Salvage radiotherapy of prostate cancer : retrospective analysis of 10 years' experience in the Department of oncology and radiotherapy University hospital of Split

Radosevic, Sebastian

UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

Sebastian Radosevic

SALVAGE RADIOTHERAPY OF PROSTATE CANCER. RETROSPECTIVE ANALYSIS OF 10 YEARS' EXPERIENCE IN THE DEPARMENT OF ONCOLOGY AND RADIOTHERAPY UNIVERSITY HOSPITAL OF SPLIT

DIPLOMA THESIS

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TABLE OF CONTENTS:

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1. INTRODUCTION

1.1 PROSTATE CANCER

1.1.1 EPIDEMIOLOGY AND ETIOLOGY

Prostate cancer (PC), is the most common malignancy in males with an incidence of 2141 cases in 2015 in Croatia and is the third most common cause of death (1). Changes in the prostate increase with age with an increased incidence of PC in the population older than 70 years. It occurs more often in the African-American male population than in white men (2). There is a familial factor in the development of cancer with a two times increased risk if one first-degree relative is affected and a four times increased risk if two or more relatives are affected (2).A BRCA2 mutation leads to a fivefold increased risk of PC (2). Additionally, there is a chance of being affected by PC as well as benign prostatic hyperplasia (BPH). The risk of developing PC is 1 in 10.000 for men younger than forty, 1 in 103 for men 40-59 years of age and 1 in 8 for men between 60 and 79 years (3). PC presents with 83 new cases each year and leads to 9 confirmed deaths per year, leading to a mortality/incidence ratio of 0.38 (1).

1.1.2 PATHOLOGY

The vast majority of PC are adenocarcinomas. The remaining part can be subdivided into epithelial and non-epithelial tumors with sarcomas, small cell carcinomas, neuroendocrine tumors and transitional cell tumors being the most common. The long-term use of androgen deprivation therapy can lead to the development of neuroendocrine tumors (4).

On cytology, PC is cytologically characterized by hyperchromatic, enlarged nuclei with prominent nucleoli, mitotic figures, and amphophilic cytoplasm (5). The cytoplasm is usually abundant. Architectural features include small glands which infiltrate between benign surrounding glands, and regions with an increased number of glands which is not inflamed which can be cancer (5). An additional factor to differentiate PC from a normal gland or benign prostatic hyperplasia is that in cancer the basal cell layer is missing. Prostate intraepithelial neoplasia (PIN) and atypical small acinar proliferation (ASAP) are now considered to be premalignant states with PIN having a strong association with PC on biopsies (6). Intraductal dysplasia is considered as a precursor to PC because the frequency of PCs is high in prostate

glands with multiple locations of dysplasia (7). Staining for acid phosphatase and prostate-specific antigen is characteristic for a PC (3).

Most of the high-grade prostatic intraepithelial neoplasia develop in the peripheral zone of the prostate gland, being the most common location for PC (5). 10-20% develop in the transition zone and 5-10% in the central zone (3). Around 85% of these tumors are multi-focal. Cancers involving the central zone of the prostate gland are highly malignant and have a different route of spread compared to PC in other zones (8). Furthermore, androgen and progesterone receptors have been found on the surface of PC cells (9).

1.1.3 Natural history of disease

PC invades locally into the gland and then through the prostatic capsule into the surrounding structures. Invasion can include the seminal vesicles which leads to a higher likelihood of local recurrence or distant disease. If the tumor invades the bladder trigone, symptoms of ureteral obstruction will develop. Rectal invasion is possible but rare due to the Denonvilliers' fascia. Lymph node metastases are more common in advanced stages and affect the obturator, external iliac, and internal lymph node chains. PC usually spreads to distant sites via retrograde venous spread through the vertebral plexus. The axial skeleton, especially the lumbar spine is most commonly affected. The resulting bone lesions are osteoblastic and can result in pathologic fractures. If the metastases involve the vertebral body, this can lead to spinal cord compression. Lung, liver, adrenal glands are the most common affected internal organs (2,9).

1.1.4 Clinical findings

Usually, PC is asymptomatic. If symptoms are present, these often suggest local infiltration or metastatic spread of the disease. Symptoms caused by prostatic outflow obstruction are hesitancy, frequency, poor stream and nocturia (3). Haematospermia and erectile dysfunction are possible. These symptoms can also be caused by benign prostatic hyperplasia. Metastatic disease affecting the bones will cause bone pain or spinal cord compression and hyper-

calcemia. General symptoms related to malignancy are possible which include malaise, anorexia and weight loss (2).

1.1.5 Screening and diagnosis

Digital rectal examination (DRE) and prostate-specific antigen (PSA) levels are the basic tests for detecting PC. DRE is focusing on the size, consistency and abnormalities of the gland and surrounding tissues but it should not be used alone (10). The majority of these cancers appear in the peripheral part of the prostate gland and can be detected on DRE. On DRE, the cancer may be palpable through the rectum as a hard nodule or a diffusely infiltrating irregularity. A loss of the midline sulcus of the prostate gland is typical. Overall 20-25% of patients with positive DRE have cancer (2). Combining PSA measurement with DRE and ultrasound (US) show better results than rectal examination alone (11).

Today the most important test for the diagnosis of PC is the PSA test. This test is very sensitive for the prostate but relatively non-specific for PC because other non-malignant states can also increase the PSA levels in the blood (3).

Trans rectal ultrasound (TRUS) is used to guide trans rectal biopsies and other diagnostic procedures and to evaluate the primary tumor for further staging. Abnormal findings on TRUS are not necessary related to malignancy. It is important to describe the dimension of the prostate gland, volume, shape, symmetries, echogenicity and the involvement of surrounding tissues including the seminal vesicles and ampullas of the duct deferens (12).

If there is suspicion of PC due to abnormal findings in DRE and PSA values, a prostate biopsy is the next step to confirm the diagnosis. Under TRUS guidance, biopsies are taken from the peripheral part of the gland, with the possibility of including other suspicious areas as well. An extended 12-core biopsy is advised. The procedure is carried out under local anesthesia with antibiotic prophylaxis before the procedure. Indications for a TRUS guided biopsy are a PSA level ≥ 4 ng/ml on the first consultation, suspicious finding on DRE, and a suspicious rise in PSA (10). If the biopsy is negative but the PSA is abnormal, men should undergo repeated biopsy (2). A prostate biopsy can lead to haematospermia, rectal bleeding, fever above 38,5 °C (10). If systematic biopsy is compared with ultrasound-guided biopsy, the guided biopsy shows better diagnostic performance, meaning better sensitivity, specifici-

ty, and negative/positive predictive values (13). Colour Doppler and contrast-enhanced targeted biopsy show the highest sensitivity and specificity (13).

Magnetic resonance imaging (MRI) examines the prostate gland and the surrounding tissues such as rectum and bladder with better results with regard to cancer in the prostate and local extend (2). Specific rectal coils which are placed immediately adjacent to the prostate gland are used to detect PC (14). The use of multiparametric MRI (mpMRI) is able to detect PC in patients who did not have a biopsy before or in case the biopsy was negative and in addition to that a significant disease can be ruled out (15). MpMRI consists of a T2-weighted (T2w) sequence, a diffusion-weighted sequence (DWI), and a dynamic contrast-enhanced (DCE) evaluation (16).

In case of an increased PSA and positive DRE but there is a negative histologic finding on biopsy, the multiparametric MRI can be used to specify the location of the tumor. The result is more accurate with a TRUS-biopsy. In addition to that, an MRI guided biopsy is also possible.

T1-weighted (T1w) images show a high signal in adjacent lymph nodes and bone marrow. These pictures are not useful for PC detection because the normal gland appears hypointense and different zones of the prostate gland can´t be differentiated (10). An important benefit of the T1w image, is to detect post biopsy hemorrhage which is seen with a high intensity signal (17,18). If the hemorrhage exclusion sign on a T1w image is combined with a related homogenous low-signal intensity area on a T2w image, that is strongly predictive of PC (19).

The structure of the prostate gland and seminal vesicle is studied on a T2-weighted image. The normal peripheral zone of the prostate glands appears hyper intense on a T2 sequence due to the high amount of gland tissue (10). An important landmark for staging is the prostatic capsule which presents as a thin hypointense line (16). Due to the flexible amount of stromal and glandular tissue in the transitional zone, it appears heterogeneous (10). PC on a T2w picture has a low T2w signal due to the increased cell density which leads to a decreased water content (2). The differential diagnosis includes focal fibrosis or a stromal BPH node. The cell density is proportional to the aggressiveness of the tumor. The extracapsular extension can be visualized on a T2 sequence and presents with asymmetry or macroscopic invasion of the neurovascular bundle, retraction of the capsule, irregularity of the prostatic contour, change in the recto-prostatic angle, and signs for a rupture of the capsule with extension

into the periprostatic fat (16). The limitations of the T2w sequence is, that PC cannot be excluded when the lesion is less than 10 mm and < 0.3cm (20). Lesion larger than 20 mm have a detection rate of 89% (20).

DWI shows the movement of matter in space until a homogenous distribution and is therefore capable of measuring diffusion restrictions (10). It correlates with the Gleason score (GS) and the cellularity (16). The diffusion limitation is measured with the apparent diffusion coefficient (ADC) and the b-value describes the degree of diffusion weighting which enable the quantification of a diffusion map (10). B-values above 1000 is important for measuring the cellularity and therefore cell density which is specific value for the aggressiveness of PC (21). An area of low diffusion appears hypointense on an ADC map due to a low diffusion coefficient or low ADC values (16). This method does not require contrast media. Normal prostatic tissue is visible as an area with high ADC values. The ADC value shows the best correlation to the GS and the aggressiveness of the PC (22). DWI images can differentiate between a normal central zone, the peripheral zone, a prostatic cyst, BPH nodule and PC (23). The advantages of this technique are a short imaging time, no need for contrast media and relatively simple post-processing requirements (24).

DCE is a functional MRI image that shows a relationship to angiogenesis (16). This method uses low molecular weight gadolinium contrast media (10). As a result of the increased vascularity of the PC, DCE pictures show an intense and early contrast media wash-in that is followed by an intense and early wash-out (16). The normal tissue in the peripheral zone shows a slower and more progressive wash-in (16). Therefore, DCE enables the examination of the micro vascularization and neoangiogenesis of PC (10). Namimoto *et al.* found out, that the combination of DCE and postcontrast T1 sequences is 82% accurate which led to the conclusion that dynamic pictures are helpful in the evaluation of low intensity lesions in the peripheral zone (25). Endorectal dynamic imaging increased the diagnostic sensitivity from 77.8 to 88.9% in localized PC (26). In addition to that DCE together with an endorectal surface coil results in a more accurate determination of the tumor localization, penetration of the capsule, invasion of seminal vesicle, and involvement of the neurovascular bundle (27). In sum, DCE increases the specificity and sensitivity of detecting especially PC in peripheral and anterior zones and therefore decreases the rate of false-positive results (10).

The examination protocol of the prostate gland MRI should include high resolution T2-sequences in axial, coronal and sagittal planes together with an axial T1 image of the pelvis and diffusion and perfusion (T2 + DWI + DCE) imaging of the prostate (10).

CT-scan gives a better and more detailed view of the lymph node changes in the common iliac and para-aortic regions. It is used when MRI scans are contra-indicated because it has inferior sensitivity and specificity for detection of extra prostatic involvement.

18F-Fluoride PET/CT is useful for the detection of metastases in patients with high risk prostate cancer. With this technique patients who have metastases can be separated from those who do not have metastases and there can be treated with curative local radiotherapy or surgery (28).

1.1.6 UCSF Cancer of prostate Risk assessment (CAPRA) Score

The score is used to predict the recurrence risk of PC after radical prostatectomy. In order to calculate the CAPRA score, points are given for the GS, PSA level, T-stage, % of positive biopsy cores, and age getting a range from 0-10 points (3). If the score increases by 2 points that means a doubling of the risk. The disease is divided into three groups: 0-2 indicate a relatively low risk, 3-5 are intermediate, and 6-10 are high risk (3). In addition to that the CAPRA score can be used for prediction of development of metastases, prostate cancer-specific mortality, and all-cause mortality with good accuracy (29). On top of that the biochemical-recurrence-free survival at 3 years can be correctly predicted (30). Summarized, the CAPRA score primarily indicates the relative risk and helps in predicting the outcome after radical prostatectomy.

1.1.7 PSA

The PSA is a kallikrein-related serine protease with the effect of liquefying the seminal coagulum. It is produced by non-malignant and malignant epithelial cells. Therefore, the antigen is prostate-specific, not prostate cancer specific and can be used in screening as well as in risk stratification (3). In serum PSA exists complexed with a protease inhibitor or uncomplexed (free) form. The free form is rapidly eliminated from the blood via the kidneys and has a half-life of 12-18h (2). Prostatitis and BPH can increase the PSA levels in serum. Serum PSA levels are not significantly affected by DRE but a prostate biopsy can increase the levels up to tenfold (9). PSA levels should not be detectable after removal of the prostate gland for about 6 weeks. A normal PSA value is defined as ≤4 ng/ml and a positive predictive value for a value between 4 and 10 ng/ml is approximately 20-30% (3). According to a PC prevention trail there is no PSA level below which the risk of PC falls to zero. There is rather a continuum of risk (31). In addition to that, prevalence of biopsy detected prostate cancer in patients with a PSA level in normal range is not rare (32).

PSA velocity is related to the rate of change of serum PSA. The PSA doubling time points to the required time needed to double the amount of PSA. Patients with an increase in PSA levels by 0.75 ng/ml appear to be at an increased risk of developing cancer (3). To prevent misinterpretation the PSA levels should be taken by the same laboratory over a period of 18 months.

The PSA levels are elevated on average approximately 0.12 ng/ml per gram of BPH tissue and increases with age. In conditions like prostatitis and BPH, the levels are increased as well. The PSA density describes the ratio of PSA to prostate gland volume.

PSA doubling time (DT) is the time needed for the PSA level to double. It reflects the tumor growth and is especially important after prostatectomy. PSA DT is not used for diagnostics but for deciding which therapy to use and for the control of the therapy (10). The drug finasteride decreases the rate at which the tumor secretes PSA into the blood (33). A PSA DT of less than 3 months is related to a preoperative PSA velocity of < 2.0 ng/ml/yr, and a GS 7 or 8-10, which leads to a shorter survival caused by an increased prostate cancer-specific mortality (PCSM) (34).

PSA failure is the rise in PSA levels in PC patients after surgery or radiation. A rise of >0.2 ng/ml after surgery is considered failure. If there a level of >2 ng/ml above the nadir after radiation therapy, that is considered failure (35).

1.1.8 GLEASON SCORE (GS)

After taking a biopsy or radical prostatectomy, the tissue is examined under the microscope according to the growth pattern and scored in the GS. It scores the dominant and the secondary dominant pattern from 1 (well differentiated) to 5 (undifferentiated). The sum gives a total score of 2-10 points, with a score above 8 having a poor outcome. In addition to the invasion of perineural tissue and spread to extracapsular tissues as seminal vesicles, rectum and bladder. A GS of 3 resembles a low-grade disease, score of 4 resembles an intermediate-grade disease and a score of 5 resembles a high-grade disease. (3) The most important part in the Gleason score system is the primary score of the tumor because it determines the biologic risk. Epstein *et al.* introduced a new classification according to five grade groups in which group 1 has a GS ≤6; group 2 has GS 7 (3+4); group 3 – GS 7 (4+3); group 4 – GS 8 and group 5 – GS 9-10 (36).

1.1.9 STAGING AND RISK STRATIFICATION

PC is staged according to the tumor, node, metastasis (TNM) staging system (table 1). Included are stages which can be identified by an abnormal PSA (T1c), which are clinically confined to the gland but are palpable (T2) and tumors which involve adjacent or distant structures (T3 and T4) (2). In the Tx stage the primary tumor cannot be assessed and in T0 there is no evidence of a primary tumor.

Table 1: TNM staging of PC

<u>Localized disease</u>	
T1	clinically inapparent tumor, neither palpable nor visible by imaging
T1a	Tumor incidental histologic finding in >5% of resected tissue; not palpable
T1b	tumor incidental histologic finding in >5% of resected tissue
T1c	tumor identified by needle biopsy (e.g., because of elevated PSA)
T2	tumor confined within prostate
T2a	tumor involves half of the lobe or less
T2b	tumor involves more than one half of one lobe, not both lobes
T2c	tumor involves both lobes
<u>Local ex-tension</u>	
T3	tumor extends through prostatic capsule
T3a	extracapsular extension (unilateral or bilateral)
T3b	tumor invades seminal vesicle(s)
T4	tumor is fixed or invades adjacent structures (rectum, bladder, levator muscles, external sphincter, and/or pelvic wall
<u>Metastatic disease</u>	
N1	positive regional lymph nodes
M1	distant metastasis

Revised from SB Edge et al (eds): AJCC Cancer Staging Manual

PSA-level, GS and the T-stage with or without extend of the involvement of the biopsy care are important to assess the risk of cancer spread. The American Urology Association (AUA) guidelines assign men into three categories. The ***low-risk group*** constitutes a PSA ≤10 ng/ml, Gleason ≤6, and a clinical stage T1 or T2a. In ***the intermediate group*** are men with a PSA 10-20 ng/ml, Gleason score 7, or clinical T2b. ***High risk*** men have a PSA >20 ng/ml, Gleason score 8-10, or clinical stage T2c or T3a. (3) Problems with this system occur due to the missing differentiation between Gleason scores 3+4 or 4+3, which are different in terms of biologic risks.

If the stage is <T2a, Gleason score ≤6 and the PSA ≤10 ng/ml the risk of metastatic spread is low (37).

Patients with a pre-treatment PSA velocity of 2 ng/ml/year, an interval to PSA failure of <3 years and a post-treatment doubling time <3 months have an increased risk of metastatic spread and prostate cancer-specific mortality and are not suitable for salvage therapy (38).

1.1.10 TREATMENT

The therapy given to the patient depends on the stage of the tumor, age, symptoms, and condition of the patient, the capability of the therapy to provide disease -free survival.

1.1.10.1 LOCALIZED DISEASE

Local prostate cancer is stage T1-T2c without metastases and lymph node involvement. Therapy options are watchful waiting and active surveillance, radical prostatectomy, radiation therapy and cryotherapy (3).

1.1.10.1.1 Active surveillance

In active surveillance, men are followed with DRE, PSA tests, and prostate biopsies in fixed intervals to assess the progression of PC. This method is suitable for patients with PSA ≤10 ng/ml, tumor stage T1-T2a, Gleason score ≤6 (39). Treatment is introduced with the first sign of progression (3).

1.1.10.1.2 Radical Prostatectomy

The aim of a radical prostatectomy (RP) is to remove the cancer completely with a clear margin, conserve continence by maintaining the external sphincter, and to preserve potency by sparing the nerves in the neurovascular bundle (2). This method is advised for patients with a life expectancy of more than 10 years because it showed improved survival compared to active survival (40). In case of a low-risk disease, an open or robotic radical prostatectomy can be performed in which the postoperative erectile dysfunction is preserved by unilateral or bilateral cavernous nerve sparing. For the high-risk group, a non-nerve-sparing surgery is performed (41). In use are the retropubic, perineal, or robotic laparoscopic approach. In the open radical retropubic approach, the peritoneum is not opened but the lymph nodes are removed between the bilateral obturator vessels and the external iliac vein (41). The approach determines the possible complications of surgery. In the retropubic approach, urine leaks, lymphocele and urinary or rectal damage are possible. Iatrogenic ileus is a possible complication of the robotic assisted approach. For all RPs, there is a risk of urinary incontinence and erectile dysfunction. The erectile dysfunction usually comes back after about 6 months after surgery and a better recovery is related to younger age, quality of sexual function before operation and a good surgical technique (2).

After surgery, the PSA level should be <0.2 ng/ml within 6 weeks of surgery (3). If the levels rise above 0.2 ng/ml, PSA failure is present (42). In case of positive lymph node involvement, adjuvant androgen deprivation therapy should be offered (3). High risk patients with a pT3 PC or when the surgical margins were positive after RP, can be additionally treated with immediate external beam radiation to improve the progression-free survival and local control of the disease (43).

1.1.10.1.3 RADIATION THERAPY

The radiation therapy (RT) can be delivered via external beam therapy or by brachytherapy in which a radioactive source is placed close to the tumor.

Before external beam RT it is important to make three-dimensional treatment plans in order to increase the dose of radiation delivered to the prostate gland and to decrease involvement of the surrounding tissues. This technique allows safe delivery of 65 to 70 Gy to the prostate gland. With the help of newer treating plans like three-dimensional, conformal radiation therapy (3DCRT) and intensity-modulated radiation therapy (IMRT) it is possible to target the prostate gland more precisely which leads to a decrease in acute and late toxicities (3). In addition to that, the delivery of higher doses >80 Gy are possible which leads to a better biochemical outcome after treatment. The results of RT can be improved by neoadjuvant, concurrent, and adjuvant androgen deprivation therapy (ADT). A decline in PSA to <0.5 or 1 ng/ml, steady PSA levels, and a negative prostate biopsy after 2 years define cancer control (2). Biochemical failure is defined a rise in PSA by >2 ng/ml above the nadir (Phoenix definition) (44). Most of the side-effects of RT are limited in extend but radiation is associated with a higher frequency of bowel complications like diarrhea and proctitis. Other side-effects are urinary urgency, frequency, hematuria, rectal bleeding and tenesmus. Posttreatment erectile dysfunction as after surgery is as well possible after radiation therapy but it is due to a disruption of the vascular supply not due to nerve damage. Higher doses lead to an incidence of rectal toxicity and doses ≥73 Gy increase the late urinary toxicities (45). If external beam RT is combined with ADT, there is a transient loss of sexual function which improves within 9 months postoperatively (46). Combining external beam RT with brachytherapy leads to a worsening of urinary function (46). In order to decrease the size of the prostate and therefore a decreased involvement of the surrounding tissues, to increase the local control rates, and to decrease the systemic failure, neoadjuvant ADT can be given to the patient (2). Monotherapy with gonadotropin-releasing hormone (GnRH) agonists, in addition to RT showed increased survival and disease-free survival benefits in patients with increased risk of metastatic spread (47). According to Crook *et al.* there is no significant difference whether to use intermittent or continuous ADT in patients after radiotherapy (48).

Brachytherapy includes the direct implementation of a radioactive source into the prostate. These implants can be permanent with iodine 125 or palladium 103 having a lower dose rate but an overall higher total dose delivered in comparison to temporal implants (3). The therapy is based on the fact that the dose of radiation decreases with the square distance from the source. Brachytherapy is usually well tolerated but many patients experience urinary frequency and urgency.

1.1.10.2 METASTATIC DISEASE

Death due to PC is often a result of the failure of controlling the metastatic spread. PC is in most cases hormone dependent, especially to testosterone. Testosterone is the most important circulating androgen and is secreted in the testis by Leydig cells (3). Prostate cells take up this androgen and convert it to dihydrotestosterone (DHT), which is the key intracellular androgen. Interrupting this is the main focus in treatment of metastatic PC (2,3).

For symptomatic M1 patients it is recommended to perform an immediate castration to prevent the development of a further progression of the disease and palliation of symptoms (49). Asymptomatic M1 patients, the immediate castration should be offered to prevent the progression of PC (49).

1.1.10.2.1 NONCASTRATE METASTATIC PC

Metastatic hormone sensitive PC can be treated with ADT and early administration of docetaxel which shows increased survival rates but increases adverse events as well (50). In addition to that, abiraterone acetate and prednisolone can be added to ADT in order to improve the development of pain, PC symptoms and the quality of life (51).

Patients with a testosterone levels >150 ng/dL and visible metastases on imaging studies are in the state of noncastrate metastatic PC and present with pain due to osseous spread and less commonly spinal cord compression, coagulopathy or bone marrow compression (2).

The main focus of treating metastatic PC is to deplete or lower the androgen production and/or block the binding of these hormones (2). This can be achieved by testosterone lowering agents, antiandrogens, androgen deprivation therapy (ADT) or surgical treatment.

Androgen depletion is not a curative therapy because some cells are already castration resistant when PC presents for the first time. For that reason, the PSA level in 60-70% of patients will return to normal values, there is a regression of detectable lesions in about 50% (2).

Surgical orchiectomy is used to remove the testis and stop the production of testosterone (2). This technique was the "gold standard" but nowadays replaced by chemical castration (52).

1.10.2.2 TESTOSTERONE LOWERING AGENTS

Gonadotropin-releasing hormone (GnRH) agonists and antagonists induce androgen deprivation by blocking the luteinizing hormone (LH) on the pituitary level (3). Goserelin acetate, triptorelin pamoate, histrelin acetate and leuprolide acetate are approved for the treatment of PC (3). After administration of GnRH agonists, the LH and follicle-stimulating hormone levels rise initially and cause the "flare phenomenon" due to the rise in the testosterone level, which leads to bone pain, cord compression and bladder outlet obstruction (53). After this initial reaction a downregulation of receptors takes place which leads to a chemical castration (2).

GnRH antagonists like degarelix on the other hand, don´t cause the initial rise in testosterone levels and can achieve a chemical castration within 48h (2). Compared to GnRH agonists, the antagonists show a more rapid suppression of LH, RH and testosterone in addition to a better disease control with less side-effects (54).

In patients with impending spinal cord compression, bilateral orchiectomy or LHRH antagonist should be considered as first-line treatment (49).

Administration of testosterone lowering agents can lead to the androgen depletion syndrome which is characterized by fatigue, weakness, hot flushes, impotence, loss of libido, anemia, sarcopenia (2). Other side effects are a decrease in bone density and an increased risk

of diabetes and cardiovascular disease (55). By prescribing calcium, vitamin D supplements or in severe cases bisphosphonates, the bone changes can be prevented (3).

1.10.2.3 ANTIANDROGENS

Drugs like flutamide, bicalutamide, and nilutamide, block the androgen receptors in the prostate cell and therefore block the flare disease if they are given together with GnRH agonists (2). Non-steroidal antiandrogens should not be used as mono therapy due to the lacking benefits (2,49). In M1 patients with advanced metastatic disease, it is recommended to perform short-term administration of antiandrogens due their suppressive effect on the "flare phenomenon" (49).

1.10.2.4 INTERMITTENT ANDROGEN DEPRIVATION THERAPY (IADT)

IADT uses the "on- and-off" approach to decrease side effects and to prevent the prostate cells from becoming resistant to ADT (2). The intermittent deprivation seems to be as effective as the continuous use but shows tolerability and quality of life advantages (56). There is evidence that using IADT can be helpful for patients with relapsing, locally advanced, or metastatic PC with a good initial response to androgen deprivation (57).

1.1.10.3 CASTRATION RESISTANT METASTATIC PROSTATE CANCER (CRPC)

CRPC is defined as a progressing disease despite androgen suppression by surgical medical intervention, where the testosterone level was <50 ng/ml (2). Furthermore, a biochemical progression includes three following increases of the PSA level above the nadir with >2 ng/ml which are 1 week apart (49). In addition to biochemical progression, radiological progression includes the presence of two or more bone lesions on a bone scan or a progression of a soft tissue lesion (49). Transdifferentiation or androgen receptor (AR) independence, leads to the development of CRPC (58). The result is an increase in the PSA level which indi-

cates signaling through AR signaling axis despite androgen deprivation therapy (2). The prognosis of patients with CRPC is poor and needs multidisciplinary approach (59). The baseline PSA and PSA velocity independently predict the survival and development of bone metastases (60).

Docetaxel belongs to the taxane-based chemotherapeutics. In combination with prednisone it approved for the treatment of CRPC (59). In high risk patients with metastatic CRPC characterized by a PSA >114 ng/ml, visceral metastases, <12 months response to ADT and tumor related complications, first-line chemotherapy is indicated (61).

Cabacitaxel is a non-cross resistant taxane which can be offered to patients who progressed after docetaxel therapy (62). After docetaxel failure, it shows a better overall survival compared to mitoxantrone with prednisolone (61).

Sipuleucel-T is a biological agent based on autologous dendritic cells which are capable of detecting prostatic acid phosphatase (3). It may be offered to asymptomatic or minimally symptomatic patients (62).

Abiraterone acetate is a CYP17 inhibitor which leads to a decreased production of androgens in the PC, testis and adrenal glands (2). Its use shows increased radiographic progression-free survival and possible improved overall survival in patients with CRPC who did not receive chemotherapy (63). Possible side-effects are due to the long-term use of corticosteroids like inducing a loss of bone minerals and inducing osteoporosis, diabetes and central nervous system effects. On top of these effects, abiraterone acetate can lead to an increase in blood pressure, increased level of fatty acids in the blood, anemia and urinary tract infections.

Enzalutamide is a new generation nonsteroidal antiandrogen which has a higher affinity for the AR receptors and distinctively blocks nuclear location and DNA binding of the receptor complex (2). This drug improves the patient related outcomes and delays the development of the first skeletal metastases (64). Enzalutamide similarly prolongs survival if given after chemotherapy (65). The most common side effects are fatigue and hypertension (49).

1.10.4 BONE METASTASES

Painful bone metastases are a characteristic feature of CRPC. Therapy with short or long-course external beam RT is effective in treating bone lesions (66).

Alpharadin is alpha-emitting radium-223 chloride, which finds the metastatic bone lesions (2).

Bisphosphonates like zoledronic acid are used to block bone resorption mediated by osteoclasts.

Denosumab is a RANK ligand inhibitor protecting against bone loss due to androgens (2). The human monoclonal antibody targets RANKL which is an important mediator of osteoclast activity and survival (49).

1.1.11 FOLLOW-UP

Follow-Up is performed by using DRE and PSA-level examinations together with history taking specific for the disease (49).

After RP, PSA should be unobserved within 6 weeks after successful treatment. If the levels continue to be elevated, that can be due to residual cancer tissue. A rapid increase in PSA can point to distant metastases (49). The post RP PSA levels usually precede a disease progression but in some cases the disease can progress without a PSA change (67).

After RT, the PSA level drops slowly which can last up to 3 years or more. Failure is defined a PSA >2 ng/ml above the nadir (49). PSA doubling times (DT) seems to correlate with the location of recurrence, meaning local recurrence has a longer DT than distant recurrence (68).

During ADT the PSA level helps to follow the course of the PC and predict the survival (49). Patients with a PSA of <0.2 ng/ml have a median survival of 75 months, PSA 0.2-0.4 ng/ml or less have 44 months and PSA >0.4 ng/ml have 13 months (69).

1.2 Salvage radiotherapy

1.2.1 Definition

Salvage radiotherapy (SRT) is a method which uses radiation to control the recurrence (local or biochemical) of PC after RP and to avoid or delay the development of metastases which can lead to the death (70). It delivers radiation to the prostate bed and possibly to the surrounding tissues like lymph nodes (71). The outcomes after SRT are reported as biochemical recurrence, biochemical recurrence-free survival (bRFS), local recurrence, local recurrence-free survival, metastatic recurrence, metastatic recurrence-free survival (mRFS), clinical progression-free survival, cancer-specific survival, and overall survival (71).

1.2.2 Indication

SRT is indicated only for patients with PSA (biochemical) or local recurrence after RP, in whom distant metastases are not present (71). A PSA level > 0.2 ng/ml after RP is considered biochemical failure (42). Adverse pathologic findings at RP such as the invasion of the seminal vesicles, positive surgical margins, or extraprostatic invasion should be treated with adjuvant radiotherapy (71). Characteristics of the PC at time of diagnosis, PSA doubling time (PSADT) which follows the relapse, and the PSA level when the patient entered the protocol seem to be associated with progression to development of metastatic PC (72). A retrospective study found out that patients with a high-grade PC and/or a fast PSADT who naturally would progress to metastatic PC can profit from SRT treatment (73).

Postoperative radiation may not be necessary in men who have a preoperative PSA velocity of 0.5 ng/ml/yr or less, PSA level which is < 10 ng/ml, a nonpalpable PC with a GS <6 when diagnosed (74).

1.2.3 Diagnostics

Clinical history, physical examination, and the PSA kinetics are the main tests in evaluating PC recurrence after RP (75).

1.2.4 Risk of post treatment complications

SRT causes toxic effects mostly in the genitourinary (GU) and gastrointestinal (GI) system but can as well lead to secondary pelvic malignancies (70). Low doses as well as high doses (>70.2 Gy) are well tolerated but can lead to mild side-effects like diarrhea and proctitis (76). Delayed recovery of sexual function is a possible side-effect of patients treated with SRT (77). Acute GU problems tend to recover sooner after the end of RT compared bowel symptoms (78).

1.2.5 Technique and dosing

The European Association of Urology guidelines recommend doses of 64-66 Gy at a PSA of ≤ 0.5 ng/ml (79). Using the maximum radiation dose with acceptable toxic effects and a minimum dose of 64-65 Gy is recommended by the American Society of Radiation Oncology (ASTRO) (71).

Patients who have a postoperative PSA > 2 ng/ml and a pT3N0 PC are less likely to benefit from higher RT doses (80).

When performing SRT, irradiating the prostate bed with 70 Gy is recommended to accomplish the optimal disease-free survival after RP (81). Doses of 78 Gy delivered to patients at intermediate-to-high risk increase the freedom from failure but increase the toxic effects as well (82). In addition to that, Zietman *et al.* mention that high doses of 79.2 Gy are responsible for a lower risk of biochemical failure in patients with localized PC compared to conventional doses of 70.2 Gy (83). On top of that, a longer PSA disease-free survival (PSA-

DSF) is as well associated with higher radiation doses when the patients were controlled for pre-treatment PSA, biopsy GS, and clinical T stage (84).

1.2.6 Combination with androgen deprivation therapy

A retrospective study was performed on 157 patients treated with RT after receiving RP (85). Pre-RT PSA seems to be important for the outcome of SRT. Giving neoadjuvant ADT (NADT) to patients with pre-RT PSA of >0.2 ng/ml before SRT, seems to have a beneficial effect on the biochemical disease-free survival (BDFS). In addition to that, they found out, that pre-RT PSA <2.0 ng/ml, low GS and positive surgical margins are strong independent factors for the BDFS prediction.

1.2.7 Results of treatment

The prognostic response to SRT can be defined by GS, preradiotherapy PSA level, surgical margins, PSADT, and seminal vesicle invasion (73). Progression of PC can be predicted by GS 8-10, preradiotherapy PSA >2.0 ng/ml, negative surgical margins, PSADT ≤10 months, seminal vesicle invasion (73).

PSADT is especially important for the prediction of the biochemical control and disease recurrence because a short PSADT is associated with a worse chance of control (75).

The risk of developing metastases can be decreased and the survival can be increased by treating the patient with adjuvant radiotherapy (86). Stephenson *et al.* developed a nomogram in order to predict the cancer control at 6 years for patients who received SRT for recurrent PC which was defined by PSA (87). In addition to that, they found out that patients will have a long-term PSA response if SRT is started at the first sign of recurrence (87).

2. OBJECTIVES

The goal of this single center, retrospective study, was to analyze the outcome [overall survival (OS), metastases-free survival (MFS), time to second biochemical progression (SBP)] in patients with biochemical relapse after RP receiving SRT, at the Department of oncology and Radiotherapy in the University Hospital of Split. Patients treated with SRT from the years 2006 until 2015 were included into this study.

3. MATERIALS AND METHODS

3.1 DATA COLLECTION:

This retrospective cohort study is composed of 124 patients, who were treated with salvage RT at the Department of Oncology and Radiotherapy, in the University Hospital of Split between the years 2006 and 2015. Values were taken from the individual patients charts and missing data was requested from the other institutions in Zadar, Šibenik and Dubrovnik. The cut-off for data collection was the 1.2.2018.

3.2 INVESTIGATED VARIABLES:

124 patients treated with SRT were analyzed according to Initial PSA before prostatectomy in ng/ml, PSA after surgery in ng/ml, GS, initial stage, perineal invasion (yes vs. no), lymphovascular invasion (yes vs. no), biochemical relapse free survival, median time from PSA relapse to start of SRT, PSA at beginning of SRT, PSA response after SRT, dose of radiation, second PSA progression after SRT (yes vs. no), SBP, third biochemical progression after ADT, MFS, development of metastases (yes vs. no), and the OS was analyzed and summarized as medians.

3.3 STATISTICAL ANALYSIS:

Statistical analysis was performed by using the MedCalc software for Windows, version (MedCalc Software, Mariakerke, Belgium). The Kolmogorov Smirnov test was used to assess whether the data was normally distributed or not.

Categorical variables were presented using frequencies and percentages and the differences were tested using Chi squared test, while numerical variables were presented using median and 95% CI. For survival analysis, the Kaplan Meier analysis was used. The Spearman Coefficient was used in order to assess the relationships between the different variables. A Correlation was significant with a $P<0.05$.

4. RESULTS

Table 2 shows the clinical characteristics and outcomes of this study which included 124 men treated with SRT in the Department of Oncology and Radiotherapy. There was a higher PSA level before the surgery compared to the status after surgery (Table 2).

Table *2*: clinical characteristics of 124 patients included into this study

	Median	95% CI
Age at SRT in years	68	66.6 - 70.0
Initial PSA level *	9.9	8,6 - 11
PSA level after surgery *	0,068	0,04 - 0,129
Biochemical relapse free survival in months	26.00	19.15 - 30.84
Dose of radiation †	66.0	66.0 - 66.0
Second biochemical free survival in months	43.50	35,61 - 49.00
Time from PSA relapse to beginning of SRT in months	5.5	4.0 - 7.0
Beginning of ADT to progression in months	21	5.81 - 62.11
Follow-up in months	58.00	50.21 - 67.00
Metastases-free survival in months	52.50	46.61 – 59.00
Overall survival in months	53.00	47.00 – 59.39

Abbreviations: CI, confidence interval; SRT, salvage radiotherapy; PSA, prostate-specific antigen; ADT, androgen deprivation therapy

* Ng/ml

† Gray

In Table 3, categorical variables examined in this study are shown. The majority of patients presented with a Gleason score of 7. In addition to Gleason score, the TNM stage was noted with the majority of patients being staged T2(a-c)N0M0. The presence of lymphovascular and perineural invasion was mostly not documented in the patient charts.

The patients were divided into groups according to the PSA level at the beginning of SRT, leading to the majority of patients having a PSA level of less than 0.7 ng/ml. After treating the patients with SRT, the response to the therapy was measured as percental decrease of PSA and grouped according to the amount of decrease. Most of the patients had a high response of more than 90%. At the cut-off (1.2.18) of this study, the great majority of patients are still alive.

Table 3: categorization of the 124 patients included into this study

Parameter		No.	%	*P* value †
Gleason score	3-6	41	33.1	<0.001
	7	63	50.7	
	8-9	17	13.6	
	unknown	3	2.4	
Initial TNM stage	T1N0M0	8	6.5	<0.001
	T2(a-c)N0M0	63	50.8	
	T3NoMo	34	27.4	
	T3bN0M0	11	8.9	
	unknown	8	6.5	
Perineural invasion	yes	30	24.2	<0.001
	no	27	21.8	
	unknown	67	54	
Lymphovascular invasion	yes	47	37.9	<0.001
	no	6	4.8	
	unknown	71	57.3	
PSA at beginning of SRT *	<0,7	68	54.8	<0.001
	0,7-1,5	24	19.4	
	1,5-2,0	11	8.9	
	2,0-4,0	11	8.9	
	>4,0	9	7.3	
	unknown	1	0.8	
PSA response after SRT	<30%	15	12.1	<0.001
	30-50%	1	0.8	
	50-75%	7	5.6	
	75-90%	10	8.1	
	>90%	80	64.5	
	unknown	11	8.9	
Second PSA progression after SRT	yes	33	26.6	<0.001
	no	91	73.4	
Third progression (from beginning of ADT to progression)	Valid cases	8	6.45	<0.001
	No progression	116	93.55	
Development of metastases	yes	4	3.2	<0.001
	no	120	96.8	
Survival of patients until 1.2.18	Alive	112	90.32	<0.001
	Dead	12	9.68	

Abbreviations: GS, Gleason-Score; PSA, prostate-specific antigen; SRT, salvage radiotherapy
*Ng/ml † Spearman-Coefficient

In table 4 the correlations between the investigated variables are shown. The lymphovascular invasion shows to be related to the MFS (r = -0.21, CI: -0.37 to -0.04, *P* = 0.015) and to OS (r = -0.2484, CI: -0.4069 to -0.07540, *P*=0.005). Besides lymphovascular invasion, also the perineural invasion looks to related to OS (r = -0.19, CI: -0.35 to -0.014, *P* = 0.034). In addition to that, the initial TNM stage shows a relationship to the OS (r = -0.18, 95% Ci = -0.35 to -0.002, *P* = 0.047).

There was no relationship shown between the Initial stage and the metastases-free survival (*P*=0.06. Also, the biochemical relapse free survival shows no relationship to the PSA response after therapy (P=0.086), metastases free survival (P=0.269) and the overall survival (P=0.119). In addition to that, the Gleason score as well, shows no relationship to the PSA response (P=0.066), the MFS (P=0.656) and the OS (P=0.601). Furthermore, there is no significant relationship between the PSA response after SRT and the biochemical relapse free survival (P=0.086), the MFS (P=0.978) and the OS (P=0.984).

The 5-year overall survival of the patients included is 91.7% (95%CI= 85.71 to 97.90) (Figure 1); the 5-year biochemical relapse-free survival was 85.51% (95%CI = 76.68 to 94.33) (figure 2) and the 5-year metastases-free survival was 91.09% (95%CI = 85.00 to 97.35) (figure 3).

TABLE 4: Correlation between evaluated patient characteristics

	Biochemical relapse-free survival	Metastases-free survival	Overall survival	PSA re-sponse after therapy
Biochemical relapse free survival	-	0.269	0.119	0.086
Lymphovascular invasion	0.642	0.015*	0.005*	0.255
Perineural invasion	0.169	0.071	0.034*	0.064
Initial TNM stage	0.149	0.063	0.047*	0.149
Gleason Score	0.541	0.656	0.601	0.066
Dose of radiation	0.769	0.066	0.460	0.894
PSA response after therapy	0.086	0.978	0.985	-

*Correlation (Spearman Coefficient) is significant if below $P<0.05$

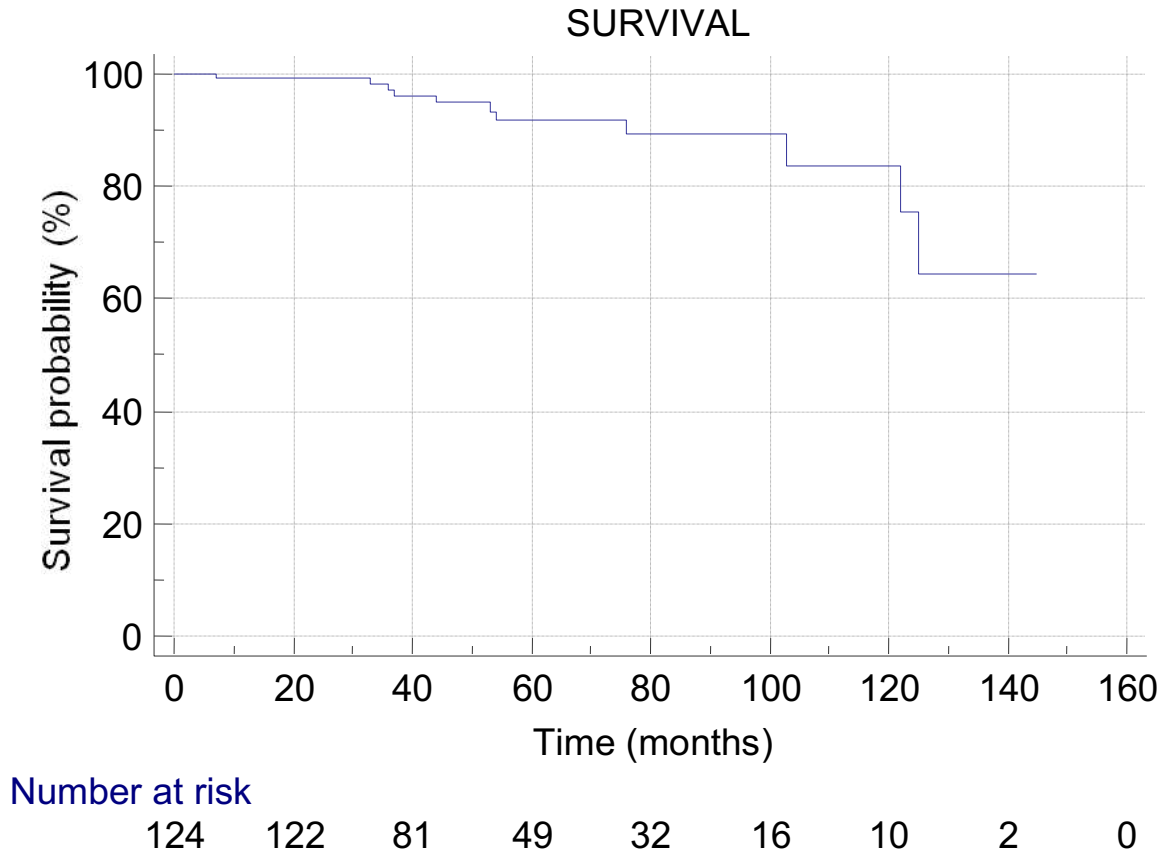

Figure 1: Kaplan-Meier survival analysis of the 124 patients included into this study

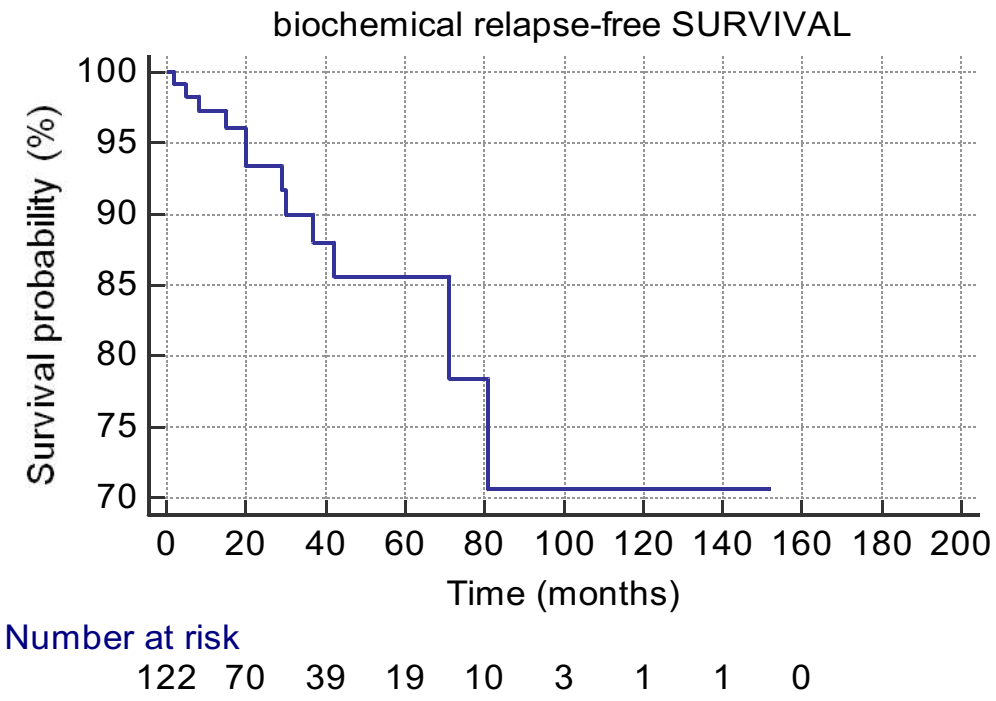

Figure 2: Kaplan-Meier analysis of the biochemical relapse-free survival of the 124 patients

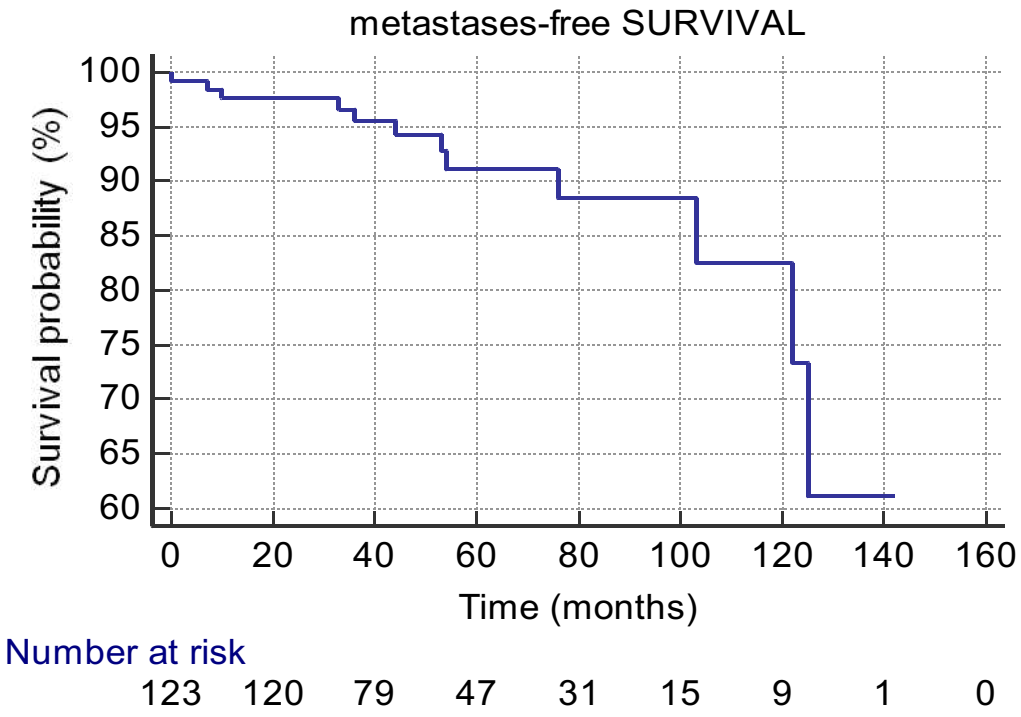

Figure 3: Kaplan-Meier analysis of the metastases-free survival of the 124 patients

5. DISCUSSION

Prostate cancer is a common problem in men with advancing age. Treating this type of cancer is therefore of great interest for the patients as well as the doctors, especially in case of failure of primary treatment. In this study we examined those patients who developed a biochemical progression after being treated with RP and for that reason received SRT. Today SRT and ADT are the only curative therapies for biochemically recurrent PC with SRT being limited to localized PC without metastatic spread.

The results of this study show, that patients achieve the best response to SRT when therapy is applied early after the biochemical relapse of the disease. Furthermore, a negative correlation between the lymphovascular invasion and MFS, OS and between perineural invasion together with the initial TNM and OS was established.

We showed, that most of patients who treated after a median time 5,5 month, responded predominantly with a decrease of the PSA level by more than 90% of the level they had before starting SRT. The study made by Choo *et al.* determined the efficacy of external beam radiation as SRT (88). The initial PSA response of 86% to 94% is consistent with the results of our study, but then dropped to a complete response of 53% to 62%. The drop in the complete response points to a difference to the response rate determined by us because patients treated with SRT did rarely develop an increase of the PSA level after the therapy and therefore maintained their results.

The PSA level at the beginning of SRT shows to be an important predictor for the response to the therapy. Macdonald *et al.* found out that patients with a PSA < 0.6 ng/ml and RT doses of more that 64.8 Gy have the best benefit from SRT (89). These results further strengthen the findings of this study, in which we found that patients with a PSA level at the beginning of SRT below 0,7 ng/ml achieve good benefits from the therapy. Treating Patients with a low PSA level at the beginning of SRT shows an improved response to the therapy which is consistent with the results from King (90).

As reported by MacDonald *et al.*, treating a biochemically relapsing PC when the PSA level is still below 0.5 ng/ml, the biochemical control rate seems to improve (89). The results we found, correlate with their findings in the way that less than one third of our patients developed a second biochemical relapse after introducing SRT and therefore are biochemically controlled.

Our findings show that out of 124 patients on 4 developed metastases during the follow-up period. The early application of SRT decreases the development of metastases and increases the metastatic-free survival. Studies performed by Stephenson *et al.* and Boorjian *et al*. show that the application of SRT improves the metastases-free survival and are therefore corresponding the before mentioned results (87,91).

During the follow-up period of the present study, the five-year survival rate of 91.7% was established. The randomized trials by Bolla *et al.* which shows a survival of 93% and Thompson *et al*. with a survival of approximately 90% in patients staged pT3 (43,86). Furthermore, the Toronto Sunnybrook Regional Cancer Centre came showed survival rates after 4 years between 89% to 94% (88). These findings confirm the results found by this study. As expected, SRT offered to patients having a biochemical relapse after RP at the Department of Oncology and Radiotherapy shows similar survival rates as the aforementioned studies.

Lymphovascular invasion seems to be negatively related to MFS and OS, meaning that no invasion may lead to better survival outcomes in patients treated with SRT. The same correlation was established when relating perineural invasion and OS. In addition to that a lower initial TNM stage, could possibly have an impact on the OS. Our findings appear to be well supported by Stephenson *et al.* who mentions, that lymphovascular invasion as a predictor of the durable response to SRT (73). In contrast to the beforementioned study in which GS, pre SRT PSA level are additional prognostic variables of the response to SRT, we could not find a significant relationship between these factors and the MFS and OS.

The majority of patients was treated with a median of 66 Gy, resulting decreased PSA level of more than 90%. Delivering doses around 66 Gy appears to be related to a good response to therapy (89,90). Combining the early start of therapy and the radiation dose, results in optimal therapy outcomes and survival. In contrast to these results, we could not establish a significant relationship between the administered dose of radiation and the PSA response after SRT, MFS and the OS.

The results produced by this study need to be interpreted with caution. On the one hand, it is due to the nonrandomized and retrospective nature of this study. On the other hand, the limitations of our study are due to the missing comparative group which is not treated with SRT to calculate the corresponding values for survival. Given the relatively small number of patients in a single institution, problems in calculating significant differences and relationships between the mentioned variables may appear and have to be interpreted with caution.

6. CONCLUSION

1. The use of SRT in treating patients with a biochemical relapse after RP leads to a good response with decreases of PSA levels of more than 90%.
2. The overall survival is similar to results achieved by other institutions.
3. The development of metastases can be prevented if therapy is started early and at an PSA level lower than 0,7 ng/ml.
4. If there is less or no involvement of the surrounding tissues in addition to a low initial TNM stage, the MFS and OS is improved.

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8. SUMMARY

Title: Salvage radiotherapy of prostate cancer, retrospective analysis of 10 years' experience in the Department of Oncology and Radiotherapy University Hospital of Split.

Objectives: We evaluated the clinical outcomes of patients treated with salvage radiotherapy (SRT) after biochemical relapse regarding the biochemical control after surgery, overall survival (OS) and metastatic-free survival (MFS).

Materials and Methods: A retrospective cohort study (from 2006 until 2015) using the data collected from patient charts in the Department of Oncology and Radiotherapy in Split with missing data requested from Zadar, Šibenik and Dubrovnik. A total of 124 patients treated with salvage radiotherapy after developing biochemical relapse following radical prostatectomy (RP) were included into this study.

Results: The median follow-up from salvage radiotherapy to the 1.2.18 was 58 months with 68 years being the median age of the patients. Therapy was started after a median of 5.5 months. Out of the 124 patients, 68 started SRT with a PSA level below 0.7 ng/ml. 80 patients responded to the therapy with drop in PSA of more than 90%. Progression after SRT was observed in 33 patients and 4 patients developed metastases. This leads to a median biochemical relapse-free survival (BRFS) of 26 months, OS of 53 months, an MFS of 52.5 months. The 5-year overall survival of the patients included is 91.7% (95%CI= 85.71 to 97.90); the 5-year biochemical relapse-free survival was 85.51% (95%CI = 76.68 to 94.33) and the 5-year metastases-free survival was 91.09% (95%CI = 85.00 to 97.35). A relationship was shown between lymphovascular invasion and MFS (P=0.015) and OS (P=0.005). Perineural invasion (P=0.034) and the TNM stage (P=0.047) show a relation to OS. Other relationships were not observed.

Conclusion: Patients treated with SRT show a good biochemical response after the therapy. If the surrounding tissues were not involved and the initial TNM stage is low, the outcomes improve leading to a better MFS and OS.

9. CROATIAN SUMMARY

Naslov: "Salvage"-radioterapija (SRT) karcinoma prostate, retrospektivna analiza desetgodišnjeg iskustva Klinike za onkologiju i radioterapiju Kliničkog bolničkog centra Split.

Ciljevi: Evaluacija ishoda liječenja pacijenata SRT kod biokemijskog recidiva nakon radikalne prostatektomije obzirom na biokemijsku kontrolu (PSA), ukupno preživljavanje (OS) i preživljavanje bez metastaza (MFS).

Materijali i metode: Retrospektivna kohortna studija (od 2006 do 2015) na osnovu podataka dobivenih iz povijesti bolesti pacijenata s Klinike za onkologiju i radioterapiju u Splitu, te s odjela onkologije OB bolnica u Zadru, Šibeniku i Dubrovniku. Ukupno je u studiji obrađeno 124 pacijenta koji su liječeni SRT zbog biokemijskog recidiva nakon radikalne prostatektomije.

Rezultati: Medijan praćenja nakon SRT je bio 58 mjeseci (do 01.02.2018), medijan dobi pacijenata iznosi 68 godina. Sa SRT se počelo u prosijeku nakon 5,5 mjeseci. Kod 68 pacijenata od ukupno 124, počelo se sa SRT kod vrijednosti PSA ispod 0,7 ng/ml. Kod 80 pacijenata je pala vrijednost PSA za više od 90%. Biokemijska progresija bolesti nakon SRT je primjećena kod 33 pacijenata, a u 4 pacijenta su se razvile presadnice. To odgovara medijanu preživljenja bez biokemijskog recidiva (bRFS) od 26 mjeseci, medijanu ukupnog preživljenja (OS) od 53 mjeseca i medijanu preživljenja bez metastaza (MFS) od 52,5 mjeseci. Stopa petogodišnjeg preživljenja iznosi 91,7% (95%CI= 85.71 do 97.90); petogodišnje preživljenje bez biokemijskog recidiva iznosi 85.51% (95%CI = 76.68 do 94.33) i petogodišnje preživljenje bez metastaza iznosi 91.09% (95%CI = 85.00 to 97.35). Postoji povezanost između limfovaskularne invazije i preživljavanja bez metastasa (MFS) (*P*=0,015) i ukupnog preživljavanja (OS) (*P*=0,005). Nadalje postoji povezanost perineuralne invazije (P=0,034) i TNM-stadija (*P*=0,047) s ukupnim preživljavanjem.

Zaključci: Salvage-radioterapija kod pacijenata s biokemijskim rezidivom nakon radikalne prostatektomije uzrokuje pad vrijednosti PSA PSA i utječe na ukupno preživljenje, preživljenje bez biokemijske progresije i preživljenje bez pojave presadnica Izostanak tumorske infiltracije okolnog tkiva i niski inicijalni TNM-stadij poboljšavaju prognozu obzirom na preživljavanje bez metastaza (MFS) i ukupno preživljavanje (OS).

10. CURRICULUM VITAE

Personal information:

Name and Surname: Sebastian Jakov Horst Radosevic

Date of birth: 30th of August 1991, in Bocholt, Germany

Nationality: German

Address: Op de Haare 19, 46397 Bocholt, Germany

E-Mail: sebastian.radosevic@gmx.net

Education:

2012-2018: University of Split School of Medicine, Split, Croatia

2009-2012: Berufliches Gymnasium für Gesundheit und Erziehung, Borken, Germany

2002-2009: Euregio-Gymnasium, Bocholt, Germany