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Risk Factors for Positive Surgical Margins in organ-confined Prostate Cancer treated with Robotic-assisted Radical Prostatectomy

Risikofaktoren für positive chirurgische Schnittränder bei Roboter-assistierter radikaler Prostatektomie bei organbegrenztem Prostatakarzinom

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1. Summary

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Prostate cancer is said to be the leading cause of solid neoplasms in males in Europe. Over the last two decades the screening for and diagnosis of prostate cancer, especially organ-confined prostate cancer, has increased dramatically, predominantly due to patient awareness and the introduction of prostate specific antigen (PSA) screening. This has also prompted the use of new treatment techniques, especially in minimally invasive surgeries, amongst which the robotic-assisted radical prostatectomy has found its place.

Organ-confined prostate cancer in patients with a life expectancy of more than 10 years should be treated curatively via surgical removal or various radiotherapy modalities.

The goal of the radical prostatectomy is to remove the entire prostate and the seminal vesicles, while at the same time attempting to preserve continence and erectile function. The surgery requires a fine balance between dissecting as close as possible to the prostate capsule in order to preserve the neurovascular bundle responsible for erectile function, but at the same time dissecting sufficiently far away from the tumour to avoid positive surgical margins. Besides lymph node dissection, the absence of a positive surgical margin is the only prognostic factor upon which the surgeon may have an impact.

The aim of this thesis is to evaluate the factors that influence the positive surgical margin rate.

The first 1200 patients who had undergone a robotic-assisted radical prostatectomy at the Department of Urology of the University Clinic of Saarland made up the study population of this research. Data capturing commenced in March 2006 when the robotic-assisted radical prostatectomy was introduced at the Department. Patient information, including data retrieved retrospectively, was saved in a central database. Additional data sets were added to the collection over time. From April 2010 onwards the “da Vinci Worksheet” was implemented as a

patient data capturing process during the preoperative and intrahospital periods. This worksheet was to be completed by the treating doctors. At the end of 2010 an audit was initiated in order to complete any missing data. Certain variables were identified as being relevant in the identification of risk factors for positive surgical margins in organ-confined disease. With the assistance of the Institute for Medical Biometry, Epidemiology and Medical Informatics of the University Clinic of Saarland, SPSS was used to determine the Fisher Exact Test, as well as the Cox Regression Model.

In total, 857 patients had organ-confined disease, of which 7,9% (n=68) had positive surgical margins. In our analysis there was a statistically significant increase in positive surgical margins when a nerve-sparing operation had been performed. A statistically significant increase could also be shown in bilateral nerve-sparing operations when compared to unilateral nerve-sparing operations. Of note was that a prostate weight of below 35g was related to a higher incidence of positive surgical margins. This was also statistically significant when examining patients who had a low prostate weight and a nerve-sparing operation (19.3% vs 8.6% p=0.009).

The learning curve across the 1200 patients showed a statistically significant decline in the positive surgical margin rate. This was also seen when only examining the nerve-sparing operations as the rate declined from 14.7% in the first 400 patients to 5.4% in the last 400 patients (p=0.011) Furthermore, when the preoperative biopsies of the prostate were ‘inadequate’ a statistically significant increase in the positive surgical margin rate was found. (‘Adequate’ biopsies entail the removal of eight or more biopsy cores and the identification of the location of the cancer).

The Cox Regression Model was used to identify independent risk factors. The two variables that remained statistically significant in the multivariable analysis were the presence of a nerve-sparing operation (p=0.003) and a low prostate weight (p=0.022).

In conclusion it can be stated that the two independent risk factors for positive surgical margins in patients with organ-confined prostate cancer undergoing a robotic-assisted radical prostatectomy, are a low prostate weight of less than 35g and a nerve-sparing operation.

1. Zusammenfassung

Risikofaktoren für positive chirurgische Schnittränder bei Roboter- assistierter radikaler Prostatektomie bei organbegrenztem Prostatakarzinom

Das Prostatakarzinom ist die häufigste maligne Tumorerkrankung des Mannes in Europa. Während der letzten 20 Jahre ist die Inzidenz des Prostatakarzinoms aufgrund einer besseren gesundheitlichen Aufklärung und dem zunehmenden Einsatz des PSA-Screening deutlich angestiegen. Heutzutage werden vor allem organbegrenzte Prostatakarzinome diagnostiziert. Dies hat auch die Entwicklung neuerer operativer Methoden wie die roboter-assisterte radikale Prostatektomie beeinflusst, einer Weiterentwicklung der minimal-invasiven laparoskopischen Operationsverfahren.

Bei Patienten mit einem organbegrenzem Prostatakarzinom und einer Lebenserwartung von mehr als 10 Jahren sollte ein kurativer Therapieansatz gewählt werden. Als Standardtherapie stehen die radikale Prostatektomie und verschiedenen strahlentherapeutische Verfahren zur Verfügung. Bei der radikalen Prostatektomie gilt es, neben dem bestmöglichen onkologischen Ergebnis mit kompletter Entfernung der tumortragenden Prostata und Samenbläschen auch den Erhalt der Lebensqualität zu gewährleisten, vor allem im Hinblick auf die Kontinenz und erektile Funktion. Der Operateur steht vor der Aufgabe, das Gefäß-Nerven-Bündel für die erektile Funktion zu schonen, welches dicht an der Prostatakapsel verläuft, ohne gleichzeitig positive chirurgische Schnittränder zu provozieren. Positive Schnittränder gelten als prognostische Faktoren für eine schlechtere Prognose und stellen damit den einzigen prognostische Faktor dar, der vom Operateur mit beeinflusst werden kann.

Ziel dieser Arbeit war es daher, mögliche Einflussfaktoren für einen positiven chirurgischen Schnitträndern, dem sogenannten R1-Status, zu identifizieren.

Die Daten der ersten 1200 Patienten wurden ausgewertet, die sich einer roboter-assistierten radikalen Prostatektomie an der Klinik für Urologie und Kinderurologie am Universitätsklinikum des Saarlandes unterzogen haben. Die prospektive Datenerhebung begann im März 2006 mit Einführung der roboter-assistierten radikale Prostatektomie . Im Laufe der Zeit erweiterten sich

die abgefragten Parameter und die Daten der ersten Patienten wurden dann retrospektiv in der zentralen Datenbank nachgetragen. Seit April 2010 wurde zur besseren Dokumentation der sog. “da Vinci Laufzettel” eingeführt. Der Laufzettel begleitet den Patienten während des gesamten Aufenthalt und wird durch die jeweils behandelnden Ärzte geführt. Im Dezember 2010 wurden die Datensätze auf Konsistenz und Vollständigkeit hin überprüft. Mit Unterstützung des Instituts für Medizinische Biometrie, Epidemiologie und Medizinische Informatik wurden einzelne Faktoren ausgewählt und statistisch geprüft, die für den R1 Status wichtig sein könnten. Diese Auswertung erfolgte mit SPSS. Der Fisher Exact Test wie auch das Cox Regression Model wurden angewandt.

Insgesamt wurden 857 Patienten mit einem organbegrenzten Prostatakarzinom identifiziert, 7,9% (n= 68) dieser Patienten hatten einen R1-Status. Mehrere verschiedene Faktoren wurden nach einer Literaturrecherche identifiziert und untersucht. Eine statistische signifikante Zunahme in der R1 Rate wurde bei einer nerverhaltenden Operation festgestellt, wobei ein signifikant höherer R-1 Status bei einem beidseitigem gegenüber einem einseitigen Nerverhalt festgestellt wurde. Ein weiterer Prognosefaktor für einen R1-Status war das Prostatagewicht unter 35g gegenüber >35g. Dieser war auch statistisch relevant bei einer nerverhaltende Operation (19.3% und 8.6% p=0.009). Die Analyse der Lernkurve fand eine statische signifikante Abnahme der R1 Rate bei organ-begrenzten Tumoren im zeitlichen Verlauf. Die Patienten mit einer nerverhaltenden Operation zeigten auch eine statische signifikante Abnahme von initial 14.7% bei den ersten 400 auf 5.4% bei den letzten 400 Patienten (p=0.011). Eine mangelnde Qualität des präoperativen Stanzbiopsiebefundes führt ebenfalls zu einer statistisch signifikant höheren R1-Rate, wobei eine ausreichende Qualität bei einer Anzahl der Stanzbiopsien ≥8 und dem Vorhandensein einer Seitenangabe für die positiven Stanzen gegeben wurde.
In der multivariaten Cox Regressions-Analyse konnten dann die nerverhaltende Operation (p=0.003) sowie ein Prostatagewicht <35g (p=0.022) als unabhängige Risikofaktoren für einen R1 Status identifiziert werden.

Zusammenfassend zeigt sich, dass Patienten mit nerverhaltender Operation und einem Prostatagewicht <35g ein signifikant erhöhtes Risiko für das Auftreten eines R1-Befundes aufweisen.

2. Introduction

2.1 The Incidence and Aetiology of Prostate Cancer

Ever since the prostate was first described, presumably, by Heròphilus in 300BC (1) it has been an organ of much interest in the urological society especially with regard to the benign enlargement of the prostate and prostate cancer.

Prostate cancer is the most common non-cutaneous malignancy in men (2) with the incidence in Europe being 87.2/100000. In Germany in 1998, 18.7% of all newly diagnosed malignancies were prostate cancers.(3) In the USA, the estimated lifetime risk of prostate cancer is 16.72% with the lifetime risk of mortality being 2.57%. The incidence increases with age and black African-Americans have a higher incidence than white Americans.(4) Scandinavian countries have a particularly high incidence and far eastern countries have a relatively low incidence.(3) The European mortality due to prostate cancer currently lies at 34.1/100000. In a recent article published by Heidenreich et al prostate cancer was said to be becoming the leading solid neoplasm in Europe, with a 15% incidence in developed countries and a 4% incidence in developing countries.(5)

The aetiology of prostate cancer is not yet understood. There is a genetic predisposition in some families, as one can demonstrate a relative risk increase according to the number of affected family members.(6) Familial prostate cancers usually have an earlier onset, predominantly under the age of 55 years.(3) As with breast cancer, carriers of the gene BRCA1 and BRCA2 have an increased risk of prostate cancer (7) and recently there has been a great focus on the hereditary prostate cancer-1 gene (HPC1).(8) Other contributing factors to the development of prostate cancer are an over expression of telomerase as well as a deficiency in Glutathion-S-transferase. Genes have also been implicated in prostatic carcinogenesis, such as a mutation of p53, vascular endothelial growth factor and a loss of E-Cadherin, to mention a few. Genes such as myc-oncogens and p27 have been attributed to the progression and metastases of prostate cancer. Numerous other enzymes, receptors and growth factors have been linked to the development of the cancer e.g. 5α-reductase-type 2 and insulin-like growth factor 1.(3)

The development of prostate cancer has also been blamed on nutrition, where the nutrition theory links certain diets in some populations to a predisposition to this type of cancer. The ingestion of animal fats, common in the western diet, may also explain the increased incidence of prostate cancer in the western world.(9) At the same time, tomatoes may be cancer-protective, whereas raised calcium levels may be carcinogenic.(3) In populations previously classified as “low risk populations”, an increase in prostate cancer was seen after immigrating to a Scandinavian country, Sweden, demonstrating the importance of environmental and possibly dietary factors.(10) There have also been proven associations between obesity and prostate cancer.(11)

The hormonal influences on prostate cancer can also not be ignored. Prostate cancer does not occur in males castrated before puberty and hormone deprivation is also a form of treatment in prostate cancer.(2, 3)

The detection, treatment and mortality rates of prostate cancer have dramatically changed, and are continuously changing, since the introduction of prostate specific antigen (PSA) screening, which has increased the detection rate and survival of patients in Europe and the United States, particularly amongst patients aged above 75 years.(12) None the less, due to the very high incidence in the male population and especially when the longer life expectancy in our population is considered, prostate cancer still remains a hot topic amongst medical personnel and researchers.

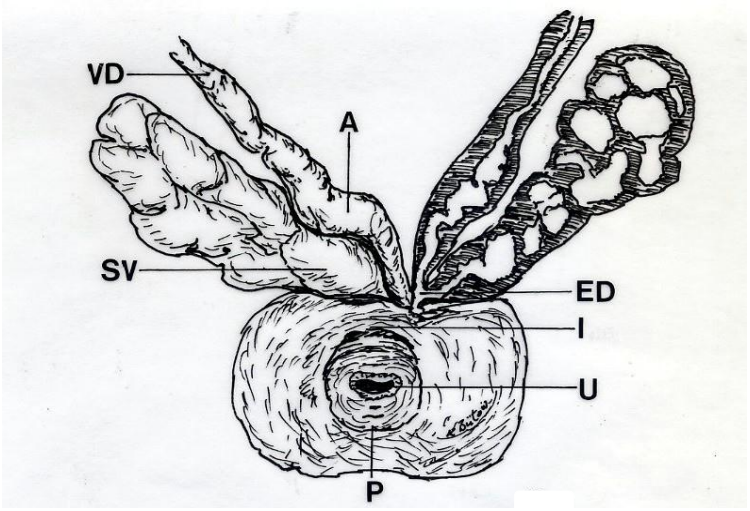
2.2 The Anatomy of the Prostate

In order to facilitate further discussions involving surgical techniques used in the treatment of prostate cancer, a short summary of the anatomy of the prostate has been drafted below.

The role of the prostate is to add prostatic secretions to the bulk of the fluid during ejaculation. The prostatic gland secretes a thin, milky fluid that contains calcium, citrate ion, phosphate ion, a clotting enzyme and profibrinolysin. The slightly alkaline characteristics of the fluid are very

important since sperm do not become optimally motile until the pH of the surrounding fluids rises to about 6.0 -6.5.(13)

The prostate is a walnut-sized gland situated at the base of the bladder. In a young male the gland weighs about 20g, but is known to enlarge over time. Certain anatomical landmarks are very important: The apex is the most inferior part of the gland and the base of the prostate is the superior part of the gland. The prostate lobes are found on either side of the prostatic urethra, which transverses the prostate. The prostatic urethra is found in the anterior part of the gland and is covered with urothelium. The urethra forms a more or less 30° angle anteriorly in the middle of the prostate and the verumontanum is just distal to this angulation.(2,14)



A = Ampulla
ED = Ejaculatory Duct
I = Isthmus
P = Prostate
SV = Seminal Vesicle
VD = Vas Deferens
U = Urethra

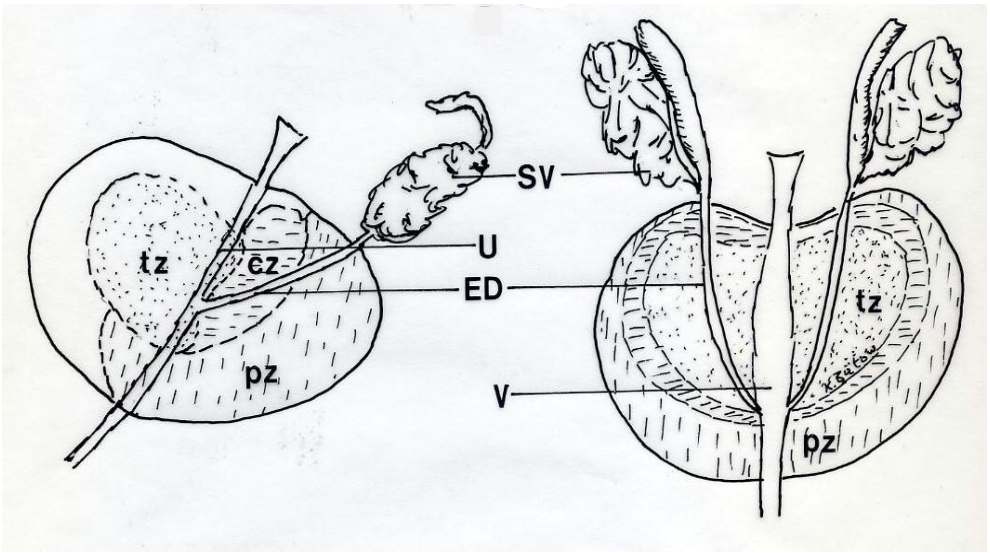
(Drawing. K-W. Bütow 2013)

Figure 1: The Prostate and Seminal Vesicles

The prostate is divided into different zones and lobes and is enclosed in a capsule made of collagen, elastin and smooth muscle.(2,14)

The central zone is a cone shaped area that surrounds the ejaculatory duct and extends from the base of the bladder to the verumontanum. Only 1-5% of all prostate cancers develop in this zone. The peripheral zone is found posteriolaterally in the prostate and also contains the most prostatic glandular tissue. Up to 70% of all adenocarcinomas of the prostate develop in this zone. The transitional zone surrounds the prostatic urethra proximal to the verumontanum. Approximately 20% of cancers arise from this area. The prostate lobes are described as lateral

and median. Enlarged periurethral tissue in the transitional zone causes hyperplasia of the lateral lobes. The hyperplastic periurethral glands bulge into the bladder neck and form a median lobe.(2, 14, 15)



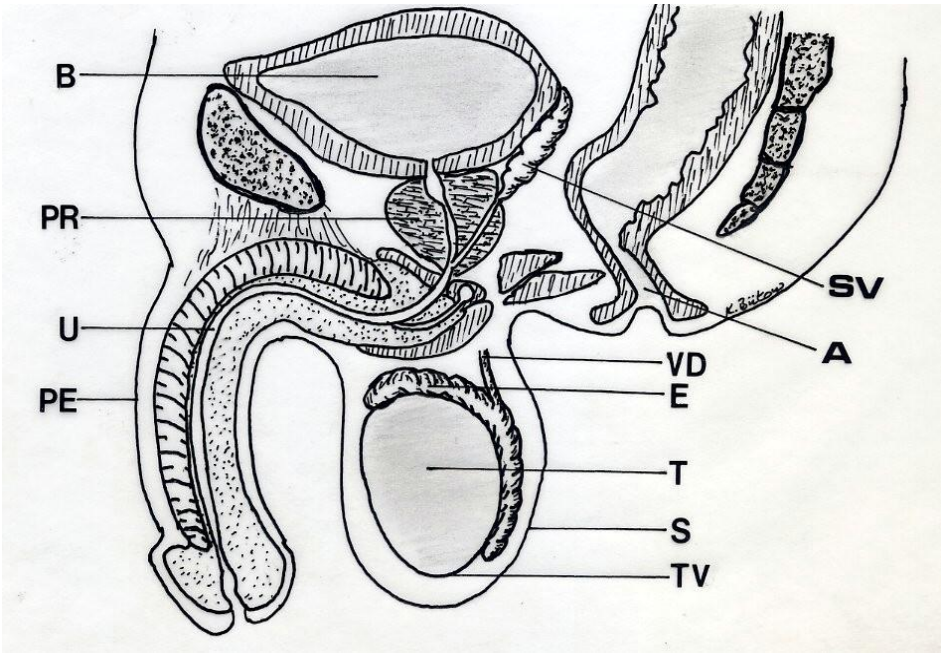
ED = Ejaculatory Duct
SV = Seminal Vesicle
U = Urethra
V = Verumontanum
cz = central zone
tz = transitional zone
pz = peripheral zone

(Drawing. K-W. Bütow 2013)

Figure 2: Schematic Representation of the zonal Anatomy

The bladder and bladder neck are situated superior to the prostate and in relation to the base of the prostate. Posterior and superior to the prostate are the seminal vesicles, which are accompanied by the ductus deferens, a continuation of the duct of the epididymis. Posterior to the prostate is the rectoprostatic fascia (Denonvilliers fascia), which lies between the prostate and the rectum. The urethral sphincter, consisting of striated muscle, is in continuation with the apex of the prostate and is found at the inferior border of the gland. On both lateral aspects of the prostate the neurovascular bundle is situated which contains the nerves derived from the pelvic plexus. Posterior to the pubic symphysis is retropubic space and the deep venous plexus. The prostate is connected to the pubic bone via the puboprostatic ligament, a continuation of the prostatic sheath.(16) The prostate's main blood supply is derived from the inferior vesicle artery, which originates from the anterior division of iliac artery. The inferior vesicle artery then divides into two main branches, which run between the layers of the lateral prostatic fascia. One of the arteries, the capsular artery continues posteriolaterally to the prostate with the cavernous nerves. The deep dorsal vein collects the venous drainage of the prostate and finally

drains into the dorsal venous plexus, which joins the lateral venous plexus. These all eventually drain by means of the pudendal, obturator and vesicle plexus into the internal iliac vein.(14, 16)



A = Anus
B = Bladder
E = Epididymis
PE = Penis
PR = Prostate
S = Scrotum
SV = Seminal Vesicle
T = Testis
TV = Tunica Vaginalis
U = Urethra
VD = Vas Deferens

(Drawing. K-W. Bütow 2013)

Figure 3. A cross-section of the male reproductive tract

2.3 Prostate Cancer Screening and Diagnosis

Prostate cancer screening usually compromises of two elements: The digital rectal examination and since the 1990's is the serum PSA level. According to two large randomized trials, namely the Prostate, Lung, Colorectal, and Ovary trail (PLCO) in the United States and the European Randomised Study of Screening for Prostate Cancer (ERSPC) trail in Europe, there is currently no evidence that widespread screening of the population for the detection of early prostate cancer is required.(17,18) This said, in most developed countries, prostate cancer screening commences from about the age of 45 years. The American Urological Association (AUA), Japanese Urological Association (JUA), and National Comprehensive Cancer Network (NCCN) recommend that all men obtain a baseline PSA at age 40.(19)

As previously mentioned most prostate cancers are located in the peripheral zone of the prostate and can be detected by digital rectal examination if they are larger than 0,2ml in

volume.(20) If there is a suspicious finding on the digital rectal examination, then a further investigation in the form of a prostate biopsy is necessary. Even where the PSA value is within the normal range, a suspicious digital rectal examination alone has a positive predictive value of 5-30%.(21) In a recent study conducted by Abdrabo *et al.*, the digital rectal examination alone had a 63,8% sensitivity and a 68% specificity for detecting prostate cancer.(22)

The other powerful tool used in the screening of prostate cancer is the PSA enzyme, which liquefies coagulated ejaculate, necessary for reproduction. An elevated PSA is specific to the prostate but may be due to numerous causes, such as prostatitis, benign prostatic hyperplasia or prostate cancer.(23) Unfortunately no PSA value is specific for the diagnosis of prostate cancer, but as a general rule a PSA value of above 4ng/ml should be regarded as suspicious. This value often however needs to be adjusted according to age and prostate volume. Between 65% to 90% of the total PSA (*tPSA*) is bound (*cPSA*) and only 10% to 35% of PSA is free PSA (*fPSA*). In some cases the free/total PSA ratio is used to try and differentiate between benign enlargement of the prostate and prostate cancer.(24) Research has been conducted on other parameters such as PSA density, PSA density in the transitional zone, age specific reference ranges, PSA velocity and free PSA, but the gold standard still remains the serum PSA.(3) PSA is a continuous parameter; the higher the value, the more likely it is due to prostate cancer. An elevated PSA level is a better predictor of prostate cancer than a digital rectal examination. A 2004 study in the USA revealed that some men may harbour prostate cancer at even low levels of serum PSA.(20)

Table 1. PSA Risk

PSA level	Risk of PCa
0-0.5	6.6%
0.6-1	10.1%
1.1-2	17.0%
2.1-3	23.9%
3.1-4	26.9%

Heidenreich *et al*.(20)

It can therefore be said that there is no optimal PSA threshold value for detecting prostate cancers.(25)

Once the digital rectal examination, PSA level and the therapeutic consequence indicate that further investigations are required, a biopsy of the prostate is done. Most prostate biopsies are guided by transrectal ultrasound, although some urologists prefer to do perineal prostate biopsies. In the past, a sextant biopsy was considered to be the gold standard, however, according to the latest research, if the prostate volume is 30-40ml, at least eight cores should be sampled. Extra sampling of a suspect lesion on transrectal ultrasound is also suggested.(20) In a prospective study, Presti *et al*. found that by using the traditional sextant biopsy, 20% of cancers were missed, but by doing an eight core biopsy (apex, mid lobar mid gland, lateral mid gland and lateral base) the cancer detection rate went up to 95%. This was irrespective of prostate size.(26)

2.4 Histopathology of Prostate Cancer

In the majority of cases the prostatic tumour is an adenocarcinoma that is well differentiated, forming an acini, tubules or cribiform pattern. The neoplastic acini invade the stroma of the gland as well as the lymphatics and occasionally the perineural areas.(27) Like most tumours, prostate cancer is defined according to the TNM classification designed by the Union of International Cancer Control (UICC).(28)

Table 2. The TNM classification:

	Primary Tumour
T1	Clinically in apparent tumour
T1a	Incidental finding, less than 5% burden on transurethral resection
T1b	Incidental finding, more than 5% burden on transurethral resection
T1c	Diagnosis on prostate biopsy, no tumour found on final histology
T2	Tumour confined to prostate
T2a	Tumour in less than 50% of a single prostate lobe
T2b	Tumour in more than 50% of a single prostate lobe
T2c	Tumour present in both lobes
T3	Tumour extends beyond prostate capsule
T3a	Extracapsular extension with bladder neck involvement
T3b	Involvement of the seminal vesicles
T4	Tumour is fixed or invades other structures besides the seminal vesicles

	Regional Lymph Nodes
N0	No regional lymph node metastases
N1	Regional lymph node metastases

	Distant Metastases
M0	No distant metastases
M1	Distant metastases

Sobin *et al*.(28)

It is important to note that the invasion of the prostate capsule is still classified as a T2 disease, as it does not spread beyond the prostate capsule.(28)

Organ-confined tumours can therefore be classified postoperatively as T1c or T2. In this thesis our focus will be on T2 tumours, as the T1c stage classification is allocated to conditions where the final histological examination shows no residual tumour.

A very unique characteristic of prostate cancer is that it can also be defined by the differentiation of the glands in the prostate cancer itself, first described by Gleason in 1966 and known as the Gleason Score. The score ranges from grade 1 to grade 5; grade 1 being a well-differentiated cellular pattern and grade 5 being a poorly-differentiated cellular pattern. The most common and second most common Gleason grades are added together to provide us with the Gleason score. The lower the score, the less aggressive the cancer is. The most recent modification of the grading system by the International Society of Urologic Pathologists was in 2005.(29)

Table 3. 2005 International Society of Urological Pathology Modified Gleason System

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 tumour 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
Pattern 4
Fused microacinar glands Ill-defined glands with poorly formed glandular lumina Large cribriform glands Cribriform glands 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

Epstein *et al*.(30)

Of note however is that there is often discordance between the Gleason Score found on the biopsy specimen and the Gleason Score found on the final specimen after radical prostatectomy. In a recent study it was shown that concordance between the two pathology

samples only occurred 58% of the time and that the Gleason Score was higher on the final prostate sample in 38% of the cases.(31)

A low Gleason Score (6 or less) on final histology is usually also associated with a low tumour stage (pT2N0 (83%), pT3N0 (14%), pT4N0 (0.1%) and pTN1 (2%)). Unfortunately this however does not preclude PSA recurrence (26% at 15years) and local recurrence (20% at 15years) at a later stage.(32)

2.5 The Treatment Options in organ-confined Prostate Cancer

The treatment advised for organ-confined and contained prostate cancer depends on numerous variables. The different options will be discussed below.

2.5.1 Watchful Waiting

0ther terms also used for this treatment option are “deferred treatment” or “symptom-guided treatment”. Increased screening worldwide, has resulted in a higher incidence of small, localised, well-differentiated prostate cancers, the treatment of which would be of no benefit to the patient.(20) It is often difficult to define which tumours can be classified into “insignificant or small”.(33) Despite this, the group of patients falling into this category have a less than 10 year life expectancy and would the prostate cancer become symptomatic, they would also only be treated symptomatically. The aim of this is to avoid overtreatment and a concomitant decrease in the quality of life, as treatment itself carries a high morbidity and is associated with an increased mortality.(20) In a study conducted in the USA, after a 7-year follow up, 41% of patients on watchful waiting remained free from any form of treatment. The remaining patients had either received radiotherapy or brachytherapy (34%), hormone therapy (16%) or even prostatectomy (10%),(34) showing that treatment could be avoided in nearly half of the patients.

2.5.2 Active Surveillance

The rationale behind this treatment option is that a very well-selected group of people with low risk disease will have a very low rate of progression. Abstinence from treatment will avoid the

unnecessary treatment of patients with a low progression rate. At the same time, close monitoring will also identify those patients requiring definitive treatment. The main difference between this approach and 'watchful waiting' is that in this approach, patients will have decisive, radical treatment if there is disease progression. Active surveillance is also often considered a strategy to "buy time", as often the quality of life post-intervention, especially with regard to potency and continence, is poorer than that before any form of intervention. Some eligibility criteria have been suggested for active surveillance, namely: clinically confined prostate cancer, a Gleason Score of 7 or below and a PSA level of less than 15-20ng/ml. Criteria used to define cancer progression are: PSA doubling time of between two and four years and a Gleason Score progression of more than or equal to 7. However these indicators are have not been properly validated and currently it is not possible to make an evidence-based recommendation on when to continue active surveillance and when to start treatment.(20) In one of the most well-designed models for a statistical analysis of factors relating to active surveillance, Epstein found that there was a 95% predictive value for identifying "significant" cancer preoperatively, but only a 66% predictive value for identifying "insignificant" cancer, demonstrating the difficulty of deciding which patients to assign to active surveillance.(2) This said, this approach is often used in patients where a diagnosis of a well-differentiated prostate cancer is made after a transurethral resection of the prostate (Stage T1a and T1b).(35) In taking this treatment option, patients need to be well informed that there is always the risk that a curable cancer may progress to being incurable while on the active surveillance program.(20) In a Finnish study, patients on active surveillance indicated that their quality of life was the same as those of the general population with regard to general, mental and physical health. The stressors of this treatment strategy did not have any influence on urinary or erectile functions, demonstrating that where patients are counselled fully in advance, they still have a good quality of life prior to the commencement of definitive treatment.(36)

2.5.3 Radical Prostatectomy

The surgical treatment of prostate cancer consists of removing the entire prostate gland, situated between the urethra and the bladder, as well as the seminal vesicles and periprostatic fat with the aim of achieving negative margins. Often a bilateral pelvic lymph node dissection is performed simultaneously. The main advantage of this procedure is that if performed skilfully,

it offers the possibility of cure with minimal damage to surrounding tissue. The other benefit being that it provides accurate pathological tumour staging as the removed specimen can be examined *ex vivo*.(2) This procedure is offered to patients with localised disease and a life expectancy of more than ten years, with the goal of eradication of the disease. Unfortunately it often entails significant morbidity with regards to continence and potency,(20) with a nerve-sparing operation (unilaterally or bilaterally) being performed to try and prevent the adverse effects on potency. The operation still remains the gold standard in the treatment of organ-confined prostate cancer. The individual surgical techniques will be discussed in Section 2.6.

2.5.4 Radiotherapy

External beam radiation therapy (EBRT) involves the use of gamma rays, usually photons, directed at the prostate. The therapy can be used on its own or in combination with hormone therapy.(37) Unfortunately there are no randomized control trails comparing EBRT with radical prostatectomy, but the general consensus is that the overall survival rate as well as the complication rate is comparable with that of radical surgery.(20) In a retrospective study by Boorijan et al high risk patients who had had a radical prostatectomy were compared to those who had undergone EBRT plus hormone therapy and EBRT alone. The 10-year cancer-specific survival rate was 92%, 92% and 88% respectively. The risk of all causes of mortality was however slightly higher in EBRT and hormone therapy group.(38) In the most advanced centres, EBRT consists of scanning the patient and transferring the 3D information on the target volume and safety margin into a planning system. At the time of irradiation, adaptations to the contours of the target volume can be done automatically. This is often a multidisciplinary approach between physicians, physicists, dosimeters, radiographers, radiologists, radiology oncologists and computer scientists. Biochemical disease-free survival is higher if the radiation dose is above 72Gy as compared to below 72Gy in low volume disease. Rarely will a radiation dose of more than 81Gy be given in the light of the danger of radiation toxicity.(20)

2.5.5 Brachytherapy

Brachytherapy is usually a safe and minimally invasive form of treatment that only requires only a short hospitalisation stay. Typically, a transperineal access, accompanied by transrectal ultrasound, is used to insert and implant iodine-125 or palladium-103 particles (often referred to as ‘seeds’) into the prostate.(2, 3) There are certain eligibility criteria that should be adhered

to when using this form of therapy. These are: a clinical tumour stage of T1b-T2a N0 M0; a Gleason Score of 6 or less on a sufficient amount of biopsies; an initial PSA of less than 10ng/ml; the presence of cancer in less than 50% of the biopsy cores; a prostate volume of less than 50cm^3 and an International Prostatic Symptom Score (IPSS) of less than 12. Patients with low risk prostate cancer are good candidates for this type of therapy. Patients who have received more than 140Gy by Day 90 have a significantly higher biochemical control rate after four years than patients receiving less than 140Gy.(20) In a recent study, the 5-year prostate specific antigen relapse-free survival for low, intermediate and high risk patients was 98%, 95% and 80%, respectively.(39)

2.5.6 Hormone Therapy

Hormone therapy is not used as the first line therapy in locally contained prostate cancer, but has found its place in advanced prostate cancer, as a therapy in recurrent disease after definitive treatment or as part of a multimodality approach. All hormone therapy is based on the fact that prostate cells are dependent on androgens for growth and proliferation and therefore tumour growth is be hampered by depriving these cells of testosterone. There are three main approaches to this therapy: (1) suppression of the secretion of testicular androgens, (2) inhibition of the action of the circulating androgens on the prostate at the level of the receptors and (3) suppression of intracellular androgen synthesis. The combination of 1+2 is known as complete (maximal or total) androgen blockade.(2, 20)

2.6 The Surgical Treatment of Prostate Cancer

Young first performed the radical prostatectomy at the beginning of the 20th century, using the perineal approach. Memmelaar and Millin were the first to perform the retropubic prostatectomy. The surgical removal of the prostate is to date the only treatment that has been shown to benefit cancer-free survival in comparison to conservative management in randomised control trials.(20) The surgical treatment of prostate cancer can be divided into three main areas: open radical prostatectomy, of which the most common is the retropubic radical prostatectomy (RRP), but which also includes the perineal radical prostatectomy; the

laparoscopic radical prostatectomy (LRP) and the newest of the surgical techniques the robotic-assisted (laparoscopic) radical prostatectomy (RARP).(2)

2.6.1 Radical retropubic prostatectomy

The Radical Retropubic Prostatectomy (RRP) is the most common performed prostatectomy, as urologists, due to its familiarity, often prefer it above other surgical techniques. It has a low risk of rectal injury and provides ready access for the pelvic lymphadenectomy. If wanted, the neurovascular bundles can be preserved in a procedure known as a nerve-sparing prostatectomy.(2)

2.6.2 Total perineal prostatectomy

This surgical approach is an acceptable one when experienced surgeons perform it. This surgery often results in less blood loss, but it does have the disadvantage that it does not provide access for pelvic lymph node dissection. It is also associated with a high rectal injury rate and a nerve-sparing procedure is often not possible.(2)

2.6.3 Laparoscopic radical prostatectomy

The Laparoscopic Radical Prostatectomy (LRP) is often referred to as being the most difficult form of prostatectomy and is only performed by surgeons experienced in the field of laparoscopy. This form of surgery is often accompanied by less bleeding, better visualisation, less postoperative pain and a shorter convalescence period. However it does require a transperitoneal approach (an extraperitoneal approach is also possible, although it is more technically challenging), which carries a greater risk for bowl injury, postoperative obstruction and vascular injury. It has often been criticised for having a higher risk of severe complications and difficulty in achieving hematostasis without thermal injury to the neurovascular bundle. Postoperative bleeding may also be more prominent due to the decrease in intra-abdominal pressure at the end of surgery.(2)

2.6.4 Robotic-assisted radical prostatectomy

Overall robotic surgery is fast becoming a leading form of surgery in many domains. Since 2007 the number of robotic surgeries worldwide has nearly tripled from 80000 to 205000, with the

radical prostatectomy leading the way.(40) This operative technique will be discussed in depth in Section 2.7.

2.7 Robotic-assisted radical prostatectomy

Robotic-surgery, here referring to the da Vinci© System produced by Intuitive surgical© Inc. Sunnyvale Cal, USA, was first introduced to the open market in 1999 and first used by cardiac surgeons. This operating technique was introduced in Urology for the first time in 2001 when Binder and Kramer performed 10 radical prostatectomies in Frankfurt.(41) Initially the goal of using this new surgical technique was to minimise blood loss, decrease postoperative pain, shorten the convalescent period and improve cosmetics. It was also hoped that it would improve urinary incontinence and potency, the two major setbacks often associated with a radical prostatectomy. Contrary to laparoscopic surgery, it is claimed that robotic surgery has a much shorter learning curve. The technical advantages above conventional laparoscopy are the 3D viewing and magnification, elimination of surgeon tremor, direct eye-hand coordination as well as instruments that facilitate fine dissection.(42) The practical advantage being that of the ease in which one can tie sutures and perform the vesicourethral anastomosis.(2) Despite all of this, superiority with regard to oncological and functional outcome has not been proven. Prospective trials are urgently required, although it seems that in the USA and in some areas of Europe, the Robotic-assisted Radical Prostatectomy (RARP) is already becoming the new gold standard in organ-confined prostate cancer surgery.(20)

2.7.1 The Surgical Technique

The original robotic surgery techniques were designed to enable trauma surgery on the battlefield, from a safe distance. The surgeon, who is seated at the console, uses finger-controlled movements to manipulate the surgical instruments at a different site. Specialised software is used to transfer the motion of the fingers, without delay, to the microsurgical instruments. A variety of instruments can be used and exchanged at the 8mm port by the surgical assistant who, scrubbed and sterile, is at the side of the patient. The instruments used have special wrist joints which allow 360° movement in the confined pelvis. Another advantage for the surgeon is that unlike in laparoscopic surgery where counterintuitive movements must

to be learnt (moving the external part of the instrument to the right moves the internal part of the instrument to the left), robotic surgery, although using laparoscopic instruments, allows the surgeon to use the same hand movements as in open surgery. Two optic lenses are aligned side by side at the end of the camera which allows the surgeon three-dimensional vision. The possible shorter learning curve in robotic surgery is credited to these factors and also explains why the company that markets robotic surgery is also called "Intuitive".(43) Criticism of the technique often focuses on the fact that unlike open surgery there is no tactile stimulation and the surgeon has to rely on visual cues only.(42) In a study designed by Tewari *et al*. to try and disprove this fact, visual cues were used to train robotic surgeons, with the end goal being the avoidance of posterolateral positive surgical margins. By following cues such as the observation of the periprostatic fascia compartment, colour and texture of tissue, periprostatic veins, signs of inflammation and visualisation of a freely, separating bloodless plane showing areolar tissue, the overall posterolateral positive surgical margin rate was 2,1%. This is extremely low.(44)

Unlike RRP, the surgical approach is usually transperitoneal. This is associated with a greater incidence of bowel injury and postoperative ileus. Haematoma and urinary leakage may also be managed easier in an extraperitoneal approach and although an extraperitoneal approach has been performed successfully used in robotic surgery, it is not the approach most commonly used. Some surgeons would view previous intra-abdominal surgery as a relative contraindication to RARP. An additional person using an extra port with laparoscopic instrumentation provides surgical assistance.(42)

2.7.2 The Outcome

Often, especially when comparing surgical techniques, the oncological control, continence and potency are discussed. In most cases the jury is still out on which radical surgical technique provides the best outcomes and many contradictory reports can be found in the literature.

In a population-based observational cohort study conducted in the USA in 2009, it was found that the amount of men undergoing minimally invasive radical prostatectomy (MIRP) in comparison to RRP increased from 9,2% in 2003 to 43,2% in 2007. Although the complication rates were lower in the MIRP group, the incontinence and erectile dysfunction rates were

higher. The oncological outcomes were the same.(45) In a study conducted by Magheli *et al*. 522 patients that had undergone RARP were matched to the same number of men that had undergone LRP and RRP. The positive surgical margin rate was 19,5%, 13,0% and 14,4% respectively, showing a statistically significant increase in positive surgical margins in patients undergoing a RARP. Attention should be drawn to the fact that this was the first experience of RARP at that centre and that the rate of biochemical recurrence for all three surgical groups was the same.(46) The international literature is scattered with contradictory reports and findings but when looking at a systematic review, performed by Ficarra *et al*., the evidence showed that LRP and RARP were more time consuming than RRP, but that all three operative techniques showed similar continence and potency rates, although a single prospective, non-randomised trail did suggest better outcomes in the RARP group. The positive surgical margin rates were comparable.(47) Ideally prospective randomized trials comparing the RARP to other surgical techniques should be conducted. However, since the RARP has in many centres already become the gold standard in radical prostatectomy surgery, it is unlikely that such a trial will be forthcoming.(48)

2.7.3 The Cost and Training Issue

Additional issues surrounding the topic of RARP include that of training and cost. The real learning curve for the RARP has not yet been fully established, although there is a general consensus that it is shorter than that required for the LRP. A question that has arisen during the introduction of this technique is when a RARP program should be initiated at a centre. Some believe that the skills learnt performing LRP and RRP procedures can be transferred to the RARP, while others believe that training courses should be attended and some even believe that fellowships in robotic training should be implemented. A major drawback in any training program is that only a single surgeon only can work at a normal console at any given point in time.(42)

Another considerable disadvantage of RARP are the costs involved. The initial cost of a da Vinci© System approaches $1,400 000, not to mention the annual technical support fees and the intraoperative expenses. The instruments also need to be exchanged after every 10 operations. This operation can therefore only be cost-effective in high volume centres.(43) The

most cost-effective surgery still remains the RRP.(42) There is some debate about the total cost per patient, as patients undergoing a RARP are often known to have a shorter hospital stay. The costs for patients undergoing a RARP or a RRP from the day of admission till one year postoperatively were calculated in a study conducted in the USA. The cost difference per patient was $1200, with the RARP being the more expensive operation.(49)

2.8 The Relevance of Positive Surgical Margins

The goal of any curative cancer surgery is to achieve local control and therefore better the oncological outcome of the patient. The definition of a positive surgical margin is tumour present at the edge of an inked pathology specimen. A positive surgical margin is created when an incision is made into an extraprostatic tumour (extraprostatic disease) or when a surgeon accidently makes an incision into a prostate with organ-confined disease (pT2).(50)

The objective of a radical prostatectomy is to completely remove the prostate cancer and therefore an important way to control locally confined cancer is clear surgical margins. Grossfeld et al described poor prognostic features with regard to cancer control as non–organ-confined disease and extracapsular tumour; perineural, lymphovascular and seminal vesicle invasion, positive surgical margins and lymph node metastases.(2) The importance and the relevance of the positive surgical margin is that it is the only poor prognostic feature of a poor outcome that can be influenced by surgical technique.

Positive surgical margins influence the prognosis of patients treated surgically for organ-confined prostate cancer. In a study performed by Kin *et al*., where the outcome of patients treated with radical prostatectomy (RRP and LRP) was analysed, a statistically significant correlation could be seen between a positive surgical margin and biochemical recurrence ($p=0.035$). This study did however not take pathological tumour staging into account.(51) A closer look at research evaluating whether positive surgical margins are an independent prognostic marker after radical prostatectomy, research done in Norway proves that in general patients with positive surgical margins, irrespective of their location or extent, are at higher risk of PSA recurrence at a mean follow-up time of 62 months. It is noteworthy that the hazard ratio

is statistically significantly higher in patients with localised (pT2) disease, in comparison to locally advanced disease (pT3/pT4). This research emphasises the importance of clear surgical margins in organ-confined disease.(52) Swindle *et al*. examined 1389 patients who had undergone a RP and found the positive surgical margin rate of pT2 tumours to be 6,8% and 23% for pT3/pT4 tumours. Overall patients with positive surgical margins had a 10-year progression free probability of 58%, whereas those patients with clear margins surgical margins had an 81% 10-year progression free probability.(50) In an article by Lake *et al*. the positive surgical margin rate in 1997 pT2 tumours that had been resected by means of a RP was supplied as 14%, of which 11,5% had focal positive surgical margins (<3mm) and 2,6% had extended positive surgical margins (>3mm). The 10-year disease free survival for patients with clear surgical margins, focal positive surgical margins and extended positive surgical margins, was 90%, 76% and 53% respectively.(53)

Based on the above information, it can therefore be said that positive surgical margins, even in organ-confined disease leads to an increased risk in biochemical recurrence and a decreased in disease free survival.

With this in mind, when looking at the literature present, many publications try to identify risk factors with regard to positive surgical margins and the radical prostatectomy. Relationships that have been examined in the past have been the nerve-sparing operation,(54, 55, 56) the learning curve (57, 58) and the prostate weight (59, 60) to mention but a few.

3. Goal Setting

Prostate cancer is still a very actual and growing topic, especially considering the rising incidence due to better screening options and an increasingly aging population. Robotic-assisted radical prostatectomy is increasingly being used to treat organ-confined prostate cancer and has become the gold standard of treatment at some centres. As with all tumour surgery the primary objective is still to provide a good oncological outcome. Positive surgical margins are a real risk in organ-confined cancer, and influence the overall disease-free survival rate. The goal of this thesis is to identify factors that can influence the positive surgical margin rate in organ-confined prostate cancer in the hope that by addressing these factors the occurrence of positive surgical margins can be curtailed and better oncological outcomes achieved.

4. Material and Methods

4.1 Patient Selection Criteria

The first robotic assisted radical prostatectomy (RARP) was performed at the University Clinic of Saarland on the 18th March 2006. As a recognized prostate cancer centre and due to the specialisation of the clinic in the operative treatment of prostate cancer, by the 26th January 2011, 1200 patients had successfully been treated with this surgical technique. All patients, irrespective of outcome, who were treated by means of the RARP during this time period were included in this study. All operations were performed by one of three surgeons. Not one of the surgeons had had prior robotic surgery experience.

All patients, irrespective of outcome, operated in this time span, were included in this study. All operations were performed by one of three surgeons. None of the surgeons had prior robotic surgery experience.

All patients operated in this time span had been diagnosed with prostate cancer on prostate biopsies. These biopsies were predominantly performed in external clinics or private practices. Only a minority of patients had had their prostates biopsied at the University Clinic of Saarland itself. Most of the biopsies had been deemed necessary after a suspicious clinical examination, a raised PSA value or an increased PSA doubling time. The patients operated upon during this time period had presented with clinical stages of T1, T2 or T3 and none of them had had any known metastases at the time of surgery. The intention of the surgery was always curative and other therapeutic options such as active surveillance, 'watchful waiting', as well as radiotherapy, had been discussed with the patients. As the University Clinic of Saarland specialises in robotic surgery, unless there was a medical contraindication, all patients undergoing a radical prostatectomy were to be treated by means of the RARP procedure. The patients were fully informed of this fact prior to surgery.

4.2 Data Retrieval

In furtherance of internal quality assessment and audit, all data from patients operated upon using this technique was collected retrospectively till April 2010 and from then onwards prospectively. The initial aim of this data-capturing strategy was to evaluate the surgical outcome and to this end data was collected and formatted in an excel spread sheet. As time progressed, additional criteria were identified and added to the excel spread sheet. As such the size of the excel spread sheet grew over time.

Currently, 83 different data sets are captured describing the preoperative, the intraoperative and the postoperative events and facts. These different data sets are manually entered into the excel spread sheet. The details of the patients undergoing a RARP could be retrieved from the theatre operating lists. Once a patient had undergone a RARP, irrespective of outcome, he would be added to the spread sheet. Most of the data that is needed can be retrieved electronically via the computer software, SAP, which is used throughout the clinic. However, not all data, particularly the preoperative data can be retrieved from the computer system. It is therefore essential that the data collection process be started upon admission of the patient to the hospital. If does not take place, valuable data could be lost.

4.3 "da Vinci Worksheet" and Data Acquisition

In order to facilitate the data collection process and to assure that no data is lost the "da Vinci Worksheet" was implemented in April 2010 (refer to Attachment no. 1). The admitting doctor records all pre-operative data on the first two pages of the worksheet on the day of the admission. On the day of discharge the discharging doctor completes the intra-operative as well as the postoperative information. In this manner the person collecting the patient data did not have to personally interview each of the patients. The admitting doctor regularly filled in most preoperative data, but often there were gaps in the data filled in by the discharging doctor as some discharges also took place over the

weekend. Luckily most operative and postoperative data could be retrieved via the discharge letters and operating reports. Data that could not be captured from these reports could be retrieved from the hard copy of the patient's file. This is especially important with regard to the preoperative prostate biopsies, which are performed in clinics outside the University clinic, since these are not recorded electronically on our computer software.

In 2011 the University Clinic of Saarland implemented the electronic capture off all patients' ward files. All patients admitted after February 2009 would have their paper files electronically scanned into the computer system. This would enable missing data to be retrieved electronically if a patient was admitted after February 2009. In some patient cases not all data could be retrieved in this manner. An attempt to retrieve the outstanding data was made by writing letters to the referring urologist. However, this process was not always successful.

Furthermore random audits of patients' data were also performed. This demonstrated that at certain times, before the establishment of the "da Vinci worksheet", the data captured was of poorer quality, especially regarding the preoperative data. As of November 2010, the data recorded before April 2010 was audited and updated using the above mentioned processes.

4.4 Excel Spread sheet Lay out

The spread sheet containing the patients information consists of 83 columns and 83 different sets of data. Not all recorded data was included in the current study. The reason for documenting all necessary data is to facilitate future audits and studies. The research described in this paper only used information of 11 data sets, namely the following:

Table 4. Preoperative Data Sets

Preoperative Data
Preoperative PSA (ng/ml)
Number of biopsies taking preoperatively
Number of left-sided positive biopsies
Number of right-sided positive biopsies
Nerve-sparing procedure: 1=no, 2= yes
Nerve-sparing location: 1 = right, 2 = left, 3 = bilateral
Biopsy Quality: 0 = inadequate, 1 = adequate*

Table 5. Postoperative Data Sets

Postoperative Data
Prostate weight (g)
Tumour stage: pT
Positive surgical margins: 1 = R0, 2 = R1, 3 = R2
Positive surgical margin location: 1 = basal, 2 = lateral, 3 = apical, 4 = seminal vesicles, 5 = multiple

Table 6. Definitions of the variables

Preoperative PSA (ng/ml): The PSA value at diagnosis, also before any form of hormone treatment
Number of biopsies taken preoperatively: The number of the prostate biopsies taken at diagnosis (Range 2 till 27)
Number of left-sided/right-sided positive biopsies: The number of positive biopsies from each prostate lobe
Nerve-sparing: The dissection and sparing of the neurovascular bundle lateral to the prostate (bilaterally, right or left)
Prostate weight: The prostate weight after surgical removal, as documented by the examining pathologist. The prostate is weighed with the seminal vesicles.
Tumour stage: According to the TNM 6^{th} (2007) and TNM 7^{th} (2010) classification
Positive surgical margins: Microscopically proven extension of the tumour into the surgical dissection or cauterization margin
Positive surgical margin location: As described by the pathologist, the area of the prostate where the extension of the tumour into the surgical margins was found. 'Multiple' refers to several separate areas where the tumour can be found in the surgical margin and not a continuous positive surgical margin.

*"Biopsy Quality" is a criterion that was designed in line with this study to quantify the quality of the preoperative biopsy, as the results of the biopsy are the basis for the decision to perform a radical prostatectomy or not. The results of the preoperative biopsy also influence the decision on whether to perform a nerve-sparing operation or not. The quality of the biopsy is very difficult to assess, especially since there is very limited information available about the different biopsy techniques used. As mentioned previously, most biopsies are performed at external clinics. Two criteria are used to evaluate whether a biopsy was of "adequate" or "inadequate" quality.

No. 1: At least 8 biopsy cores should be removed from the prostate (in line with EAU Guidelines)

No. 2: It should be possible to locate the biopsy core containing the prostate cancer (for example, left apex)

If both criteria were fulfilled the quality of the biopsy was deemed “adequate” and if none or only one criterion was fulfilled the biopsy was labelled as “inadequate”.

4.5 Statistical Evaluation of Data

The data collected for this study was used to create an excel pivot table where numerous varying parameters were compared to one another in a preliminary statistical evaluation. The data was also presented in tables and graphs for a better visualisation of the evaluation process.

Once the preliminary statistical evaluation had been completed the Institute for Medical Biometry, Epidemiology and Medical Informatics at the University Clinic of Saarland was approached to perform a formal analysis. The statistical analysis was completed with the SPSS Software for Windows. Univariate analyses were conducted, where the association of one explanatory variable with one outcome variable was examined. Pearson’s correlation test was used to assess the linear association between two continuous variables. The correlation ranged from -1 to +1, with numbers close to 0 not showing a strong correlation. Negative numbers indicated that as the one variable increased, the other variable decreased, whereas positive numbers indicated that as the one variable increased, so did the other variable. The Fisher exact test was also used to compare the outcome of two separate variables/groups as this test compares proportions between two or more groups. Outcomes were classified as statistically significant where the p value was below 0.05, as in such instances the null hypothesis had been disproven and the statistical variation could not be attributed to random chance.(61)

Since the purpose was to identify variables that would predict positive surgical margins, only variables that were statistically significant were used in the multivariable analysis. The goal of the multivariable analysis was to examine the association of multiple variables with the outcome variable so that independent risk factors for positive surgical margins could be identified. The logistic regression analysis included a 95% confidence interval as well as a corresponding p value.(61)

5. Results

5.1 Tumour Staging

Elsewhere in this thesis, it is explained that prostate cancer is staged according to the TNM classification. Only the pathological, not the clinical stage, was examined in this study. A pT2 tumour stage represents cancers that are still organ-confined and have not yet advanced extracapsularly. As previously clarified the pT1c tumour stage will not be included in our analyses as no tumour is found on the final histology specimen.

Therefore the first objective of this study was to further classify the patients with a pT2 tumour stage amongst the 1200 patients who had been selected for this study. The pT2 tumour stage was further divided into its subcategories, namely pT2a, pT2b and pT2c.

Table 7. Tumour Stage Division

Tumour stage (pT)	Number of patients (n = 1200)	Percentage (%)
1c	6	0.5%
2a	91	7.6%
2b	5	0.4%
2c	761	63.4%
3a	213	17.8%
3b	119	9.9%
4	5	0.4%

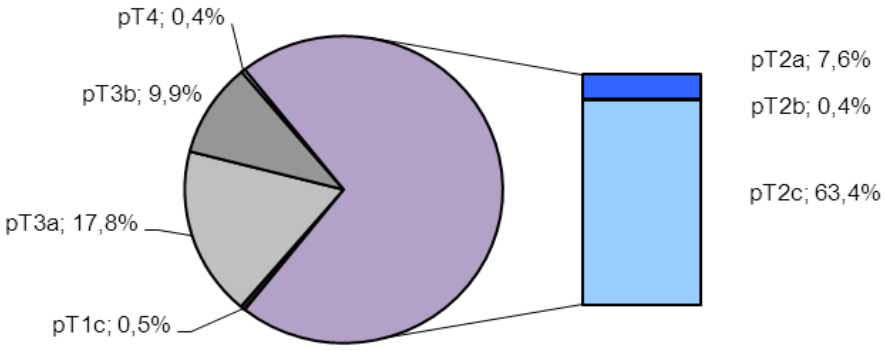


Figure 4. Tumour Stage distribution

This subdivision demonstrates that pT2 tumours are the most common tumour found in the study population, with the majority of pT2 tumours falling within the pT2c group.

5.2 Positive surgical margins

The positive surgical margin rate in patients with a pT2 tumour stage was calculated. In this analysis pT2a and pT2b were grouped together and pT2c was evaluated separately. The positive surgical margin rate for the pT2a and pT2b tumour stage as compared to the pT2c tumour stage was 4.2% and 8.4% respectively, with the total positive surgical margin rate being 7.9%, where R0 = negative surgical margins and R1 = positive surgical margins.

Table 8. Surgical margins for pT2 tumour stage

Tumour stage	R0	R1	Number of Patients (n = 857)	Percentage R1 (%)
2a + 2b	92	4	96	4.2%
2c	697	64	761	8.4%

Pearson's Correlation Test	2.101
Fisher Exact Test	0.226

This calculation demonstrates that there is no statistically significant difference in the positive surgical margin rate between the tumour stage pT2 (a and b) and pT2c.

5.3 Positive surgical margins with regard to a nerve-sparing operation

The effect of a nerve-sparing operation on the positive surgical margin rate was to be evaluated. Of the 857 patients, 546 (63.7%) had had a nerve-sparing operation. This included a bilateral as well as unilateral nerve-sparing operation. When a nerve-sparing procedure was used the positive surgical margin rate was 10.3% (56/546) whereas when no nerve-sparing procedure was used the positive surgical margin rate was only 3.9% (12/311).

Table 9. Positive Surgical Margins with a Nerve-sparing Operation

			Positive Surgical Margin		
			R0	R1	Total
Stage pT2	Non Nerve-sparing	Amount	299	12	311
		Percentage	96.1%	3.9%	100%
	Nerve-sparing	Amount	490	56	546
		Percentage	89.7%	10.3%	100%
Total			789	68	857
			92.1%	7.9%	100%

Pearson's Correlation Test	11.476
Fisher Exact Test	0.001

The above-mentioned values demonstrate that there is a statistically significant increase in the positive surgical margin rate when a nerve-sparing operation is performed.

5.4 The Bilateral and Unilateral Nerve-sparing Operation

5.4.1 The relationship between a Positive Surgical Margin Rate and a Unilateral or Bilateral Nerve-sparing Operation

Prior to performing a nerve-sparing operation, the surgeon must choose between a bilateral or unilateral (right or left-sided) nerve-sparing procedure. The majority of patients in this study underwent a bilateral nerve-sparing procedure, 62.5% (341/546). The positive surgical margin rate for a bilateral nerve-sparing procedure is 12.3% (42/341). The remaining patients who had the unilateral nerve-sparing operation, were left with a positive surgical margin rate of 6.8% (14/205).

Table 10. The Positive Surgical Margin Rate and a Unilateral and Bilateral Nerve-sparing Operation

			Positive Surgical Margin		
			R0	R1	Total
Stage pT2	Bilateral Nerve-sparing	Amount	299	42	341
		Percentage	87.7%	12.3%	100%
	Unilateral Nerve-sparing	Amount	191	14	205
		Percentage	93.2%	6.8%	100%
Total			490	56	546
			89.7%	10.3%	100%

Pearson's Correlation Test	4.259
Fisher Exact Test	0.042

The above calculation demonstrates that there is a statistically significant increase in the positive surgical margin rate where a bilateral nerve-sparing operation is performed in comparison to a unilateral nerve-sparing operation.

5.4.2 The Relationship between a Positive Surgical Margin rate and a left-sided versus a right-sided Nerve-sparing Operation

Table 11. Left-sided versus Right-sided Nerve-sparing Operation

			Positive Surgical Margin		
			R0	R1	Total
Stage pT2	Left-sided Nerve-sparing	Amount	116	12	128
		Percentage	90.6%	9.4%	100%
	Right-sided Nerve-sparing	Amount	75	2	77
		Percentage	97.4%	2.6%	100%
Total			191	14	205
			93.2%	6.8%	100%

Pearsons Correlation Test	3.422
Fischer Exact Test	0.086

No statistically significant difference was found between positive surgical margin rate and a left-sided or right-sided nerve-sparing procedure.

5.5 Prostate weight

5.5.1 Prostate Weight Distribution

All specimens sent for pathological evaluation postoperatively were weighed. The prostate and the seminal vesicles were weighed as one unit. Six prostate weight categories were established in order to facilitate all further calculations.

Table 12. Prostate Weight Categories

Prostate weight category	Weight	Number of patients
Category 1	≤35g	114
Category 2	35.1-45g	158
Category 3	45.1-55g	213
Category 4	55.1-65g	145
Category 5	65.1-75g	92
Category 6	>75g	135

The mean prostate weight was 52g and the average prostate weight was 55.8g, ranging from 3g to 158g.

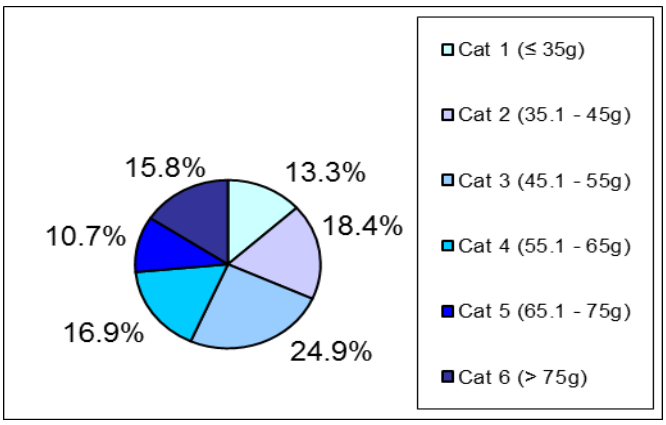


Figure 5. Prostate weight distribution

5.5.2 The relationship between a Positive Surgical Margin Rate and Prostate Weight

In order to ascertain whether the prostate weight had any bearing on the positive surgical margin rate, the positive surgical margin rate was calculated for each weight category. Marked differences were found in the positive surgical margin rate depending on the prostate weight.

Table 13. Positive Surgical Margins and the Prostate Weight

			Positive Surgical Margin		
			R0	R1	Total
Stage pT2	Weight Category 1 ≤35g	Amount	97	17	114
		Percentage	85.1%	14.9%	100%
	Weight Category 2 35.1-45g	Amount	146	12	158
		Percentage	92.4%	7.6%	100%
	Weight Category 3 45.1-55g	Amount	197	16	213
		Percentage	92.5%	7.5%	100%
	Weight Category 4 55.1-65g	Amount	140	5	145
		Percentage	96.6%	3.4%	100%
	Weight Category 5 65.1-75g	Amount	84	8	92
		Percentage	91.3%	8.7%	100%
	Weight Category 6 >75g	Amount	125	10	135
		Percentage	92.6%	7.4%	100%
Total			789	68	857
			92.1%	7.9%	100%

Pearson's Correlation Test	11.795
Fisher Exact Test	0.045

This calculation demonstrates that the positive surgical margin rate has a statistically significant correlation to the prostate weight (p=0.045). It is noteworthy that the first weight category (under 35g) has the numerically highest positive surgical margin rate. This finding was followed-up by further calculations comparing the patients in category 1 (prostatic weight of under 35g) to those in the rest of the study population.

5.5.3 The Influence of a Low Prostate Weight on the Positive Surgical Margin Rate

As previously demonstrated, the prostate weight does have an impact on the positive surgical margin rate. Of note is the very high positive surgical margin rate in patients with a low prostate weight. For this reason two separate categories for weight were created, namely those patients with a prostate weight equal to or less than 35g and those with a prostate weight of more than 35g.

Table 14. Positive Surgical Margins and a low Prostate Weight

			Positive Surgical Margin		
			R0	R1	Total
Stage pT2	Weight Category 1 ≤35g	Amount	97	17	114
		Percentage	85.1%	14.9%	100%
	Weight Category 2 >35g	Amount	692	51	743
		Percentage	93.1%	6.9%	100%
Total			789	68	857
			92.1%	7.9%	100%

Pearson's Correlation Test	8.764
Fisher Exact Test	0.008

The above calculation demonstrates a statistically clear correlation between a low prostate weight of under 35g and positive surgical margins.

5.5.4 The Relationship between Positive Surgical Margins, Prostate Weight and a Nerve-sparing Operation

Once the correlation between a nerve-sparing operation and the positive surgical margin rate was observed, the question arose as to whether this would also be true of the prostate weight and whether one specific weight category was at particular risk when a nerve-sparing operation was performed. The patients were first divided into groups of those who had not undergone a

nerve-sparing operation and those who had. Once again the positive surgical margin rate per weight category was calculated.

Table 15. The Positive Surgical Margins relating to Prostate Weight and a non Nerve-sparing Operation

Non nerve-sparing operation			Positive Surgical Margin		Total
			R0	R1	
Stage pT2	Weight Category 1 ≤35g	Amount	30	1	31
		Percentage	96.8%	3.2%	100%
	Weight Category 2 35.1-45g	Amount	37	0	37
		Percentage	100%	0%	100%
	Weight Category 3 45.1-55g	Amount	70	2	72
		Percentage	97.2%	2.8%	100%
	Weight Category 4 55.1-65g	Amount	56	1	57
		Percentage	98.2%	1.8%	100%
	Weight Category 5 65.1-75g	Amount	40	4	44
		Percentage	90.9%	9.1%	100%
	Weight Category 6 >75g	Amount	66	4	70
		Percentage	94.4%	5.7%	100%
Total			299	12	311
			96.1%	3.9%	100%

Pearson's Correlation Test	6.323
Fisher Exact Test	0.236

When a non nerve-sparing operation was performed no significant relationship between the prostate weight and the positive surgical margin rate could be demonstrated.

Table 16. The Positive Surgical Margins relating to Prostate Weight and a Nerve-sparing Operation

Nerve-sparing operation			Positive Surgical Margin		Total
			R0	R1	
Stage pT2	Weight Category 1 ≤35g	Amount	67	16	83
		Percentage	80.7%	19.3%	100%
	Weight Category 2 35.1-45g	Amount	109	12	121
		Percentage	90.1%	9.9%	100%
	Weight Category 3 45.1-55g	Amount	127	14	141
		Percentage	90.1%	9.9%	100%
	Weight Category 4 55.1-65g	Amount	84	4	88
		Percentage	95.5%	4.5%	100%
	Weight Category 5 65.1-75g	Amount	44	4	48
		Percentage	91.7%	8.3%	100%
	Weight Category 6 >75g	Amount	59	6	65
		Percentage	90.8%	9.2%	100%
Total			490	56	546
			89.7%	10.3%	100%

Pearson's Correlation Test	10.755
Fisher Exact Test	0.056

As with the non nerve-sparing operation the prostate weight does not seem to be statistically significant when evaluating the above-mentioned six categories in patients who have undergone a nerve-sparing operation.

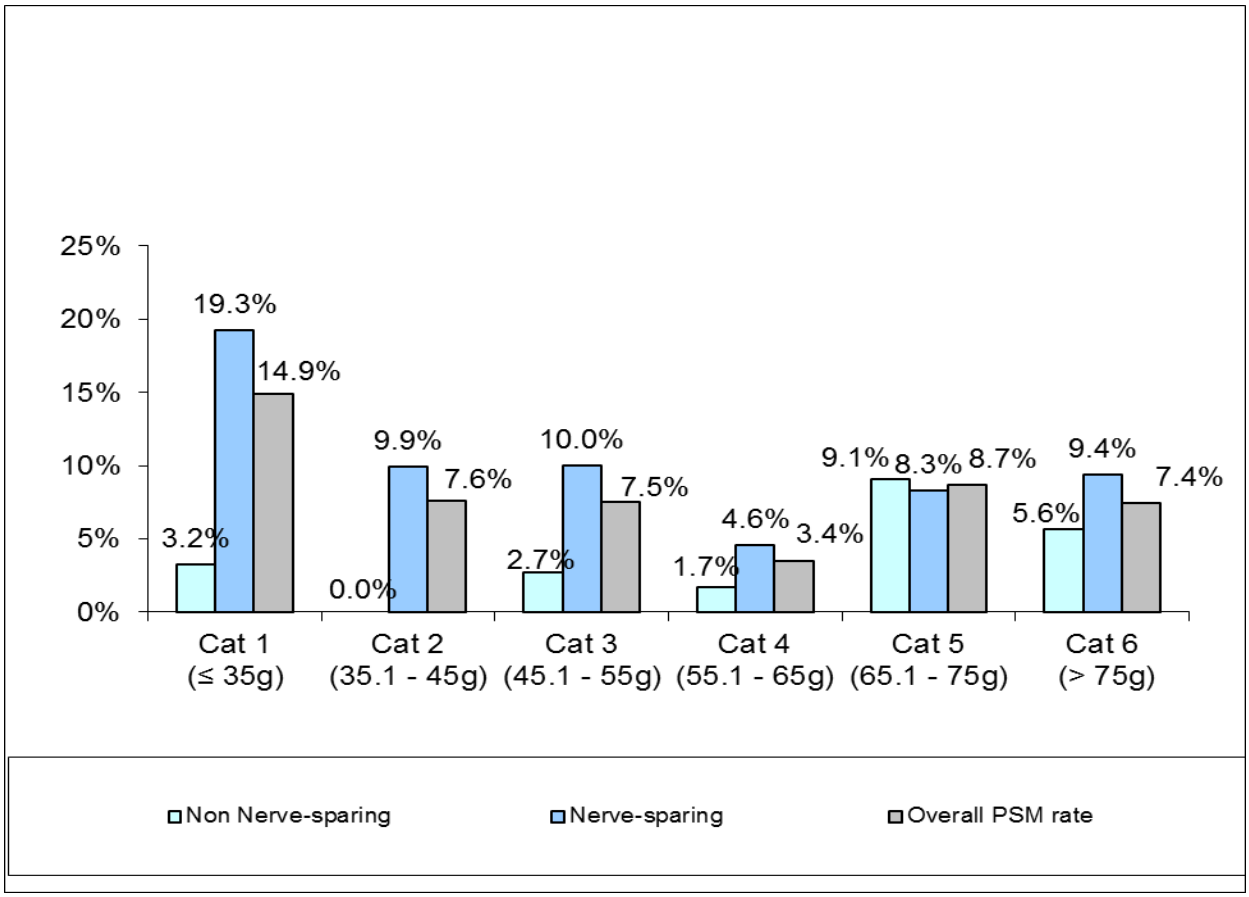


Figure 6. Positive surgical margin distribution according to prostate weight and the nerve-sparing operation

5.5.5 The Influence of a Low Prostate Weight and a Nerve-sparing Operation on the Positive Surgical Margin Rate.

Since the positive surgical margin rate in the prostate weight category of equal to or less than 35g was found to be statistically significant, a decision was made to compare this weight category to the above 35g weight category, taking the nerve-sparing and non nerve-sparing operation into consideration.

Table 17. The Positive Surgical Margins relating to a low Prostate Weight and a non Nerve-sparing Operation

Non Nerve-sparing			Positive Surgical Margin		Total
			R0	R1	
Stage pT2	Weight Category 1 ≤35g	Amount	30	1	31
		Percentage	96.8%	3.2%	100%
	Weight Category 2 >35g	Amount	269	11	280
		Percentage	96.1%	3.9%	100%
Total			299	12	311
			96.2%	3.8%	100%

Pearson's Correlation Test	0.033
Fisher Exact Test	1.000

When a non nerve-sparing procedure is performed no correlation can be found between the positive surgical margin and the prostate weight can be found.

Table 18. The Positive Surgical Margins relating to a low Prostate Weight and a Nerve-sparing Operation

Nerve-sparing			Positive Surgical Margin		Total
			R0	R1	
Stage pT2	Weight Category 1 ≤35g	Amount	67	16	83
		Percentage	80.7%	19.3%	100%
	Weight Category 2 >35g	Amount	423	40	463
		Percentage	91.4%	8.6%	100%
Total			490	56	546
			89.7%	10.3%	100%

Pearson's Correlation Test	8.512
Fisher Exact Test	0.009

A statistically significant increase in the positive surgical margin rate is found when a nerve-sparing operation is performed in a patient with a low prostate weight of equal to or less than 35g.

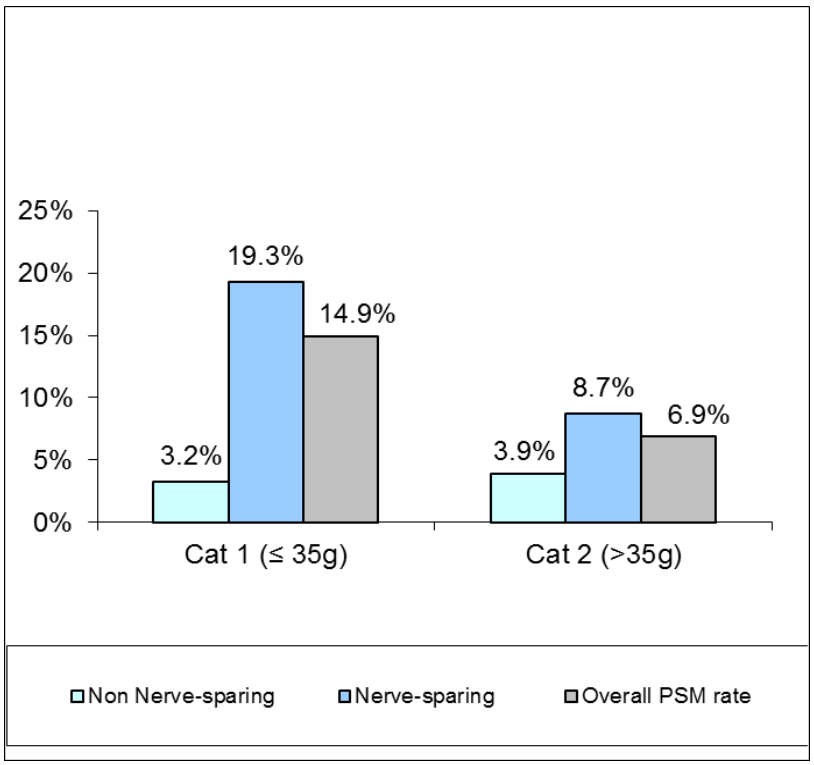


Figure 7. Positive surgical margin distribution in a low prostate weight group

5.5.6 The Relative Risk

The relative risk for patients with a low prostate weight of having positive surgical margins after their surgical procedures when compared to patients with a higher prostatic weight, is calculated as:

Formula

Percentage PSM if ≤35g/Percentage PSM if >35g

14.9/6.9

= 2.1

The relative risk in having positive surgical margins, for the patient with a prostate weight of equal to or less than 35g, in comparison to a patient with a prostate weight of above 35g, is 2.1 fold.

5.6 Localisation of positive surgical margins

This study also identified the anatomical area(s) of the prostate where the most positive surgical margins were found. These areas were identified by the pathologist on the specimen itself. Four specific areas of the prostate were identified, namely: the apex, the base, the lateral areas and the seminal vesicles. If several positive margins were seen on the specimen, the positive surgical margin area was classified as 'multiple'.

5.6.1 Distribution of the localisation of the positive surgical margins

Table 19. Localisation of Positive Surgical Margins

Localisation of positive surgical margin	Number	Percentage
Apex	40	58.8%
Base	19	27.9%
Lateral	5	7.4%
Seminal Vesicles	1	1.5%
Multiple	3	4.4%
Total	68	100%

Only a very small number of patients had positive surgical margins within the lateral, seminal vesicular and multiple areas. For statistical purposes, it was therefore decided that all further calculations involving these parameters would be divided into three groups, namely: apex, base and 'other', where the third category or group would encompasses all the remaining localisations.

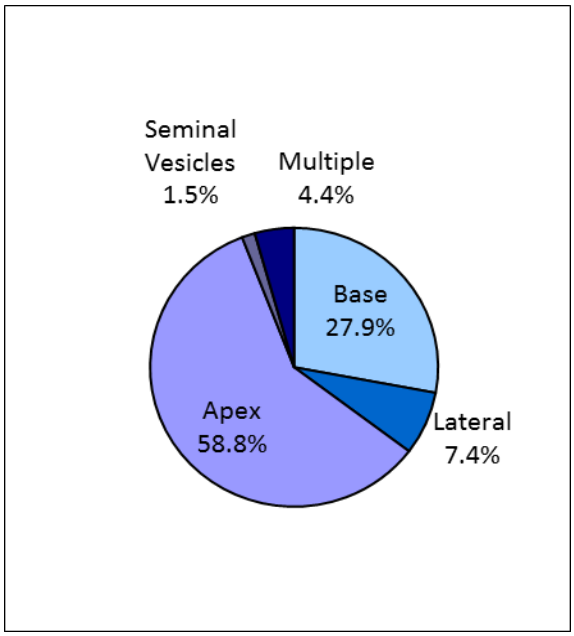


Figure 8. Distribution of positive surgical margins

5.6.2 The Relationship between a Nerve-sparing Operation and the Localisation of the Positive Surgical Margin

An attempt was made to identify whether a nerve-sparing operation would have any bearing on the localisation of the positive surgical margins. Once again the patients were divided into separate groups depending on whether a nerve-sparing operation was performed or not, with the following results:

Table 20. The Nerve-sparing Operation and the Localisation of the Positive Surgical Margin

			Localisation			Total
			Apex	Base	Other	
Nerve-sparing	Without	Amount	10	1	1	12
		Percentage	83.3%	8.3%	8.3%	100%
	With	Amount	30	18	8	56
		Percentage	53.6%	32.1%	14.3%	100%
Total		Amount	40	19	9	68
		Percentage	58.8%	27.9%	13.2%	100%

Pearson's Correlation Test	3.758
Fisher Exact Test	0.153

These calculations were not statistically significant and a relationship between the localisation of the positive surgical margin and a nerve-sparing operation could not be determined.

5.7 The Learning Curve and pT2 Tumours

5.7.1 Number of pT2 Patients operated

In order to establish whether a positive trend could be seen in relation to the positive surgical margin rate over time, the 1200 patients were divided into three groups of 400 patients each. Each subsequent group showed a steady decline in the number of pT2 patients, as over time more patients with advanced pathological stages received operations.

Table 21. Number of pT2 Patients operated over Time

Patient Number	Number of patients with pT2 Tumours	Percentage
1-400	306	76.5%
401-800	297	74.3%
801-1200	254	63.5%
Total	857	71.4%

5.7.2 The Amount of Nerve-sparing Operations over Time.

Not only had the number of pT2 tumours decreased over time. There was also a steady decline in the number of patients who had undergone a nerve-sparing operation.

Table 22. Nerve-sparing Operations over Time

			Nerve-sparing		
			Without	With	Total
Patient Nr	1-400	Amount	74	232	306
		Percentage	24.2%	75.8%	100%
	401-800	Amount	112	185	297
		Percentage	37.7%	62.3%	100%
	801-1200	Amount	125	129	254
		Percentage	49.2%	50.8%	100%
Total			311	546	857
			36.3%	63.7%	100%

Pearson's Correlation Test	38.005
Fisher Exact Test	<0.0001

These calculations demonstrate that there is a statistically significant decrease over time in the number of patients who have received a nerve-sparing operation.

5.7.3 The Amount of Bilateral Nerve-sparing Operations performed

Furthermore, since as previously demonstrated, there was a difference in the positive surgical margin rate depending on whether a bilateral or unilateral nerve-sparing operation had been performed, the amount of bilateral versus unilateral nerve-sparing operations was also calculated over time.

Table 23. The Amount of Bilateral Nerve-sparing Operation over Time

			Nerve-sparing		
			Unilateral	Bilateral	Total
Patient Nr	1-400	Amount	92	140	232
		Percentage	39.7%	60.3%	100%
	401-800	Amount	68	117	185
		Percentage	36.8%	63.2%	100%
	801-1200	Amount	45	84	129
		Percentage	34.9%	65.1%	100%
Total			205	341	546
			37.5%	62.5%	100%

Pearson's Correlation Test	0.879
Fisher Exact Test	0.644

Although there was a decrease in the percentage rate of patents who had undergone a nerve-sparing operation, there was a steady increase in the percentage rate of patients who had had a bilateral nerve-sparing operation over time. This was, however, not statistically significant.

5.7.4 The Positive Surgical Margin Rate over Time

The global positive surgical margin rate over time was calculated in order to ascertain whether there had been a positive learning curve as demonstrated by a decrease in the positive surgical margin rate. The positive surgical margin rate of the pT2 tumours per 400 patients operated upon was once again calculated, with the following results:

Table 24. Positive Surgical Margin rate over Time

			Positive surgical margin		Total
			Negative	Positive	
Patient Nr	1-400	Amount	269	37	306
		Percentage	87.9%	12.1%	100%
	401-800	Amount	279	18	297
		Percentage	93.9%	6.1%	100%
	801-1200	Amount	241	13	254
		Percentage	94.9%	5.1%	100%
Total			789	68	857
			92.1%	7.9%	100%

Pearson's Correlation Test	11.424
Fisher Exact Test	0.003

A statistically significant decrease in the number of pT2 patients with positive surgical margins over time could be demonstrated.

5.7.5 The Relation between a Nerve-sparing Operation and the Positive Surgical Margin Rate over Time

Having proven the decrease in the overall positive surgical margin rate, the impact of the nerve-sparing as well as the non-nerve-sparing operations on the positive learning curve was evaluated.

Table 25. The Positive Surgical Margin Rate in Relationship to the non Nerve-sparing Operation over Time

Non-nerve-sparing operation			Positive surgical margin		Total
			Negative	Positive	
Patient Nr	1-400	Amount	71	3	74
		Percentage	95.9%	4.1%	100%
	401-800	Amount	109	3	112
		Percentage	97.3%	2.7%	100%
	801-1200	Amount	119	6	125
		Percentage	95.2%	4.8%	100%
Total			299	12	311
			96.1%	3.9%	100%

Pearson's Correlation Test	0.727
Fisher Exact Test	0.695

There was no decrease in the positive surgical margin rate in patients who had undergone a non-nerve-sparing operation.

Table 26. The Positive Surgical Margin Rate in Relationship to the Nerve-sparing Operation over Time

Nerve-sparing operation			Positive surgical margin		Total
			Negative	Positive	
Patient Nr	1-400	Amount	198	34	232
		Percentage	85.3%	14.7%	100%
	401-800	Amount	170	15	185
		Percentage	91.9%	8.9%	100%
	801-1200	Amount	122	7	129
		Percentage	94.6%	5.4%	100%
Total			490	56	546
			89.7%	10.3%	100%

Pearson's Correlation Test	9.074
Fisher Exact Test	0.011

Patients that had undergone a nerve-sparing operation showed a steady decline in positive surgical margins over time. This calculation proved a statistically significant positive learning curve.

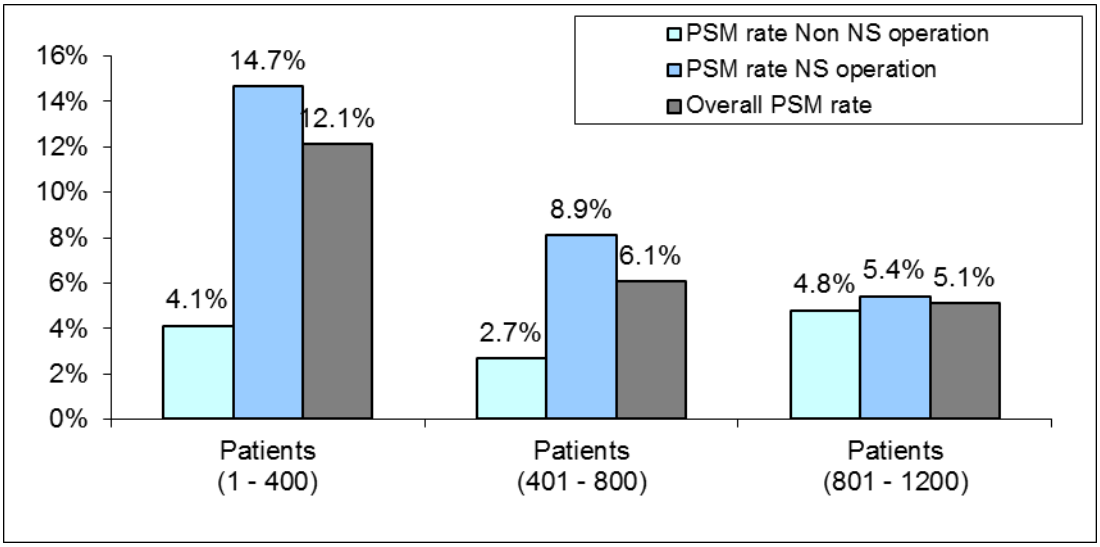


Figure 9. Positive surgical margin rate over time, depending on the nerve-sparing operation

5.8 The Quality of the Preoperative Biopsy

As explained earlier in this thesis, the quality of the prostate biopsy was described as either adequate or inadequate. All biopsies were divided into one of these two groups and further statistical analyses were performed.

5.8.1 Assessing the Number of adequate prostate biopsies

The first priority was to evaluate how many preoperative biopsies could be defined as being "adequate" according to the criteria described in Section 4.4.

Table 27. Number of Adequate Prostate Biopsies

	Number of biopsies	Percentage
Adequate	449	52.4%
Inadequate	408	47.6%
Total	857	100%

5.8.2 The influence of the quality of the biopsy on the positive surgical margin rate

The next analysis of interest was the determination of whether a preoperative prostate biopsy of poor quality could negatively influence the positive surgical margin rate. The positive surgical margin rate in preoperative biopsies which were considered adequate, was compared to that of biopsies of which the quality thereof was considered inadequate, with the following results:

Table 28.The Positive Surgical Margin Rate as influenced by the Biopsy Quality

			Positive surgical margin		
			Negative	Positive	Total
Biopsy	Adequate	Amount	422	27	449
		Percentage	94%	6%	100%
	Inadequate	Amount	367	41	408
		Percentage	90%	10%	100%
Total			789	68	857
			92.1%	7.9%	100%

Pearson's Correlation Test	4.766
Fisher Exact Test	0.032

The above table demonstrates that there is a statistically significant increase in the positive surgical margin rate when the surgeon does not have adequate preoperative information concerning tumour localisation and tumour volume.

5.8.3 The Positive Surgical Margin Rate as influenced by the Quality of the Biopsy in a Nerve-sparing and a non Nerve-sparing Procedure

The decision to perform a nerve-sparing operation or not depends on numerous variables of which one of the most important is the result of the preoperative biopsy of the prostate. A nerve-sparing procedure will only be considered where the pre-operative biopsy reveals a very low tumour volume. The aim of the following analysis was to identify whether an inadequate preoperative biopsy would influence the positive surgical margin rate in either or both the non nerve-sparing and nerve-sparing procedures.

Table 29. The Positive Surgical Margin Rate as influenced by the Biopsy Quality and a non Nerve-sparing Operation

Non Nerve-sparing			Positive surgical margin		Total
			Negative	Positive	
Biopsy	Adequate	Amount	173	9	182
		Percentage	95,1%	4,9%	100%
	Inadequate	Amount	126	3	129
		Percentage	97,7%	2,3%	100%
Total			399	12	311
			96,1%	3,9%	100%

Pearson's Correlation Test	1,396
Fisher Exact Test	0,190

Patients with a preoperative biopsy of adequate quality have a higher positive surgical margin rate than biopsies of inadequate quality, but this difference is not statistically significant.

Table 30. The Positive Surgical Margin Rate as influenced by the Biopsy Quality and a Nerve-sparing Operation

Nerve-sparing			Positive surgical margin		Total
			Negative	Positive	
Biopsy	Adequate	Amount	249	18	267
		Percentage	93,3%	6,7%	100%
	Inadequate	Amount	241	38	279
		Percentage	86,4%	13,6%	100%
Total			490	56	546
			89,7%	10,3%	100%

Pearson's Correlation Test	7.013
Fisher Exact Test	0.006

A statistically significant impact was observed in cases where a nerve-sparing procedure is performed in a patient with a pre-operative prostate biopsy of inadequate quality. The relative risk increase is 2.03 (13,6%/6,8%).

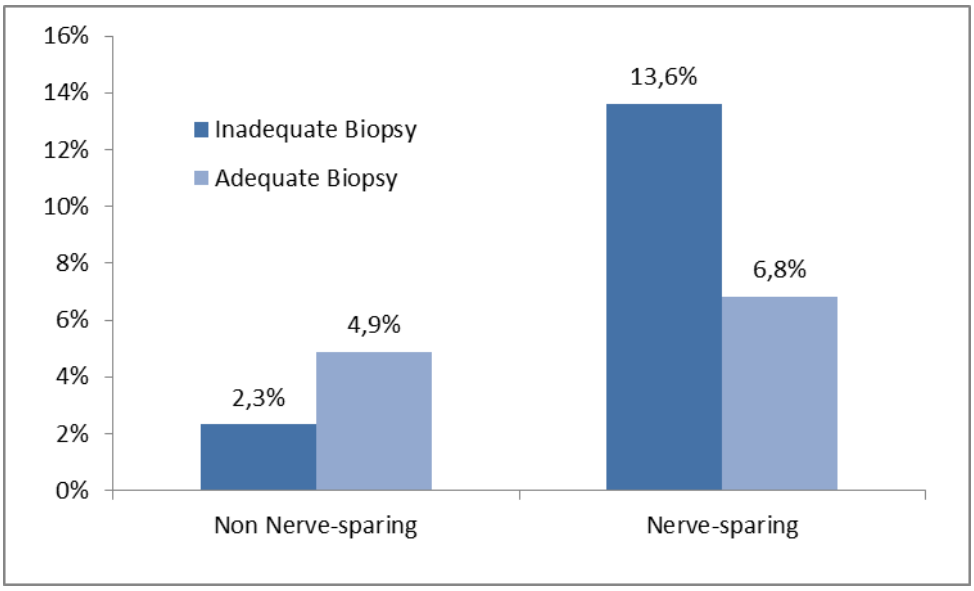


Figure 10. Positive Surgical Margin distribution depending on quality of biopsy

5.9 The preoperative PSA value as a risk factor for positive surgical margins

The positive surgical margin rate was calculated in relation to the PSA value on the basis of the theory that an elevated tumour volume is associated with a higher PSA value, even in organ-confined prostate cancer. The patients were divided into three categories dependent on their PSA value. Category 1 was confined to PSA values of below 6ng/ml, Category 2 to between 6ng/ml and 10ng/ml and Category 3 to values above 10ng/ml. The PSA values used in this calculation were those obtained at diagnosis and before any form of hormonal treatment.

Table 31. The Positive Surgical Margin Rate as per PSA Category

			Positive surgical margin		
			Negative	Positive	Total
PSA	Category 1 <6ng/ml	Amount	411	28	438
		Percentage	93.6%	6.4%	100%
	Category 2 6-10ng/ml	Amount	239	23	262
		Percentage	91.2%	8.8%	100%
	Category 3 >10ng/ml	Amount	139	17	156
		Percentage	89.1%	10.9%	100%
Total			789	68	857
			92.1%	7.9%	100%

Pearson's Correlation Test	3.586
Fisher Exact Test	0.159

The results demonstrate that there is no statistically significant increase in the positive surgical margin rate the higher the PSA value.

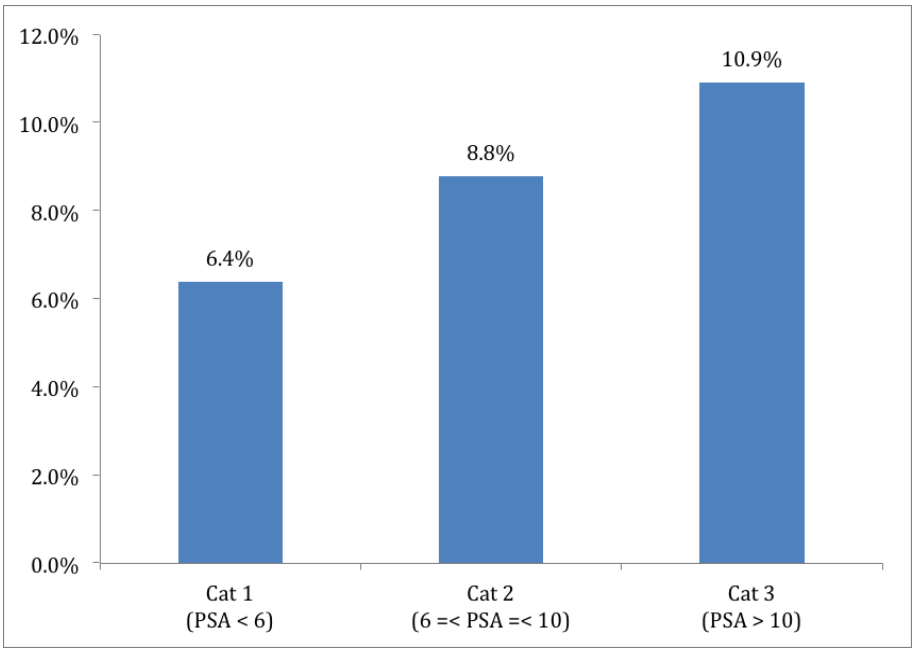


Figure 11. Positive Surgical Margin Rate according to PSA (ng/ml)

5.10 Multivariable analysis

The above-calculated results were used to perform a multivariable analysis in order to determine which factors were independent risk factors for an increased positive surgical margin rate in patients with pT2 tumours. The three variables included in this analysis were the nerve-sparing operation, a low prostate weight (under 35g) and the quality of the preoperative prostate biopsy.

Table 32. Multivariable Analysis

	Regression Co-efficient	Wald Chi Quadrant	Significance
Biopsy Quality	-0.398	2.267	0.133
Nerve-sparing	0.967	8.648	0.003
Prostate Weight	-0.707	5.259	0.022

Table 33. Multivariable Analysis and Confidence Interval

		95% Confidence Interval	
	Exp (B)	Lower Value	Upper Value
Biopsy Quality	1.672	0.400	1.128
Nerve-sparing	2.630	1.381	5.009
Prostate Weight	0.493	0.270	0.902

The two factors that were proven to be independent risk factors for positive surgical margins were a nerve-sparing operation and a low prostatic weight.

6. Discussion

6.1 The Importance of Positive Surgical Margins and their Relation to Surgical Technique

Positive surgical margins in organ-confined prostate cancer result in an increased risk of biochemical failure as well as tumour recurrence.(62) A study conducted in Hamburg evaluated such risk in 4490 patients who had undergone a radical prostatectomy. When positive surgical margins were present the five-year risk of a biochemical remission-free increased from 12% to 18%. In pT2 tumours alone the five-year biochemical remission free rate decreased from 95% to 83%. The relative risk increase for a biochemical remission in pT2 tumours in the presence of positive surgical margins was 2,9. The biochemical prognosis of a patient with a pT2 tumour and positive surgical margins is worse than that of pT3a tumour stage and negative surgical margins.(63) The overall PSM rate in the study, which is the subject matter of this thesis, was 7.9%. In other centres where RARP is performed, the PSM rate for organ-confined tumours resembled our own and ranged from 9.4% to 14%.(64, 65, 66)

Several studies have compared the results of the RRP to those of the RARP. Most studies, however, do not demonstrate a clear advantage of the RARP with regard to the positive surgical margins rate in pT2 tumours.

Table 34. Studies comparing the Positive Surgical Margin Rate of the RRP to the RARP in organ-confined cancer

	RRP PSM(%)	RARP PSM(%)
Smith *et al* (2007)(64)	24.1	9.4
Weizer *et al* (2010)(65)	12	14
Laurila *et al* (2009)(66)	14	13

However, of importance is that high volume urological centres usually publish the data mentioned above and not the community hospitals. In an independent report, compiled by Cancer Care Ontario, 1346 pathologists' reports were evaluated in 2005 and 2006. Irrespective

of surgical technique the overall pT2 positive surgical margin rate in 43 different hospitals was 33%.(67)

6.2 Staging, the preoperative PSA and the localisation of the Positive Surgical Margin

Most radical prostatectomies are performed on patients with a pT2 tumour stage, as this tumour stage can be cured if treated surgically. The data in this study mirrors that of international centres as 71,4% of the 1200 patients that were operated had a pT2 tumour, furthermore the pT2c tumour stage was the most common amongst the pT2 tumours.(68)

In this study, an increase in the PSA value was not associated with a statistically significant increase in the PSM rate. Other studies have shown that an increased PSA can lead to a higher rate of positive surgical margins, however those studies are not specific to organ-confined tumours.(51, 69) The examination of organ-confined prostate cancer only, did not reveal an association between an elevated PSA level and an increased risk of biochemical recurrence. However, the relationship between a positive surgical margin and the PSA was not examined.(70)

In nearly 60% of the patients in this study, the positive surgical margin was found at the apex. The second highest incidence, almost 30%, was situated basally. Positive surgical margins were rarely found in the other locations. Irrespective of surgical technique, most other studies have also found the apex to be the most common location for a positive surgical margin.(52, 71, 72)

The relationship between the localisation of the positive surgical margin and a nerve-sparing operation was also evaluated in this study. Patients without a nerve-sparing operation had an apical positive surgical margin in 83.3% of the time and a basal positive surgical margin in 8.3% of the time. In comparison, patients who had had a nerve-sparing prostatectomy had an apical positive margin rate of 53.6% and basal positive surgical margin rate of 32.1%. The difference between these two population groups was not statistically significant (p=0.176). Marchetti *et al* described patients who had undergone a RARP with a bilateral nerve-sparing operation. The overall localisation of the positive surgical margin, irrespective of pathological stage, was

posterolateral in 43%, apical in 39% and basal in 17% of patients. Unfortunately no comparison could be made to patients who had not undergone a nerve-sparing procedure.(73)

6.3 Positive Surgical Margins and the Nerve-sparing Operation

In this study, the nerve-sparing operation was associated with an increase in the PSM rate from 3.8% to 10.3%, which was statistically significant.

Research conducted of large databases (Budäus *et al*.(63), Nelles *et al*.(74)) have, when not taking the surgical technique and tumour stage have not been taken into account, have not found a correlation between the positive surgical margin rate and the nerve-sparing operation. When organ-confined tumours in RRP patients were examined however, Ahyai *et al* found a statistically significant increase from 7.8% to 13.9% in the positive surgical margin rate when a nerve-sparing procedure was performed.(75) With regard to the RARP, Liss *et al* found an increase in the rate of positive surgical margins from 3.3% to 5.9% when a nerve-sparing operation was performed. However this was not statistically significant, nor specific for pT2 tumours.(76) Coelho *et al* examined 876 patients who had undergone a RARP by a single surgeon who had already had the experience of operating more than 1500 cases. He found amongst the pT2 tumours the positive surgical margin rate for patients that had not had a nerve-sparing procedure to be 8.51%, patients who had received a bilateral nerve-sparing operation had a positive surgical margin rate of 8.15% and patients who had received a unilateral nerve-sparing operation had a positive surgical margin rate of 6.14%. These values were not statistically significant.(77)

Furthermore the analysis in this study revealed that a unilateral nerve-sparing procedure had a positive surgical margin rate of 6.8% and a bilateral nerve-sparing procedure a positive surgical margin rate of 12.3%. This difference is statistically significant, with p=0.042.

As stated previously, the only study that used the same criteria as this study to evaluate the RARP group, namely by Coehlo *et al*, could not find a statistical difference in the positive surgical margin rate after a unilateral or bilateral nerve-sparing operation.(77) Although Greco

et al found that when examining patients, with pT2 tumours, who had undergone a Laparoscopic radical Prostatectomy (LRP) the positive surgical margin rate rose from 5.3% to 8.2% when a bilateral instead of a unilateral nerve-sparing procedure was performed. However, this difference was once again not statistically significant.(78)

6.4 Prostate Weight

The average prostate weight for a pT2 tumour stage operated by means of a RARP at the University Clinic of Saarland was 55.8g, with the median prostate weight being 52g. Independently of tumour stage the average prostate weight, in an article published by Zorn *et al* describing 375 patients that had undergone a RARP, was 51.8g.(79) In a study by Msezane *et al* the average prostate weight of 709 patients who had had a RARP was 52.9g.(80)

When the RARP program was first introduced in the University Clinic of Saarland, patients with larger prostates (>60g) where excluded from the initial surgeries as it was thought that a larger prostate would lead to more difficult intra-operative conditions. This exclusion criterion was, however, lifted after 10 operations.(81) Conversely other studies have shown that a low prostate weight in RRP specimens is associated with an increase the positive surgical margins rate.(82) It was for this reason that prostate weight in patients undergoing a RARP was also investigated in this study. Due to the large number of patients in this study, six distinct weight categories were established: ≤35g, 35.1-45g, 45.1-55g, 55.1-65g, 65.1-75g and >75g. The prostate weight did have an impact on the positive surgical margin rate ($p=0.045$). This was especially true when patients with a very low prostate weight (≤35g) were compared to the rest of the population in the cohort (14.9% vs 6.9%, $p= 0.008$). The overall relative risk increase for a positive surgical margin when a patient has a low prostate weight is 2.1.

In his 2007 article, Zorn *et al* showed similar trends with patients who had undergone a RARP for pT2 tumours. He found that the prostate weight group of less than 50g had a significantly increased risk of having a positive surgical margin.(79) Another study, conducted by Skolarus *et al* evaluated 885 patients who had undergone a RARP were evaluated for positive surgical margins. Irrespective of the tumour stage the patients were divided into three groups according

to the prostate weight. The first category was that of patients with a prostate weight of less than 50g, the second of between 50g and 100g and the third category encompassed patients who had a prostate weight of more than 100g. The positive surgical margin rate was 19%, 11,1% and 0%, respectively.(83) Ficarro *et al* also demonstrated in 2009 that in his evaluation of preoperative risk factors for positive surgical margins in patients undergoing a RARP, that a prostate volume of less than 40cc was a risk factor for an increased incidence of positive surgical margins.(84) A similar study conducted by Frota *et al* in patients undergoing a LRP were divided into three groups depending on the prostate weight: under 30g, between 30g and 75g and above 75g. The positive surgical margin rate was 39%, 16% and 27% respectively.(85) The results found in the fore-mentioned study were confirmed in another study where patients who underwent a RRP, had a higher positive surgical margin rate the smaller the prostate weight, irrespective of pathological stage: 14% if <40g, 12% for 41g-50g, 10% for 51g-65g and 10% for >65g respectively. These figures were statistically significant.(86) In a study examining the biochemical recurrence rate of pT2 tumours Cho *et al* noted that a low prostate volume of under 30g was associated with an increased risk of biochemical recurrence. Unfortunately the positive surgical margin rate was not calculated in Cho's study.(87)

Although the authors of a recent publication recommended that the prostate specimen should be used as the preferred method of measuring prostate size in prostatectomy studies,(88) the question arises whether the postoperative prostate weight can adequately be determined pre-operatively. It has been proven that prostate volume can be equated to prostate weight where the seminal vesicles have been removed.(89) Preoperatively most urologists depend on transrectal ultrasound, the accuracy of which is operator dependent.

In this study at the University Clinic of Saarland, the effect of the combination of a low prostate weight and a nerve-sparing operation was examined. The patients were divided into two categories, those who had not had a nerve-sparing operation and those who had. Examination of the prostate weight in the cases of non nerve-sparing operations revealed no statistical correlation between the non nerve-sparing and the positive surgical margin rate. In the weight category less than or equal to 35g and above 35g, the positive surgical margin rate was 3.2% and 3.9% respectively, with $p = 1.000$. Evaluation of the nerve-sparing procedures over all the

weight categories, did not reveal any statistically significant difference when it came to the positive surgical margin rate (p = 0.081). However, when a comparison was made between patients with a nerve-sparing operation and a prostate weight of less than or equal to 35g, compared to that of above 35g, the positive surgical margin rate was 19.3% and 8.7% respectively, with p = 0.009. This demonstrates that nearly 20% of all patients who undergo a nerve-sparing operation with a low prostate weight and an organ-confined tumour will have a positive surgical margin.

Studies demonstrating this exact correlation could not be found, but a study by Marchetti *et al*, that examined organ-confined tumours and a bilateral nerve-sparing procedure demonstrated that the predicted probability of a positive surgical margin of a prostate of 25g, 50g, 100g and 150g was 22%, 13%, 5% and 1% respectively.(73)

6.5 The Quality of the Preoperative Prostate Biopsy

The diagnosis of prostate cancer is usually made on a prostate biopsy. Indications for a prostate biopsy are usually found on the digital rectal examination as well as on the raised PSA level in serum. Other factors, which may indicate that a prostate biopsy is required, are the free/total PSA ratio and the PCA3 marker, although these are rarely used as independent screening tools. Once the decision has been made to perform a prostate biopsy, two methods can be used, either a transrectally guided biopsy or a perineal biopsy. According to the European Association of Urology (EAU) both methods have similar cancer detection rates, although most urologist prefers the transrectal approach. Certain guidelines should be adhered to while taking the biopsies:

- The sample site should be as far posterior and lateral in the peripheral zone as possible
- Additional cores should be removed from the areas of suspicion
- Prostate glands with volumes of 30-40ml, should have at least 8 cores removed
- There does not seem to be a benefit to removing more than 12 cores(20)

According to the British Prostate Testing for Cancer and Treatment Study Group, when testing for prostate cancer, 10 cores should be removed for an accurate diagnosis.(90)

On the basis of aforesaid, it was decided in this study that the quality of the preoperative prostate biopsies of the patients operated upon at the University Clinic of Saarland were to be examined in the light of whether they were of assistance in properly preparing the surgeon for the operation. This unit retrospectively used two criteria to determine whether the biopsy was of adequate quality:

- The biopsy should comprise of at least eight cores
- The location of the positive biopsy core should be stipulated

This information was also used to decide whether a nerve-sparing procedure should be performed, either unilaterally or bilaterally, or whether it was in the patient's best interests to abstain from a nerve-sparing procedure. The aim is to have as much information as needed about the tumour burden and location of the tumour in any given prostate lobe. According to this criteria 52.4% of the patients had an adequate prostate biopsy and 47.6% had an inadequate prostate biopsy.

Whereas the positive surgical margin rate was found to be 6% in cases where an adequate biopsy was taken, in cases of an inadequate prostate biopsy, it rose to 10%, which was statistically significant, with $p = 0.032$. Several different studies regarding prostate biopsies have been conducted although few attempt to identify the quality of the biopsy. Frota *et al* conducted a study comparing the prostate biopsies that were positive for cancer and the final pathology after radical laparoscopic prostatectomy. In his study, the average amount of cores removed was 10.3 (6-24). However, he found that the correlation between the preoperative biopsy results and the final pathology was very poor. Only 37% of the patients had a positive prostate biopsy bilaterally, whereas on the final specimen 86% of the patients had cancer bilaterally and 58% of them had significant cancer bilaterally. The positive surgical margin rate did also not relate to the positive biopsy cores. In patients with positive biopsy results in the right lobe only, the contralateral (left) lobe had positive surgical margins in 10% of the cases, extracapsular extension in 11% and significant cancer in 5%. The same assessment was performed on patients who had a positive biopsy in the left lobe only, who on final pathology also showed in the contralateral (right) lobe positive surgical margins in 12% of the cases, extracapsular extension in 8% and significant cancer in 7%. In 24% of the patients only six needle core biopsies were taken, in 63% of the patients 7-12 needle core biopsies were taken

and in 13% of the patients more than 12 needle core biopsies were taken. Unfortunately, however no correlations were drawn between the amount of preoperative biopsies and the positive surgical margin rate.(91) In a similar study Bulbul *et al* also showed that 66% of patients who had unilateral disease on prostate biopsy had in fact bilateral disease on the final pathological specimen.(92) Sfakianos *et al* suggests that the amount of biopsies taken should be decided by the size of the prostate. In his study the prostate volume to biopsy core ratio (volume/number of cores) was calculated. It was found that the median prostate volume/number of cores was 3.5 in patients diagnosed with prostate cancer whereas those who were not diagnosed with cancer had a ratio of 4.7, the difference being statistically significant. It was therefore suggested that the prostate cancer detection could be enhanced by reducing the ratio between prostate volume and the number of core biopsies taken, i.e. the larger the prostate, the more cores should be removed.(93) Hashimoto *et al* also proved the relationship between the percentage of positive core biopsies and the rate of positive surgical margins. If more than 35% of the biopsies were involved with cancer, there was a statistically significant increase in the positive surgical margin rate, emphasising the importance of good preoperative biopsies.(69)

In this study as far as the nerve-sparing procedure is concerned, those patients who had had adequate preoperative prostate biopsies had a positive surgical margin rate of 6.7%, whereas those who had not, had a positive surgical margin rate of 13.6%. This difference was statistically significant, $p = 0.006$. This difference was not found when non nerve-sparing operation was performed. This result indicates that where the surgeon has inadequate preoperative information and a nerve-sparing procedure is performed, the patient has a worse oncological outcome. This leads us to conclude that a standardised, international biopsy method is essential and that if it has not been adhered to, a nerve-sparing procedure should be reconsidered.

6.6 The Learning Curve of the pT2 Tumours

The learning curve of the pT2 tumours over time was evaluated. As stated in the beginning of this thesis 1200 patients were evaluated in this study, although only 857 had a pT2 tumour. The

1200 patients were divided into three equal groups of 400 patients each and the learning curve of the pT2 tumours was evaluated for each group of 400 patients. Of importance was that over time the number of patients with a pT2 tumour per 400 patients decreased steadily form 306, to 297 to 254. During this same period of time there was a steady increase in the number of patients with pT3 tumours who were treated surgically. This trend was, however, not statistically significant.

Another variable that was analysed over time was the amount of nerve-sparing operations that were performed in pT2 tumours. In the first 400 patients 75.8% of all patients with a pT2 tumour received a nerve-sparing operation. In the next 400 patients only 62.3% received a nerve-sparing operation and in the last 400, only 50.8% had undergone an nerve-sparing operation, thus showing a steady decline in the number of patients receiving this procedure ($p < 0.0001$). The nerve-sparing procedure became a more selected procedure over time. We know from previous calculations that this procedure has a statistically significant increased risk of contributing to positive surgical margins. Unfortunately, to our knowledge no literature could be found analysing the trend in nerve-sparing operations over time.

Furthermore the learning curve with regard to the positive surgical margin over time in pT2 tumours was analysed. This analysis delivered the following results: the positive surgical margin rate in the first category of 400 patients, of whom 307 had a pT2 tumour was 12.1%. In the next 400 patients, of whom 297 had a pT2 tumour, the positive surgical margin rate was 6,1% and in the last 400 patients, of whom 254 had a pT2 tumour, the positive surgical margin rate was only 5.1%, giving an average rate of 7.9%. The decrease in the positive surgical margin rate was statistically significant with $p = 0.003$.

Learning curves and benefits of surgical volumes can usually be demonstrated in all surgical modalities. This was shown by Chun *et al* who examined the positive surgical margin rate depending on surgical volume for RRPs. One surgeon who had performed 1293 RRP's was compared to 10 other surgeons who had operated between 1 and 237 open radical prostatectomies. The positive surgical margin rate for the experienced surgeon was 20.2%,

whereas the positive surgical margin rate for the remaining surgeons was 22.6% the difference being statistically significant.(94)

Often in contemporary literature a new surgical technique is critisized for “sacrificing the initial patients during the learning curve”, since these early cases often do have a worse oncological outcome than if they were operated by a more conventional surgical technique. As far back as 2009, White *et al* compared the postitve surgical margins of patients undergoing either a RRP or a RARP at a single center, operated upon by a single urologist during the initiation stage of a robotics programme. In total 63 patients underwent a RRP and 50 a RARP. The positive surgical margin rate was 36% in the RRP group and 22% in the RARP group. When only the pT2c tumours cases were examined the positive surgical margin rate in the RRP group was 42.8% and 22.8% in the RARP group, demonstrating that even in the initial phase RARP does not have a higher positive surgical margin rate.(95) Rocco *et al* also compared 120 patients who had undergone an RARP to a historical control group of consecutive patients who had undergone an RRP. The positive surgical margin rate for the RARP group was 22% and for the RRP group 25%, respectively. There was no statistically significant difference. When only the pT2 tumours were evaluated 15% in the RARP group and 17% in the RRP group had positive surgical margins, once again not demonstrating a statistically significant difference.(96)

Studies examing the experience in a surgical technique have also been conducted demonstrating once again that the more experience one has in a surgical technique, the less positive surgical margins are present. The results of surgeons performing a RARP who either have experience in the robotic surgery or laparoscopic surgery (LRP) have been compared in their rate of positive surgical margins. In total 286 operations were performed; 121 by surgeons experienced in RARP and 165 by surgeons experienced in LRP. The positive surgical margin rate for the surgeons experienced in LRP was 34.6%, whereas those experienced in RARP had a positive surgical margin rate of 24.0%, which was statistically significant. Unfortunately this difference could not be replicated when the results of surgery on pT2 tumours were analysed, but none-the-less the overriding conclusion is that experience in a surgical technique does lead to better results.(97)

Atug *et al* examined the learning curve in RARP in a small group of patients. The first 100 patients who had undergone a RARP by the same surgical team were evaluated for the learning curve, with focus on the positive surgical margin rate. The patients were divided into three groups of 33,33 and 34 patients respectively. The overall positive surgical margin rate declined from 45.4%, to 21.2% to 11.7%. When the positive surgical margin rate of patients with a pT2 tumour stage only were evaluated, the positive surgical margin rate was as follows: 38.4%, 13.7% and 3.6% respectively. The analysis was performed on a very small group of patients, but the difference was statistically significant (p=0.0035).(98) Liss *et al* published one of the few articles about RARP with contradicting results. Of the first 216 patients that were operated via a RARP as well as over the first 149 that had a pT2 tumour stage, no decrease in the positive surgical margin rate could be seen (p=0.371). There was, however, a statistically significant decrease in the positive surgical margin rate for pT3 tumours.(76)

In total it is however safe to say that there seems to be a very short learning curve with regard to the RARP.

Furthermore, in this study the positive surgical margin rate of the patients who had undergone a nerve-sparing operation and a non nerve-sparing operation were also evaluated. Where patients who had not had a nerve-sparing procedure were concerned, the positive surgical margin rate varied from between 4.1%, 2.7% and 4.8% in the three groups respectively. No clear trend could be established and no statistical significance could be drawn from this information. The 546 patients who had undergone a nerve-sparing procedure were also evaluated over time. In total 232 patients had received a nerve-sparing procedure in the first 400 patients, 185 in the next 400 patients and 129 patients had received a nerve-sparing procedure in the last 400 patients. The positive surgical margin rate was 14.7%, 8.9% and 5.4% respectively, thus demonstrating a statistically significant decline in the positive surgical margin rate over time in patients undergoing a nerve-sparing procedure. It can therefore be said that the positive surgical margin rate of patients who do not undergo a nerve-sparing procedure remains stable and that there is no learning curve. The true learning curve over time is reflected in the nerve-sparing procedure (p = 0.011). Unfortunately no literature could be found where

the positive surgical margin rate over time in patients who have undergone a nerve-sparing procedure were evaluated.

6.7 Multivariable analysis

The multivariable analysis was used in this study assess the variables that are significant in the prediction of positive surgical margins in patients with organ-confined prostate cancer who undergo a RARP. The reasoning behind the use of this analysis was to identify patients who are at risk of having positive surgical margins, at the preoperative stage already. Three variables were identified as being of current importance: the nerve-sparing operation, a low prostate weight (less than or equal to 35g) and the quality of the preoperative biopsy. A regression analysis was used to evaluate these three parameters along with the Wald test. Only two of the variables were statistically significant: the nerve-sparing operation and the prostate weight ($p=0.003$ and $p=0.022$ respectively). The confidence interval for all three variables was calculated, with a 95% confidence interval for the nerve-sparing operation from 1.381 to 5.009 and the prostate weight from 0.270 to 0.902, respectively.

With the above given information we can confidently say that men with a low prostate weight of less than 35g and men undergoing a nerve-sparing operation are at increased risk of having positive surgical margins in organ-confined prostate cancer.

6.8 Limitations of this Study

This study has a few limitations. One of them would be the identification of which men have organ-confined disease prior to surgery. Unfortunately only an educated guess may be ventured, although there are a number of tools to guide the clinician, such as the digital rectal examination, a PSA of less than 10ng/ml and the D'Amico risk stratification which groups patients into low, intermediate and high risk categories. Although this risk stratification is not failsafe, in a study by Hernandez *et al*, the five-year biochemical recurrence-free survival for the low, intermediate and high-risk groups according to D'Amico's criteria were 94.5%, 76.6% and

54.6% respectively, thereby providing the relevance of such a risk stratification process.(99) Ideally normograms should be designed that accurately predict organ-confined disease based on preoperative information. In one such a study by Huang *et al*, the 2007 Partin Tabels model was used to design the „Partin Normogram“ to try and predict just that. Based on the patient's preoperative clinical stage, the tPSA and the biopsy Gleason Score, Huang's study attempted to predict organ-confined disease, extracapsular extension, seminal vesicle invasion and positive lymph node disease. The aim of the study group is to design a computer programme to facilitate these predictions.(100) Despite this and other studies, a 100% accurate prediction will never be possible when it comes to identifying patients who only have organ-confined cancer.

Another limitation is that although prostate volume and prostate weight can be equated postoperatively (89) (as previously discussed) an accurate preoperative prostate volume cannot always be determined accurately. Most patients who undergo a radical prostatectomy will have their prostate volume measured by transrectal ultrasound at time of the biopsy. As we know, sonographic measurements are very operator dependent. In a study conducted by Nunaz-Nateras *et al* the preoperative prostate volume of 302 patients was measured by a group of urologists and radiologists. The preoperative volume was than compared to the postoperative prostate volume after RARP. It was found that the preoperative measurement was within 17%-22% of the postoperative weight, thus demonstrating that a preoperative ultrasound is a relatively good estimate of the postoperative volume.(101) Unfortunately not all ultrasound operators work as accurately as the aforementioned and instead of advocating an absolute cut off value of 35g, which was the statistically proven value in this study, it would be more realistic to caution surgeons about patients with low prostate weights of approximately 35g.

This University Clinic of Saarland study proves that patients with organ-confined disease undergoing a nerve-sparing operation and patients with organ-confined disease and a low prostate weight are at greater risk of positive surgical margins than other patients when a robotic-assisted radical prostatectomy is performed.

7. Table of Figures

8. Tables

9. Abbreviations

EAU European Association of Urology

ERBT External Beam Radiation Therapy

LRP Laparoscopic Radical Prostatectomy

PSM Positive Surgical Margin

PSA Prostate Specific Antigen

RARP Robotic-assisted Radical Prostatectomy

RRP Retropubic Radical Prostatectomy

R0 Negative surgical margins

R1 Positive surgical margins

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11.Attachments

Da Vinci Laufzettel

Patientenaufkleber

Patienten Daten

Alter		Aufnahme Datum	
Aufgenommen durch		Überwiesen durch	
Präoperative Arbeit 0 = Nein 1 = Ja		Arbeit 1=selbstständig, 2=angestellt	

Prätherapeutische Daten

Komorbidität			
Vordiagnosen			
Voroperationen			
Gewicht (kg)		BMI	
Grösse (cm)			
ASA		NYHC	
Präop Hb		Präop Hkt	
Präop CRP			
Antikoagulation 0=nein 1=Marcumar 2=ASS 3=Plavix 4=Heparin 5=andere		Antik. Pausiert (d)	

Inzidentelles Prostatakarzinom 0=nein 1=pT1a (<5%) 2=pT1b (>5%)			
Präop. Stanze 1=bei uns 2=auswärts		Anzahl Stanzen	
Anzahl pos. Stanzen li		Anzahl pos. re	
Präop Gleason		Präop Gleason Score	

Datum Stanze			
Skelett Szinti 0=nein 1=positiv 2=negativ			
Präop TNM			
PSA präop		PSA bei Diagnosestellung (neoadjuvant therapierte Patienten)	
Vorbehandlung 0=Nein 1=LHRH 2= perpheres Antiandrogen 3= perpheres Antiandrogen (steroidal) 4= 5α Reduktasehemmer 5=Chemotherapie 6=Brachytherapie 7=andere		Dauer (Monate)	

TRUS			
Prostata Volumen		Adenom Volumen	
Echoarmer Bereich 0=nein 1=rechts 2=links 3=beide		Kapseldurchbruch 0=nein 1=rechts 2=links 3=beide	
SB dilatiert 0=nein 3=rechts 2= links 3=beide		SB infiltriert 0=nein 1=rechts 2=links 3=beide	
Tastbefund suspekt 0 = Nein 1=ja			

Präop. Kontinenz 0=nein 1=ja		Präop. Potenz 0=nein 1=ja	
IIEF Score		ICSSF Score	
QLQ 30			

Operation

OP Datum		Operateur 1=Stöckle 2=Siemer 3=Kamradt 4=Gerber 5=Becker 6=Ohlmann 7=Kopper 8=Akcetin	
OP-Zeit (Schnitt-Naht) [Min.]		Blutverlust (ml)	
Nervsparing 0=nein 1=ja		Nervsparing 1=rechts 2=links 3=beidseits	
Erhalt der puboprostatischen Bänder mit anteriorer Präparation des/der neurovaskulären Bündel 0=Nein 1=Ja			
Rocco Anastomose 0= Nein 1= Ja			
Postop Hb (5 Tag)		Postob Hkt	
CRP			
Komplikationen (intraoperativ) 0=nein 1=ja		Konversion 0=nein 1=ja Technisches Problem 2=ja OP Problem	
Ableitung 1=BK, 2=BK und Zystofix, 3=nur Zystofix			

Histologische Daten

Prostatavol. (ml)			
pT		pN	
Anzahl entfernten Lymphknoten		Anzahl tumorokupierte Lymphknoten	
M			
postoperativer Gleason		postop. Gleason-Score	
R 0=R0 1=R1 2=R2		R 1=basal 2=lateral 3=apikal 4=Samenblase 5=Ductus	
R 1=fokal 2=ausgedehnt			

Postoperative Daten

Entlassungstag Datum			
Blasenkatheterentferung Datum			
Entlassung 0=ohne Ableitung, 1= mit Zystofix, 2= mit BK, 3=mit BK und Zystofix		Grund f. längere Katheterdauer 1= Paravasat, 2= Andere (Erklären)	
Zystofixentferung Datum			
Kontinenz 1=gute Frühkontinenz 2=mäßige/schlechte Kontinenz		Anzahl Pads gebraucht in erste 24h nach Katheter Ex	
Komplikationen (postoperativ) 0=nein 1=ja (Welche?)		Komplikation Grad (1-5)	
Besonderheiten			

12. Publications

The results of this thesis were presented at the following congresses and included as asbracts in their congress procedings publications:

12/2010 Deutsches Robotisches Urologie Symposium
Poster Presentation: Ergebnisse der Roboter-assistierten Prostatektomie im Bezug auf Tumorstadium und R1 Rate

04/2011 52. Jahrestagung der Südwestdeutschen Gesellschaft für Urologie
Presentation: Ergebnisse der Roboter-assistierten Prostatektomie, in Bezug auf Tumorstadium, R1-Rate und Outcome bei nerverhaltender Operationstechnik

09/2011 63. Jahrestagung der Deutschen Gesellschaft der Urologie
Presentation: Positive Schnittränder bei roboter-assistierter (da Vinci)-Prostatektomie in einem high-volume Zentrum: Zusammenhang zwischen Tumorstadium und nerverhaltender Operationstechnik

10/2011 31st Annual Congress of the Société Internationale d'Urologie
Evaluation of the learning curve of robotic assisted radical prostatectomies with focus on the positive surgical margin rate

02/2012 27th Annual Congress of the European Association of Urology
Presentation: Evaluation of the learning curve in robotic assisted radical prostatectomy for patients with organ confined prostate cancer

02/2012 27th Annual Congress of the European Association of Urology
Presentation: The impact of prostate weight and a nerve-sparing operation on the positive surgical margin rate in organ confined prostate cancer in patients undergoing a robotic assisted radical prostatectomy

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14.Lebenslauf

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BERUFLICHER WERDEGANG

Seit 11. 2012 Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg (Südafrika)
Department of Surgery, division of Trauma (Prof. KD. Boffard)
- **Assistenzärztin (Supernumerary Registrar)**

11.11 – 10.12 Centre Hospitalier Universitaire Tenon, Paris (Frankreich)
Department d'Urologie (Prof. F. Haab)
- **Assistenzärztin (Faisant Function Intèrne)**

07.11 – 10.11 University of Stellenbosch, Tygerberg, (Südafrika)
Department of Urology (Prof. C. Heyns)
- **Assistenzärztin (Supernumerary Registrar)**

10.09 – 06.11 Universitätsklinikum des Saarlandes, Homburg (Saar)
Klinik und Poliklinik für Urologie und Kinderurologie (Prof. M. Stöckle)
- **Assistenzärztin**

2009 Pietermaritzburg (Südafrika)
- **Assistenzärztin Allgemeinmedizin (Internship)**
  - Jan. – Feb. 2009: Anästhesie
  - Mär. – Apr. 2009: Orthopädie
  - Mai – Aug. 2009: Pädiatrie

2006 Le Centre contre la Lutte du Cancer, (Clermont Ferrand, Frankreich)
Abteilung für Nuklearmedizin (Prof. J. Maublant)
- **Famulatur**

2005 Universität von Pretoria
Institut für Physiologie (Prof. D. Van Papendorp)
- **Tutor**

AUSBILDUNG

2011	**Approbation als Ärztin**	Landesamt für Gesundheit und Verbraucherschutz
2003-2008	**MBChB** (Südafrikanisches Staatsexamen, *cum laude* (Oberste 4% des Jahrgangs)	Universität von Pretoria (Südafrika)
1997-2001	**Matrix** (Allgemeine Hochschulreife) (Senior Certificate)	Crawford College Pretoria
1989-1996	**Grundschule**	Deutsche Schule Pretoria

Berufliche Weiterbildung

2013	Advanced Trauma Life Support	Trauma Society of South Africa
2012	Definitive Surgical Trauma Care	International Association for Trauma Surgery and Intensive Care
2012	Advanced Cardiovascular Life Support Basic Life Support certificate	Resuscitation Council of South Africa /American Heart Association
2012	Seminar: Bildgebende Systeme: TRUS Kurs	Akademie der Deutschen Urologen (DEGUM-zertifiziert)
2011	Knotenkurs	German Society of Residents in Urology (GeSRU)
2011	TUR Intensiv Kurs	TUR Schulen
2010	Urologie Kompaktkurs – BPS/Kinderurologie Hands-on-Training Laparoskopie	Akademie der Deutschen Urologen
2010	Spezialkurs in Strahlenschute (Fachkunde) Grundkurs in Strahlenschutz	Krankenhaus Beratungs- und Seminargesellschaft im Universitätsklinikum Homburg
2008	Paediatric advanced life support certificate Basic life support certificate	Resuscitation Council of South Africa /American Heart Association
2005	HIV/AIDS Clinical Management Program	Foundation for Professional Development
2004	HIV/AIDS Foundation Course	Centre for Study of AIDS

Akademische Erfolge

2008	MBChB *cum laude*	Universität von Pretoria
2007	Merit Certificate (Durchschnitt im Jahr >75%)	Universität von Pretoria
2005	Preis – Superior Scholastic Attainment and Outstanding Academic Merit	Golden Key International Honour Society (USA)
2005	Merit Certificate (durchschnitt im Jahr >80%)	Universität von Pretoria

Stipendien

2006	Meritus Stipendium	Universität von Pretoria
2005	Meritus Stipendium	Universität von Pretoria
2005	Superior Scholastic Attainment and Outstanding Academic Merit	Golden Key International Honour Society
2004	Meritus Stipendium	Universität von Pretoria
2003	Meritus Stipendium	Universität von Pretoria

Vorträge

Feb 2012	Vortrag: The impact of prostate weight and a nerve-sparing operation on the positive surgical margin rate in organ confined prostate cancer in patients undergoing a robotic assisted radical prostatectomy	27th Jahrestaugung der European Association of Urology
Feb 2012	Vortrag: Evaluation of the learning curve in robotic assisted radical prostatectomy for patients with organ confined prostate cancer	27th Jahrestaugung der European Association of Urology
Oct 2011	Poster Vortrag: Evaluation of the learning curve of robotic assisted radical prostatectomies with focus on the positive surgical margin rate	31. Jahrestaugung der Société Internationale d'Urologie

Sept 2011	Vortrag: Positive Schnittränder bei roboter-assistierter (da Vinci)-Prostatektomie in einem high-volume Zentrum: Zusammenhang zwischen Tumorstadium und nerverhaltender Operationstechnik	63. Jahrestagung der Deutschen Gesellschaft der Urologie
April 2011	Vortrag: Ergebnisse der Roboter-assistierten Prostatektomie, in Bezug auf Tumorstadium, R1-Rate und Outcome bei nerverhaltender Operationstechnik	52. Jahrestagung der Südwestdeutschen Gesellschaft für Urologie
Dec 2010	Poster Vortrag: Ergebnisse der Roboter-assistierten Prostatektomie im Bezug auf Tumorstadium und R1 Rate	Deutsches Robotisches Urologie Symposium
Mai 2010	‚Wiederspenstige Nierensteine'	Kolliquium: Uniklinik Homburg
Mai 2010	Poster Vortrag : 'Das muzinöse Adenokarzinom als Spätfolge nach Harnblasenekstrophie-Rekonstruktion. Fallbericht und Literaturübersicht'	51. Jahrestagung der Südwestdeutschen Gesellschaft für Urologie

Publications

May 2012	Robotic-assisted laparoscopic radical cystectomy: Surgical and oncological outcomes	Int Braz J Urol Vol. 38 (3): 324-329; May - June, 2012
März 2011	A Single Center Prospective Study: Prediction of Postoperative General Quality of Life, Potency and Continence after Radical Retropubic Prostatectomy	J Urol 2011 May;185(5):1681-5.

MITGLIEDSCHAFTEN VON VEREINEN

2010	European Association of Urology
2010	German Society of Residents in Urology
2005	South African HIV Clinicians Society
2005	Golden Key International Honour Society