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Persistent PSA after radical prostatectomy and its impact on oncologic outcomes

Dissertation

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Research question

Being Europe´s most common malignancy in men and the 2nd most common in the world, prostate cancer (PCa) has gained an important interest in the last decades for public health policies. [1]

The clinical use of prostate specific antigen (PSA) , a serine protease from the kallikrein family, as a tumor marker in the decade of 1980´is considered one of the most important achievements in detection of prostate cancer.[2]

According to the European Association of Urology (EAU) guidelines the use of digital rectal exam along with PSA measurement are consider the first approach when considering PCa.[3].

As for the treatment, radical prostatectomy (RP) is offered as a gold standard in selected patients offering good long term oncological results in those patients with localized and locally advanced prostate cancer.[4,5]

The follow-up guidelines until 2018 included the measurement of PSA 3-months after RP but in 2019 an update included the possible value of persistent PSA at 6 week after RP. [3,6]. Nevertheless recent evidence has shown that PSA values could be undetectable 6 weeks after surgery.[7] This finding has been subject of different investigations that discuss clinical value of persistent PSA, defined as ≥0.1ng/ml, and it´s impact in terms of recurrence, metastasis as well as mortality.[8–10] Unfortunately the available data is scarce and offers some limitations that impede us to set new clinical standards.

The aim of this research was to established the real impact of persistent PSA at 6 weeks in long term oncological outcomes and to assessed the factors that could lead to persistent PSA values after radical prostatectomy. For these reasons we included 11,604 patients that underwent RP in a high volume center (Martini Klinik, Hamburg) between 1992-2016.

The patients were stratified in two different groups, according to their PSA values at 6 weeks after RP; either persistent PSA (≥0.1ng/ml) or undetectable PSA (≤0.1ng/ml). Then both groups have been compared in terms of metastasis-free survival (MFS), overall survival (OS) and cancer-specific survival (CSS) rates.

Generalities

Anatomy of prostate

The prostate is the largest male accessory gland and is located in the pelvis anterior to the rectum, posterior to the pubic symphysis and distal to the bladder. Usually described as "walnut-shaped", the prostate measures approximately 4x3x3cm. and has a conical form with the base attached to the bladder, the apex pointing the urogenital diaphragm and perforated by the urethra.[11,12] Laterally, the prostate is embedded into the endopelvic fascia along with the levator ani muscle fibers. Posteriorly, the Denovillier´s fascia is the anatomical limit between the rectum and prostate.

The prostate derives from the urogenital sinus during the embryological stage approximately at ten weeks and its development is promoted by the presence of testicular androgens.[13]. The glandular components merge from the endoderm while muscle and stroma do so from the mesoderm.

The prostate is divided into three main zones: central, transition and peripheral zones, which represent 25%, 70% and 5% of the gland´s volume, respectively. The peripheral zone is where most cancers develop accounting for approximately 70% of the cases followed by the transition zone (20-25%) and central zone (5-10%). Beside these zones, a fibromuscular stroma is described as a thickened area localized at the apex, which lacks glandular tissue and is primarily composed of connective tissue and muscle fibers. Finally, the gland is surrounded by a pseudo-capsule composed of a thin layer of connective tissue mainly elastin and collagen. [11]

The blood supply of the prostate usually arises from two different pathways, commonly derived from the gluteopudendal artery, which are the vesiculo-prostatic artery responsible for the cranial irrigation and the prostatic artery for the caudal section. The venous drainage is given mainly by the capsular vessels which end into the dorsal venous complex also known as "Santorini complex" located posterior to the pubis. Auxiliary drainage is given by anteroinferior and deferential veins. The lymphatics drain mainly into the obturators and internal iliac node chains. Additionally, secondary drain pathways lead to external iliac and presacral nodes. [11,14] The "Batson" venous plexus has been suggested to be a possible pathway for bone metastases and is represented by a group of valveless veins that connect the internal iliac to the vertebral plexus.

The prostate innervation is provided by the prostatic plexus which includes sympathetic and parasympathetic fibers. The sympathetic fibers emerge from the hypogastric plexus between T10 and L2, whereas the parasympathetic arise between S2 and S4.[14]

Running from superior to inferior at the posterolateral sides of the prostate, the neurovascular bundles contain nerves which are responsible for the erectile function. These structures should be identified when a nerve sparing surgery is intended in order to maximize benefits regarding functional outcomes.[15,16]

The seminal vesicles (SV) are paired sacs located posterior to the bladder base arranged in a highly coiled structure and have a volume capacity of 3-4 ml. . Arising from the Wolffian duct, the SV´s development depends on the presence of testosterone. The ducts arising from the seminal vesicles merge with the vas deferens and give rise to the ejaculatory duct, which ends in the verumontanum inside the prostatic urethra.[11] The arterial supply is provided by the vesiculo deferential artery, a branch of the umbilical artery, and the seminal vesicle´s lymphatics drain into internal iliac nodes. [17]

Hypothalamic Pituitary Gonadal axis

Testosterone is the major circulating androgen, of which 95% is produced in the testes by Leydig cells upon luteinizing hormone (LH) stimulation. It is a steroid hormone and is responsible for male sexual differentiation.

Gonadotropin-releasing hormone (GnRH), secreted by the hypothalamus in a pulsatile way, stimulates the biosynthesis of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the adeno-hypophysis. These hormones will act in the testes in order to maintain testosterone production and spermatogenesis. Negative feedback given by testosterone itself to inhibit GnRH secretion, is one of the mechanisms to maintain hormone production in normal levels.[18]

With a relative short half-life of about 12 minutes, testosterone can be found free in blood in small amounts. The remaining circulating testosterone is either loosely bound to albumin or tightly bound to sex hormone-binding globulin (SHBG). It follows a pulsatile secretion cycle, with a peak during the morning. The term “bioavailable testosterone” refers to the amount of free hormone plus the one bound to albumin and is about 2% . [19]

Testosterone binds to the androgen receptor (AR) which is then internalized to the nucleus in order to enhance the production and secretion of growth factors.[19]

Approximately 5% of testosterone is converted into dihydrotestosterone (DHT) by the 5α-reductase enzyme. DHT binds with greater affinity to the AR and with a 5-fold faster dissociation rate when compared to testosterone. Due to its stronger effects, DHT has a determinant action regarding prostate growth.

Histology

The prostate epithelium is a two layered cell epithelium where luminal or secretory cells and basal cells are present. Between the basal-cell layer, neuroendocrine cells can be found. The prostatic stroma is composed of fibroblasts, smooth muscle cells and nerves.

The most popular histological grading system is called the "Gleason score" and was proposed by Dr. Donald Gleason in 1966. It ranges from 1 to 5 based on the extent of glandular differentiation and pattern of growth, where 1 is the most differentiated and 5 the least. One

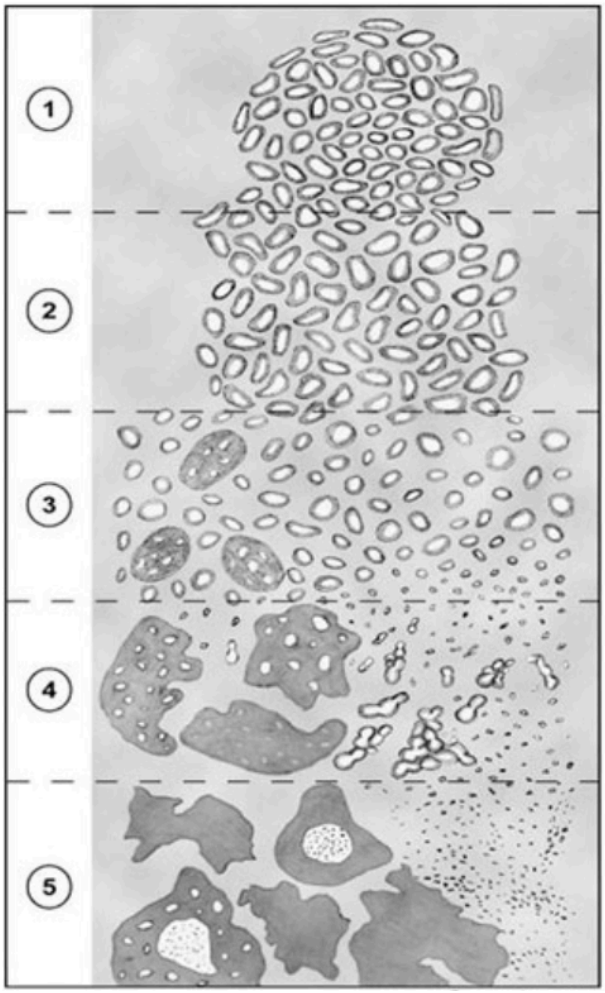


Figure 1 Modified Gleason system. Note cribriform glands are only seen in patterns 4 and 5. Poorly formed glands are also component of pattern 4. Courtesy (Jonathan I. Epstein 2010)[22]

interesting feature of the grading system is that the final score is based not just on the worst grade but on the sum of the two most common patterns. [20] [21]. In 2005, a modification to this grading system was proposed by the International Society of Urological Pathology (ISUP) Consensus Conference. As result of this modification, the ISUP consensus agreed on modifying criteria for the cribriform pattern, avoid reporting low grade cancer diagnoses (Gleason pattern 1 or 2) done by needle biopsy, ignore low grade cancer < 5% when it coexists with high grade cancers, report tertiary grade when present and how to deal with multiple Gleason patterns in several cores. [22] .

Based on the Gleason Score, in 2013 a new grading scale was developed to ensure a better and more accurate prognosis. The authors established 5 groups (I-V) as follows: Gleason score ≤6 (grade group I), Gleason score 3+4=7 (grade group II), Gleason score 4+3=7 (grade group III), Gleason score 4+4=8 (grade group IV) and Gleason score 9-10 (grade group V). This new grading system appears to be more accurate in grade stratification and offers a simplified grading, I being the lowest possible grade instead of 6 as the commonly used Gleason score. [23] [24]

Epidemiology

Being the second most common malignancy in men and the 6th leading cause of death, PCa has gained wide interest in public health policies. [1]

PCa incidence has been continuously increasing, which may be attributed to various reasons. Firstly, it is an age-related cancer, as the population´s life expectancy increases, so does the incidence of PCa. Secondly, numerous public health programs for PCa detection have been adopted in an effort to promote disease awareness and early detection. Finally, better diagnostic tools have been introduced in the market with a direct impact in PCa incidence.

Since the introduction of prostate-specific antigen (PSA) as biomarker in late 1980´s, the incidence rate has risen. A shift in detecting early stage prostate cancer was noticed, which in turn caused a direct effect in the mortality rate. [25]

The highest incidence rates are observed in developed countries such as Australia, North America and Western Europe. However, the world´s PCa overall mortality seems to be decreasing due to two main factors: a shift toward early diagnosis, raising patients´ chances for

receiving curative treatment, and the improvement of new treatments such as radical prostatectomy, hormonal or radiation therapies. On the other hand, an increase in the mortality rate observed in some countries has been explained by the limited access to healthcare services and screening.[26]

The most important PCa risk factors are: advanced age, African-American race and hereditary factors including the number of first-grade affected relatives. [27] More recently, an association between PCa and hereditary breast cancer has been described. The increased risk for PCa of 21% suggests an important role of BRCA gene mutations in carcinogenesis. This risk seems to be greater if a relative´s diagnosis was done at a younger age (<60 years) and may carry a more aggressive disease. [28]

Prevention and chemoprevention

Several studies have tried to identify factors that could prevent PCa, unfortunately the results have not been as successful as expected. This is the case of the SELECT trial, which tried to elucidate the beneficial impact of vitamin E (alpha tocopherol) and/or selenium supplementation in the incidence of PCa incidence. The trial failed to prove any benefit and was suspended before the final phase. Further analysis found an increased risk of prostate cancer in the vitamin E supplementation group of about 17%.[29]

Other examples of chemoprevention worth mentioning are the Prostate Cancer Prevention Trial (PCPT) and the REDUCE trial which intended to demonstrate the PCa incidence reduction after the administration of a 5α-reductase inhibitors.

The PCPT trial showed a decrease in prostate prevalence after a 7-year period of finasteride administration, which is a type-2 DHT inhibitor. The researchers reported up to 24.8% prevalence reduction in patients receiving finasteride. The second study called "Reduction by Dutasteride of Prostate Cancer Events" (REDUCE) described similar results when administrating dutasteride as a dual DHT-inhibitor (Type and Type 2). [3031]

No recommendations followed these findings because after careful analysis the greater effect was observed in low grade tumors that can generally be managed in a conservative manner avoiding unnecessary drug-related secondary effects. It also raised special concern when a

higher number of high-grade (Gleason 8-10) cancers were detected which was explained by the prostate´s volume reduction making easier to be discovered by DRE and biopsy.

Other factors such as obesity and prostatic chronic inflammation as promoters of carcinogenesis are being currently investigated[32]

Population screening

Early detection of PCa is one of the cornerstones of successful treatment. As previously discussed, many factors may modify PSA values making it cancer unspecific and dependent on multiple conditions. The arbitrary limit for the total PSA in serum has been set to 4ng/ml, nevertheless a recent study proposed new cut-off values to improve detection while reducing 7.5% of unnecessary prostate biopsies. In this study, the number needed to screen in order to avoid one biopsy was 13.3 using a PSA value of 1.75ng/ml for men <49 and 50-59 years, 2.25 ng/ml for men between 60-69 years and 3.25ng/ml for men over 70. [33]

Diagnosis

Prostate cancer suspected on the basis of abnormal DRE and/or PSA elevation. However, a definitive diagnosis is only reached through histopathological analysis.

Digital rectal examination

DRE is a clinical diagnostic method, in which the physician assesses the prostate in search for abnormalities such as nodules, tissue induration and/or asymmetry. Less than 20% of PCa cases are detected with DRE alone but its positive predictive value is enhanced when PSA values are >4 ng/ml [3435]. DRE cannot be obviated because up to 8% of patients may have an abnormal DRE despite the PSA value being normal.[36]

PSA

Serum PSA is a serine protease belonging to the kallikrein family, also known as human Kallikrein peptidase 3 (h*K*3) and is synthesized exclusively in the prostate gland by epithelial cells. Although it was first described in 1970, it was until the late 1980´s when it became clinically important as a diagnostic tool for PCa.[2] PSA is responsible for the dissolution of the seminal gel through its action on semenogelin and fibronectin.

Being a biomarker that is only produced by prostatic tissue, it has gained an important role in screening, diagnosis and follow-up not just for monitoring patients in active surveillance but

also after radiotherapy or surgical treatment. Nevertheless, one of its major drawbacks as a tumor marker is that it lacks specificity and can be altered by benign processes such as infections, gland size, activities, infections, benign conditions and/or gland stimulation (i.e. after a DRE).

After PSA was introduced in the 1980´s, it increased the incidence of prostate cancer and created a shift to early-stage diagnosis. [37].
Due to the above-mentioned PSA disadvantages, efforts have been made to accurately detect PCa while avoiding overtreatment, in other words, to increase the specificity for detecting high-grade cancers.

The majority of circulating PSA is found bound to protease inhibitors (complex PSA) while a small percentage (5-10%) is found in the free state (unbound) also known as free PSA (fPSA). The complex PSA molecule is mainly bound to ∝ -1-antichymotrypsin (ACT) (65-95%) and in a lower percentage to ∝ -1-protease inhibitor (API) (5-10%) and ∝ -2-macroglobulin (A2M) (1-2%). [38]

The fPSA to total ratio is routinely used to increase PSA specificity in detecting PCa and to avoid unnecessary biopsies. When setting a cut-off value of 25%, this ratio was able to detect up to 95% of prostate cancers while avoiding up to 20% of unnecessary biopsies in patients with normal DRE and PSA between 2-10.0 ng/ml [39].

A precursor of PSA , "proPSA" has emerged as a potential PCa serum marker. In normal prostate tissue, other forms of proPSA containing propetides of 2,4 and 7 amino acids coexist named (-2)proPSA, (-4)proPSA, and (-7)proPSA, respectively. These precursors have shown to be useful in improving PCa detection, especially in patients with PSA in the 'grey zone'. (-2)-proPSA has gained particular interest due to its overexpression in PCa patients and even being able to discriminate between PCa and benign prostatic hyperplasia (BPH).[40]

PSA density (PSAD) is a quotient of serum PSA and prostate volume (where *prostate volume= length X width X depth X 0.5)* and has shown to be clinically useful to distinguish between PCa and BPH. [41] More recently, a correlation between PSAD and PCa aggressiveness has been shown and used as a predictor of surgical outcomes. [42]

PSA kinetics refers to mathematical formulas that assess PSA changes over time. The most accepted are PSA velocity (PSAV) and PSA doubling time (PSADT). The PSAV is expressed in ng/ml/year and the PSADT refers to the number of months that it takes for the PSA level to increase two-fold its value. These calculations have clinical applications, specially PSADT might be useful for diagnostic, prognostic, choosing secondary treatment and follow-up. On the other hand, the true clinical value of PSAV in decision-making has been questioned [43][44].[45][46]. Today, many different methods to calculate PSADT have been described and some institutions offer online calculators that can be accessed free of charge. (https://www.mskcc.org/nomograms/prostate/psa_doubling_time). [47]

Other available biomarkers in Prostate cancer

- Prostate health index *PHI® (Beckman Coulter*): A mathematical model using total PSA (tPSA), % free PSA and a isoform of PSA proenzyme [−2]proPSA (p2PSA)] to enhance specificity in PCa detection. [48]
- 4K Score : Uses a panel of four different kallikreins tPSA, %fPSA, PSA and hK2 along with age and clinical findings in the DRE. [49] Although it showed to decreased unnecessary biopsies, it still missed 12% of high grade cancers. [50]
- SelectMDX® (MDx Health, Irvine, USA): Test based on a urine sample after DRE. It measures mRNA of a 3-gene panel (TDRD1, DLX1 and HOXC6). Apart from the laboratory results, the test includes clinicopathologic data (i.e. PSA, age, transrectal ultrasound (TRUS) results, prostate volume, history of prostate biopsies, clinical TNM stage and family history). It has been accepted as a less invasive diagnostic tool for detecting PCa particularly in patients with Gleason score >7 .[51] [52]
- ConfrimMDx® (MDx Health, Irvine, USA): Biomarker test that focused on the methylation status of gluthathion-S-transferase P1(GSTP1), adenomatous polyposis coli (APC) and Ras association domain-containing protein 1 (RASSF1) through a multiplex quantitative methylation specific polymerase chain reaction assay, indirectly reflecting the level of cancer present in the DNA even when normal histology is reported. The test enhanced prostate cancer detection and reduced the number of re-biopsies with a negative predictive value of 90% (senility 68%, specificity 64%) [53]
- PCA3 (Progensa, Bedford, USA): Urine test performed after a 15-30 second prostatic massage where the first 20-30 ml of voided urine are collected for analysis. It has a sensitivity of 74% and specificity of 91% for predicting a positive biopsy in patients

with PSA levels less than 4 ng/ml and might play a role as a prognostic factor in active surveillance.[54]

- Mi prostate score urine test MiPS (University of Michigan, Ann Arbor, USA): Based on the findings regarding an augmented fusion rate between Transmembrane protease serine 2 (TMPRSS2) and members from the ETS transcription family (ERG and ETV1) in prostate cancer. MiPS combines PCA3 and TMPRSS2:ERG as a predictor for the presence of PCA and also high-grade PCa on biopsy [55] [56]
- ExoDx® Prostate intelliscore (EPI; exosome diagnostics Boston , USA): Urine samples without DRE are analyzed to extract exosomal RNA to quantitively measure PCA3 and gen ERG using reverse transcription. The sum of normalized PCA3 and ERGRNA levels (called EXO106) might offer a benefit to men with serum PSA in the "grey zone" and translate in fewer unnecessary biopsies. [57]

Prognostic Markers

- Oncotype Dx genomic prostate score® (Genomic health, Redwood City, USA): Gene expression signature that measures 12-cancer related genes and 5 reference genes that are algorithmically combined. A Genomic Prostate Score (GPS) is obtained by these 17-genes which are quantified using reverse transcriptase polymerase chain reaction. The score, which ranges from least aggressive to most aggressive (0-100) intents to improve the decision-making process in active surveillance by reducing undersampling.[58] [59]
- Polaris® (myriad Genetics Inc. Salt Lake City USA): Quantitative measure of the expression of 31 genes using reverse transcriptase polymerase chain reaction (RT-PCR). These values are then used in a mathematical score called cycle progression score (CCP-score), which takes into account overexpression and underexpression of cell cycle regulators. The score has shown to be a useful tool for predicting biochemical recurrence, metastatic disease, patient stratification and cancer specific survival in patients undergoing watchful waiting. [586061]
- ProMark® (metalmark, Cambridge, USA).- Using a quantitative proteomics approach, this test uses 12-biomarkers that predict "lethal disease" and "cancer aggressiveness", in terms of surgical Gleason and TNM stage.[62]
- DNA-Ploidy: Based on the rationale that a normal cell which contains two sets of equivalent chromosomes "diploidy", any addition or deletion of chromosomes is conceived as "aneuploidy". Aneuploidy has been linked to a negative impact or poor

prognosis in the cases of high Gleason scores. The measurement of ploidy might enhance prognostic values when added to available models.[63]

- Decipher® (GenomeDX, Vancouver, Canada): The test analyzes 22 genes involved in aggressive PCa. The specific gene expression patterns were first proposed as a guide in decision-making for patients with recurrent disease.[64] It has also been studied as predictor for biochemical recurrence and distant metastasis, and might lead to significant changes regarding therapy in high-risk patients. [6566]

Prostate biopsy

It is a confirmatory test for PCa when suspicious persistently elevated PSA or DRE is abnormal. It is worth mentioning that a single abnormally elevated PSA must never trigger a biopsy and should be confirmed after a few weeks while other causes of elevation should be excluded (ejaculation, manipulation , infection)[3]

Although patient preparation prophylaxis has been a subject of controversy, the administration of a single-dose antibiotic to decrease the risk of infectious complications is widely accepted [67]. Fluoroquinolones are the most commonly used drugs but others have also been described, such as trimethoprim-sulfamethoxazole, both of them showing benefit in decreasing urinary tract infections ($p < 0.02$, < 0.05 respectively) when compared to placebo.[68]

In general, pain related to transrectal ultrasound-guided prostate biopsy (TRUS biopsy) is well tolerated after the infiltration of 10-ml of lidocaine 1% at the apex and/or neurovascular bundles, significantly reducing pain when compared to placebo.[69]
Besides pain and infection, the most common complication is self-limited bleeding evident as hematuria or hematospermia. Other common complications, such as erectile dysfunction (ED) or lower urinary tract symptoms (LUTS) usually resolve completely after a short period of time.[70]

The relationship between the number of cores and the complication rate has been subject of debate, making it unclear to determine the exact number of cores to be taken in order to avoid missing the diagnosis while also lowering related complications.

The sextant method described in late 1980´s by Hodges, is a random systematic sampling that substituted the TRUS targeted biopsies of hypoechoic lesions. [71] Later on, adding samples to

the standard sextant scheme was proposed by taking them from the lateral and medial aspect which in turn traduced into a better diagnostic yield.[7273] On the other hand, a modified 8-core scheme showed similar cancer detection rates when compared to a 10-core scheme.[74] The guidelines establish bilateral biopsies from apex to base and as far posterior and lateral as possible for small prostates and a total of 10-12 cores.[3]

Repeat biopsy should be considered in men with continued suspicion of PCa either by DRE findings, PSA level or PSA kinetics including PSAD, PSAV, and PSA derivatives can be helpful in selected patients.

The use of magnetic resonance imaging (MRI) for targeting biopsy, also known as fusion biopsy (FBX), might show cancer detection benefits and has gained acceptance with a cancer detection rate (CDR) of 26.3% vs 4.4% (p=<0.001) in patients with suspicious imaging and previous negative biopsy.[75]

Saturation biopsy refers to the process in which cores are systematically obtained in order to achieve ≥18 cores. This exhaustive technique is not accepted for an initial biopsy. A 2013 meta-analysis suggested a benefit to patients with PSA <10ng/dl and prostate volume (PV) >55 ml. [76]

A prostate biopsy (Pbx) can be performed either through the transperineal or transrectal route, the first one having a theoretical advantage for longitudinal sampling of the peripheral zone, better anterior sampling and avoidance of the rectum and its flora thereby reducing severe infectious complications like sepsis.[77] The major drawbacks of the transperineal approach are the need of a special template for each patient depending on the prostate size and for it to be performed under general anesthesia or sedation combined either with local or regional anesthesia.[78] Both approaches have revealed to have similar diagnostic rates when performed under expert hands and some authors even propose to combine both approaches to increase the overall cancer detection.[7980]

Staging

PCa staging is essential in deciding treatment options and predicting functional and oncological outcomes. The tumor, node, metastasis (TNM) classification system [81] can be divided into clinical cTNM and pathological pTNM . The 8th and most recent edition published by the

American Joint Committee of Cancer (AJCC) lists the most significant changes compared to previous editions: 1) Organ confined disease is classified as pT2 and no further subdivision is needed. 2) Both Gleason score and Gleason grade groups should be reported. 3) Prognostic stage III can include organ confined disease when PSA >20 ng/dl or GS 9-10. [82]

In the 1990´s, Epstein and colleagues developed clinical and pathological criteria that attempted to identify insignificant tumors which may benefit from non-surgical treatment as the first approach. These criteria include PSA and needle biopsy-related results, including PSAD <0.15 ng/ml, Gleason ≤6 and the presence of fewer than 3 cores in which PCa is present in no more than 50% per core.[83] The National Comprehensive Cancer Network (NCCN) has a grading system for patient stratification based on TNM, Gleason-grade group (GG), and PSA. For the "very low" and "very high" groups, additional variables like PSAD, number of positive cores and % of PCa were included. (Table-1)

Risk group	Clinical/pathologic features		
Very low	• T1c AND • Grade Group 1 AND • PSA <10 ng/mL AND • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[g] AND • PSA density <0.15 ng/mL/g		
Low	• T1-T2a AND • Grade Group 1 AND • PSA <10 ng/mL		
Intermediate	Has no high- or very-high-risk features and has one or more intermediate risk factors (IRF): • T2b-T2c • Grade Group 2 or 3 • PSA 10-20 ng/mL	Favorable intermediate	• 1 IRF and • Grade Group 1 or 2 and • <50% biopsy cores positive[g]
		Unfavorable intermediate	• 2 or 3 IRFs and/or • Grade Group 3 and/or • ≥50% biopsy cores positive[g]
High	• T3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL		
Very high	• T3b-T4 OR • Primary Gleason pattern 5 OR • >4 cores with Grade Group 4 or 5		

Table-1 Data from NCCN guidelines 2019[84]

Initially developed to predict biochemical recurrence in patients undergoing retropubic radical prostatectomy, radiotherapy or brachytherapy in patients with localized disease, the D´Amico risk group stratification has been widely adopted. It uses a pretreatment value of PSA, biopsy Gleason score and the T stage from the AJCC. Stratifying patients as low-, intermediate- and high-risk [85].

Patient stratification according to D´Amico			
	T	PSA	Gleason Score
Low risk	T1c- T2a	≤10ng/ml	≤6
Intermediate risk	T2b	>10ng/ml- ≤20ng/ml	7
High Risk	T2c	PSA>20ng/ml	≥8

Table 2 D'Amico et al. 2006[85]

The EAU risk group classification is essentially based on D´Amico´s classification system but distinguishes between localized and locally advanced disease, the latter having cT3-4 or cN+ as criteria for this category.

Treatment

When choosing optimal treatment, the decision is based on the patient´s risk stratification, patient´s characteristics such as life expectancy as well as patient´s own preferences. The NCCN guidelines offer a good and simple tool for decision-making depending on the risk groups.[84]

Active surveillance (AS)

Treatment strategy for low-risk patients where the patient will be continuously monitored until disease progression is detected and only then an election for definitive treatment can be made. It aims to avoid overtreatment without losing the time frame for curative treatment. Active surveillance in favorable-risk patients has a similar risk for developing metastatic disease and mortality (1.5%) compared to active treatment in long term cohorts. [86] This strategy intends to avoid unnecessary treatments and side effects. Even though the criteria between hospitals might change, it is generally accepted that AS is reserved for low-risk patients or insignificant disease.

Patient´s characteristics usually include PSA<10ng/ml, Gleason ≤ 6, clinical stage ≤T2, PSA density <0.15 NG/ml/g, and ≤3 positive cores ≤ 50%.

Patient´s follow-up protocol is not universal and also depends on each institution´s criteria. Commonly DRE, TRUS and PSA control every 3-6 months have been traditionally accepted as monitoring protocols. For re-biopsy most programs will recommend performing it between 12-15 months. Nevertheless, this criteria is not yet standardized and other parameters are taken

into consideration in an effort to improve decision-making, such as PSA kinetics or other biomarkers whose use is still under debate. [87]

To trigger treatment, evidence of disease progression during follow-up, such as higher Gleason score, number of positive scores or % of cancer in each of the cores are considered.

Watchful waiting (WW)

WW is a type of conservative management, where the patient is followed until he develops local or systemic progression that translates into disease-related symptoms. It is a strategy without curative intention and the main benefit for the patient is lowering treatment-related toxicity. Usually in this group men who are included have life expectancy <10 years, suffering from other severe comorbidities or those who simply refuse treatment.

Active treatment has shown advantages over WW, a study with a long-term follow-up of 29 years showed lower overall mortality, lower prostate cancer and a lower metastasis rate in patients who underwent radical prostatectomy compared to those in watchful waiting with a 2.9 years of life gained.[88]

Radical Prostatectomy

Considered the gold standard of prostate cancer definitive treatment, radical prostatectomy has been described in numerous techniques including open, laparoscopic, robotic with perineal or retropubic approach. It consists in removing the prostate, seminal vesicles and, depending on the risk stratification, the pelvic lymph nodes.

The robotic prostatectomy is currently one of the most common approaches in developed countries. Even though it has shown no benefit in terms of functional neither oncological outcomes that justifies the systematic use of the robotic approach, further investigations are needed. In the USA in 2010, more than 60% of radical prostatectomies were performed robotically. [89].

Extended lymph node dissection (eLND)

eLND has demonstrated great advantage in the staging and prognosis of prostate cancer patients. Nevertheless, it is a time consuming procedure and carries associated morbidity in around 20% of cases.[90] The use of predictive tools, such as nomograms, is a clinical strategy

that aims to identify patients with risk of lymph node invasion (LNI) and reducing the associated complications of unnecessary procedures.

By combining preoperative serum PSA, clinical TNM stage and biopsy Gleason Score, the Partin tables provide an individualized risk for extra prostatic extension and lymph node invasion.[91]

The Briganti nomogram and an online tool from the Memorial Sloan Kattering Cancer Center are available to calculate the risk of LN invasion based on clinical and standard systematic biopsies achieving an area under the curve (AUC) of 82% and 81% respectively [9293].

Additional imaging information provided by MRI and subsequent targeted biopsies have allowed for new models, that might be adopted in the near future, to offer higher AUC (86%) while sparing 57% of eLND and missing only 1.6% of LNI. [94]

Radiotherapy (RT)

RT is a treatment modality that applies a cytotoxic amount or radiation to a desired tissue and can be broadly divided into two large groups according to how energy is delivered: either external or internal (brachytherapy).

Adjuvant radiotherapy ART is indicated in those patients who underwent RP and pathological analysis revealed positive margins. Salvage radiotherapy (SRT) is considered when patients have detectable and rising PSA ≥0.1 ng/dl after RP with no evidence of nodal or distant metastasis.

External Radiotherapy

External beam radiotherapy generally involves the use of gamma radiation beams which are directed at the prostate. Since the photons may induce damage to the surrounding tissues, mainly rectum and bladder, efforts have been made to develop equipment able to focus radiation specifically on the prostate while reducing radiotoxicity to the adjacent tissues. 3D conformal radiotherapy (3D-CRT), intensity-modulated therapy (IMRT) and more recently image guided radiation therapy (IGRT) are some of these examples.

Physicians search for the best balance between delivering an effective dose of radiation and lowering complications and side effects.

Hypofractionation refers to delivering a higher dose per session 2.1-3.5Gy/ fraction for 25 min 5 times a week, during 4 weeks making a total of 52-72 Gy by the end of treatment. Extreme hypofractionation, also known as stereotactic body radiation therapy (SBRT), has been offered to low-risk disease patients and delivers >6.5 GY/daily during 5 or fewer visits. This approach is associated with lower treatment costs but might be linked to higher genitourinary (GU) toxicity. [95]

Brachitherapy

It refers to the transperineal implantation of radioisotopes in the prostate through a hollow needle to deliver radiation at a constant rate. There are mainly two groups of radioisotopes: low dose (LDR) and high dose (HDR). Brachytherapy is not recommended for patients suffering from LUTS, an International Prostatic Symptom Score (IPSS) >12, maximum urinary flow-rate of <15 ml/sec, and for prostates with a size >50cc.[3] In LDR, the most commonly used radioisotopes are iodine^{-125} and palladium^{-103}, and the dose is delivered over a 1-2 month period.[96]

HDR, on the other hand, uses iridium^{-192} and the difference when compared to LDR is that radiation is delivered during temporal implant sessions [96]

Hormone therapy (HT)

It is well known that PCa cell proliferation is affected when low serum levels of androgens are maintained. [97] In line with this rationale, surgical treatments such as bilateral orchiectomy and more recently pharmacological agents targeting the androgen axis, such as luteinizing hormone-releasing hormone LHRH agonists/antagonists have been used as first line choices for hormone dependent PCa. The objective is to reach testosterone levels <50ng/dl, however, recently lower levels <20ng/dl have been recommended.[3]

Either alone or combined with RT, ADT also plays a role as adjuvant therapy. Approximately 30% of the patients who undergo RP may experience an increase in PSA level during follow-up.[9899] ADT, in combination with RT after RP, has shown improvement in oncological outcomes in terms of overall survival, lower incidence of metastatic cancers and deaths from PCa. [100] Nevertheless, the administration of ADT is associated with side effects, such as sexual dysfunction, hot flashes, fatigue and cardiovascular morbidity among many others. For these

reasons, intermittent ADT was investigated as a therapeutic option in selected patients. Intermittent therapy might be beneficial to avoid or minimize side effects in patients with no more than 1 of the following factors: pT stage ≥pT3b, pathological Gleason score ≥8 and PSA >0.5ng/ml at the time of RT. [101]

No matter which therapeutic strategy is selected, most of the tumor cells will react to hormone deprivation´s state through one of the multiple and described biochemical mechanisms, giving rise to castration resistant prostate cancer CRPC.[102] Even for patients with localized CRPC the prognosis is unfavorable since up to 60% will eventually develop metastasis in the first 5 years.[103]

Choosing therapies in patients with CRPC is complex and must be done in an individualized manner, where localization and whether it is hormone sensitive play a fundamental role. Since the discussion of these topics goes beyond the scope of this revision, we will mention agents accepted for the treatment of metastatic castration sensitive prostate cancer, non-metastatic CRPC or metastatic CRPC, such as apalutamide, enzalutamide, docetaxel and abiraterone.[104105106107]

Patients and methods

Study population

After Institutional Review Board approval, patients that underwent radical prostatectomy (RP) (1992-2016), from our institution´s database (Martini-Klinik Prostate Cancer Center, Germany), were identified.

Patients were stratified according to persistent (PSA ≥0.1 ng/ml at six weeks after RP) vs. undetectable PSA (PSA <0.1 ng/ml).

RP was performed with use of an open retropubic or robot-assisted approach, as previously described. [108] Moreover, neurovascular bundle preservation was performed with the intraoperative frozen section technique, as previously described [109110]. All RP specimen were evaluated by dedicated uro-pathologists.

Exclusion criteria consisted of metastasis at time of RP (n=24), unknown pathologic tumor stage (n=11), unknown surgical margin status (n=293), neoadjuvant (n=1,109) and adjuvant androgen deprivation treatment (n=356). Finally, patients with unknown PSA at six weeks after RP (n=8,626) were excluded.

These selection criteria yielded 11,604 patients, which represented the focus of the current analysis.

Outcomes

Metastasis was diagnosed by positive imaging for persistent PSA or biochemical recurrence (BCR) (two consecutive PSA values ≥0.2ng/ml after surgery). Imaging procedures consisted of bone scan and/or computed tomography and/or abdominal magnetic resonance imaging and/or 11C-choline positron emission tomography/computed tomography scan (PET/CT) and/or 18F-choline PET/CT and/or Ga-68-PSMA PET/CT. MFS was calculated as time from RP to metastasis or last follow-up. OS was calculated as time from RP to death or last follow-up. Finally, CSS was calculated as time from RP to death attributed to PCa or last follow-up.

Covariates

Covariates consisted of age, year of surgery, preoperative PSA, biopsy/pathologic Gleason grade group (GG), clinical/pathologic tumor stage, surgical margin status and pathologic lymph node status. SRT was defined as radiotherapy delivered for persistent PSA or BCR. The decision to undergo SRT was at the discretion of the urologist. Information on the SRT field (prostatic bed vs. whole pelvis) was unavailable. Median SRT dose was 46 Gray with a median number of 37 fractions and 2 Gray per fraction. However, in 835 SRT patients' (46.0%) detailed information on SRT was unavailable. Information about receipt and duration of androgen deprivation during SRT was not available for all patients.

Statistical analyses

Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges were reported for continuously coded variables. The Chi-square test examined the statistical significance in proportions' differences. The Mann-Whitney U test examined the significance of medians' differences.

Two sets of multivariable logistic regression models tested the relationship between tumor characteristics and persistent PSA. Within the first model adjustment was made for clinical tumor characteristics. Within the second model adjustment was made for pathological tumor characteristics.

Kaplan-Meier analyses depicted MFS, OS and CSS. Three sets of multivariable Cox regression models were fitted to test the relationship between PSA persistence and the oncologic outcomes. Specifically, the first set tested the relationship between persistent PSA and MFS, the second the relationship between persistent PSA and OS and the third the relationship between persistent PSA and CSS. All multivariable Cox models were adjusted for pathological tumor characteristics and Charlson comorbidity index (CCI). Subsequently, multivariable Cox regression models were repeated in the subgroup of patients with exclusively persistent PSA. Finally, 1:1 propensity score matching (PSM) was performed to test the impact of SRT vs. no RT on OS and CSS in patients with persistent PSA. Due to missing data, PSM was not performed to test the impact of SRT on MFS. Matching was performed for tumor characteristics, namely: pathologic Gleason, surgical margin, pathologic tumor stage and lymph node status. With the use of a caliper of 0.4 no significant differences between tumor characteristics were recorded between patients without and with SRT (Study-Table 1).

	Before 1:1 matching			After 1:1 matching		
	No RT (n=455)	**SRT (n=570)**	**p-value**	**No RT (n=253)**	**SRT (n=253)**	**p-value**
Year of surgery, median (interquartile range)	2010 (2004-2014)	2011 (2008-2013)	<0.01	2011 (2003-2014)	2011 (2008-2013)	0.4
Age, yrs, median (interquartile range)	64.4 (59.8-68.8)	65.0 (59.9-69.4)	0.2	64.3 (59.9-68.4)	64.7 (59.5-68.5)	0.8
Preoperative PSA, ng/ml, median (interquartile range)	10.0 (6.1-19.0)	12.1 (7.5-20.0)	<0.001	10.9 (6.5-19.4)	10.6 (6.5-18.6)	0.7
PSA six weeks after RP, ng/ml, median (interquartile range)	0.4 (0.1-2.6)	0.3 (0.1-1.0)	0.6	0.2 (0.1-0.5)	0.2 (0.1-0.4)	0.6
Pathologic Gleason, n (%)						
GG1-2	230 (50.5)	154 (27.0)	<0.001	108 (42.7)	97 (38.3)	0.4
GG3-5	225 (49.5)	416 (73.0)		145 (57.3)	156 (61.7)	
Pathologic tumor stage, n (%)						
pT2	186 (40.9)	89 (15.6)	<0.001	69 (27.3)	82 (32.4)	0.3
pT3a	126 (27.7)	161 (28.2)		99 (39.1)	82 (32.4)	
pT3b	143 (31.4)	320 (56.2)		85 (33.6)	89 (35.2)	
Positive surgical margin, n (%)	121 (26.6)	319 (56.0)	<0.001	75 (29.6)	85 (33.6)	0.4
pN1, n (%)	110 (24.2)	199 (34.9)	<0.001	61 (24.1)	66 (26.1)	0.8

Study-Table 1: Descriptive tumor characteristics of RP patients with persistent PSA at six weeks after RP (≥0.1 ng/ml), stratified according to no RT and SRT, before and after 1:1 matching. Abbreviations: GG – Gleason grade group; PSA – prostatic specific antigen; RP

R software environment for statistical computing and graphics (version:3.4.4) was used for all statistical analyses. All tests were two sided with a level of significance set at $p < 0.05$.

Results

Descriptive Statistics

Of 11,604 identified patients, 8.8% (n=1,025) vs. 91.2% (n=10,579) harbored persistent or undetectable PSA, respectively (Study-Table 2). 10% (n=125) of patients with persistent PSA at six weeks had an undetectable PSA in the subsequent PSA testing. The median follow-up was 61.8 vs. 46.4 months for patients with undetectable and persistent PSA. Patients with persistent PSA were older (median age: 64.6 vs. 64.2 years, p=0.006), more frequently had pathologic GG5 (19.6 vs. 2.5%, p<0.001), more frequently harbored positive surgical margins (42.9 vs. 15.1%, p<0.001), as well as pathologic tumor stage T3b (45.2 vs. 8.1%, p<0.001) and lymph node invasion (pN1) (30.2 vs. 3.7%, p<0.001) compared to patients with undetectable PSA. Moreover, patients with persistent PSA more frequently received SRT (55.6 vs. 11.8%, p<0.001). 16% (n=1,694) of patients with undetectable PSA developed BCR, median time to BCR was 53.0 months.

	Persistent PSA (n=1,025, 8.8%)	**Undetectable PSA (n=10,579, 91.2%)**	**p-value**
Age, yrs, median (IQR)	64.6 (59.9-69.1)	64.2 (59.2-68.3)	<0.01
Preoperative PSA, ng/ml, median (IQR)	11.2 (6.8-19.8)	6.6 (4.7-9.7)	<0.001
Year of surgery, median (IQR)	2011 (2007-2013)	2009 (2005-2012)	<0.001
Pathologic Gleason grade group, n (%)			
1	75 (7.3)	2748 (26.0)	<0.001
2	309 (30.2)	6042 (57.2)	
3	419 (40.9)	1433 (13.5)	
4	21 (2.0)	82 (0.8)	
5	201 (19.6)	265 (2.5)	

Pathologic tumor stage, n (%)			
≤pT2c	275 (26.8)	7565 (71.5)	<0.001
pT3a	287 (28.0)	2156 (20.4)	
pT3b	463 (45.2)	858 (8.1)	
Surgical margin status, n (%)			
Negative	585 (57.1)	8977 (84.9)	<0.001
Positive	440 (42.9)	1602 (15.1)	
Pathologic lymph node status, n (%)			
pN0	566 (55.2)	6516 (61.6)	<0.001
pNx	150 (14.6)	3673 (34.7)	
pN1	309 (30.2)	390 (3.7)	
Salvage radiotherapy performed, n (%)	570 (55.6)	1245 (11.8)	<0.001

Study-Table 2: Descriptive characteristics of patients treated with radical prostatectomy, stratified according to postoperative PSA (persistent PSA vs. undetectable PSA).

Risk characteristics for persistent PSA

In multivariable models, testing the relationship between clinical tumor characteristics and persistent PSA (Study-Table 3), higher preoperative PSA value, advanced clinical tumor stage and more aggressive biopsy GG, were associated with an increased risk for persistent PSA (all $p<0.01$). Conversely, more contemporary year of surgery was associated with lower risk for persistent PSA ($p<0.001$).

In multivariable models, testing the relationship between pathological tumor characteristics and persistent PSA (Study-Table 3), higher preoperative PSA, more advanced pathologic tumor stage, pathologic GG3-5, positive surgical margins and pN1 were associated with an increased risk for persistent PSA (all $p<0.01$). Conversely, older age was associated with lower risk for persistent PSA ($p=0.04$).

	OR	95%-CI	p-value
Clinical model			
Year of surgery	1.04	1.02-1.05	<0.001
Age	0.99	0.99-1.01	0.8
Preoperative PSA	1.05	1.04-1.05	<0.001
Clinical tumor stage T1c (referent)	1.00	-	-
Clinical tumor stage T2a	1.50	1.24-1.8	<0.001
Clinical tumor stage T2b	2.43	1.93-3.03	<0.001
Clinical tumor stage ≥T2c	3.50	2.50-4.88	<0.001
Biopsy GG1 (referent)	1.00	-	-
Biopsy GG2	1.52	1.25-1.85	<0.001
Biopsy GG3	2.73	2.19-3.39	<0.001
Biopsy GG4	3.96	3.12-5.03	<0.001
Biopsy GG5	5.06	3.85-6.64	<0.001
Pathological model			
Year of surgery	1.01	0.99-1.03	0.1
Age	0.99	0.98-0.99	0.04
Preoperative PSA	1.02	1.02-1.03	<0.001
Pathologic stage ≤T2c (referent)	1.00	-	-
Pathologic stage T3a	1.96	1.61-2.38	<0.001
Pathologic stage T3b	3.76	3.02-4.7	<0.001
Pathologic GG 1 (referent)	1.00	-	-
Pathologic GG2	1.25	0.95-1.66	0.1
Pathologic GG3	3.51	2.58-4.82	<0.001
Pathologic GG4	3.96	2.16-7.0	<0.01
Pathologic GG5	4.95	3.41-7.24	<0.001
Negative surgical margin (referent)	1.00	-	-
Positive surgical margin	1.66	1.40-1.95	<0.001
Pathologic lymph node status N0 (referent)	1.00	-	-
Pathologic lymph node status N1	2.32	1.88-2.85	<0.001
Pathologic lymph node status Nx	1.04	0.84-1.28	0.7

Study-Table 3: Multivariable logistic regression models predicting persistent PSA (≥0.1 ng/ml) at six weeks after radical prostatectomy. Abbreviations: GG – Gleason grade group; OR- Odds Ratio; CI – Confidence interval; PSA – prostatic specific antigen.

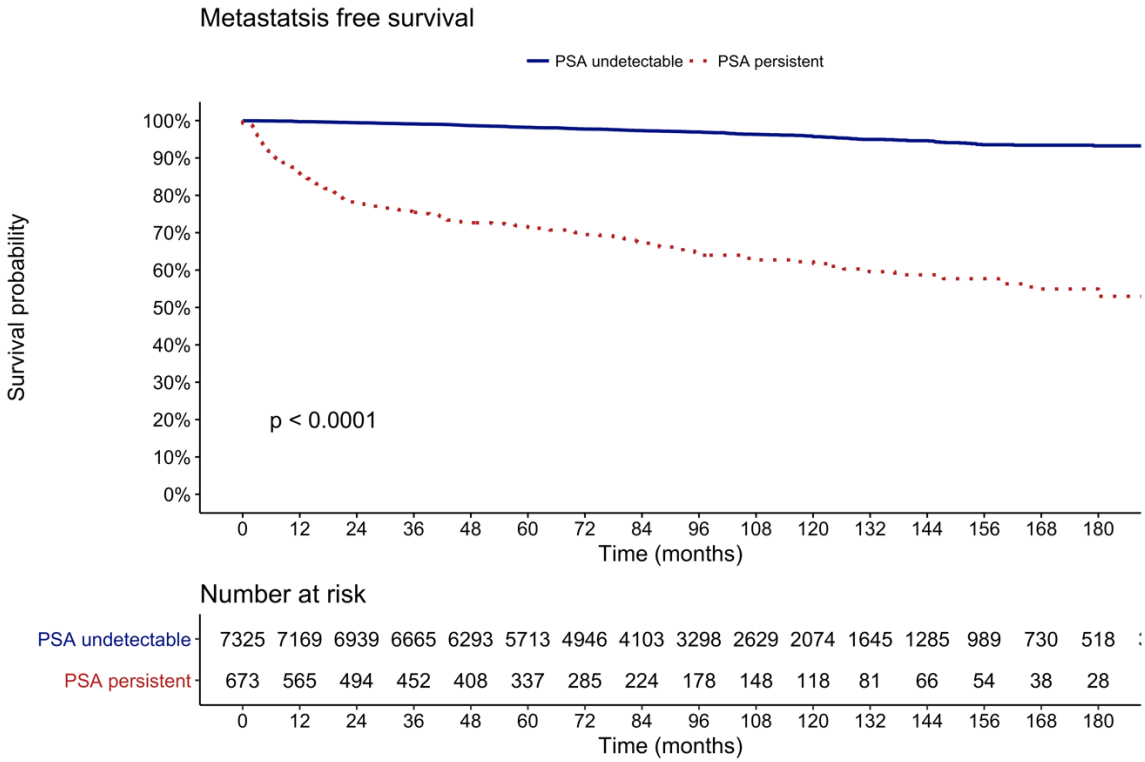
Effect of PSA persistence on MFS

Overall, 221 (21.6%) and 250 (2.4%) patients with persistent and undetectable PSA developed metastasis (p<0.001). Patients with persistent PSA who developed metastasis most frequently harbored M1a disease (n=102). Conversely, patients with undetectable PSA at six weeks who developed metastasis most frequently harbored M1b disease (n=118) (Study-Table 4).

	PSA undetectable	PSA persistent
No metasases	10306 (92.8)	802 (7.2)
Local only	28 (84.8)	5 (15.2)
M1a	101 (49.8)	102 (50.2)
M1b	118 (54.9)	97 (45.1)
M1a+M1b	2 (33.3)	4 (66.7)
M1a+M1b+M1c	1 (33.3)	2 (66.7)
M1a+M1b+M1c +local	2 (100)	0 (0)
M1b+local	0 (0)	2 (100)
M1b+M1c	11 (68.8)	5 (31.2)
M1a+M1b+local	1 (100)	0 (0)
M1c	8 (61.5)	5 (38.5)
unknown	1 (50)	1 (50)

Study-Table 4: Location of metastases stratified according to persistent vs. undetectable PSA at six weeks after RP

At 15-years after RP, MFS (Study-Figure 1) was 53.0 vs. 93.2% ($p<0.001$) for persistent vs. undetectable PSA, respectively. In multivariable Cox regression models, testing the relationship between PSA persistence and metastasis (Study-Table 5), persistent PSA achieved an independent predictor status of metastasis (Hazard ratio[HR]:3.59, 95%-confidence interval[CI]:2.83-4.57, $p<0.001$), after adjustment for all covariates.



Study-Figure 1: 15 year metastasis free survival undetectable PSA vs Persistent PSA

	Predicting metastasis			**Predicting death**			**Predicting cancer-specific death**		
	HR	**95%-CI**	**p-value**	**HR**	**95%-CI**	**p-value**	**HR**	**95%-CI**	**p-value**
Undetectable PSA postoperative	1.00	-	-	-	-	-	-	-	-
Persistent PSA postoperative	3.59	2.83-4.57	<0.001	1.86	1.41-2.45	<0.001	3.15	1.92-5.18	<0.001
Year of surgery	1.23	1.19-1.28	<0.001	0.99	0.96-1.01	0.3	0.92	0.87-0.97	<0.01
Age	0.98	0.96-0.99	0.02	1.08	1.06-1.09	<0.001	1.02	0.99-1.06	0.2
Preoperative PSA	1.00	0.99-1.01	0.7	0.99	0.98-1.01	0.3	0.99	0.98-1.01	0.6
Pathologic stage ≤T2c (referent)	1.00	-	-	1.00	-	-	1.00	-	-

Pathologic stage T3a	2.14	1.56-2.93	<0.001	1.03	0.81 - 1.31	0.8	1.16	0.60-2.25	0.6
Pathologic stage T3b	3.87	2.77-5.41	<0.001	1.63	1.22 - 2.16	<0.001	4.00	2.16-7.38	<0.001
Pathologic GG1-2 (referent)	1.00	-	-	1.00	-	-	1.00	-	-
Pathologic GG3-5	3.60	2.71-4.79	<0.001	1.56	1.22 - 1.99	<0.001	3.36	2.01-5.63	<0.001
Negative surgical margin (referent)	1.00	-	-	1.00	-	-	1.00	-	-
Positive surgical margin	1.05	0.84-1.33	0.7	1.26	1.02 - 1.57	0.03	1.72	1.10-2.68	0.02
Pathologic lymph node status N0 (referent)	1.00	-	-	1.00	-	-	1.00	-	-
Pathologic lymph node status N1	1.48	1.14-1.92	<0.01	1.38	0.95 - 1.99	0.1	1.38	0.78-2.46	0.3
Pathologic lymph node status Nx	0.44	0.30-0.64	<0.001	1.02	0.83 - 1.26	0.8	0.90	0.52-1.56	0.7
CCI 0 (reference)	1.00	-	-	1.00	-	-	1.00	-	-
CCI 1	0.80	0.59-1.08	0.1	1.62	1.28 - 2.07	<0.001	1.35	0.80-2.28	0.3
CCI ≥2	0.85	0.60-1.21	0.4	2.38	1.91 - 2.98	<0.001	0.47	0.20-1.11	0.1

Study-Table 5: Multivariable Cox regression models predicting metastasis, death and cancer-specific death in the entire study cohort.Abbreviations: CCI – Charlson comorbidity index; GG – Gleason grade group; HR- Hazard Ratio; CI – Confidence interval; PSA – prostatic

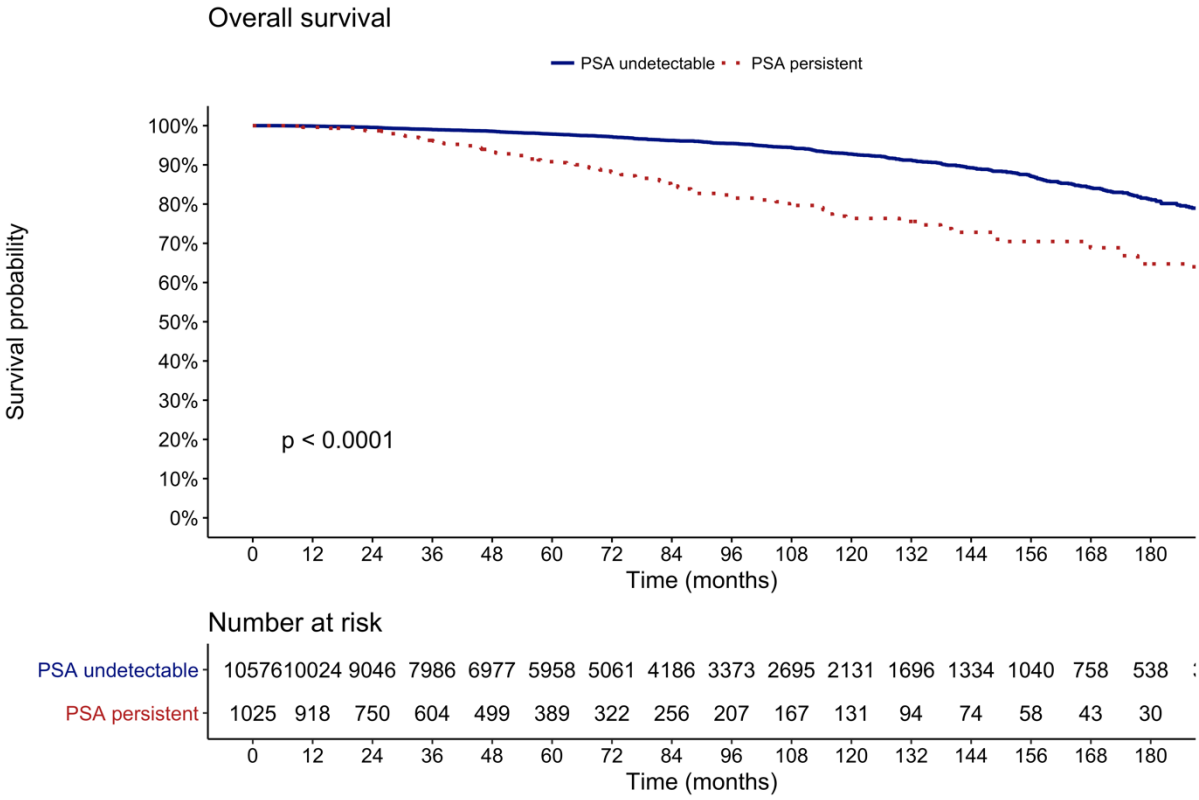
In subgroup analyses, focusing exclusively on patients with PSA persistence (Study-Table 6), pathologic tumor stage T3b (HR:2.01, 95%-CI:1.21-3.35, p<0.01), pathologic GG3-5 (HR:3.17, 95%-CI:1.92-5.24, p<0.001), year of surgery (HR:1.23, 95%-CI:1.17-1.30, p<0.001) and age (HR:0.97, 95%-CI:0.95-0.99, p=0.02) were all associated with higher metastasis risk.

	Predicting metastasis			**Predicting death**			**Predicting cancer-specific death**		
	HR	**95%-CI**	**p-value**	**HR**	**95%-CI**	**p-value**	**HR**	**95%-CI**	**p-value**
Year of surgery	1.23	1.17-1.30	<0.001	0.96	0.91-1.02	0.2	0.91	0.85-0.98	<0.01
Age	0.97	0.95-0.99	0.02	1.03	0.99-1.07	0.2	1.03	0.98-1.10	0.3
Preoperative PSA	1.01	0.99-1.01	0.4	0.98	0.97-1.01	0.1	0.99	0.97-1.01	0.3
Pathologic stage ≤T2c (referent)	1.00	-	-	1.00	-	-	1.00	-	-
Pathologic stage T3a	1.59	0.95-2.66	0.1	1.77	0.70-4.49	0.2	1.95	0.38-10.03	0.4
Pathologic stage T3b	2.01	1.21-3.35	<0.01	2.92	1.16-7.33	0.02	4.48	0.93-21.72	0.1
Pathologic GG1-2 (referent)	1.00	-	-	1.00	-	-	1.00	-	-
Pathologic GG3-5	3.17	1.92-5.24	<0.001	2.49	1.30-4.77	<0.01	5.05	1.76-14.46	<0.01
Negative surgical margin (referent)	1.00	-	-	1.00	-	-	1.00	-	-
Positive surgical margin	0.93	0.67-1.27	0.6	1.60	0.98-2.62	0.1	1.50	0.77-2.93	0.2
Pathologic lymph node status N0 (referent)	1.00	-	-	1.00	-	-	1.00	-	-
Pathologic lymph node status N1	1.32	0.96-1.83	0.1	1.49	0.87-2.54	0.1	1.46	0.71-2.99	0.3
Pathologic lymph node status Nx	0.68	0.35-1.30	0.2	0.79	0.39-1.63	0.5	1.09	0.41-2.86	0.9
CCI 0	1.00	-	-	1.00	-	-	1.00	-	-
CCI ≥1	0.89	0.63-1.25	0.5	1.82	1.07-3.13	0.03	1.06	0.51-2.21	0.9

Study-Table 6: Multivariable Cox regression models predicting metastasis, death and cancer specific mortality in the subgroup with postoperative persistent PSA (≥0.1ng/ml at six weeks after RP).Abbreviations: CCI – Charlson comorbidity index; GG – Gleason grade group.

Effect of PSA persistence on OS

During the study period, 106 (10.3%) vs. 531 (5.0%) patients with persistent and undetectable PSA (p<0.001) died. At 15-years after RP, OS (Study-Figure 2) was 64.7 vs. 81.2% (p<0.001) for persistent vs. undetectable PSA, respectively. In multivariable Cox regression models, testing the relationship between PSA persistence and OS (Study-Table 5), persistent PSA achieved independent predictor status of death (HR:1.86, 95%-CI:1.41-2.45, p<0.001).



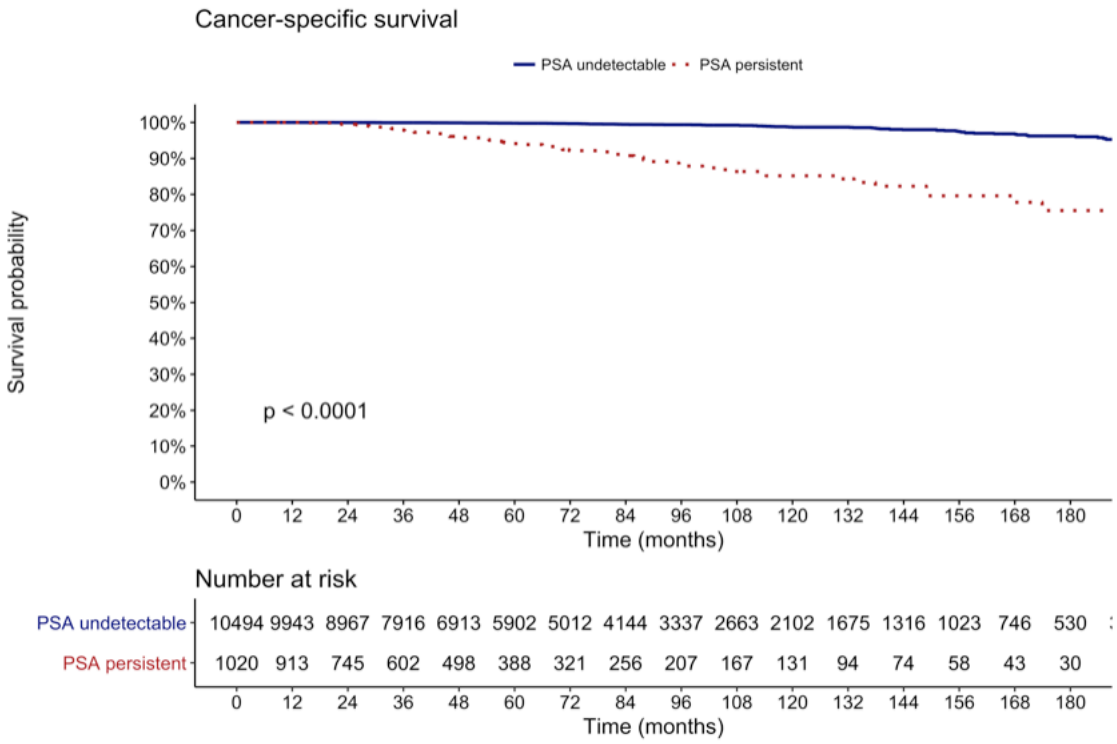
Study-Figure 2: Overall Survival: Undetectable PSA vs persistent PSA

Finally, in subgroup analyses, focusing exclusively on patients with PSA persistence (Study-Table 6), pathologic tumor stage T3b (HR:2.92, 95%-CI:1.16-7.33, p=0.02), GG3-5 (HR:2.49, 95%-CI:1.30-4.77, p<0.01) and CCI ≥1 (HR:1.82, 95%-CI:1.07-3.13, p=0.03) represented independent predictors for death.

Effect of PSA persistence on CSS

Of all death that occurred during the study period, 64 (6.2%) and 84 (0.8%) were attributed to PCa (p<0.001), respectively. At 15-years after RP, CSS (Study-Figure 3) was 75.5 vs. 96.2% (p<0.001) for persistent vs. undetectable PSA, respectively. In multivariable Cox regression models, testing the relationship between PSA persistence and CSS (Study-Table 5), persistent

PSA achieved independent predictor status of cancer-specific death (HR:3.15, 95%-CI:1.92-5.18, p<0.001).

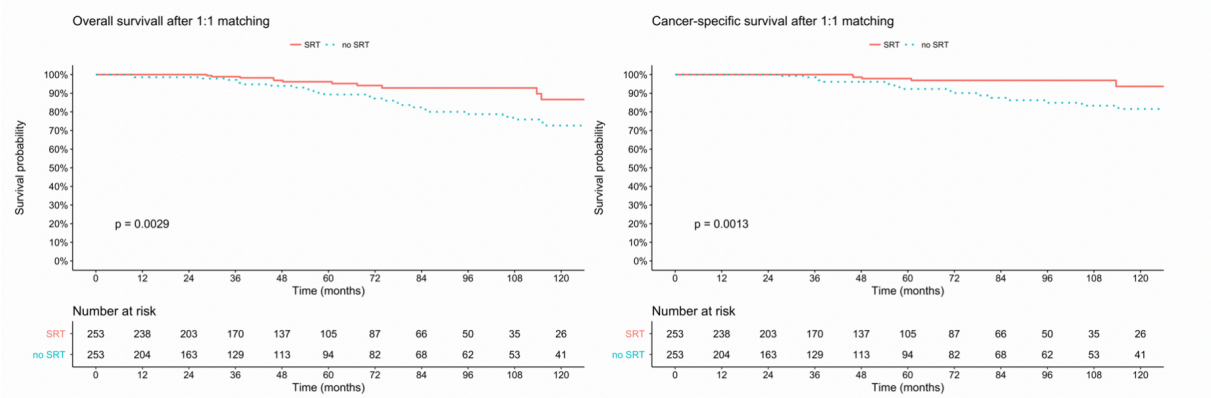


Study-Figure 3: Cancer-specific survival Undetectable PSA vs persistent PSA

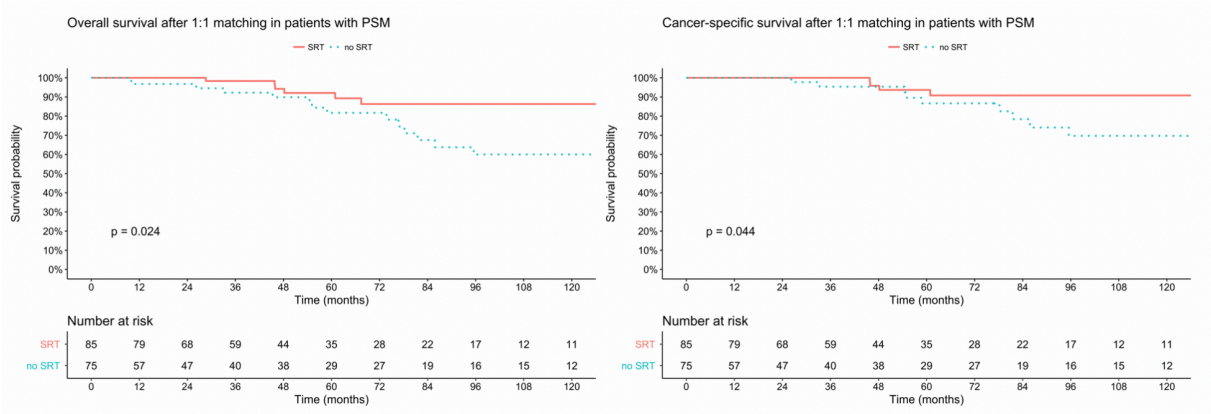
Finally, in subgroup analyses, focusing exclusively on patients with PSA persistence (Study-Table 6), GG3-5 (HR:5.05, 95%-CI:1.76-14.46, p<0.01) and year of surgery (HR:0.91, 95%-CI:0.85-0.98, p<0.01) represented independent predictors for cancer-specific death.

Effect of SRT on OS and CSS

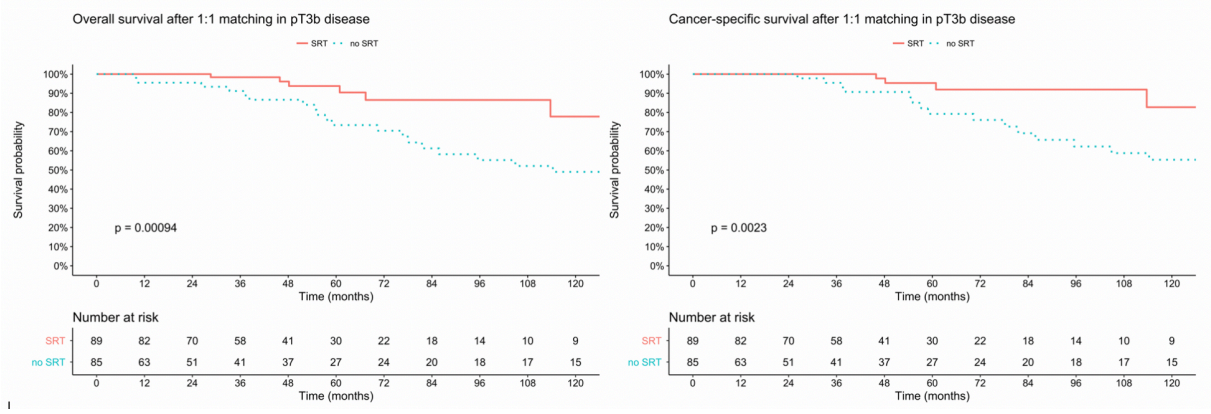
In the subgroup of patients with persistent PSA, after 1:1 PSM between patients with SRT vs. no RT, OS at 10 years after RP was 86.6 vs. 72.6% in the entire cohort (p<0.01) (Study-Figure 4), 86.3 vs. 60.0% in patients with positive surgical margin (p=0.02) (Study-Figure 5), 77.8 vs. 49.0% in pT3b disease (p<0.001) (Study-Figure 6), 79.3 vs. 55.8% in GG3-5 disease (p<0.01) (Study-Figure 7) and 87.4 vs. 50.5% in pN1 disease (p<0.01) (Study-Figure 8), for SRT and no RT respectively. Moreover, CSS at 10 years after RP was 93.7 vs. 81.6% in the entire cohort (p<0.01) (Study-Figure 4), 90.8 vs. 69.7% in patients with positive surgical margin (p=0.04) (Study-Figure 5), 82.7 vs. 55.3% in pT3b disease (p<0.01) (Study-Figure 6), 85.4 vs. 69.7% in GG3-5 disease (p<0.01) (Study-Figure 7) and 96.2 vs. 55.8% in pN1 disease (p<0.01) (Study-Figure 8), for SRT and no RT respectively. The median time to SRT was 5.4 months.



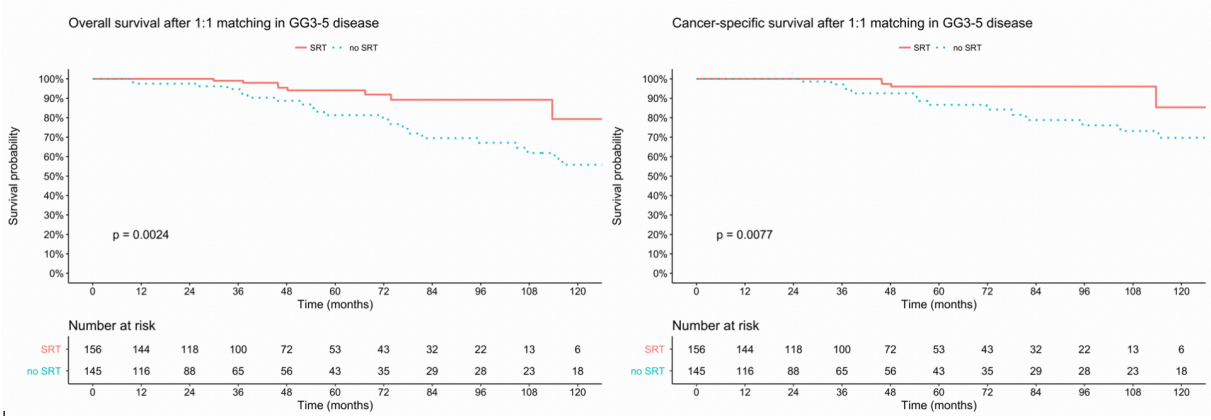
Study-Figure 4: Left: Entire cohort overall survival. *Right: Entire cohort Cancer-specific survival*



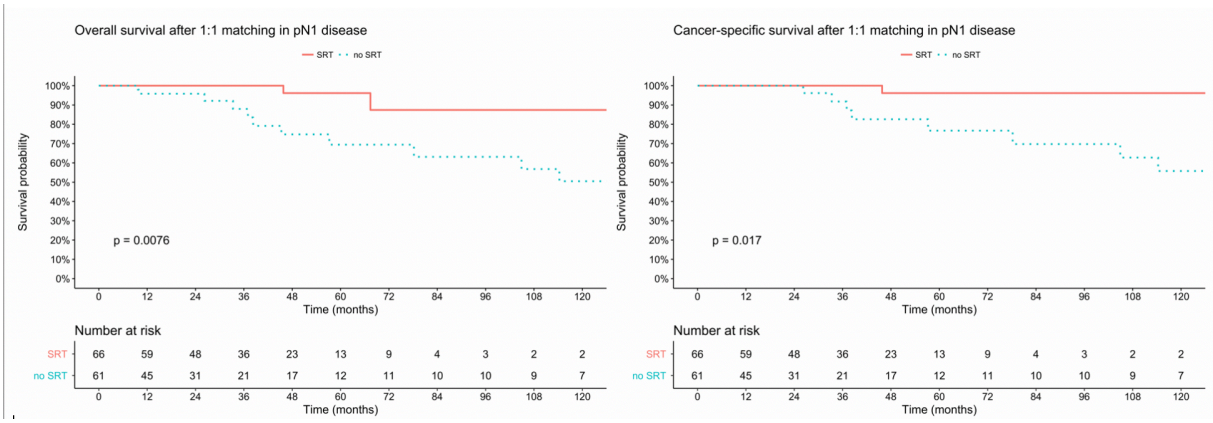
Study-Figure 5 : Overall survival(left) and Cancer-specific survival (right)in patients with positive surgical margins who received SRT vs no SRT



Study-Figure 6: Overall survival(left) and Cancer-specific survival (right) in patients with pT3b disease who received SRT vs no SRT.



Study-Figure 7: Overall survival(left) and Cancer-specific survival (right) in patients with Gleason Grade3-5 who received SRT vs no SRT.



Study-Figure 8: 4 Overall survival(left) and Cancer-specific survival (right) in patients with positive lymph node invasion (pN1) who received SRT vs no SRT.

In multivariable Cox regression models, after PSM, SRT was associated with lower risk for death (HR:0.37, 95%-CI:0.16-0.83, p=0.02) and cancer-specific death (HR:0.12, 95%-CI:0.03-0.47, p<0.01) (Study-Table 7).

	Predicting death			**Predicting cancer-specific death**		
	HR	**95%-CI**	**p -value**	**HR**	**95%-CI**	**p -value**
SRT	**0.37**	**0.16-0.83**	**0.02**	**0.12**	**0.03-0.47**	**<0.01**
Year of surgery	0.98	0.91-1.05	0.6	0.99	0.90-1.09	0.9
Age	0.98	0.92-1.03	0.4	0.94	0.87-1.01	0.1
Preoperative PSA	0.94	0.91-0.97	<0.001	0.91	0.87-0.96	<0.001
Pathologic stage ≤T3a (referent)	1.00	-	-	1.00	-	-
Pathologic stage T3b	4.45	2.09-9.50	<0.001	15.64	4.66-52.49	<0.001
Pathologic GG1-2 (referent)	1.00	-	-	1.00	-	-

Pathologic GG3-5	2.78	1.27-6.03	0.01	2.14	0.75-6.16	0.2
Negative surgical margin (referent)	1.00	-	-	1.00	-	-
Positive surgical margin	1.99	1.04-3.84	0.04	2.86	1.17-6.98	0.02
Pathologic lymph node status N0/Nx (referent)	1.00	-	-	1.00	-	-
Pathologic lymph node status N1	2.61	1.23-5.53	0.01	5.54	1.94-15.80	<0.01
Charlson comorbidity index 0 (referent)	1.00	-	-	1.00	-	-
Charlson comorbidity index ≥1	2.38	1.10-5.15	0.03	2.08	0.63-6.88	0.2

Study-Table 7: Multivariable Cox regression models predicting death and cancer-specific death in the subgroup with postoperative persistent PSA (≥0.1ng/ml at six weeks after RP) after 1:1 propensity score matching. Abbreviations: GG – Gleason grade group; HR-Hazar risk.

Discussion

PSA after RP represents the cornerstone in follow-up of PCa patients. Specifically, early PSA values after RP could help to identify patients at risk for worse oncologic outcome. Moreover, early PSA after RP could help to identify patients who benefit from further treatment. However, few previous studies tested the impact of persistent PSA on long-term oncologic outcomes. To address this void, we investigated the relationship between persistent PSA at six weeks and the long-term oncologic outcomes after RP. Additionally, we focused on the subgroup of patients with persistent PSA to identify candidates who may benefit from SRT. Our analyses revealed several noteworthy findings.

First, of 11,604 identified patients, 8.8% (n=1,025) harbored persistent PSA. This result demonstrates that persistent PSA represents a common finding early after RP. This result is different from previous studies. Our proportion of patients with persistent PSA is lower than the one reported by Bianchi (26.0%). [10] However, Bianchi relied on a cohort that exclusively consisted of pN1 patients, which have a higher risk for persistent PSA as reported by Sengupta et al [111]. One reason for the lower proportion of patients with persistent PSA in our study may be the rate of patients with missing information. However, our results corroborate the findings by McDonald et al., who reported a proportion of 9.2% with persistent PSA, which is similar to our rate [112]. Moreover, 10% (n=125) of patients with persistent PSA at six weeks had an undetectable PSA in the subsequent PSA testing. One explanation could be related to receipt of androgen deprivation in these patients.

Second, in multivariable logistic regression several pre- and postoperative tumor characteristics represented independent predictors for persistent PSA. These results demonstrate the direct relationship between more advanced pre- and postoperative tumor characteristics and persistent PSA and can help to identify those with an increased risk.

Third, patients with persistent PSA had worse oncological outcomes compared to patients with undetectable PSA. Specifically, at 15-years after RP, MFS, OS and CSS was better for persistent vs. undetectable PSA, respectively. Moreover, in multivariable models persistent PSA remained an independent predictor for metastasis (HR:3.59, $p<0.001$), death (HR:1.86, $p<0.001$) and cancer-specific death (HR:3.15, $p<0.001$). These findings corroborate the report by Fossati et al. within pN0 patients treated with SRT, who reported a HR of 4.64 for persistent PSA to develop metastasis [8]. Moreover, our findings also corroborate the report by Bianchi et al., who reported higher risk for development of metastasis and cancer-specific mortality in pN1 patients with persistent PSA .

Fourth, in analyses focusing on patients with persistent PSA, after PSM between patients with SRT vs. no RT, SRT was associated with better OS and CSS at 10 years after RP, in the entire cohort, in patients with positive surgical margin, pT3b disease, GG3-5 disease and pN1 disease. Moreover, in multivariable models, SRT was associated with lower risk for death (HR:0.37, $p=0.02$) and cancer-specific death (HR:0.12, $p<0.01$). These results are important in clinical decision-making to select best candidates for SRT. Therefore, patients with persistent PSA after RP and additional risk factors, such as pT3b, GG3-5, positive surgical margin or pN1 disease appear to have a survival benefit by SRT. Moreover, to the best of our knowledge, our study, including 1,025 patients with persistent PSA after RP, is the largest study which addressed this topic.

Taken together, our results demonstrated that persistent PSA at six weeks is an independent predictor for death and development of metastasis. Up to 2018 EAU guidelines recommend first PSA value after RP at three month. However, earlier PSA measurement can help in clinical practice to identify patients with unfavorable outcome. Moreover, earlier PSA measurement can help identifying candidates who may benefit from SRT and result in a shorter delay to salvage treatment. Since the half-life of PSA is approximately 3.15 days, serum PSA values of ≤50ng/ml should be undetectable within four weeks after RP. [113] PSA testing at six weeks following RP, should be considered to identify patients with persistent PSA after RP and worse

oncologic outcome. Moreover, future prospective studies, testing the impact of SRT after RP should consider persistent PSA, since it can provide important information.

Our study is not devoid of limitations. First and foremost, PSA testing after RP was performed with multiple methods, which could have influenced our results. Ideally, ultra-sensitive PSA testing should be performed. In regard of MFS, differences in performed imaging modalities might have influenced our results. It is reasonable that in patients with persistent PSA more advanced imaging modalities were used. However, detailed information on performed imaging for each patient was unavailable. Moreover, despite relying on multivariable adjustments and PSM a selection bias may still exist. Additionally, detailed information on SRT regimens were not available for all patients. With a median dose of 46 Gray in our cohort, the dose was lower than SRT regimens from contemporary reports, which could have influenced our results[114]. Moreover, ADT duration during SRT was unavailable, which could have biased our findings, since short-, as well as long-term ADT during SRT has been shown to result in a survival benefit. [114115] Finally, toxicity related to SRT was not covered by our database. It is of note that although SRT resulted in improved OS and CSS, quality of life may have been negatively influenced by SRT related toxicity and needs to be considered in decision-making.

Conclusion

Persistent PSA at six weeks after RP represents a strong prognostic predictor for development of metastasis and death after RP. Therefore, early measurement of PSA can be useful in clinical practice to identify patients with high risk for worse oncologic outcome. Moreover, SRT was associated with improved OS and CSS in patients with persistent PSA. In those with persistent PSA and additional risk factors, such as pT3b, GG3-5, positive surgical margin or pN1, SRT should be considered.

**Disclaimer: The author of this dissertation wants to state that these results have been already published in a scientific journal where he shares authorship.* [116]

Summary & Conclusion

Persistent prostatic specific antigen (PSA) represents a poor prognostic factor for recurrence after radical prostatectomy (RP).

The aim of this thesis is to investigate the impact of persistent PSA at six weeks after RP on long-term oncologic outcomes and to assess patient characteristics associated with persistent PSA.

From our institutional database (Martini-Data), we identified patients who harbored persistent (≥0.1ng/ml) vs. undetectable PSA (<0.1ng/ml) at six weeks after RP. Patients with neo- and/or adjuvant androgen deprivation therapy (ADT) were excluded.

As for statistical analysis, logistic regression models tested for prediction of persistent PSA. Kaplan-Meier analyses and Cox regression models tested the effect of persistent PSA on metastasis-free survival (MFS), overall survival (OS) and cancer-specific survival (CSS) rates. Propensity score matching was performed to test the impact of salvage radiotherapy (SRT) on OS and CSS in patients with persistent PSA.

A total of 11,604 patients were identified, 8.8% (n=1,025) harbored persistent PSA. At 15-years after RP, MFS, OS and CSS were 53.0 vs. 93.2% ($p<0.001$), 64.7 vs. 81.2% ($p<0.001$) and 75.5 vs. 96.2% ($p<0.001$) for persistent vs. undetectable PSA, respectively. In multivariable Cox regression models, persistent PSA represented an independent predictor for metastasis (HR:3.59, $p<0.001$), overall mortality (HR:1.86, $p<0.001$) and cancer-specific mortality(HR:3.15, $p<0.001$). SRT was associated with improved OS (HR:0.37, $p=0.02$) and CSS (HR:0.12, $p<0.01$) after 1:1 propensity score matching. The main limitation was missing postoperative PSA data and the duration of salvage ADT.

We conclude that persistent PSA is associated with worse oncologic outcomes after RP, namely metastasis, mortality and cancer-specific mortality. In patients with persistent PSA, SRT resulted in improved OS and CSS.

Zusammenfassung und Fazit

Eine PSA (Prostata spezifisches Antigen) -Persistenz stellt nach radikaler Prostatektomie (RP) einen ungünstigen Prognoseindikator für das Auftreten eines Rezidivs dar.

Das Ziel dieser Arbeit ist die Auswirkung einer PSA-Persistenz, sechs Wochen nach RP, auf das langfristige onkologische Outcome zu untersuchen und Charakteristika von Patienten zu bewerten, die eine PSA-Persistenz aufweisen.

Wir nutzten unsere interne Datenbank (Martini-Data), um Patienten mit PSA-Persistenz (≥0.1ng/ml) denjenigen Patienten mit nicht nachweisbarem PSA (<0.1ng/ml) sechs Wochen nach RP gegenüberzustellen. Patienten mit neo- oder adjuvanter Androgendeprivationstherapie (ADT) wurden aus den Kollektiven ausgeschlossen.

Bei der statistischen Datenanalyse verwendeten wir logistische Regressionsmodelle zur Bestimmung des prädiktiven Werts einer PSA-Persistenz. Kaplan-Meier Kurven und Cox-Regressionsmodelle wurden herangezogen, um den Stellenwert einer PSA-Persistenz hinsichtlich des metastasenfreien Überlebens (MFS, metastasis-free survival), des Gesamtüberlebens (OS, overall survival) und des krebsspezifischen Überlebens (CSS, cancer-specific survival) zu beurteilen. Durch ein Propensity score matching bewerteten wir den Einfluss einer salvage-radiatio (SRT) auf das OS und CSS bei Patienten mit PSA-Persistenz.

Von 11.604 untersuchten Patienten wiesen 8,8 % (n=1.025) eine PSA-Persistenz auf. 15 Jahre nach RP lag das MFS, OS und CSS bei 53.0 vs. 93.2% (p<0.001), 64.7 vs. 81.2% (p<0.001) und 75.5 vs. 96.2% (p<0.001) entsprechend für Patienten mit PSA-Persistenz vs. Patienten mit nicht nachweisbarem PSA. In der multivariaten Cox-Regressionsanalyse stellte die PSA-Persistenz einen unabhängigen Prädiktor für die Metastasierung (HR:3.59, p<0.001), Gesamtmortalität (HR:1.86, p<0.001) und krebsspezifische Mortalität (HR:3.15, p<0.001) dar. Eine SRT war mit einem besseren OS (HR:0.37, p=0.02) und CSS (HR:0.12, p<0.01) nach 1:1 propensity score matching assoziiert. Beschränkungen in der Auswertung bestanden aufgrund teils fehlender Angaben bezüglich postoperativer PSA-Daten und der ADT-Dauer nach SRT.

Wir schlussfolgern, dass PSA-Persistenz mit einem schlechteren onkologischem Outcome nach RP assoziiert ist, insbesondere bezüglich des Metastasierungsrisikos, der Gesamtmortalität und

der krebsspezifischen Mortalität. Bei Patienten mit PSA-Persistenz führte eine SRT zu einer Verbesserung des OS und des CSS.

Abbreviations

3D-CRT conformal radiotherapy
A2M alpha2-macroglobulin
ACT alpha1-antichymotrypsin
ADT androgen deprivation therapy
AJCC American joint Committee of Cancer AJCC
APC adenomatous polyposis coli
API alpha1-protease inhibitor
AR androgen receptor
AS active surveillance
AUC area under the curve
BCR biochemical recurrence
BPH benign prostatic Hyperplasia
cc cubic centimeters
CCI Charlson comorbidity index
CCP score cell cycle progression score
CDR cancer detection rate
CI confidence interval
cm centimeters
CRPC castration resistant prostate cancer
CSS cancer-specific survival
CT computed tomography scan
DFHT dihydrotestosterone
DRE digital rectal exam
FBX fusion biopsy
fPSA free PSA
FSH follicle-stimulating hormone
GG Gleason-grade group
GPS Genomic Prostate Score
GSTP1 glutathione-S-transferasa P1
Gy gray
HDR high dose radioisotopes
hK human Kallikrein
IGRT image guided radiation therapy
IMRT intensity-modulated therapy
IPSS international prostatic symptom score
ISUP International Society of Urological Pathology
LDR low dose radioisotopes
LH luteinizing hormone
LHRH luteinizing hormone-releasing hormone
LND Lymph node dissection
LNI lymph node invasion
LUTS lower urinary tract symptoms
MFS metastasis-free survival
MiPS Mi-prostate score urine test MiPS
ml milliliters
MRI magnetic resonance imaging
mRNA messenger RNA
NCCN The National comprehensive Cancer Network
ng nanograms

OS overall survival
PBx prostate biopsy
PCa Prostate Cancer
PCA3 prostate cancer antigen 3
PCPT prostate cancer prevention trial
PET/CT positron emission tomography/computed tomography scan
PCPT Prostate Cancer Prevention Trial
PSA prostate-specific antigen
PSAD Prostate specific Antigen density
PSADT PSA doubling time
PSAV The PSA velocity
PSM propensity score matching
RASSF1 Ras association domain-containing protein 1
REDUCE reduction by dutasteride of prostate cancer events
RP radical prostatectomy
RT radiotherapy
RT-PCR reverse transcriptase protein chain reaction (RT-PCR).
SBRT stereotactic body radiation therapy
sec seconds
SHBG sex hormone-binding globulin
SRT salvage radiotherapy
SV seminal vesicles
TNM tumor, node, metastasis classification
tPSA total prostate-specific antigen
TRUS transrectal ultrasound
WW watchful waiting

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