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Comparison of the Functional and Oncological Outcomes of the Sub-trigonal Versus Conventional Robotic Radical Prostatectomy for Prostate Cancer

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Abbreviations

BCR	Biochemical recurrence
BMI	Body mass index
ICIQ	International Consultation on Incontinence modular Questionnaire
IIEF	International Index of Erectile Function
IRB	Internal review board
NS	Nerve sparing
NVB	Neurovascular bundle
PCa	Prostate cancer
PSA	Prostate specific antigen
PSM	Positive surgical margin
RARP	Robotic assisted radical prostatectomy
RP	Radical prostatectomy
STRP	Subtrigonal radical prostatectomy
TPRP	Transperitoneal radical prostatectomy
TRUS	Trans-rectal ultrasound
TURP	Trans-urethral resection of the prostate

1. Introduction

1.1. Epidemiology, Risk Factors and Pathology of Prostate Cancer

1.1.1. Epidemiology

Prostate cancer (PCa), or carcinoma of the prostatic gland, is a malignant transformation within the prostatic gland. It is considered as the second most common cancer and the sixth leading cause of cancer death in men worldwide (Center, 2012). Around 15% of men today are expected to be diagnosed with PCa in future (Siegel, 2014). From 1975 to 1980, the annual incidence rate had increased by 2%. This was explained by the incidental detection of PCa after the transurethral resection of the prostate for benign prostatic hyperplasia (Potosky et al., 1990). After the introduction of prostate-specific antigen (PSA) and screening programs for PCa, the incidence rates had dramatically increased between 1989 and 1992 (Siegel et al., 2014). With the detection of undiagnosed cases, the incidence rates then decreased between 1992 and 1995, followed by a return to baseline detection rates (Stephenson et al., 1996). PCa has displayed a wide variation of incidences worldwide; it is the most common type of non-skin malignancy which affects men in USA and Europe. Incidences range up to 249 cases per 100,000; especially in African Americans who have a 59% higher incidence rate than whites (Siegel et al., 2014). On the other hand, the lowest incidence rate (1.9 cases per 100,000) was detected in China (Jemal et al., 2006; Parkin et al., 2005). PCa can be incidentally found during a histopathological examination of radical cystoprostatectomy specimens after a radical cystectomy for muscle invasive bladder cancer, with a suggested pathological correlation between both malignancies (Fahmy et al., 2017).

In general, PCa is a slow-growing cancer. Among the common solid malignancies, PCa is associated with the lowest mortality rate (Liu et al., 2013). Before 1991, it was the single leading cause of death among men diagnosed with PCa (35%) After 1991, a decline of the mortality rate was observed, which was

explained by the introduction of PSA in screening, as well as increased utility of effective curative treatments (Epistein, 2012). Mortality rates due to PCa widely vary between countries and ethnic groups; the highest rates were reported in the Caribbean (28 per 100,000 yearly); however, in China and North Africa, the mortality rate is less than 5 per 100,000 yearly (Parkin et al., 2005). Over the last 2 decades, the mortality rate has decreased in 27 out of 53 analysed countries; however, in contrast, 10 countries have displayed an increase. The downward trend is mainly present in high-income countries where PSA-screening programs are well-established. On the other hand, an increased mortality rate was noticed in central and eastern Europe, Asia and Africa (Rebbeck, 2013). The average age of death due to PCa has remained stable at 77 years over the last three decades (Epstein et al., 2012).

Currently, no clear data can explain the observed variation in the incidence and mortality rate due to PCa, which is likely due to a multi-factorial process. People of the same race who live in different countries have varied rates of diagnosed PCa. For example, Chinese and Japanese men who immigrated to the US are at higher risk of PCa than those living in China and Japan. This could be due to different lifestyles, or environmental and dietary factors (Shimizu et al., 1991).

1.1.2. Risk factors

Various aspects were investigated as risk factors for PCa; for instance, age, family history, genes, race, inflammation and infection, hormones, sexual activity, vasectomy, diet, obesity, smoking and alcohol consumption. Among these factors, increasing age, heredity and ethnic origin are the main three well-known risk factors for PCa (Mottet et al., 2015).

Most PCa cases occur for those above the age of 50 at the time of diagnosis. Only 2% are diagnosed before the age of 50 (Jani et al., 2008). Prior to the introduction of PSA, the median age of diagnosis was 70 years. Over the past two

decades, it decreased to 67 years, and 63% of cases were diagnosed after the age of 65 (Ries et al., 2008). Currently, the percentages of diagnosed PCa for men below 55, 55-64, 65-74, 75-84 and above 85 are 10%, 30%, 35%, 20% and 4%, respectively (Brawley et al., 2012).

A strong familial component for PCa was demonstrated by many epidemiological and genetic studies. Germline factor is considered to be responsible for about 15% of PCa cases (Carter et al., 1992). Suggestions for higher risk among first-degree relatives began early at the mid of the previous century (Woolf et al., 1960). If the father is affected, the relative risk is 2.17 and it increases to 3.34 if the brother is affected. The risk further increases at least 5- folds if more than one first-degree relative is affected (Jansson et al., 2012; Hemminki et al., 2012). Early genetic studies had identified several genes expected to be responsible for PCa prevalence (HPC1, RNASEL, HPC2/ELAC and MSR1), yet the roles of these genes are not fully understood (Eeles et al., 2014). RNASEL alleles, in a population-based study, was identified as a predictive gene for PCa mortality (Lin et al., 2011). Recently, a new technique to identify PCa-associated alleles, named genome wide associated studies (GWAS), had identified alleles on chromosomes 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 17, 19, 22 and
X. Yet, the predictive value for each allele is about 1.5 times the baseline risk, which makes the clinical benefit for identifying people at risk of PCa very limited (Choudhury et al., 2012; Eeles et al., 2014). Studies on African-Americans and Japanese populations have identified extra specific alleles for these groups, however the evidence is incomplete (Takata et al., 2010; Haiman et al., 2011).

In general, chronic inflammation caused by infection can cause cancer by the induction of cellular hyperproliferation. This process is approved in cancer of the colon, stomach, bladder and liver (Coussens & Werb, 2002; DeMarzo et al., 2007). A similar mechanism for PCa was suggested after the frequent identification of proliferative inflammatory atrophy (PIA) in prostate specimens. Usually, PIA is found adjacent to the high-grade prostatic intraepithelial neoplasm

(HGPIN) or early PCa lesions (Shah et al., 2001; Nakayama et al., 2003). Furthermore, genetic alteration of genes responsible for inflammatory response and DNA repair were suggested to contribute to inflammation induced PCa (Klein & Silverman, 2008). Sexual activity has been suggested as a cause of prostatic inflammation with subsequent PCa. This was based on the increased incidence of PCa observed among uncircumcised men, and those with history of sexually transmitted diseases; especially syphilis (Sutcilffe et al., 2010). Despite the extensive effort conducted to isolate or identify specific infectious agents which may have a direct link with PCa initiation, currently, no infectious agent has been proven to cause PCa.

Numerous studies have investigated dietary factors and obesity as causes of PCa after an increased incidence in the first generation of immigrants (from Asia to USA) was observed (Muir et al., 1991; Shimizu et al., 1991). However, until now, no study could show an association between food and PCa or establish any role between healthy food and the minimisation of risk of this disease.

Obesity is a known risk factor for cancers, such as breast and colon cancers. White fat in human bodies is considered an endocrine organ that secretes cytokines and substances with cytokine-like activities (Madigan et al., 1998). Prospective studies suggest that obesity increases the risk of high-grade PCa but is also associated with lower risks of the low-grade disease (Gong et al., 2006). Obesity is further linked with higher rates of biochemical failure after radiotherapy or radical prostatectomy (Masko et al., 2013).

Smoking is also a risk factor for PCa because it increases the circulating androgens and cadmium exposure. Moreover, it causes cellular oxidative stress (Huncharek et al., 2010). Based on recent studies, smokers are at higher risk of metastasis in comparison to non-smokers (Moreira et al., 2014). Alcohol consumption also demonstrated a controversial relation to PCa; epidemiological

studies have suggested higher risk of high-grade PCa in heavy drinkers (Zuccolo et al., 2013), while others suggested a protective role (McGregor et al., 2013).

1.1.3. Pathology

Adenocarcinoma is the most common type of PCa (Mottet et al., 2015). Mucinous adenocarcinoma is a rare subtype of adenocarcinoma with more liability to bone metastasis; however, the prognosis is similar to non-mucinous variants (Osunkoya et al., 2008). Sarcomas very rarely affect the prostate (less than 0.2%) and are more likely to be rhabdomyosarcoma or liomysarcoma in childhood or adult aged patients, respectively (Sexton et al., 2001; Cheville et al., 1995).

Clinically undetectable tumours are staged as T1a/b if the cancer is incidentally found in the prostatic tissue after transurethral resection of the prostate (TURP), or after open prostatectomy for benign hyperplasia. This depends on the percentage of malignant tissue (T1a less than 5%; T1b more than 5%). Tumours detected after prostatic biopsy due to high PSA levels are staged as T1c (Epstein et al., 2007). After radical prostatectomy, preoperative T1 stages will be upstaged to T2 if the tumour is confined to the prostate, T3a if the tumour has extracapsular extension, or T3b if the tumour invades seminal vesicle. The degree of extracapsular extension correlates with the risk of disease progression after radical prostatectomy (Epstein et al., 2001). The tumour can extend to the seminal vesicle, more commonly through invasion of the periseminal vesicle's soft tissue rather than direct extension through the ejaculatory duct (Villers et al., 1989). Seminal vesicle infiltration is a strong predictor for disease progression after surgery and is associated with a 65% progression rate within five years (Pierorazio et al., 2011). Most tumours are located in the posterior part of the prostate, in the peripheral zone. Only 15% of tumours arise from the anterior part, the transitional zone (Al-Ahmadie et al., 2008). In about 90% of cases, the tumour is multi-focal with a prominent nodule most often larger in size with higher grade and stage; however, other tumours are usually small and low grade (Yoon et al., 2008). The

most common sites for metastasis of PCa are the lymph nodes, bones and lungs. The less common sites include the bladder, liver and adrenal gland (Hess et al., 2006). In general, the volume of the tumour correlates with the stage. Tumours less than 0.5 cm^3 are unlikely to extend beyond the capsule. In most cases, tumours less than 4 cm^3 are not associated with lymph node metastasis. However, the location of the tumour also affects the volume; for instance, transitional zone tumours extend beyond the capsule at larger volumes compared to peripheral zone tumours (McNeal et al., 1990).

Grading of PCa is based on the Gleason system, which is founded on the glandular pattern of the tumour under low magnification. The pattern is graded from 1 to 5, which is the most undifferentiated architecture (Gleason & Mellinger, 1974). Currently, the Gleason score is the sum of the most common and highest grade patterns instead of the sum of the first and second common patterns. If the tumour only has a single pattern, the score will be double the present pattern grade (Epstein et al., 2005). It is not advisable to grade a cancer as Gleason score of 2 to 4 based on needle biopsy because almost all tumours would be graded higher after radical prostatectomy (Steinberg et al., 1997).

Different techniques can be used for prostate specimen sampling after radical prostatectomy. Whole-mount technique is the preferred method for teaching and publication purposes, however, the information provided is identical to those obtained from other techniques in which the prostate is not completely embedded (Sehdev et al., 2001).

1.2. Surgical Anatomy of the Prostate

The prostatic gland is an ovoid-shaped organ that lies below the bladder in the retropubic space and is traversed by the prostatic urethra; the junction between the bladder neck and membranous urethra. It has anterior, posterior and lateral surfaces with the prostatic base facing the bladder neck upwards, while the apex faces downwards. The deep position of the apex and the close relation to the

striated sphincter and the neurovascular bundle makes the apical dissection the most challenging step in RP.

1.2.1. Prostatic capsule and endo-pelvic fascia

The prostatic gland is surrounded by three separate layers of fascia: Denonvilliers fascia, the levator fascia and the prostatic fascia, which is also called the prostatic capsule. Denonvilliers fascia is a connective tissue layer that separates the prostate from the anterior wall of the rectum. Cranially, it becomes more dense and prominent; however, causally, it becomes thinner and terminates in the striated urethral sphincter. Prostatic fascia is in direct contact with prostatic parenchyma, anteriorly and laterally. The average thickness of the prostatic capsule is 0.5 mm and may be pierced in some areas by the glandular tissue. Laterally, the prostate is covered by the visceral endopelvic fascia, and the lateral divisions of the dorsal venous plexus are located between the prostatic capsule and the endopelvic fascia just below the arcus tendineus fascia pelvis (the juncture of the parietal and visceral endopelvic fascia). During classical radical prostatectomy, endopelvic fascia should be incised laterally to this junction to avoid injury of the venous plexus.

1.2.2. Neurovascular bundle (NVB)

Understanding the arterial and venous blood supply of the prostate is crucial to minimise intraoperative blood loss, as well as for proper visualisation of the prostatic apex and membranous urethra. Prostatic veins drain into the Santorini plexus. The superficial dorsal vein travels between the puboprostatic ligaments and can be easily visualised in the retropubic space over the prostate and bladder neck. The common trunk and the lateral venous plexus run between the prostatic fascia and endopelvic fascia. The lateral plexus has free communications with the pudendal, obturator and vesical plexuses and communicates with the internal

pudendal vein through small branches that penetrate the pelvic sidewall muscles near the puboprostatic ligament.

Arterial supply for the prostate originates from the inferior vesical artery, a branch of the internal iliac artery through two large groups of arteries; the urethral and capsular groups (Flucks, 1937). The urethral branches enter the prostate at the posterolateral aspect of the bladder neck and supply the periurethral part of the gland. The capsular branches run posterolateral to the prostate, in the lateral pelvic fascia, and send dorsal and ventral branches to the prostate and pelvic floor. These capsular branches are the anatomical landmark for identifying the neurovascular bundle intraoperatively (Walsh et al., 1983).

The cavernous nerve fibres run with the arterial supply of the prostate to form the NVB, which is mainly located at the posterolateral aspect of the prostate and pierce the prostate at 5 and 7-o'clock positions near the base. Approaching the apex, the NVB follows a spray-like distribution and pierces the prostate at 1 and 11-o'clock positions. The nerve fibres are difficult to identify intraoperatively; the accompanying vessels are usually used as a landmark to preserve NVB during nerve sparing radical prostatectomy.

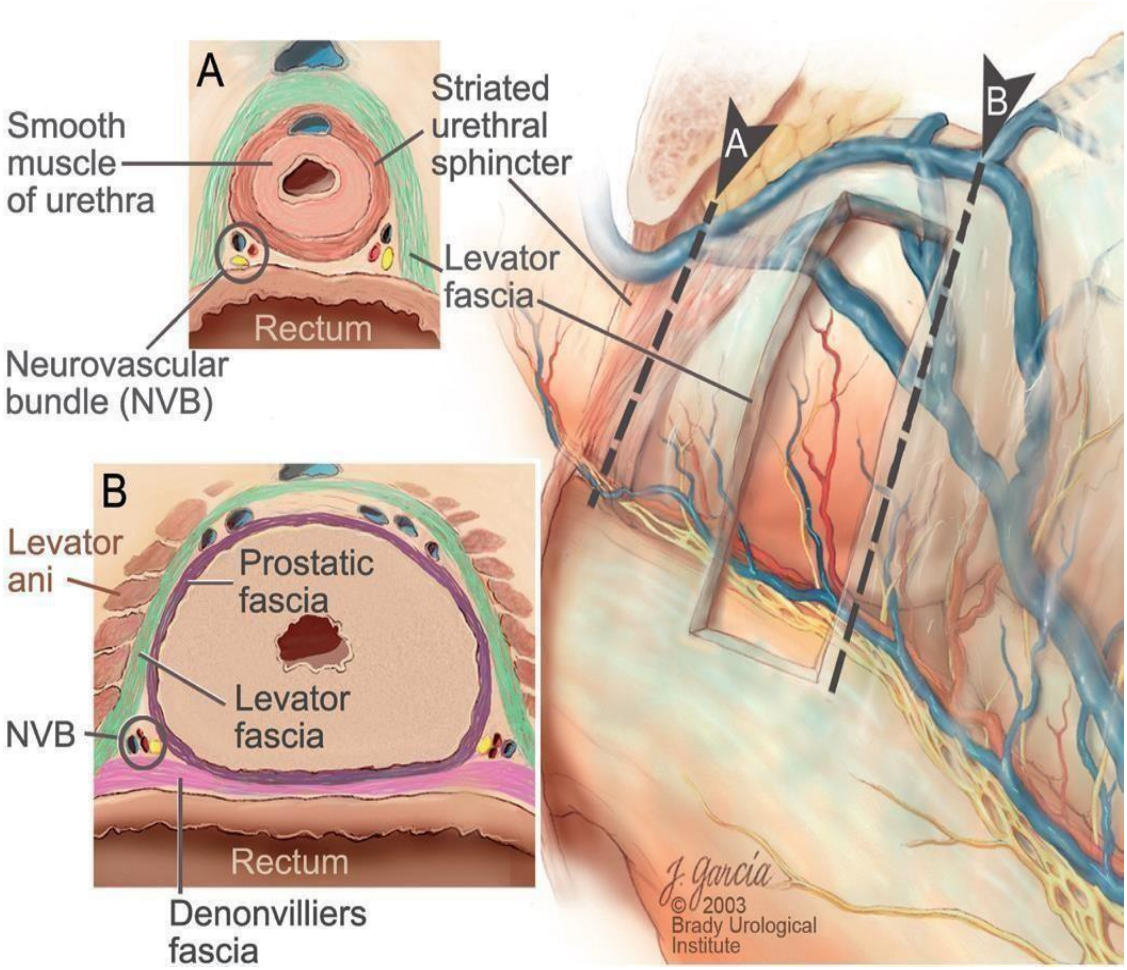


Figure 1(A)**:** A cross section through the apex of the prostate demonstrating that the neurovascular bundles are posterolateral to the circumferential striated sphincter of the urethra. Figure 1(B): A cross section through the midportion of the prostate demonstrating that the neurovascular bundles are located between the layers of the levator fascia and prostatic fascia (Campbell-Walsh et al., 2012).

Although the previous pattern is common for NVB distribution, anatomical variations in the distribution pattern of NVB around the prostate is not uncommon. In the literature, there is some evidence that nerve tissue is distributed not only in the posterolateral aspect, but also anteriorly (Eichelberg et al., 2007; Sievert et

al., 2008; Ganzer et al., 2008; Lee et al., 2008), and is even shown to have functionality (Hisasue et al., 2010).

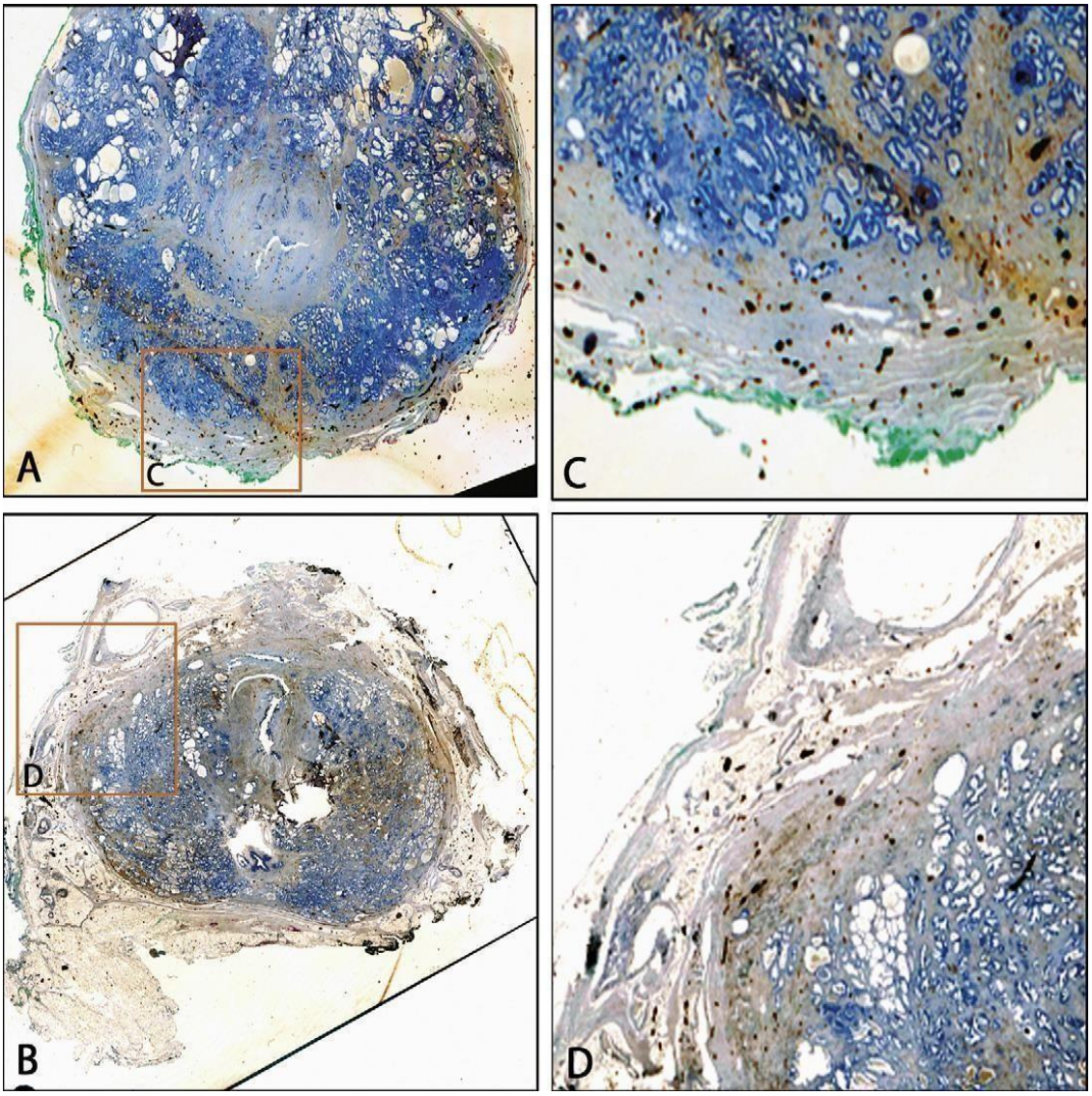


Figure 2: Distribution of periprostatic nerves. Transverse whole-mounted sections of the prostate from the apex (A) and the middle (B). Magnifications: (C) dorsal periprostatic and capsular nerves at the apex; (D) ventrolateral periprostatic nerves in the middle (Ganzer et al., 2008).

1.2.3. External urethral sphincter

The striated urethral sphincter is located at the level of the membranous urethra. With the surrounding fascia, the sphincter forms a vertically-oriented tubular sheath around the membranous urethra and extends to the perineal muscle before the development of the prostate. After the prostate develops from the urethra, it invades the sphincter and causes some atrophy to the muscle fibres (Oelrich, 1980). In adults, the sphincter fibres form a horse-shoe shape around the membranous urethra and the apex of the prostate. This orientation is critical during the dissection of the apex to preserve the sphincter (Walsh et al., 1990). Apart from the Levator ani muscle, it also surrounds the membranous urethra and prostatic apex and is inserted posteriorly in the perineal body (Myers, 1994). These muscle fibres are responsible for voluntary active continence and are innervated at the striated sphincter by the pudendal nerve. The striated sphincter is responsible for passive continence through its fatigue-resistant, slow twitch fibres. Preoperative instructions for the patient to contract the levator ani muscle can help strengthen the external sphincter as well (Centemero et al., 2010).

1.3. Role of Radical Prostatectomy in Treatment of PCa

Radical prostatectomy (RP) is the surgical treatment for PCa. It involves the removal of the whole prostatic gland between the urethra and bladder, including the seminal vesicles and sufficient surrounding tissue, to obtain a negative margin. Many years ago, radical prostatectomy was recognised as the gold standard treatment for localised PCa (Christopher et al., 2016). This operation was developed in 1945 by an Irish surgeon, Terence Millin (Millin et al., 1945), and was refined in 1982 by Patrick C. Walsh when he developed the modern nerve-sparing, retropubic prostatectomy with minimal blood loss to preserve the potency of patients (Walsh et al., 1983). The most common approach is to make an incision in the skin between the umbilicus and top of the pubic bone. Since the initial

description by Walsh, technical advancements have been made, and the incisional length has decreased to between 8–10 cm.

Patients who undergo RP for low risk PCa can obtain better metastasis-free and progression-free survivals in comparison to patients who undergo watchful waiting of their disease (Hamdy et al., 2016). In intermediate risk disease, RP can significantly improve the overall survival, but not disease-specific survival, for PCa patients (Wilt et al., 2012). In high-risk PCa, RP can still be offered as a treatment option, however, it should be as part of a multi-modal treatment plan (Fahmy et al., 2017). For patients who develop local recurrence after radiotherapy, salvage RP is the preferred option for local control of the disease, yet the rate of complications is expected to be higher than primary RP due to the impact of previous RT on the tissues (Chade et al., 2012).

Commonly, this operation is accompanied by bilateral pelvic lymph node dissection; however, the indication for lymphadenectomy depends on the risk stratification of the disease. In low risk patients, pelvic lymph node dissection is not required since the chance of lymph node involvement in this group is very low. In intermediate-risk men, the chance of lymph node involvement is between 3.7% to 20% (Studer et al., 2008). Pelvic lymphadenectomy should be performed if the risk of lymph nodes being positive is more than 5% (Studer et al., 2008). In all high-risk patients, lymphadenectomy should be routinely performed due to the high risk of lymph node involvement (15%-40%) (Studer et al., 2008). This includes, at least, the removal of lymph nodes around the external iliac vessels, medial and lateral to the internal iliac artery, and within the obturator fossa. Perisacral and common iliac lymph nodes can also be removed to maximise the chance of complete clearance of up to 97% (Mattei et al., 2008).

1.4. Robotic Assisted Radical Prostatectomy (RARP)

The first laparoscopic prostatectomy was performed in 1991 by William Schuessler et al. in Texas to minimise the morbidity of open surgery and overcome

the difficult exposure of the retropubic space during open radical prostatectomy (Schuessler et al., 1997). In 2000, the first RARP was performed by Binder et al. in Frankfurt, Germany (Binder et al., 2001) and by Abbou et al. in Creteil, France (Abbou et al., 2000). It then gained popularity over time (Frota et al., 2008). In 2010, Bocciardi described the subtrigonal approach through the Douglas space, following a completely intrafascial plane without any dissection of the anterior compartment (Galfano et al., 2010). Currently, 80-85% of radical prostatectomies in USA are performed using robotic assistance; however, this proportion is lower in Europe (Naomi, 2014).

RARP began in the urology department at University Hospital Tuebingen in 2008 and was performed using transperitoneal radical prostatectomy (TPRP) approach. In June 2013, the Tuebingen group switched to subtrigonal radical prostatectomy (STRP). This study compares the outcome of both techniques regarding the oncological and functional aspects.

2. Methodology

2.1. Study Design and Data Collection

For this study, the approval of the internal review board (IRB) and ethical committee in Tuebingen University was obtained (project number 709/2013BO2). All patients who underwent STRP in Tuebingen university hospital were identified from the beginning of this technique (June 2013) until January 2015. The research in the database displayed 92 patients treated with STRP between the specified timeframe. The first 30 patients who were operated in the second half of 2013 were excluded from the study since they were considered to be from the starting phase during the learning curve of this technique. Thus, 62 patients who underwent operation between January 2014 and January 2015 were included as the experimental group and were assigned to group B. To compare the outcomes of STRP versus TPRP, all patients who underwent operation using the TPRP technique in the last 18 months before starting STRP (from January 2012 to June 2013) were identified as the control group and assigned to group A. 127 patients were retrieved for this group. A total of 189 patients were identified for both groups; 127 patients from group A that underwent TPRP, and 62 patients from group B that underwent STRP. One patient was excluded from group A since TPRP was intraoperatively converted to open surgery due to severe adhesions from multiple previous surgeries. Finally, 188 patients were included in this study. No patients were excluded from the study based on preoperative or postoperative assessments.

Data was prospectively collected from the database of Tuebingen University Hospital. The retrieved data included patients' name, contact data, age, BMI, preoperative PSA, preoperative and postoperative haemoglobin level, digital rectal examination findings, preoperative Gleason score, TRUS estimated prostatic volume and potency status before surgery. The applied risk stratification was based on D' Amico (D' Amico et al., 1998). Operative data included console time

(the time taken by the surgeon on the robotic console), nerve sparing (either unilateral or bilateral) and intraoperative complications classified according to the Clavien-Dindo classification (Clavien et al., 2009). Blood loss was calculated by the difference between pre and post-operative haemoglobin levels. The final pathology data included the final Gleason score, prostatic specimen volume, margin status and lymph node status. Oncological outcomes were retrieved from the database which included the PSA relapse (biochemical recurrence was defined as the PSA level of ≥0.2 ng/ml), development of metastasis and further treatment after surgery. Regarding functional outcomes, the data were collected from patients through phone calls or correspondences, as will be explained later.

2.2. Surgical Technique

All patients included in this study were treated with RARP for PCa after proper and full preoperative assessment. A well-informed written consent was obtained from every patient, including possible postoperative complications and the discussion of radiotherapy as an alternative treatment. TPRP was performed in the first group, while STRP was the employed technique in the second group.

2.2.1. Conventional robotic assisted radical prostatectomy

Under general anaesthesia, the patient is positioned in a supine position with semi-flexion and abduction of both hip joints, as well as flexion of the knee joints. A 20F Foley catheter is inserted to deflate the bladder. Five laparoscopic ports are fixed in the abdominal wall in the following distribution: a 12 mm port at the umbilical ring for the robotic camera. After insufflation of Co2 of up to 15 mmHg pressure inside the abdominal cavity, two 8 mm ports on the line between the umbilicus and the anterior superior iliac spine are placed one hand breadth apart from the camera port on the line. One 5 and one 12 mm ports are on the right side for the assistant; the 5 mm port is between the camera and the 8 mm port and is used for suction. The 12 mm port is 8 cm below and lateral to the right 8 mm port and is used for the introduction of different surgical instruments employed by the

assistant surgeon. The patient's position is changed from supine to deep Trendelenburg position after the fixation of all ports.

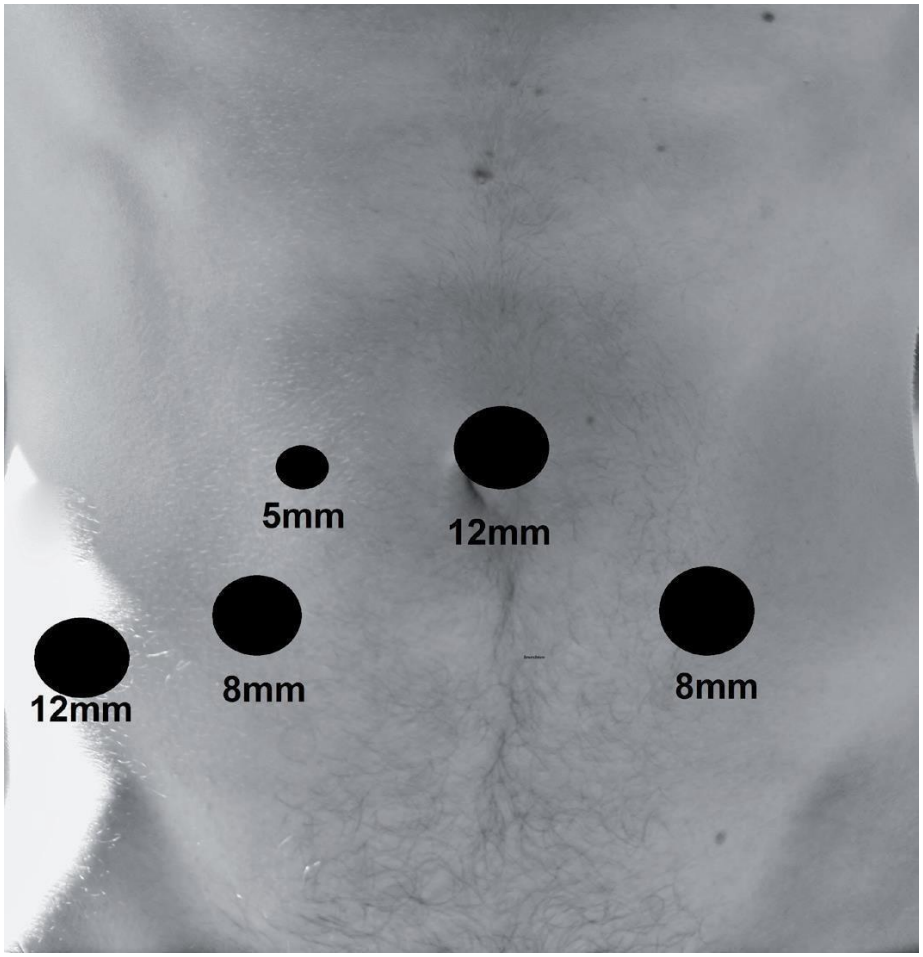


Figure 3: A diagram demonstrating the distribution of laparoscopic ports in the abdominal wall (Fahmy et al., 2015).

The pelvic cavity is inspected, and the release of adherent bowel is performed if necessary. An incision in the lower part of the anterior wall of the Douglas pouch using monopolar scissors is created. Next, the vas deference is identified as well as the seminal vesicle, which lies immediately lateral to it. Dissection of the seminal vesicle is performed by using minimal electrocautery and metal hemoclips to avoid thermal injury of the nearby NVB. Then, the retropubic

space is reached through the dissection of the perivesical fat. After controlling the dorsal venous plexus by using bipolar electrocautery, the bladder neck is dissected from the prostatic base using monopolar scissors. During this time, intermittent caudal retraction of the urethral catheter balloon is performed by the assistant surgeon to identify the proper plane for bladder neck dissection. Dissection is then continued towards the prostatic apex, and the urethra is sharply cut just above the concavity of the prostatic apex.

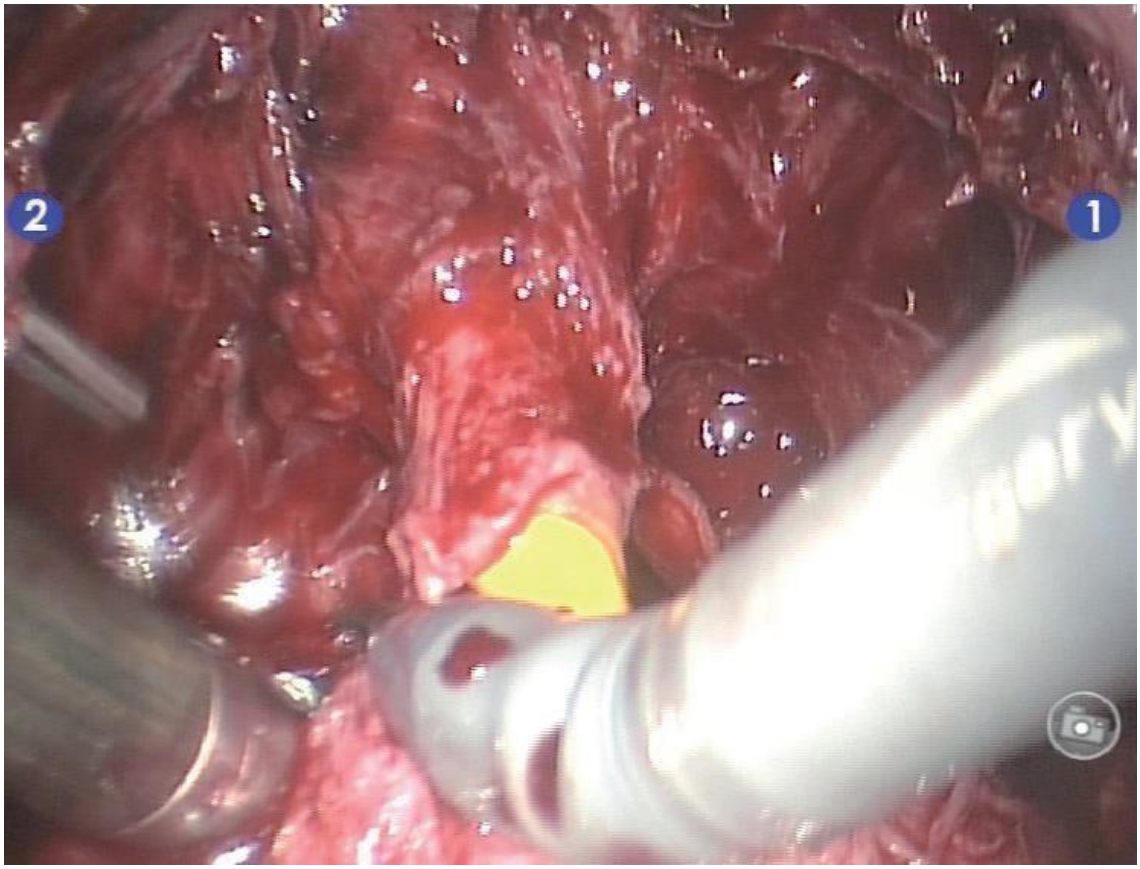


Figure 4: Sharp dissection of the urethra from the prostatic apex (Fahmy et al., 2015).

Anterior traction over the vas and seminal vesicle is performed by the assistant surgeon to identify the space between the prostate and the rectum. After that, Denonvilliers fascia is incised just behind the junction of the ejaculatory duct

and prostate to reach the perirectal fat plane. Metallic clips are used to control the neurovascular bundles when nerve sparing was planned. After the complete dissection of the prostate, the remnant Denonvilliers fascia and posterior part of the bladder neck are approximated to the striated sphincter behind the urethral stump using the V-LocTM suture. With the same suture, a continuous tension-free vesico-urethral anastomosis is performed over a 20 Fr. Silicone catheter. The catheter balloon is then inflated with 8cc water. The anastomosis is tested for leakage by inflation of the bladder through the urethral catheter with 100 cc normal saline.

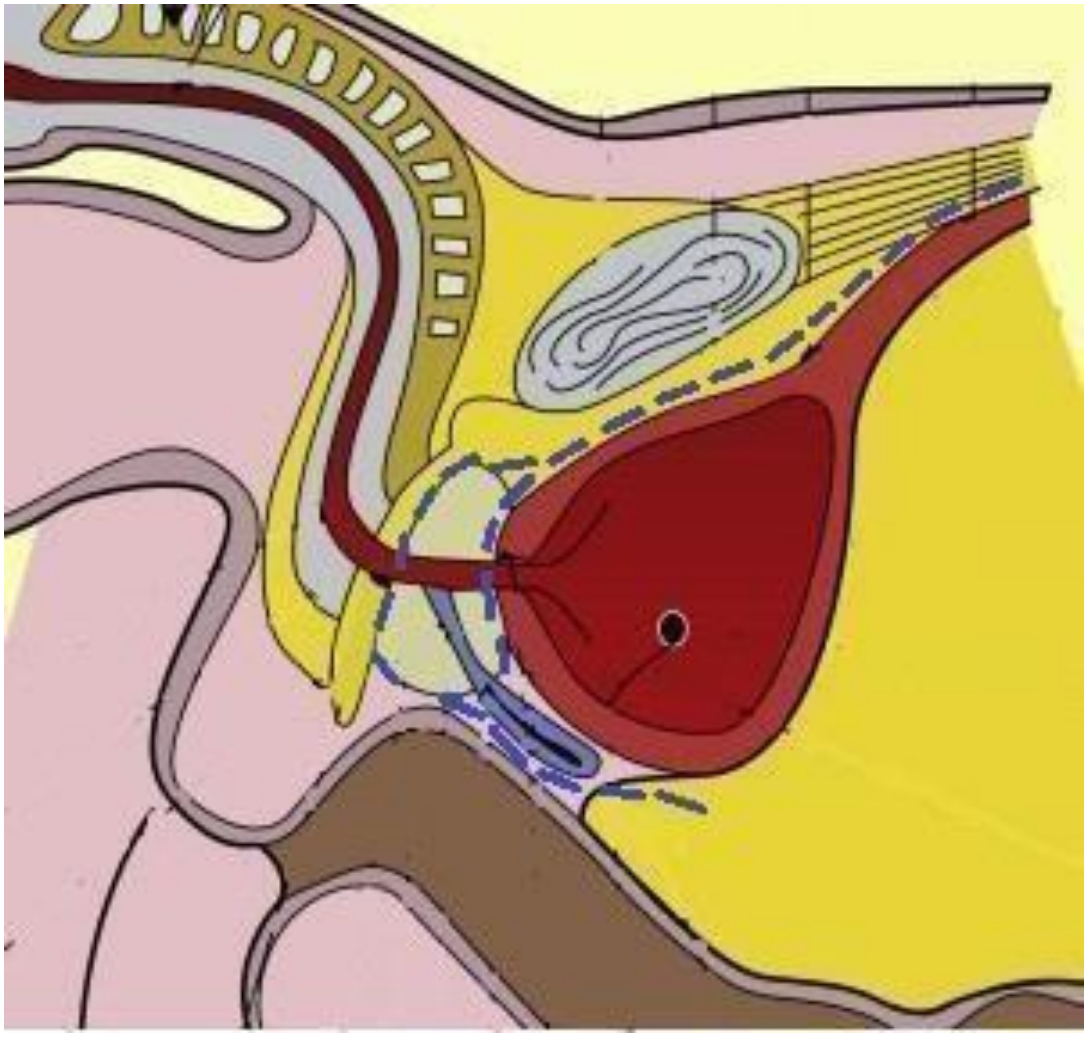


Figure 5: A diagram demonstrating the dissection planes in TPRP marked in the interrupted blue line (Patel & Chapple., 2008).

2.2.2. Subtrigonal robotic assisted radical prostatectomy

The patient's position and distribution of the laparoscopic ports are the same as in conventional RARP. Seminal vesicles are directly approached through a lower transverse incision at the anterior wall of the Douglas pouch. After the dissection of the seminal vesicles and cutting of the vase deferentia bilaterally, the assistant surgeon applies upwards traction on the seminal vesicles to facilitate the incision of the posterior layer of the Denonvelliers fascia. The plan between the prostate and the rectum is opened just below the ejaculatory duct (Fahmy et al., 2015).

Subsequently, nerve sparing is achieved by retracting one seminal vesicle upwards and medially , and creating various holes in the periprostatic fascia and applying metal clips over the tissue bundles. The same technique is made on the contralateral side. After that, the base of the prostate is dissected form the bladder neck, starting form 6 o'clock , and continue bilaterally until 12 o'clock (Fahmy et al., 2015).

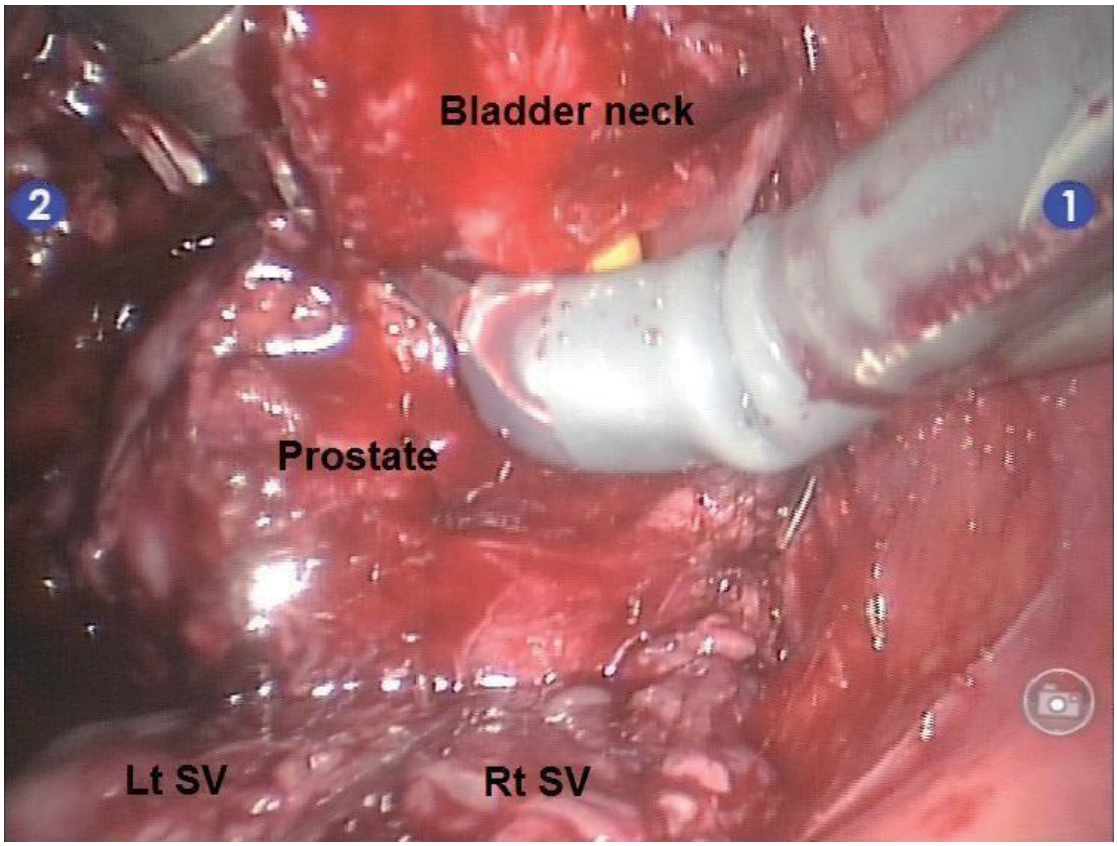


Figure 6: Bladder neck dissection from 6 o'clock until 12 o'clock (Fahmy et al., 2015).

Lastly, external sphincter muscle fibers are peeled downward from the prostatic apex before cutting the urethra to minimize the sphincter injury . Then, the urethra is sharply cut just a few millimetres above the concavity of the prostatic apex. With this technique, the operation is completely performed through the Douglas pouch without entering the retropubic space or disruption of the peri-vesical tissue. The urethrovesical anastomosis is performed as described in the conventional technique. (Fahmy et al., 2015).

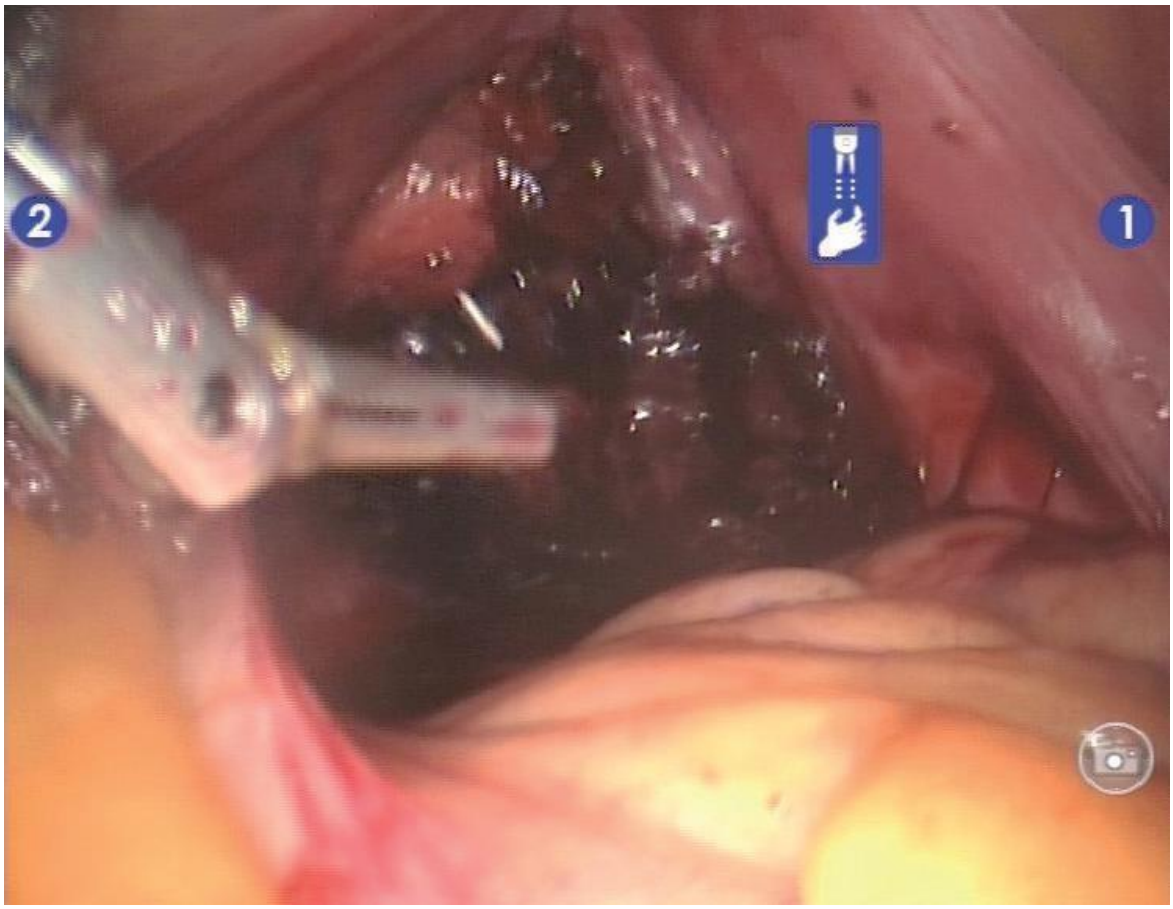


Figure 7: The view of the prostatic bed after complete extraction of the prostate with intact perivesical tissue (Fahmy et al., 2015).

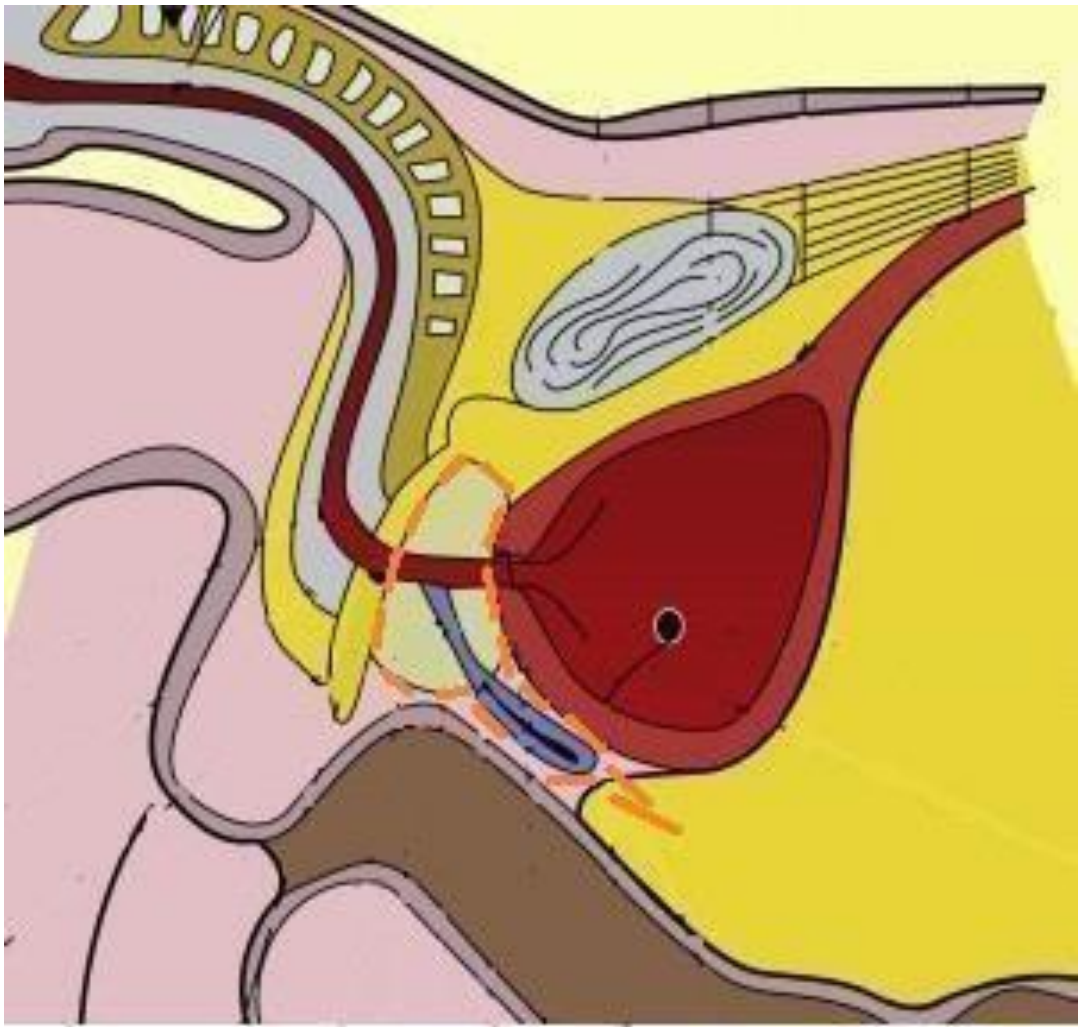


Figure 8: A diagram demonstrating the dissection planes in STRP marked in the interrupted orange line (Patel & Chapple., 2008).

2.3. Follow-up

For patients treated with TPRP, the median follow-up time was 34 months (24-39). For STRP patients, the median follow-up time was 9 months (3-15). The data for perioperative outcomes including operative time, blood loss, intra- operative complications, hospital stay, anastomotic complications, duration of catheterisation and postoperative complications were collected from the database

records of Tuebingen University Hospital. Surgical complications were classified according to the Clavien-Dindo classification (Clavien et al., 1992). Marginal status was obtained from the histopathological examination of prostatic specimens using the whole-mount technique. BCR was defined as the PSA value of 0.2 ng/mL or greater with a second confirmatory laboratory value (Cookson et al., 2007). Functional outcomes were evaluated using ICIQ and IIEF scores for continence and potency, respectively. Incontinence was defined as using at least one pad per day. Immediate post-operative continence was defined as the no usage of pads within one week of catheter removal. Postoperative potency was defined as the ability of the patient to get enough erection for penetration with or without medications. Data for ICIQ and IIEF scores of patients were collected through telephone calls. Only patients with preoperative potency and bilateral nerve sparing surgery were subjected to IIEF scoring. Questionnaires were sent by post to patients who could not be reached by phone. The questionnaires were translated to the German language since it is the native language for the included patients.

2.3.1. ICIQ

ICIQ is a brief, fully validated questionnaire launched after the International Consultation on Incontinence meeting in 1999. This score is composed of the sum of three questions after the selection of one answer for each question. The first question is how often the patient leaks urine. The patient should select one of six answers (never, once a week, 2-3 times a week, once a day, several times a day or all the time) and score from 0 to 5. The second question is how much urine the patient leaks, and the answer is one of four (none = 0, small amount = 1, moderate amount = 2, large amount = 3). The third question is how much does leaking urine interfere with the patient's everyday life, and the answer is a score between 0 and 10. The ICIQ score is the sum of the previous three answers, and the degree of incontinence is classified into: no incontinence = 0, mild = 1-5, moderate = 6-10 and severe = 11-21.

2.3.2. IIEF score

The International Index of Erectile Function (IIEF) is a validated questionnaire used for clinical assessment of erectile dysfunction and treatment outcomes (Rosen et al., 1997). The first five questions in the IIEF questionnaire assess the erectile function of patients. A score between 0-5 is awarded for each question. The first question is how often the patient can get an erection during sexual activity. The second is how often the erections were hard enough for penetration. The third is how often the patient was able to penetrate. The fourth is how often the patient was able to maintain his erection after penetration. The last question is how often the patient could maintain his erection to the completion of intercourse.

2.4. Statistical Analysis

For this study, statistical analysis was performed using the jmp V.12 software® (SAS Inc. Cary, USA). All data were presented as median and range for continuous variables, and as percentages for categorical variables. Mann- Whitney-U and Pearson x2 tests were employed to compare the continuous and categorical variables, respectively. Kaplan Meier curves were used to present the survival data with the Log-rank test for comparison. A p-value of <0.05 is regarded as significant.

3. Research Questions and Hypothesis

The study aims to answer the following questions: is there any difference between conventional or subtrigonal techniques for RARP regarding operative time, intraoperative and postoperative complication rates? Can the preservation of the dorsal venous plexus decrease the intraoperative blood loss? What is the impact of the anatomical preservation of the retropubic and perivesical areas on functional outcomes? Is STRP oncologically safe as TPRP or not?

The hypothesis of this study is that STRP is associated with less blood loss and carries better functional outcomes regarding postoperative continence and erectile function. It is also oncologically safe with similar oncological outcomes in comparison to TPRP. The rationale for this hypothesis was based on the fact that the subtrigonal approach is more anatomically preservative than the conventional one since the prostatic gland is completely excised from the Douglas pouch with the preservation of perivesical tissues; this is expected to improve functional outcomes.

4. Results

4.1. Patient Criteria

Group A included 126 patients who underwent operation between January 2012 and June 2013 using TPRP. The median age of this group is 64 years (45-76), the median BMI is 27.2 kg/m^2 (20.9-40) and the median preoperative PSA is 7.4 ng/ml (0.4-28). Regarding the clinical staging of PCa, 44 (34.9%), 19 (15.0%) and 1 (0.07%) patients are T1, T2 and T3, respectively. The other 62 patients (49.2%) have clinical stages between T1-T3, however, the specific stage was unknown. D' Amico risk stratification was applicable for only 61/126 patients as the following: Low 14 (23%), Moderate 36 (59%) and High 11 (18%). In this group, 26 (21%), 47 (37%) and 53 (42%) had bilateral, unilateral or non-nerve sparing surgery, respectively.

Group B included 62 patients who underwent operation between January 2014 and January 2015 using STRP with a median age of 62.5 years (48-77), BMI median of 26.7 kg/m2 (21.2-37.8) and preoperative PSA median of 7.0 ng/ml (1.2-26.8). In this group, T1, T2 and T3 clinical stages are 22 (35.5%), 11(17.7%) and 0 (0%), respectively. The other 29 (46.8%) patients were unknown. Risk stratification was Low, Moderate and High for 6 (19%), 17 (53%) and 9 (28%) patients, respectively. 8 (13%), 32 (52%) and 22 (35%) patients had bilateral, unilateral or non-nerve sparing radical prostatectomy. Both groups were matched in all previous variables with no significant difference detected (see Table 1).

Table1: Preoperative criteria of patients involved in the study, including the p-value of the difference between both groups

Patients criteria	Group A	Group B	P
Age (y)	64 (45-76)	62.5 (48-77)	*0.13*
BMI (kg/m^2)	27.2 (20.9-40)	26.7 (21.2-37.8)	*0.33*

Pre-Op PSA (ng/ml)	7.4 (0.4-28)	7.0 (1.2-26.8)	*0.80*
Clinical stage*			
cT1	44 (34.9%)	22 (35.5%)	
cT2	19 (15.0%)	11 (17.7%)	*0.43*
cT3	1 (0.07%)	0	
Unknown	62 (49.2%)	29 (46.8%)	
D' Amico risk stratification*			*0.53*
Low	14 (23%)	6 (19%)	
Moderate	36 (59%)	17 (53%)	
High	11 (18%)	9 (28%)	
Nerve sparing			
No	53 (42%)	22 (35%)	
Unilateral	47 (37%)	32 (52%)	*0.11*
Bilateral	26 (21%)	8 (13%)	

*Data were not available for all patients, ** Significant p-value

4.2. Perioperative Outcomes

The console time was comparable in both groups. In group A, the median time was 167 minutes (90-267) versus 163 (72-273) for group B (p=0.65). No difference was detected in blood loss between both groups; the median of haemoglobin drop was 2.73 (0-9.2) for group A versus 2.70 (0.5-6.6) in group B (p=0.80). The median time of post-operative catheterisation was 5.7 days (4-20) in

group A versus 5.5 (4-9) in group B (p=0.96); and the median hospital stay after surgery until discharge was 7 days (3-24) in group A and 7 days (5-14) in group B. The pathological findings were comparable in both groups; in group A, 17 (14%), 74 (59%), 28 (22%) and 7 (6%) patients had the Gleason score of ≤6, 3+4, 4+3 and ≥8, respectively, versus 10 (16%), 30 (48%), 19 (31%), 3 (5%) in group B. 97 (77.0%) and 25 (19.8%) patients in group A displayed pT2 and T3 versus 45 (72.6%) and 14 (22.6%) in group B (p=0.96). Pathological staging was missed in the pathology report for the other patients (4 and 3 patients in group A and B, respectively). pNx, N0 and N1 lymph node statuses were 1 (1%), 120 (95%) and 5 (4%) in group A and 1 (1.6%), 58 (93.6%) and 3 (4.8%) in group B (p=0.58). Only the prostatic volume displayed a significant difference which was 46.5 g (14-173) in group A versus 38.5 g (16-84) in group B (p-value = 0.018).

Table 2: Perioperative and pathological outcomes of patients involved in the study, including the p-value of the difference between both groups

Perioperative outcomes	**Group A**	**Group B**	***P***
Console time (min)	167 (90-267)	163 (72--273)	*0.65*
Blood loss by Hb diff.	2.73 (0-9.2)	2.70 (0.5-6.6)	*0.80*
Intra op. complications	1	1	*0.42*
Days of cath.	5.7 (4-20)	5.5 (4-9)	*0.96*
Hospital stay (day)	7 (3-24)	7 (5-14)	*0.06*
final Gleason			
<=6	17 (14%)	10 (16%)	*0.16*
3+4	74 (59%)	30 (48%)	

4+3	28 (22%)	19 (31%)	
>=8	7 (6%)	3 (5%)	
Pathological Stage*			
pT2	97 (77.0%)	45 (72.6%)	
pT3	25 (19.8%)	14 (22.6%)	*0.96*
Unknown	4 (3.2%)	3 (4.8%)	
LN			
pNx	1 (1%)	1 (1.6%)	
pN0	120 (95%)	58 (93.6%)	*0.58*
pN1	5 (4%)	3 (4.8%)	
Prostatic weight (g)	46.5 (14-173)	38.5 (16-84)	*0.018***

*Data were not available for all patients, ** Significant p-value

Table 3: Postoperative complications classified according to the Clavien-Dindo classification

Clavien	Group A	No. (%)	Group B	No. (%)
I	-		-	
II	Blood transfusion	1 (0.007%)		
IIIa			Retention + suprapubic catheter fixation	1 (1.6%)

IIIb	Lymphocele + Laparoscopic fenestration	6 (4.8%)	Lymphocele + Laparoscopic fenestration	1 (1.6%)
IVa	Angina + ICU admission	1 (0.007%)		
IVb	-		-	
V	-		-	

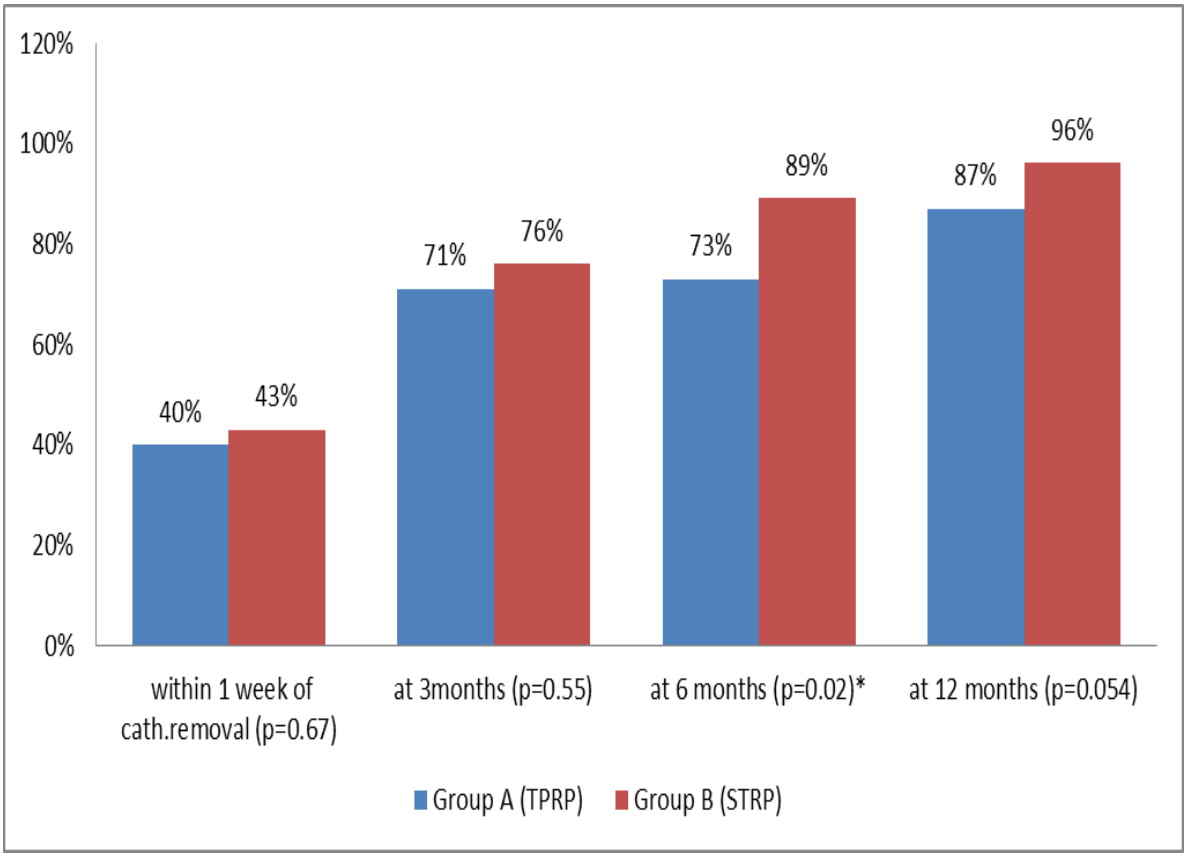
Regarding complications, one patient in each group developed intra- operative complications; obturator nerve injury in group A and left ureteral injury in group B. For postoperative complications, 8 patients (6.3%) developed postoperative complications in group A; one patient required blood transfusion, 6 patients developed pelvic lymphocele and treated with laparoscopic fenestration later on and one patient developed angina pectoris and was admitted to the intensive care unit for 2 weeks. On the other hand, only 2 patients developed post-operative complications in group B; one patient had acute urine retention due to urethral catheter blockage and was managed by supra pubic catheter fixation. The other patient developed pelvic lymphocele treated by laparoscopic fenestration. The difference in the complication rate between the two groups was not significant (p-value= 0.34). Postoperative complications according to the Clavien-Dindo classification are presented in Table 3.

4.3. Functional Outcomes

4.3.1. Continence

From the included 188 patients, 146 (77.7%) patients responded to our contact trials and answered the ICIQ questionnaire; 96 patients answered the phone calls and the other 50 patients completed the questionnaire form and sent it back by post. Group distribution was 93 patients in group A and 53 patients in group B. In group A, 37/93 patients (40%) could achieve immediate postoperative continence versus 23/53 patients (43%) in group B (p-value = 0.67).

At 3, 6 and 12-month intervals, the continence recovery rates were 71%, 73% and 87% in group A versus 76%, 89% and 96% in group B. P-values were0.55, 0.02 and 0.054, respectively, with a significant difference at 6 months interval and near significant difference at 12 months. The median number of pads used per day was 0.4 in group A versus 0.6 in group B (p-value = 0.20).



*significant p-value

Figure 9: Differences in continence rates between group A (blue) and group B (red) after catheter removal at 3, 6 and 12-month intervals after surgery.

4.3.2. Erectile function

A total number of 22 patients were eligible for postoperative assessment of erectile function; 15 patients in group A with the median age of 61 years (45-75), and 7 patients in group B with the median age of 59 years (48-69). In group A, 2/15 (13%) patients could achieve enough erection for penetration versus 3/7 (43%) in group B; however, the difference was not significant (p-value = 0.13). The median IEFF score was 7.4 (1-25) in group A versus 11.6 (1-25) in group B (p-value = 0.72).

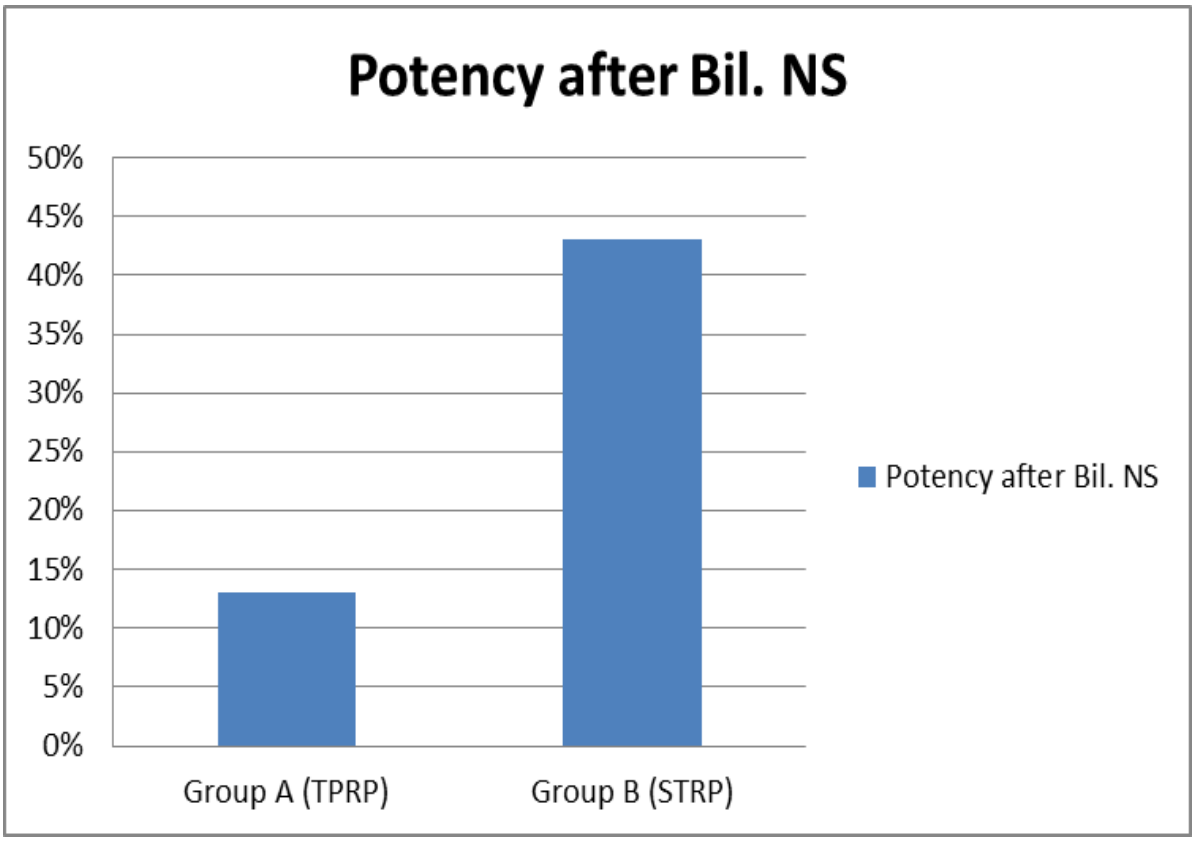
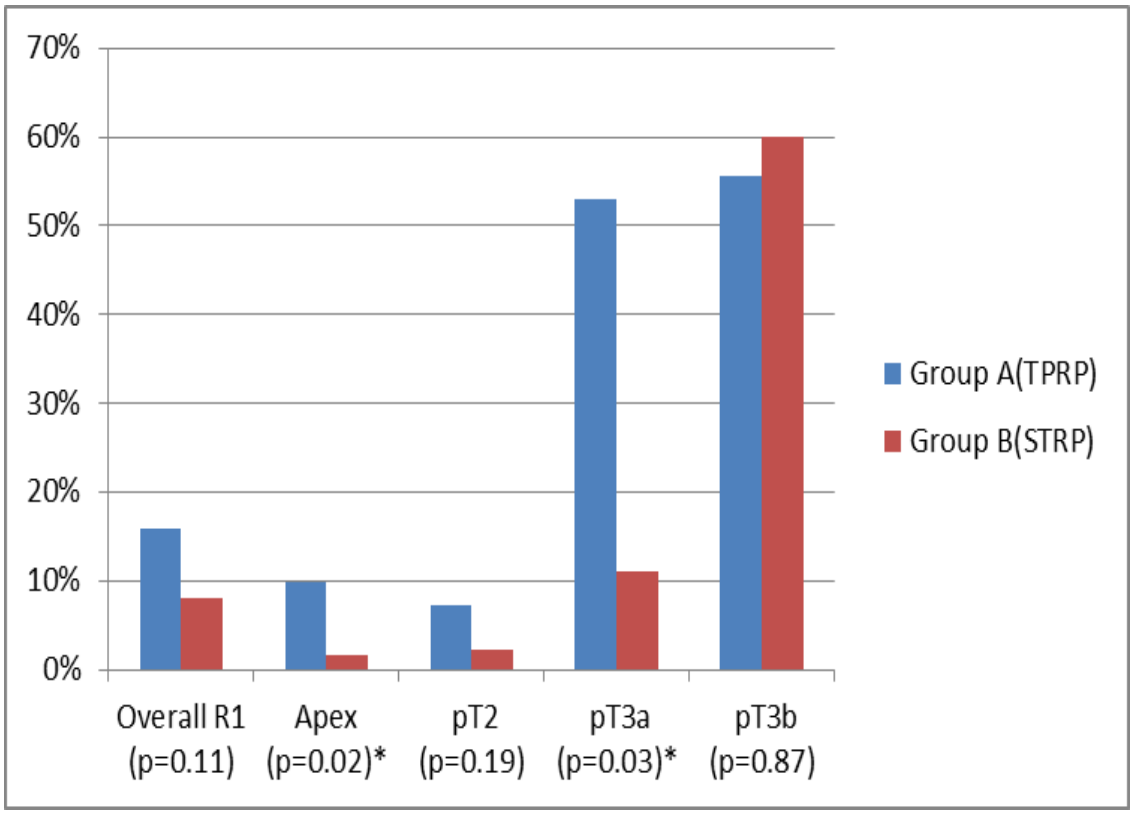


Figure 10: The percentage of patients in each group that were able to penetrate after bilateral nerve sparing surgery.

4.4. Oncological Outcomes

Positive surgical margin rates and BCR were used to compare the oncological outcomes in both groups. Overall, the positive surgical margin (PSM) rate was 16% in group A versus 8% in group B, (p-value = 0.11). When the PSM was compared in each pathological stage, the rates in pT2, pT3a and pT3b were 7.2%, 53% and 55.6% in group A versus 2.2%, 11% and 60% in group B, respectively (p-values = 0.19, 0.03 and 0.87). The PSM in pT3a was significantly lower in group B than in group A. With the comparison of the PSM rate at the prostatic apex, group A was 9.8% versus group B which was 1.6%, with a significant difference (p-value = 0.02).



*significant p-value

Figure 11: The difference in PSM rates between both groups; the columns demonstrate the total PSM rates at the apex and in each pathological stage.

After a median follow-up time of 34 months (24-39) for group A and 9 months (3-15) for group B, the BCR 1y-free survival was 91% in group A compared to 94% in group B. Kaplan Meier curve in Figure 12 illustrates the BCR-free survival in both groups (Log-rank p-value = 0.57).

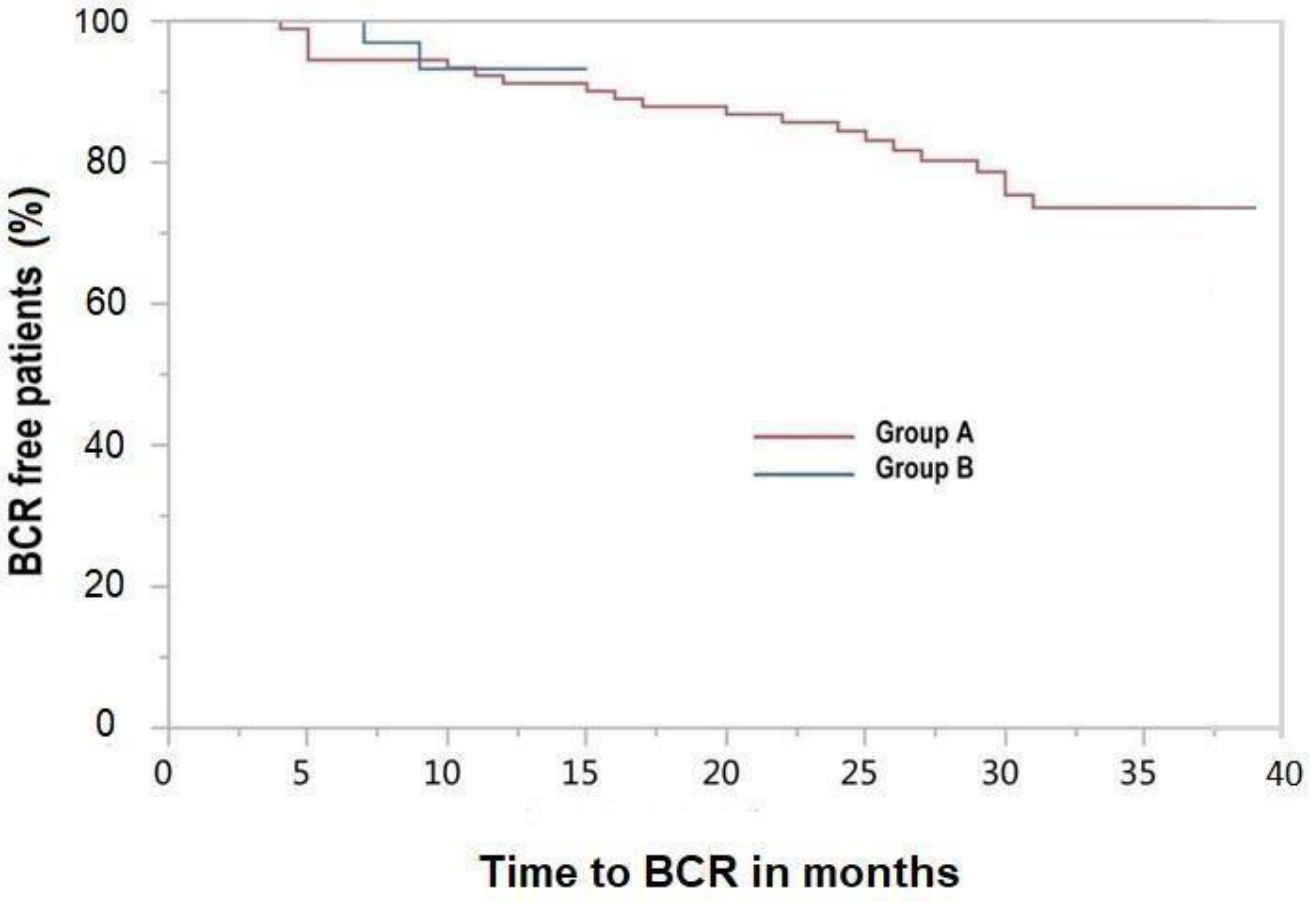


Figure 12: Kaplan Meier diagram demonstrating the 1-year BCR-free survival; the red line represents group A and the blue line represents group B.

5. Interpretation and Discussion

Although PCa is not aggressive in most cases, surgical treatment by RP in intermediate or high-risk diseases was approved to provide longer overall and disease-specific survivals for patients with localised PCa when compared to conservative treatment (Bill et al., 2014). Even in locally advanced PC with regional lymph node metastasis, RP was suggested to improve the survival outcomes (Engel et al., 2010; Fahmy et al., 2017). Despite being the preferred treatment option in localised PCa with a life expectancy of more than 10 years (Droz et al., 2010), there is no specific age limit for this operation and it shouldn't be denied on the basis of age alone (Albertsen et al., 2011). Patients with high risk PCa or with a life expectancy of <10 years included in this study were operated after discussing other non-surgical therapeutic modalities. Despite higher financial cost, RARP replaced open RP as a gold standard treatment for localised PCa in USA and this trend is extending to Europe and other parts of the world (Naomi, 2014).

The functional outcome, in the form of potency and continence, is the main concern for patients requiring RP, as well as the main reason to avoid this operation. Nerve sparing during RP can improve the functional outcome and can be safely performed in all patients with low-risk disease (Walsh, 2001). Even in patients with preoperative impotence, nerve sparing may help in continence preservation (Nilson et al., 2003). It is not recommended for patients with high-risk diseases, or those suspected of extracapsular extension due to higher risk of residual tumour (Steuber et al., 2006). Nerve sparing can be initially planned with the use of nomograms or Partin tables that can predict the involvement of NVB or based on preoperative multiparametric MRI scan (Partin et al., 1997; Iversen et al., 2010). However, the decision can be changed according to the intra-operative findings. Some techniques are very useful in making intra-operative decisions; frozen section analysis is very helpful for making a proper decision regarding nerve sparing (Beyer et al., 2014). Any induration detected by intra-operative palpation of the NVB area, which is an advantage for open surgery over

laparoscopic surgery, is highly suspicious of NVB invasion and should then be excised.

RP can be performed open, laparoscopic or robotic assisted. The clear advantages of laparoscopic or robotic assisted versus open are reduced blood loss, faster recovery, earlier discharge and less operative pain, yet early oncological and functional outcomes are comparable to open surgery (Yaxley et al., 2016). The magnification and 3-dimensional vision provided in RARP make the challenging steps of nerve sparing and urethra-vesical anastomosis more feasible, and this is the main factor for the increasing popularity of RARP. Most commonly, RARP is performed through the transperitoneal approach, which is preferred by many surgeons due to the larger working space compared to the extraperitoneal approach. In this study, both used techniques are transperitoneal, however, the subtrigonal one is more anatomical preserving as the prostate is completely removed through the cul-de-sac.

Only preliminary data is available in the literature about the outcome of STRP. In 2013, Bocciardi and group reported their results using STRP on 200 patients (Galfano et al., 2013). Another group presented their results at the Italian urology meeting in 2015 on 45 patients (Al-Shali et al., 2015). In contrast to our study, both reports did not compare subtrigonal to conventional RARP. Recently, a randomized controlled trial including 120 patients suggested that STRP can result in earlier recovery of continence in comparison to TPRP (Dalela et al., 2017).

5.1. Perioperative Outcomes

In general, the reported rates for perioperative complications after RARP are very low. For example, bladder neck contracture, anastomotic leak and post-operative ileus are about 1%. Other organ injury and deep venous thrombosis are less than 1% (Ramsay et al., 2012). We employed the Clavien-Dindo classification, the most commonly used classification in urological procedures, to report our postoperative complications (Clavien et al., 1992).

In this study, patients who underwent operation in the first 6 months after the switch to STRP were excluded from the start since it was during the learning phase of the new technique. The switch to STRP did not affect the perioperative outcomes regarding the operative time, blood loss, intra or postoperative complications. In STRP, the creation of vesico-urethral anastomosis is a challenging step due to the narrow working space in comparison to TPRP in which the bladder is mobilised; however, no anastomotic complications were recorded in our patients.

Theoretically, operative time for RARP is the time starting from port fixation until the closure of port sites after the performance of surgery. Usually, port insertion and removal are conducted by assistant surgeons. In this study, port insertion and removal were the same in both cohorts. That is why we only compared the console time in both groups to investigate the impact of changing the operative technique on time. The estimation of blood loss during surgery can be done through different methods; by direct measurement from the surgical suction, or by weighing the gauzes and towels. It can also be estimated in the laboratory by comparing the pre and postoperative haemoglobin levels. Visual estimation (photometry) can also be used (Schorn, 2010). In Tuebingen's database, blood loss in the surgical suction and pre and postoperative haemoglobin levels were recorded. We compared blood loss between TPRP and STRP by by the difference between pre and postoperative haemoglobin levels as we consider this method more clinically relevant than suction measures.

5.2. Functional Outcomes

5.2.1. Continence

Functional outcomes in terms of urinary continence and potency is the main concern of patients regarding RP. After surgery, the prevalence of incontinence at 1 month is high, ranging from 4% to 87%. However, incontinence tends to diminish with time, and recovery is observed in most cases during 1 to 6 months following

surgery (Cespedes et al., 1999; Jonler et al., 1996). By 12 months after surgery, 90% of patients are continent, and this percentage can increase after one more year (Walsh et al., 1998; Catalona et al., 1999). About 6% of patients require surgical treatment for incontinence after RP (Kim et al., 2013). The severity of incontinence and the timeline of urinary function recovery depends on many preoperative and intraoperative factors. Preoperative factors include age, preoperative voiding function, reduced bladder compliance, detrusor hypertrophy, bladder outlet obstruction and neurological disorders. Body mass Index (BMI), especially if more than 30 Kg/m^2, is associated with a higher rate of incontinence (Anast et al., 2005). Anatomical variations between patients can affect the outcome as well; some patients have underdeveloped striated sphincter with less muscle fibres and more collagen (Burnett & Mostwin, 1998; Strasser et al., 1999). The length of membranous urethra might have a direct impact on the continence rate after the removal of the prostate (Cambio & Evan, 2006). Normally, urine continence is maintained by the bladder neck and the external sphincter near the prostatic apex. Removal of the prostate through surgery disrupts the way the bladder holds urine and can result in urine leakage. This may be due to improper dissection of the prostatic base from the bladder neck. Post RP incontinence is usually secondary to intrinsic sphincter deficiency, which can be injured during the dorsal venous complex ligation and division. Preservation of a supple bladder neck without too large diameter is crucial for postoperative incontinence (Horrie et al., 1999). Using large and deep sutures for vesicourethral anastomosis can damage the continence provided by the urethral smooth muscles. Striated sphincter injury during the dissection of the prostatic apex should be avoided by careful apical dissection. Furthermore, pubovesical/puboprostatic ligaments are considered to play a role in the continence mechanism by stabilising the prostate, bladder and urethra in their positions (Steiner et al., 1994; Presti et al., 1990; Deliveliotis et al., 2002; Burnett et al., 1998). Preservation of NVB was suggested to not only preserve potency, but also improve continence outcome (Walz et al., 2016).

The subtrigonal approach for RP was first described by Bocciardi in 2010 as the most anatomically preserving approach for this operation (Galfano et al., 2010); by this technique, the prostate can be completely excised through the Douglas pouch with the preservation of all peri-vesical tissues, the Retzius space and the dorsal venous complex. All these structures were suggested to be involved in the continence mechanism, as mentioned above. Based on the evidence of variability in NVB distribution (Eichelberg et al., 2007; Sievert et al., 2008; Ganzer et al., 2008; Lee et al., 2008), NS through the subtrigonal approach is expected to preserve the entire circumferentially located fibres around the prostate, which is supposed to improve the functional outcome.

The severity of the incontinence can be estimated by the number of pads used per day. In this study, incontinence was defined as using at least one pad per day. The assessment of post RP incontinence is a comprehensive process and should ideally be continuous at different time intervals, not only to assess the presence of incontinence, but also to accurately detect the change of symptoms with time. Even for research purposes, continence function should be preoperatively assessed to predict the outcome which depends on many factors, as previously mentioned. Despite not being routinely required, urodynamic study is a useful tool to detect the cause of post prostatectomy incontinence, and to assess the compliance of the bladder (Singla & Singla, 2014). Some conservative measures can help patients to faster recovery of incontinence after RP which can even be started before the operation; for example, weight reduction and pelvic floor exercises (Kegel exercises) (Kampen et al., 2000). Other measures include lifestyle modifications in the form of reduced fluid intake, avoidance of bladder irritants such as caffeine and alcohol as well as biofeedback (Goode et al., 2011). Furthermore, pharmacological agents such as anti-muscarinic agents can improve symptoms (Singla & Singla, 2014).

In this study, the immediate postoperative continence after catheter removal was nearly similar in both the subtrigonal group and the conventional group.

Recoverability of continence was faster in the subtrigonal group. After 12 months, the continence rate was also higher in this group. Bocciadri and Al-Shali reported higher immediate postoperative continence (90% and 63%, respectively) than our results, however, this can be explained by the difference in patient criteria. Most of our patients (77.0%) were intermediate or high-risk PCa versus the 45% in Bocciardi's report that theoretically may require more dissection and affect the urethral length (Hoyland et al., 2014). Our continence rate after one year was nearly similar to Bocciardi's results. Due to the absence of detailed preoperative assessment of our patients' continence status, all were supposed to be fully continent before surgery.

Despite being promising, the results of our study should be cautiously interpreted because some important data about other factors were irretrievable. It was not documented whether any of the patients began pelvic floor exercises before or after RP, and if anyone followed a certain lifestyle plan to improve their symptoms. Furthermore, the data were collected from patients only once at a certain time, and patients depended on their memory to answer the given questionnaire. Therefore, the accuracy of the data given by patients might be affected.

5.2.2. Erectile dysfunction

Erectile dysfunction is one of the common side effects for RP and it can affect more than 60% of patients treated with this operation (Chung & Brock, 2013). The definition of erectile dysfunction varies among studies. It was defined as the ability to develop spontaneous erection (Ficarra et al., 2009), or the ability to have satisfying intercourse (Willis et al., 2012). Preservation of erectile function after RP requires sparing of the neurovascular bundle. The feasibility of nerve sparing depends on numerous factors; firstly, the risk stratification of PCa. It is not advised to preserve the NVB in high-risk or palpable intraoperative tumour at the apex of the prostate due to the higher rate of positive margins in these cases (Steuber et

al., 2006). In addition, the anatomical variation in the distribution of NVB makes nerve sparing difficult if the nerve fibres are distributed all around the prostate or partially impeded inside the prostatic tissue (Ganzer et al., 2008; Lee et al., 2008). Regardless, the used surgical approach, cauterization, must be avoided to prevent thermal injury during NVB dissection; alternatively, it can be controlled by hemoclips (Salomon et al., 2004). Avoidance of traction and direct manipulation of NVB can minimise cavernous nerve injury. In addition, one of the main advantages of RARP is the magnification of the field and better visualisation of the prostatic apex and NVB.

In the literature, there are some debates that postoperative fibrotic changes which occur in the corpus cavernosum are one of the causative factors of erectile dysfunction (Joseph et al., 2006). Indeed, cavernous nerve injury in animal models is associated with penile fibrosis and structural changes in the penis (Podlasek et al., 2001). In animal models, cavernous nerve injury resulted in severe neuropraxia with subsequent apoptosis of penile smooth muscle fibres and endothelium. This can cause increased production of transforming growth factor- beta and other fibroproliferative cytokines. Eventually, it can lead to the loss of smooth muscles and fibrosis. Rehabilitation after RP is more involved in postoperative management for faster recovery of erectile function and the prevention of penile shrinkage (Jae K and Seung L, 2015). Variable options can be used, for instance, phosphodiesterase-5 inhibitors, vacuum bumps and intracavernosal or intraurethral prostaglandin injections (Sheng Q et al., 2016).

Although potency recoverability was higher in the subtrigonal group (43% versus 13% in the conventional group), the difference was not statistically significant since only patients who underwent bilateral NS with no history of ED (11.7%) were included in this comparison. Preoperative assessment of erectile function was only based on medical history. No IIEF score-based assessment was performed before surgery, which should be considered in future studies to assess potency outcomes after RP. This may add some limitation to our potency results. Furthermore, there are no available data of our patients practicing any kind of

penile rehabilitation using medications or vacuum devices. The data was collected at a certain point in time, not at different time intervals as for continence data. Moreover, our results regarding postoperative sexual function was lower than the reported results by Al-Shali et al. (51%) and Bocciardi et al. (75%).

5.3. Oncological Outcomes

5.3.1. Marginal status

The best local control of PCa can be achieved by the complete removal of the prostate and the surrounding adventitia without breaching the tumour to avoid any residual malignant cells. Because most prostate adenocarcinomas arise from the peripheral zone, there is some chance for positive surgical margins. In fact, marginal status can be affected by several factors. For instance, localised tumours (pT2 or less) have much lower positive margin rates compared to locally advanced stages (T3 or higher). In high-volume centres, the reported positive margin rates for pT2 ranged between 4% and 10%, and between 21% to 35% for pT3 (Patel et al., 2008; Stolzenburg et al., 2008). Surgical technique and experience can also affect the marginal status. As previously mentioned, apical dissection is a very challenging step to obtain a proper urethral length and to preserve the striated sphincter. This is why the prostatic apex is the most common site for positive margins (Touijer et al., 2005). Furthermore, several authors have proven that the technique used for histopathological examination of the prostate specimen affects marginal results. Some studies only used biopsies of remaining tissue after the removal of the surgical specimen to assess margin status, while others employed step-sectioned routine or whole-mount histology. Routine sectioning detected a higher rate of positive margins because the tissue slices are thinner than that of the whole-mount technique and up to 12% of positive margins can be missed when the whole-mount technique is used (Cohen MB et al., 1994).

In this study, all specimens were examined by the whole-mount technique for both groups, and surgical experience would unlikely affect the PSM results since

RARP has been well-established for many years in Tuebingen University hospital. The difference in PSM between the two groups is clearly due to the difference in surgical technique. Theoretically, the subtrigonal approach is expected to have only functional benefits since it is considered the least anatomically disturbing approach for RARP. Our oncological outcomes displayed obvious reduction in PSM rates, especially at the apex and in patients with extra-capsular tumours (pT3a). Our patients' overall PSM after the subtrigonal approach was 8% versus 25.5%, as reported by Bocciardi (Galfano et al., 2013). The marked reduction of PSM at the apex and pT3a in STRP in comparison to TPRP can be explained by the difference in the peri-prostatic dissection; in STRP we used the "*single plane continuous dissection*". After the dissection of the bilateral seminal vesicles, the dissection around the entire prostate is performed from the same plane guided by the prostatic capsule. Therefore, only one plane for dissection is first created on the seminal vesicles away from the prostate itself. The counter traction applied by the assistant surgeon on the seminal vesicles makes it easier to identify the prostatic capsule and the suspected macroscopic extracapsular extension of the tumour. On the other hand, the dissection in TPRP is the "*multiple planes interrupted dissection*". After the dissection of the bilateral seminal vesicles and the posterolateral aspects of the prostate, we created another plane anteriorly through the retro-pubic space. No specific landmarks can identify the proper plane away from the prostate as in the case of the seminal vesicles, which may increase the probability of exceeding the capsule during the identification of the proper plane. This can further explain the high PSM rate in pT3b (seminal vesicle invasion) in both groups where the plane is created, with the high probability of dissecting through the tumour during the identification of the dissection plane.

5.3.2. Biochemical recurrence

After RP, the PSA level should be undetectable provided that the entire prostatic tissue was removed. In general, about 25% to 41% of patients can

develop increased PSA within 10 years after RP, however, this doesn't mean that these patients will develop clinical progression or metastasis (Roehl et al., 2004). A slight rise of PSA can be due to residual benign or malignant prostatic tissue or may be due to non-prostatic origin of PSA (Diamandis & Yu, 1995). Nonetheless, a raised PSA should be considered as an indicator for residual or recurrent tumour unless it is very low and shows plateau levels on serial follow-ups. Surgical margin status, with consideration of pathological stage, is an important predictor for BCR. Patients with pT2 disease and positive margins have a 12% higher risk of BCR than those with same stage and negative margins. This risk can increase to 18% in the pT3b stage (Budaus et al., 2010). The median time to develop metastasis after BCR is about 8 years, but this also depends on the PSA doubling time and the postoperative Gleason score (Antonarakis et al., 2012). The impact of time between RP and BCR on metastasis and mortality is controversial in the available reports; the prostate cancer–specific mortality risk decreases by 24% for every year delayed from surgery to BCR, (Freedland et al., 2006). On the other hand, in a cohort of patients with BCR who did not receive either adjuvant therapies, the time from prostatectomy to biochemical recurrence was not significantly associated with systemic progression (Boorjian et al., 2011).

An accurate definition of BCR was a matter of debate for many years. In fact, more than 50 definitions were reported in the literature (Zincke et al., 1994; Moul et al., 1996; Cookson et al., 2007). Different values for PSA were used as a cut-off for the definition of BCR. Eventually, the American Urological Association (AUA) guidelines panel defined BCR as a PSA of 0.2 ng/mL or greater with a second confirmatory reading (Cookson et al., 2007). Currently, this the most commonly used definition in clinical practice, and it was applied in our study as well.

In this study, we only compared the 1-year BCR-free survival as the maximal follow-up for the subtrigonal group, which was 15 months. Our results in the subtrigonal group was 94% BCR-free survival in comparison to the 90% reported by Bocciardi. This is considered a short period; a longer follow-up must be considered in future studies.

In conclusion, the more anatomical preservation by using STRP was suggested to increase the postoperative continence recoverability. This study approved the oncological safety of STRP, even in locally advanced cases. Surprisingly, the subtrigonal approach displayed a reduction of PSM; especially at the apex and in tumours with extra-capsular extension. The results of this study should be interpreted with consideration of the highlighted limitations in the discussion, as well as the short duration of the follow-up. Prospective studies that include a larger number of patients and with longer follow-ups are mandatory to confirm or deny these results.

6. Abstract/Summary

6.1. Background

The subtrigonal approach for robotic assisted radical prostatectomy was first described in 2010 as the most anatomically preserving technique, in which the prostate can be completely removed through the Douglas pouch. This technique was introduced in the Urology Department of Tuebingen University Hospital in June 2013 after many years of performing the conventional transperitoneal robotic prostatectomy, however few data is available regarding its outcome.

6.2. Objectives

The aim of this study is to compare the functional and oncological outcomes of subtrigonal approach versus the conventional approach for robotic radical prostatctomy

6.3. Methods

Consecutive groups of patients who underwent TPRP (n=126) from 01/2012 to 05/2013, and those who switched and underwent STRP (n=62) from 01/2014 to 01/2015 were compared;. Functional outcomes were evaluated using ICIQ and IIEF of both groups by questionnaire and telephone protocols. Oncological outcomes were assessed regarding positive surgical margins and biochemical recurrence free survival (PSA ≥ 0.02 ng/ml) using the Kaplan Meier curve. Postoperative complications were classified using the Clavien-Dindo system. Statistical analysis was performed using the jmp v.12 software®. Mann-Whitney-U and Pearson x^2 tests were employed to compare the continuous and categorical variables, respectively. The Kaplan Meier curve was applied to present the survival data

6.4. Results

The median age and follow-up time in the TPRP and STRP groups were 64 and 62.5 years and 34 and nine months, respectively. Within 7 days of catheter removal, 37/93 patients (40%) in group A were continent compared to 23/53 (43%) in group B (p-value = 0.67). At 3, 6 and 12-month intervals, the continence recovery rates were 71%, 73% and 87% in group A versus 76%, 89% and 96% in group B. The p-values were 0.55, 0.02 and 0.054, respectively. 15 and 7 patients in group A and B, respectively, underwent bilateral nerve sparing surgery (NS). In group A, 2/15 (13%) could achieve enough erection for penetration versus 3/7 (43%) in group B; (p-value = 0.13). The overall positive surgical margin (PSM) rate was 16% in group A versus 8% in group B (p-value = 0.11). According to the pathological stage, PSM rates in pT2, pT3a and pT3b were 7.2%, 53% and 55.6% in group A compared to 2.2%, 11% and 60% in group B, respectively (p-values = 0.19, 0.03 and 0.87). PSM in pT3a was significantly lower in group B. When comparing the PSM rate at the prostatic apex, it was 9.8% in group A versus 1.6% in group B; with a significant difference (p-value = 0.02). The BCR 1y-free survival was 91% in group A versus 94% in group B (Log-rank p-value = 0.57).

6.5. Conclusion

The anatomical preservative sub-trigonal approach for RARP increases the post-operative continence recoverability. Our results approved the oncological safety of this technique even in locally advanced cases. Sub-trigonal approach displayed reduction of PSM especially at the apex and in tumors with extra-capsular extension. Prospective randomized studies including bigger cohorts of patients with longer follow up are mandatory to confirm these results.

7. Abstrakt / Zusammenfassung

7.1. Hintergrund

Der subtrigonale Ansatz zur robotergestützten radikalen Prostatektomie wurde erstmals in 2010 als die am besten die Anatomie erhaltende Technik beschrieben. Hierbei wird die Prostata vollständig durch den Douglas-Raum entfernt.. Diese Technik wurde im Juni 2013 in der Urologischen Klinik des Universitätsklinikums Tübingen eingeführt, nachdem viele Jahre lang die konventionelle transperitoneale robotische Prostatektomie durchgeführt worden war. Es liegen jedoch nur wenige Daten zum Ergebnis der neuen Technik vor.

7.2. Ziele

Das Ziel dieser Studie ist es, die funktionellen und onkologischen Ergebnisse des subtrigonalen Ansatzes mit dem konventionellen Ansatz für die robotische radikale Prostatektomie zu vergleichen.

7.3. Methoden

Konsekutive Gruppen von Patienten, die einer TPRP (n = 126), von 01/2012 bis 05/2013, unterzogen wurden und diejenigen, die einer STRP (n = 62) von 01/2014 bis 01/2015 unterzogen wurden, wurden verglichen. Funktionelle Ergebnisse wurden mittels ICIQ und IIEF beider Gruppen, erhoben durch Fragebogen und Telefonprotokollen, ausgewertet. Die onkologischen Ergebnisse wurden hinsichtlich der positiven chirurgischen Ränder und des biochemischen rezidivfreien Überlebens (PSA ≥ 0,02 ng/ml) mittels Kaplan-Meier-Kurve bewertet. Postoperative Komplikationen wurden nach dem Clavien-Dindo-System klassifiziert. Die statistische Analyse wurde mit der Software jmp v.12 durchgeführt. Mann-Whitney-U- und Pearson-x2-Tests wurden verwendet, um die kontinuierlichen bzw. kategorischen Variablen zu vergleichen. Die Kaplan-Meier- Kurve wurde angewendet, um die Überlebensdaten darzustellen.

7.4. Ergebnisse

Das mittlere Alter und die Nachbeobachtungszeit in den Gruppen TPRP und STRP betrugen 64 bzw. 62,5 Jahre und 34 bzw. 9 Monate. Innerhalb von 7 Tagen nach Katheterentfernung waren 37/93 Patienten (40%) in Gruppe A kontinent verglichen mit 23/53 (43%) in Gruppe B (p-Wert = 0,67). In 3, 6 und 12-Monats- Intervallen waren die Kontinenzraten 71%, 73% und 87% in Gruppe A und 76% (p-Wert = 0,55), 89% (p-Wert = 0,02) und 96% (p-Wert = 0,054) in Gruppe B. Bei 15 bzw. 7 Patienten der Gruppen A und B wurde eine bilaterale nervenschonende Operation (NS) durchgeführt. In der Gruppe A konnten 2/15 (13%) eine ausreichende Erektion für die Penetration erzielen, gegenüber 3/7 (43%) in der Gruppe B; (p-Wert = 0,13). Die Rate der positiven Absetzungsränder (PSM - positiv surgical margin) betrug in der Gruppe A 16% hingegen 8% in der Gruppe B (p-Wert = 0,11). Nach dem pathologischen Stadium betrugen die PSM-Raten 7,2%, beipT2, 53% bei pT3a und 55,6% bei pT3b Gruppe A und im Vergleich 2,2% (p-Wert = 0,19), 11% (p-Wert = 0,03) und 60% (p-Wert = 0,87) in Gruppe B. PSM in pT3a war in Gruppe B signifikant niedriger. Beim Vergleich der PSM-Rate am Apex der Prostata betrug sie 9,8% in Gruppe A gegenüber 1,6% in Gruppe B; mit signifikantem Unterschied (p-Wert = 0.02). Das Ein-Jahres-BCR-freie Überleben betrug 91% in Gruppe A gegenüber 94% in Gruppe B (logarithmischer Rang p-Wert = 0,57).

7.5. Schlussfolgerung

Der subtrigonale anatomische Konservierungsansatz für RARP erhöht die postoperative Kontinenzwiederherstellbarkeit. Unsere Ergebnisse bestätigten die onkologische Sicherheit dieser Technik auch in lokal fortgeschrittenen Fällen. Der subtrigonale Ansatz zeigte eine Reduktion des PSM, insbesondere am Apex und bei Tumoren mit extrakapsulärer Extension. Prospektive randomisierte Studien einschließlich größerer Kohorten von Patienten mit längerer Nachbeobachtung sind obligatorisch, um diese Ergebnisse zu bestätigen.

8. References

- Abbou CC, Hoznek A, Salomon L, et al. Remote laparoscopic radical prostatectomy carried out with a robot. Report of a case. Prog Urol 2000;10:520–3.
- Al-Ahmadie HA, Tickoo SK, Olgac S, et al. Anterior-predominant prostatic tumors: zone of origin and pathologic outcomes at radical prostatectomy. Am J Surg Pathol 2008;32:229–35.
- Albertsen PC, Moore DF, Shih W, et al. Impact of comorbidity on survival among men with localized prostate cancer. J Clin Oncol 2011;29(10):1335-41.
- Al-Shali Y, Topazio L, Autieri D, et al. Trans douglas robotic radical prostatectomy: our experience . Italian Association of Urology Meeting 2015. http://nazionale2015.auro.it/abstract/trans-douglas-robotic-radical-prostatectomy-our-experience/
- Anast JW, Sadetsky N, Pasta DJ, et al . The impact of obesity on health related quality of life before and after radical prostatectomy (data from CaPSURE). J Urol. 2005; 173(4):1132-8.
- Antonarakis ES, Feng Z, Trock BJ, et al. The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. BJU Int 2012;109:32–9.
- Beyer B, Schlomm T, Tennstedt P, et al. A feasible and time-efficient adaptation of NeuroSAFE for da Vinci robot-assisted radical prostatectomy. Eur Urol, 2014. 66: 138.
- Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med 2014;370(10):932-42.

- Binder J, Kramer W. Robotically assisted laparoscopic radical prostatectomy. BJU Int 2001;87:408–10.
- Boorjian SA, Thompson RH, Tollefson MK, et al. Long-term risk of clinical progression after biochemical recurrence following radical prostatectomy: the impact of time from surgery to recurrence. Eur Urol 2011;59:893–9.
- Brawley OW. Trends in prostate cancer in the United States J Natl Cancer Inst Monogr. 2012 (45):152-6.
- Budaus L, Isbarn H, Eichelberg C, et al. Biochemical recurrence after radical prostatectomy: multiplicative interaction between surgical margin status and pathological stage. J Urol 2010;184:1341–6.
- Burnett AL, Mostwin JL. In situ anatomical study of the male urethral sphincteric complex: relevance to continence preservation following major pelvic surgery. J Urol 1998;160:1301–6.
- Cambio AJ, Evans CP. Minimising postoperative incontinence following radical prostatectomy: considerations and evidence. Eur Urol. 2006; 50(5):903-13.
- Campbell, Meredith F., Wein, Alan J.Kavoussi, Louis R. (Eds.) (2012) Campbell-Walsh urology /editor-in-chief, Alan J. Wein ; editors, Louis R. Kavoussi ... [et al.]Philadelphia : W.B. Saunders,
- Carter BS, Beaty TH, Steinberg GD, et al. Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci U S A 1992;89:3367–71.
- Catalona WJ, Carvalhal GF, Mager DE, et al. Potency, continence and complication rates in 1,870 consecutive radical retropubic prostatectomies. J Urol 1999;162:433–8.
- Centemero A, Rigatti L, Giraudo D, et al. Preoperative pelvic floor muscle exercise for early continence after radical prostatectomy: a randomised controlled study. Eur Urol. 2010;57(6):1039-43.
- Center MM, Jemal A, Lortet-Tieulent J, et al. International variation in prostate cancer incidence and mortality rates. Eur Urol 2012;61: 1079–92.

- Cespedes RD, Leng WW, McGuire EJ. Collagen injection therapy for postprostatectomy incontinence. Urology. 1999;54:597-602.
- Chade, D.C., Eastham J, Graefen M, et al. Cancer control and functional outcomes of salvage radical prostatectomy for radiationrecurrent prostate cancer: a systematic review of the literature. Eur Urol, 2012. 61: 961.
- Cheville JC, Dundore PA, Nascimento AG, et al. Leiomyosarcoma of the prostate. Report of 23 cases. Cancer. 1995 15;76(8):1422-7.
- Christopher J.D.W, Refik S, Richard C, et al. Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol 2016;70:21-30.
- Chung E, Brock G. Sexual rehabilitation and cancer survivorship: a state of art review of current literature and management strategies in male sexual dysfunction among prostate cancer survivors. J Sex Med. 2013; 10 Suppl 1():102-11.
- Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. Surgery. 1992;111(5):518-26.
- Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience Ann Surg. 2009;250(2):187-96.
- Cohen MB, Soloway MS, Murphy WM. Sampling of radical prostatectomy specimens. How much is adequate? Am J Clin Pathol 1994;101:250-2.
- Cookson MS, Aus G, Burnett AL, et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. J Urol 2007;177:540–5.
- Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860–7.

- Dalela D, Jeong W, Prasad MA, et al. A Pragmatic Randomized Controlled Trial Examining the Impact of the Retzius-sparing Approach on Early Urinary Continence Recovery After Robot-assisted Radical Prostatectomy. Eur Urol. 2017;72(5):677-685.
- D'Amico AV, Desjardin A, Chen MH, et al. Analyzing outcome-based staging for clinically localized adenocarcinoma of the prostate. Cancer. 1998 15;83(10):2172-80.
- Deliveliotis C, Protogerou V, Alargof E, Varkarakis J. Radical prostatectomy: bladder neck preservation and puboprostatic ligament sparing—effects on continence and positive margins. Urology 2002;60:855– 8.
- De Marzo AM, Platz EA, Sutcliffe S, et al. Inflammation in prostate carcinogenesis. Nat Rev Cancer 2007;7:256–69.
- Diamandis EP, Yu H. New biological functions of prostate-specific antigen? J Clin Endocrinol Metab 1995;80:1515–7.
- Droz JP, Balducci L, Bolla M, et al. Background for the proposal of SIOG guidelines for the management of prostate cancer in senior adults. Crit Rev Oncol Hematol 2010;73(1):68-91.
- Eeles R, Goh C, Castro E, et al. The genetic epidemiology of prostate cancer and its clinical implications. Nat Rev Urol 2014;11:18–31.
- Eichelberg C, Erbersdobler A, Michl U, et al Nerve distribution along the prostatic capsule. Eur Urol. 2007;51(1):105-10.
- Engel J, Bastian PJ, Baur H, et al. Survival benefit of radical prostatectomy in lymph node-positive patients with prostate cancer. Eur Urol. 2010;57(5):754-61.
- Epstein JI. Pathologic assessment of the surgical specimen. Urol Clin North Am 2001;28:567–94.

- Epstein JI, Allsbrook WC Jr, Amin MB, et al. The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol 2005;29:1228–42.
- Epstein JI, Srigley J, Grignon D, et al. Recommendations for the reporting of prostate carcinoma. Hum Pathol 2007;38:1305–9.
- Epstein MM, Edgren G, Rider JR, et al. Temporal trends in cause of death among Swedish and US men with prostate cancer. J Natl Cancer Inst 2012;104:1335–42.
- Fahmy O, Khairul-Asri MG, Schubert T, Renninger M, Stenzl A, Gakis G. Clinico-pathological features and prognostic value of incidental prostatic adenocarcinoma in radical cysto-prostatectomy specimens: a systematic review and meta-analysis of 13140 patients. J Urol. 2017;197(2):385-390.
- Fahmy O, Zahran M, Khairul-Asri M, Stenzl A, Schwentner C. Trans- Douglas approach for intra-fascial nerve sparing Robotic Assisted Radical Prostatectomy. Robotics, Lap and Endosurg 2015; 1: 1-4.
- Fahmy O, Khairul-Asri MG, Hadi SHSM, Gakis G, Stenzl A. The Role of Radical Prostatectomy and Radiotherapy in Treatment of Locally Advanced Prostate Cancer: A Systematic Review and Meta-Analysis Urol Int. 2017;99(3):249-256.
- Ficarra V, Novara G, Fracalanza S, et al. A prospective, non-randomized trial comparing robot-assisted laparoscopic and retropubic radical prostatectomy in one European institution. BJU Int 2009b;104:534–9.
- Flocks RH. Arterial distribution within prostate gland: its role in transurethral prostatic resection. J Urol 1937;37:524–48.
- Freedland SJ, Humphreys EB, Mangold LA, et al. Time to prostate specific antigen recurrence after radical prostatectomy and risk of prostate cancer specific mortality. J Urol 2006;176:1404–8.

- Frota R, Turna B, Barros R, Gill IS. Comparison of radical prostatectomy techniques: open, laparoscopic and robotic assisted. Int Braz J Urol. 2008;34:259–269.
- Ganzer R, Blana A, Gaumann A, et al. Topographical anatomy of periprostatic and capsular nerves: quantification and computerised planimetry. Eur Urol. 2008;54(2):353-60.
- Galfano A, Ascione A, Grimaldi S, et al. A New Anatomic Approach for Robot-Assisted Laparoscopic Prostatectomy: A Feasibility Study for Completely Intrafascial Surgery Eur Urol 2010; (58): 457–461.
- Galfano A, Di Trapani D, Sozzi F, et al. Beyond the learning curve of the Retzius-sparing approach for robot-assisted laparoscopic radical prostatectomy: oncologic and functional results of the first 200 patients with ≥ 1 year of follow-up. Eur Urol. 2013;64(6):974-80.
- Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol 1974;111:58–64.
- Gong Z, Neuhouser ML, Goodman PJ, et al. Obesity, diabetes, and risk of prostate cancer: results from the Prostate Cancer Prevention Trial. Cancer Epidemiol Biomarkers Prev 2006;15:1977–83.
- Goode PS, Burgio KL, Johnson TM 2nd, et al. Behavioral therapy with or without biofeedback and pelvic floor electrical stimulation for persistent postprostatectomy incontinence: a randomized controlled trial. JAMA. 2011 12; 305(2):151-9.
- Haiman CA, Chen GK, Blot WJ, et al. Genome-wide association study of prostate cancer in men of African ancestry identifies a susceptibility locus at 17q21. Nat Genet 2011;43:570–3.
- Hamdy, F.C., Donovan J.L, Lane J.A, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med, 2016. 375: 1415.

- Hemminki K. Familial risk and familial survival in prostate cancer. World J Urol 2012;30(2):143-8.
- Hess KR, Varadhachary GR, Taylor SH, et al. Metastatic patterns in adenocarcinoma. Cancer 2006;106:1624–33.
- Hisasue S, Hashimoto K, Kobayashi K, et al. Baseline erectile function alters the cavernous nerve quantity and distribution around the prostate. J Urol. 2010 184(5):2062-7.
- Horie S, Tobisu KI, Fujimoto H, et al. Urinary incontinence after non–nervesparing radical prostatectomy with neoadjuvant androgen deprivation. Urology 1999;53:561–7.
- Hoyland K, Vasdev N, Abrof A, Boustead G. Post-Radical Prostatectomy Incontinence: Etiology and Prevention. Rev Urol. 2014; 16(4):181–188.
- Iversen, P, McLeod DG, See WA, Morris T, Armstrong J, Wirth MP. Antiandrogen monotherapy in patients with localized or locally advanced prostate cancer: final results from the bicalutamide Early Prostate Cancer programme at a median follow-up of 9.7 years. BJU Int, 2010. 105:1074.
- Jae Heon Kim, Seung Wook Lee. Current status of penile rehabilitation after radical prostatectomy Korean J Urol. 2015; 56(2): 99–108.
- Jani AB, Johnstone PA, Liauw SL, et al. Age and grade trends in prostate cancer (1974-2003): a Surveillance, Epidemiology, and End Results Registry analysis. Am J Clin Oncol 2008;31:375–8.
- Jansson KF, Akre O, Garmo H, et al. Concordance of tumor differentiation among brothers with prostate cancer. Eur Urol 2012;62(4):656-61.
- Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ. Cancer statistics, 2006. CA: a Cancer J Clin. 2006;56(2):106–130.
- Jonler M, Madsen FA, Rhodes PR, et al. A prospective study of quantification of urinary incontinence and quality of life in patients undergoing radical retropubic prostatectomy. Urology. 1996;48:433-440.

- Joseph E, Jesse N, Hari K, Randall B .Penile Rehabilitation After Radical Prostatectomy: Important Therapy or Wishful Thinking? Rev Urol. 2006 Fall; 8(4): 209–215.
- Kim PH, Pinheiro LC, Atoria CL, et al. Trends in the use of incontinence procedures after radical prostatectomy: a population based analysis. J Urol 2013;189:602–8.
- Klein EA, Silverman R. Inflammation, infection, and prostate cancer. Curr Opin Urol 2008;18:315–9.
- Lee SB, Hong SK, Choe G, Lee SE. Periprostatic distribution of nerves in specimens from non-nerve-sparing radical retropubic prostatectomy. Urology. 2008;72(4):878-81.
- Leitzmann MF, Rohrmann S. Risk factors for the onset of prostatic cancer: age, location, and behavioral correlates. Clin Epidemiol 2012;4:1-11.
- Lin DW, FitzGerald LM, Fu R, et al. Genetic variants in the LEPR, CRY1, RNASEL, IL4, and ARVCF genes are prognostic markers of prostate cancerspecific mortality. Cancer Epidemiol Biomarkers Prev 2011; 20:1928–36.
- Liu PH, Wang JD, Keating NL. Expected years of life lost for six potentially preventable cancers in the United States. Prev Med 2013;56:309–13.
- Madigan MP, Troisi R, Potischman N, et al. Serum hormone levels in relation to reproductive and lifestyle factors in postmenopausal women (United States). Cancer Causes Control 1998;9:199–207.
- Masko EM, Allott EH, Freedland SJ. The relationship between nutrition and prostate cancer: is more always better? Eur Urol 2013;63:810–20.
- Mattei A, Fuechsel FG, Bhatta Dhar N, et al. The template of the primary lymphatic landing sites of the prostate should be revisited: results of a multimodality mapping study. Eur Urol. 2008;53(1):118-25.
- Mavis N. Schorn CN. Measurement of Blood Loss: Review of the Literature January 2010Journal of midwifery & women's health 55(1):20 –27.

- McGregor SE, Courneya KS, Kopciuk KA, et al. Case-control study of lifetime alcohol intake and prostate cancer risk. Cancer Causes Control 2013;24: 451–61.
- McNeal JE, Villers AA, Redwine EA, et al. Histologic differentiation, cancer volume, and pelvic lymph node metastasis in adenocarcinoma of the prostate. Cancer 1990;66:1225–33.
- Millin, T. "Retropubic prostatectomy: A new extravesical technique report; report of 20 cases". Lancet. 1945; 2 (6380): 693–696.
- Moreira DM, Aronson WJ, Terris MK, et al. Cigarette smoking is associated with an increased risk of biochemical disease recurrence, metastasis, castration-resistant prostate cancer, and mortality after radical prostatectomy: results from the SEARCH database. Cancer 2014;120:197–204.
- Mottet N, Bellmunt J, Briers E, et al . European guidelines for prostate cancer. 2015. https://uroweb.org/wp-content/uploads/EAU-Guidelines- Prostate-Cancer-2015
- Muir CS, Nectoux J, Staszewski J. The epidemiology of prostatic cancer. Geographical distribution and time-trends. Acta Oncol 1991;30:133–40.
- Myers RP. Radical prostatectomy: pertinent surgical anatomy. Atlas Urol Clin North Am 1994;2:1–18.
- Nakayama M, Bennett CJ, Hicks JL, et al. Hypermethylation of the human glutathione S-transferase-π gene (GSTP1) CpG island is present in a subset of proliferative inflammatory atrophy lesions but not in normal or hyperplastic epithelium of the prostate: a detailed study using lasercapture microdissection. Am J Pathol 2003;163:923–33.
- Naomi Lee. Robotic surgery: where are we now? The Lancet, 2014; 384 (9952): 1417.
- Nelson WG, De Marzo AM, Isaacs WB. Prostate cancer. N Engl J Med 2003 ;349(4):366-81.

- Nelson CP, Montie JE, McGuire EJ, et al. Intraoperative nerve stimulation with measurement of urethral sphincter pressure changes during radical retropubic prostatectomy: a feasibility study. J Urol 2003;169:2225–8.
- Nirmish S and Ajay K. Singla2. Post-prostatectomy incontinence: Etiology, evaluation, and management. Turk J Urol. 2014; 40(1): 1–8.
- Oelrich TM. The urethral sphincter muscle in the male. Am J Anat 1980; 158:229–96.
- Osunkoya AO, Carter HB, Epstein JI. A clinicopathologic study of preoperative and postoperative findings with minute Gleason 3+3=6 cancer at radical prostatectomy. Urology. 2008 ;72(3):638-40.
- Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74-108.
- Partin AW, Kattan MW, Subong EN, et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. JAMA 1997;277:1445–51.
- Patel AK, Chapple RC. Anatomy of the lower urinary tract. Renal and urology. 2008; 26 (4):127-132.
- Patel VR, Palmer KJ, Coughlin G, et al. Robot-assisted laparoscopic radical prostatectomy: perioperative outcomes of 1500 cases. J Endourol 2008;22:2299–305.
- Podlasek CA, Gonzalez CM, Zelner DJ, Jiang HB, McKenna KE, McVary KT. Analysis of NOS isoform changes in a post radical prostatectomy model of erectile dysfunction. Int J Impot Res. 2001; 13 Suppl 5():S1-15.
- Potosky AL, Kessler L, Gridley G, et al. Rise in prostatic cancer incidence associated with increased use of transurethral resection. J Natl Cancer Inst 1990;82:1624–8.
- Presti Jr JC, Schmidt RA, Narayan PA, Carroll PR, Tanagho EA Pathophysiology of urinary incontinence after radical prostatectomy. J Urol 1990;143:975–8.

- Ramsay C, Pickard R, Robertson C, et al. Systematic review and economic modeling of the relative clinical benefit and cost effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localized prostate cancer. Health Technol Assess, 2012;16(41):1-313.
- Rassweiler J, Schulze M, Teber D, et al. Laparoscopic radical prostatectomy with the Heilbronn technique: oncological results in the first 500 patients. J Urol 2005;173:761–4.
- Rebbeck TR, Devesa SS, Chang BL, et al. Global patterns of prostate cancer incidence aggressiveness, and mortality in men of African descent. Prostate Cancer 2013;2013:560857.
- Ries LAG, Melbert D, Krapcho M, et al, editors. SEER Cancer Statistics Review, 1975-2005. Bethesda (MD): National Cancer Institute; 2008. https://seer.cancer.gov/archive/csr/1975_2005/
- Roehl KA, Han M, Ramos CG, et al. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. J Urol 2004;172:910–4.
- Rosen R, Riley A, Wagner G, et al. The International Index of Erectile Function (IIEF): A multidimensional scale for assessment of erectile dysfunction. Urology 1997;49 822-830.
- Salomon L, Sebe P, De la Taille A, et al. Open versus laparoscopic radical prostatectomy. I, II. BJU Int 2004;94:238–50.
- Schuessler, WW; Schulam, PG; Clayman, RV; Kavoussi, LR. Laparoscopic radical prostatectomy: Initial short-term experience. Urology 1997. 50 (6): 854–857.
- Sehdev AE, Pan CC, Epstein JI. Comparative analysis of sampling methods for grossing radical prostatectomy specimens performed for nonpalpable (stage T1c) prostatic adenocarcinoma. Hum Pathol 2001;32:494–9.

- Sexton WJ, Lance RE, Reyes AO, Pisters PW, Tu SM, Pisters LL. Adult prostate sarcoma: the M. D. Anderson Cancer Center Experience. J Urol. 2001;166(2):521-5.
- Shah R, Mucci NR, Amin A, et al. Postatrophic hyperplasia of the prostate gland: neoplastic precursor or innocent bystander? Am J Pathol 2001;158: 1767–73.
- Sheng-Qiang Qian, Liang Gao, Qiang Wei, Jiuhong Yuan. Vacuum therapy in penile rehabilitation after radical prostatectomy: review of hemodynamic and antihypoxic evidence. Asian J Androl. 2016; 18(3): 446–451.
- Shimizu H, Ross RK, Bernstein L, et al. Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles county. Br J Cancer 1991;63:963–6.
- Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin 2014; 64:9–29.
- Sievert KD, Hennenlotter J, Laible I et al. The periprostatic autonomic nerves--bundle or layer? Eur Urol. 2008 54(5):1109-16.
- Singla N, Singla AK. Post-prostatectomy incontinence: Etiology, evaluation, and management. Turk J Urol. 2014;40(1):1-8.
- Steinberg DM, Sauvageot J, Piantadosi S, et al. Correlation of prostate needle biopsy and radical prostatectomy Gleason grade in academic and community settings. Am J Surg Pathol 1997;21:566–76.
- Steiner MS. The puboprostatic ligament and the male urethral suspensory mechanism: an anatomic study. Urology 1994;44: 530–4.
- Stephenson RA, Smart CR, Mineau GP, et al. The fall in incidence of prostate carcinoma. On the down side of a prostate specific antigen induced peak in incidence—data from the Utah cancer registry. Cancer 1996;77: 1342–8.

- Steuber T, Graefen M, Haese A, et al. Validation of a nomogram for prediction of side specific extracapsular extension at radical prostatectomy. J Urol. 2006;175(3 Pt 1):939-44.
- Stolzenburg JU, Rabenalt R, Do M, et al. Endoscopic extraperitoneal radical prostatectomy: the University of Leipzig experience of 2000 cases. J Endourol 2008;22:2319–25.
- Strasser H, Tiefenthaler M, Steinlechner M, et al. Urinary incontinence in the elderly and age-dependent apoptosis of rhabdosphincter cells. Lancet 1999;354:918–9.
- Sutcliffe S. Sexually transmitted infections and risk of prostate cancer: review of historical and emerging hypotheses. Future Oncol 2010;6:1289–311.
- Takata R, Akamatsu S, Kubo M, et al. Genome-wide association study identifies five new susceptibility loci for prostate cancer in the Japanese population. Nat Genet 2010;42:751–4.
- Touijer K, Kuroiwa K, Saranchuk JW, et al. Quality improvement in laparoscopic radical prostatectomy for pT2 prostate cancer: impact of video documentation review on positive surgical margin. J Urol 2005;173:765–8.
- Van Kampen M, De Weerdt W, Van Poppel H, De Ridder D, Feys H, Baert L. Effect of pelvic-floor re-education on duration and degree of incontinence after radical prostatectomy: a randomised controlled trial. Lancet. 2000; 355(9198):98-102.
- Villers A, McNeal JE, Redwine EA, et al. The role of perineural space invasion in the local spread of prostatic adenocarcinoma. J Urol 1989;142: 763–8.
- Walsh PC, Lepor H, Eggleston JC. Radical prostatectomy with preservation of sexual function: anatomical and pathological considerations. Prostate. 1983;4(5):473-85.

- Walsh PC, Quinlan DM, Morton RA, et al. Radical retropubic prostatectomy: improved anastomosis and urinary continence. Urol Clin North Am 1990;17:679.
- Walsh PC. Anatomic radical prostatectomy: evolution of the surgical technique. J Urol 1998;160:2418–24
- Walsh PC. Nerve grafts are rarely necessary and are unlikely to improve sexual function in men undergoing anatomic radical prostatectomy. Urology 2001;57:1140–4.
- Walz J, Epstein J, Ganzer R, et al. A Critical Analysis of the Current Knowledge of Surgical Anatomy of the Prostate Related to Optimisation of Cancer Control and Preservation of Continence and Erection in Candidates for Radical Prostatectomy: An Update. Eur Urol 2016; 70 (2): 301-311.
- Willis DL, Gonzalgo ML, Brotzman M, et al. Comparison of outcomes between pure laparoscopic vs robot-assisted laparoscopic radical prostatectomy: a study of comparative effectiveness based upon validated quality of life outcomes. BJU Int 2012;109:898–905.
- Wilt TJ, Brawer MK, Jones KM, et al. Prostate Cancer Intervention versus Observation Trial (PIVOT) Study Group. N Engl J Med. 2012 Jul 19;367(3):203-13.
- Woolf CM. An investigation of the familial aspects of carcinoma of the prostate. Cancer 1960;13:739–44.
- Yaxley, J.W, Coughlin GD, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. Lancet, 2016. 388: 1057.
- Yoon GS, Wang W, Osunkoya AO, et al. Residual tumor potentially left behind after local ablation therapy in prostate adenocarcinoma. J Urol 2008;179:2203–6.

- Zincke H, Oesterling JE, Blute ML, et al. Long-term (15 years) results after radical prostatectomy for clinically localized (stage T2c or lower) prostate cancer. J Urol 1994;152:1850–7.

8. Declaration on own contribution

This study was conducted in Urology Department, Tuebingen University Hospital. Professor Dr. med. Arnulf Stenzl was involved in the design and conception of this study and the thesis was written under his supervision as a father doctor.

Professor Dr. Gakis supervised the writing of the thesis

Mr. Jörg Hennenlotter participated in designation of the study, data analysis, preparation of the questionnaires and contact of the patients.

Mr. Julian Heinkele conducted the questionnaires with the patients through telephonic interviews.

Dr. Niklas Harland participated in interpretation of the results and revision of the thesis.

Omar Ahmed, the author of the thesis participated in the designation of the study and constitution of the hypotheses, collected the data from data base records of Tuebingen University Hospital, Prepared the questionnaires, conducted the statistical analysis and wrote the whole thesis including tables and charts.

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Place, Date, Signature

Acknowledgement:

At the end of my doctorate thesis, I would like to give many thanks to my father doctor, Professor Dr.med. Arnulf Stenzl, for giving me the chance to do this novel study on this interesting topic.

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Also I would like to thank Mr. Julian Heinkele for performing the questionnaires through telephonic interviews with the patients.

Finally I would like to thank Dr. Niklas Harland for his help during thesis revisions

Sincere thanks to my parents and my wife who have supported me mentally and morally during my studies and doctoral thesis

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January 2014 – June 2016 : Clinical Fellow in urological surgery– *Tuebingen University Hospital* (*Germany*).
December 2011 – Dec 2013: Surgeon of urology – *Zagazig University* (*Zagazig, Egypt*).
March 2011 – Dec 2011: Surgeon of Urology – *Al Ahrar Governmental Hospital & El Obour International Hospital* - (*Zagazig, Egypt*).

Sep 2010 – Feb 2011: Visitor Doctor - *Urology & Nephrology Centre (UNC) –* (*Mansoura, Egypt*).
April 2007 – July 2010: Resident Doctor in Urology Surgery Department – *Zagazig University Hospital* - (*Zagazig, Egypt*).
March 2006 – Feb 2007: House officer – *Zagazig University Hospital* - (*Zagazig, Egypt*).

Training courses

***** Hands-on training course Laparoscopic nephrectomy, **Kuala Lumpur, Malaysia** (Mar 2018).
***** Short-term clinical training on minimal invasive urological surgery, **Kunming, China** (October 2017).
***** Hands-on training course on MRI Fusion Biopsy (EAU 31stmeeting) **Munich, Germany** (Mar 2016).
***** Hands-on training course on Thulium laser for vaporesection of prostate (EAU 31stmeeting) **Munich, Germany** (Mar 2016).
***** Nerve sparing radical cystectomy course of the European School of Urology (EAU 31stmeeting) **Munich, Germany** (Mar 2016).
***** Urethral stricture advanced course of the European School of Urology (EAU 31stmeeting) **Munich, Germany** (Mar 2016).
* Basic Life Support course of European Resuscitation Councel (ERC) **Tuebingen, Germany** (Feb 2014).
* The International training course on Minimally Invasive Operating Techniques "SILS in urology '' **Cairo University** (May 2013).
* The International training course on Minimally Invasive Operating Techniques in "Single-Portal Laparoscopic Surgery'' **Cairo University**(November 2012).
* The 14th International Training Course on Uro-laparoscopy **Mansoura(** November 2012).
* The 1st Urology Club Laparoscopy Workshop, **Zagazig University** (September 2012) ***(Participant & one of the co-organizers).***
* The 12nd International Applied Laparoscopic Urology Course, **Cairo University** (October, 2011)
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- Research Team Management.
- Communication Skills in different Modalities of Learning.
- Scientific Conferences Organization.
- Technology Application in Teaching.
- International Scientific publication.
- Quality Parameters in Teaching Process. **Zagazig ,** (August, 2011)

* The International Urology and Nephrology Centre (UNC) Course: "New Techniques in Reconstructive Urology" **Mansoura** (January, 2010).

* The European School of Urology Course:" Urolithiasis and Endourology for Beginners", **Cairo** (December, 2009).
* The International Urology and Nephrology Center (UNC) Course: "The Recent Advances in Urologic Oncology", **Mansoura** (November, 2009) .
* The International Urology and Nephrology Center (UNC) Course: "Renal and Ureteric Stones and Strictures: Role of Open Surgery", **Mansoura** (May, 2009) .
* The European Resuscitation Council Course: "The Advanced Trauma Life Support (ATLS) ", **Cairo** (January, 2007) .

★ Publications Published

* Y pouch neobladder - a simplified method of intracorporeal neobladder after robotic cystectomy *J Endourol. 2015*
* Feasibility of penis-preserving surgery for urethral melanoma: proposal for a therapeutic algorithm. *Clinical Genitourinary Cancer 2015*
* Role of Laparoscopy in uretero-pelvic junction obstruction with concomitant pathology *Central European Journal of Urology 2015*
* Current status and feasibility of intracorporeal ileal neobladder after robotic assisted radical cystectomy. *Journal of Surgical Onchology 2015*.
* Trans-Douglas Approach for intra-fascial nerve sparing robotic assisted radical prostatectomy. *Robotics,Laparoscopy and endourology 2015*
* Laparoscopic radical nephrectomy with inferior vena cava thrombectomy: highlight of key surgical steps *(International British Journal of Urology 2015*)
* Ten years of complete remission of pulmonary metastasis after post-cystectomy palliative cisplatin-gemcitabine chemotherapy with gefitinib for muscle invasive bladder cancer : a case presentation .*Urologia Internationalis 2016.*
* Algorithm for optimal urethral coverage in hypospadias and fistula repair: a systematic review *(European Urology 2016)*
* Systemic anti-CTLA-4 and intravesical Bacille-Calmette-Guerin therapy in non-muscle invasive bladder cancer: is there a rationale of synergism?. *(Medical Hypotheses 2016)*
* The current status of checkpoint inhibitors in metastatic bladder cancer. *(Clinical and Experimental Metastasis 2016)*
* Effect of androgen and estrogen receptor signaling pathways on bladder cancer progression. *(Bladder Cancer 2016)*
*Systematic Review and Meta-Analysis on the impact of Hexaminolevulinate- Versus White-Light Guided Transurethral Bladder Tumor Resection on Progression in Non- Muscle Invasive Bladder Cancer *(Bladder Cancer 2016)*
* Clinico-pathological features and prognostic value of incidental prostatic adenocarcinoma in radical cysto-prostatectomy specimens: a systematic review and meta-analysis of 13140 patients. *(Journal of Urology 2016)*
* Female sexual dysfunction after radical cystectomy and neobladder substitution. *(Climacteric 2016)*
* Finasteride loaded biodegradable nanoparticles: Near infra-red quantification of plasma and prostate levels

* Update on targeted therapy of bladder cancer (*Clinics in Oncology 2016*)

* The role of radical prostatectomy and radiotherapy in treatment of locally advanced prostate cancer: A systematic review and meta-analysis *(Urologia internationalis 2017)*
* Total proximal ureteral substitution using buccal mucosa.*(International Journal of Urology 2017)*
* Survival after Metastasectomy for Metastatic Urothelial Carcinoma: A Systematic Review and Meta-Analysis. *(Bladder Cancer 2017)*

* Optical improvements in the diagnosis of bladder cancer: Implications for clinical practice *(Therapeutic Advances in Urology. 2017)*
* Urethral recurrence after radical cystectomy for urothelial carcinoma: A systematic review and meta-analysis *(Urol Oncol. 2018)*
* A systematic review and meta-analysis on the oncological long-term outcomes after trimodality therapy and radical cystectomy with or without neoadjuvant chemotherapy for muscle-invasive bladder cancer. *(Urol Oncol. 2018)*

Conference papers:

1. Infection of the entire genitourinary system - a severe form of tuberculosis
   25th Malaysian Urological Conference, (MUC)2016. BJUI Supplement

2. Open extraction of a ureteral stent after endoscopic fixation due to neglect for six years
   25th Malaysian Urological Conference (MUC)2016. BJUI Supplement

3. Segmental ureteral substitution using tubularized buccal mucosal graft
   25th Malaysian Urological Conference (MUC)2016. BJUI Supplement

4. Bilateral torsion of intra-abdominal seminoma presented with acute abdomen and hemorrhagic shock.
   26th Malaysian Urological Conference (MUC)2017. BJUI Supplement

5. Long-term outcome after trimodality therapy and radical cystectomy with or without neoadjuvant chemotherapy for muscle-invasive bladder cancer.
   113th American Urological Association conference (AUA2018), San Francisco. J Urol