Aus der Klinik für Urologie und Kinderurologie
(Direktor: Prof. Dr. K.-P. Jünemann)
im Universitätsklinikum Schleswig-Holstein, Campus Kiel
an der Christian –Albrechts-Universität zu Kiel

Extended salvage pelvic lymph nodes dissection in patients with recurrent prostate cancer. Data base of the Department of urology and pediatric urology, University Hospital Schleswig-Holstein, Campus Kiel.

Inauguraldissertation
zur
Erlangung der Doktorwürde
der Medizinischen Fakultät
der Christian-Albrechts-Universität zu Kiel

vorgelegt von
ALEXEY V. AKSENOV

aus Novosibirsk, Russische Föderation

2015 Kiel

1. Berichterstatter: Prof. Dr. K.-P. Jünemann *(Referent)*

2. Berichterstatter: Prof. Dr. J. Dunst *(Korreferent)*

Tag der mündlichen Prüfung: 11.05.2015 *(Datum)*

Zum Druck genehmigt, Kiel, den 11.05.2015 *(Datum der mündlichen Prüfung)*

gez.: PD Dr. C.M. Naumann *(Vorsitzender der Prüfungskommission)*

CONTENTS

GLOSSARY

ADT	- androgen deprivation therapy
BCR	- biochemical recurrence
BPH	- benign prostate hyperplasia
BCRF	- biochemical recurrence freedom
BR	- biochemical response
BRFS	- biochemical recurrence-free survival
CAB	- combined androgen blockade
CRFS	- clinical recurrence-free survival
CSM	- cancer-specific mortality
CSS	- cancer-specific survival
EBRT	- external beam radiotherapy
EPCA-2	- early prostate cancer antigen-2
ePLND	- extended pelvic lymph node dissection
GS	- Gleason score
iPSA	- initial prostate specific antigen
HDR-BT	- high-dose rate brachytherapy
LHRH	- luteinizing hormone-releasing hormone
LN	- lymph node(s)
LND	- lymph node dissection
lPLND	- limited pelvic lymph node dissection
OS	- overall survival
PCa	- prostate cancer
PET/CT	- positron emission tomography /computerized tomography
PIN	- prostate intraepithelial neoplasia
PNLD	- pelvic lymph node dissection
PSA	- prostate specific antigen
PSA-DT	- PSA doubling time
PSM	- positive surgical margin
RS	- relative survival
PW TRUS	- power doppler transrectal ultrasonography
RP	- radical prostatectomy
RT	- radiotherapy
SePLND	- salvage extended pelvic lymph node dissection
SgPLND	- sentinel-guided pelvic lymph node dissection
sRP	- salvage radical prostatectomy
sRT	- salvage radiotherapy

INTRODUCTION

Prostate cancer (PCa) treatment has been one of the crucial issues in urology for decades. According to the U.S. «Cancer statistics 2009», the overall cancer death rates in men decreased by 19.2% between 1990 and 2005, with a decrease in prostate cancer deaths by 24% (Jemal et al. 2009). According to «Cancer statistics 2010», PCa is the most common malignant tumor in the male population (estimated new cases 217730, or 28%), and presents the second most frequent cause of death from cancer (11%) among Americans *(Figure 1a)* (Jemal et al. 2010, 2011).

The incidence of PCa increases much faster with age than the incidence of other malignant tumors, and unlike them it has no peak (Jemal et al. 2005). Thus the risk of accidental PCa among 50-year-old men is 27% (found during autopsy after decease from other causes), among 80-year-olds it is 63%. The risk of PCa detection with a clinical manifestation is 3.6%. Only 20% of the diagnosed prostate cancer cases dies from it. The risk of death from PCa among the whole men population lies at 2.0% (Stemmermann et al. 1992). Clinical manifestation of PCa is often asymptomatic and does not always present a threat to the life of the patient. Occasionally this disease may proceed aggressively, especially in young patients, and - in the absence of timely diagnosis and treatment – it may lead to death (Presti 2000).

According to the 2011 cancer register of Schleswig-Holstein, the number of new PCa cases in 2008 was 2450 (25.6% of the overall male cancer rate), mortality rate – 443 (11.5% of the overall cancer-related death rate) *(Figure 1b)*. In Germany, the number of new PCa cases in 2008 was 65582, making it the most frequently diagnosed type of cancer in men (26.7%) (Pritzkuleit et al 2011).

PCa usually proceeds from the peripheral zone of the gland (65%-90%). Invasive cancer is often preceded by PIN (prostatic intraepithelial neoplasia). In contrast to PCa, the basal layer of the epithelium is safe during PIN (Godoy and Taneja, 2008).

The choices of treatment are relatively well standardized. But treatment of PCa recurrence and advanced disease has encouraged a discussion concerning the optimal method of treatment. It is well-known, that in some patients the disease takes a particularly stubborn drift that remains resistant to treatment or is prone to recur shortly after treatment (Roberts and Han 2009, Moreira et al. 2010).

The character of PCa clinical development is primarily determined by the characteristics of the tumor itself: the disease stage according to the TNM-classification, the Gleason score (GS) of cell differentiation, the level of the prostate specific antigen (PSA), and the PSA doubling-time (PSA-DT). The prognosis is determined by the presence of metastases in the regional lymph nodes (LN) (stage N), and by the presence of distant metastases (stage M). The latter can be determined,

respectively to the main types of PCa metastasis. The initial metastatic spread of PCa is to the distant LN, the secondary spread concerns the bones and sometimes other internal organs (Heidenreich et al. 2012).

Apart from the LN, the most frequent location of PCa metastases is in the bones. The axial skeleton is involved in 85% of those patients who die from PCa (Whitmore et al. 1984). Previously, bone scintigraphy was always considered necessary during PCa diagnostics, but later it became clear that this is not required at PSA levels under 20 ng/ml and in asymptomatic patients with well- or moderately-well (GS up to 7a=3+4) differentiated tumours (Lee et al. 2000).

PSA-levels below 10ng/ml were observed in 66% of PCa primary patients according to one of studies. If the initial PSA level was between 4ng/ml and 10ng/ml, PCa was found by biopsy in 26%-35% patients. In these cases it is important to measure the free/total PSA ratio and PSA density (Horninger et al. 2000, Ito et al. 2003).

In other words, no carcinoma is detected in 64%-75% of patients with «gray scale» PSA levels. Therefore, the number of tissue samples in per biopsy was recently increased from 6 to 10, even in low-risk patients. The Vienna nomogram is a clinical algorithm, which can be used as a guideline for diagnosis and treatment of such patients (Heidenreich 2007). This nomogram determines the optimal number of prostate biopsies based on the patient’s age and the prostate volume (Remzi et al. 2005).

The degree of PCa tissue differentiation is commonly judged by the system proposed by Dr. D.F. Gleason (Gleason et al. 1988). It is based on the microscopic structure of the glands at a small enlargement. The degree of differentiation is determined by two principal histological patterns – firstly the dominance, i.e. identification of the pattern that occupies the largest area, and the secondly, by the size of the pattern. Each of these aspects is estimated by a 5-point scale. By summing up both values, the total amount of points is obtained. Thus, the GS can range from 2 to 10. According to many authors, the GS is fundamental for the prognosis of the course of the disease and life expectancy, along with the PSA level and TNM stage (Roach 2003, Dall'Oglio et al. 2005, Hsy et al. 2009).

The Partin Coefficient Tables are another important tool in guiding decisions on effective treatment options for PCa. It is a way of predicting the cancer's pathologic stage, which can only be determined after the prostate gland has been removed by surgery and examined by a pathologist. There are several Partin tables (nomograms) depending on the PSA level. In one of the first nomograms based on data from 4133 men treated for PCa, it was shown that the probability of having one of the following

pathologic stages of PCa depends on PSA level, GS and clinical stage (Partin et al. 1997):

- Organ-confined disease: PCa completely confined to the prostate gland
- Established capsular penetration: PCa extended into and possibly through the prostatic capsule
- Seminal vesicle involvement
- LN involvement.

PSA has been used as a marker since the 1990s, but despite its remarkable performance, it becomes clear that it is not an ideal cancer-specific marker (Jurincic et al. 1990). High PSA levels can also be observed in patients with benign prostate hyperplasia (BPH) or chronic inflammation processes in the prostate. Special PCa subgroup consists of patients with so called PSA-negative tumors. In most of cases these tumors are aggressive including bone metastases. Due to this, some authors point out the necessity of new PCa markers and use the term “post-PSA era”. It would be better, if simple samples (e.g. blood, urine) could more accurately predict disease progression. For example, it was reported in 2007 that a new blood test for early prostate cancer antigen-2 (EPCA-2) may be able to predict PCa and its aggressiveness. Research on this still continues (Hansel et al. 2007, Margreiter et al. 2008, Bickers and Aukim-Hastie 2009).

Another subject of studies has been the influence of genetic mutations on PCa course. The largest study that has investigated the clinical characteristics and outcome of patients with PCa with and without germ line BRCA mutations included 1940 noncarriers and 79 BRCA carriers (61 BRCA-2 and 18 BRCA-1). Pathogenic mutations in BRCA-1 and BRCA-2 genes confers a more aggressive PCa phenotype with a higher probability of locally advanced and metastatic disease and hypothesizes that the presence of a germline BRCA-2 mutation is a prognostic marker associated with poorer survival (Castro et al. 2013, Narod et al. 2008).

Currently, there are many PCa treatment methods that have been developed and put into practice; the main methods and “gold standards” today are radiotherapy (RT) (brachytherapy or external beam radiotherapy (ERBT)), radical prostatectomy (RP) (open surgical: retropubic or perineal, and minimally invasive: conventional laparoscopic and robot-assisted laparoscopic (Heer et al. 2011)), as well as antiandrogen deprivation therapy (ADT) (Heidenreich et al. 2012). Many publications are devoted to the efficiency of only one these methods individually, i.e. as separate treatment methods.

Radiation therapy.

A large number of studies is devoted to RT. RT of urinary tract tumors and of genital organ tumors has a more than 100-year history. In 1895, W. K. Röntgen discovered the rays named after him. In 1899, the first patient was cured of skin cancer by radiation, and in the next 10 years, radiation therapy began to be applied in PCa (Röntgen 1895, Jantsch 1984).

According to the generally accepted hypothesis, ionizing radiation affects tumor and normal cells, causing irreparable damage to the double-stranded DNA molecule. In 2/3 of the cases, this damage occurs due to oxygen-free radicals resulting from rupture of the covalent bond in the water molecule, and 1/3 of the cases the effect is directly due to the ionizing radiation on DNA. Radiation damage occurs only with the entry of cells into mitosis. Moreover, there are data indicating that ionizing radiation stimulates apoptosis (Perez 1998).

There are several types of RT, which are differentiated by the way that ionizing energy is administered to the prostate.

1. Dose-escalated EBRT, the most modern variety of which is 3D-conformal RT.
2. External beam radiotherapy combined with a radioactive seed implantation (EBSeeds).
3. High-dose rate brachytherapy (HDR-BT).
4. Low-dose rate brachytherapy (LDR-BT).

There are many studies on the efficiency of RT as a monomethod and on comparing the efficiency of its various types (Pieters 2009). Thus, HDR-BT before EBRT with a reduced dose from the EBRT produces a comparable survival outcome and genitourinary toxicity, but significantly less gastrointestinal toxicity for PCa patients (Fang et al. 2008). The 5-year biochemical recurrence-freedom (BCRF) rates for EBRT + HDR versus EBRT-alone were 67% versus 44% (Kestin et al. 2000).

The efficiency of RT in locally advanced PCa could not be confirmed - the average 5-year survival after RT varies between 45% and 86% according to different sources (Fiorica et al. 2010, Kälkner et al. 2007, Roach et al. 1999). However, the most significant therapeutic factor affecting biochemical recurrence-free survival (BRFS) rates after RT is the radiation dose (Khuntia et al. 2004).

Our data based on 278 patients with a 3 year follow-up after RT showed that BCR developed in 98 (35.2%) patients during the first 1.5 years after RT. The BRFS in patients with cT2 and cT3 stage differs significantly (75% and 44% respectively); mean time to achieve BCR after RT was 2 and 1 year respectively (Juenemann, 2004).

How should patients with positive surgical margins (PSM) to be treated? In these cases, the 3-year BRFS has been reported to be 73%-90% which is comparable to BRFS levels in patients with negative margins (Rabbani et al. 2009). According to the other studies, PSM increases the risk of biochemical recurrence (BCR) after RP by 2- to 4-folds (Stephenson et al 2009). But the other side of the question is – when should RT be performed in the case of PSM?

In one of the studies, the 7-year BCRF probability was 60% in patients with PSM. A PSM was significantly associated with BCR (HR 2.3, $p<0.001$) after adjusting for age, PSA level, pathological GS, pathological stage and year of surgery. Authors have pointed out that the empirical prognostic usefulness of sub-classifications of PSM (solitary vs. multiple, focal vs. extensive and apical location vs. other) is limited (Stephenson et al. 2009).

In a cohort of 1943 patients who underwent RP, it was shown that PSM is significantly predictive for PSA failure and thus the need for salvage therapy as well as cancer-specific survival (CSS). The 5-year BRFS was 84.4% in men with negative margins compared to 57.5% with PSM (Ploussard et al. 2011). The length of PSM is significantly associated with disease progression. GS and the extent of PSM can be used to stratify the risk for recurrence in patients with a positive margin (Ochiai et al. 2008). The 5-year risk of BCR was 20% resp. 55% for less than 3 mm resp. 3 mm or greater (Chuang et al. 2007).

The prostate weight was found to be significantly and inversely related to the PSM rate in this cohort of RP patients. Patients with smaller prostate volumes (<50g) should be counseled preoperatively that they are at higher risk for a PSM when undergoing RP (Goetzl et al. 2009).

In the case of PSM after RP, RT can be used as a second (adjuvant) treatment option. 50%-60% of the patients with tumor stage pT_3R_1 after RP, who do not receive adjuvant therapy, develop BCR. Three randomized trials have shown that an absolute improvement of 20% in the 5-year BRFS could be achieved by administering adjuvant RT with 60 Gy in patients with tumor stage pT_3R_1, even if the PSA-level was close to zero after RP. Also, there are numerous, albeit retrospective studies, which provide evidence that salvage radiotherapy (sRT) after a PSA increase is an effective treatment, but with higher total doses of 66-70 Gy and a higher rate of late effects (Bottke and Wiegel 2008).

All the above-mentioned results show the necessity to clarify the indications for RT and adjuvant RT (Higano 2009). In case of a pR1 stage, it is necessary to perform radiation at least over a period of 6 weeks (Wiegel et al. 2009). The length of the PSM

should be taken into consideration when defining the indications for sRT (Chuang et al. 2007).

sRT as a treatment option for recurrent PCa is also not devoid of complications. In a cohort of 308 patients, late toxicity occurring more than 90 days after EBRT completion was identified in 13%. 12 (3.9%) of the patients had grade 2 urethral strictures and were treated with urethral dilation, 3 (1.0%) patients suffered from grade 3 cystitis, and one patient from grade 4 rectal complications (Peterson 2009). Another study reports that the average perioperative complication levels of salvage RT (both HDR-BT, EBRT and their combination) was 9.1% (Heidenreich et al. 2010).

The risk of RT complications depends on the total and single focal dose. Meta-analysis of randomized dose escalation trials demonstrates that late toxicity rates increase with the RT dose (Ohri et al. 2012). In the case of urogenital tract tumors, the total focal dose should be no less than 65 Gy. In postoperative RT, doses of 45-50 Gy are sufficient (Spate and Roach 2000).

One of the latest studies on a cohort of 1903 patients shows that the incidences of acute genitourinary and gastrointestinal toxicities were 35%, 49%, and 55% for brachytherapy alone, resp. EBRT, resp. EBRT+HDR ($p < 0.001$). Late genitourinary toxicities were present in 22%, 21%, and 28% for brachytherapy alone, EBRT, and EBRT+HDR ($p=0.01$), respectively. Patients receiving EBRT+HDR had a higher incidence of urethral stricture and urinary retention, while dysuria was more common in patients receiving BT. Late gastrointestinal toxicities were 2%, 20%, and 9% for BT, EBRT, and EBRT+HDR respectively ($p<0.001$). Differences were the most pronounced regarding rectal bleeding, with 3-year rates of 0.9%, 20%, and 6% ($p<0.001$) for BT, EBRT, and EBRT+HDR respectively (Mohammed et al. 2012).

Most patients with PCa cT3 undergo neoadjuvant hormonal therapy followed by RT. The importance of radiating both the prostate and the seminal vesicles by using the new HDR-BT boost technique for cT3b PCa was pointed out in one of the studies. Compared to radiation of the prostate alone, this type of HDR-BT increases the 3-year BRFS from 57% to 79% and decreases the impotence rate from 35% to 24%, at comparative toxicity (Rades et al. 2007).

Radical prostatectomy.

The risk of PCa progression after surgical treatment depends on the degree of differentiation, the morphological stage and the extent of germination of the prostate capsule. LN invasion was also shown to be one of the predicting factors. The number of removed LN plays an important role in the length of the BCRF period, specific and overall survival (OS) (Allaf et al. 2004, Bader et al. 2003, Osmonov et al. 2013).

Today, the choice of treatment tactics takes into consideration the degree of differentiation and stage of the tumor, the patient's age, the prognosis of the long-term relapse-free period, the risk of complications, as well as the preferences of the patient and the physician's experience. Based upon these points, 3 groups of patients are distinguished based on the risk of BCR: low-risk, intermediate-risk and high-risk. The criteria by which these groups are differentiated (D'Amico et al 1993) are as follows:

Low risk	**Intermediate risk**	**High risk**
PSA <10 ng/ml *and* GS <7 *and* cT1–cT2a	PSA 10–20 ng/ml *or* GS=7 *or* cT2b	PSA >20 ng/ml *or* GS >7 *or* cT2c–cT3

We have analysed several large studies (with patient cohorts of approximately 1000 or more) to find out the comparative efficiency of primary PCa operative treatment vs. primary RT. To this end, we considered the 5-year BRFS level. Results are showed in *Table 1* (Partin et al. 1993, Catalona et al. 1994, Zincke et al. 1994, Paulson et al. 1994, Kuban et al. 1995, Zietmann et al. 1995, Khuntia et al. 2004, Sylvester et al. 2006, Bastide et al. 2006, Hernandez et al. 2007, Yoshioka et al. 2009, Burdick et al. 2009, Loeb et al. 2010). The variation in 5-year BRFS after RT is much higher than in surgery. The primary differences lie in the toxicity profiles of the treatments. Generally, the BRFS, the clinical recurrence-free survival (CRFS), and the PCa CSM are nearly identical in the patient groups after surgery and after RT (Ciezki and Klein 2009).

A further problem is hormone resistant PCa, based on a change in the androgen receptors. Luteinizing hormone-releasing hormone (LHRH) inhibitors, castration and anti-androgens are frequently combined into a total androgen blockade or a combined androgen blockade (CAB), the most aggressive form of hormonal treatment used for advanced PCa. Although it may take many years, hormone therapy will eventually fail. The time of failure is variable - some men (approximately one in five) have recurrent growth within a year from starting hormone treatment, whereas others have no sign of recurrent disease after 10 years of treatment (Walsh 1997). The average time to PSA evidence of regrowth (i. e. hormone resistance) is 2.5 years (Buchan and Goldenberg 2010). One way to prolong BRFS is to give hormones in an on/off-mode over several months. This is called intermittent androgen deprivation therapy and some authors conclude it as an acceptable treatment at different stages of PCa. The duration of the

cycle is decreased progressively during the therapy. Age, GS and PSA are factors predicting mortality (Prapotnich et al. 2009).

In advanced cases monotherapy of PCa is often not effective and the disease recurs: overall 40% of the patients have BCR within 10 years of follow-up after RP; however, the cancer-specific mortality (CSM) rate after 10 years is as low as 6% (Isbarn et al. 2010).

It is important to define, what should be considered as a BCR, therefore requiring initiation of salvage therapy. Urologists are usually guided by the level of PSA and PSA-DT as implied by the term “biochemical recurrence”. In these cases, dynamic control of the PSA level after the operation is absolutely required. Clearly standardized critical levels of PSA have not yet been set down, but there is a tendency to reduce the currently applied level.

In the studies by Heidenreich et al. (2009) and Parapel et al. (2008), the authors defined disease progression by two consecutive PSA values of >0.2 ng/ml. The use of any adjuvant treatment (primarily ADT) was also considered to be a treatment failure. Another study defines BCR as a PSA level above 0.5 ng/ml and/or a PSA-DT of less than 10 months (Stephenson et al. 2007).

Yet other authors suggest that BCR is best defined as two successive PSA levels > or = 0.4 ng/ml, as this correlates most accurately with clinical progression. PSA-DT and GS are the variables that best predict the development of distant metastasis and CSM. Prognostic models based on these and other variables are useful for assessing the need for salvage therapy and the anticipated outcome following local salvage therapy (Simmons et al. 2007).

According to EAU Guidelines 2014, there is international consensus that recurrent cancer following RP may be defined by two consecutive PSA values of > 0.2 ng/ml (Moul 2000).

Regarding the terms of follow-up, PSA measurements are recommended at the following intervals (according to EAU Guidelines 2009 and to last EAU Guidelines 2014): 3, 6 and 12 months postoperatively, and every 6 months thereafter for the next 3 years, and then annually (Heidenreich et al. 2009).

Treatment of the disease is the most complicated in patients with recurrent PCa. What method of treatment should be offered to the patient in each individual case? This question cannot be always answered with confidence. Unfortunately, the actual choice is often influenced by the available equipment, the physician’s experience and the «commitment» of the clinic to a treatment policy (Kupelian et al. 1997, Kimura et al. 2010).

Salvage therapy.

Salvage treatment of PCa presents a further chapter in PCa management. That question is currently highly topical, often causing controversial discussions on international congresses. These difficulties are due to the fact that not many studies are devoted to salvage therapy for recurrent PCa (Heidenreich et al. 2009, 2010, Leonardo et al. 2009, Parapel et al. 2009, Kimura et al. 2010, Chade et al. 2011, Rigatti et al, 2011, Suardi et al. 2011).

There are only a few studies devoted to salvage radical prostatectomy (sRP) and salvage extended pelvic lymph node dissection (SePLND). The volume of such studies is much smaller than that on sRT because salvage surgery is not a standard procedure. Moreover, the number of patients included in these studies is very small in general. The indications for this type of treatment, as well as the pre-operative prognostic risk factors for further progression of the disease are not clear (Hautmann 2006, Paparel et al. 2009).

One of the largest prospective analyses of the SePLND impact on the prognosis of patients with BCR and nodal pathologic 11 C-choline PET/CT scan after RP includes only 72 patients. 56.9% of these patients had a BCR. The 5-yr BCR-free survival rate was 19%. Preoperative PSA <4 ng/ml, time to BCR <24 months, and negative lymph nodes at previous RP represented independent predictors of BCRF. 5-yr CSS was 75% (Rigatti et al, 2011).

The latest international, multi-institutional cohort analysis was performed on 404 men with radiation-recurrent PCa who underwent sRP between 1985 and 2009. There was a median follow-up of 4.4 yrs following sRP. Freedom from clinical metastasis was observed in >75% of patients 10 yrs after surgery. 5 yrs after sRP the rates were as follows: free from BCR: 48% (42-53), free from metastasis: 83% (78-87), free from CSM: 92% (88-95). 10 yrs after sRP the rates were: free from BCR: 37% (31-43), free from BCR: 37% (31-43), free from metastasis: 77% (71-82), free from CSM: 83% (76-88) (Chade et al, 2010).

sRP is considered as a surgically challenging, but effective secondary local treatment of radiorecurrent PCa with a curative intent (Abdollah et al 2012, Osmonov et al. 2013). The identified predictive parameters will help to select patients most suitable for sRP with a long-term cure and good functional outcome (Heidenreich et al. 2010). SePLND for selected patients with BCR and clinically recurrent nodal disease on ADT can achieve an immediate complete PSA response in roughly one third of the patients (Osmonov et al. 2013).

The most appropriate candidates for sRP are patients with organ-confined disease, BCR after primary RT and strongly wishing a therapy. In experienced hands, morbidity

after sRP is low with a continence rate of 83%-96%. Long-term oncological control can be achieved in more than 80% of the patients (Heidenreich et al. 2008).

The complication rates of salvage surgical methods (SePLND and especially sRP) have decreased as technical applications have improved considerably within the last few years (different fixed holding systems and tissue-coagulating systems). Main complications are rectal injury (3.6-6.0%), stricture of bladder / urethral anastomosis (10.9-18.0%), urinary incontinence (20-50%), and, very rarely, severe complications such as iatrogenic damage to the ureter or large blood vessels (Hautmann 2006, Heidenreich et al. 2009).

The EAU guidelines recommend extended pelvic lymph node dissection (ePLND) or sentinel-guided PLND (SgPLND) for LN staging in PCa. However, many authors point out, that SgPLND offers the advantage of selective removal of sentinel LN. The additional expenditure and increased morbidity of ePLND has led to a limitation of the PLND area and so to a reduced detection of metastases in many clinics (Winter et al. 2011).

The Munich Cancer Registry study based on a cohort of 35629 men with prostate cancer has shown that RP should be performed in patients with positive LN, as LN-positive patients with complete RP had improved survival rates compared to patients with abandoned RP. Thus, the overall survival (OS) of patients with RP at the 5 yr- and the 10 yr-interval was 84% and 64% respectively; but only 60% and 28% respectively, in patients with aborted RP. The relative survival of patients with RP at the 5 yr and 10 yr interval was 95% and 86% respectively; and 70% and 40% respectively, with abandoned surgery (Engel et al. 2010).

In our previous study it was shown that LN metastases were detected in 15 of 106 patients (14.15%) during RP. Positive sentinel LNs were detected in 11 of these 15 patients (73.3%). The average number of removed LN was 20.5 (range +/-5). It was shown that routine use of ePLND leads to increased detection of histologically positive LN, while the number of complications is not increased (Osmonov et al. 2011).

There are controversial opinions that the data available to date do not justify the use of SePLND outside clinical trials due to the small number of patients included, the lack of control groups as well as the short-term follow-up (Suardi et al. 2011). We believe however, that the standard technique of ePLND needs to be revised and supplemented by additional dissection areas such as the triangle of Marcille, the sacral LN, and the preprostatic area (Osmonov et al. 2011).

The technique of RP is well-known, and all steps of this operation have already been standardized (Rassweiler et al. 2006, Stolzenburg et al. 2008, Walsh 1988). The technique of ePLND by contrast, is extremely dependent on the institution and the surgeon's experience (Briganti et al. 2008). In our earlier studies, we have recommended standardizing ePLND and suggested a practical guideline for surgeons (Osmonov et al. 2011, 2013).

Diagnostics of nodal metastases has been significantly improved; 11C-choline-positron emission tomography /computerized tomography (PET/CT) play the main roles in BCR management. The diagnostic accuracy of choline PET in detecting the sites of PCa relapse has been investigated by several authors, and the overall reported sensitivity ranges between 38% and 98%. It has been demonstrated that the choline PET positive detection rate improves with increasing PSA values. The routine use of 11C-choline PET/CT cannot be recommended for PSA values <1 ng/ml (Picchio et al. 2011).

Our own recent data show that the reliability of 11C-choline PET/CT imaging for detection of LN metastases is limited by a high false-positive rate. Specificity and sensitivity of 11C-choline PET/CT in detecting of LN metastases appeared to be 22.7% and 85.1% respectively (Osmonov et al. 2013).

Besides general surgical complications there are also specific potential complications associated with ePLND. These include lymphoceles, which make up 10.6% of all complications after ePLND (in comparison, limited PLND (lPLND) has a 9% lymphocele rate). Another possible complication is lymphedema of the lower extremities, but fortunately this occurs only rarely (Heidenreich et al. 2002).

The definition of ePLND is disputable. How many LN should be removed during primary RP? Our recent data based on 174 patients with intermediate and high-risk prostate cancer show that at least 15 LN in the intermediate risk group and at least 18 LN in high risk group should be removed to detect the a maximum number of metastases. If fewer LN are removed, the probability of non-detected metastases increases. In intermediate risk patients (n=115) the average number of LN removed was 20.5; LN metastases were found in 15 patients (13%). In high-risk patients (n=59) the average number of LN removed was 23.9, LN metastases were found in 19 patients (32%) (Osmonov et al. 2013).

SePLND significance in case of BCR will be shown in the course of this study.

Issues addressed by the study:

1. How can the surgical method be optimized in patients with advanced PCa?
2. What is to be done in case of BCR? Is sRP a valid treatment option after RT?
3. What is the role of ePLND, especially in patients with recurrent disease?
4. In how far does the number of removed LNs correlate with BRFS and cancer-specific survival (CSS)?
5. How can the site/role of pre- and postoperative RT in patients with recurrent PCa be best identified?
6. When is the best time to initiate ADT after primary treatment?
7. What is the influence of ADT on BCRF?
8. What is the frequency and relevance of salvage-therapy complications?

PATIENTS AND METHODS

Study population and data

In our study we represent the single-center retrospective analysis of surgical salvage procedures (SePLND and sRP) in patients with PCa recurrence. A cohort of 41 patients from our department has been included in our study.

Inclusion criteria:

- Histological proof of PCa.
- BCR and/or suspiciously low PSA-DT.
- Salvage therapy of PCa (sRP, SePLND, sRT or combinations thereof).
- Absence of bone metastases at the time of salvage therapy.

There is still no definition of PCa relapse or progression. We defined PCa progression as a PSA cut-off of ≥0.5 ng/ml and/or PSA-DT <6 months. So, we considered progress of the disease as a BCR. We described the situation as a biochemical response (BR), if after salvage operation PSA level was below the preoperative level and continued to fall, even it was above BCRF criteria. Taking into consideration the variable sequence of different treatment methods, we formed several groups, which will be discussed below.

To evaluate the efficiency of treatment we took into account the following indicators:

a) the patients' age
b) the degree of tumor differentiation by GS
c) the risk stratification according to D'Amico classification
d) the initial PSA (iPSA) at the time of primary treatment
e) the stage of the disease according to TNM-classification (including the R stage)
f) the PSA-DT, both before and after salvage therapy in relation with presence/absence of ADT
g) duration of the BCRF-period
h) CSS
i) localization and number of metastases in removed LN
j) the type and dose of RT
k) the presence/absence of distant metastases
l) complications connected with sRP and SePLND

The Results section has been structured on the basis of the above-listed parameters.

Among 41 patients included in the study, 40 primarily or secondary underwent RP. This operation was the primary method of treatment in 30 (73.2%) patients, whereas in 10 (24.4%) patients it was secondary treatment option (sRP). In one patient it turned out intraoperative that preparation of the prostate was impossible due to changed tissue properties (frozen pelvis) after primary RT, therefore only SePLND was performed.

In Group 1 (sRP) surgery of the prostate included ePLND in all cases. In group primary RP just 19 (63.3%) RPs were supported by ePLND. 66.7% of the primary RPs had been performed in external departments.

All primary and salvage prostatectomies performed at our department were done according to the classic technique of RP (Walsh 1988). Access was retropubic, the operation time was 180 minutes on average and the average blood loss was 300 ml. In those patients with intact erectile function, the primary RP is usually performed with bilateral preserve of the neurovascular bundle, in contrast to sRP. Anastomosis is formed by six sutures. The obligatory frozen section practice is performed in all patients immediately after the prostate has been removed. If necessary, PSM resection is performed. In most cases (63.3%), primary RP was supplemented by regional PLND on both sides.

Diagnostic methods

We imaged the prostatic gland and the tumor-suspect areas in the peripheral zone of the prostate by means of preoperative power doppler transrectal ultrasonography (PW TRUS; Nemio XG Premium, model SSA-580A, Toshiba, Japan) prior to primary RP. We compared these findings with the histological biopsy report. Subsequently, we injected the radioactive marker Tc-99 into the peripheral zone into both prostate lobes to enable intraoperative usage of C-Trak gamma probe (AEA Technologies, Morgan Hills, CA, USA) for sentinel LN detection. The method consists of intraoperative scanning of the lymphatic pathways to identify the location of the sentinel LN groups in the depth of the wound, as well as to remove paravasal and pelvic LN tissue. An increase of the index up to more than 20 cps (counts per second) indicates excessive accumulation of Tc-99 in the scanned area. Thus, probability of metastasis is higher in this area; this also helps to improve intraoperative orientation at the stage of ePLND and increases the probability of histological tumor cell detection in the removed LNs. Scintigramms are performed prior to surgery, which provide the opportunity to visualize increased accumulation of the radioisotope drug. On scintigramms or sentinel scan a sharply intensified signal from the prostate itself is always seen.

Figures 2 and 3 present the 11C-choline PET/CT and scintigramm resp., which show sentinel LNs on the left side, in addition to the increased accumulation of radioisotope drug in the prostate.

When BCR was diagnosed, we performed an 11C-choline PET/CT (Siemens, Germany). If the regional LNs were suspect for metastases in 11C-choline PET/CT after primary treatment failure, SePLND was indicated. This diagnostic method has a relatively high sensivity, as choline is accumulated mainly by tumor tissue and is almost absent in normal LN tissue.

All the patients included in the study underwent bone scintigraphy to exclude distant metastases in the skeleton. Patients with evidence of bone metastases were excluded from the study. In spite of this, 4 (9.8%) patients were found to have bone metastases during the follow-up. All of them received Zometa and were under complete androgen blockade.

Surgical technique

Regardless of whether PLND was included in the RP, or whether it was an independent method of salvage therapy, there was a standard approach for LN removal, schematically presented in *Figure 4*. We distinguished the following groups of regional LNs for the prostate (Osmonov et al. 2011):

- LN dissection (LND) in the fossa obturatoria;
- Sacral LND;
- LND in the region of external iliac artery;
- LND in the region of internal iliac artery;
- LND in the region of common iliac artery;
- LND dissection in presciatic area or the “triangle Marcille”.

Technical features of ePLND and details of LN differentiation on above-mentioned groups were well-described in a recent publication from our institution (Osmonov et al. 2011). We performed SePLND as follows: choosing a transperitoneal access, we defined landmarks such as the iliac vessels before beginning with the dissection. The ureter was identified and separated carefully from the surrounding tissue. LN dissection was then performed systematically from top downwards. Small or medium

clips were used to avoid extensive ligation. We used the Harmonic Scalpel® (Ethicon Endosurgery, USA) to seal the LN vessels and to shorten the operation time. Standard operating routine includes the following *(Figure 4)*:

1. The patient was in the supine position and rotated to the side of LN dissection. The wound was exposed in the region of the fossa obturatoria by means of a Book-Walter retractor.

2. Margins of the LN dissection in the fossa obturatoria: the upper margin is the top edge of the external iliac vein, the lower margin is the obturator nerve; the angle between the lower edge of the external iliac vein and the pubic bone is cranial, and the bifurcation of the common iliac artery is caudal.

3. The upper margin of sacral LN dissection is the obturator nerve, the lower margin is the lateral edge of the neurovascular bundle (NVB) of the prostate, the cranial margin is the foramina obturatoria, and the caudal margin is the ureter.

4. LN dissection in the so-called presciatic area includes the last one-third of the backside area of the external iliac vein close to the bifurcation of the common iliac vein.

5. LN dissection along the common iliac artery is performed as follows: Dissection and clipping is done in the same way in the caudal direction, with a careful stump separation of the LN down from the pelvic wall using a mini-swab. We recommend pulling the external iliac artery to lateral after reaching three-quarters of the dissection length, to clear the surface of the common iliac vein. We recommend removal of LN tissue of at least 3 cm along the common iliac artery or up to the ureter crossing point (Osmonov et al. 2011).

The dissection areas of SePLND were as follows: 1. LND paraaortal, 2 LND interiliacal, area between the right and left common iliac artery, 3. LND in the region of the common iliac artery on the both sides, 4. LND around the promontorium, 5. LND in the presciatic area or the “triangle Marcille”, 6. LND in the region of the internal iliac artery, 7. LND in the fossa obturatoria. 8. LND in the region of the external iliac artery. 9. LND in the sacral area *(Figure 4)*.

Additionally we also attempted to standardize SePLND in view of the operative limitations of salvage surgery due to the scar formation after primary therapy and the presence of easily damageable structures like pelvic vessels and nerves.

Dividing into groups

We included 41 patients in this study, who underwent a various combinations of salvage treatment of their PCa-BCR prior to salvage surgery between November 1997 and June 2011. We formed 3 groups of patients according to the type and combination of salvage therapy options being performed for subsequent analysis. The common in all three groups was SePLND as the only salvage treatment or as a part of it. Schematic sequence of treatment options in each group is shown in *Figure 5*.

Group 1 (n=10) consists of patients with primary RT and subsequent salvage RP with ePLND. Median follow-up after the sRP was 40.0 ± 11.2 months (24-59 months).

Group 2 (n=22) consists of patients with primary RP and subsequent SePLND. Median follow-up after SePLND was 32.3 ± 27.0 months (1 - 90 months).

Group 3 (n=9) consists of patients with primary RP and subsequent sRT. Median follow-up after sRT was 60.2 ± 24.5 months (24 - 112 months) (*Figure 5, Table 2*).

Across the groups RT was performed in 33 (80.5%) patients. In 10 of them RT was the primary treatment for PCa and in 23 patients RT was performed as salvage treatment.

We also analysed the influence of ADT on the follow-up. Thirty (73.2%) from the total of 41 patients received ADT at some stage of their treatment. Taking into consideration that all patients had a BCR prior to salvage surgery and 25 (61.0%) received an ADT prior to salvage surgery; these 25 (61.0%) patients had a hormone resistant PCa at the time of salvage surgery. Terms of ADT and correlation with other treatment methods were analysed.

We would like to point out that 27 of 41 patients, received one or more secondary salvage treatments (out of these there were 22 secondary SePLND, 3 secondary cases of salvage RT, 3 secondary cases of salvage adjuvant RT and one secondary salvage RP). For example, 3 patients from Group 2 underwent SePLND twice and one patient even three times. Two patients in the same group underwent adjuvant RT (shortly after the SePLND) and 3 further patients underwent sRT as a secondary salvage treatment. Still in this same group, 7 SePLNDs were considered as secondary salvage options as they follow the adjuvant RT. In Group 3 eight patients underwent SePLND and one patient sRP as secondary salvage treatments. In Group 1 one patient received sRP as a second salvage treatment.

Our goal is to analyse the overall results of salvage therapy, therefore we will not distinguish between primary and secondary salvage treatments in the following analysis. Thus, we present only the above-mentioned three groups of patients (*Diagram 1*). BCRF, CSS and the influence of ADT were analysed according to the goals of our study.

RESULTS

The results are structured according to the previously mentioned goals of the study.

a) **Patient age:** The distribution of the patient age is presented in *Table 2*. Group 1 contained the oldest patients on average, the lowest average age was found in Group 2. Overall, the average age of the patients at the time of primary treatment was 62.3 ± 8.7 years (49-74 years); at the point of salvage treatment it was 66.1 ± 6.5 years (54-78 years).

b) **Degree of tumor differentiation:** Distribution of the patients by Gleason Score (Diagram 2) showed that the dominant score was 7 (43.9% of patients), then score 9 (22.0%), score 8 (17.1%), score 6 (9.8%), score 10 (2.4%). In two patients (4.9%) in, the GS could not be determined according to the histological analysis. Relying on this indicator, it can be said that the percentage of patients with low-risk was no more than 9.8%, patients with intermediate- and high-risk clearly dominated. This is not coincidental, as all patients included in the study sooner or later had a PCa recurrence. This can also be seen as further proof of the relevance of the GS in BRFS prognosis.

c) **Risk stratification:** According to the D'Amico risk classification, there were 3 (7.5%) patients with low-risk, 13 (32.5%) patients with intermediate risk and 24 patients (60.0%) with high-risk prostate cancer. In one patient from Group 1, it was impossible to determine the risk category. In Group 1, high-risk patients (77.8%) predominated, with only two intermediate-risk patients. The risk distribution (low-intermediate-high) in Group 2 was 2 – 6 - 14 (resp. 9.1% - 27.3% - 63.6%); in Group 3 it was 1 -5 - 3 (resp. 11.1% - 55.6% - 33.3%). The clear predominance of high-risk patients in Groups 1 and 2 and of intermediate-risk patients in Group 3 has been analysed (Diagram 3).

d) **Initial PSA values:** The iPSA level was also different in the three patient groups (Diagram 4). In Group 1, it was 33.2 ng/ml, in Group 2 – 19.0 ng/ml, in Group 3 – 12.1 ng/ml. The prevalence of a high iPSA level in Group 1 could be seen as predicting potentially less favourable postoperative results. This hypothesis will be proved or disproved in following analysis.

e) **TNM-classification:** It has been mentioned above that the stage of the disease by TNM classification is also important in predicting the risk of PCa recurrence. Among the studied patients, stage cT1 was not identified. Stage cT2 was diagnosed in 17 (42.5%) patients; regarding the distribution of cT2a - cT2b - cT2c, the latter was dominating with 3 - 5 - 9 patients respectively. Stage cT3 was diagnosed in 21 (52.5%) patients with cT3a and cT3b found almost equally in 10 resp. 11 patients. In 2 patients it was not possible to define the stage by the TNM classification.

f) **PSA-DT and ADT:** We considered the PSA-DT as the primary index of treatment efficiency. Based upon PSA levels, we analysed the PSA-DT in all three groups of patients. First we calculated the PSA-DT **before salvage treatment**. As mentioned above, all of patients who received ADT before salvage surgery (n=25; 61.0%) had BCF and therefore were hormone resistant at the time of salvage surgery. We also attempted to take into consideration the influence of ADT on the PSA-DT level (*Diagram 5*).

In Group 1, the mean level of PSA-DT prior to sRP was 13.8 months (without ADT) and 12.3 months (with ADT). Furthermore, 2 patients showed a PSA regress after ADT was prescribed, but the PSA level remained ≥0.5 ng/ml. In 5 patients (50%) we observed a BCR-free period from 16 to 75 months (mean BCRF period in this group was 34 months) (*Diagram 5*).

In Group 2, the mean level of PSA-DT prior to SePLND was 9.2 months (without ADT) and 11.3 months (with ADT). In 11 patients (50%) we observed a BCR-free period of 10 to 92 months (mean BCRF period in this group was 40.6 months) (*Diagram 5*).

In Group 3, the mean level of PSA-DT prior to sRT was 18.1 months (without ADT). Just one patient in this group underwent ADT, his PSA-DT was 4 months. In 3 patients (33.3%) we observed BCR-free period from 32 to 72 months (mean BCRF period in this group was 50.3 months) (*Diagram 5*).

Moreover, we analysed the PSA-DT in all groups **after the first salvage treatment (salvage surgery in Group 1 + 2, sRT in Group 3)** (*Diagram 5*).

In Group 1 four patients (40%) needed to receive hormonal therapy after salvage sRP. In this group, 6 of 10 (60%) patients had a BCRF period of 6 to 43 months (the mean BCRF period in this group was 27.2 months), 3 patients (30%) continue to be BCR-free at the time of analysis (35, 27, 43 months). The average duration of PSA-DT after sRP without application of ADT treatment was 4.5 months. From the time that ADT was initiated, one patient had a BCRF of 43 months and the level of PSA continues to remain below 0.5 ng/ml. In a further patient the PSA level – although not meeting BCRF criteria - showed a significant regress by 78% after ADT initiation. Another patient achieved a PSA-DT of 7 months with ADT. Only one patient developed bone metastases 2 years after sRP (*Diagram 5*).

As mentioned before, SePLND was performed twice resp. three times in 3 pts. resp. one patient. Therefore, we evaluated the results of 27 SePLNDs in this group. Initially no ADT was prescribed postoperatively, but then 11 out of 24 (40.7%) patients had to undergo hormonal treatment. Overall, the results in Group 2 were favourable – 63% patients had a BCR-free period of 2 to 60 months (mean BCRF period in this group was 17.5 months). The remaining three patients a of PSA regress which remained

above BCRF criteria. It is important to mention that in 5 out of 17 (29.4%) patients BCRF continued at the time of analysis (for 2, 3, 3, 5, 12 months). The majority of these patients underwent salvage surgery in 2011; therefore their BCRF follow-up was only 2-5 months so far.

The mean level of PSA-DT after SePLND without application of ADT treatment was 6.1 months; in patients who received ADT the PSA-DT was 9.0 months. After ADT was initiated, three patients had BCRF and the other two patients had a regress of PSA level, but remained over BCRF criteria for 15 and 30 months.

In 3 patients from Group 2 secondary sRT was performed after SePLND, and we decided to further analyse to these 3 cases. It appears that all of them sooner or later received ADT treatment, and all of them had a BCRF-period of 35 to 45 months (mean period was 40.7 months). One of these patients unfortunately died of pancreas cancer, despite of good PCa control.

In Group 3, four patients (44.4%) needed to receive hormonal therapy. With ADT, 3 of the 9 patients (33.3%) had a BCR-free period of 12 to 26 months (average BCRF was 17.6 months), thus 2 patients (22.2%) have continued BCR-free at the time of analysis (15 and 26 months). In all of them, BCRF started after ADT therapy was initiated. The average PSA-DT after sRT without ADT treatment was 12.6 months. Three patients (33.3%), who did not receive ADT treatment, showed a regress of the PSA level, which remained over BCRF criteria, but decreased by 1.6 times on average **i**n compared with the PSA level before sRT.

When calculating the PSA-DT, we combined Groups 2 and 3 because SePLND was performed as a final salvage treatment in both these groups (*Diagram 5*).

g) **BCRF survival:** In total, BCR-freedom was observed in 23 of 41 patients (56.1%) after salvage surgery. As many as 75.6% of all patients showed a BR, i.e. a decrease of the PSA-level. We summarized all obtained results after salvage treatment in *Tables 3, 4*.

We also performed statistical analysis of all three groups in total (n=41). The average BCRF-survival was 21.4 months (95% CI 16.768 – 26.024; Std. error 2.361).

h) **Cancer-specific survival:** CSS analysis was also performed for all three groups. We included in CSS analysis only those patients, whose follow-up was more than 24 months (n=23). The results were as follows: 95% confidence interval of 5-years CSS = 66.97%-100%; Hazard-Ratio = 0.006683 (95% CI = 0 – 0.006683); median CSS = 103.7 months. It is statistically irrational to calculate CSS for each group because the small number of patients included in the study. The small number of patients also causes the wide margins of the 95% confidence interval.

i) **Number and localisation of metastases in removed LNs:** We have calculated the number of removed LN in all SePLNDs and combined sRP+SePLND, additionally taking into consideration their localization. In each group of LN the number of metastases was determined. These data are shown in *Diagram 6*.

The frequency of finding LNs and a share of metastases among them were calculated for each group. These data are presented in *Diagram 7*.

In total, N1 stage was established after 13.3% RP operations, after 30.0% sRP operations and after 58.3% SePLND –operations *(Diagram 8).*

We found the number of detected LN metastases to be ca. 5.6 times higher after salvage surgery than after primary RP (14.8% and 2.65% respectively). Thus the frequency of finding metastases in removed LNs during sRP is comparable with SePLND (15.0% and 14.7% respectively) *(Diagram 9, 10)*. It has turned out that most metastases during salvage surgery were found in the a. iliaca communis LNs and the presacralis LNs (total 17.9% and 15.4% respectively), followed by LNs from the region of the a. iliaca externa (12.2%), a. iliaca interna (12.1%), and the Marcille triangle (10.0%). The least frequent detection of metastases was in the obturator LNs (4.3%). Although a relatively large number of nodes (116) was removed from this area – which is standard in lLND-, the percentage of LN metastases is very low. More LNs were only removed in the a. iliaca communis area (190) and the a. iliaca externa (172), but there the percentage of positive LNs was as high as 17.9% resp. 12.2%.

Actually the most frequent metastases by far were found in the group “Other LNs” (27/84, or 32.1%) – this group juts out because it mainly includes LNs that were not related to the regional LNs - mostly paraaortal, paracaval and interaortocaval -, which had previously been identified as distant metastases in the preoperative PET-CT. The number of removed LNs and the frequency of metastases per LN group when comparing the Groups 1 and 2 were almost equal.

In SePLND (Groups 2+3) 16.6 (2-36) LNs were removed per patient, and 14.7% of these were positive. In sRP (Group 1) as many as 18.0 (9-26) LNs were removed per patient and 15.0% of these harboured metastases. In contrast, only 7.8 (0-36) LNs were removed per patient during primary RP, and only 2.65% of these were positive. When comparing primary RP (with lLND) and SePLND, it becomes clear that both the number of removed LNs and the percentage of positive LNs found is much higher in SePLND. (*Diagram 11*).

j) **Type and dose of RT:** 33 RT treatments were performed in 41 (80.5%) patients. Among these, 14 were performed in Group 2: as adjuvant RT after primary RP (8), as adjuvant RT after SePLND (2), as sRT after SePLND (3), and as a primary treatment option (1). *Diagram 12* shows the distribution by RT type, with a prevalence

of external RT (66.7%). This fact may indirectly point towards a greater risk of late postoperative complications. The radiation doses for each patient are also known.

k) **Distant metastases:** As mentioned above, distant metastases were found by bone scintigraphy in four patients during the post-salvage follow-up period. All of them received ADT and Zometa. In one patient, however, abnormal accumulation of the radiopharmaceutical drug was observed in the pelvic LNs, and therefore the RP included the removal of distant LN from paraaortal region in addition to regional ePLND. As a result, 8 out of 8 removed paraaortal LNs were found to be positive for metastases (100%). In the same patient, 5 LN metastases were found in the 18 regional LNs (27.8%), so the ratio of positive LNs was almost twice as high as the average ratio (14.8%). 28 months after the operation the level of PSA, which had previously been >100 ng/ml, dropped down to 37.7 ng/ml. After ADT initiation, the level of PSA dropped to 1.6 ng/ml, then slowly rose to the current level of 6.9 ng/ml. In the further course bone metastases were diagnosed, and the patient additionally received Zometa. The second patient with bone metastases had a PSA level of 5.5 ng/ml at the time of analysis. The last two patients with distant metastases had PSA levels of 59.4 resp. >100 ng/ml despite treatment with chemotherapy (Docetaxel). These patients require further observation.

l) **Complication rate:** We have also analysed all complications that occurred intra- and postoperatively. In the following they will be only listed, but there will be a detailed discussion of complications in the chapter below *(Table 5).*

Two of the 41 patients (4.9%) included in the study, underwent re-laparotomy was performed (2^{nd} resp. 3^{rd} day after the primary operation) to stop bleeding and to remove the hematoma. In one case, the source of bleeding were the epigastric vessels, in the second case the active source of bleeding was not found. Intraoperative ureteral injury had occurred in the latter patient, caused by difficulties with ureter isolation and suspicion of a metastatic LN in the projection of the ureter. Prompt diagnosis of the iatrogenic injury led to immediate ureter neoimplantation by Boari technic, and intraoperative double-J catheter-stent (6,32 Ch) placement. Thereby we were able to avoid more serious complications, such as an otherwise necessary reoperation.

In one patient (2.4%) a rectovesical fistula was diagnosed after surgery, which required further surgery one month after RP and partial resection of the anterior rectum wall with insertion of a protective double sigmoidostoma, and, a week later, abdomen-perineal closure of the fistula and suprapubic bladder drainage installing. We suppose that the previous RT in this patient increased the risk of such a complication, due to the tissue-changing properties of radiation. It must be kept in

mind that surgical preparation in pre-irradiated patients can lead to complications and intraoperative difficulties.

Two patients (4.9%) developed postoperative lymphoceles, which required surgical treatment. Lymphoceles are not uncommon in patients after RP (up to 20% in primary operations), as well as due to ePLND if the deep lymphatic vessels are touched upon. Lymphoceles lead to swelling, stagnation of the liquids, or even thromboemboly of lower extremities. To prevent lymphoceles, the peritoneum is not fully closed, because it resorbs liquid – thus surgeons make a fenestration (i. e. leave "windows" in peritoneum). After the salvage operation we intentionally did not restore the integrity of peritoneum, and therefore the number of lymphoceles is relatively small in comparison to primary RP. Moreover, lymphocele correction is now usually done laparoscopic at our department.

DISCUSSION

We believe that there is still no treatment option, which could prevent PCa relapse. Therefore, the main aim in PCa treatment is to minimize these relapses and to effectively deal with clinically evident recurrences. So far the main treatment options in case of BCR have been ADT and/or RT. Salvage surgery (sRP resp. SePLND) are rarely considered due to the lack of data and the fear of surgical complications.

We studied the results of PCa salvage treatment in our institution. 25 (61.0%) patients were hormone resistant at the time of salvage surgery. 16 patients have not received any ADT prior to salvage surgery at all. Although the number of patients is relatively small, this study has high clinical relevance, due to the limited data on salvage treatment of recurrent PCa (Rigatti et al. 2011, Jilg et al. 2012). The patients were divided into three groups in order to evaluate the effect of SePLND (resp. sRP+SePLND) on patients with different primary (Groups 1+2) and previous salvage treatment (Group 3). BRFS analysis is one of the key-points of our study; the survival data are presented in a Kaplan-Maier curve (*Diagram 13)*. According to our results, we are able to note some differences between these groups.

Thus, Group 1 (n=10) with sRP after primary RT, demonstrates surprising results after sRP: we observed BCRF in 60% of the patients of an average duration of 27.2 months; 50% of the latter continue to have PSA levels of below 0.5 ng/ml. None of these patients required further salvage treatment, but profited from adding only ADT in case of PSA progress. The iPSA level was the highest in this group: almost two times higher than in the other two groups. This fact points to a more severe initial course of the oncological process and increases the value of the high treatment success rate achieved in this group in comparison with the others groups.

Analysis of Group 2 (n=22; SePLND after primary RP) also showed unexpectedly favourable results. This group with 22 out of 41 patients (53.7%) was the largest one in our study and demonstrates similar results as Group 1: 63.6% of the patients achieved BCR-freedom with an average duration of 17.5 months, and 28.6% of the latter continue with PSA levels under 0.5 ng/ml. This BCRF-survival includes the data of patients who received ADT after salvage surgery.

In Group 3 (n=9; SePLND after RP and sRT), BCRF was registered in 33.3% patients with an average duration of 27.2 months, and 2 out of the 3 latter patients still have PSA levels of below 0.5 ng/ml. Three other patients in this group showed a PSA regress, but with levels over BCR criteria (0.5 ng/ml). The mean PSA-DT before ADT therapy in this group was with 12.6 months higher than in the previous two groups. The aim of salvage treatment in Group 3 was to stop or minimize biochemical progression after sRT by means of sRP + SePNLD. Thus, 8 out 9 patients (88.9%) from Group 3 underwent SePLND after sRT. Retrospectively, sRT in this group of

patients may not have been the optimal treatment choice, and in these cases it would have been better to perform SePLND as soon as the PCa BCR was diagnosed.

The above-mentioned results of sRP in Group 1 indicate the role of SePLND, as a part of sRP. The importance of ePLND during sRP is confirmed by the following finding: LN metastases were found in 15.0% of all removed LN during sRP with SePLND and in 14.7% of all removed LN during SePLND alone. Therefore, as we have mentioned before, the frequency of metastases finding during salvage surgery (summary sRP and SePLND) is almost 5.6 times higher than in primary RP (14.8% in salvage surgery vs. 2.65% in primary RP respectively). N1 stage was established after 58.3% of all SePLND performed in our study, which is more than 4 times more often than after primary RP.

The number of positive LNs found during primary RP seems to be an important factor for CSS. This has been suggested by data from Bader and colleagues, which show a correlation between survival and the number of positive LNs found during primary RP with ePLND. Of 39 patients with only one positive LN, 15 (39%) remained without signs of clinical or chemical progression. On the other hand, only 6 out of 49 (12%) patients, who had at least two positive LNs, remained disease-free (Bader et al. 2003).

In general we suppose that the removal of more LNs results in more positive LNs that will be found (Osmonov et al, 2013). Thus BRFS after ePLND is superior to lPLND as shown in a comparative study: the 5-year PSA progression-free rate was 43% for ePLND versus 10% for lPLND ($p=0.01$) (Allaf et al, 2004) - despite the still relatively small number of removed LNs in the ePLND group (mean 11.6 vs 8.9, $p<0.0001$).

Comparing the average number of removed LNs in each group, we found that the rate of LN metastases detected in salvage procedures is much higher than in primary RP. Thus, during primary RP only 7.8 LNs (2.65% LN+) per patient were removed on average, while 18 LNs during sRP (15% LN+), resp. 16.3 LNs during SePLND (14.7% LN+) were removed per patient.

More than every other LN (51.7%) removed during primary RP was taken from the fossa obturatoria. Traditionally, most of surgeons limit ePLND just to this LN location, considering that further expansion of ePLND volume leads to an increase of the number of complications. But in our study among 117 obturatoric LN removed during primary RP, just in 3 (2.6%) metastases were found.

Mattei and colleagues studied primary prostatic lymphatic landing sites by using a multimodality technique and found that PLND for PCa should not only include the external and obturator regions as well as the portions medial and lateral to the internal iliac vessels, but also the common iliac LN at least up to the ureteric

crossing. Thus it is possible to remove approximately 75% of all nodes potentially harbouring metastasis (Mattei et al. 2008).

The frequency of positive LNs in our study increases with the number of removed LNs per operation. These results correlate with a parallel study from our department based upon 174 patients (115 intermediate risk and 59 high risk), where results of all primary RPs are analysed. Our results have shown that the more LNs are removed, the more metastases are found. Thus, the maximum number of metastases was detected only if more than 15 LNs were removed in the intermediate-risk and 18 LNs in high-risk group (Osmonov et al. 2013).

The question still remains and continues to provoke controversy during urology expert meetings – what should be the extent of LN dissection in PCa surgery? The prevalence of metastases in the LNs of paraaortal and communis region in patients who have a PCa relapse convinces us of the necessity to perform a maximally extended ePLND, which includes not only the fossa obturatoria, but also the a. iliaca interna, externa and communis regions, the Marcille triangle, the parasacral LNs, and even reaching into aorta bifurcation area. It has been shown in previous studies from our department (Osmonov et al. 2011) and has been proved again in the current study.

We propose that at least 15 LNs in the intermediate-risk group and at least 18 LNs in the high-risk group should be removed during ePLND. This is only a relative number and the actual number of removed LNs can also depend on further factors such as the condition of the patient, the experience of the surgeon, or the priorities and specifics of different surgical schools (Osmonov et al. 2013, Briganti et al. 2008).

However, it needs to be noted that we have a different situation in salvage cases in compared to primary surgical treatment. A significant predominance of positive LNs in salvage surgery has clearly been shown by our data.

Although salvage LN surgery follows essentially the same surgical approach as primary ePLND, there are some differences regarding the higher challenge to the surgeon as well as the surgical outcome with respect to the number of positive LNs. A significantly higher rate of positive LNs in salvage surgery has clearly been shown by our data.

Moreover, the frequency of LN metastases per LN group differs significantly from the typical LN excision areas in primary surgery. During the salvage procedure, we found only 4.4% LN metastases in the fossa obturatoria – less than in any other LN region. More than 50% of all LN metastases were found in LNs of the a. iliaca communis (29.9%) and in the LN group labeled “other LN” (23.7%), mostly consisting of

paraaortal, paracaval and aortocaval LNs (situated above the typical area of LN dissection), as well as interiliacal, promontorium and mesenterical LNs.

In all three groups we were able to observe that the PSA-DT increased after ADT was started. ADT is an effective treatment option which carries both good cancer control and clinical response in patients who were castration-resistant prior to salvage surgery.

Therefore we have pointed out in the introduction that the BRFS after RP and RT are approximately equal *(Table 1).*

On the other hand, salvage surgery can prolong the time until ADT initiation. ADT has often been shown to cause negative side effects such as loss of libido and fatigue, thus postponement of ADT can help to improve the quality of life. We have found, moreover, that the moment of hormone resistance is observed at a later time in salvage-operated patients. Unfortunately, it is not always possible to determine the starting point and duration of ADT, which makes it difficult to draw a valid conclusion.

Our data in conjunction with BCRF levels show that more than a half patients can live in average nearly 2 years without BCRF after salvage surgery of recurrent PCa *(Table 3).* We consider the prolongation of BRFS, CSS and the postponement of ADT initiation as the key-points of our study as they illustrate the necessity of SePLND. The high risk of LN metastases also documents the necessity to prevent metastatic spread at an early stage of the disease, thus intermediate and high risk PCa patients initially should always undergo ePLND during primary RP. Although PET-CT remains relevant, it is not a safe method of LN diagnostics with a sensitivity/specificity of only 85.1%/22.7% as shown in a recent analysis (Osmonov et al. 2013). In the absence of reliable preoperative diagnostics, ePLND and SePLND currently remains the only method of combatting LN metastatic spread. Therefore, we believe that refusal of SePLND cannot be justified by fear of complications.

Some authors have pointed out that BCR frequency is in inverse ratio with an increase of the radiation dose (Mohammed et al. 2012). In our opinion, the long-term consequences and complications of high-dose radiation have not been sufficiently examined yet. It is often impossible to estimate the frequency and severity of high-dose radiation complications due to the required long-term follow-up. Depending on the type of RT, late genitourinary toxicities are present in ca. 21%-28% patients, late gastrointestinal toxicities in 2% of brachytherapy patients and in up to 20% of EBRT patients (Mohammed et al. 2012). The quality of life and the general condition suffers in these often old-age patients. In urological practice, radiation-caused cystitis and proctitis have been observed at a mean follow-up of 6-8 years after RT (Osmonov et al. 2006).

Moreover, the effects of ionizing radiation on the tumor area and normal tissue in impact zone are also not fully known currently, and there are only scarce publications on this issue (Riley 1994). The underlying logic of relapse emergence after RT is based on the hypothesis that viable tumor cells remain, which are capable of uncontrolled division, leading to an oncological progression. In our opinion, the hypothesis that viable tumor cells remain in the body after RT, requires further confirmation or refutation. In practice, this is a very difficult issue because patients do not undergo prostate biopsy after RT. It is only indicated if the finding of a local recurrence affects the treatment decision (Heidenreich et al. 2012). The reason for this has indirectly been given above: today BCR progress (increase of PSA level) is seen as a synonym for PCa progress. However, even if control biopsies are performed, the above question will remain unanswered, as it is not possible to histologically examine the entire volume of irradiated tissue. Therefore, even if the biopsy negative it is not possible to conclude that there are no viable tumor cells (Serag et al. 2012).

The above-mentioned uncertainty of cell status after RT remains a general problem which also applies to primary PCa diagnostics, especially in the early stages, when tumor cells are often not detected in the first or even second biopsy, despite a rise of PSA level. Even if a PCa diagnosis is achieved in one of the subsequent biopsies, the tumor is given more time to progress while the start of treatment is delayed. Extended and saturation biopsy schemes should be performed followed by repeated biopsies if necessary (Scattoni et al. 2007).

When planning the salvage surgery, the patient's overall condition, his PSA level, GS, risk classification, PSA-DT should be taken into account. In general, however, it seems that salvage surgery should be considered as a valid treatment option in a much larger share of patients than to date, especially when contrasting the severe long-term follow-up complications after RT (radiation cystitis/proctitis, bleedings) with the relatively limited and short-term complications associated with salvage surgery.

According to our experience the number of such complications is relatively small (in total 17.0%), which can expand the indications for performing salvage surgery in patients with recurrent PCa and ePLND during primary surgical treatment. We would still like to emphasize that the operation is relatively difficult and should therefore be performed by an experienced surgeon. Randomized clinical trials are necessary to determine the value of different types of salvage therapy.

The improvements of RP technique during the last decade including the new possibilities opened by robot-assisted surgery have generally reduced the level of complications and of long-term side effects. This also has implications for salvage surgery techniques. We have been able to show that sRP and SePLND are not just

“PSA cosmetics”, but efficient alternatives and valid treatment options in patients with PCa relapse. The indications for sRP should be therefore expanded.

Moreover, ePLND should be performed in all cases both during sRP as well as during primary RP in patients with intermediate- and high-risk prostate cancer with the aim of preventing cancer progression and metastasizing. We believe that salvage surgery of patients with biochemical PCa relapse is feasible and relatively safe treatment method, that it prolongs the BRFS period, life expectancy and cancer-specific survival in these patients.

We realize that the presented study has it’s limitations, such as the relatively low number of patients included and the retrospective single-center design. Multi-centric prospective randomized trials are required.

SUMMARY

Treatment of patients with biochemical PCa relapse is generally difficult and without valid therapy options. These patients commonly receive salvage RT (sRT) and/or ADT. A further potential treatment method is salvage extended PLND (SePLND). This treatment option is still rarely performed and there are no reliable long-term data. We have retrospectively analysed the outcome of SePLND performed at our department since 2003 in 41 patients with a BCR. Moreover, we have performed an extensive review of the literature on salvage treatment of PCa recurrence.

We divided the cohort into three groups according to the type of primary treatment (Group1: primary RT; Group 2, primary RP; Group 3: primary RP+ sRT). All 41 patients underwent SePLND; Group 1 additionally underwent sRP. Indications for salvage treatment were BCR of PCa and/or a shortening of PSA-doubling time, a positive PET-CT scan, as well as absence of bone metastasis. We observed PSA, PSA-velocity, localization of LNs and LN+, BRFS, CSS and OS.

There were 3 (7.5%) patients with low-risk, 13 (32.5%) patients with intermediate-risk and 24 patients (60.0%) with high-risk PCa. Thirty (73.2%) from the total of 41 patients received hormonal therapy at some stage before or after salvage surgery. 56.1% of patients had an average BCRF-period of 21.4 months after salvage surgery. This means that more than half of the patients were BCR-free for almost 2 years. 75.6% of all patients showed a biochemical regress, i.e. a PSA drop-down after salvage surgery.

The rate of detected LN metastases was ca. 5.6 times higher in salvage surgery than in primary RP (14.77% and 2.65% respectively). The average number of removed LNs per patient was 7.8 (0-36) during primary RP, 16.6 (2-36) during SePLND and 18.0 (9-26) during sRP. We suggest that it is better to remove the maximum possible number of LNs in the initial procedure than to perform re-operations in the same patient due to later evidence of LN metastases. Our proposal is strengthened by the fact the number of salvage surgery complications was relatively small (17.0%). We believe that our results clearly underline the necessity of ePLND and SePLND respectively.

Due to the relatively small number of patients we cannot at this stage recommend SePLND implementation in all patients with BCR. In absence of a control group, it can so far only be stated that SePLND is a feasible and relatively safe treatment option and has a promising outcome. SePLND can prolong BCRF survival and postpone ADT initiation, while its influence on CSS remains yet unclear. We believe that more data will be accumulated in the future in multi-center randomized prospective studies. On this basis the role of salvage surgery can be more clearly defined and enhanced. It will also be necessary to develop clear recommendations for salvage surgery and to define the indications. Ultimately, it will help to treat patients with recurrent PCa more effectively, to prolong the life of these patients, and to reduce PCa mortality.

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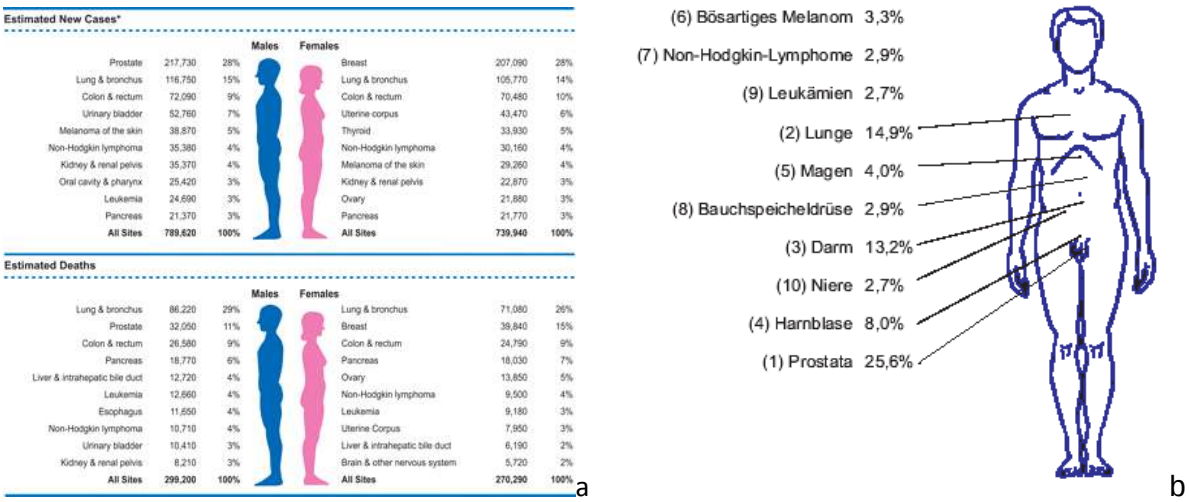
SUPPLEMENT (Graphic material)

Figure 1. ***Estimated cancer new cases and deaths in a) USA (according to Cancer Statistics 2010) and b) Schleswig-Holstein (Germany)***



Estimated New Cases*

	Males			Females		
Prostate	217,730	28%		Breast	207,090	28%
Lung & bronchus	116,750	15%		Lung & bronchus	105,770	14%
Colon & rectum	72,090	9%		Colon & rectum	70,480	10%
Urinary bladder	52,760	7%		Uterine corpus	43,470	6%
Melanoma of the skin	38,870	5%		Thyroid	33,930	5%
Non-Hodgkin lymphoma	35,380	4%		Non-Hodgkin lymphoma	30,160	4%
Kidney & renal pelvis	35,370	4%		Melanoma of the skin	29,260	4%
Oral cavity & pharynx	25,420	3%		Kidney & renal pelvis	22,870	3%
Leukemia	24,690	3%		Ovary	21,880	3%
Pancreas	21,370	3%		Pancreas	21,770	3%
All Sites	**789,620**	**100%**		**All Sites**	**739,940**	**100%**

Estimated Deaths

	Males			Females		
Lung & bronchus	86,220	29%		Lung & bronchus	71,080	26%
Prostate	32,050	11%		Breast	39,840	15%
Colon & rectum	26,580	9%		Colon & rectum	24,790	9%
Pancreas	18,770	6%		Pancreas	18,030	7%
Liver & intrahepatic bile duct	12,720	4%		Ovary	13,850	5%
Leukemia	12,660	4%		Non-Hodgkin lymphoma	9,500	4%
Esophagus	11,650	4%		Leukemia	9,180	3%
Non-Hodgkin lymphoma	10,710	4%		Uterine Corpus	7,950	3%
Urinary bladder	10,410	3%		Liver & intrahepatic bile duct	6,190	2%
Kidney & renal pelvis	8,210	3%		Brain & other nervous system	5,720	2%
All Sites	**299,200**	**100%**		**All Sites**	**270,290**	**100%**

a

b

Figure 2. ***11C-choline PET/CT. Suspicion of left-side pelvine LN metastasis.***

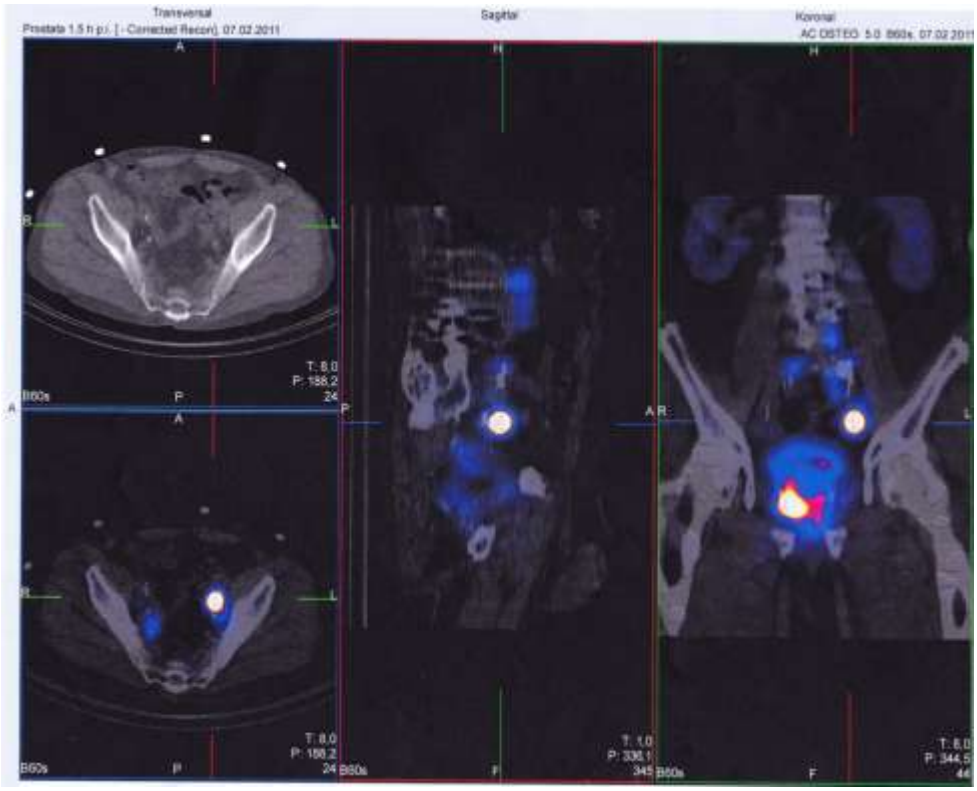


Figure 3. ***Pelvine scintigramm. Suspicion of left-side pelvine LN metastasis.***

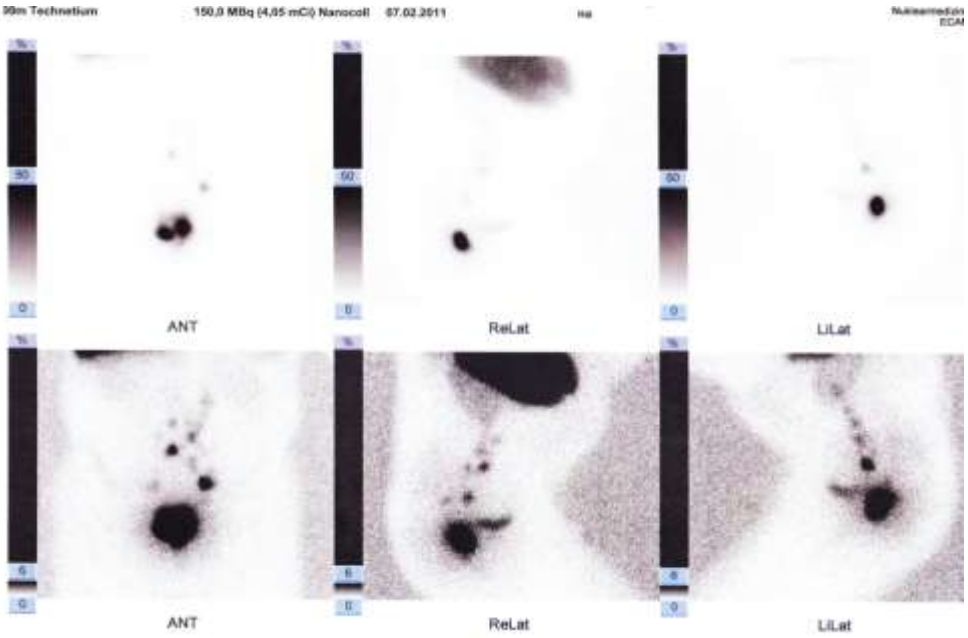


Figure 4. ***Groups of LNs, removed during ePLND.***

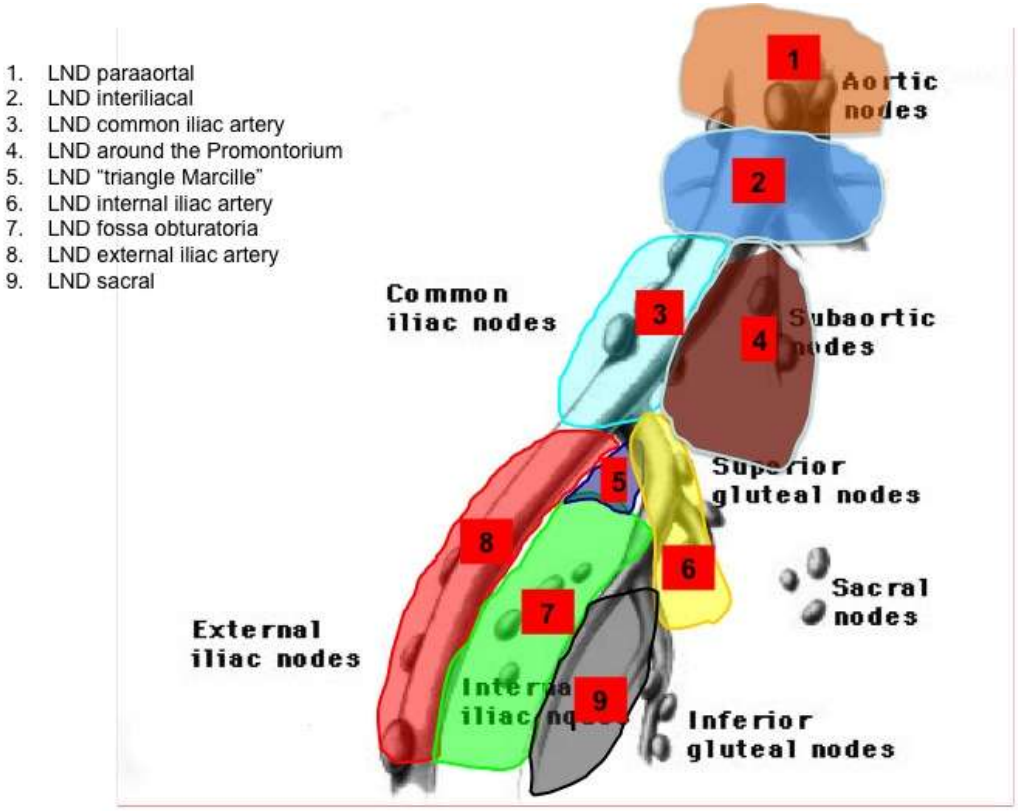


Figure 5. ***Three groups of patients, n=41.***

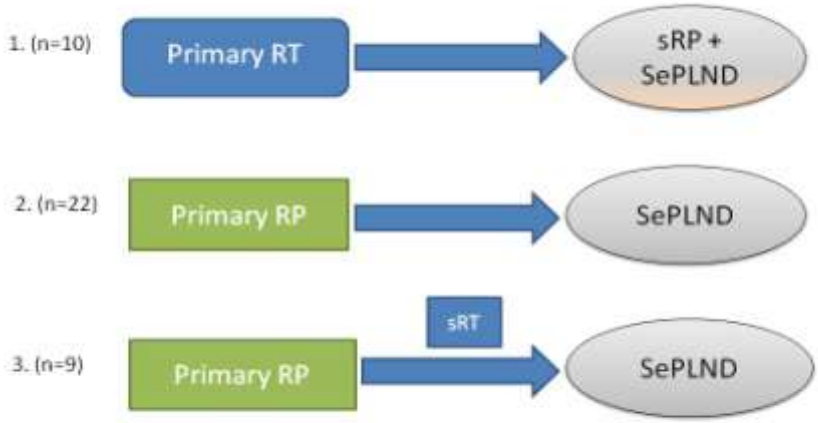


Table 1. ***5-year BRFS level after RP vs. RT treatment of PCa.***

	Low-risk	Intermediate-risk	High-risk
Radical prostatectomy	85-94%	68-77%	55-(68**)%
Radiotherapy	66-86%	51-78%	29-(67*)%

* - 10-years BRFS
**- 15-years BRFS

(The table reflects the results from the following studies: Partin et al. 1993, Catalona et al. 1994, Zincke et al. 1994, Paulson et al. 1994, Kuban et al. 1995, Zietmann et al. 1995, Khuntia et al. 2004, Sylvester et al. 2006, Bastide et al. 2006, Hernandez et al. 2007, Yoshioka et al. 2009, Burdick et al. 2009, Loeb et al. 2010.)

Table 2. ***Median age at moment of treatment in each patient group (age range).***

Groups of patients	Age (yrs) at time of primary treatment	salvage treatment
RT ⇨ sRP (Group1)	64.2 ± 3.6 (60-70)	68.2 ± 4.1 (63-76)
RP ⇨ SePLND (Group2)	61.8 ± 7.2 (52-74)	65.2 ± 7.5 (54-78)
RP ⇨ sRT ⇨ S ePLND (Group3)	61.4 ± 7.6 (52-73)	66.0 ± 6.7 (54-74)
Summary	62.3 ± 8.7 (49-74)	66.1 ± 6.5 (54-78)

Table 3. ***Results after Salvage treatment in all three groups (n=41).***

	n	BCR-free patients after salvage	Biochemical regress	Mean BCR-free period (months)	Patients with ADT
Group 1	10	60.0%	70.0%	27.2	40.0%
Group 2	22	63.6%	82.1%	17.5	40.7%
Group 3	9	33.3%	66.6%	17.7	44.4%

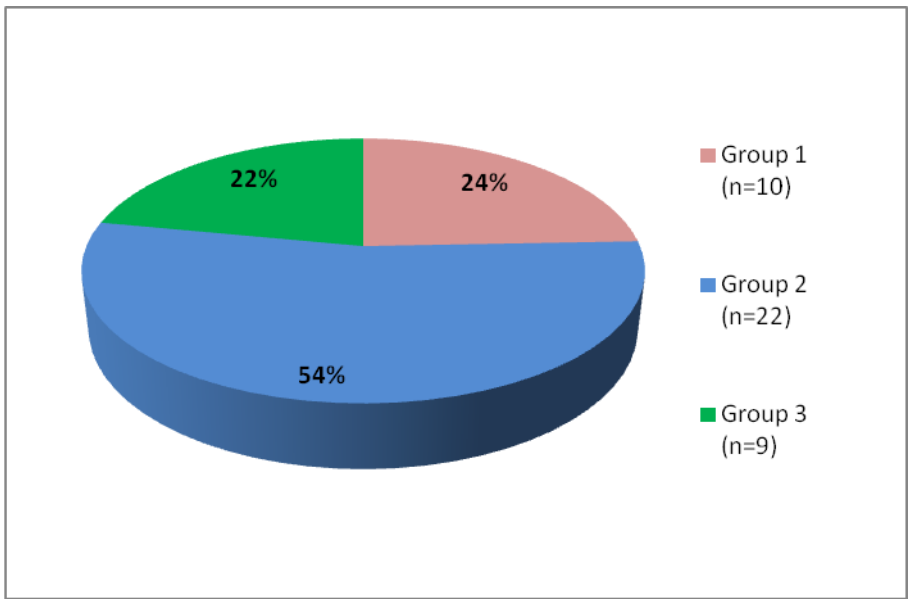
Table 4. ***Results after salvage treatment: patients with- vs. without ADT.***

	Patients with ADT			Patients without ADT		
	BCR-free patients after salvage	BCR-free period (months)	PSA-DT (months)	BCR-free patients after salvage	BCR-free period (months)	PSA-DT (months)
Group 1	50.0%	26.5	7.0	66.7%	27.5	4,5
Group 2	81.8%	16.8	9.0	60.0%	13.0	6.1
Group 3	75.0%	17.7	-	0%	-	12.6

Table 5. ***Complications of salvage treatment (n=41).***

Complication	Frequency
Intra-/early postoperative period	
Bleeding	**2 (4.9%)**
Ureteral injury	**1 (2.4%)**
Late postoperative period	
Lymphocele	**2 (4.9%)**
Ureteral stricture	**1 (2.4%)**
Rectovesical fistula	**1 (2.4%)**

Diagram 1. ***Distribution of patients in groups and follow-up (n=41).***



Median Follow-up (months)	
Group 1	***40.0 ± 11.2***
Group 2	***32.2 ± 27.0***
Group 3	***60.2 ± 24.5***

Diagram 2. ***Gleason score in all patients (n=41).***

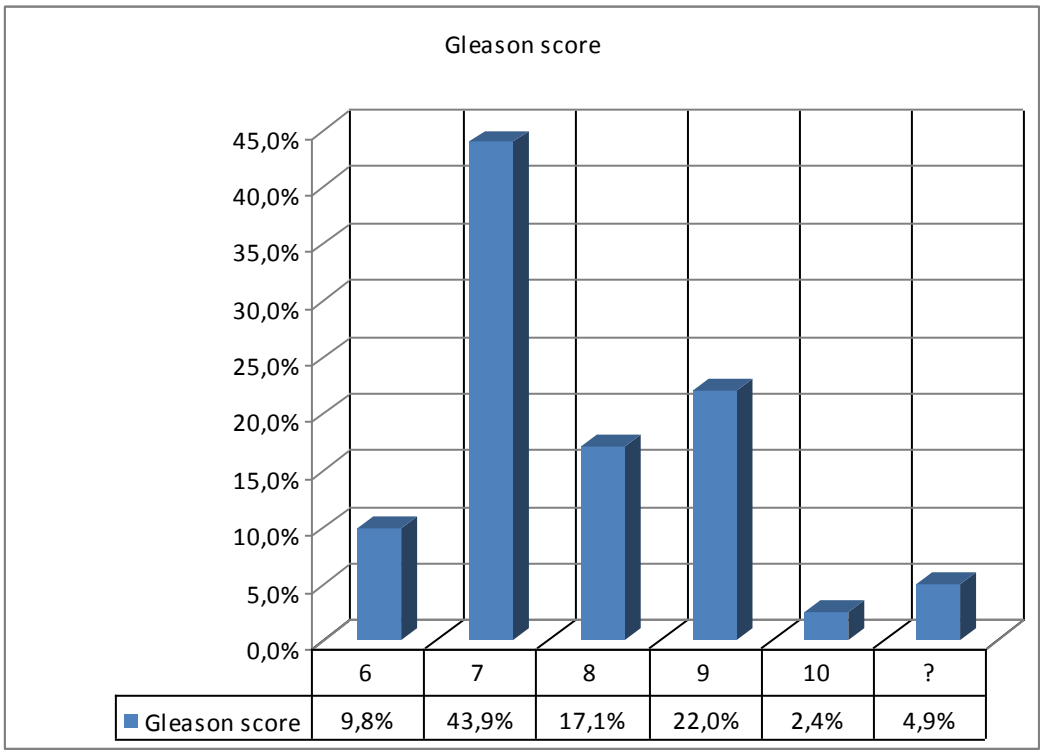


Diagram 3. ***Risk groups according to D'Amico classification in all patients (n=41).***

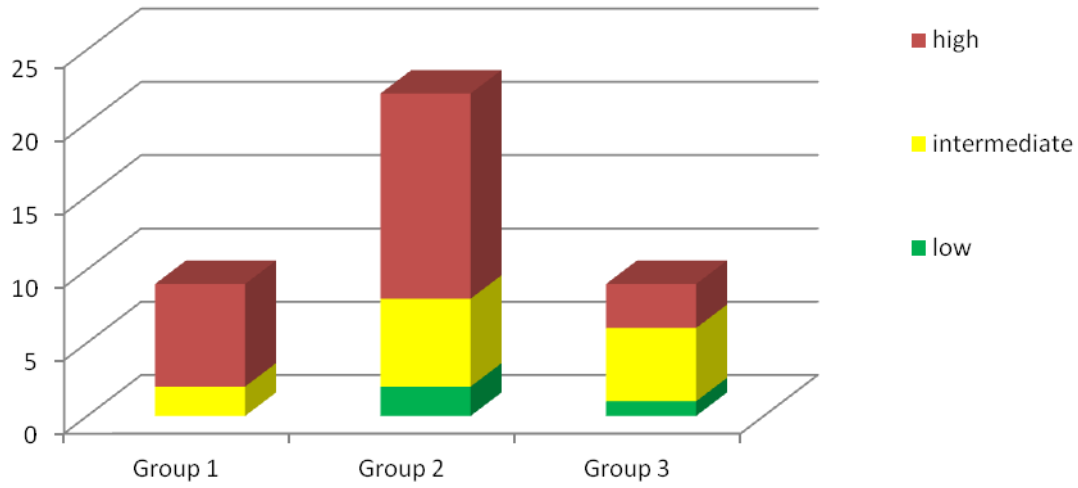


Diagram 4. ***iPSA level in all patients groups (n=41).***

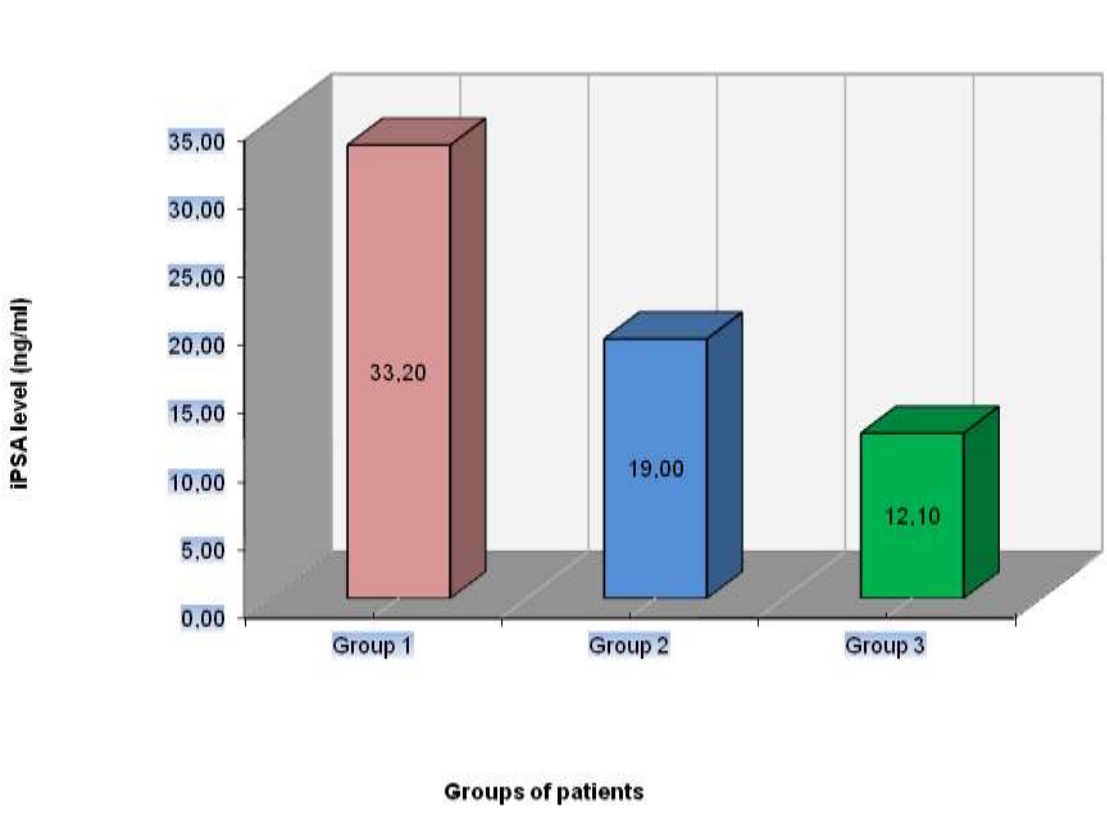
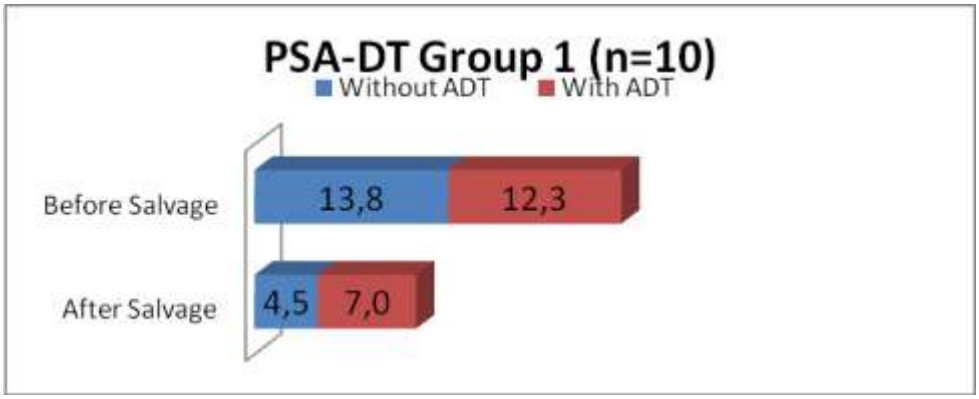


Diagram 5. ***Dynamic of PSA-DT in months.***



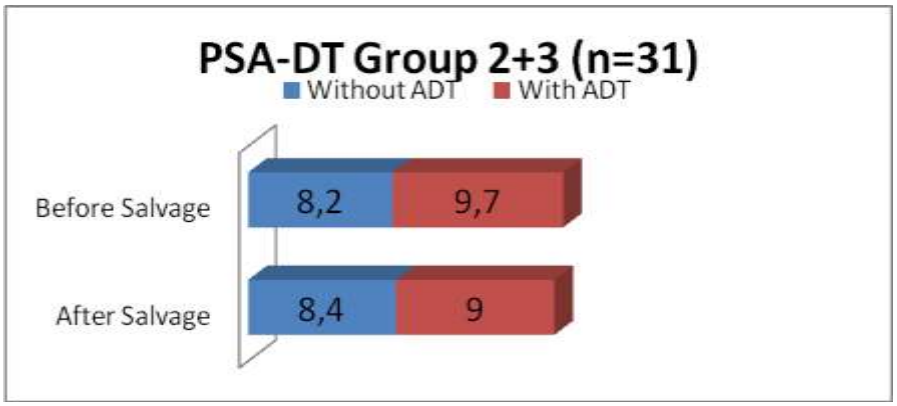
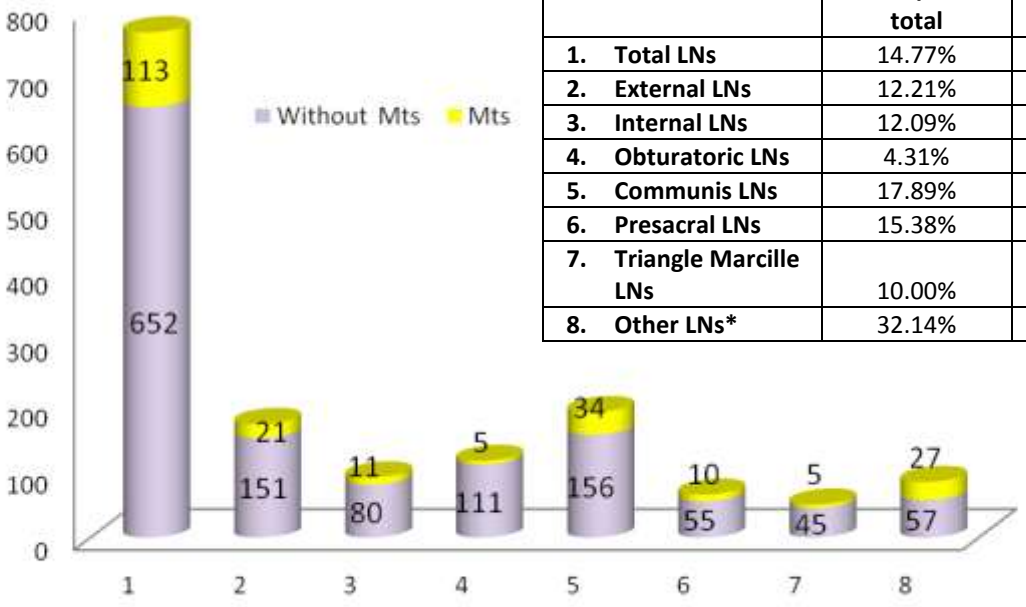


Diagram 6. ***Localisation of LN Metastasis (in all 41 patients after sRP and SePLND in a total of 46 salvage operations). Average of removed LNs per operation: 16.6. n=765 (LNs in total).***



	LNs+ / LNs total	n LNs
1. Total LNs	14.77%	765
2. External LNs	12.21%	172
3. Internal LNs	12.09%	91
4. Obturatoric LNs	4.31%	116
5. Communis LNs	17.89%	190
6. Presacral LNs	15.38%	65
7. Triangle Marcille LNs	10.00%	50
8. Other LNs*	32.14%	84

** interiliacal (26/4), paraaortal (43/16), paracaval (6/5), promontorium (6/2), mesenterical (3/0)*

Diagram 7. ***Localisation of LN metastasis (in all 41 patients after sRP and SePLND in a total of 46 salvage operations). n=113 (LNs+ in total)***

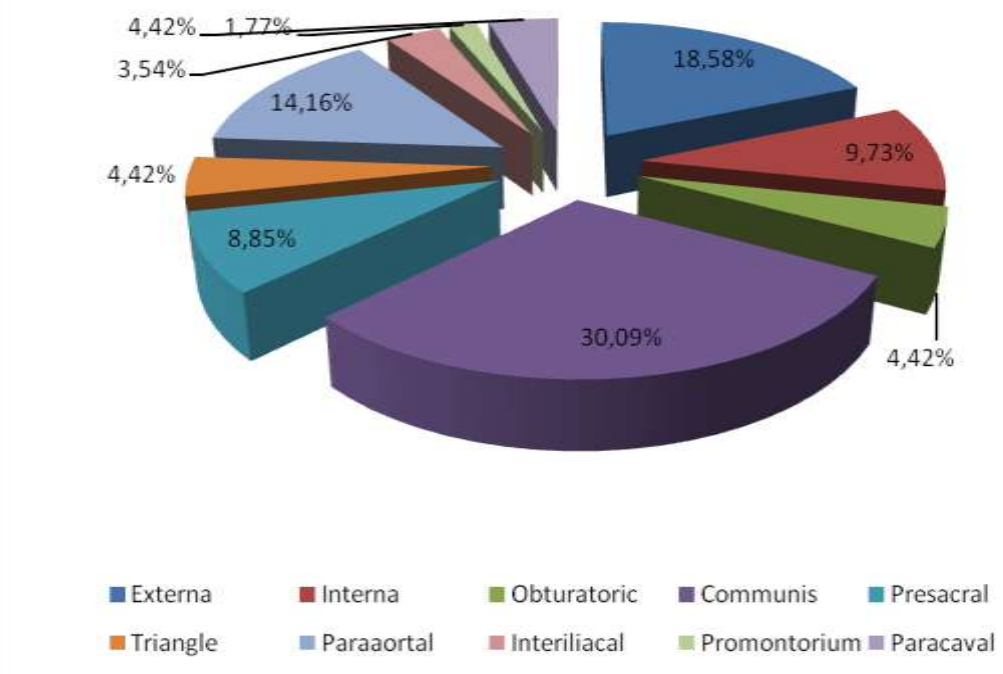


Diagram 8. ***Frequency of N1 stage after all operations.***

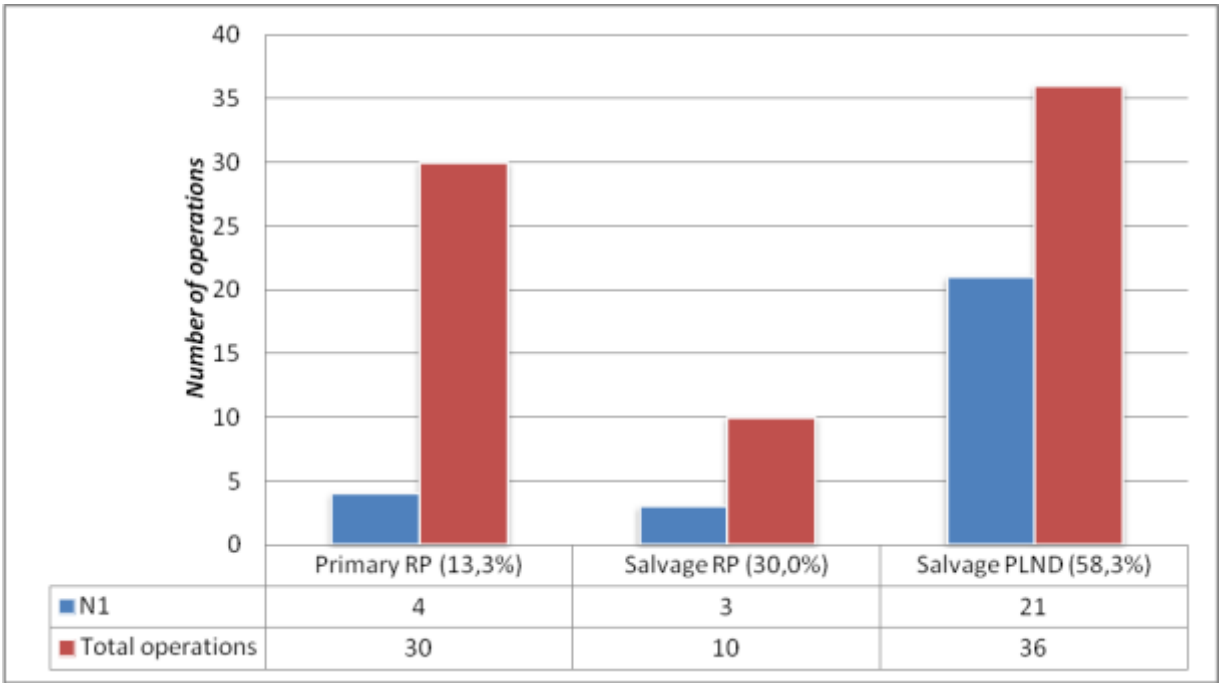


Diagram 9. ***Total number of removed LNs in different operations (n=991 LNs).***

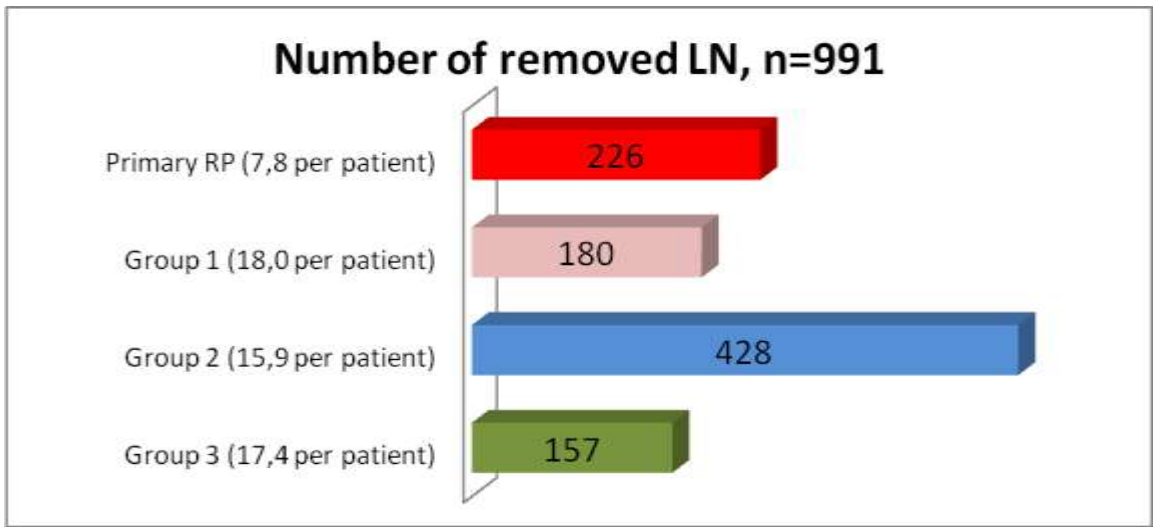


Diagram 10. ***Frequency of positive LNs in all operations (n=991 LN).***

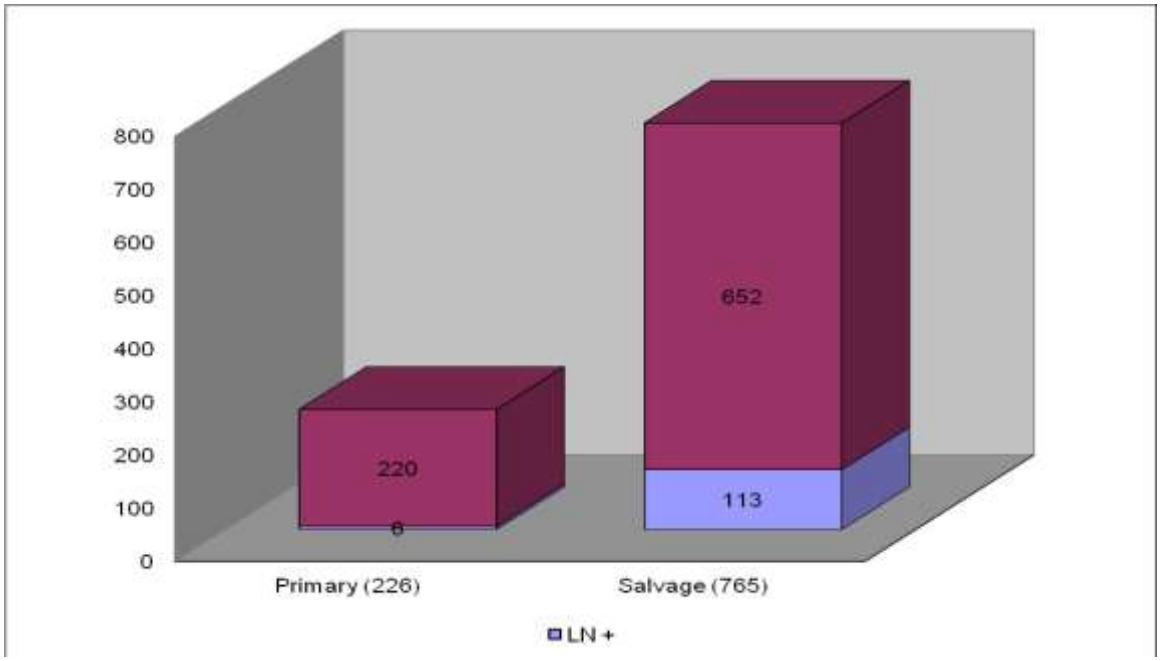


Diagram 11. ***Correlation between the number of removed LNs per operation and frequency of positive LNs.***

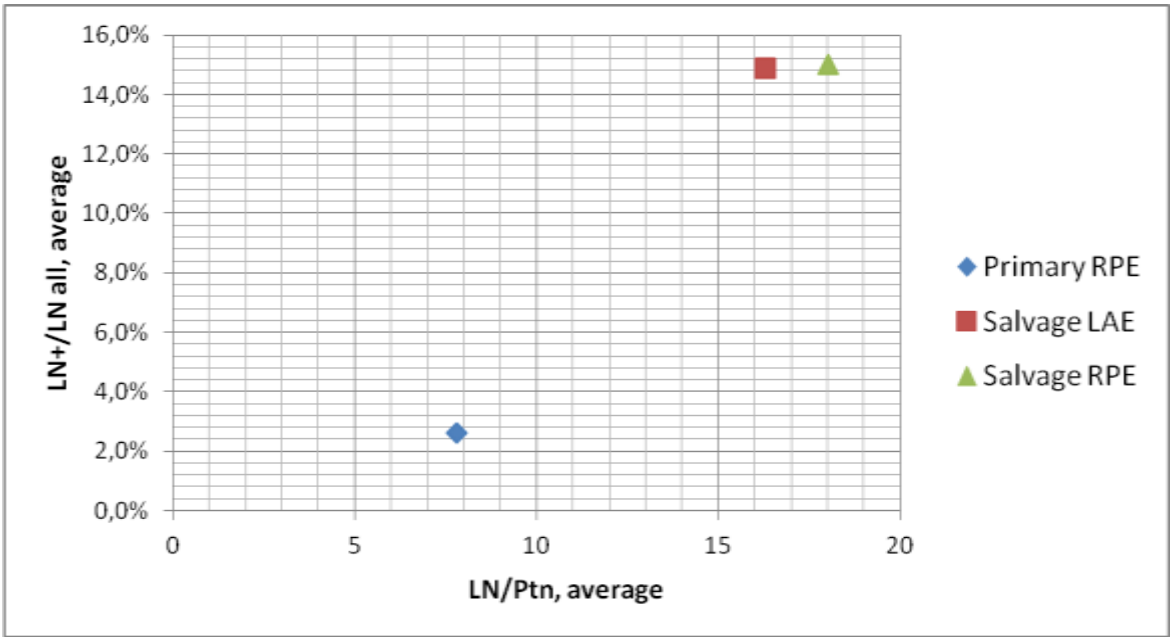


Diagram 12. ***Types of radiotherapy used in study.***

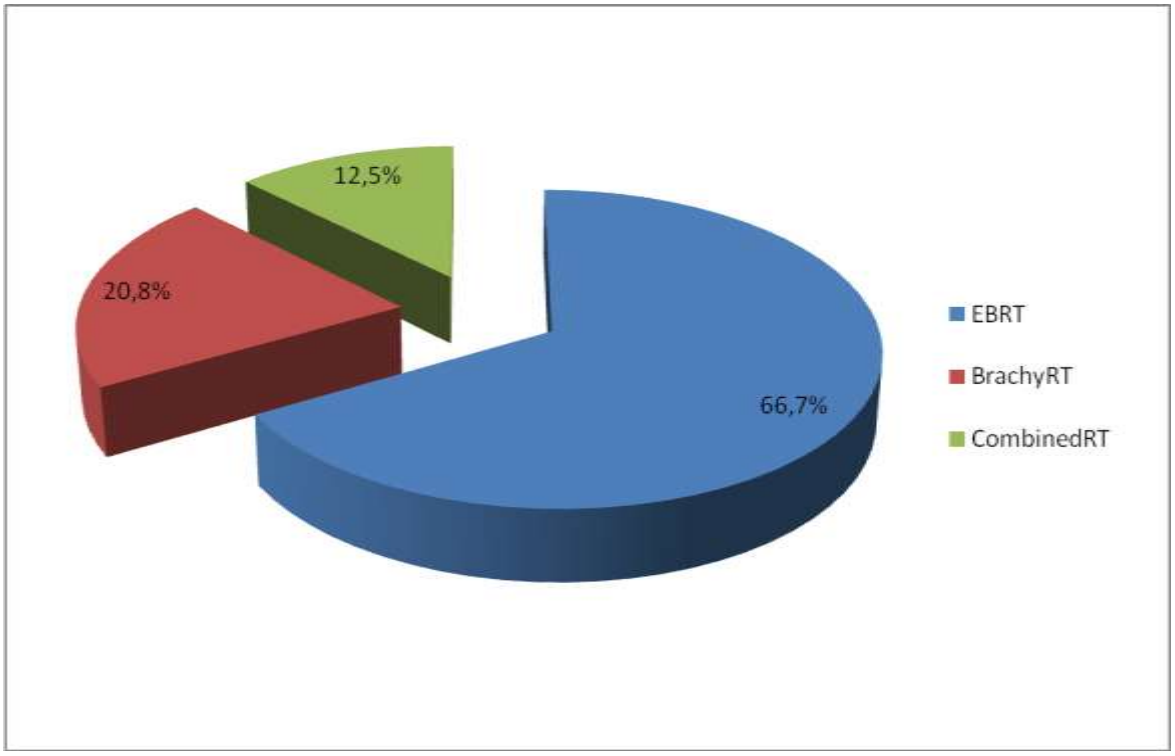
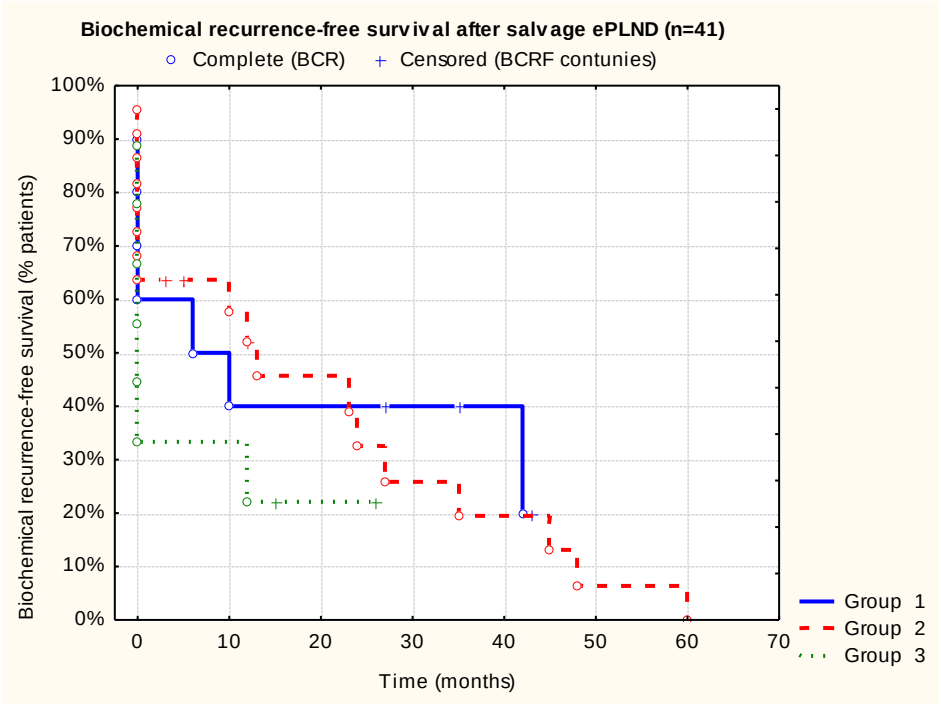


Diagram 13. ***Kaplan-Meier curve with analysis of BRFS in 3 groups (n=41).***



ACKNOWLEDGEMENTS

I would like to heartily thank Dr. D.K. Osmonov for the opportunity to be involved in this study, to perform the operations together, for his consistent support, his sage advice and teaching. He instilled in me the belief that the work will be carried through. Without him this study would not have been possible.

I would like to express my deep gratitude to Prof. Dr. K.-P. Jünemann for the opportunity to be involved in this study, for his support and interest in this work, for wise advice and improvement. I hope to continue my work under his guidance.

I would like to sincerely thank Ms. Kalz for her kind editing of the English text, for the extensive work that she has kindly done.

I would like also to thank Prof. Andrey N. Gerasimov from the First Moscow State Medical University I.M. Sechenov for his professional help in the statistical analysis of our data.

Furthermore, I would like to sincerely thank all staff members of the Department of Urology and Pediatric Urology in Kiel for the friendly attitude and assistance.

I am also very grateful to my family for moral support.

I hope that the obtained results will help patients with recurrent prostate cancer in prolonging their lives and in improving their quality of life.

SHORT BIOGRAPHY

Name: Aksenov Alexey Vyacheslavovich.

Date of birth: November 01 1983.

Birth place: Novosibirsk, Russia.

Status: Married, 1 Child.

Contacts: mob. +49 1523 3967656 (Germany); +7 (916) 654 74 36 (Russia).

alexey.aksenov@uksh.de aksenov.1@mail.ru

Education: 2014 – completed the radiological protection course (Kiel, Germany).

2013 – completed the german approbation examination in human medicine.

From 12.06.2012 – resident in University Hospital Schleswig-Holstein, Campus Kiel, Department of urology and pediatric urology.

01.02.2011 – 10.05.2012 - worked as urologist in Clinic of Urology (First Moscow State Medical University I.M. Sechenov, former Moscow Medical Academy), Moscow, Russia.

2011 – completed the «Ultrasound in urology» course.

18.04.2011: become a PhD degree in Russia.

2008 – 2011: doctorand at the Department of Urology, Moscow Medical Academy I.M. Sechenov.

September 2009 – February 2010: scientific and practical training period in University Hospital Schleswig-Holstein, Campus Kiel, Department of urology and pediatric urology. Begin to work in postgraduate thesis, sighed up as doctorand in Kiel University.

2008 – completed the «Basics of Andrology» course.

2009 – completed and defended a course paper at the Department of Paedogogics, Moscow Medical Academy I.M. Sechenov; got a certificate «High School Teacher».

2006-2008 – resident at the Department of Urology, Moscow Medical Academy I.M. Sechenov.

2000-2006 – student at the Medical Faculty, Moscow Medical Academy I.M. Sechenov.

Research experience: 2009 – present: working on the doctoral thesis in University Hospital Schleswig-Holstein, Campus Kiel, Department of urology and pediatric urology.

2008 – 2011: worked on the post-graduate thesis and 18.04.11 become a degree PhD in Moscow, Russia. Also took part in research works dealed with the immunohistochemistry of hydronephrotic kidney, the minimal-invasive treatment of urolithiasis. Participated at number of conferences and forums. Co-author of twenty scientific articles.

Speciality: Urology.

Post-graduate thesis: Complications of endoscopic operations on the ureter, their prophylaxis and treatment (Russia).

Extended salvage pelvic lymph nodes dissection in patients with recurrent prostate cancer. Database of Kiel University (Germany).

Clinic (base): Since 06/2012 - University Hospital Schleswig-Holstein, Campus Kiel, Department of urology and pediatric urology (head by Prof. Dr. Juenemann K.-P.).

Till 05/2012 - Clinic of Urology, First Moscow State Medical University I.M. Sechenov (head by Prof., Corresponding Member of the Russian Academy of Medical Science, President of Russian Urological Society Y.G. Alyaev).

Scientific advisor: Dr. D.K. Osmonov (Ger); Prof. Dr. L.M. Rapoport (Rus).

Foreign languages: Studied English in Moscow („Advanced English for medical students" (4 semesters) - excellent mark) Completed post-graduate English course for medical professionals. 1999 – studied English at Suzanne Sparrow Language School, Plymouth, UK.

Studied German in Germany, Kiel University; in Moscow Goethe-Institute (has obtained Goethe-Certificate B2, Kiel University-Certificate C1).

Articles in central medical press: 20.