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# OUTCOMES AFTER SURGICAL TREATMENT OF LOCALIZED PROSTATE CANCER WITH FOCUS ON URINARY INCONTINENCE AND SHORT TERM COMPLICATIONS

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# Outcomes after surgical treatment of localized prostate cancer with focus on urinary incontinence and short term complications

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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*"You only see what you are looking for and you only look for what you know"*

*Patrick Walsh*

# ABSTRACT

**Background:** Urinary incontinence is a significant long-term complication after radical prostatectomy. The aim was to evaluate clinically significant definitions of urinary incontinence and to investigate its potential predictors. Robot-assisted radical prostatectomy has become a widespread surgical technique in prostate cancer despite the lack of randomised trials showing its superiority compared to open surgery. A further aim was to compare short-term results three months after the two surgical techniques.

**Material and methods:** Data for this thesis derives from two sources. The first cohort is a consecutive series of 1411 men who underwent radical prostatectomy at Karolinska University Hospital from 2002 to 2006 and completed a study-specific validated questionnaire. The second cohort derives from the LAPPRO study, a multicentre, prospective controlled trial of men who underwent radical prostatectomy between 2008 and 2011 (n=4003). Data was collected prospectively with validated patient questionnaires and case report forms which were completed by health-care personnel.

**Results:** Urinary leakage as a long-term side effect after radical prostatectomy proved to cause the patient a lot of bother. Even a proportion of those who had occasional leakage reported significant bother. Increased age at surgery increases the risk of urinary incontinence one year after surgery and this increases exponentially with age. Furthermore patients with preoperative urinary leakage have an increased risk of postoperative incontinence. When evaluating short-term outcomes and comparing open radical prostatectomy to robot-assisted radical prostatectomy, re-operation during initial hospital stay was more frequent after open surgery. Men operated by open surgery also sought medical care more frequently compared to men operated by robot-assisted surgery within three months after surgery. Men who underwent lymph-node dissection proved to have an increased risk for readmission as well as a greatly increased risk for thromboembolic events, such as deep venous thrombosis and pulmonary embolism. Regardless of whether lymph-node dissection was preformed or not, men who underwent open prostatectomy appeared to have an increased risk of thromboembolic events compared to those who had robot-assisted surgery.

**Conclusions:** If the definition of continence consists of the use of pads, a certain number of men that are bothered significantly by urinary leakage will be defined as continent. When planning a patient for radical prostatectomy, one must take age and preoperative urinary leakage into consideration as risk factors for postoperative incontinence. The robot-assisted radical prostatectomy is a safe procedure and has some short-term advantages compared to open surgery. Lymph-node dissection during radical prostatectomy increases the risk for thromboembolic events, the risk is higher in open surgery compared to robot-assisted surgery.

# LIST OF SCIENTIFIC PAPERS

I. **Wallerstedt A**, Carlsson S, Nilsson AE, Johansson E, Nyberg T, Steineck G, Wiklund N. P.
Pad use and patient reported bother from urinary leakage after radical prostatectomy.
*The Journal of urology* 2012;187:196-200.

II. **Wallerstedt A**, Carlsson S, Steineck G, Thorsteinsdottir T, Hugosson J, Stranne J, Wilderäng U, Haglind E, Wiklund N. P.
Patient and tumour-related factors for prediction of urinary incontinence after radical prostatectomy.
*Scand J Urol* 2013;47:272-81.

III. **Wallerstedt A**, Tyritzis S, Thorsteinsdottir T, Carlsson S, Stranne J, Gustafsson O, Hugosson J, Bjartell A, Wilderäng U, Wiklund N. P, Steineck G, Haglind E.
Short term results after robot-assisted laparoscopic radical prostatectomy compared to open radical prostatectomy.
*European Urology* 2014. 10.1016/j.eururo.2014.09.036.

IV. Tyritzis SI, **Wallerstedt A**, Steineck G, Nyberg T, Hugosson J, Bjartell A, Wilderäng U, Thorsteinsdottir T, Carlsson S, Stranne J, Haglind E, Wiklund N. P.
Thromboembolic complications in 3544 patients undergoing radical prostatectomy with or without lymph node dissection.
*The Journal of urology* 2014. 10.1016/j.juro.2014.08.091.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| RR | Relative risk |
| CI | Confidence interval |
| IQR | Interquartile range |
| LAPPRO | Laparoscopic Prostatectomy Robot Open Study |
| TURP | Transurethral resection of the prostate |
| PSA | Prostate specific antigen |
| GS | Gleason score |
| BMI | Body mass index |
| OR time | Operating room time |
| ASA score | American Society of Anesthesiologists score |
| IPSS | International Prostate Symptom Score |
| OR | Odds ratio |
| NA | Not applicable |
| UTI | Urinary tract infection |
| DVT | Deep venous thrombosis |
| AMI | Acute myocardial infarction |
| PE | Pulmonary embolism |
| LND | Lymph-node dissection |
| ORP | Open radical prostatectomy |
| RARP | Robot-assisted laparoscopic radical prostatectomy |
| LRP | Laparoscopic radical prostatectomy |

# 1 INTRODUCTION

Hippocrates, the father of western medicine, once stated “Primum, non nocere” - “First, do no harm”. Today this statement is still highly relevant in the surgical treatment of prostate cancer. Studies have shown that we have to operate on eight men to prevent one from dying from prostate cancer.[1] Currently there is a substantial overtreatment of prostate cancer as we have little understanding of which prostate cancers will lead to death. The operation, in turn, can lead to life-long side effects such as urinary incontinence and impotence, and the risk of overtreatment must be weighed up against the risk of complications.

In light of "First, do no harm", the overall objective of this thesis was to investigate the harm that we cause the patient by performing prostate cancer surgery. As urinary incontinence is a common long-term complication after radical prostatectomy, we wished to identify patients at risk of this complication as well as quantify its effect on patient morbidity. Secondly we evaluated whether short-term complications could be reduced by the use of a new surgical technique.

# 2 BACKGROUND

## 2.1 PROSTATE CANCER

### 2.1.1 Epidemiology

In 1853 the English surgeon J. Adams was the first to describe a case of prostate cancer and he concluded his report with the words "a very rare disease".[2] Today prostate cancer is the most common type of cancer in Sweden, followed by breast cancer, skin cancer and colon cancer.[3] About one third of all cancers in men are prostate cancer and the probability of developing prostate cancer is 13% before 75 years of age.[4]

#### 2.1.1.1 Incidence

In Sweden, 9663 men were diagnosed with prostate cancer in 2012.[3] In the US there were 238,590 estimated new cases in 2013 (28% of all cancers), accounting for the most common cancer in men before lung and colorectal cancers.[5] When the measurement of prostate-specific antigen (PSA) became more common there was a substantial increase in the incidence of prostate cancer in the US.[6] The incidence peaked in 1992 approximately 5 years after the introduction of PSA screening. The increased use of PSA in diagnosis of prostate cancer led to many clinically non-significant prostate cancers being diagnosed. It has been shown that about 30% of men in their 60s and in 50% of men in their 80s have prostate cancer when performing microscopic examination during autopsy or cysto-prostatectomy for bladder cancer in men without a history of prostate cancer.[7] There was a sharp decrease in incidence after the peak in 1992 (4.4% per year between 2001 and 2005) which may reflect a stabilisation of PSA-testing or that many of the latent cancers already had been detected.

The incidence of prostate cancer varies widely between different parts of the world and between different ethnicities, disease rates differ by more than 100-fold between populations. Prostate cancer is most common among Black Americans (272 cases per 100,000), second most common among White Americans and Scandinavians, while the disease is unusual in Southeast Asia (1.9 cases per 100,000 in China).[8] This pattern suggests that life-style factors and heredity play a role in the development of prostate cancer. It has been shown that men with germ line mutations in breast cancer genes BRCA1 and BRCA2, have an increased risk of prostate cancer.[9,10] Both incidence and mortality are higher in Black Americans compared to White Americans.[11] This has been attributed to the acculturation of Black Americans into US White society.[12] However, research suggests that Black Americans receive less aggressive therapy.[13] Other risk factors for prostate cancer that have been proposed are obesity, high intake of animal fat, red meat and dairy products; whilst a high intake of antioxidants and phytoestrogens such as tomatoes, cabbages, onions, soya beans and green tea appear to decrease the risk of prostate cancer.[14,15,16] Certain medications such as aspirin, statins and metformin have also been suggested to reduce the risk of prostate cancer diagnosis.[17,18,19] However, others have found no such association.[20,21] The evidence have

thus not been strong enough to provide recommendations in order to prevent the development of prostate cancer.

#### 2.1.1.2 Mortality

Mortality rates also vary widely across different countries and Sweden has among the highest morality rate in the world.[22] Prostate cancer is the second most common cause of death in men in Sweden after cardiovascular death.[23] The age-standardized mortality rate from prostate cancer has decreased over the last fifteen years. The decline has been most prominent in men under 75 years of around 35 percent. In contrast, the actual number of men who die of the disease every year in Sweden has been relatively stable at around 2,400 during the past decade. One reason is that the number of elderly men in the population increases with increasing life expectancy (Figure 1).[24]

In the US there were 29,720 estimated deaths from prostate cancer in 2013. The death rates in the US have also been declining since the early 1990s and is the second most common cancer related cause of death after lung cancer.[5]

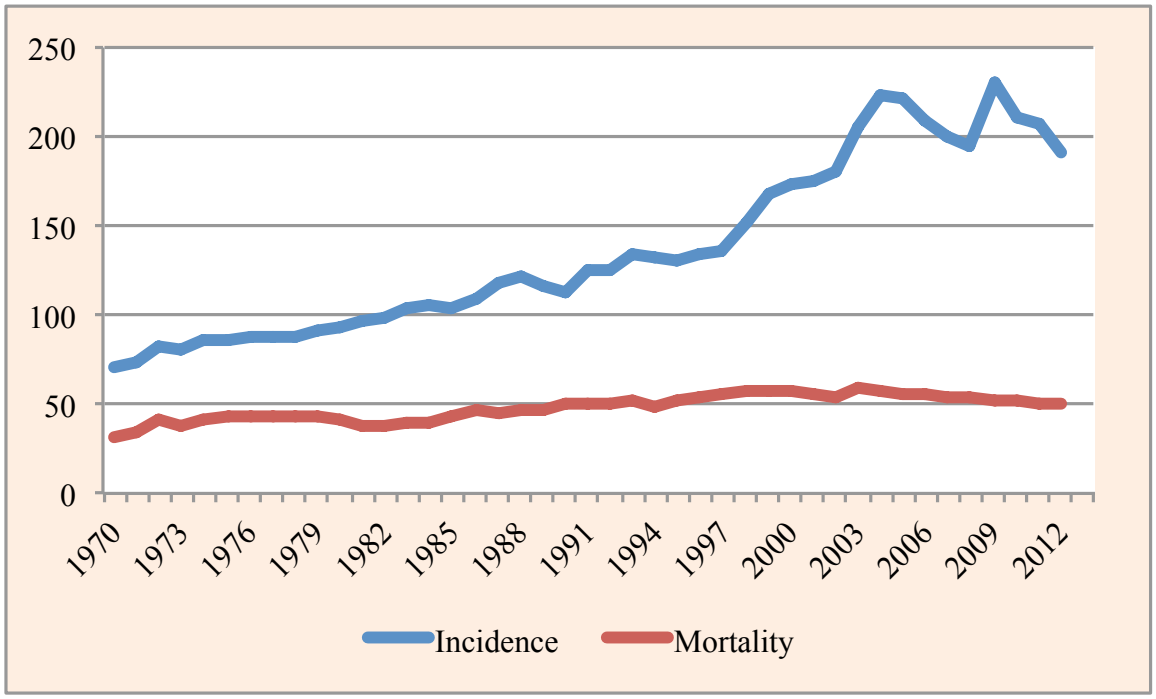



*Figure 1. Prostate cancer incidence and mortality in Sweden between 1970 and 2012. Annual numbers of new prostate cancer cases and prostate cancer deaths per 100 000 persons, crude rate.*
*Graphical illustration: A Wallerstedt. Data adapted from NORDCAN Association of the Nordic Cancer Registries and the Swedish National Board of Health and Welfare.*

#### 2.1.1.3 Survival rates

The relative 5-year survival rate for prostate cancer is over 90 percent in Sweden today.[4] The survival rates have increased significantly in all age categories in most recent years (Figure 2). One reason for improved survival rates could be due to longer life expectancy, a further reason may be that men are diagnosed with a "latent" prostate cancer late in life through PSA

testing. Another reason could of course be the improvements in treatment and that nowadays cancers are treated that previously were considered too advanced to cure. Also in the US survival rates have markedly increased for prostate cancer with 5 year relative cancer survival rates from 68% in the years 1975-1977 to 99% in the years 2002-2008.[5]

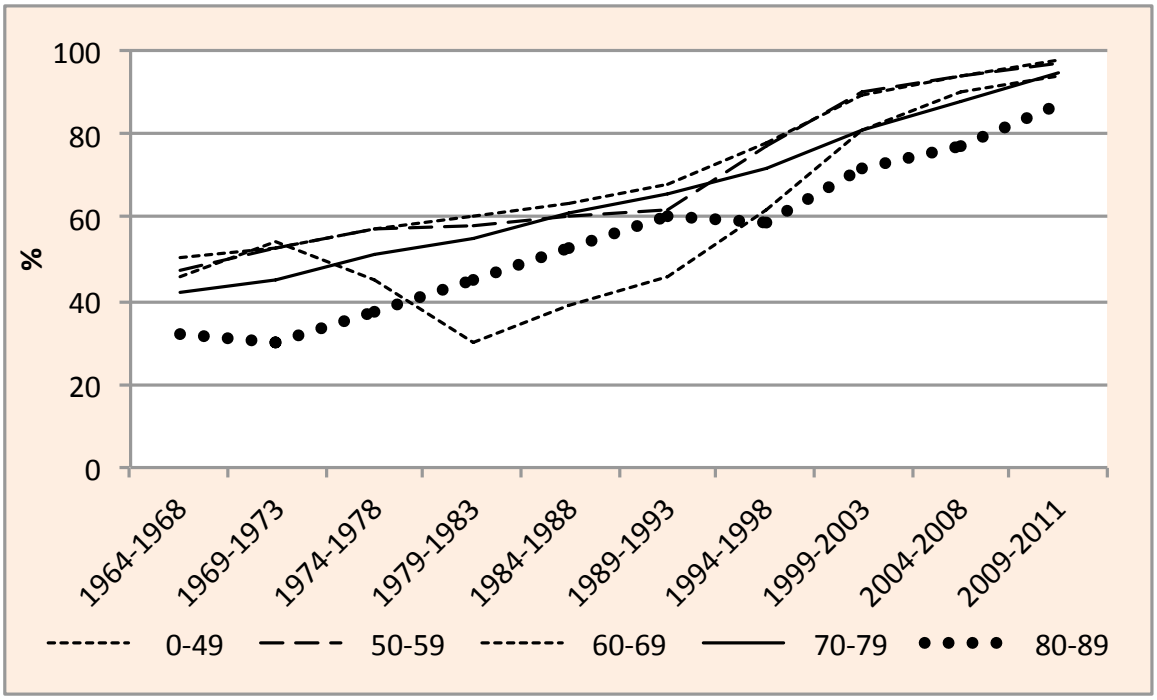



*Figure 2. Five year relative survival from prostate cancer in Sweden between 1964-2011. Graphical illustration: A Wallerstedt. Data adapted from NORDCAN Association of the Nordic Cancer Registries.*

### 2.1.2 Diagnosis

Investigation of early detection of prostate cancer includes Digital Rectal Examination (DRE), Prostate-Specific Antigen (PSA) blood test, Trans-Rectal Ultrasound (TRUS), needle biopsy and in some cases imaging with Magnetic Resonance Imaging (MRI).

#### 2.1.2.1 Digital rectal examination (DRE)

A digital rectal exam should always be performed when investigating lower urinary tract symptoms in men. The purpose of palpation is to estimate the size of the prostate and to identify palpable tumour lesions. However, DRE is a test with only fair reproducibility among urologists.[25] Furthermore DRE misses a substantial proportion of cancers and detects the cancers often in a late stage. Studies have shown that an abnormal DRE has a sensitivity of 44%, a specificity of 68% and a positive predictive value of 46% for detecting prostate cancer on biopsies.[26] The positive predictive value of DRE is improved by PSA-testing. If a suspected nodule is palpated it should be classified according to the TNM classification e.g. whether the tumour is confined within the prostate, extends through the prostatic capsule and if it is separated from the organs next to it (Table 1).[27]

| T | | Primary tumour |
|---|---|---|
| TX | | Primary tumour cannot be assessed |
| T0 | | No evidence of primary tumour |
| T1 | | Clinically inapparent tumour not palpable or visible by imaging |
| | T1a | Tumour incident histological finding in 5% or less of tissue resected |
| | T1b | Tumour incident histological finding in more than 5% of tissue retracted |
| | T1c | Tumour identified by needle biopsy (eg because of elevated PSA) |
| T2 | | Tumour confined within prostate |
| | T2a | Tumour involves one half of one lobe or less |
| | T2b | Tumour involves more than half of one lobe, but not both lobes |
| | T2c | Tumour involves both lobes |
| T3 | | Tumour extends through the prostatic capsule |
| | T3a | Extracapsular extension (unilateral or bilateral) |
| | T3b | Tumour invades seminal vesicles(s) |
| T4 | | Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, or pelvic wall |
| **N** | | **Regional lymph nodes** |
| | NX | Regional lymph nodes cannot be assessed |
| | N0 | No regional lymph nodes metastasis |
| | N1 | Regional lymph node metastasis |
| **M** | | **Distant metastasis** |
| | MX | Distant metastasis cannot be assessed |
| | M0 | No distant metastasis |
| | M1 | Distant metastasis |
| | M1a | Non-regional lymph nodes(s) |
| | M1b | Bone(s) |
| | M1c | Other site(s) |

*Table 1. TNM classification, seventh edition*.[27]

#### 2.1.2.2 Prostate-specific Antigen (PSA)

PSA is a protein produced in the prostate and secreted in high concentrations in the seminal fluid where it is involved in the liquefaction of the seminal coagulum.[28] PSA circulates in serum both bound and unbound. The blood levels of PSA typically rises in a man with prostate cancer. However, some of the worst tumours deform the prostate cells to the extent that they are unable to produce PSA. The level of PSA also rises due to many other factors apart from cancer, thus an elevated PSA is not on its own a strong predictor for prostate cancer. Furthermore, there is no real cut-off point for PSA where the sensitivity and specificity rises. Studies have shown that the sensitivity for detecting prostate cancer is different for different cut-off points; PSA level of 1.1, 2.1, 3.1 and 4.1 ng/mL yielded sensitivities of 83.4%, 52.6%, 32.2% and 20.5% respectively and specificities of 38.9%, 72.5%, 86.7% and 93.8% respectively.[29] Other reasons for elevated PSA are age, benign prostate hyperplasia (BPH), urinary tract infection, urinary retention, renal failure and iatrogenic examinations of the urinary tract such as cystoscopy and TRUS with biopsies.

In conclusion, there are a lot of factors to consider when evaluating an elevated PSA and deciding whether to further investigate with trans-rectal ultrasound (TRUS) and biopsies. To help with this decision there are a number of factors with PSA that are significantly associated with prostate cancer aggressiveness such as the rate of change of PSA (PSA velocity and doubling time), the PSA density (serum PSA divided by prostate volume) and the percentage of PSA in the free or complex isoforms.[30,31,32,33,34,35] In men with prostate cancer a greater proportion of the PSA is attached to macromolecules compared to men with only BPH. The higher the ratio, the lower the risk for prostate cancer.

Screening with PSA has been widely debated and no country has yet introduced a national PSA-based screening program. However, many countries use frequent PSA testing 'opportunistic screening' although it is currently unknown whether it reduces prostate cancer mortality or not. Recent results from the Göteborg Randomized Population-based Prostate Cancer Screening Trial showed that organized screening reduces prostate cancer mortality but is associated with overdiagnosis.[36]

#### 2.1.2.3 Trans-Rectal Ultrasound (TRUS)

TRUS is performed to measure the size of the prostate, the shape (e.g. if there is a lobus tertius) and to detect areas suspicious for tumour or extra-prostatic growth. If the investigation raises suspicion of prostate cancer, needle biopsies are performed with TRUS under local anaesthesia. The recommendation in Sweden is to initially take 10-12 systematic biopsies from the peripheral zone where most cancers are located.[24] The histopathology from the biopsy cores is then evaluated by the pathologist. More than 95% of all cancers in the prostate are acinic adenocarcinomas, the remaining 5% are represented by subtypes of prostate adenocarcinoma such as ductal, mucinous, small cell carcinoma, primary translational cell carcinoma and sarcoma.[37] If the histopathology report is benign but there is a persisting clinical suspicion of prostate cancer, repeat biopsies are performed with additional cores from the transitional zone.

#### 2.1.2.4 Gleason score

A grading system for the evaluation of prostatic adenocarcinoma was originally developed by Donald F. Gleason in 1966.[38] It was based on the glandular pattern of the tumour at low magnification. This system categorises patterns into five different grades. The Gleason score is then expressed as a sum of the grade which occurs most frequently in the biopsy, and the highest grade that can be detected e.g. 3+4=7. The system has been modified several times in 1967, 1974, 1977 and in 2005. The grading currently used is based on the latest modification done in 2005 by the ISUP International Society of Urological Pathology.[39] Figure 3 describes the characteristics for each Gleason pattern.

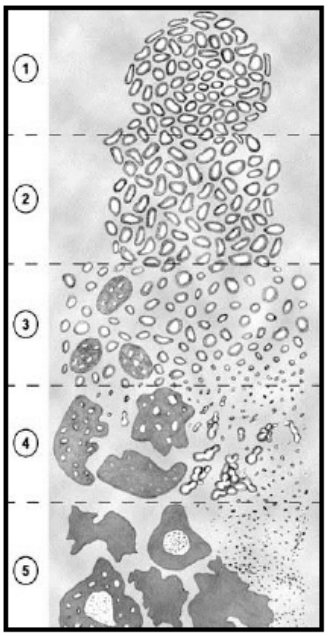



*Figure 3. 2005 ISUP Modified Gleason System*[39]

Pattern 1: Circumscribed nodule of closely packed but separate, uniform, rounded to oval, medium-sized acini (larger glands than pattern 3)

Pattern 2: Like pattern 1, fairly circumscribed, yet at the edge of the tumor nodule there may be minimal infiltration. Glands are more loosely arranged and not quite as uniform as Gleason pattern 1

Pattern 3: Discrete glandular units. Typically smaller glands than seen in Gleason pattern 1 or 2. Infiltrates in and amongst non-neoplastic prostate acini. Marked variation in size and shape. Smoothly circumscribed small cribriform nodules of tumor

Pattern 4: Fused microacinar glands, Ill-defined glands with poorly formed glandular lumina. Large cribriform glands. Cribriform glands with an irregular border. Hypernephromatoid.

Pattern 5: Essentially no glandular differentiation, composed of solid sheets, cords, or single cells. Comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid masses.

The Gleason score has a fairly good inter-observer reproducibility among uropathology experts, however not so good when compared to general pathologists.[40,41,42] Berg et al. reports that a general and an expert uropathologist reports the same Gleason score (GS) in 78% of cases.[43] This highlights the need for using experts in the field of uropathology when evaluating histology in prostate biopsies since the urologist bases a great deal of the treatment decision (i.e. what kind of treatment, nerve-sparing surgery, lymphadenectomy and preoperative MRI or bone scintigraphy) on the pathology report. Data from the same study showed that there was an acceptable correlation between the grade of biopsy and the subsequent radical prostatectomy with 68% concordance. In the non-matched cases the GS was significantly higher in the prostatectomy specimens. Two thirds of men with GS = 6 had a higher GS in their prostatectomy specimen, however the level of agreement was higher in GS $\geq$ 7.[43] The under-grading reflects the sampling error that can not be eliminated because biopsies only represent a small fraction of the prostate.[44] Increasing the number of core biopsies taken increases the sample size, thus reducing this discrepancy. Currently in Sweden it is recommended to take 12 cores the first round of biopsies.

The ultimate value of a grading system would be its prognostic capability. The Gleason score has been proven to have a strong correlation with prognosis of prostate cancer. In a register-based nationwide cohort of over 12000 men with locally advanced prostate cancer (defined as local clinical stage T3, T4 or alternatively T2 with serum levels of PSA 50-99 ng/ml, without signs of metastases) the prostate cancer specific mortality at 8 years of follow-up was 28% for GS 2-6, 41% for GS 7, 52% for GS 8 and 64% for GS 9-10 without any treatment.[45] An important cut-off in predicting prognosis with GS is Gleason pattern 4 and 5. These tumours are much more aggressive as compared to Gleason pattern 1-3 and this is reflected in a strongly increased risk for lymph-node metastases and death.[46,47] High GS is also associated with higher risk of extra prostatic tumour extension.[48]

#### 2.1.2.5 Magnetic Resonance Imaging (MRI)

Over the past decade, imaging of prostate cancer has been developed and improved. MRI is used for diagnostic purposes to determine the stage of the disease in prostate cancer (T and N stage). However, there is currently no strong scientific evidence regarding the usefulness of MRI and whether it leads to increased survival. To detect prostate cancer multi-parametric MRI is needed which includes a combination of T2-weighted imaging, dynamic contrast-enhanced MRI and diffusion-weighted imaging.[49,50] Detection of highly differentiated cancers, i.e. with low Gleason grade, has lower sensitivity with MRI compared to the low differentiated cancers that should preferably be treated.[51] There is a strong belief that MRI will have an increasing role in the staging of prostate cancer in the future. It could help provide even better knowledge of the localization of the tumour before the treatment decision is made and also guide how treatment for a specific patient should optimally be performed. To get a good sensitivity and specificity it is of great importance to have an experienced team of radiologists, urologists and pathologists with a high patient load. The latest use of MRI is in combination with trans-rectal ultrasound, where the MRI images are transferred to the ultrasound machine and linked to the ultrasound images in real time. This enables biopsies to be targeted towards suspicious areas visualised on MRI, thus allowing for fewer biopsies to be taken overall to detect prostate cancer. This technique is still under development but shows promising results compared to systematic biopsies in prostate cancer detection and might play an important role in the future.[52]

### 2.1.3 Treatment options in localized prostate cancer

In recent years, the number of diagnosed prostate cancer cases have increased significantly, partly due to expanded and improved diagnosis of prostate cancer with the introduction of PSA and partly because of the increased life expectancy of the population. This has led to more men today being offered curative treatment following early diagnosis when the cancer is still localized. PSA testing has resulted in lead-time bias, since cancers are detected about 9 to 13 years earlier than previously.[53] However, increasing numbers of harmless cancers will be diagnosed. The natural course of prostate cancer is unpredictable, and as a result clinicians are still today unable to differentiate between aggressive prostate cancer that poses a threat to the patient's life, and those cancers which are slow growing and will not affect the patient within his lifetime. A lot of biological and histological research is being done in the search for the prediction tumour behaviour.[54]

However, we know today that there are a number of factors that predict prognosis and aggressiveness of the tumour. As mentioned previously the PSA level including the total PSA, the change of PSA over time and PSA ratio are significantly associated with the aggressiveness of the tumour. Furthermore certain information from the biopsy correlates with cancer aggressiveness. The Gleason score is the most important factor but also number of cores with cancer, the distribution and volume of cancer in the cores, the presence of perineural space invasion, lymphovascular invasion, or ductal or neuroendocrine

differentiation.[45,55,56] To assist the urologist in the assessment of all these variables nomograms (prediction tables) have been developed.[57]

Prostate cancer is considered incurable if: metastasis exists, PSA-level is above 100 ug/l, if there is wide spread lymph-node invasion, or the cancer is stage T4 with invasion of other organs except for the seminal vesicles. Untreated prostate cancer without metastasis is divided into four risk groups which are correlated with prognosis and will aid in the treatment decision (Table 2).[58]

| Risk | Stage | Grade | PSA (ng/ml) | |
|---|---|---|---|---|
| **Very low risk** | T1c | ≤ 6 | <10 | cancer in 1-4 of a total of 8-12 biopsy cores, maximum of 8 mm total cancer length in 8-12 biopsy cores, PSA density <0.15 ug / l / $cm^3$ |
| **Low risk** | T1-T2a | ≤ 6 | <10 | |
| **Moderate 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 all biopsy cores) |

*Table 2. Swedish national guidelines risk classification of prostate cancer*[58]

Curative treatment of localized prostate cancer consists of radiotherapy or surgery with radical prostatectomy. A Swedish randomized trial of radical prostatectomy, the SPCG-4 study, showed that radical prostatectomy had an absolute risk reduction of 11% in mortality compared to watchful waiting.[1] The awareness that radical prostatectomy improves survival has contributed to surgery becoming the most common form of treatment in Sweden. A third option for localized prostate cancers is active surveillance for patients with very low risk cancers which allows delayed primary treatment until monitoring shows any signs of cancer progression, thus avoiding "unnecessary" treatment. In the section below these three different treatments are described in more detail.

#### 2.1.3.1 Radical prostatectomy

Radical prostatectomy was the first treatment for prostate cancer and it has been performed for over 100 years.[59] The operation involves removal of the prostate gland and seminal vesicles and in more advanced cases also includes removal of the lymph-nodes that drain the prostate. It is a technically difficult operation to perform due to its inaccessible location in the small pelvis. Despite this the radical prostatectomy is today the gold standard treatment for localized prostate cancer.[60] Radical prostatectomy as primary treatment of prostate cancer has increased over the latest decades in Sweden, mostly since the introduction of PSA which led to an increase in the incidence of mainly localized cancers which are curable. Figure 4 shows the total number of radical prostatectomies as primary treatment in Sweden between 1998

and 2013. The reason for the decline since around 2010 is believed to be due to more patients with low-risk cancers being put on active surveillance instead of treatment with radical prostatectomy.

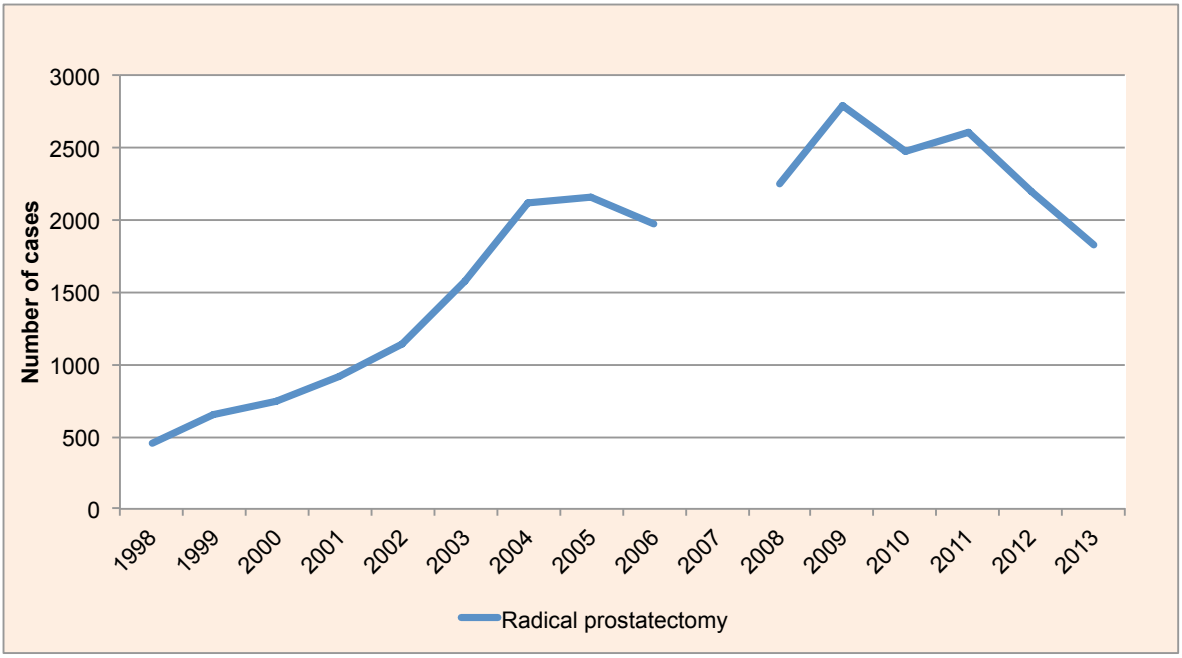



*Figure 4. Total number of radical prostatectomies as primary treatment per year of diagnosis in Sweden between 1998 and 2013. Information for year 2007 is not available. Graphical illustration: A Wallerstedt. Data adapted from NPCR.*

Potential advantages of radical prostatectomy over radiotherapy are that treatment failure is more easily identified and that it provides more accurate tumour staging by pathological examination of the surgical specimen. In addition lymph-node dissection can be performed which is the most accurate and reliable nodal staging procedure as available imaging techniques currently still have rather low sensitivity.[51,61,62] When compared to watchful waiting, prostatectomy significantly reduced local progression, distant metastases and improved cancer-specific and overall survival rates in the Scandinavian randomized trial, SPCG-4.[63] Radical prostatectomy is described more in detail in chapter 2.2.

#### 2.1.3.2 Radiotherapy

External beam radiotherapy uses beams of gamma radiation, usually photons, directed at the prostate and the surrounding tissues to treat prostate cancer. Radiotherapy has been evolving and today it is possible to give radiation with higher precision enabling higher doses to be delivered with stronger effect but also lower risk for side-effects.[64,65] Three different randomized trials have shown that radiotherapy in combination with endocrine treatment decreases mortality in locally advanced prostate cancer.[66,67,68] Today there exists no randomized controlled trials that compares radiotherapy with radical prostatectomy. The studies that are available are difficult to draw any conclusions from because of possible selection bias and because the endpoints for determining treatment success or failure are different for radiotherapy and surgery.[69] High risk prostate cancers have more than 15-20%

risk for lymph-node metastasis, and it may therefore be appropriate to treat with radiation.[70] However, there is no strong evidence that radiation therapy is effective against lymph-node metastasis. Standard treatment for external beam radiation in Sweden is currently 78 Gy in 39 fractions, which has shown to improve cancer control.[71]

The side effects after radiation therapy are related to microvasculature damage of the tissue in the bladder, rectum, striated sphincter and urethra. Short-term side effects are irritative urinary symptoms, flatulence, loose stools and mucus or bleeding from the rectum. In a prospective study 9% of patients reported distress related to bowel function one year after radiotherapy or brachytherapy.[72] Urinary symptoms can also be persistent.[73] Approximately 50% of patients develop erectile dysfunction a few years after radiation therapy.[37] This is caused by injury to the vasculature of the cavernous nerves and to the corpora cavernosa.

External beam radiation is often combined with long-term hormonal therapy in locally advanced prostate cancers and localized high-risk disease since studies have shown benefit in terms of overall survival.[74] There are some relative contraindications for the use of external beam radiation as well as brachytherapy. Patients with severe obstructive urinary symptoms are not suitable because of the increased risk for acute urinary retention. Patients with prior TURP are unsuitable if the cavity in the prostate is too large because it leads to technical difficulties in administrating the radiation treatment. Inflammatory bowel disease is a relative contraindication due to the risk of worsening gastrointestinal symptoms.

In brachytherapy radioactive sources are planted directly into the prostate gland. There are two sorts of brachytherapy, low dose-rate brachytherapy (also known as "seeds") and high dose-rate brachytherapy. Low dose-rate brachytherapy is suitable for low and intermediate-risk prostate cancers with limited distribution of Gleason grade 4. The treatment is performed over 2-3 hours under general or spinal anaesthesia. Iodine seeds are deposited in the prostate using needles under trans urethral ultrasound guidance and fluoroscopy. The seeds consist of iodine-125 with a half-life of 60 days. The radiation dose is approximately 145 Gy, which is substantially higher than the dose used in external beam radiotherapy. Observational studies have shown that the effect is comparable with external beam radiation and radical prostatectomy in low and intermediate risk cancers.[75,76,77] Side-effects after brachytherapy are mostly urinary symptoms especially in patients with coexisting prostatic hyperplasia.[77] To avoid these problems it is important to choose patients who fulfil the following criteria: prostate volume < 50 cc, no urinary residual, International Prostate Symptom Score <8 and no median lobe. The risk of long-term side effects is thought to be lower in brachytherapy compared to external beam radiation and radical prostatectomy besides more frequent urination. Persistent urinary symptoms occur in approximately 10% and erectile dysfunction in 15 to 50% of patients depending on the erectile function prior to treatment.[58]

External beam radiation and high dose-rate brachytherapy can be given in combination. There are currently no randomized trials investigating its effect however there are observational studies that show a good effect particularly on high-risk cancers.[78,79] The treatment is initiated with 3-5 weeks of external beam radiation followed by high dose-rate

brachytherapy which is performed with almost the same method as low dose-rate brachytherapy. The difference is that needle's are implanted in the prostate only temporarily during 10-20 minutes while the treatment is performed. The radiation dose to the surrounding organs is less and thus decreases the risk of side-effects compared to external beam radiation. The side-effects among most patients receiving this mode of treatment are irritative urinary symptoms and rectal symptoms. Many develop erectile dysfunction a few years after treatment to a greater extent compared to those who had received brachytherapy as monotherapy.[58]

#### 2.1.3.3 Active surveillance

At the time of diagnosis not all prostate cancers are suitable for curative treatment. There has been a substantial increase in the incidence of prostate cancer since the introduction of PSA and it has contributed to the detection of many low risk, clinically insignificant cancers. It has been shown in studies that most men who die within 10-15 years after a diagnosis of low or intermediate risk prostate cancer will die from causes other than from the cancer itself.[80,81] Some reports have shown overdiagnosis (cancers detected by screening that would never cause the patient disability or death) in as much as 50% or more in older men.[53] In a randomized controlled trial radical prostatectomy did not significantly reduce all-cause or prostate cancer mortality compared with observation after 12 years of follow-up.[82] Furthermore, there is uncertainty as to whether Gleason grade 3 has the ability to metastasize, and if this is so, the question remains whether such cancers should be treated at all.[83] Some argue that it should not.[84] However there is a correlation between the propagation of Gleason grade 3 and the risk for simultaneous Gleason grade 4 cancer.[85] Considering all the evidence, there is a place for active surveillance in selected cases of prostate cancer.

In Sweden active surveillance is recommended for patients with very low risk prostate cancer and an expected survival of 10 years or more.[58] This is to avoid overtreatment, as well as the potential side effects the treatment causes. The longer expected survival of the patient, the more important it is to perform a thorough investigation to exclude the possibility of a more aggressive cancer before committing a patient to active surveillance, since about 30 percent of all Gleason 3+3 in biopsies are upgraded to a higher Gleason grade after surgery due to sampling error.[43] Based on this, about one third of all patients are understaged on their initial prostate biopsy, one biopsy alone is not sufficient to offer the patient active surveillance as an alternative.[86] Therefore a re-biopsy has to be performed before commencing active surveillance. Active surveillance should not be mistaken for watchful waiting, which is the monitoring of a patient until he develops metastatic disease that requires palliative treatment.

Active surveillance according to Swedish National Guidelines consists of:

- a new biopsy with 10 cores within 2-6 months after the initial biopsy, preferably in the anterior part of the prostate[87]
- PSA repeated every 3-4 month
- DRE repeated every 6-8 months for 2 years
- PSA and DRE repeated every 6 months after the initial 2 years of active surveillance
- re-biopsy every 2-3 years including 10 cores
- optional re-evaluation of the primary pathology report
- optional multi-parametric MRI

The longer the expected survival of the patient, the lower the threshold for recommending treatment if monitoring shows any signs of more aggressive cancer. Active surveillance is not optimal for a patient with anterior cancer, a large prostate, a PSA ratio <0.1, prostatitis/UTI or family history of prostate cancer.[58] Active surveillance can induce patient anxiety, as it causes the patient to live with an untreated cancer. This in it self may be a reason to initiate treatment.[88,89] A potential downside of recommending active surveillance to men with low-risk cancers that are still curable is that such cancers could progress over time where potentially the opportunity for curative treatment could be missed. Furthermore multiple biopsies could complicate future attempts at nerve-sparing surgery through potential distortion of the anatomy. A randomized clinical trial, the SPCG-4 study, showed that patients treated with watchful waiting had shorter cancer-specific and overall survival compared to patients operated with radical prostatectomy.[90] However, average self-assessed quality of life was similar between the two groups after 12 years of follow-up.[91]

Active surveillance should be stopped when the patient is no longer a candidate for curative treatment and then the patient should be converted to watchful waiting for possible future hormonal treatment.

## 2.2 RADICAL PROSTATECTOMY

### 2.2.1 Historical background

The history of radical prostatectomy takes its beginning back in 1866 when Kuchler first described the perineal approach to remove prostate cancer.[59] Kuchler only performed the operation on cadavers but the year after the famous surgeon Theodor Billroth was the first one to perform the operation on a patient to treat urinary obstruction at the University of Zurich and later described this in a medical journal.[92] However, the outcome of the operation was poor as the patient died from complications. Later, in 1904 Professor Hugh Hampton Young performed a radical perineal prostatectomy in Johns Hopkins Hospital and he published data from his first operations in 1905.[93] However, the peri- and postoperative morbidity was still very high. In 1945 Terence Millin was the first to describe the radical retropubic prostatectomy.[94] The indication was initially treatment for prostatic obstruction. Patients were only mobilised four days after surgery and discharged 14 days postoperatively. Still the operation was associated with high mortality and complications such as substantial blood loss, severe urinary incontinence, erectile dysfunction and stricture of the vesicourethral anastomosis. The diagnosis of prostate cancer during this period of time was often reached through digital rectal examination finding a palpable prostatic nodule. At this stage the cancer had frequently already spread beyond the prostate and was not curable by prostatectomy. The discovery of prostate-specific antigen (PSA) in 1970 by Ablin et al. was revolutionary and led to a stage migration of prostate cancer towards smaller, potentially curable tumours and thus the demand for curative treatment options increased.[95] During this period of time efforts were initiated to decrease the peri- and postoperative complications. Reiner and Walsh described the anatomy of the dorsal venous complex in 1979 and a few years later Walsh and Donker improved understanding of the periprostatic anatomy, especially the existence and function of the neurovascular bundles.[96,97] They developed the anatomic radical retropubic prostatectomy which allowed the dissection to be performed with good visualization and preservation of cavernosal nerves and the external sphincter muscle, leading to lower rates of postoperative erectile dysfunction and incontinence. Walsh described the first prostatectomy with nerve-sparing technique in 1983.[98] Other significant updates in the surgical technique was the knowledge of the anatomy of the puboprostatic ligaments[99], urinary sphincter, prostate shape[100] and the posterior rhabdosphincter[101]. The development of the surgical technique had started and it is still today continually enhanced to decrease postoperative morbidity.

### 2.2.2 Anatomy of the prostate

A detailed knowledge of the anatomy of the prostate and the surrounding tissues is mandatory when performing a radical prostatectomy to ensure reliable oncological and functional outcomes. Patrick Walsh once said: "You only see what you are looking for and you only look for what you know". Thus, it is of great importance to have precise knowledge of all relevant anatomical structures to facilitate surgical orientation and dissection during radical

prostatectomy since the surgical anatomy of the prostate and adjacent tissues is very complex.

The prostate is a walnut-sized gland in men that is located between the bladder and the penis with the urethra running through the gland. The size of the gland increases with age. The prostate is divided into five zones: three glandular (the peripheral zone, the transitional zone and the central zone) and two non-glandular (the peri-urethral zone and the fibromuscular stroma). The peripheral zone constitutes almost 75% of the normal prostate gland and occupies the distal prostate gland, the area around the urethra distal to the seminal colliculus (an elevation in the wall of the urethra where the seminal ducts enter). This zone is were most cancers are located in the prostate. The transitional zone lies superior to the seminal colliculus, lateral to the proximal urethra, and posterior to the fibromuscular stroma. Benign prostate hyperplasia (BPH) is caused by enlargement of the transitional zone, compressing the peripheral zone or displacing it laterally. The central zone lies posterior to the urethra and superior to the seminal colliculus. The peri-urethral zone is a midline structure of cylindrical, internal smooth muscle sphincter that runs from the base of the seminal colliculus to the back of the bladder neck. This is the site of origin of the large median lobe of BPH. The anterior fibromuscular stroma forms the anterior surface of the gland. In close proximity behind the prostate lies the rectum. The prostate can therefore be examined via the rectum by a digital rectal exam or by transrectal ultrasound.

The function of the prostate is to produce the majority (95%) of the seminal fluid, together with the seminal vesicles and the bulbourethral glands. The secretions produced by the prostate nourishes and protects the sperm produced in the testicles. There are two seminal vesicles located posterior-laterally to the prostate where the fluid from the prostate is collected. During ejaculation the seminal fluid is squeezed into the urethra from the seminal vesicles, the prostate and the spermatic duct.

The prostate is covered with three fascial layers: Denonvilliers' fascia, the prostatic fascia and the levator fascia. Denonvilliers' fascia is located between the anterior walls of the rectum and prostate whilst the prostatic fascia is located anteriorly and antero-laterally in direct continuity with the capsule of the prostate. Laterally the prostatic fascia fuses with the levator fascia, which covers the pelvic musculature, to form the lateral pelvic fascia. The puboprostatic ligaments are paired fibrous bands originating from the visceral endopelvic fascia and their function is to stabilize the prostate, urethra and bladder to the pubic bone. They are considered an important part of the suspensory system of the continence mechanism.[102] The dorsal venous complex or the Santorini's plexus covers the prostate ventrally and drains blood from the penile veins.[103] The prostate is surrounded by a capsule-like structure, however it is not a well-defined capsule in an anatomic sense but rather a layer of fibro muscular fascicles, primarily smooth muscle.[104]

The inferior hypogastric plexus or pelvic plexus innervates the mechanism of erection, ejaculation and urinary continence and contains sympathetic fibres that derive from the

hypogastric nerves originating mainly from T11-L2.[105] The plexus also contains parasympathetic fibres primarily from the pelvis and sacral splanchnic nerves and originate from the ventral rami of S2-4. The nerves are located in two neurovascular bundles that are located on the lateral and anterolateral surface of the prostate.[97,106,107] The bundles are not a distinct structure but consist of multiple finely dispersed fibres.[108] The fascial and neural anatomy of the prostate are of special interest when performing a radical prostatectomy with nerve sparing surgery to improve functional outcome.[109] The dissection can be performed in three different planes: intrafascial, interfascial and extrafascial (Figure 6). In the first case all the nerves are intended to be spared and in the third case the largest amount of tissue around the prostate is excised. Extrafascial dissection is the most safe approach for ensuring good oncological outcomes but carries with it a high probability of erectile dysfunction. The external urethral sphincter is located distal to the prostate apex and is innervated by autonomic branches from the pelvic plexus. The sphincter consists of two different muscle types. The outer muscle layer consists of striated muscle fibres and has been described as having a horseshoe appearance, often called the rhabdosphincter.[110] The inner muscle layer surrounds the urethra completely and consists of smooth muscle and elastic tissue.[111]

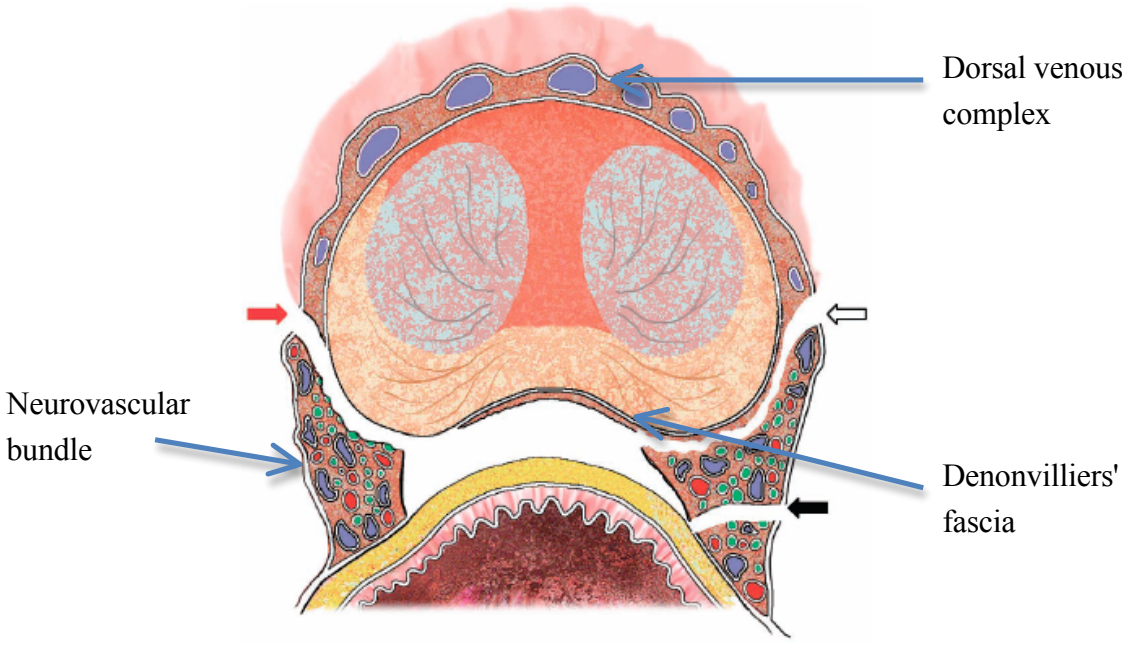



*Figure 6. Schematic drawing of different dissection techniques for preservation of the neurovascular bundles. The left neurovascular bundle is preserved with an intrafascial technique (red arrow). The right neurovascular bundle is dissected in an interfascial plane (white arrow). Also demonstrated is the extrafascial dissection of the right neurovascular bundle (black arrow).*[112]

Lymphadenectomy in radical prostatectomy can be performed in two ways: limited or extended. In the limited version nodes in the obturator fossa located cranial and caudal to the obturator nerves are removed where as in the extended version the nodes overlying the external iliac artery, vein and nodes medial and lateral to the internal iliac artery are also

excised.

### 2.2.3 Different types of radical prostatectomy

Radical prostatectomy is today performed in three different ways in Sweden: open retropubic, laparoscopic and robot-assisted radical prostatectomy. There is also a fourth approach: the radical perineal prostatectomy, which is not performed in Sweden today. A disadvantage with this technique is that the lymph-nodes cannot be removed through this approach. Furthermore, studies have shown that the technique is associated with higher incidence of rectal injuries.[113]

#### 2.2.3.1 Retropubic radical prostatectomy

Retropubic radical prostatectomy was previously the most commonly used technique for many decades. It provides wide exposure of the operative field and direct access for pelvic lymphadenectomy and prostate excision with possibility of preservation of the neurovascular bundles. When performing a radical retropubic prostatectomy a midline incision is made from the symphysis pubis up toward the umbilicus. Careful suturing of the dorsal venous complex is made with suture-ligatures both distally above the apex of the prostate and proximally below the bladder neck. The apex dissection aims to free the urethral sphincter and the neurovascular bundles from the prostate without damaging them. It is important to visualize the transition between the urethra and the prostate as the risk of a positive margin is greatest in this area. The nerve-sparing dissection is then continued to free the neurovascular bundles dorsolaterally from the prostate. Diathermy should preferably not be used due to the risk of irreversible damage to the autonomic nerves.[114] If extraprostatic growth of the tumour is suspected the resection is made wider, thus not sparing the nerves. The dissection of the bladder neck is made either with a wide dissection in case of an advanced cancer or alternatively with bladder neck sparing technique. Then the anastomosis between the bladder neck and the distal urethra is performed with 4 to 6 single sutures.

#### 2.2.3.2 Laparoscopic radical prostatectomy

The laparoscopic approach was introduced to improve visualization of anatomy and with the belief that it would be associated with less bleeding, less postoperative pain and shorter convalescence compared to open surgery.[115] However, this operative technique proved to be difficult with a long learning curve. Although perioperative bleeding is less, this technique has been debated to be associated with more postoperative complications such as ureteral injuries and anastomotic strictures.[116,117]

Laparoscopic prostatectomy is performed with five laparoscopic ports that are surgically inserted through the abdominal wall and subsequently the abdominal cavity is inflated with carbon dioxide to form a pneumoperitoneum. Pneumoperitoneum is usually referred to as the cause for less bleeding in laparoscopic operations compared to open operations. Usually, a posterior dissection from the Pouch of Douglas is performed to dissect the vas deferens and the seminal vesicles. The urinary bladder is then taken down from the abdominal wall and the

space of Retzius is developed. The dorsal venous complex is then sutured with ligatures whereafter the prostate is freed from the bladder neck. Then the dissection of the neurovascular bundles is performed. If the cancer is poorly differentiated, is locally advanced or if the patient is preoperatively impotent, nerve sparing surgery is normally not performed to avoid the risk of a positive margin. Then the urethra is freed from the apex of the prostate. It is important not to make a too wide excision of the prostate so as not to damage the external sphincter as this might cause postoperative incontinence. However, the risk for positive margins is highest at the apex of the prostate so the dissection can not be too close either. Lastly the anastomosis between the bladder neck and urethra is made by 10-14 continuous sutures. The prostate is removed from the abdomen in an endobag through an incision at the umbilical port.

#### 2.2.3.3 Robot-assisted radical prostatectomy

Robotics in the practice of surgery started to evolve in the late 20th century. The first surgical application of a robot was in neurosurgery to orientate a needle for a brain biopsy under computerized tomography (CT) guidance.[118] However the original prototype for the robot we use today for radical prostatectomy was created for military purposes to mount onto an armoured vehicle.[119] Intuitive Surgical Inc. acquired the prototype from the military and gave birth to the da Vinci® robotic system. The system is based on the concept of *immersive telepresence*, which means that the surgeon operates on the patient remotely but still feels that he is in the operating room.

In 2000, the first robot-assisted radical prostatectomy was performed in the world.[120] The operative technique is the same as in traditional laparoscopic prostatectomy except that the surgeon controls the camera and two or three operating arms from the controls of a robotic console. Robotic technology was thought to provide better results due to improved visualization through better lighting, improvement of magnification and a three-dimensional image of the abdomen. Robotic instruments have also increased mobility with 7 degrees of freedom and more precise motor control in comparison with the conventional laparoscopic instruments that enables a more accurate dissection technique. Another advantage with the robotic technique is the improved ergonomics for the surgeon as compared to both the open and laparoscopic technique. The technology makes it easier to visualize the urethra and to sew an anatomically correct anastomosis without damaging the outer micturition sphincter, which is believed to result in reduced postoperative incontinence. The neurovascular bundles innervate the penis are attached to the prostate capsule and should be preserved to maintain potency after surgery. The robotic approach's good visualization and extended mobility is thought to allow preservation of the nerves in a better way than with open surgery and thus lead to lower levels of impotence. In recent studies it has also been shown that preservation of the nerves is associated with lower rates of incontinence one year after radical prostatectomy.[121,122] This evidence could widen the indication for nerve sparing surgery not only for preservation of potency but also preservation of continence.

The robotic technique has been proven to cause less perioperative bleeding, less transfusions and shorter hospital stay compared to open surgery.[123] However the total cost is higher. With respect to long-term functional and oncological outcomes most studies have shown no difference between the techniques.[124,125] However, in a meta-analysis Ficarra et al. showed a statistically significant advantage in favour for the robotic technique concerning 12 months urinary continence recovery and potency rates.[126,127] A more important factor for the functional and oncological results is the individual skill and experience of the surgeon.[128,129,130] Thus, it is of great importance that radical prostatectomy is performed by a select number of surgeons with a high annual volume of cases to be able to improve and maintain their surgical skills. A further potential advantage is that the robot-assisted technique seems to have a shorter learning curve when compared to laparoscopic and open surgery.[131,132,133]

Today, there are no high-quality published studies in which open radical prostatectomy and robot-assisted radical prostatectomy are compared. Despite this, many surgeons adopted the robotic-assisted technology and it became more widely used, based on promising preliminary reports both in terms of postoperative morbidity and oncological results.[134,135] Today the robotic technique is the most commonly used technique for radical prostatectomy in Sweden, about 65% of all prostatectomies in Sweden in 2013 were performed robotically (Figure 5).[24] In the US the numbers are even higher with 85% of all prostatectomies in 2011. Given the increased use of robotics there is a great need for evidence-based data proving that the robotic technique is at least as good or a better method than the conventional open technique.

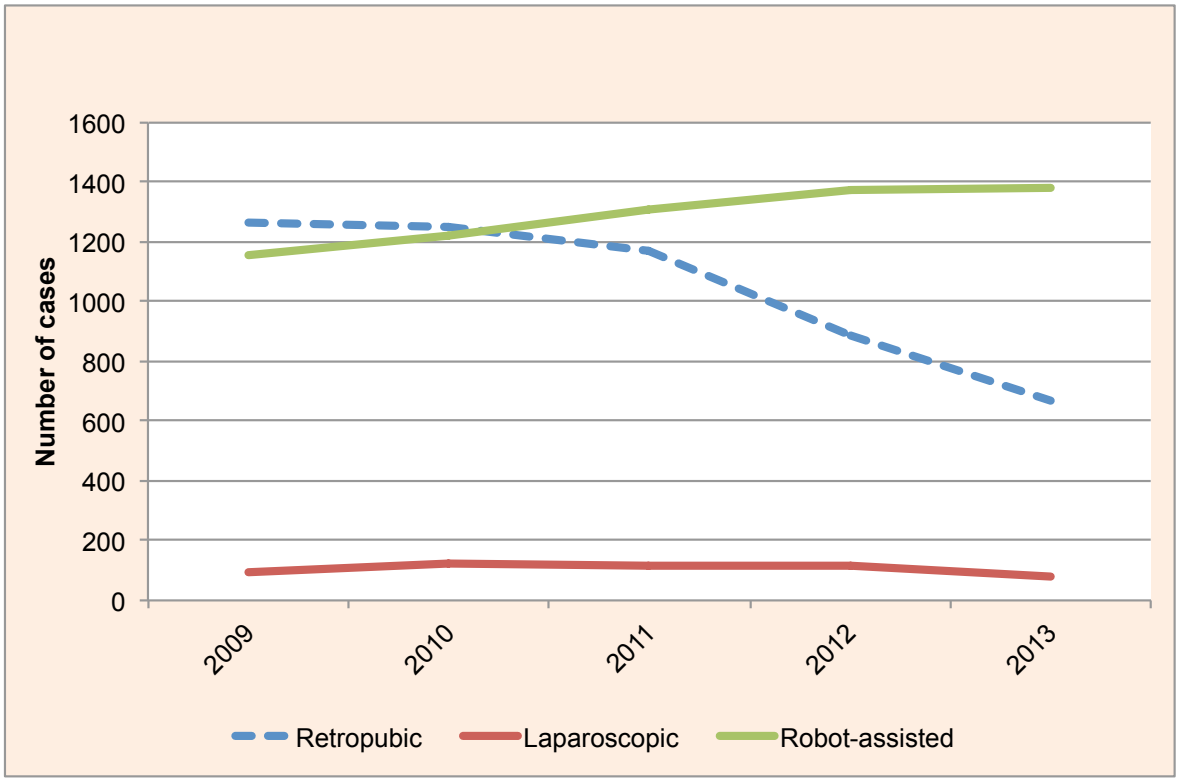



*Figure 5. Type of radical prostatectomy as primary treatment in Sweden between 2009 and 2013.*
*Graphical illustration: A Wallerstedt. Data adapted from NPCR.*

### 2.2.4 Complications

Surgical technique should be as atraumatic as possible to reduce the risk of complications from surgery. Over the years the surgical technique has improved with increasing experience and the risk of side effects are decreasing. However, there is still a significant risk of complications after prostate cancer surgery. The two most common long-term side effects are urinary incontinence and erectile dysfunction that also have a significant impact on quality of life.[136]

#### 2.2.4.1 Short-term complications

Short-term complications within 30 days of surgery was assessed in a meta analysis by Tewari et al in 2012 with data obtained from 400 articles representing 286,876 patients who had undergone radical prostatectomy, either open, laparoscopic or robot-assisted. Patients operated by robot-assisted prostatectomy had significantly lower PSA preoperatively and a lower percentage of men with pT3 disease compared to men operated by open or laparoscopic surgery.[137] Bleeding is the most common complication of radical prostatectomy. In the meta analysis the robotic approach had significantly less bleeding and transfusion rates compared to both open and laparoscopic surgery (RARP 188 ml; 1.8%, ORP 745 ml; 16.5%, LRP 378 ml; 4.7%).[137] There is substantial evidence that laparoscopic techniques cause less bleeding which is usually explained by the formation of a pneumoperitoneum during surgery.[138,139] Hospital stay was also significantly shorter in men operated by robotic technique (RARP 4.0 d, ORP 9.9 d, LRP 6.3). Rates of mortality were very low and no differences were noted between the groups (RARP 0.04%, ORP 0.1%, LRP 0.04%).[137] Studies have shown that the most common cause of death within 30 days of the operation is acute myocardial infarction.[140] Overall there was lower morbidity for robotic patients in the meta analysis with lower readmission, reoperation and total perioperative complication rates. The perioperative injuries that occurred with the robotic technique were nerve injuries (0.4%), ureteral injuries (0.1%), ileus (0.8%), rectal injuries (0.3%) and bowel injury (0.09%). Anastomotic leakage occurred in 3.5% in the same group. Wound infection (2.8% vs. 0.7%), hematomas (1.6% vs. 0.7%) and lymphoceles (3.2% vs. 0.8%) were significantly more common with the open technique compared to the robotic technique.[137] The results from this meta analysis must be interpreted with care since the differences in patient characteristics described might explain differences in outcomes between the surgical techniques. However, in the absence of a randomized controlled trial this meta analysis provides a high level of evidence that the robot-assisted technique is at least comparable to the open technique.

Thromboembolic events are also a known complication of radical prostatectomy. However the rates for deep venous thrombosis were lower for the robotic patients compared to open technique in the meta analysis (0.3% vs. 1.0%).[137] Lymph-node dissection during radical prostatectomy increases the risk for thromboembolic events, especially in patients with previous thromboembolic diseases.[141] The causes for the increased risk during lymph-node dissection could be due to potential intimal injuries, hematomas or postoperative

lymphoceles.[142] In the open surgery thromboembolic events could be due to the extra peritoneal approach.[143,144,145] Lymph-node dissection also leads to an increased risk of lymphocele formation, especially after open surgery.[146]

#### 2.2.4.2 Long-term complications

*Urinary incontinence*

Urinary incontinence after radical prostatectomy is a significant long-term complication that affects quality of life.[147] Incontinence rates vary a lot in the existing literature, in a review using the definition of continence as *no pad*, incontinence rates ranged from 4% to 31% with a mean value of 16%.[126] The large variation in incontinence depends on many different factors. Studies have shown that predictors of urinary incontinence in patients who underwent robot-assisted radical prostatectomy are patient age[148,149,150,151,152,153], severe lower urinary tract symptoms (LUTS)[151,154], comorbidities[150] and preoperative erectile dysfunction[149]. Other factors that have been discussed as predictors are prostate volume[155], obesity[156,157,158] and surgeon experience[159,160].

Different surgical aspects have been discussed to improve the recovery of urinary continence. In a study by Freire et al. bladder neck preservation was associated with improved continence rates at 4 months after surgery compared to bladder neck resection and reconstruction, however no difference was seen at one or two years of follow-up.[161] Also selective dorsal venous complex division[162], nerve-sparing technique[121,122] and posterior musculofascial reconstruction[163,164] as well as anterior restoration of the pelvic space[99,165] have been discussed as potential surgical aspects to reduce the risk of urinary incontinence after robot-assisted radical prostatectomy. Comparing surgical techniques, a cumulative analysis of five studies in a review by Ficarra et al. showed a statistically significant advantage in favour of robotic surgery compared to both open and laparoscopic surgery in terms of 12 months urinary continence recovery.[126] The absolute risk reduction was 3.8%.

*Erectile dysfunction*

The most common long-term complication after radical prostatectomy is erectile dysfunction. In a review of the literature the mean values of potency recovery was 70% at 12 months and 79% at 24 months after surgery.[127] However, erectile dysfunction is only a part of the impaired sexual health that affects many men after radical prostatectomy. There is also a significant loss in orgasmic function in many men which can consist of absence of orgasm (anorgasmia), painful orgasm (dysorgasmia)[166] and urine loss occurring during orgasm (climacturia)[167]. One cause that has been reported for dysorgasmia is bilateral sparing the tips of the seminal vesicles.[168] Sparing the tips of the seminal vesicles during nerve-sparing radical prostatectomy has been believed to cause less damage to the pelvic nerves as they are located about 3-10 mm from the nerves.[169] Impairment of the orgasmic function has been related to reduction in physical and emotional satisfaction which in turn may lead to sexually avoidant behaviour and disharmony in a relationship.[170]

The erectile dysfunction after radical prostatectomy is caused by damage of the autonomic nerves supplying the cavernosus which mediates the erection. With improving surgical technique it is today possible to preserve the neurovascular bundles which cover the surface of the prostate.[98] The extension of nerve-sparing has an impact on potency rates.[171] In a systematic review from Ficarra et al. bilateral preservation of the nerves was associated with a lower risk of erectile dysfunction after robot-assisted radical prostatectomy.[127] Intrafascial technique has also shown a significant improvement in potency rates.[172] Another aspect of the surgical technique in nerve-sparing is the level of the incision of the levator ani fascia that has been debated to play a role in the recovery of potency.[173]

The risk for erectile dysfunction is thought to depend on several other factors such as comorbidities[174] and preoperative potency status[149,171]. It has been shown that many men (30-70%) are already impotent before their surgery and that the rates increases with age.[175,176] Age in itself is also predictor for postoperative erectile dysfunction.[149,174] Conflicting results have been presented concerning the effect of obesity on potency outcomes.[129,177,178] The experience of the surgeon has been discussed as a predictor for potency outcomes, however in a study by Zorn et al. no difference could be seen between inexperienced and experienced surgeons.[160]

One can observe a large heterogeneity for the definition of potency which also can be an explanation for the variation in potency rates between different cohorts. The most common definition is *an erection sufficient for intercourse regardless of the use of phosphodiesterase type 5 inhibitors*. Many also use the SHIM score (Sexual Health Inventory for Men) which is more objective and reproducible. However, the cut-off value for what is considered normal has no consensus. A standardized classification has been proposed with SHIM 17 as a cut-off value.[179]

There are many surgical aspects apart from nerve-sparing that have been thought to influence the potency recovery after robot-assisted radical prostatectomy. A study comparing extraperitoneal to transperitoneal approach in robot-assisted radical prostatectomy where all patients were preoperatively potent and received bilateral nerve-sparing surgery, showed no differences after 12 months follow-up.[180] Many studies have evaluated thermal compared to athermal dissection of the neurovascular bundles as the classic nerve-sparing technique described by Walsh et al. was based on the idea that thermal dissection was harmful to the cavernous nerves.[97,181] Experiments on dogs supported this belief.[114] A meta analysis showed significant advantages in terms of early potency recovery in favour of athermal dissection.[127] However, conflicting results have been reported concerning longer follow-up in comparative studies.[182] These results should also be contrasted to those results of numerous robotic surgeons that have used monopolar and bipolar energy for the dissection of the nerves and have still had good results with respect to potency.[149,174] Today with the existing evidence, no definitive conclusion can be drawn concerning the use of energy during dissection of the cavernous nerves. Another aspect that has been debated is traction of the cavernous nerves

during nerve dissection that could lead to neuropraxia, however there is no strong evidence that it has any effect on potency outcomes.[171]

In a review comparing operation techniques the cumulative analysis showed significant advantages in terms of 12 months potency recovery after robot-assisted technique compared to open technique.[127] In contrast, Hu et al. reported significantly higher prevalence of erectile dysfunction after minimally invasive radical prostatectomy compared to open prostatectomy, however the results have been debated to be influenced by the learning curve for the minimally invasive technique.[183]

# 3 AIMS

The aims of this thesis were:

1. To evaluate the definition of postoperative urinary continence after radical prostatectomy using self reported urinary bother and urinary leakage.

2. To identify patient and tumour related factors that could predict incontinence after 12 months after radical prostatectomy.

3. To report the frequency of certain pre-specified short-term results and adverse events after both robot-assisted radical prostatectomy and retropubic radical prostatectomy, and to investigate potential differences between the two procedures.

4. To investigate the association of lymph-node dissection to postoperative morbidity and incidence of thromboembolic events, by comparing patients operated with retropubic radical prostatectomy or robot-assisted radical prostatectomy with or without lymph-node dissection.

# 4 MATERIAL AND METHODS

## 4.1 KS COHORT

A consecutive series of 1411 prostate cancer patients from Karolinska University Hospital underwent radical prostatectomy (open or robot-assisted) between January 2002 and December 2006. No exclusion criteria were set and only patients with follow-up longer than one year were included in the study. Data was collected prospectively on clinical stage, biopsy Gleason score, PSA and routine pathology reports provided data on prostate weight. Validated patient questionnaires assessed the functional outcomes postoperatively. The development of the questionnaires was based on previous experience from our cancer survivorship program and it was refined after in-depth interviews with patients who underwent radical prostatectomy.[184] Face-to-face validation ensured that the questions and answering alternatives were understood correctly. Informed consent was obtained from each included patient.

Urinary incontinence was evaluated with three different questions. The two first questions were included in one main questionnaire whereas the third question was included in a questionnaire that was sent out 12 months postoperatively to a subgroup of the cohort (541 of 1,179 patients). The main questionnaire also contained a question about urinary bother, to be able to evaluate the effect of postoperative incontinence. The main consecutive series of 1411 is referred to as cohort 1 while the subgroup of 541 men from cohort 1 is referred to as cohort 2. The questionnaires were collected by a neutral third party. The study was approved by the ethics committee.

**Urinary leakage questions:**

1) During the past six months how often did you change your protective pad during a typical day?

- Not applicable, I don't use any protective pad
- Less than 1 pad/day
- About 1 pad/day
- About 2-3 pads/day
- About 4-5 pads/day
- About 6 pads or more/day

2) During the past six months how much urine did you leak in the daytime?

- Not applicable, I don't leak urine in the daytime
- Little
- Moderate
- Much

3) Do you have urinary leakage?

- Never
- Leakage when coughing, sneezing or using pad during physical activity
- Pad used continuously but not always wet
- Pad used continuously and had to be changed because they are wet
- Continuous leakage and need to change pads continuously

**Urinary bother question:**

1) During the past six months, if you have had urinary leakage daytime and you would have to live with it the rest of your life, how would you find that?

- Not applicable – I don't have any leakage
- It wouldn't bother me at all
- It would bother me slightly
- It would bother me moderate
- It would bother me much

## 4.2 LAPPRO

LAPPRO (Laparoscopic Prostatectomy Robot Open) is a prospective, non-randomized, controlled trial with the aim to compare outcomes after retropubic radical prostatectomy to robot-assisted radical prostatectomy. Fourteen centres in Sweden included patients in the study, where seven centres performed the open approach and seven centres performed the robot-assisted approach, between September 1, 2008 and November 7, 2011. Geographical location decided what operation technique was to be used for the majority of the patients, not patient or surgeon preference. The primary endpoint for the LAPPRO study is urinary incontinence. The three studies included in this thesis with data from the LAPPRO study are sub studies to the main study which is not yet published. The study was approved by the Gothenburg regional ethical review board and the trial is registered in the Current Controlled Trials database (ISRCTN06393679).

Patients completed validated questionnaires preoperatively and at 3, 12 and 24 months postoperatively. The questionnaires were validated face-to-face in a clinical setting by experts and prostate cancer patients for mutual understanding and contained questions concerning the primary and secondary endpoints together with possible confounders and effect modifiers. Patient-reported data was prospectively collected by a neutral third party. Health-care professionals completed validated clinical record forms (CRF) before, during and 1.5-3, 12 and 24 months after surgery. The questionnaires and CRF:s were further tested in a pilot study (n=100) after which final revisions were made. A detailed description of the study design and procedure including the development of the CRF:s and questionnaires has previously been published.[185] All data was manually entered into a secured electronic database. To ensure quality assurance of the collected data approximately 1% of the data was re-entered in the database and cross checked. The recruiting sites were regularly monitored by two research nurses.

Inclusion criteria were tumour stage cT1, cT2 or cT3 (TNM Classification of Malignant Tumors)[27], no clinical signs of metastatic disease, PSA <20 ng/ml, age < 75 years, no previous malignancy, fitness for prostatectomy, informed consent and ability to read and write Swedish.

### 4.2.1 Predictors of urinary incontinence

The population for this sub study was all patients included in the LAPPRO study during the first 17 months, a total of 1529 patients. They had undergone their prostatectomy between September 1, 2008 and January 31, 2010 with a follow-up of 12 months. The focus of this

analysis was to find potential confounders for the primary endpoint, urinary incontinence. In order not to interfere with the results of the primary endpoint of the LAPPRO study the cohort for this paper was not divided into operating techniques. In the present study the inclusion criteria were fitness for prostatectomy, signed informed consent and ability to read and write Swedish.

The primary endpoint, urinary incontinence, was evaluated with the following question: "How often do you change pad, diaper or sanitary aid during a typical day (24 h)? with response alternatives "Not applicable, I don't use any protective pad; Less than once/day; About 2-3 times/day; About 4-5 times/day; About 6 times or more/day". Incontinence was defined as the change of one pad or more per day. This definition was predefined in the study protocol of LAPPRO.

### 4.2.2 Short-term complications

The patient-reported adverse events were measured three months postoperatively. To avoid including results from the learning curve only patients operated by a surgeon with experience from at least 100 operations as primary surgeon were included in the present study.

To evaluate adverse events we asked at 3 months; "Have you sought medical care for any of the following disorders after surgery?" with 22 specified disorders as answering categories, followed by "Yes" and "No". We used the same question to calculate the probability of seeking health care by dichotomizing between "never" and "once or more". Readmission was evaluated with the following question at 3 months; "Have you been readmitted to the hospital after the surgery?" with answer categories "Yes" or "No". After the patient could specify in free writing the cause for readmission. These answers were then classified into groups in a blinded fashion.

### 4.2.3 Complications after lymph-node dissection

In this paper the inclusion criteria were the same as for the whole LAPPRO study. The time point for measuring the adverse events was three months postoperatively. Either limited or extended lymph-node dissection was preformed and extended was done in most patient with high risk disease according to the D'Amico tables.[186] During limited dissection the obturator nodes were removed and during extended dissection also the nodes overlying the external iliac artery and vein, nodes in the obturator fossa located cranial and caudal to the obturator nerve and nodes medial and (at some centres) lateral to the internal iliac artery were removed.

Postoperative care consisted of early ambulation on the evening of the operation, stockings and low molecular weight heparin. Heparin were administered in the dose of 5,000 U for either 5-7 days or 10 days or more depending on centre preference and the patients risk for thromboembolic events (previous thrombosis, obesity and smoking).

## 4.3 STATISTICAL ANALYSIS

### 4.3.1 KS cohort

To calculate the proportion of patients with moderate or much bother from urinary leakage a statistical analysis was done. Comparison between groups were done by calculating relative risk, defined as the ratio of proportions, and it was estimated according to the log binomial regression model, presented with the 95% confidence interval. Missing data on one or more questions under consideration were excluded from each respective calculation. SAS®, version 9.2 was used for all calculations.

### 4.3.2 LAPPRO

#### 4.3.2.1 Predictors for urinary incontinence

Relative risk was used as effect measure for the analysis of the association between the preoperative factors and postoperative urinary incontinence. The relative risk was defined as the ratio of proportions, estimated according to the log binomial regression model and presented with 95% confidence intervals. Bivariate regression analysis with age added was done to calculate the age-adjusted relative risk. The estimates for the exponential curve describing the increased probability of leakage with age were obtained in the log binomial model of age at surgery and urinary incontinence. In the same figure we also present a step function showing the proportion in each age group changing their pad at least once a day. The figure was created in the free software R. Individuals with missing data were excluded in each respective calculation. For the statistical analysis the data were first entered into EpiData 3.1 and then exported to SAS 9.2 (SAS Institute Incorporated, Cary, NC, USA).

#### 4.3.2.2 Short-term complications

For the main LAPPRO study a power calculation was done to detect a difference on the primary endpoint; urinary leakage at 12 months (significance level $p = 0.05$, 80% power, two-sided test). Concerning the short-term results, to reduce the risk of significant effects that arise by chance, all the outcomes were defined before the start of the study. However, no adjustment was made for multiple testing and can be seen as a limitation of the study.

The results are presented unadjusted and after three different adjustments (A, B, and C). Adjustment A is the use of stringent confounders. Adjustment B refers to all factors in A with the addition of tumour-related factors that are confounders, but may also be mediating factors, since they can affect the surgery differently in the respective surgical groups. Adjustment C refers to A and B with the addition of lymph-node dissection, which should also be considered a confounder, but may also be a mediating factor due to differences in technique in the respective surgical groups.

Fifty data sets were made and imputation was performed for variables considered possible confounders in the statistical freeware R utilizing Multiple Imputations by Chained Equations (MICE).[187] Missing information on prostate weight was imputed by making a linear

regression model of postoperative prostate weight, predicted by preoperative prostate volume from men who had information on both variables. For each endpoint, possible confounders were selected from 20 probable risk factors by choosing the variables that was statistically significantly associated ($p<0.20$). Relative risks were calculated as the proportion of patients from the robot-assisted group divided by patients from the open group. Log binomial regression models provided 95% confidence intervals for the unadjusted relative risks. We also calculated odds ratios, modelled by logistic regression, with the adjusted ratios calculated as a pooled estimate from the 50 imputed datasets. The statistical analysis was performed using SAS 9.3 for Windows (SAS Institute Incorporated, Cary, NC, USA).

#### 4.3.2.3 Complications after lymph-node dissection

Log linear regression was used to calculate relative risks. Successive formation of logistic regression models (forward selection with the inclusion criterion $p <0.10$) was used to identify those of the possible confounders that were most strongly associated with the outcome of DVT and/or PE. The identified predictors were used to adjust the association between operation technique with or without LND, and DVT and/or PE. To perform the statistical analysis data were entered in EpiData 3.1 and exported to SAS 9.2 (SAS Institute Incorporated, Cary, NC, USA).

# 5 RESULTS

## 5.1 URINARY INCONTINENCE

### 5.1.1 Bother from urinary incontinence

#### 5.1.1.1 Patient characteristics

Questionnaires were received from 1,288 patients (91%), and 1,179 among them had a follow-up of one year or more. Open radical prostatectomy was done in 411 patients, including 6 patients in cohort 2 and robot-assisted radical prostatectomy was done in 768 patients, including 535 patients in cohort 2. Median age at surgery was 63 (range 37-78) and median follow-up was 2.2 years (range 1-5), however in cohort 2 the median follow-up was 1.7 (range 1-4). Concerning clinical characteristics median PSA was 6.9 (range 0.4-117) and clinical stage was T1 702 (60%), T2 422 (36%) and T3 55 (5%).

#### 5.1.1.2 Pad use and urinary leakage in correlation to urinary bother

The results show that 775 (67%) out of 1,163 patients reported no pad use while 123 (11%) reported less than 1 pad and 143 (12%) reported 1 pad used per day. When evaluating urinary bother correlated to how many pads the patient used the results showed that patients who used security pads had a more than 5 times higher risk for moderate or much urinary bother compared to men using no pads (RR 5.2, CI 95% 3.5–7.7) (Table 3). With increasing number of pads we could see an increasing risk for urinary bother (Figure 7). The same trend was noted for all three of the urinary leakage questions.

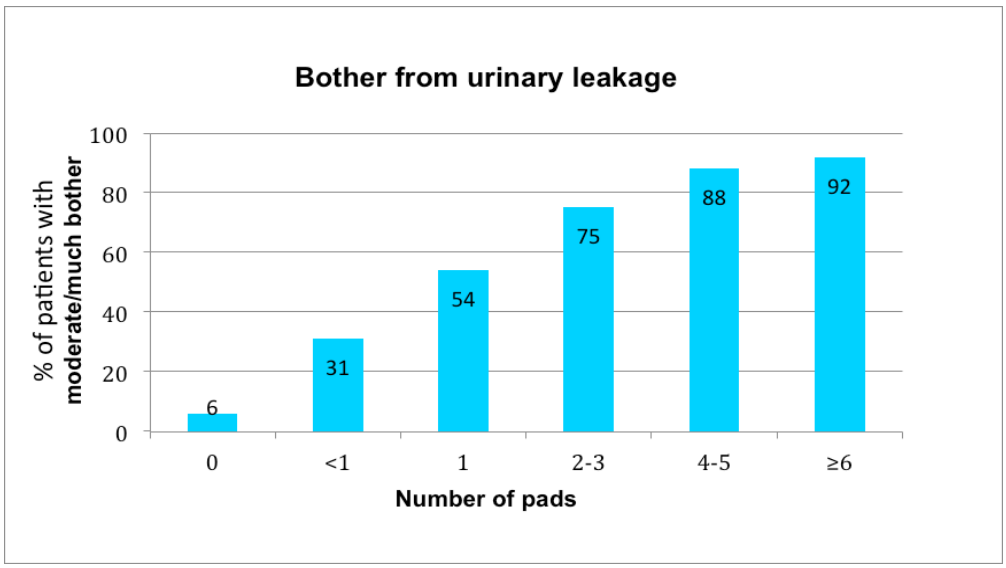
| Bother from urinary leakage 12 months after radical prostatectomy | | | | | | |
|---|---|---|---|---|---|---|
| **a) PADs** | **N/A** | **No** | **Little** | **Moderate** | **Much** | **RR moderate/much bother (95% CI)** |
| ≥6 | 0/12 | 0/12 | 1/12 | 3/12 | 8/12 | 15.4 (11.1-21.4) |
| 4-5 | 0/25 | 1/25 | 2/25 | 7/25 | 15/25 | 14.8 (10.8-20.3) |
| 2-3 | 0/85 | 3/85 | 18/85 | 25/85 | 39/85 | 12.7 (9.4-17.2) |
| 1 | 2/143 | 13/143 | 51/143 | 39/143 | 38/143 | 9.1 (6.6-12.5) |
| <1 | 8/123 | 23/123 | 54/123 | 23/123 | 15/123 | 5.2 (3.5-7.7) |
| 0 | 542/775 | 88/775 | 99/775 | 23/775 | 23/775 | 1.0 reference |
| **b) Urinary leakage** | | | | | | |
| Much | 0/42 | 1/42 | 2/42 | 5/42 | 34/42 | 70.8 (33.8-148.6) |
| Moderate | 0/80 | 1/80 | 12/80 | 25/80 | 42/80 | 63.9 (30.4-134.2) |
| Little | 49/504 | 111/504 | 198/504 | 89/504 | 57/504 | 22.0 (10.5-46.7) |
| No leakage | 499/534 | 15/534 | 13/534 | 2/534 | 5/534 | 1.0 reference |
| **c) Urinary leakage** | | | | | | |
| Continuous pad change | 2/12 | 0/12 | 2/12 | 2/12 | 6/12 | 27.5 (10.6-71.3) |
| Wet pad | 2/16 | 0/16 | 3/16 | 2/16 | 9/16 | 28.3 (11.2-71.6) |
| Safety pad | 4/78 | 4/78 | 28/78 | 23/78 | 19/78 | 22.2 (9.1-54.0) |
| Pad at physical activity | 79/214 | 43/214 | 60/214 | 19/214 | 13/214 | 6.1 (2.4-15.5) |
| Never urinary leakage | 165/206 | 20/206 | 16/206 | 3/206 | 2/206 | 1.0 reference |

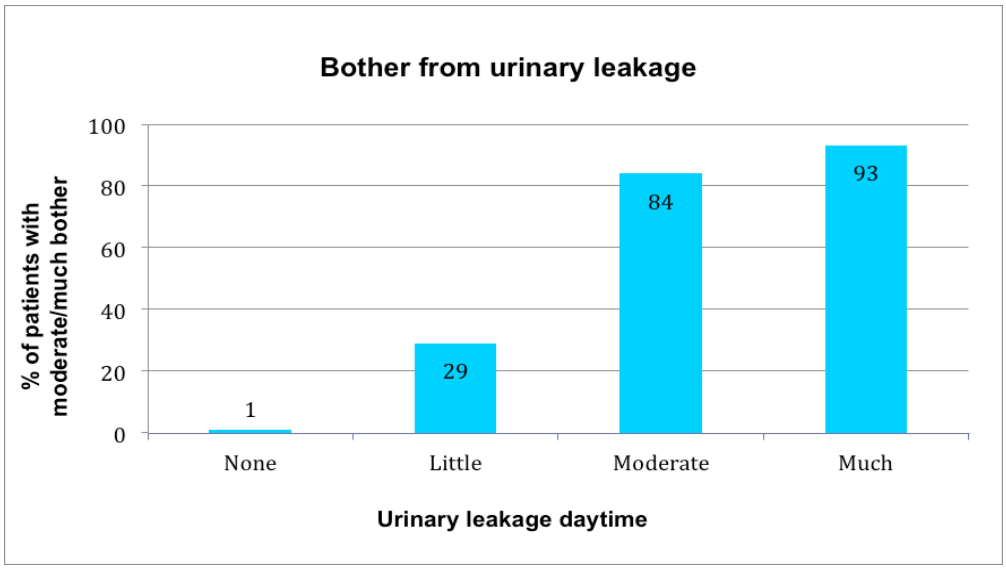
For exact wording of the questions see material and methods

Urinary leakage question a) and b) survivors answered 2.2 years postoperatively (range 1-5)

Urinary leakage question c) survivors answered 1 year postoperatively

*Table 3. Bother from urinary leakage 12 months after radical prostatectomy.*



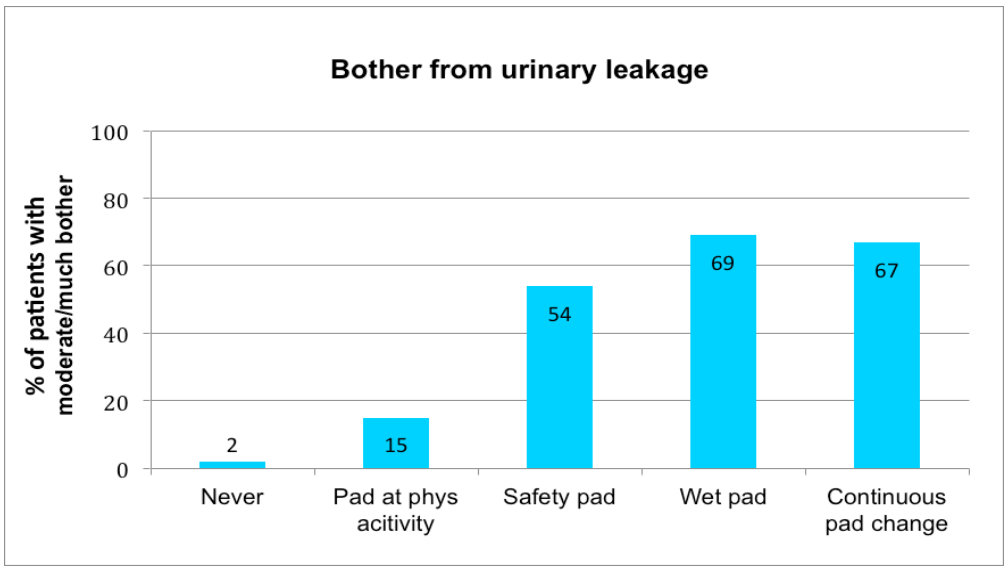




*Figure 7. Bother from urinary leakage 12 months after radical prostatectomy measured with three different questions for urinary leakage.*

### 5.1.1.3 Cross-tabulation

To further evaluate the rate of urinary incontinence after radical prostatectomy we compared the answers for the urinary leakage questions using a cross-tabulation. The results show that there is a wide variety in how men report the use of pads despite the same answer for urinary leakage. Of 776 men reporting no pad use, 514 (66%) reported no leakage and 255 (33%) reported little urinary leakage. Men that reported little urinary leakage also reported very different answers on pad requirements, 255 (51%) used 0, 101 (20%) used fewer than 1 and 104 (21%) used 1 pad per day (Table 4).

**Cross tabulation of urinary leakage and pad requirement**

| | Daily pad requirement | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 [a] | < 1 [b] | 1 | 2-3 | 4-5 | ≥6 | Not stated | Total |
| **Urinary leakage daytime past 6 months** | | | | | | | | |
| No leakage | 514 | 14 | 5 | 0 | 0 | 0 | 3 | 536 |
| Little | 255 | 101 | 104 | 37 | 3 | 3 | 3 | 506 |
| Moderate | 3 | 8 | 31 | 31 | 5 | 2 | 0 | 80 |
| Much | 0 | 0 | 1 | 17 | 17 | 7 | 0 | 42 |
| Not stated | 4 | 0 | 2 | 0 | 0 | 0 | 9 | 15 |
| Total | 776 | 123 | 143 | 85 | 25 | 12 | 15 | 1179 |
| **Urinary leakage** | | | | | | | | |
| Never | 201 | 2 | 1 | 3 | 0 | 0 | 3 | 210 |
| Occational pad-use during physical activity | 148 | 43 | 18 | 4 | 0 | 0 | 2 | 215 |
| Safety pad | 6 | 17 | 38 | 14 | 3 | 0 | 0 | 78 |
| Wet pad | 2 | 2 | 5 | 5 | 2 | 0 | 0 | 16 |
| Continues leakage | 2 | 0 | 4 | 3 | 1 | 2 | 0 | 12 |
| Not stated | 5 | 3 | 2 | 0 | 0 | 0 | 0 | 10 |
| Total | 364 | 67 | 68 | 29 | 6 | 2 | 5 | 541 |

[a] Not applicable, I don't use any protective pad

[b] Less than 1 pad/day

*Table 4. Cross tabulation of urinary leakage and pad requirement.*

### 5.1.2 Predictors of urinary incontinence

#### 5.1.2.1 Patient characteristics

The response rate was 89% consisting of 1360 men with a follow-up of 12 months. Patient characteristics showed median age at surgery; 64 years (range 41 to 77), clinical stage; T1 771 (58%), T2 490 (37%), T3 32 (2%) and median preoperative PSA of 6.4 (range 0.1 to 99.0).

#### 5.1.2.2 Age and preoperative urinary leakage as predictors for postoperative urinary incontinence

The results show that patient age at surgery and preoperative urinary leakage were significantly associated with 12-months postoperative incontinence. Comparing men in the oldest age group (70 to 80) with 38% incontinence at 12 months postoperatively to the youngest age group (40 to 54) with 13% incontinence, the relative risk for incontinence was 3.0 (95% CI 1.8-5.0) (Table 5). The risk for incontinence increases with age in a non-linear way and can be described with an exponential function (Figure 8).

Among men having urinary leakage before their prostate cancer diagnosis 40% (27/67) were incontinent 12 months postoperatively compared to 22% (258/1149) in the group without urinary leakage before their prostate cancer diagnosis resulting in an age-adjusted relative risk of 1.8 (95% CI 1.3-2.4) (Table 6).

| Incontinence 12 months postoperatively | Groups | No. incontinent/Total No. (%) | RR (95% CI) | Age-adjusted RR (95% CI) |
|---|---|---|---|---|
| **Age at surgery** | **40-54** | 15/118 (13%) | reference | |
| | **55-59** | 37/271 (14%) | 1.1 (0.6-1.9) | |
| | **60-64** | 105/436 (24%) | 1.9 (1.1-3.1)* | |
| | **65-69** | 112/388 (29%) | 2.3 (1.4-3.7)* | |
| | **70-80** | 55/145 (38%) | 3.0 (1.8-5.0)* | |
| **Educational level** | **> 13** | 95/464 (20%) | reference | reference |
| **(years in school)** | **12-13** | 46/153 (30%) | 1.5 (1.1-2.0) | 1.4 (1.0-1.8) |
| | **10-12** | 79/353 (22%) | 1.1 (0.8-1.4) | 1.1 (0.9-1.5) |
| | **≤ 9** | 63/234 (27%) | 1.3 (1.0-1.7) | 1.2 (0.9-1.6) |
| **Employment status** | **Employed** | 123/671 (18%) | reference | reference |
| | **Retired** | 138/458 (30%) | 1.6 (1.3-2.0)* | 1.0 (0.7-1.3) |
| | **Sick leave** | 14/44 (32%) | 1.7 (1.1-2.8)* | 1.7 (1.1-2.7)* |
| | **Unemployed** | 3/11 (27%) | 1.5 (0.6-4.0) | 1.4 (0.5-3.7) |
| **BMI** | **18.5-25** | 109/439 (25%) | reference | reference |
| | **25-30** | 135/626 (22%) | 0.9 (0.7-1.1) | 0.9 (0.7-1.1) |
| | **>30** | 39/139 (28%) | 1.1 (0.8-1.5) | 1.2 (0.9-1.6) |
| **Heredity** | **No** | 251/1006 (25%) | reference | reference |
| | **Yes** | 73/352 (21%) | 0.8 (0.7-1.0) | 0.9 (0.7-1.2) |
| **Prostate weight** | **0-20** | 2/8 (25%) | 1.5 (0.4-5.0) | 0.6 (0.2-1.9) |
| **(gram)** | **20-40** | 65/380 (17%) | reference | reference |
| | **40-60** | 125/435 (29%) | 1.7 (1.3-2.2)* | 0.9 (0.3-2.9) |
| | **60-80** | 35/133 (26%) | 1.5 (1.1-2.2)* | 0.8 (0.2-2.5) |
| | **>80** | 81/340 (24%) | 1.4 (1.0-1.9)* | 0.7 (0.2-2.3) |
| **Preop PSA** | **<5** | 99/412 (24%) | reference | reference |
| | **5-6.8** | 62/326 (19%) | 0.8 (0.6-1.0) | 0.8 (0.6-1.0) |
| | **6.9-9.7** | 68/292 (23%) | 1.0 (0.7-1.3) | 0.9 (0.7-1.2) |
| | **>9.7** | 90/301 (30%) | 1.2 (1.0-1.6) | 1.1 (0.8-1.4) |
| **T-stage** | **T1** | 159/771 (21%) | reference | reference |
| | **T2** | 138/489 (28%) | 1.4 (1.1-1.7)* | 1.2 (1.0-1.5)* |
| | **T3** | 9/31 (29%) | 1.4 (0.8-2.5) | 1.3 (0.7-2.2) |
| **Gleason score, preop** | **≤6** | 196/871 (23%) | reference | reference |
| | **3+4** | 69/297 (23%) | 1.0 (0.8-1.3) | 1.0 (0.8-1.2) |
| | **4+3** | 30/96 (31%) | 1.4 (1.0-1.9)* | 1.2 (0.9-1.7) |
| | **≥8** | 29/94 (31%) | 1.4 (1.0-1.9) | 1.3 (0.9-1.7) |

*= a statistically significant association on a 95% confidence level

*Table 5. Effect of patient and tumour-related factors on urinary incontinence after radical prostatectomy 12 months postoperatively*

### 5.1.2.3 Other factors

Men previously operated on for inguinal hernia had a statistically significant increased age-adjusted relative risk of 1.4 (95% CI 1.2-1.8) for incontinence 12 months postoperatively (p = 0.0012). However, when doing a multivariable regression analysis and additionally adjusting for preoperative urinary leakage the relative risk was diminished, 1.0 (95% CI 0.8-1.4). Presence of kidney disease, depression and mental disorders also showed a significant increased age-adjusted relative risk for 12 months postoperative incontinence, however these groups were small (Table 6). We further evaluated 36 factors including BMI, previous TURP and factors concerning clinical data, comorbidity and previous surgery and found no statistically significant association to postoperative incontinence.

| Incontinence 12 months postoperatively | Groups | No. incontinent/Total No. (%) | RR (95% CI) | Age-adjusted RR (95% CI) |
|---|---|---|---|---|
| **Neurological disease** | **No** | 283/1204 (24%) | reference | reference |
| | **Yes** | 4/14 (29%) | 1.2 (0.5-2.8) | 1.0 (0.5-2.3) |
| **Diabetes** | **No** | 261/1134 (23%) | reference | reference |
| | **Yes** | 25/83 (30%) | 1.3 (0.9-1.8) | 1.2 (0.8-1.6) |
| **Hypertension** | **No** | 187/826 (23%) | reference | reference |
| | **Yes** | 101/390 (26%) | 1.1 (0.9-1.4) | 1.0 (0.8-1.3) |
| **Heart failure** | **No** | 286/927 (24%) | reference | reference |
| | **Yes** | 1/4 (25%) | 1.1 (0.2-5.8) | 0.9 (0.2-4.7) |
| **Angina pectoris** | **No** | 277/1184 (23%) | reference | reference |
| | **Yes** | 8/32 (25%) | 1.1 (0.6-2.0) | 0.9 (0.5-1.7) |
| **Respiratory disease** | **No** | 277/1190 (23%) | reference | reference |
| | **Yes** | 10/25 (40%) | 1.7 (1.1-2.8)* | 1.4 (0.9-2.3) |
| **Gastrointestinal disease** | **No** | 282/1194 (24%) | reference | reference |
| | **Yes** | 5/21 (24%) | 1.0 (0.5-2.2) | 1.0 (0.5-2.1) |
| **Kidney disease** | **No** | 282/1211 (23%) | reference | reference |
| | **Yes** | 5/9 (56%) | 2.4 (1.3-4.3)* | 2.4 (1.4-4.1)* |
| **Depression** | **No** | 277/1195 (23%) | reference | reference |
| | **Yes** | 10/23 (43%) | 1.9 (1.2-3.0)* | 1.7 (1.1-2.7)* |
| **Mental disorders** | **No** | 280/1200 (23%) | reference | reference |
| | **Yes** | 7/19 (37%) | 1.6 (0.9-2.9) | 1.8 (1.0-3.0)* |
| **Inguinal hernia** | **No** | 256/1109 (23%) | reference | reference |
| | **Yes** | 28/76 (27%) | 1.2 (0.8-1.6) | 1.0 (0.8-1.5) |
| **Previous operation for inguinal hernia** | **No** | 206/973 (21%) | reference | reference |
| | **Yes** | 70/214 (33%) | 1.5 (1.2-1.9)*[a] | 1.4 (1.2-1.8)*[b] |
| **Previous TURP** | **No** | 260/1147 (23%) | reference | reference |
| | **Yes** | 9/28 (32%) | 1.4 (0.8-2.5) | 1.2 (0.7-2.0) |
| **Preop urinary leakage** | **No** | 258/1149 (22%) | reference | reference |
| | **Yes** | 27/67 (40%) | 1.8 (1.3-2.4)*[c] | 1.8 (1.3-2.4)*[d] |

*= a statistically significant association on a 95% confidence level, a P value= 0.0003, b P-value= 0.0012, c P-value= 0.0008, d P-value= 0.0002

*Table 6. Effect of comorbidities and previous surgery on urinary incontinence after radical prostatectomy 12 months postoperatively*

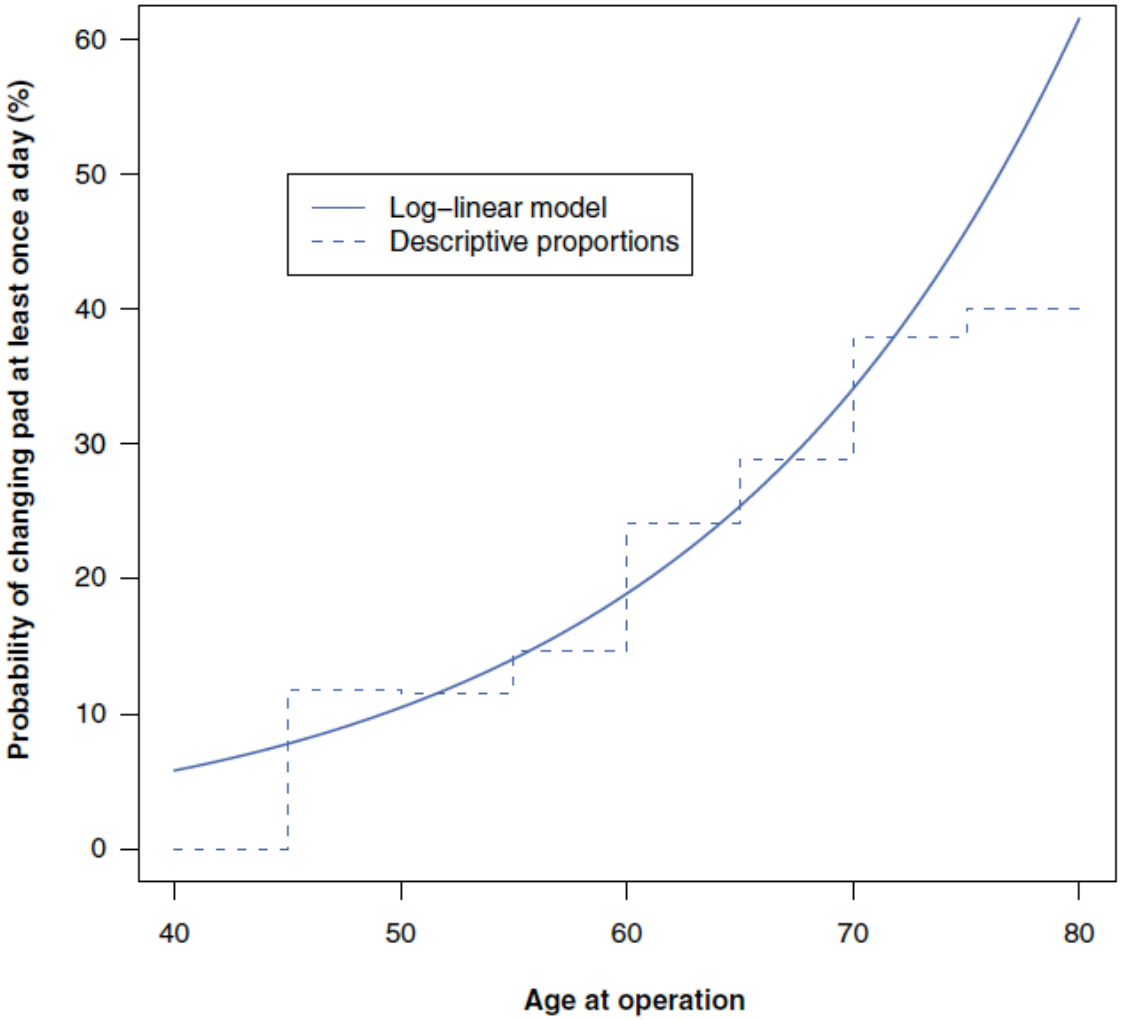



*Figure 8. Likelihood of 12 months postoperative urinary incontinence with increasing age at surgery*

## 5.2 COMPLICATIONS AFTER RADICAL PROSTATECTOMY

### 5.2.1 Short-term complications

The LAPPRO study collected in total data from 4003 men. For this study 1378 men were excluded; 980 because their surgeon had preformed less than 100 operations and 398 for not meeting inclusion criteria's and other causes, as stated in the flow chart (Figure 9). Questionnaires were received from 2506 (95%) men and of these 745 were operated by open surgery and 1761 by robot-assisted surgery.

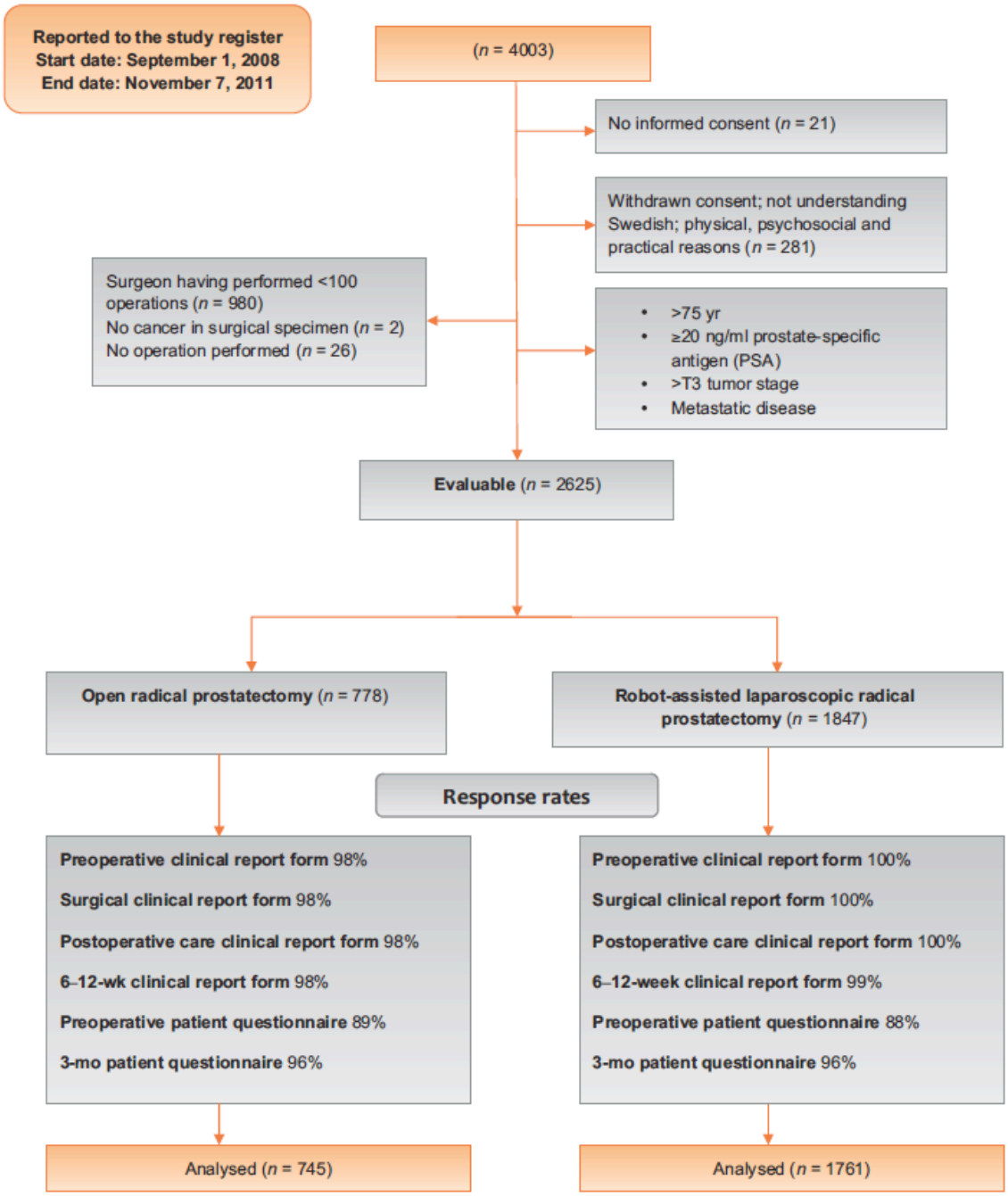



*Figure 9. Flow chart for the analysis of short-term results of the LAPPRO trial. Numbers may not total correctly, because the same individual may have fulfilled more than one exclusion criteria.*

#### 5.2.1.1 Patient characteristics

Men operated by robot-assisted surgery had significantly higher level of education, higher ASA score, higher clinical tumour stage and total length of cancer in their prostate biopsy compared to men operated by open surgery. Nerve-sparing surgery was more frequently performed during robot-assisted surgery, also after adjustment for tumour characteristics. Concerning lymph-node dissection, limited lymph-node dissection was done significantly more during open procedures whereas extended lymph-node dissection was more common in the robotic group. There was no statistically significant difference between the groups concerning comorbidities. When evaluating predictors for patient-reported readmission to hospital in our data we found that the factors that significantly increased the risk for readmission were PSA level, lymph-node dissection, prostate weight, clinical tumour stage, tumour stage of prostatectomy specimen, Gleason score on pathology specimen and a history of mental disorder.

#### 5.2.1.2 Parameters during hospital stay

Robot-assisted surgery was associated with significantly less perioperative bleeding (185 vs. 683 ml, $p < 0.001$) and shorter hospital stay (3.3 vs. 4.1 days, $p < 0.001$) compared to open surgery. However, the operation time was significantly shorter with the open technique (103 vs. 175 min, $p < 0.001$). Reoperation during initial hospital stay was significantly more frequent after open surgery (1.6 vs. 0.7 %) which gives an odds ratio of 0.31 (CI 95% 0.11-0.90) when adjusting for tumour factors and lymph-node dissection. No patient died during hospital stay (Table 7). Three patients died within three months of surgery in the robot-assisted group and no one in the open group which resulted in no statistically significant difference, $p = 0.56$.

| Variable | Open surgery [b] Mean (range) Median (IQR) | Robot-assisted surgery [c] Mean (range) Median (IQR) | *p* value |
|---|---|---|---|
| Perioperative bleeding (ml) | 683 (50–8000)<br>550 (350–800) | 185 (0–5200)<br>100 (50–200) | <0.001 |
| OR [d] time (min) | 103 (40–428)<br>89 (74–125) | 175 (45–575)<br>168 (144–201) | <0.001 |
| Time in recovery unit (h) | 6.7 (1–90)<br>4.0 (2.8–7.0) | 4.5 (0–45)<br>4.0 (3.0–5.0) | 0.054 |
| Length of hospital stay (d) | 4.1 (1–17)<br>4 (3–5) | 3.3 (2–53)<br>3 (2–4) | <0.001 |

| | Open surgery, [b] *n* (%) | Robot-assisted surgery, [c] *n* (%) | Unadjusted RR (CI 95%) Unadjusted OR (CI 95%) | Adjusted for nontumour confounders [d,e] OR (CI 95%) | Adjusted for A + tumour-specific confounders [f] OR (CI 95%) | Adjusted for A + B + lymph node dissection [g] OR (CI 95%) |
|---|---|---|---|---|---|---|
| Reoperation during initial hospital stay | 8 (1.6) | 13 (0.7) | 0.47 (0.20–1.13)<br>0.47 (0.19–1.13) | 0.46 (0.19–1.14) | 0.32 (0.12–0.90) | 0.31 (0.11–0.90) |
| Mortality during hospital stay | 0 (0) | 0 (0) | NA | NA | NA | NA |

OR time = operating room time "skin to skin"; IQR = interquartile range; RR = relative risk; CI = confidence interval; NA = not applicable.
[a] Total may not add up to 100 due to rounding of percentages.
[b] Denotes retropubic radical prostatectomy.
[c] Denotes robot-assisted laparoscopic radical prostatectomy.
[d] Possible confounders to be used in adjustments for each outcome were selected as variables significantly associated (*p* value <0.20) with the specific outcome.
[e] Adjustment A: employment status preoperatively, postoperative irradiation, previous operation for inguinal hernia, previous transurethral resection of the prostate (TURP), pulmonary disease, mental disorder, or kidney disease.
[f] Adjustment B: Adjustment A + tumour factors (preoperative prostate-specific antigen level, clinical tumour stage, tumour stage of prostatectomy specimen, Gleason score on biopsy cores, Gleason score pathology on specimen).
[g] Adjustment C: Adjustment A + B + lymph node dissection.

*Table 7. Comparison between open surgery and robot-assisted surgery concerning parameters during hospital stay* [a]

#### 5.2.1.3 Patient-reported adverse events and readmissions three months after surgery

Men operated with open technique were more likely to seek health care compared to men operated with robotic technique (p = 0.03) within three months after surgery. Specifically, it was significantly more common to seek health care for cardiovascular reasons in the open group after adjusting for non-tumour and tumour-specific confounders, OR 0.63 (CI 95% 0.42-0.94). The two cardiovascular diseases that caused the difference were pulmonary embolism (0.8 vs. 0.3 %) and deep venous thrombosis (1.9 vs. 0.2 %). Psychological reasons for seeking health care was significantly more frequent in the open group, with OR 0.72 (CI 95% 0.53-0.96) after adjusting for non-tumour and tumour specific confounders (Table 8). There was no statistically significant difference in readmission rates three months after surgery between the operating techniques (Table 9).

| Adverse event | Open surgery, [b] *n* (%) | Robot-assisted surgery, [c] *n* (%) | Unadjusted RR (CI 95%) Unadjusted OR (CI 95%) | Adjusted for nontumour confounders [d,e] OR (CI 95%) | Adjusted for A + tumour-specific confounders [f] OR (CI 95%) | Adjusted for A + B + lymph node dissection [g] OR (CI 95%) |
|---|---|---|---|---|---|---|
| Infection | 121 (16.4) | 309 (17.6) | 1.08 (0.89–1.31)<br>1.09 (0.87–1.38) | 1.03 (0.81–1.32) | 0.91 (0.70–1.18) | 0.90 (0.69–1.18) |
| Infection in the operation wound | 42 (5.6) | 59 (3.3) | – | – | – | – |
| Pneumonia | 5 (0.7) | 8 (0.5) | – | – | – | – |
| Urinary tract infection | 89 (11.9) | 262 (14.8) | – | – | – | – |
| Cardiovascular | 58 (7.9) | 101 (5.8) | 0.74 (0.54–1.01)<br>0.72 (0.52–1.01) | 0.69 (0.47–1.00) | 0.63 (0.42–0.94) | 0.65 (0.43–1.00) |
| Pulmonary embolism | 6 (0.8) | 5 (0.3) | – | – | – | – |
| Hypertension | 34 (4.6) | 70 (4.0) | – | – | – | – |
| Acute myocardial infarction | 1 (0.1) | 2 (0.1) | – | – | – | – |
| Arrhythmia or other heart diseases | 12 (1.6) | 24 (1.4) | – | – | – | – |
| Deep venous thrombosis | 14 (1.9) | 4 (0.2) | – | – | – | – |
| Stroke | 0 (0.0) | 0 (0.0) | – | – | – | – |
| Surgical | 187 (25.2) | 392 (22.3) | 0.88 (0.76–1.03)<br>0.85 (0.70–1.04) | 0.84 (0.67–1.04) | 0.81 (0.64–1.03) | 0.85 (0.66–1.08) |
| Pain in the operation wound | 49 (6.6) | 42 (2.4) | – | – | – | – |
| Pain in the lower abdomen | 58 (7.8) | 149 (8.4) | – | – | – | – |
| Pain in the upper abdomen | 20 (2.7) | 57 (3.2) | – | – | – | – |
| Bleeding from the operation wound | 37 (5.0) | 46 (2.6) | – | – | – | – |
| Bleeding from the urinary tract | 66 (8.8) | 162 (9.2) | – | – | – | – |
| Inguinal hernia | 14 (1.9) | 33 (1.9) | – | – | – | – |
| Catheter blockage | 58 (7.8) | 100 (5.7) | – | – | – | – |
| Gastrointestinal | 138 (18.7) | 264 (15.1) | 0.81 (0.67–0.97)<br>0.77 (0.62–0.97) | 0.78 (0.61–1.01) | 0.76 (0.60–1.01) | 0.77 (0.58–1.03) |
| Nausea | 17 (2.3) | 35 (2.0) | – | – | – | – |
| Impaired appetite | 37 (5.0) | 64 (3.6) | – | – | – | – |
| Loose or frequent stools | 48 (6.4) | 99 (5.6) | – | – | – | – |
| Constipation | 84 (11.2) | 138 (7.8) | – | – | – | – |
| Psychological | 122 (16.6) | 228 (13.1) | 0.79 (0.64–0.97)<br>0.76 (0.60–0.96) | 0.81 (0.62–1.06) | 0.72 (0.53–0.96) | 0.78 (0.58–1.06) |
| Depressed mood | 92 (12.3) | 156 (8.8) | – | – | – | – |
| Worry | 94 (12.6) | 187 (10.6) | – | – | – | – |

OR = odds ratio; RR = relative risk; CI = confidence interval.
[a] Total may not add up to 100 due to rounding of percentages.
[b] Denotes retropubic radical prostatectomy.
[c] Denotes robot-assisted laparoscopic radical prostatectomy.
[d] Possible confounders to be used in adjustments for each outcome were selected as variables significantly associated ( $p$ value <0.20) with the specific outcome.
[e] Adjustment A. Readmission adjusted for: employment status preoperatively, International Prostate Symptom Score (IPSS), neurologic disease, mental disorder, kidney disease, and prostate weight. Infection adjusted for: previous transurethral resection of the prostate (TURP), IPSS, cardiovascular disease, pulmonary disease, neurologic disease, mental disorder, and prostate weight. Cardiovascular adjusted for: age at surgery, educational level, employment status preoperatively, body mass index (BMI), IPSS, diabetes, cardiovascular disease, pulmonary disease, mental disorder, prostate weight. Surgical adjusted for: employment status preoperatively, BMI, IPSS score, IPSS, cardiovascular disease, pulmonary disease, mental disorder, kidney disease, and prostate weight. Gastrointestinal adjusted for: age at surgery, educational level, employment status preoperatively, BMI, postoperative irradiation, coronary bypass surgery, smoking, IPSS, diabetes, cardiovascular disease, pulmonary disease, mental disorder, and prostate weight. Psychological adjusted for: age at surgery, educational level, employment status preoperatively, physical exercise, postoperative irradiation, coronary bypass surgery, smoking, IPSS, mental disorder, and prostate weight.
[f] Adjustment B: Adjustment A + tumour factors (preoperative prostate-specific antigen level, clinical tumour stage, tumour stage of prostatectomy specimen, Gleason score on biopsy cores, and Gleason score pathology on specimen).
[g] Adjustment C: Adjustment A + B + lymph node dissection.

*Table 8. Comparison between open and robot-assisted surgery concerning patient-reported adverse events three months after surgery* [a]

| Readmission and readmission causes | Open surgery, [b] *n* (%) | Robot-assisted surgery, [c] *n* (%) | Unadjusted RR (CI 95%) Unadjusted OR (CI 95%) | Adjusted for nontumour confounders [d,e] OR (CI 95%) | Adjusted for A + tumour-specific confounders [f] OR (CI 95%) | Adjusted for A + B + lymph node dissection [g] OR (CI 95%) |
|---|---|---|---|---|---|---|
| Readmission | 57 (7.7) | 163 (9.3) | 1.21 (0.91–1.62)<br>1.23 (0.90–1.69) | 1.26 (0.89–1.78) | 1.21 (0.83–1.77) | 1.39 (0.94–2.06) |
| Infection | 10 (1.3) | 37 (2.0) | 1.56 (0.78–3.12)<br>1.57 (0.78–3.17) | 1.61 (0.75–3.43) | 1.44 (0.64–3.21) | 1.68 (0.73–3.85) |
| UTI | 7 (0.9) | 21 (1.1) | – | – | – | – |
| Deep infections | 2 (0.3) | 7 (0.4) | – | – | – | – |
| Sepsis | 0 (0.0) | 7 (0.4) | – | – | – | – |
| Wound infection | 1 (0.1) | 2 (0.1) | – | – | – | – |
| Cardiovascular | 9 (1.2) | 5 (0.3) | 0.23 (0.08–0.70)<br>0.23 (0.08–0.69) | 0.32 (0.09–1.16) | 0.28 (0.07–1.09) | 0.32 (0.08–1.27) |
| Pulmonary embolism | 5 (0.6) | 3 (0.2) | – | – | – | – |
| DVT | 2 (0.3) | 0 (0.0) | – | – | – | – |
| Chest pain | 1 (0.1) | 1 (0.1) | – | – | – | – |
| AMI | 1 (0.1) | 1 (0.1) | – | – | – | – |
| Surgical | 15 (1.9) | 55 (3.0) | 1.54 (0.88–2.72)<br>1.56 (0.88–2.78) | 1.54 (0.82–2.87) | 1.48 (0.75–2.92) | 1.77 (0.87–3.60) |
| Catheter blockage and retention after catheter removal | 7 (0.9) | 19 (1.0) | – | – | – | – |
| Anastomotic leakage | 1 (0.1) | 14 (0.8) | – | – | – | – |
| Bleeding | 1 (0.1) | 9 (0.5) | – | – | – | – |
| Lymphocele | 4 (0.5) | 3 (0.2) | – | – | – | – |
| Abdominal pain | 2 (0.3) | 10 (0.5) | – | – | – | – |
| Miscellaneous | 4 (0.5) | 25 (1.4) | 2.63 (0.92–7.54)<br>2.66 (0.92–7.65) | 2.34 (0.78–6.99) | 1.63 (0.54–4.96) | 1.44 (0.47–4.45) |
| Operation hernia | 0 (0.0) | 4 (0.2) | – | – | – | – |
| Other likely related to procedure | 1 (0.1) | 13 (0.7) | – | – | – | – |
| Other not likely related to procedure | 2 (0.3) | 6 (0.3) | – | – | – | – |
| Psychological | 1 (0.1) | 2 (0.1) | – | – | – | – |
| Readmission leading to reoperation | 13 (1.7) | 29 (1.6) | 0.94 (0.49–1.80)<br>0.94 (0.49–1.82) | 1.07 (0.54–2.13) | 1.22 (0.54–2.73) | 1.44 (0.62–2.34) |
| Readmission not leading to reoperation | 36 (4.6) | 116 (6.3) | 1.36 (0.94–1.95)<br>1.38 (0.94–2.03) | 1.45 (0.95–2.22) | 1.34 (0.85–2.11) | 1.56 (0.97–2.50) |

OR = odds ratio; RR = relative risk; CI = confidence interval.
[a] Total may not add up to 100 due to rounding of percentages.
[b] Denotes retropubic radical prostatectomy.
[c] Denotes robot-assisted laparoscopic radical prostatectomy.
[d] Possible confounders to be used in adjustments for each outcome were selected as variables significantly associated ($p$ value $< 0.20$) with the specific outcome.
[e] Adjustment A. Infection adjusted for: age at surgery, employment status preoperatively, physical exercise, previously operated for inguinal hernia, previous transurethral resection of the prostate (TURP), International Prostate Symptom Score (IPSS), cardiovascular disease, mental disorder, kidney disease, and prostate weight. Cardiovascular adjusted for: IPSS, pulmonary disease, neurologic disease, and prostate weight. Surgical adjusted for: age at surgery, employment status preoperatively, coronary bypass surgery, IPSS, mental disorder, and prostate weight. Miscellaneous adjusted for: age at surgery, postoperative irradiation, previously operated for inguinal hernia, IPSS, kidney disease, and prostate weight. Readmission leading to reoperation adjusted for: age at surgery, postoperative irradiation, and prostate weight. Readmission not leading to reoperation adjusted for: employment status preoperatively, previously operated for inguinal hernia, previous TURP, IPSS, mental disorder, and prostate weight.
[f] Adjustment B: Adjustment A + tumour factors (preoperative prostate-specific antigen level, clinical tumour stage, tumour stage of prostatectomy specimen, Gleason score on biopsy cores, and Gleason score pathology on specimen).
[g] Adjustment C: Adjustment A + B + lymph node dissection.

*Table 9. Comparison between open and robot-assisted surgery concerning patient-reported readmissions three months after surgery* [a]

### 5.2.2 Complications after lymph-node dissection

#### 5.2.2.1 Patient characteristics

Questionnaires were received from 3544 (96%) of the patients. Open radical prostatectomy and robot-assisted radical prostatectomy was performed in 863 (24%) respectively 2681 (76%) of the cases. Lymph-node dissection was done in 547 patients (15%), 266 (49%) out of these were limited and 281 (51%) were extended. Extended LND was performed significantly more than limited LND in the robotic group compared to the open group (73% vs. 22%). Open patients had less aggressive tumours with higher proportions of cT1 and Gleason score 6 tumours.

Positive lymph-nodes were found in 49 men (9.5%). Extended lymph-node dissection resulted in higher lymph-node yield and the robot-assisted technique had higher lymph-node yields in both limited and extended lymph-node dissection compared to the open technique (Table 10).

| LND stratified characteristics | | LND + ORP (232 pts) | | LND + RARP (315 pts) | |
|---|---|---|---|---|---|
| | Overall | Limited | Extended | Limited | Extended |
| **No. N stage (%)** | | | | | |
| **N0** | 436/515 (84.7) | 147/163 (90.2) | 39/45 (86.7) | 73/82 (89.0) | 177/225 (78.7) |
| **N1** | 49/515 (9.5) | 2/163 (1.2) | 5/45 (11.1) | 3/82 (3.7) | 39/255 (17.3) |
| **Nx** | 30/515 (5.8) | 14/163 (8.6) | 1/45 (2.2) | 6/82 (7.3) | 9/225 (4.0) |
| **No. Lymph nodes excised** | | | | | |
| **Mean (range)** | 16.3 (1.0-76.0) | 6.1 (1.0-22.0) | 18.3 (5.0-48.0) | 9.2 (2.0-31.0) | 21.5 (2.0-76.0) |
| **Median (IQR)** | 14.0 (7.0-24.0) | 5.0 (3.5-8.0) | 16.0 (12.0-26.0) | 8.0 (6.0-13.0) | 20.0 (13.0-29.0) |
| **Mean positive nodes in N1 (range)** | 2 (0-8.0) | 1 (1.0-1.0) | 3.5 (2.0-8.0) | 1 (1.0-1.0) | 2.2 (0-7.0) |

*Table 10. Lymph-node dissection stratified characteristics*

#### 5.2.2.2 Complications and readmissions within 90 days

Men treated with LND reported more wound complications (pain, bleeding and infections), cardiovascular (DVT and PE) and psychological events (anxiety and depression) (Table 11). Concerning readmissions, lymph-node dissection was associated with more frequent readmissions related to infectious, cardiovascular and surgical complications. Lymph-node dissection was also associated with increased risk of reoperation (Table 12).

#### 5.2.2.3 Thromboembolic events

In the cardiovascular group, lymph-node dissection was specifically associated with a highly increased risk for DVT and PE compared to men who did not undergo lymph-node dissection, age-adjusted RR 7.8 (95% CI 3.51-17.32) and 6.29 (95% CI 2.11-18.73) (Table 11). When evaluating predictive factors for DVT and/or PE we found that a history of thrombosis, stage pT4 disease and Gleason score 8 or greater increased the risk while low alcohol consumption (once per week) on the other hand was protective. Open surgery overall

resulted in a statistically significantly higher risk for DVT and/or PE compared to robot-assisted surgery, RR 3.46 (95% CI 1.74-6.89). When only looking at men who did not undergo lymph-node dissection and comparing the surgical techniques, we saw that open surgery was significantly associated with an increased risk for DVT and/or PE compared to robot-assisted surgery, RR 3.20 (95% CI 1.16-8.83) (Table 13).

| | | | RR (95% CI) | |
|---|---|---|---|---|
| **Complication** | **No. No LND (%)** | **No.LND (%)** | **Unadjusted** | **Age adjusted** |
| **Overall** | 2873 | 526 | - | - |
| **Genitourinary (at least one)** | 635 (22.1) | 128 (24.3) | 1.10 (0.93-1.30) | 1.11 (0.93-1.31) |
| **UTI** | 383 (13.3) | 74 (14.1) | 1.05 (0.84-1.33) | 1.06 (0.84-1.34) |
| **Blockage in the catheter** | 161 (5.6) | 34 (6.5) | 1.15 (0.81-1.65) | 1.16 (0.81-1.66) |
| **Hematuria** | 246 (8.6) | 41 (7.8) | 0.91 (0.66-1.25) | 0.93 (0.68-1.28) |
| **Operation wound (at least one)** | 408 (14.2) | 115 (21.9) | 1.54 (1.28-1.85)* | 1.56 (1.29-1.87)* |
| **Pain** | 93 (3.2) | 29 (5.5) | 1.70 (1.13-2.56)* | 1.78 (1.19-2.68)* |
| **Pain lower abdomen** | 210 (7.3) | 63 (12.0) | 1.64 (1.26-2.14)* | 1.67 (1.28-2.18)* |
| **Pain upper abdomen** | 77 (2.7) | 21 (4.0) | 1.49 (0.93-2.39) | 1.52 (0.94-2.45) |
| **Bleeding** | 91 (3.2) | 29 (5.5) | 1.74 (1.16-2.61)* | 1.79 (1.19-2.69)* |
| **Infection** | 107 (3.7) | 31 (5.9) | 1.58 (1.07-2.33)* | 1.64 (1.11-2.43)* |
| **Hernia** | 47 (1.6) | 14 (2.7) | 1.63 (0.90-2.93) | 1.56 (0.86-2.81) |
| **Respiratory (at least one)** | 10 (0.3) | 4 (0.8) | 2.18 (0.69-6.94) | 2.32 (0.72-7.41) |
| **Pneumonia** | 10 (0.3) | 4 (0.8) | 2.18 (0.69-6.94) | 2.32 (0.72-7.41) |
| **Cardiovascular (at least one)** | 163 (5.7) | 49 (9.3) | 1.64 (1.21-2.23)* | 1.57 (1.16-2.14)* |
| **Hypertension** | 113 (3.9) | 22 (4.2) | 1.06 (0.68-1.66) | 1.02 (0.65-1.59) |
| **Acute myocardial infarction** | 4 (0.1) | 1 (0.2) | 1.36 (0.15-12.19) | 1.21 (0.14-10.82) |
| **Arythmia** | 40 (1.4) | 10 (1.9) | 1.37 (0.69-2.71) | 1.32 (0.66-2.62) |
| **DVT** | 10 (0.3) | 15 (2.9) | 8.19 (3.70-18.14)* | 7.80 (3.51-17.32)* |
| **PE** | 6 (0.2) | 7 (1.3) | 6.37 (2.15-18.89)* | 6.29 (2.11-18.73)* |
| **Stroke** | 2 (0.1) | 0 | NA | NA |
| **Gastrointestinal (at least one)** | 432 (15.0) | 95 (18.1) | 1.20 (0.98-1.50) | 1.18 (0.96-1.44) |
| **Nausea** | 51 (1.8) | 12 (2.3) | 1.28 (0.69-2.39) | 1.27 (0.68-2.36) |
| **Impaired appetite** | 96 (3.3) | 38 (7.2) | 2.16 (1.50-3.11)* | 2.14 (1.48-3.08)* |
| **Loose or frequent stools** | 168 (5.9) | 31 (5.9) | 1.0 (0.69-1.46) | 0.98 (0.67-1.42) |
| **Constipation** | 233 (8.1) | 53 (10.1) | 1.24 (0.94-1.65) | 1.20 (0.91-1.60) |
| **Psychological[a] (at least one)** | 377 (13.1) | 95 (18.1) | 1.37 (1.12-1.69)* | 1.40 (1.14-1.72)* |
| **Anxiety** | 307 (10.7) | 76 (14.4) | 1.35 (1.07-1.71)* | 1.40 (1.11-1.77)* |
| **Depression** | 267 (9.3) | 64 (12.2) | 1.31 (1.01-1.69)* | 1.34 (1.03-1.73)* |
| **Other** | 299 (10.4) | 71 (13.5) | 1.30 (1.02-1.65)* | 1.30 (1.02-1.66)* |

* = a statistically significant association on a 95% confidence level
[a] = please not that in the published paper this heading was incorrecty named "Neuro-musculoskeletal"

*Table 11. Patient reported 90-day adverse events by system unadjusted and adjusted by age.*

| | | | RR (95% CI) | |
|---|---|---|---|---|
| **Readmission cause** | **No. No LND (%)** | **No.LND (%)** | **Unadjusted** | **Age adjusted** |
| **Overall** | 2856 | 524 | - | |
| **Infectious:** | 43 (1.5) | 19 (3.6) | 2.41 (1.41-4.10)* | 2.39 (1.40-4.08)* |
| **Urinary tract** | 27 (1.0) | 13 (2.5) | 2.62 (1.36-5.05)* | 2.61 (1.35-5.05)* |
| **Deep** | 6 (0.2) | 3 (0.6) | 2.72 (0.68-10.86) | 2.79 (0.70-11.21) |
| **Sepsis** | 7 (0.3) | 3 (0.6) | 2.34 (0.60-9.00) | 2.27 (0.59-8.79) |
| **Wound** | 3 (0.1) | 0 | NA | NA |
| **Cardiovascular:** | 4 (0.1) | 9 (1.7) | 12.26 (3.79-39.67)* | 11.75 (3.62-38.17)* |
| **Pulmonary embolism** | 4 (0.1) | 7 (1.3) | 9.54 (2.80-32.47)* | 9.22 (2.69-31.52)* |
| **DVT** | 0 | 2 (0.4) | NA | NA |
| **Other cardiovascular** | 4 (0.1) | 1 (0.2) | 1.36 (0.15-12.17) | 1.24 (0.14-11.08) |
| **Chest pain** | 2 (0.1) | 0 | NA | NA |
| **Myocardial infarction** | 2 (0.1) | 1 (0.2) | 2.72 (0.25-30.00) | 2.48 (0.23-27.32) |
| **Surgical:** | 107 (3.8) | 40 (7.6) | 2.04 (1.43-2.89)* | 2.06 (1.45-2.94)* |
| **Catheter blockage and retention after catheter removal** | 31 (1.1) | 5 (1.0) | 0.88 (0.34-2.25) | 0.88 (0.34-2.25) |
| **Anastomotic leakage** | 15 (0.5) | 5 (1.0) | 1.82 (0.66-4.98) | 1.86 (0.68-5.11) |
| **Bleeding** | 10 (0.3) | 2 (0.4) | 1.09 (0.24-4.96) | 1.20 (0.26-5.50) |
| **Lymphocele** | 0 | 8 (1.5) | NA | NA |
| **Abdominal Pain** | 19 (0.7) | 4 (0.8) | 1.15 (0.39-3.36) | 1.12 (0.38-3.29) |
| **Reoperation** | 32 (1.1) | 16 (3.1) | 2.72 (1.51-4.93)* | 2.71 (1.50-4.92)* |
| **Miscellaneous** | 32 (1.1) | 9 (1.7) | 1.53 (0.74-3.19) | 1.54 (0.74-3.22) |
| **Operation hernia** | 3 (0.1) | 2 (0.4) | 3.63 (0.61-21.69) | 3.23 (0.54-19.30) |
| **Other:** | | | | |
| **Likely related to procedure** | 15 (0.5) | 5 (1.0) | 1.82 (0.66-4.98) | 1.87 (0.68-5.16) |
| **Not likely related to procedure** | 11 (0.4) | 2 (0.4) | 0.99 (0.22-4.46) | 1.00 (0.22-4.53) |
| **Psychological** | 3 (0.1) | 0 | NA | NA |
| **Rehozpitalization:** | | | | |
| **Leading to reoperation** | 32 (1.1) | 16 (3.1) | 2.73 (1.51-4.93)* | 2.71 (1.50-4.92)* |
| **Not leading to reoperation** | 147 (5.2) | 60 (11.5) | 2.22 (1.67-2.96)* | 2.23 (1.67-2.97)* |

*= a statistically significant association on a 95% confidence level

*Table 12. Patient reported 90-day readmission causes by system unadjusted and adjusted for age.*

| **DVT and PE by ORP vs RARP** | | | | | **DVT + PE Prediction** | |
|---|---|---|---|---|---|---|
| | **No. Pts** | **No. DVT (%)** | **No. PE (%)** | **No. DVT + PE (%)** | **Unadjusted RR (95% CI)** | **Adjusted RR (95% CI)[a]** |
| **ORP** | 827 | 15 (1.8) | 6 (0.7) | 18 (2.2) | 3.43 (1.76-6.70)* | 3.46 (1.74-6.89)* |
| **RARP** | 2572 | 10 (0.4) | 7 (0.3) | 16 (0.6) | 1.0 | 1.0 |
| **LND:** | | | | | | |
| **ORP** | 224 | 10 (4.5) | 3 (1.3) | 10 (4.5) | 12.67 (5.05-31.77)* | 10.57 (4.01-27.85)* |
| **RARP** | 302 | 5 (1.6) | 4 (1.3) | 8 (2.6) | 7.52 (2.84-19.88)* | 5.80 (2.00-16.86)* |
| **No LND:** | | | | | | |
| **ORP** | 603 | 5 (0.8) | 3 (0.5) | 8 (1.3) | 3.76 (1.42-9.99)* | 3.20 (1.16-8.83)* |
| **RARP** | 2270 | 5 (0.2) | 3 (0.1) | 8 (0.4) | 1.0 | 1.0 |

[a] Adjusted for thrombosis history, stage pT4 and Gleason score 8 or greater identified by forward selection.
* = a statistically significant association on a 95% confidence level

*Table 13. DVT and PE by ORP vs. RARP with vs. without LND according to patient reported 90-day adverse events unadjusted and adjusted for possible confounders.*

# 6 DISCUSSION

This thesis has evaluated complications after surgery for prostate cancer. In the first two papers we investigate urinary bother and predictors for postoperative incontinence. We found that even small occasional amounts of urinary leakage can cause the patient much bother and that the use of no pads is not equivalent with no leakage. Considering this, if continence is defined by pad use (e.g. safety pad) then a certain number of men who experience much bother from urinary leakage will nevertheless be considered continent. Increased age at surgery and preoperative urinary leakage proved to be significant predictors for incontinence one year after surgery. In papers three and four we evaluated two different surgical techniques for treatment of prostate cancer concerning short-term complications within three months of the surgery. The results showed that men operated by robot-assisted surgery were less likely to be re-operated during initial hospital stay and less likely to seek health-care within three months of the surgery compared to men operated by open surgery. The open technique had shorter operating time but resulted in more perioperative bleeding and longer hospital stay compared to the robot-assisted technique. There was no statistically significant difference in readmission rates between the groups within 3 months after the operation. Lymph-node dissection during radical prostatectomy increased the incidence of deep venous thrombosis or pulmonary embolism sevenfold. Open surgery increased the risk threefold compared to robot-assisted surgery.

## 6.1 METHODOLOGICAL CONSIDERATIONS

### 6.1.1 Validity

Validity is the extent to which the endpoint of a study corresponds accurately to the real world. Validity can be divided into internal and external validity. Internal validity is an expression of how well a study measures what it is intended to measure. Internal validity is affected by systematic errors such as selection bias, information bias and confounding. External validity, or generalizability, indicates the degree to which one can generalize the results obtained to other populations or situations. To describe the validity of the results in this thesis this discussion will start with considering systematic errors that could arise in these studies. Overall, the studies in this thesis have high internal validity as the risk of systematic errors are relatively low due to the study designs and the methods used to overcome potential confounders. The results of the LAPPRO study has high external validity because data is derived from 14 different centres, thus is more representative of real life practice compared to a single specialised institution.

### 6.1.2 Selection bias

Selection bias is a systematic error that can occur in the recruitment of a study population. Selection bias cannot be corrected for in the analysis and therefore it can influence the internal validity. In our studies the risk for selection induced problems were lowered by including a consecutive series of men in both cohorts used. Non-participation can be a risk

for selection bias if such individuals have different characteristics compared to those who do participate. A strength of the two cohorts used in this thesis is the high participation rate which reduces the risk of selection bias. Another strength is that inclusion to each respective technique was decided upon geographical location rather than patient or surgeon preference. This is because the Swedish Health Care is organized by county, and patients are not free to seek health care across county borders by their own inclination. The risk for selection-induced problems would be reduced by this fact since all patients will be treated with one method only based on where they live rather than the preference of the different surgeons.

### 6.1.3 Information bias

Information bias is a systematic error that occurs when the information is collected in different ways for the different groups that are intended to be compared. Data collection errors can occur for either the exposure or outcome. The term misclassification is often used for this concept. Recall bias, measurement bias and detection bias are different types of information bias. One type of information bias that could arise in the first and second article is pads status as the subjective method for measuring urinary incontinence. When the outcome is urinary bother one can imagine that the pads status question blurs the effect when the patients personality plays a role in the number of pads used. One patient could be very bothered and use many pads despite experiencing little urinary leakage, compared to another patient experiencing the same amount of leakage and yet is less bothered by these symptoms, thus using less protection. On the other hand, if the outcome is operation technique it would be more important to have a more objective method for measuring incontinence. However, making the evaluation more objective, for example, by using urodynamic assessment, would have been difficult in such a large cohort. Furthermore, pads status is currently widely recognized as a method for evaluating postoperative incontinence. Today more emphasis is placed on the patients' experience, which is a further reason to evaluate incontinence by questionnaires answered by patients. Another potential source of information bias is that no discrimination was made between urge and stress incontinence. Urge incontinence is usually caused by overactive bladder is not typically incurred after prostate cancer surgery. Not to exclude these patients may have affected our outcomes.

Incontinence was defined as *the change of one pad or more per day* in paper II. This definition is not as strict as what we propose in paper I after having evaluated urinary leakage and urinary bother. However, the definition was predefined from the study protocol for LAPPRO and the decision was taken through consensus among the research group based on the clinical practice at that time. This definition will also be used for the final analysis of the primary endpoint of LAPPRO.

In paper III and IV there is a lack of a standardized tool for the assessment of the adverse events which could lead to information bias. However, at the time when the study was designed and initiated, the now widely used Clavien-Dindo system of systematic grading of adverse events after surgical procedures, was not generally recognized.[188,189] The Clavien-Dindo classification requires data on the management of the complications and this

information was unfortunately not included in the clinical report forms. Additionally, there was no standardized postoperative clinical pathway in the study which might have influenced the data on hospital stay. Furthermore, since health-care professionals were not blinded the reports could be influenced by their preference for the surgical technique used in their centre. The ‘‘I want to please my surgeon’’ attitude among patients however, is possibly not related to surgical technique and should largely be avoided when using questionnaires.[190,191]

The risk for information bias in the present studies are minimized by the large populations evaluated and by using validated self-assessed patient-questionnaires where one question is used for one phenomenon, to strive for a clear and mutual understanding. The information has been obtained and collected in the same way for both surgical groups. Furthermore, questionnaires were collected by a neutral third party to prevent interviewer related problems.

### 6.1.4 Confounding

An effect-measure can erroneously be deviated by extraneous risk factors for the outcome we study, and this source of error is often cited as confounding. Confounding can either strengthen or weaken an association. If the prevalence of the confounding factors are different in the groups that are compared then the observed association can be misrepresented. To overcome the effect of confounders there are five different methods: randomization, restriction, matching, stratification and adjustment.

Surgical experience and surgical technique are potential confounders when evaluating urinary incontinence after radical prostatectomy. However, these factors were not analysed as predictors for incontinence in paper II as only preoperative patient- and tumour-related factors for postoperative incontinence were evaluated. This might be seen as a limitation but the aim of the study was to identify potential confounding factors for the final analysis of LAPPRO with the primary endpoint of urinary incontinence 12 months after surgery. Although no distinction was made between high- and low-volume centres in the analysis, most of the operations were performed at high-volume centres. High- and low-volume centres could be confounders when evaluating surgical complications in paper III and IV. But one can also say that using all centres and not dividing them into groups could increase the generalizability of the study.

In our studies we have been highly diligent at collecting data on all possible confounders in the validated questionnaires and from the clinical data. To overcome the possible effect of confounders in our papers we used adjustments. In paper III, of the possible confounders, those who were significant at the 20% level in log binomial regression analysis were assumed to be confounders and were adjusted for in each outcome respectively. Furthermore, data from paper III is presented with three different adjustments because tumour-related factors and lymph-node dissection can either be seen as confounders or as mediating factors due to differences in technique in the respective surgical groups. In paper IV statistical models with forward selection were used to identify those confounders that were most strongly associated with the outcome from a list of possible confounders. The identified predictors were used for

adjustment.

## 6.2 LATEST EVIDENCE

### 6.2.1 Bother from urinary incontinence

Our data shows a highly increased risk for urinary bother even at small rates of urinary leakage. Of men reporting use of no pads 6% reported much or moderate bother compared to 31% in the group wearing a safety pad. This results in a relative risk of 5.2 (95% CI 3.5-7.7). These 6% of men who were bothered despite using no pads could be explained by the fact that use of no pads is not equivalent to no leakage. Two recent studies confirm the highly increased risk for urinary bother after radical prostatectomy. The Prostate Cancer Outcomes Study (PCOS) reported that, in a cohort of 1655 men who had undergone radical prostatectomy had significantly more urinary incontinence and urinary bother compared to men undergoing radiotherapy at 2 and 5 years, however no significant differences were apparent 15 years after diagnosis.[192] Two years after surgery 11% of the men who had undergone prostatectomy were bothered 'moderately' or 'much' from their urinary incontinence. Similarly results from the CaPSURE registry showed that men undergoing nerve sparing and non-nerve sparing radical prostatectomy reported 30 vs. 31% urinary bother two years after surgery.[193]

### 6.2.2 Predictors of urinary incontinence

Our data shows that with increased age there is a higher prevalence of incontinence one year after surgery which increases exponentially. There are a lot of studies investigating the predictors of incontinence after radical prostatectomy and several studies have found age to be an independent predictor for the return of urinary continence.[150,158,194,195,196,197] However, others have found no association between the two.[198,199,200] Nilsson et al. reported similar results that age at surgery predicted long-term urinary incontinence in an exponential manner with a 6% relative increase every year.[148] In our study we also found preoperative urinary leakage to be an independent predictor of postoperative incontinence at 12 months. In a national prospective study including 844 patients Holm et al. confirmed these results and found that preoperative urinary incontinence and sexual dysfunction were the strongest predictors for urinary incontinence 12 months after radical prostatectomy.[201] In recent years there has been discussion as to whether nerve-sparing surgery has any effect on urinary incontinence beyond its benefit on potency. Kaye et al. published a prospective study with a cohort of 102 preoperatively potent men undergoing either laparoscopic or robot-assisted radical prostatectomy.[122] Their results showed that completely sparing at least one neurovascular bundle along with its supportive tissue had a large beneficial effect on the recovery of urinary continence. Recent results from the LAPPRO study supports these results. The data showed a strong association between the degree of nerve sparing and urinary continence one year after surgery.[121] However, a meta-analysis including 27 longitudinal cohort studies demonstrated an association between nerve-sparing and improved urinary continence only up to six months postoperatively.[202]

### 6.2.3 Robot-assisted radical prostatectomy vs. open radical prostatectomy

The primary endpoint of the LAPPRO study which is urinary incontinence 12 months after surgery in men undergoing robot-assisted radical prostatectomy vs. men undergoing open radical prostatectomy, has not yet been published. The results are expected to be published in the beginning of 2015. A similar study was recently presented at the EMUC meeting (European Multidisciplinary Meeting on Urological Cancers) in November 2014 in Lisbon. Ong et al. presented a prospective study with data from the Victorian Prostate Cancer Registry (PCR) including 2333 men undergoing robot-assisted or open radical prostatectomy.[203] Their results showed no significant differences at 12 months in urinary and sexual function, however the robotic patients had significantly better short-term oncological outcomes (PSM and BCR) compared to open patients. Contradicting theses results, in the annual report of the National Prostate Cancer Registry of Sweden 2013 data showed that men who had undergone radical prostatectomy and were potent prior to surgery had significantly less erectile dysfunction one year after robot-assisted surgery compared to those men operated by open surgery (66% vs 79%, p = 0.01).[24]

### 6.2.4 Short-term complications

The results from LAPPRO showed that men operated by robotic surgery were less likely to be re-operated during initial hospital stay and also less likely to seek health-care within three months after surgery compared to men operated by open surgery. The robot-assisted technique was also associated with less perioperative bleeding and shorter hospital stay compared to the open technique. A recent multi-institutional retrospective study comprising data from 5471 men undergoing either open (20.1%) or robot-assisted (79.9%) radical prostatectomy, showed that open surgery was associated with higher rates of overall complications (23.25% vs. 5.62%, p = <0.001), but not higher rates of reoperations (1.09% vs. 0.96%, p = 0.689) compared to robot-assisted surgery.[204] Unlike the LAPPRO results, this study found a difference in readmission rates favouring the robotic technique (5.47% vs 3.48%, p = 0.002). However, Gandaglia et al. found no significant differences concerning overall complications or readmission rates in 2439 men undergoing either open or robot-assisted radical prostatectomy. Nevertheless, the robot-assisted technique was associated with a higher probability of experiencing 30- and 90-day genitourinary and miscellaneous complications but with lower risk for blood transfusions and prolonged length of hospital stay.[205]

### 6.2.5 Complications after lymph-node dissection

Results from the LAPPRO trial showed that lymph-node dissection during radical prostatectomy was associated with a sevenfold increased incidence of deep venous thrombosis or pulmonary embolism and that open surgery increased this risk more than robot-assisted surgery. A study by Van Hemelrijck et al. which assessed the risk of thromboembolic events in 45,065 patients undergoing different types of urological surgery, found that laparoscopic and open radical prostatectomy with lymph-node dissection was strongly associated with thromboembolic events (HR for pulmonary embolism 8.1 (95% CI

2.9-23.0) and 7.8 (95% CI 4.9-13)).[141] There are several possible mechanisms that could explain the association between deep venous thrombosis and pulmonary embolism to lymph-node dissection. Lymphocele formation, which has been reported as the most frequent complication after lymph-node dissection (0-8%) could lead to significant pressure on the iliac veins as the retroperitoneal space is limited.[206] The same effect could be caused by hematoma. Moreover, excessive bleeding which requires blood transfusion can cause hyper coagulation. Other factors that could play a role are malignancy, pelvic manipulation, patient age, operating time and comorbidities. In LAPPRO we found a history of thrombosis, pT4 stage cancers and Gleason scores of 8 or greater to be predictive factors for thromboembolic events.

It is known that the larger the extension of the lymphadenectomy, the greater the chance of finding a positive node.[60,206,207] Furthermore, the overall numbers of positive nodes increases along with the total number of nodes removed.[208] However, the number of nodes removed is related more to the experience of the surgeon than the surgical technique.[209] The latest review in the field showed that extended lymph-node dissection revealed positive lymph-nodes in up to a third of patients.[210] With this evidence and consideration of the significant morbidity caused by lymph-node dissection, combined with the strive towards treating more advanced cancers surgically, there must be further deliberation by the surgeon when selecting patients for lymph-node dissection. It would be better to strategically remove lymph-nodes that are important rather than removing as many lymph-nodes as possible. One technique that is already in development is the sentinel node technique, which can be optimised with fluorescence guidance.[211] The concept is to identify the lymph-nodes that are most likely to contain metastatic cells (sentinel node).

# 7 CONCLUSIONS

Despite a great development in the surgical technique for prostate cancer in the recent decades, the surgery still leads to a significant risk of postoperative complications. Urinary incontinence is a long-term side effect that negatively impacts quality of life. The definition of continence is today often based on the number of pads the patient uses, however a standardized definition does not presently exist. In our data we saw a wide variation in pad use for the same amount of leakage as well as a high increased risk of urinary bother even at a small rate of urinary leakage. The use of no pads was not equivalent to total urinary continence. When considering this, pad status as a definition of continence is not without limitations.

Our research has highlighted that there is need for a standardized definition of continence in the field of surgical treatment of prostate cancer. This would facilitate comparison between different surgical cohorts but also take the patient perspective into consideration. Furthermore, our research has shown that men with preoperative urinary leakage and those of older age at surgery are at higher risk of postoperative urinary leakage and that this must be taken into consideration prior to any treatment decision.

When comparing the two surgical techniques of open and robot-assisted radical prostatectomy our large prospective study showed that despite a longer operating time, patients operated by robot-assisted surgery had significantly less bleeding and shorter hospital stay compared to patients operated by open surgery. Patient-reported data at three months showed that patients operated by the robot-assisted technique had a lower risk of re-operation during initial hospital stay and were less likely to seek health-care compared to patients operated by the open technique. Lymph-node dissection during radical prostatectomy increased the risk for thromboembolic events (deep venous thrombosis and pulmonary embolism), however the risk was significantly higher in men operated by open technique compared to the robot-assisted technique. Patients with previous thrombosis and high risk disease (pT4 stage and Gleason ≥8) especially had an increased risk for thromboembolic events. Since the morbidity from particularly pulmonary embolism is clinically significant, our findings highlight that these procedures may warrant prolonged prophylaxis and screening during and after surgery. In light of this there must be a strong indication for including this procedure during radical prostatectomy.

In conclusion, we have found that there are certainly some significant short-term advantages of the robotic technique over the open prostatectomy. However, evaluating the pros and cons of robot-assisted radical prostatectomy as compared with open surgery involves further assessment of a large number of short- and long-term outcomes, including economic consequences and cure rates. These aspects will be addressed by the forthcoming results from the LAPPRO study.

# 8 FUTURE PERSPECTIVES

In this thesis we can conclude that men undergoing radical prostatectomy due to localized prostate cancer have a significant risk of long-term urinary incontinence and that even small rates of incontinence may cause a lot of bother. The advantages of a multicentre study is that it provides data that is more likely to represent a generalizable incidence of incontinence rather than results from a single centre of excellence that could be influenced by a number of systematic errors. Furthermore we conclude that robot-assisted technique as compared to open technique has advantages on short-term outcomes such as lower risk for reoperation, thromboembolic events and the need to seek health-care after the operation.

In the future, how can we reduce the risk of morbidity after surgery for prostate cancer? The best way to avoid complications would be not to operate at all. However, since we know that mortality is reduced by surgery in especially intermediate and high risk prostate cancers the most important issue to reduce the overall morbidity would be to select our patients better and only operate those with true benefit from the surgery. We know today that there is a substantial overtreatment, thus causing many men life-long side effects from treatment of asymptomatic prostate cancer that could have remained undiagnosed.[212] The problem is that today we detect too many innocuous cancers. The latest update from the SPCG4 study showed that radical prostatectomy lowers the mortality primarily from intermediate-risk cancers, whereas patients with low-risk cancers had at most 10% risk of dying from prostate cancer without any treatment and the patients with high-grade disease usually developed metastasis despite surgery. Furthermore, young men had more to gain from surgery compared to older men.[1] Thus, the future in prostate cancer diagnostics lies in detecting only the patients with intermediate and high risk cancers that would have the most benefit from the surgery. The 13 years follow-up of the ERSPC study, which is a multicentre randomized screening trial with PSA, concluded that the main weakness of screening is overdiagnosis and overtreatment although they showed significant reductions in prostate cancer mortality where 781 must be screened or 27 prostate cancers detected to avert one death.[213] However, the benefits of screening were even greater in the Swedish cohort from the Göteborg Randomized Population-based Prostate Cancer Screening Trial where only 139 needed to be screened or 13 prostate cancers detected to avert one death.[36] Diagnostics could improve substantially through the use of MRI and today there are interesting on-going trials with the aim to investigate whether MRI in combination with PSA could improve the detection of more advanced cancers, leaving the low-risk cancers undetected. Another important part of improving diagnostics is the research into new biomarkers for prostate cancer with high specificity and sensitivity, especially for detection of high-grade cancers.[54,214,215] Furthermore, improved preoperative staging could increase the surgeons knowledge of the localization and distribution of the tumour when planning surgery to minimize the risk of postoperative morbidity. An example is preoperative MRI that provides the surgeon better knowledge of the localization of the tumour in order to spare as much as possible the nerves affecting both postoperative continence and potency. Another example of 'perioperative

staging' is the NeuroSAFE that enables frozen section of the prostate during surgery and thus lowers the risk for positive surgical margins and increases the extent of nerve sparing.[216]

A second important issue of incontinence after radical prostatectomy is that the definition of incontinence varies across the world and thus makes data comparison between different cohorts complex. The future research of surgical technique in prostate cancer relies on an international consensus in defining continence and quantifying it. According to our results a suggestion for an international definition of continence could be *pad and leak free* to avoid including any patients with bother from urinary leakage being defined as continent. A desired future development would be to use a more objective method for evaluating postoperative incontinence, especially when comparing operation techniques with the outcome of incontinence to avoid information bias. An example would be to improve the technology to measure the actual leakage through simplified methods for weighing pads or with a urine sensor placed in the underwear similar to those used in enuresis alarms. However, when evaluating other outcomes such as patient bother from urinary leakage, then pads status could be used for measurement of urinary leakage and it would be of less importance to use a more objective method. Moreover, age and preoperative urinary leakage should always be considered when planning a patient for radical prostatectomy as our research has shown that they have an increased risk of postoperative incontinence.

There is evidence to continue the implementation of robot-assisted surgery since our data showed that robotic surgery has several favourable outcomes short-term outcomes compared with open surgery and has not demonstrated any substantial adverse outcomes within three months. Given that lymph-node dissection is associated with an increased risk of deep venous thrombosis and pulmonary embolism these patients should in the future be treated with an extended treatment period of low molecular heparin, especially patients undergoing open surgery, those who have had a previous thrombosis and those with high-risk tumours with pT4 or GS ≥8. Patients who undergo lymph-node dissection should also be thoroughly informed of the risk of thromboembolic events in order for them to seek health-care at an early stage if symptoms occur.

It is of importance to continue to evaluate and improve the surgical technique in the treatment of prostate cancer to further reduce the risk of postoperative complications both in the short and long-term. This can be done with future epidemiological studies in which the surgeon documents how the different steps of the surgery are performed and prospectively follow-up the short and long-term functional outcomes. To decrease the rate of postoperative incontinence it would be useful to continue evaluating the possible effect of posterior musculofascial reconstruction and anterior restoration of the pelvis as well as to further study whether the length of the urethra plays a role in urinary continence. Recent data from the LAPPRO study has shown that nerve-sparing also has a positive effect on postoperative continence.[121] To gain a deeper understanding of this relationship future studies could focus on further mapping the anatomy of the nerves and to evaluate their impact on the function of the urethral sphincter and the micturition reflex.

A radical prostatectomy is intended to be curative and we expect most patients to remain active and live many years after the procedure. Thus, reduced complication rates would improve quality of life and reduce suffering for many years for a significant number of patients.

# 9 SVENSK SAMMANFATTNING

Prostatacancer är den vanligaste cancerrelaterade dödsorsaken hos män i Sverige idag. Varje år insjuknar ca 9000 män och ca 2400 av dessa avlider till följd av sjukdomen. På senare år har antalet diagnostiserade fall ökat markant, dels p.g.a. utökad och förbättrad diagnostik av tidig prostatacancer genom introduktionen av PSA samt dels p.g.a. en ökad livslängd hos befolkningen. Detta har lett till att fler män idag kan erbjudas kurativ behandling när man på ett tidigt stadium diagnostiserar cancern då den fortfarande är lokaliserad.

Kurativt syftande behandling utgörs av strålbehandling alternativt radikal prostatektomi. En stor svensk randomiserad studie om radikal prostatektomi, SPCG-4 studien, har visat en signifikant skillnad i dödlighet i prostatacancer från 28,7 % i gruppen som följdes aktivt (”watchful waiting”) till 17,7 % i den opererade gruppen efter 18 år.[1] Denna kunskap om att operation förbättrar överlevnaden har bidragit till att kirurgi har blivit den vanligaste behandlingsformen i Sverige. Antalet radikala prostatektomier har de senaste 10 åren ökat från ett hundratal till över två tusen per år. I SPCG-4 studien såg man att den absoluta effekten av radikal prostatektomi i prostatacancerspecifik dödlighet var relativt låg, siffrorna visade att man behöver operera 8 män för att en ska förhindras från förtidig död.[1] Sannolikt är antalet ännu högre idag då vi nu använder PSA som screening och hittar patienter tidigare i sjukdomsförloppet samt att det i dagsläget inte finns någon säker diagnostik avseende vilka cancrar som progredierar till avancerad sjukdom. Detta är ett stort dilemma med lokaliserad prostatacancer att många patienter lever många år utan progress eller symtom från sin cancer och att de i många fall dör av andra orsaker.

De vanligaste komplikationerna till radikal prostatektomi är inkontinens och erektil dysfunktion (impotens). En genomgång av litteraturen har visat att mellan 4-31% har bestående urinläckage 12 månader efter operationen, dock är risken för allvarlig inkontinens låg.[126] Risken för erektil dysfunktion av någon grad är högre och har visat siffror mellan 10-46% ett år efter operationen.[127] Risken för överbehandling måste vägas mot komplikationerna som ingreppet ger. Således riskerar prostatacancerpatienten idag förutom en risk för överbehandling dessutom att drabbas av postoperativ morbiditet i form av inkontinens och erektil dysfunktion. Genom att minska komplikationsriskerna kan man tillåta en högre grad av överbehandling.

Radikal prostatektomi syftar till att avlägsna hela prostatan och därmed avlägsna tumören radikalt. Operationstekniken ska vara så atraumatisk som möjligt för att minska riskerna för komplikationer till operationen. Operationstekniken har förbättrats med ökande erfarenhet och risken för patientskador har blivit lägre. I slutet av 90-talet introducerades laparoskopisk operationsteknik av radikala prostatektomier i Frankrike.[115] Förhoppningen var då att man genom den nya metoden skulle minska morbiditeten av den kurativa kirurgin. År 2000 genomförde Binder i Tyskland den första robotassisterade radikala prostatektomin i världen.[120] Robottekniken skulle ge ytterligare bättre resultat p.g.a. en bättre visualisering av operationsområdet via bättre ljussättning samt en tredimensionell bild i buken.

Robotinstrumenten har dessutom en ökad rörlighet i jämförelse med de konventionella laparoskopiska instrumenten som möjliggör en mer exakt dissektionsteknik. Den kärlnervsträng som försörjer erektionen ligger an mot prostatakapseln och bör bevaras för att bibehålla potensen efter operation. Robotteknikens goda visualisering och utökade rörlighet möjliggör sannolikt detta på ett bättre sätt än vid öppen kirurgi. Tekniken gör det även lättare att visualisera uretra samt att sy en anatomiskt korrekt anastomos utan att skada den yttre miktionssfinktern, vilket tros leda till minskad postoperativ inkontinens. Utöver bättre visualisering och mer exakt dissektionsteknik så kommer man med robottekniken lättare åt nere i det lilla bäckenet där utrymmesbrist föreligger. I amerikanska operationsmaterial med robotassisterad teknik kunde man tidigt visa goda resultat med låga frekvenser av erektil dysfuntion, inkontinens samt en hög tumörradikalitet.[138,217]

Idag finns det inga högkvalitativa publicerade studier där de olika operationsmetoderna jämförs. Trots detta har många valt att satsa på den robotassisterade tekniken och den används i allt större utsträckning, utifrån lovande preliminära rapporter både avseende postoperativ morbiditet samt onkologiskt resultat. I USA utförs idag ca 85 % av alla radikala prostatektomier med robotteknik. I Sverige gjordes 65% av alla prostatektomier med robot år 2013. Med tanke på den ökade användning av robottekniken föreligger ett stort behov av evidensbaserade data som styrker att detta är en lika bra eller bättre metod än den konventionella öppna tekniken. Med anledning av detta startade ett samarbete mellan Sahlgrenska Universitetssjukhuset samt Karolinska Universitetssjukhuset 2007 då man påbörjade en prospektiv icke-randomiserad, öppen jämförande studie av robotassisterad laparoskopisk och öppen radikal prostatektomi, LAPPRO. Studien avser att utvärdera den robotassisterade tekniken avseende onkologiskt och funktionellt resultat samt även patientupplevd livskvalitet och ekonomiska aspekter. Hypotesen var att robotassisterad teknik medför en lägre andel komplikationer avseende inkontinens och impotens utan att påverka det onkologiska resultatet. Studien ligger till grund för tre av avhandlingens fyra arbeten (Studie II-IV).

**Studie I**

Den första studien baseras på 1411 män med prostata cancer som opererades på Karolinska Universitetssjukhuset mellan år 2002 och 2006. Studien visar att män besväras kraftigt av urinläckage som uppstår efter operationen och att även små mängder läckage är mycket besvärande. Definitionen av kontinens brukar baseras på hur många droppskydd patienten använder, t.ex. ≤1 skydd/dag. Denna studie visar att antalet droppskydd som männen använder varierar mycket oberoende av mängden urinläckage vilket gör att droppskydd är ett dåligt mått för att definiera kontinens. Bedömningen skulle bli enklare om definitionen av kontinens var "inga droppskydd".

**Studie II**

Den andra studien baseras på data från LAPPRO studien med de patienter som inkluderades under de första 17 månaderna. Studien visar att hög ålder vid operation för prostata cancer

ger högre risk för inkontinens 1 år efter operationen. Risken stiger exponentiellt med åldern. Patienter som uppger att de läcker innan operationen har en ökad risk för inkontinens efter operationen. Ytterligare 36 faktorer undersöktes inklusive högt BMI och tidigare transuretral resektion av prostatan och ingen av dessa gav någon statistiskt säkerställd ökad risk för inkontinens efter operationen.

**Studie III**

Den tredje studien baseras på data från LAPPRO studien och visar att män opererade med robotassisterad teknik hade mindre blödning under operationen och kortare vårdtid jämfört med män opererade med den öppna tekniken som i sin tur hade en kortare operationstid. Reoperation under vårdtiden var vanligare hos män som opererades med öppen teknik och dessa patienter sökte även sjukvård oftare under de tre första månaderna efter operationen jämfört med män som opererades med robottekniken. Det var ingen skillnad mellan grupperna i hur ofta patienterna återinlades på sjukhus inom tre månader efter operationen.

**Studie IV**

Den fjärde studien baseras på data från LAPPRO studien och visar lymfkörtelutrymning vid radikal prostatektomi är associerat med en kraftigt ökad risk för djup ventrombos och lungemboli. Risken var ännu större vid operation med öppen teknik jämfört med robotassisterad teknik. Risken för djup ventrombos och lungemboli ökade om patienten hade haft en tidigare propp eller hade en högrisk prostatacancer. Studien visade även att lymfkörtelutrymning ökar risken för att patienten återinläggs på sjukhus inom tre månader efter operationen.

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