatomy improved. The American urologist Patrick Walsh and colleagues described the dorsal venous complex in 1979 and, later, the existence and function of the neurovascular bundles and the external urinary sphincter (95, 96). Walsh developed the modern surgical approach (RRP) that allowed better visualization and preservation of the neurovascular bundles and external sphincter, leading to decreased complications of incontinence and ED (97). Further anatomical and technical development to RRP followed with better knowledge about the puboprostatic ligaments (98), prostate shape (99) and urinary sphincter complex (100).

As for many other surgical procedures, the laparoscopic technique was introduced in prostate cancer surgery in the late 1990s with the belief that it would lead to less bleeding and shorter convalescence than the open approach (101, 102). However, laparoscopic radical prostatectomy (LRP) never had a great impact on prostate cancer surgery because it became associated with a long learning curve and potentially more postoperative complications than RRP (103, 104). Instead, the paradigm shift arrived in the beginning of this millennium when RALP was introduced. The first RALP was performed in Germany in year 2000, and since then the development has been rapid (105). In 2018, more than 3000 RPs were performed in Sweden. Of these, 88% were performed by RALP, 11% by RRP and only 2% by

LRP (10). The trend between the different surgical approaches is shown in Figure 5, illustrating the rapid implementation of the robotic-assisted approach.
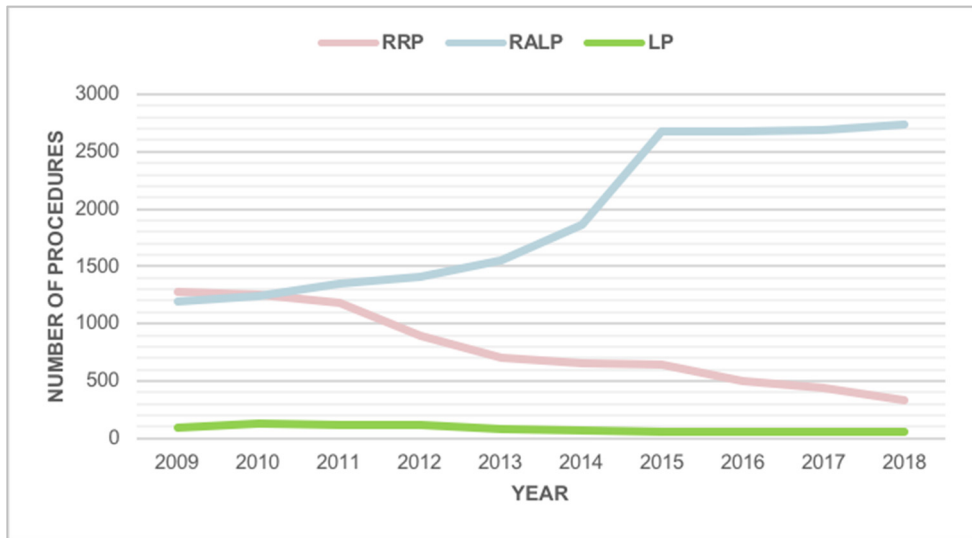
Figure 5. Type of radical prostatectomy in Sweden between 2009 and 2018 (10).

Surgical anatomy of the prostate

The prostate is located in the male pelvis between the bladder, rectum and penis, with the urethra running through the center of the gland (Figure 6). It is often described as being walnut-sized, but the size varies between individuals and increases with age. The two seminal vesicles are located posterior-laterally to the prostate and connect with the vas deferens to form the ejaculatory ducts, which run through the prostate and converge at the urethra at the seminal colliculus. The external urethral sphincter is located distal to the prostate apex and consists of two different types of muscle types, an outer layer of striated muscle fibers that forms a horseshoe-like structure and an inner layer of smooth muscle that surrounds the urethra.
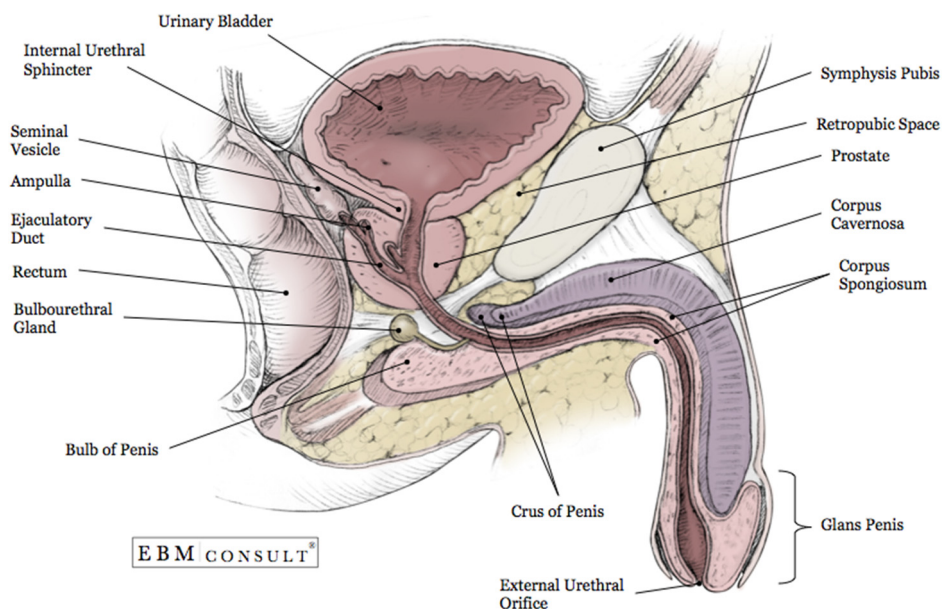
Figure 6. Male pelvic anatomy. Image provided by EBM Consult.

The prostate is composed of different histological zones, and based on these zones, the gland is divided into anatomical zones (Figure 7), three glandular zones (peripheral, central and transitional zones) and two nonglandular (peri-urethral zone and anterior fibromuscular stroma). The peripheral zone is the largest, making up almost 75% of a normal prostate and is the place where most cancers originate. Benign prostatic hyperplasia is caused by enlargement of the transitional zone.

The prostate is surrounded by a capsule-like structure consisting of fibromuscular fascicles (106) and three fascial layers: Denonvillier's fascia, located dorsally between the rectum and prostate; the prostatic fascia, located anteriorly and anterior-laterally; and the endopelvic fascia, located laterally. The puboprostatic ligaments are paired structures that support the prostate, bladder and urethra to the pubic bone and are considered to have a role in the continence mechanism (107, 108). Ventrally, the prostate is covered by the dorsal venous complex, which drains blood from the penile veins. Both parasympathetic and sympathetic nerves from the pelvic plexus run lateral and posterolateral on the prostatic surface in two neurovascular bundles (109, 110). The bundles are not distinct structures but consist of multiple dispersed nerve fibers. The nerves innervate structures of the erectile mechanism but have also been shown to play a role in continence (111) and are of special interest when performing a radical prostatectomy to preserve the functional outcome. A nerve-sparing procedure can be performed in three different surgical planes: intra-, inter- or extrafascial. In the extrafascial approach, the dissection plane is farthest from the

prostatic surface, and the bundles are not preserved. From an oncologic perspective, this could be the safest approach but comes with a high risk of ED. In the intra or interfascial techniques, the intention is to spare the nerves, resulting in a higher probability of preserved erectile function.
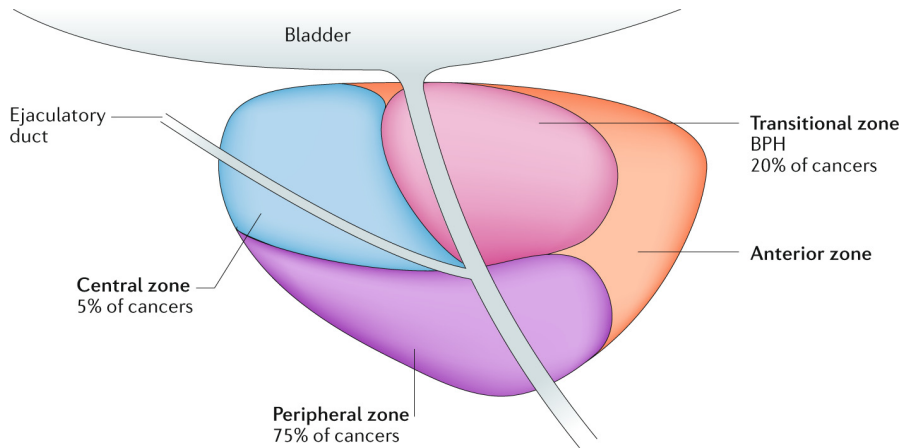
Figure 7. Anatomical zones of the prostate. Reprinted from (47), with permission from Springer Nature.

Retropubic radical prostatectomy

As previously described, surgical treatment of prostate cancer has been shown to be superior to watchful waiting (6). The evidence rests on the open retropubic approach, and RRP has been the gold standard in the surgical treatment of prostate cancer for the last few decades.

RRP is primarily performed as an extraperitoneal procedure. Good exposure to the operative field in the pelvis is made by a midline incision between the pubic bone and up towards the umbilicus. The dorsal venous complex is divided after suture ligatures have been placed both proximal and distally, and the apex of the prostate is carefully dissected from the urethral sphincter and neurovascular bundles. The apex dissection is challenging since the surgeon has to balance preserving functional outcomes and the risk of not radically removing the tumor. If the intention is nerve-sparing surgery, the dissection of the neurovascular bundles is continued laterally and dorsally from the prostate. Preferably, diathermy should be avoided in the dissection of the nerve bundles to avoid irreversible damage to the nerves (112). If an extrafascial technique is used, the resection is widened, and the nerves are not spared. The procedure continues with the dissection of the bladder neck, and the prostate is removed. Finally, a vesicourethral anastomosis is performed by single intermucosal sutures. The goal is to create a precisely aligned, watertight, tension-

and stricture-free anastomosis without interfering with the integrity of the external sphincter mechanism.

Robot-assisted radical prostatectomy

The concept of robotic surgery was first explored in the 1970s by the U.S. National Aeronautics and Space Administration (NASA) and other U.S. military organizations (113). The idea was to perform remote surgery on astronauts in orbit and on wounded soldiers on the battlefield while the surgeon was distant. Although neither of those ideas were realized, the technical advantages developed formed the start of robotic surgery. In addition to remote control, one goal of robotic surgery was to minimize unwanted motion from hand tremor, and in 1985 a robot was used in stereotactic brain surgery to insert a needle into the brain for biopsy (114). Inspired by conventional laparoscopic surgery in the 1980s and 1990s, the robots were developed and adapted to be compatible with minimally invasive surgery. This was achieved with the launch of the da Vinci® system by Intuitive Surgical Inc. in the late 1990s. The Da Vinci system offered advantages to open and conventional laparoscopic surgery with a three-dimensional visualization, better optical magnification, elimination of unwanted motions and a wristed motion that mimics the human hand to allow better dexterity, all theoretically appealing features when operating in tight spaces, such as when performing a RP in the narrow male pelvis.

RALP is performed via five laparoscopic ports through the abdominal wall. The abdominal cavity is inflated with carbon dioxide to form a pneumoperitoneum which is considered to cause less bleeding than open surgery. Except for the intraperitoneal approach, RALP is performed by the same basic principles as RRP. Traditionally, it has been performed by an anterior approach, first gaining exposure to the space of Retzius by detaching the bladder from the abdominal wall, but more recently, a posterior approach has been suggested to yield improved early postoperative continence (115-117). In this approach, the dissection starts at the pouch of Douglas, first dissecting the seminal vesicles and progressing behind the prostate, to avoid the anterior supporting structures. The technological advantages of the robotic-assisted technique was thought to make it easier for the surgeon to perform crucial parts of the procedure, such as the vesicourethral anastomosis and preservation of the neurovascular bundles, thereby improving postoperative functional outcomes. Despite the lack of high-quality studies comparing outcomes between RRP and RALP, surgeons and centers rapidly adapted the robotic technique based on early reports indicating superior short-term outcomes (118, 119) and RALP soon came to be the leading surgical approach in many countries.

The primary goal of RP is to simultaneously radically excise the tumor and preserve the functional outcomes as much as possible. However, men with localized PC have

a long remaining life expectancy even without treatment, and comparative studies between different treatment options, such as RALP and RRP, need long follow-up times to draw solid conclusions about the oncologic outcome. In PC surgery, the oncologic outcome can be measured as PC-specific survival but also as the rate of or time to BCR. Most comparative studies investigating the oncologic outcome between RRP and RALP are observational and in generally suffer from short follow-up times in the assessment of the oncologic outcome.

Complications to radical prostatectomy

Despite technical improvements to the procedure, there is still a high risk of severe side effects after RP with a significant impact on quality of life (84). The major long-term complications are urinary incontinence and ED.

Short-term complications

In general, the short-term mortality and morbidity in relation to RP are low. Perioperative mortality has been reported to be as low as 0.1% and is often related to cardiovascular events (120-122). The most common complication is intraoperative bleeding. Several studies have reported significantly less bleeding during RALP (and LRP) compared to RRP, which can be explained by the pneumoperitoneum created during laparoscopic surgery (120, 123-125).

In a meta-analysis from 2019, Cao reported perioperative outcomes from eight studies comparing minimally invasive RP (LRP or RALP) and RRP (124). The authors reported an advantage for the minimally invasive techniques regarding intraoperative blood loss, perioperative transfusions and length of hospital stay. The total operative time was lower after RRP. The rate of overall and major complications (grade III-V according to the Clavien-Dindo classification) did not differ significantly between the surgical techniques.

In 2014, Wallerstedt et al reported 90-day outcomes from the Swedish LAPPRO trial comparing RRP and RALP (120). Men treated with RRP were significantly more likely to seek health care within 90 days of surgery compared to RALP. Specifically, the groups differed in the frequency of cardiovascular events (most commonly related to pulmonary and deep venous thrombosis). However, no significant difference was observed in the readmission rate within 3 months after RP.

Urinary incontinence

Urinary incontinence after RP is related to the proximity of the prostate to the external urinary sphincter. In the existing literature, the rate of long-term incontinence varies considerably, partly explained by the use of different definitions and cutoffs for the outcome. In a systematic review from 2012 that defined incontinence based on the use of protective pads, the long-term incontinence rate varied between 4% to 31% with a mean value of 16% (126). Important factors in predicting postoperative incontinence are age (127, 128), severe LUTS (129), membranous urethral length (130), body mass index (BMI) (131), medical comorbidities (127, 132) and prostate volume (132). Increasing age has been reported to predict incontinence with an estimated relative risk of 6% per year (128).

Since the introduction of the retropubic RP by Walsh in the 1980s, several technical modifications have been suggested to improve postoperative continence. Promising results have been observed for a better long-term continence rate after bladder neck preservation (133, 134). In a randomized trial from 2017, both the short- and long-term incontinence rate was improved without compromising the oncologic outcome (134). However, concerns have been raised regarding oncological safety for tumors involving the prostate base, and in a systemic review from 2017, a significant increase in positive surgical margins was reported after bladder neck preservation (135). Nerve-sparing surgery has also been associated with improved postoperative incontinence rates (111, 136). This has been suggested to be more related to the dissection technique in nerve-sparing surgery than the actual sparing of nerves (137). Either way, the results indicate that preservation of the neurovascular bundles could also be meaningful in elderly and impotent men. Other surgical aspects, such as urethral length preservation (130), anterior and posterior reconstruction (138-144), Retzius-sparing dissection during RALP (115, 117) and handling of the dorsal venous complex (145) have all been discussed as potential technical modifications to improve postoperative incontinence.

Erectile dysfunction

To some extent all men suffer from impaired erectile function after RP. As previously described, this is caused by damage to the two neurovascular bundles containing the autonomic nerves innervating the cavernous erectile mechanism. The incidence of ED after RP varies greatly in the existing literature, partly explained by the use of different definitions and cohorts with different patient characteristics. In a meta-analysis of 15 RP series, the overall ED rate ranged from 10% to 74% and from 6% to 53% at 1 and 2 years, respectively, after surgery (146). A significantly

higher incidence has been reported in several later studies reporting ED in 65% to 81% at 2 years after surgery (147-150).

Several patient-related factors, such as age (151, 152), medical comorbidities (152) and preoperative potency status, (151, 152) have been shown to predict postoperative ED.

Both the degree (intra- or interfascial) and extent (uni- or bilateral) of nerve-sparing have been shown to be associated with postoperative ED (153, 154). Furthermore, other technical aspects, such as a retrograde nerve-sparing approach and athermal and traction-free dissection of the nerve bundles have been suggested to reduce ED (155-157).

Surgeon heterogeneity

In addition to technical aspects, long-term outcomes after RP depend on the individual surgeons. Significant variation between individual surgeons, referred to as surgeon heterogeneity or variability, has been shown for both the oncologic and functional outcomes after RP. In 2002, Begg, Scardino and colleagues were the first to report that complication rates varied significantly between individual surgeons. Among 159 surgeons who performed at least 20 RPs during the study period (4 years), they observed a large, statistically significant, variation in complications, including long-term incontinence (158). A later single-center study by Vickers et al. confirmed these results, observing a 30% to 40% absolute difference in erectile and urinary function between 11 participating surgeons (159). In a multicenter study from 2010, significant surgeon heterogeneity was also found with regard to the oncologic outcome at 5 years after surgery (160). Seven experienced surgeons had a PC recurrence rate less than 10% while another 5 experience surgeons had a rate exceeding 25%. A Swedish population-based study looking at the effects of surgeon variability on oncologic and functional outcomes, also reported a significant heterogeneity regarding incontinence after RRP, but not for ED or recurrence (161). Furthermore, Huynh et al showed a 10-fold variation in the 3-month continence rate when comparing 5 surgeons (162).

Surgeon experience has in several studies been shown to predict both incontinence, ED and oncologic outcome (104, 163-166). In a learning curve study for RRP by Vickers et al., a plateau for the BCR rate was reached after the surgeons had performed approximately 250 RPs. Learning curve studies for RALP and LRP have not revealed corresponding plateaus, but rather a continuing improvement up to higher experience levels (166, 167).

Taken together, it is well established that surgeon heterogeneity has a significant impact on both oncologic and functional outcomes after RP. However, little is known about which and to what extent, underlying surgeon-related factors such as experience influence the observed differences between surgeons.

Aims of the thesis

The overall objective of this thesis was to investigate how outcomes after radical prostatectomy are affected by the surgical technique and performance of individual surgeons. The specific aims were as follows:

- To assess whether long-term urinary incontinence and ED differ between RRP and RALP.

- To compare RRP and RALP with regard to cancer recurrence and mortality up to 8-years after surgery.

- To investigate the impact of surgeon heterogeneity on functional and oncologic outcomes after RP.

- To assess which underlying factors connected with the surgeons are of importance for surgeon heterogeneity.

- To evaluate how surgeon heterogeneity affects the comparison between RALP and RRP for functional and oncologic outcomes.

Patients and Methods

LAPPRO

LAParoscopic Prostatectomy Robot Open (LAPPRO) is a prospective, controlled, nonrandomized trial comparing outcomes after RRP and RALP (149, 168). In total, 4 003 patients were enrolled from seven centers performing RALP and seven centers performing RRP between September 2008 and November 2011. For the majority of patients, geographical location decided what type of technique was used. All men diagnosed with PC and scheduled for RP at the participating centers were screened for possible inclusion according to prespecified criteria (age <75 years, clinical tumor stage ≤T3, no signs of distant metastases, PSA value <20 ng/mL, ability to read and write Swedish and written informed consent).

Patients completed validated questionnaires preoperatively and at 3 months and 1, 2 and 8 years postoperatively. The extensive questionnaires included several questions about the functional and oncologic outcomes as well as questions related to possible confounders. Clinical data were collected by health care personnel from validated case record forms (CRFs) preoperatively and 3 months, 1 year and 2 years postoperatively. At 6 years after surgery, a structured telephone interview was conducted including questions on PSA values and adjuvant treatments. A detailed description of the study protocol and questionnaires was published in 2011 (168).

Information on the participating surgeons was received from a perioperative CRF where each surgeon stated their previous caseload of the current procedure in categories (up to 150 procedures). Surgeons who had performed more than 150 procedures were contacted retrospectively and asked for the total number of RPs (RRP or RALP) before entering the LAPPRO trial.

The primary endpoint in LAPPRO was patient-reported urinary incontinence 1 year after surgery. The questionnaires included several questions related to urinary leakage, but to evaluate the primary endpoint, patients were asked, ''How many times do you change pads, diapers, or other sanitary protection devices during a typical 24 hours?'' with seven response alternatives. Incontinence was defined as the change of one pad or more per day.

For the secondary endpoint of self-reported ED, a Swedish translation of question three from the International Index of Erectile Function questionnaire (IIEF) was used. Patients were asked "When you had erections with sexual stimulation, how

often was your erection hard enough for penetration during the last 3 months?" with six response options. ED was defined as "an erection insufficient for intercourse more than half of the time".

For the oncologic outcome, several definitions were used. Residual disease was defined as a PSA value of >0.25 ng/mL at the first postoperative measurement. BCR was defined as an initial PSA value <0.25 ng/mL, followed by a PSA-value of >0.25 ng/mL at 1, 2, 6 or 8 years after surgery with a repeated value at the same or a higher level. The combined not cured endpoint consists of residual disease, BCR and/or adjuvant or salvage treatment. The date of death and cause of death were retrieved from the National Cause of Death Register (National Board of Health and Welfare) of Sweden.

The four papers constituting this thesis are based on the LAPPRO cohort. Inclusion criteria, data collection and outcome definitions are identical to those described above.

Statistical analysis

The sample size for LAPPRO was determined to evaluate the primary endpoint of incontinence at the 1-year follow-up. After an interim analysis, group sizes were set at 700 patients in the RRP group and 1 400 in the RALP group to yield 80% power.

Analyses were adjusted for potential confounders and mediators (Table 3). The confounders for incontinence and erectile dysfunction were selected in a stepwise manner (forward selection). For each outcome, imputation was performed for variables considered as possible confounders (17 for incontinence and 19 for ED). With a level of significance set at 0.20, any factor included in more than 25 of 50 imputed models was taken to be a possible confounder. In addition, separate models including adjustment for preoperative tumor-related factors and the degree of nerve-sparing surgery were made. These were also considered confounders but may also have been mediating factors since they could have affected the operation differently in RRP and RALP. For oncologic outcomes the statistical models were adjusted as shown in Table 3.

Table 3. Adjustments for confounders for different outcomes

Outcome	Adjustment A	Adjustment B	Adjustment C
Incontinence	age at surgery, preoperative continence, body mass index (BMI), history of inguinal hernia, prior abdominal surgery, diabetes, history of pulmonary disease, history of mental disorder, pathology prostate weight	clinical T stage, preoperative PSA, biopsy Gleason grade, length of cancer in biopsy cores	degree of nerve-sparing surgery
Additional at 8 years	Cardiovascular diseases		
Erectile dysfunction	age at surgery, preoperative potency, diabetes, history of inguinal hernia, smoking status, relationship status, history of cardiovascular disease	clinical T stage, preoperative PSA, biopsy Gleason grade, length of cancer in biopsy cores	degree of nerve-sparing surgery
Additional at 8 years	pulmonary disease, history of mental disorder		
Residual disease, BCR, Not cured	pathology Gleason grade, pathology T stage, preoperative PSA, and pathology prostate weight	surgeon prior experience, surgeon annual caseload	
At 8 years	clinical T stage, preoperative PSA, biopsy Gleason grade, length of cancer in biopsy cores, pathology prostate weight		
PC-specific mortality	age at surgery, preoperative PSA, biopsy Gleason grade		
All-cause mortality	age at surgery, preoperative PSA, biopsy Gleason grade	cardiovascular diseases, pulmonary disease, history of mental disorder	

Paper I

In paper I, functional and oncologic outcomes were assessed after 2 years of follow-up in the LAPPRO trial. To avoid bias from surgeons still on their learning curve, inclusion was limited to patients operated on by experienced surgeons with a previous case load of at least 100 RPs. For the comparison between RALP and RRP, logistic regression models were used, and the results were presented as odds ratios (ORs). For functional outcomes, the results were presented after three different sets of adjustments (Table 3, Adjustment A, A+B and A+B+C) and are identical to those used in the previously published 1-year follow-up (149). The oncologic outcome was presented as the combined not cured endpoint.

The patient questionnaires included several questions about urinary leakage and ED, and as secondary analyses, six further endpoints for urinary leakage and ED were defined and analyzed (Figure 9 in the Results section).

Paper II

In paper II, surgeon heterogeneity, i.e., the variability between individual surgeons, was investigated from three different perspectives 2 years after surgery: (i) how it affected incontinence, ED and cancer recurrence; (ii) which underlying factors connected with the surgeons were of importance; and (iii) how surgeon heterogeneity affected the comparison between RALP and RRP.

To evaluate surgeon heterogeneity for each outcome measure, logistic regression models were built, and surgeons with at least 20 surgeries during the study period were included as a fixed effect. The models were used to create forest plots and to test for surgeon heterogeneity (likelihood ratio test). Analyses were repeated for surgeons with a prior experience of at least 250 radical prostatectomies. The models were adjusted for patient and tumor factors (Table 3).

In the assessment of underlying surgeon-dependent factors, three factors were analyzed: the surgeons' prior experience (number of RRPs or RALPs performed prior to the current procedure), the surgeons' annual caseload during the LAPPRO trial and the degree of nerve-sparing surgery. For these analyses, all patients who met the inclusion criteria, irrespective of surgeon experience, were included. Each of the surgeon-dependent factors was added to logistic regression base models (Adjustment A+B and Adjustment A for functional and oncologic outcomes, respectively), and the change as a percentage of the standard deviation was recorded. Large changes indicated that the factor was related to much of the observed heterogeneity.

Finally, we performed analyses to assess whether surgeon-dependent factors modified our assessment of RALP vs RRP. The models described above were repeated after including a covariate for the type of surgery performed, and the results were presented as ORs and 95% confidence intervals (CIs).

Paper III

In Paper III, the oncologic outcome 6 years after surgery was investigated. As described above, the outcome was reported as residual disease, BCR and as the combined not cured endpoint. Secondary objectives were to analyze risk factors for residual and recurrent disease and to report the rate of PC-specific and all-cause mortality at 6 years after surgery. In accordance with earlier LAPPRO reports, subgroup analyses on patients operated on by surgeons with a stated experience of more than 100 RPs before entering the trial were performed. In a second subgroup analysis, the oncologic outcome was reported stratified by risk groups based on the D'Amico risk classification.

The results were presented as relative risks (RRs) for each oncologic outcome. The logistic regression models were adjusted for tumor-related factors as described in Table 3 (adjustment A). In addition, a second model was built with adjustments also for the surgeon's prior experience and annual caseload of RPs (Adjustment A+B).

Paper IV

In paper IV, cancer recurrence, mortality and functional outcomes were analyzed 8 years after surgery. In addition to data from earlier follow-ups, data were collected from a patient questionnaire completed 8 years postoperatively. The questionnaire included patient-reported information on functional outcome as well as oncologic information such as PSA, metastases and adjuvant treatment.

The main analysis included all evaluable patients meeting the inclusion criteria. Two prespecified subgroup analyses were performed to assess treatment heterogeneity across subgroups: patients operated on by surgeons who had performed at least 100 RPs prior to the LAPPRO trial and those stratified according to the D'Amico risk classification categories. The results, comparing RALP and RRP, are presented as RRs or hazard ratios (HRs) and 95% CIs. The adjustments for possible confounding factors are described in Table 3.

Results

Paper I

Out of 4 003 men included in the LAPPRO trial 2 625 were eligible for the current analyses, 1 847 after RALP and 778 after RRP. The response rate to self-reported patient questionnaires at 2 years after RP was high (96%).

For our primary definition of incontinence, after adjustment for patient and preoperative tumor factors (A+B), there was a small, although not statistically significant, difference between RALP and RRP (19% vs 16%; OR 1.29, 95% CI 1.00-1.67; p=0.053). When adjusting only for patient-related factors (A) or adding the degree of nerve sparing (A+B+C), the results did not substantially change, but the difference between groups reached statistical significance in favor of RRP. Using other definitions of incontinence did not significantly change the results (Figure 9).

Regarding ED, after adjustment for patient and preoperative tumor factors (A + B), there was a significant difference between the groups favoring RALP (68% vs 74%; OR 0.72, 95% CI 0.57–0.91; p = 0.006). When using different adjustments (A alone or A+B+ C) or definitions, the results were largely unchanged and the significant difference remained (Figure 9).

Only 88 patients (4%) had biochemical recurrence after an initial undetectable PSA value at 6-12 weeks. In total, 274 of 2 157 men (13%) were not cured according to our definition (see Patients and Methods). When adjusted for tumor factors (Adjustment A), there was no significant difference between the surgical procedures for the rate of not cured patients (12.5% for RALP vs 13.1% for RRP; OR 0.79, 95% CI 0.59–1.07).
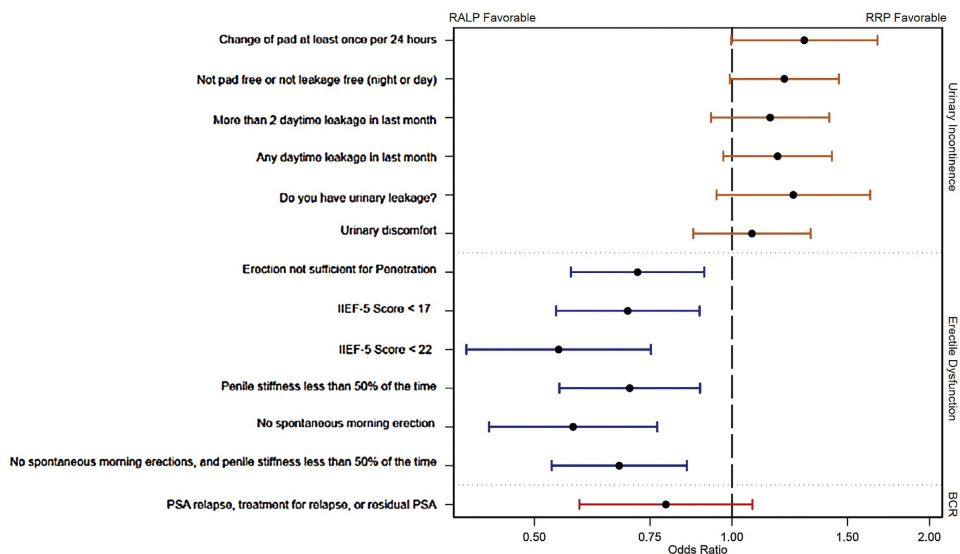
Figure 9. Forest plots showing adjusted odds ratios (point estimates) and 95% confidence intervals (horizontal lines) for comparison between RALP and RRP for different outcome definitions.

Paper II

In paper II, 3 443 men were evaluable for the analyses, 2 617 after RALP and 826 after RRP. The prostatectomies were performed by 68 surgeons. Those operating with the robotic-assisted technique were less experienced (median n=62) but had a higher annual caseload (median n=41) than surgeons operating with the open technique (prior experience median n=148 and annual case load median n=6).

The heterogeneity among surgeons with at least 20 operations performed during the study period is illustrated in Figure 10. The incontinence rate varied from 5% to 30%, representing statistically significant heterogeneity (p=0.001). The ED rate varied from 61% to 93% (p<0.001) and that of recurrent disease varied from 4% to 35% (p<0.001). The statistically significant heterogeneity remained when analyses were restricted to surgeons with a prior experience of at least 250 prostatectomies (incontinence, p=0.008; erectile dysfunction, p<0.001; not curded, p=0.03).
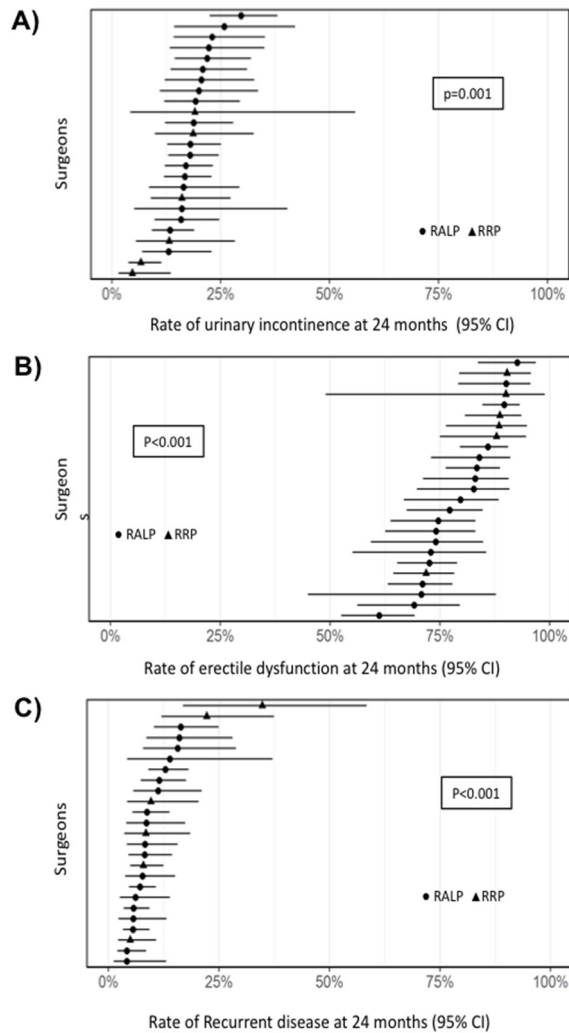
Figure 10. Surgeon heterogeneity for A) urinary incontinence B) Erectile dysfunction and C) Recurrent disease (not cured). Rates (point estimates) and 95% CIs (horizontal lines) are adjusted for baseline patient and tumor characteristics (A+B for functional outcomes and A for the oncologic outcome).

The surgeons' prior experience was the most important factor explaining surgeon heterogeneity for functional outcomes, accounting for 42% of the observed heterogeneity for incontinence (p=0.003) and 11% for ED (p=0.03). The degree of nerve sparing explained 5% of the heterogeneity for both incontinence and ED (p=0.002 and p=<0.001, respectively). Neither prior experience nor the degree of nerve-sparing had any significant influence on the observed heterogeneity for the recurrence. Annual caseload did not significantly influence incontinence or ED but accounted for 19% of the heterogeneity regarding recurrence (p= 0.01).

The base models comparing RRP and RALP for incontinence and ED (Adjustment A+B) were significantly affected when accounting for surgeon-dependent factors (Figure 11). The additional adjustment for the surgeon's prior experience had the most significant effect, changing whether or not the differences between techniques were statistically significant. Regarding the oncologic outcome (not cured), no statistically significant difference was seen between surgical techniques in the base model (Adjustment A), and the additional adjustments did not change this.

Urinary incontinence

Erectile dysfunction

Figure 11. Surgeon heterogeneity and differences by surgical modality. Adjusted odds ratios (point estimates) and 95% confidence intervals (horizontal line) for functional outcomes. The y-axis indicates which additional variables were included in the logistic regression model. The x-axis is the odds ratio for RRP vs RALP.

Paper III

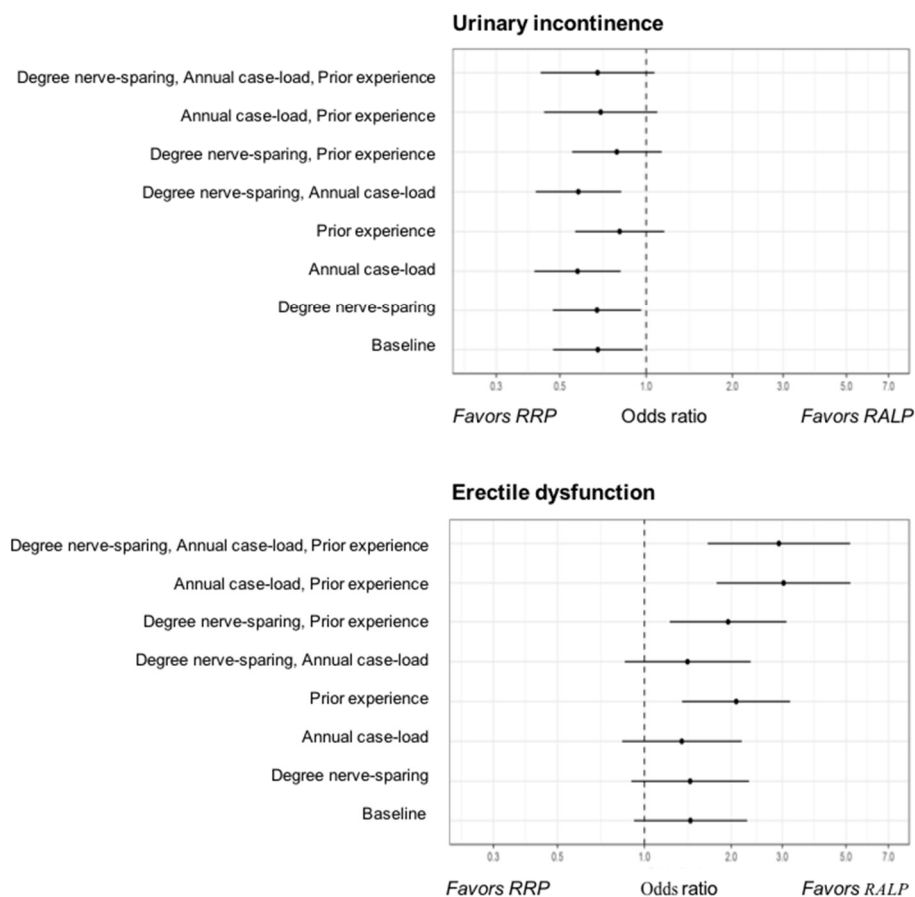After the telephone interviews at 6 years, the evaluable cohort consisted of 2 970 patients. A total of 614 patients were excluded, as they could not be reached or were unable to answer the questions. For the subgroup analysis restricted to experienced surgeons, 2 178 patients were identified.

At 6 years, the rate of not cured patients was 22% after RALP and 23% after RRP (Table 4). For BCR and not cured, no statistically significant difference was observed between RALP and RRP. There was a statistically significant lower risk for residual disease after RALP when adjustments for surgeon annual volume and prior experience were included in the statistical models (adjustment A+B). When analyses were performed only for patients operated on by experienced surgeons, there were no significant differences between groups irrespective of adjustment.

Table 4. Oncologic outcome at the 6-year follow-up

Cohort and Outcome			Adjustment A		Adjustment B	
	RALP n/N (%)	RRP n/N (%)	RR (95% CI)	p-value	RR (95% CI)	p-value
All patients						
Residual disease	51/2203 (2)	19/681 (3)	0.75 (0.45-1.26)	0.3	0.46 (0.23-0.93)	0.03
BCR	321/2244 (14)	113/717 (16)	0.93 (80.71-1.23)	0.6	0.77 (0.56-1.06)	0.1
Not cured	483/2174 (22)	157/687 (23)	0.96 (0.73-1.25)	0.8	0.82 (0.6-1.11)	0.2
Experienced surgeons						
Residual disease	37/1504 (2)	13/569 (2)	0.97 (0.55-1.72)	0.9	0.69 (0.31-1.55)	0.4
BCR	218/1538 (14)	98/631 (16)	0.89 (0.65-1.21)	0.5	0.86 (0.57-1.29)	0.5
Not cured	334/1492 (22)	131/611 (21)	0.97 (0.71-1.32	0.9	0.86 (0.56-1.33)	0.5

In the second subgroup analysis, in which patients were stratified by D'Amico risk groups, an advantage for RALP was observed for all outcome measures in the high-risk group when the models were adjusted for surgeon volume factors (Adjustment B). When only adjusted for patient and tumor factors (Adjustment A), no significant differences were seen for BCR or not cured. In the intermediate- and low-risk groups, no significant differences were observed irrespective of adjustment.

The all-cause mortality was 3% (n=96) and PC–specific mortality was 0.6% (n=21) in the total cohort of 3584 patients. After RALP, 8 of 2 698 (0.3%) patients died of prostate cancer, and 13 of 886 (1.5%) after RRP.

Paper IV

A total of 3 584 patients were eligible for the 8-year analysis. The response rate from the patient questionnaires at 8 years after surgery was 75%.

The rates of residual disease, BCR and not cured patients did not differ significantly between surgical techniques in the main analysis (all patients) or in the subgroup of patients operated on by experienced surgeons (Table 5).

Both the all-cause and PC-specific mortality rates were significantly lower after RALP in the main analysis. When the analysis was restricted to patients operated on by experienced surgeons the differences were not statistically significant (Table 5).

Table 5. Oncologic outcome 8 years after surgery. RRs are adjusted for Adjustment A (Table 3). HRs for PC-specific mortality are adjusted for Adjustment A+B and for all-cause mortality for Adjustment A.

Outcome	Overall			Experienced surgeons		
	RALP n/N (%)	RRP n/N (%)	RR or HR (95% CI)	RALP n/N (%)	RRP n/N (%)	RR or HR (95% CI)
BCR	452/1706 (27)	169/558 (30)	0.98 (0.84-1.15)	310/1170 (27)	144/489 (29)	1.00 (0.84-1.19)
Not cured	583/1971 (30)	199/656 (30)	1.07 (0.93;1.23)	410/1366 (30)	164/570 (29)	1.12 (0.96;1.31)
All-cause mortality	155/2699 (5.7)	73/885 (8.2)	0.72 (0.54-0.95)	99/1847 (5.4)	57/778 (7.3)	0.77 (0.55-1.07)
Prostate cancer-specific mortality	40/2699 (1.5)	25/885 (2.8)	0.56 (0.34-0.93)	28/1847 (1.5)	21/778 (2.7)	0.64 (0.36-1.12)

When the patients were stratified by D'Amico risk groups, differences in oncologic outcomes between techniques were mainly seen in the high-risk D'Amico group. At 8 years after surgery, the risk of positive surgical margins (21% vs. 34%), BCR (51% vs. 69%) and PC-specific mortality (6% vs. 14%) was lower after RALP.

For functional outcomes at 8 years, the results comparing RRP and RALP were largely unchanged compared to previous follow-ups (at 1 and 2 years), showing a small significant advantage for RALP regarding ED and no significant difference regarding incontinence. Among patients operated on by experienced surgeons, 63% had ED after RALP, and 69% had ED after RRP. The corresponding incontinence rates were 24% after RALP and 27% after RRP.

Discussion and future perspectives

In this thesis, outcomes after RP were investigated from two main perspectives: (i) how long-term outcomes differed between robotic and open RP and (ii) how outcomes were affected by individual surgeons' skill and experience.

In general, our results show that only small differences exist between the robotic and open techniques regarding both functional and oncologic outcomes up to 8 years after surgery. A small but statistically significant advantage for robotic surgery in ED was seen throughout the follow-up period, while the incontinence and recurrence rates were similar between techniques. Differences among all individual surgeons and among very experienced surgeons were large for all outcomes and had a significant impact on the comparison between RALP and RRP.

Incontinence

In the LAPPRO trial, the incontinence rate for patients operated on by experienced surgeons (>100 prior RPs) was 18% at 2 years and 25% at 8 years after surgery. The increase was partly expected since it is well established that age is a risk factor for incontinence (128, 169). The 2-year rate was an improvement compared to the previously reported 1-year rate of 21 % (149), showing that a long follow-up time is also needed for functional outcomes when evaluating RP.

When comparing RRP and RALP among experienced surgeons we did not observe any significant difference regarding incontinence at either follow-up time. However, the results were sensitive to the surgeon's experience, and at the 2-year follow-up we observed a statistically significant benefit for RRP when all patients and surgeons were included (paper II). This is likely explained by the difference in surgeon experience between groups, with open surgeons being more experienced than robotic surgeons in LAPPRO.

Our findings are in line with other studies also reporting no or only small differences in incontinence rates between techniques. In the only randomized trial comparing RRP and RALP, equally randomizing 326 men between techniques, no significant difference was seen either at 1 and 2 years postoperatively (123, 170). In a systemic review from 2012, including 5 studies published between 2008 and 2010, Ficcara and colleagues reported a statistically significant benefit for RALP regarding

incontinence (126). However, in a meta-analysis published in 2019, including 5 more recent studies, the 1-year incontinence rate was 28.4% after RALP and 29.2% after RRP, with no statistically significant differences between techniques (124). Additionally, the results from a prospective U.S. multicenter study found a small benefit for open surgery at the 1 year follow-up, but no significant difference between techniques at the 2 and 3 year follow-ups (171). Another recent study by Haese et al reported a modestly higher continence rate at 1 year postoperatively with RALP than with RRP (90.3% vs. 88.8%) (172).

Erectile dysfunction

After 2 years, the incidence of ED was 70% versus 64% after 8 years. Since the risk of ED normally increases with age, this improvement might indicate that recovery of erectile function can continue even more than 2 years after surgery. Compared with the rate 1 year postoperatively, the 2 year rate was basically unchanged (149).

Throughout the follow-ups in the LAPPRO trial 1, 2 and 8 years after RP, we have observed a statistically significant benefit for the robotic technique when analyzing experienced surgeons with a prior caseload of more than 100 procedures. In absolute numbers, the incidence of postoperative ED was approximately 6% lower after RALP with respect to RRP. As for incontinence, the results for ED at the 2-year follow-up were sensitive to the surgeon's prior experience and when including also inexperienced surgeons in the analyses, the difference was no longer statistically significant.

Previous studies comparing ED after RRP and RALP have reported somewhat diverging results. In concordance with our findings, some studies have reported a small advantage of the robotic technique (149, 164, 173, 174). However, in the randomized trial by Coughlin et al., no statistically significantly difference between RALP and RRP was observed in erectile function scores at 1 or 2 years postoperatively (170). Additionally, also in contrast to our findings, compared with that of RRP, Hu reported an increased risk of ED after minimally invasive techniques (RALP or LRP) in a retrospective study from 2009 evaluating 8837 men after RP (175).

Oncologic outcome

As expected, the rates of recurrent disease increased during our follow-up periods. Two, 6 and 8 years after surgery, the incidences were 13%, 22% and 30%, respectively. This includes all signs of cancer recurrence according to our definition of not cured. If stratified by risk group, the majority (59%) of men in the high-risk group had recurrence after 8 years. The corresponding incidence in the low risk group was 17%. As expected, the high recurrence rates were not reflected in the death rates. After 6 and 8 years, only 21 (0.6%) and 65 (1.8%), respectively, out of 3 584 men had died as a direct cause of the disease. Although low, these rates are higher than those observed in the ProtecT study, where the surgical arm presented with a 1% (5/553) PC-specific mortality at the 10-year follow-up (85). A possible explanation is the larger proportion of low-risk prostate cancers in the ProtecT study than in the LAPPRO trial.

Comparing surgical techniques, the groups did not differ significantly in recurrence rate at 2, 6 and 8 years. However, after 8 years, we observed a small significant advantage for robotic surgery in both all-cause and PC-specific mortality, but only when analyzing all patients, not taking the surgeons' experience into account. The differences in the oncologic outcomes between techniques were most prominent in the D'Amico high-risk group. At 8 years the risks of positive surgical margins, BCR, and PC-specific mortality were lower after RALP for high-risk PC.

In the randomized trial by Coughlin and co-workers, the oncologic outcome at the 2-year follow-up was reported in 2018 (123, 170). They reported a statistically significant benefit for RALP regarding BCR; in total, 13 men (9%) had BCR after RRP, and 4 (3%) had BCR after RALP. However, the authors recommended caution in the interpretation of the results since there was no standardization in the postoperative management, including the use of adjuvant treatments. In a recent meta-analysis, Cao and colleagues assessed 5 studies with follow-up times up to 2 years and found no significant difference in BCR rates between RALP and RRP (124). Another meta-analysis from 2015, assessing 10 studies published between 2008 and 2015, reported that RALP had better BCR-free survival than RRP (176). However, when only studies with balanced baseline characteristics between groups were included, the groups were no longer significantly different. In a recent single-center study, Haese et al retrospectively analyzed outcomes among more than 10 000 men after RALP or RRP and reported no significant difference in the 4-year BCR rate (172).

Taken together, based on our results and the existing literature, robotic and open radical prostatectomy seems to have comparable oncologic outcomes in the short and intermediate term. The possible survival benefit after robotic surgery we observed after 8 years is interesting, but because of the natural history of PC the number of events regarding mortality outcomes is still low 8 years after surgery and

our results have to be interpreted with caution. This was also the case for the randomized trial from 2018 (170). Even though the risk of BCR significantly differed (3% to 9%) at 2 years, the total number of events was low, making the results uncertain. Hypothetically, a possible explanation for the observed differences in mortality could be that the technical advantages with robotic surgery, such as superior visualization and better accessibility, give better control of the dissection planes and thereby increased the chances of radically removing the tumor, leading to fewer positive surgical margins, a lower incidence of residual and recurrent disease and, finally, lower mortality. However, to draw firm conclusions regarding a potential survival benefit there is a need for longer follow-up data from randomized trials or large prospective studies. Such studies should preferably take surgeon volume factors and potential differences between risk groups into account.

Surgeon heterogeneity

We found an unexpectedly large variation between individual surgeons for both functional and oncologic outcomes. The heterogeneity was statistically significant and remained for very experienced surgeons with a prior case-load of more than 250 RPs. When investigating underlying surgeon-dependent factors, we found that only part of the observed heterogeneity was explained by differences in prior experience, annual caseload and degree of nerve-sparing among surgeons. Our results support previous findings that revealed that surgeon heterogeneity and surgeon experience significantly affect outcomes after RP. However, our findings show that the greater part of the observed heterogeneity was unexplained even after surgeon volume was considered. This means that a large experience and high volume does not guarantee a favorable outcome after RP. Further studies with detailed information about the participating surgeons and the different steps during the operation are needed to better understand surgeon heterogeneity.

Based on the current knowledge, efforts to decrease the wide heterogeneity among surgeons, irrespective of surgical approach, are warranted. Such efforts can be facilitated by continuously reporting and monitoring outcomes during and after surgery in quality registers. Better organized training for new surgeons, defined basic skills criteria, a minimum number of annual cases performed, and peer-to-peer observation in the operating room are examples of other measures that could be effective in reducing surgeon heterogeneity and improving PC care.

In papers II, III and IV, our results showed that surgeon volume had a significant impact on the comparison between RRP and RALP. In paper II, we showed that accounting for prior experience changed whether the difference between techniques in functional outcomes was statistically significant at 2 years after RP. The same effect was seen for the oncologic outcome in papers III and IV. When additional

adjustments for surgeon volume were added to the base model at 6 years, we observed a significant benefit for RALP for residual disease in the main analyses and for recurrent disease in the high-risk group. The opposite was seen for mortality rates at 8 years, where a significant benefit for robotics was observed when all surgeons were included but not when the analysis was restricted to those with a prior experience of 100 cases. This clearly demonstrates that in comparative analyses between RRP and RALP, detailed knowledge is needed not only of the patient and tumor characteristics but also of the surgeons to avoid analyzing differences between surgeons rather than true differences between surgical techniques.

Strengths and limitations

The strengths of the LAPPRO trial are the prospective design, the large number of included patients and the high response rates to questionnaires. Due to the multicenter design involving hospitals of different sizes and the large number of participating surgeons, the collected data represent real-life PC care in Sweden, making the result generalizable to the broader society. Furthermore, the validated questionnaires were extensive, and in addition to questions related to the main endpoints, contained demographic and surgery-related information making it possible to adjust for confounders.

The main limitation of the LAPPRO trial is the lack of randomization between the compared groups (RALP vs. RRP). However, the groups were in generally well matched regarding both patient and tumor characteristics. Furthermore, in the Swedish health care system, patient residence, not patient preference, decides where patients have PC surgery. Patients living in a certain area received treatment at the same hospital, and since the included centers almost exclusively performed either RRP or RALP, the setting in the LAPPRO trial to some extent mimics that of a randomized trial.

The large number of participating surgeons with a wide range of prior experience and annual case-loads is a strength of the study but could also be a limitation. To account for surgeons still on their learning curves, the initial reports from LAPPRO were restricted to patients operated on by surgeons with a prior caseload of more than 100 RPs. However, after the design of these studies was settled, it was reported that the learning curves for RP plateaued first after a larger number of procedures and differed for RRP and RALP (104, 163, 166). Even with detailed knowledge about the surgeons, this makes our results comparing surgical modalities somewhat uncertain.

Because of differences between the laboratories connected to the participating centers, we have used a PSA cutoff of 0.25 ng/mL for the endpoint measures connected to the oncologic outcome. However, many laboratories (all during the

later follow-up periods) reported PSA values below this level, and patients in clinical practice could have been considered as having recurrent disease and been given salvage or adjuvant treatments without having a PSA over our cutoff value. This is a limitation since patients may have been misclassified as having residual disease or BCR, or not being cured. For this reason, the oncologic outcomes in this thesis were primarily reported as the not cured endpoint, including residual disease, BCR and adjuvant treatments.

Another potential bias is the use of patient-reported oncological outcomes at the 6-year telephone interview and of the questionnaire at the 8-year follow-up. However, since patients are naturally concerned about cancer recurrence after surgery, we believe that the collected data were accurate. Furthermore, in a previous publication from the LAPPRO trial, the coherence between patient-reported data and that from the CRFs was found to be good regarding additional treatments due to local recurrence or metastases (177).

Finally, the lack of standardized postoperative management for the included patients is a potential limitation. For instance, the use and timing of adjuvant therapies could at time have differed between centers and physicians and potentially affected the oncologic outcomes. However, at the 6- and 8-year follow-up, the groups did not differ significantly with regard to salvage and adjuvant therapies, and thus, the lack of standardized postoperative management should not have significantly affected the outcomes, at least not the combined not cured endpoint.

Conclusions

The main conclusion of this thesis is that there seems to be a small advantage for RALP over RRP, but the difference between techniques is diminished by the large differences among individual surgeons. From a patient perspective, who is performing the surgery is more important than whether it is an open or robotic-assisted procedure.

For ED, a small and statistically significant advantage for robotic surgery was seen throughout the different follow-up periods up to 8 years after surgery. Regarding incontinence and cancer recurrence, no significant differences were observed between RALP and RRP during the same follow-up period.

Our results 8 years after surgery indicate that there might also be an advantage for RALP regarding recurrence and mortality, especially for patients with high-risk tumors. However, the number of events was low, and longer follow-up is needed to draw firm conclusions.

A large, statistically significant heterogeneity was observed for both functional and oncologic outcomes among all participating surgeons, as well as among very experienced surgeons with more than 250 prior RPs. Some of the observed heterogeneity was explained by differences in the surgeon's prior experience and annual caseload, but the larger part remained unexplained.

Surgeon heterogeneity had a large impact on the comparison between RALP and RRP and needs to be accounted for in future comparative analyses to avoid comparing individual surgeons instead of surgical techniques.

Populärvetenskaplig sammanfattning

Årligen drabbas mer än 10 000 män av prostatacancer i Sverige vilket gör sjukdomen till den vanligaste cancerformen hos män. Sjukdomens förlopp är varierande men många tumörer är långsamväxande och orsakar vare sig symtom eller påverkar livslängden hos de drabbade männen. En del tumörer har dock ett mer aggressivt växtsätt och prostatacancer är idag, trots den generellt goda prognosen, den vanligaste cancerrelaterade dödsorsaken hos män i Sverige. Totalt orsakades cirka fem procent av dödsfallen hos svenska män 2018 av sjukdomen.

Behandlingsstrategin är beroende av hur långt gången sjukdomen är vid diagnostillfället, tumörens aggressivitet, samt patienternas ålder och samsjuklighet. För män med tumörer där utbredningen är begränsad till prostatakörteln och som har en lång förväntad kvarvarande livslängd är den vanligaste behandlingsmetoden kirurgi. Vid operationen, så kallad radikal prostatektomi, tas prostatan och viss kringliggande vävnad bort. Varje år utförs cirka 3 000 av dessa operationer runt om i Sverige. Resultaten är generellt goda avseende återfall och långtidsöverlevnad men operationen är förknippad med biverkningar som impotens och urininkontinens.

Den moderna kirurgiska tekniken vid radikal prostatektomi utvecklades på 1980-talet som ett traditionellt öppet kirurgiskt ingrepp (retropubisk radikal prostatektomi) där tillgång till operationsområdet skapas genom ett hudsnitt på nedre delen av buken. Tekniken gör det bland annat möjligt att bevara de nervbanor som är viktiga för potensen. Teknikutvecklingen har dock gått snabbt de senaste decennierna och urologkliniker i Sverige och övriga delar av västvärlden har gjort stora investeringar i ny teknik. Idag är den vanligaste operationsmetoden i Sverige en robotassisterad titthålsoperation (robotassisterad radikal prostatektomi) som nästan helt har ersatt den traditionella öppna metoden. Detta metodskifte är dock något kontroversiellt då det saknas starka vetenskapliga bevis för att robotmetoden ger någon fördel för patienten, det vill säga minskad risk för återfall i cancer och minskad risk för biverkningar.

Oavsett vilken kirurgisk teknik som används är radikal prostatektomi en utmanande operation för kirurgerna. En radikal resektion av tumören ställs mot att spara så mycket vävnad som möjligt för att minska risken för biverkningar. Det är visat i tidigare studier, både svenska och internationella, att det förekommer stora skillnader mellan enskilda kirurger för risken att få återfall och att drabbas av urininkontinens och impotens. Detta område är dock dåligt studerat och det är i stort

okänt vilka underliggande faktorer som ligger bakom de stora skillnaderna och hur dessa påverkar jämförelsen mellan operationsteknikerna.

LAPPRO studien

LAPPRO (LAParoscopic Prostatectomy Robot Open) är en svensk studie som jämför robotassisterad och öppen radikal prostatektomi. Totalt medverkar över 4 000 män som genomgick operation på grund av prostatacancer mellan 2008 och 2011 vid 14 svenska sjukhus. På sju av sjukhusen utfördes robotassisterade operationer och på de resterande sju öppna operationer. Information samlades in från patienterna via utförliga frågeformulär och telefonintervjuer, samt via sjukvårdspersonal vid förutbestämda tidpunkter upp till åtta år efter operationen.

Samtliga delarbeten i denna avhandling baseras på LAPPRO studien. Utfallet efter operation gällande återfall i cancer, dödlighet, urininkontinens och impotens undersöktes vid uppföljningar två, sex och åtta år efter operation. Förutom potentiella skillnader mellan robotassisterad och öppen kirurgi har de individuella kirurgernas påverkan på utfallen efter operationerna utvärderats.

De två huvudsakliga långtidsbiverkningarna urininkontinens och impotens undersöktes vid två och åtta år efter operation (Arbete I, II och IV). Två år efter operation var andelen inkontinenta män 18 procent och åtta år efter operationen var andelen 25 procent. Ökningen mellan uppföljningarna var delvis förväntad eftersom det är välkänt att förekomsten av urininkontinens ökar med stigande ålder. Det förelåg endast små, inte statistiskt säkerställda, skillnader mellan den robotassisterade och öppna operationsmetoden gällande urininkontinens. För förekomsten av impotens var däremot skillnaderna mellan operationsmetoderna något större. Vid två års uppföljning var 68 procent av patienterna impotenta efter robotassisterad operation medan 74 procent var det efter öppen operation. Skillnaden var statistiskt säkerställd och kvarstod åtta år efter operation.

Risken för canceråterfall undersöktes i samtliga delarbeten och steg som förväntat under uppföljningstiden. Efter två år var risken för återfall 13 procent, efter sex år 21 procent och slutligen efter åtta år 30 procent. Även gällande återfallsrisken var skillnaderna mellan robotassisterad och öppen operation små och generellt förelåg inga statistiskt säkerställda skillnader. Antalet män som avled som en direkt följ av prostatacancer var få (totalt 1,8 procent efter åtta år) vilket förklaras av att även vid återfall efter radikal prostatektomi har prostatacancer ofta en relativt långsam progress. Det sågs dock en skillnad mellan operationsmetoderna och andelen män som avlidit som en följd av prostatacancer var större efter den öppna operationsmetoden. Skillnaden mellan metoderna var särskilt påtaglig hos män med mer aggressiva tumörer vid diagnostillfället (högrisktumörer) men då det totala antalet fall var få är resultaten osäkra och måste tolkas med försiktighet. För att

kunna dra mer säkra slutsatser angående en eventuell överlevnadsfördel efter robotassisterad operation krävs längre uppföljningstid.

De enskilda kirurgernas påverkan på utfallen efter operation utvärderades i detalj i det andra delarbetet (Arbete II). Vid uppföljningen efter två år var skillnaderna i utfall mellan de deltagande kirurgerna stora oavsett om patienterna blivit opererade med robotassisterad eller öppen teknik. När kirurger som utförde minst 20 operationer under studietiden jämfördes varierade förekomsten för urininkontinens mellan 5 och 30 procent. Motsvarande skillnad för impotens var mellan 61 och 93 procent och för canceråterfall mellan 4 och 35 procent. Skillnaderna var statistiskt säkerställda och kvarstod även när enbart mycket erfarna kirurger med mer än 250 tidigare ingrepp jämfördes.

För urininkontinens och impotens var kirurgernas tidigare erfarenhet (det totala antalet tidigare utförda operationer med den aktuella tekniken) den viktigaste förklarande faktorn till den stora spridningen mellan kirurgerna, medan antalet utförda operationer per år hade störst inflytande på återfallsförekomsten. Dessa faktorer förklarade dock bara en del av den stora spridningen mellan de enskilda kirurgerna som till största delen fortsatt är oförklarad. Detta visar att erfarenhet och stor operationsvolym är viktigt men ingen garanti för ett gynnsamt resultat efter radikal prostatektomi.

Skillnaderna mellan de enskilda kirurgerna hade även ett stort inflytande på jämförelsen mellan operationsmetoderna. Kirurgerna som utförde de robotassisterade ingreppen var i genomsnitt mindre erfarna men hade en högre årlig operationsvolym. När detta togs i beaktande i de statistiska analyserna påverkades resultaten för jämförelsen mellan den robotassisterade och öppna tekniken påtagligt, vilket illustrerar vikten av god detaljkännedom även om de deltagande kirurgerna för att kunna göre en rättvis jämförelse mellan operationsmetoder.

Slutsatser

Resultaten från avhandlingen visar att det verkar finnas en liten fördel med den robotassisterade operationsmetoden då risken att drabbas av impotens var något lägre. Den viktigaste slutsatsen är dock att de små skillnader som observerades mellan operationsmetoderna överskuggas av de stora skillnaderna mellan de enskilda kirurgerna. Ur patientsynvinkel är det viktigare vem som gör operationen än vilken metod som används. Åtgärder för att minska de stora skillnaderna mellan kirurger borde prioriteras för att kunna ge en bättre och mer jämlik prostatacancervård i Sverige.

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