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UROLOGICAL ONCOLOGY

The long-term outcomes of radical prostatectomy for very high-risk prostate cancer pT3b-T4 N0-1 on definitive histopathology

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Introduction The study aimed to assess long-term outcomes in patients with very high-risk prostate cancer (PCa) – pT3b-T4 N0-1 using the definitive histopathology following radical retropubic prostatectomy (RRP).
Material and methods We have analyzed 114 patients with very high-risk PCa who underwent RRP between 1995 and 2012. Biochemical and clinical progression-free survival (BPFS, CPFS), cancer-specific and overall survival (CSS, OS) curves were constructed according to the Kaplan-Meier method. Univariate and multivariate Cox regression analysis was utilized to determine predictability of clinical and pathological parameters.
Results At the 5 and 10 year mark, the BPFS was 71.3% and 35%, respectively; the CPFS was 86.8% and 69.2%, respectively; the CSS was 98% and 76.3%, respectively and the OS was 90.3% and 62.4%, respectively. Sixteen patients (14%) had lymph-node involvement. Positive surgical margins were present in 64 (56.1%) patients. Neo-adjuvant androgen deprivation therapy (ADT) was received by 22 (19.3%) patients. Adjuvant ADT alone or in combination with external radiotherapy was received by 59 (51.8%) patients. No adjuvant treatment was needed in 29 (25.4%) patients. In univariate and multivariate analysis, neo-adjuvant ADT was associated with an increased risk of BPFS and CPFS.
Conclusions Therapy applied in patients with very high-risk PCa was multimodal in most cases, with RP usually being the first step. The study confirmed that very high-risk PCa is a heterogeneous disease. A significant subset of patients remain without adjuvant therapy treatment.

Key Words: very high-risk prostate cancer ‹› radical prostatectomy ‹› radiotherapy ‹› androgen deprivation

INTRODUCTION

Despite the ability to diagnose low-risk prostate cancer (PCa) by screening based on prostate-specific antigen (PSA), high-risk patients comprise a significant group of population between 26% to 39% [1, 2, 3]. According to the European Association of Urology (EAU) Guidelines [4], high-risk PCa is defined as localized diseases having the clinical stage T2c, a Gleason score (GS) of 8–10 or a PSA >20 ng/ml and locally advanced PCa T3-T4, any Gleason score, any PSA or cN+ disease can be referred to as a very high-risk disease. These criteria, originating from the risk group stratification by D'Amico et al. [5], was later modified to be helpful for the identification of patients who were at very high risk of biochemical recurrence and disease progression after definitive local therapy. Optimal treatment of the high- and very high-risk PCa remains controversial, and standardized treatments currently do not exist for such patients [6]. Traditionally, radical prostatectomy (RP) is not preferred, especially due to suboptimal

oncological disease control reflecting a higher incidence of positive surgical margins, more frequent local recurrence and possible occurrence of undetected metastasis [7]. As a result, the treatment has focused on combinations of external radiotherapy and androgen deprivation therapy (ADT), which has become the standard care for these patients [4, 8, 9]. However, in the last decade, the published data suggests that patients with very high-risk PCa treated with RP show excellent local tumor control and similar oncological results, especially in conjunction with multimodal treatments involving androgen deprivation and radiotherapy [10–17]. Consequently, the EAU supports optional treatment for the selective group of patients without PCa fixed to the pelvic wall, rectum and sphincter muscle by RP, with extended pelvic lymph node dissection in the context of multimodal treatment [4].

Previously, clinical evaluation of local staging of PCa was based mainly on digital rectal examination. Currently, clinical evaluations also include magnetic resonance imaging (MRI) and computer tomography (CT), which help define the local extent of the disease. Cutting-edge technologies, such as multiparametric magnetic resonance imaging (mpMRI), allow further improvement in the disease staging. The mpMRI sensitivity and specificity in detecting different stages of PCa, according to literature, varies between 33–93% and 82–98%, respectively [18]. However, the accuracy of these methods is not perfect, and therefore, some patients are classified into the locally advanced stages of PCa (T3a, T3b and T4) on the definitive histopathology following RP [6]. The aim of this study was to evaluate long-term outcomes in patients with very high-risk PCa pT3b-T4N0-1 on the definitive histopathology following radical RP.

MATERIAL AND METHODS

We have retrospectively analyzed the results of radical retropubic prostatectomy (RRP) in 114 patients who underwent surgery between 1995 and 2012 and had very high-risk PCa of pT3b, pT4 and N0-1 on definitive histopathology and had pre-surgically unfixed PCa in the pelvic wall and the surrounding tissues. Their Eastern Cooperative Oncology Group (ECOG) performance status was 0–1. PCa was diagnosed according to the standard procedures including increased PSA or positive digital rectal examination (DRE) with subsequent transrectal ultrasonography (TRUS) guided biopsy of the prostate. Local extent of disease was assessed by the same urological surgeon according to DRE, in some patients also using CT examination. No patients had any evidence of lymph node involvement. All patients had a bone scan that did not reveal metastases. RRP and standard pelvic lymphadenectomy without frozen sections was performed by a single surgeon. Patients' information was retrieved from the patient medical records and from cooperating urologists from urological clinics. Histological examination of the prostate, seminal vesicles and pelvic lymph nodes was performed by two pathologists. The RP specimens were weighted, measured, stained and fixed in whole with 10% neutral formalin solution within 24 hours. Conventionally, 36 tissue blocks containing the apex and including the prostate base were examined. Cut tissue slices were stained with haematoxylin and eosin (H & E) using a standard procedure. Pathological stage and histological grading were evaluated according to the 2002 UICC TNM system [19]and the Gleason grading system [20]. Positive surgical margins were recorded when tumour cells were present at the resection lines [21]. Biochemical progression was defined when the PSA value increased ≥0.2 ng/ml in two consecutive measurements. Clinical progression was recorded according to local recurrence of disease or distant metastases using bone scan and CT examination.

After the surgery, serum PSA and physical examination was performed every 3 months in the first year, then every six months up to the end of five years and annually thereafter. Examination intervals were adjusted individually at biochemical and clinical progression.

Adjuvant treatment was started within 3 months after radical prostatectomy. The decision about adjuvant treatment by radiotherapy of prostatic fossa alone or/and androgen deprivation therapy was made by the urologist in cooperation with the oncologist. The patients with pGS 8–9, positive surgical margins and positive lymph nodes were treated immediately. The patients with pGS 7, negative surgical margins, without lymph node involvement were regularly followed-up and was further treated if they developed disease progression.

Continuous variables were summarised with descriptive statistics (N, Mean, STD, Minimum, Median, and Maximum). Discrete variables were displayed in frequency tables (N, %). BPFS, CPFS, CSS, OS were determined using the Kaplan-Meier analysis. Univariate and multivariate (method enter) Cox regression analysis was used for the determination of predictive clinical and pathological parameters. Input parameters were PSA before surgery, GS, positive lymph nodes, positive surgical margins, pathological stage, neoadjuvant ADT and continual ADT. All testing performed were two-sided tests with the criteria set at $\alpha = 0.05$. A p-value of <0.05 was considered statistically significant. We used the statistical software IBM SPSS.

RESULTS

The mean age of patients at the time of surgery was 62.6 ±5.9 years. Median follow-up was 62 months (range 4–205). Median PSA was 10.5 ng/ml (range 3.2–100). The clinical stage cT2 had 19 (16.7%), and cT3 had 95 (83.3%) patients. The biopsy GS of 6 had 36 (31.6%) patients, the biopsy GS of 7 had 45 (39.5%) patients, the biopsy GS of 8 had 21 (18.4%) patients and the biopsy GS of 9 had 12 (10.5%) patients. Following surgery, pathological stage pT3b was confirmed in 107 patients (93.9%) and pT4 in 7 patients (6.1%). The specimen GS of 6 was confirmed in 3 patients (2.6%), the specimen GS of 7 in 55 patients (48.2%), the specimen GS of 8 in 18 patients (15.8%) and the specimen GS of 9 in 38 patients (33.3%). Positive lymph nodes were found in 16 (14.0%) patients. The mean number of removed lymph nodes was 7. Positive surgical margins were confirmed in 64 patients (56.1%). Neoadjuvant ADT in the period of 3–6 months had 22 patients (19.3%) from whom 15 continued on adjuvant ADT. Continual adjuvant ADT had 59 patients (51.8%). This treatment in combination with radiotherapy had 41 patients (36.0%). Adjuvant ADT alone after biochemical progression had 17 patients (14.9%), and adjuvant ADT with radiotherapy after biochemical progression had 8 patients (7.0%). Biochemical progression with median of 38 months was noted in 39 patients (34.2%) and clinical progression with a median of 50 months in 17 patients (14.9%). Deaths associated with prostate cancer were recorded in 11 patients, and a further 15 patients died of unrelated causes. Thirty patients remained without neoadjuvant and adjuvant therapy until the end of the monitored period (26.3%). The patients' characteristics are outlined in Table 1.

Table 1. *Patient characteristics*

Patient age at RP (years), mean ±SD	62.6 ±5.9
Follow-up (months), median (range)	62 (4–205)
PSA (ng/ml), median (range)	10.5 (3.2–100)
Clinical stage	
cT2 n (%)	19 (16.7)
cT3	95 (83.3)
cT4	0 (0.0)
Biopsy Gleason score	
Gleason 6, n (%)	36 (31.6)
Gleason 7	45 (39.5)
Gleason 8	21 (18.4)
Gleason 9	12 (10.5)
Gleason 10	0 (0.0)
Pathological stage	
pT3b, n (%)	107 (93.9)
pT4	7 (6.1)
Specimen Gleason score	
Gleason 6, n (%)	3 (2.6)
Gleason 7	55 (48.2)
Gleason 8	18 (15.8)
Gleason 9	38 (33.3)
Gleason 10	0 (0.0)
Positive lymph node, n (%)	16 (14.0)
Positive surgical margin, n (%)	64 (56.1)
Neoadjuvant ADT, n (%)	22 (19.3)
Continual ADT and/or RT, n (%)	59 (51.8)
Salvage ADT and/or RT, n (%)	25 (21.9)
No therapy, n (%)	30 (26.3)

RP – radical prostatectomy; PSA – prostate-specific antigen; ADT – androgen deprivation therapy; RT – radiotherapy

The BPFS at 3, 5 and 10 years was 83.6%, 71.3% and 35.0%, respectively, the CPFS was 93.8%, 86.8% and 69.2%, respectively, the CSS was 98.0%, 98.0% and 76.3%, respectively, and the OS were 93.2%, 90.5% and 62.4%, respectively (Figure 1–4).

The univariate Cox regression analysis determining BPFS showed that neoadjuvant ADT increases the risk of biochemical ($p = 0.004$) and clinical progression ($p = 0.001$), the adjuvant ADT decreases the risk of biochemical progression ($p = 0.005$) and the other parameters do not influence biochemical progression. The multivariate Cox regression analysis determining BPFS showed the following relationships. The GS increases the risk of biochemical progression ($p = 0.007$). Similarly, the neoadjuvant ADT increases the risk of biochemical progression ($p = 0.001$), and in contrast, the adjuvant ADT decreases the risk of biochemical progression ($p = 0.001$). The multivariate Cox regression analysis determining CPFS survival demonstrated that both positive lymph nodes ($p = 0.078$) and neoadjuvant ADT increased the risk of clinical progression ($p = 0.003$) (Tables 2, 3).

DISCUSSION

Radical prostatectomy in very high-risk PCa patients as a treatment option remains controversial. Usually, these patients are treated with a combination of external radiotherapy and ADT. However, EAU guidelines recommend primary RP with extensive pelvic node dissection in the context of a multimodality treatment setting for selected patients [4]. Recommendations are based on several published studies, which showed good results considering CSS, OS and CSM. CSS over a 10-year period was 88%, OS was 71% [11,17] and CSM ranged from 5.6% to 12.9% [22]. The aim of this study was to document our experience in managing the patients with very high-risk PCa on definitive histopathology after RP.

Optimal management of patients with high-risk PCa requires accurate preoperative clinical staging that is often due to differences in used methods and impre-

cise criteria and hence may not reflect the true nature of tumor pathology [23]. In our cohort, determining the clinical stage was based on a digital rectal examination in the majority of our patients. The clinical and pathological stage was identical in 78% of patients and in 22% patients was understaged. Improvement of clinical staging can be achieved through mpMRI that has reported sensitivity in the detection of extracapsular extension of 43% to 72%, specificity of 77% to 84%, positive predictive value of 79% to 86% and negative predictive value of 52% to 59%, sensitivity in detecting seminal vesicle invasion of 35% to 73%, detection specificity of 94% to 95%, positive predictive value of 62% to 95% and negative predictive value of 73% to 83% [24, 25]. In some patients, however, definitive disease stage can be determined only after RP by histopathological evaluation of the specimen that eventually allows for better stratification and optimal induction of adjuvant therapy and in some cases preventing potentially harmful treatment [18]. The evaluation of GS biopsy and specimen show even more significant discrepancy. In our cohort, the GS agreed only in 47%, in 4% was overestimated and in 48% was underestimated. The inaccuracy in risk assessment of PCa patients can lead to inadequate treatment options, e.g. bypassing extensive pelvic lymph node dissection in patients who had underestimated the risk of PCa according the clinical stage and the biopsy of GS. According to the EAU guidelines, neoadjuvant ADT before RP is not recommended because this was not associated with improved disease-free survival or OS [4]. Despite this, it is frequently used, especially in patients with locally advanced PCa with the aim to achieve down-staging, prostate size reduction, decrease in positive surgical margins and numbers of positive lymph nodes. In our study the neoadjuvant ADT was used in 22 (19.3%) patients. Univariate and multivariate Cox regression analysis evaluating BPFS and CPFS showed that neoadjuvant ADT significantly increases the risk of biochemical and clinical progression. These observations are in contrast to the published results obtained from meta-analysis using neoadjuvant ADT before RP that showed no deterioration or improvement in the OS [26].

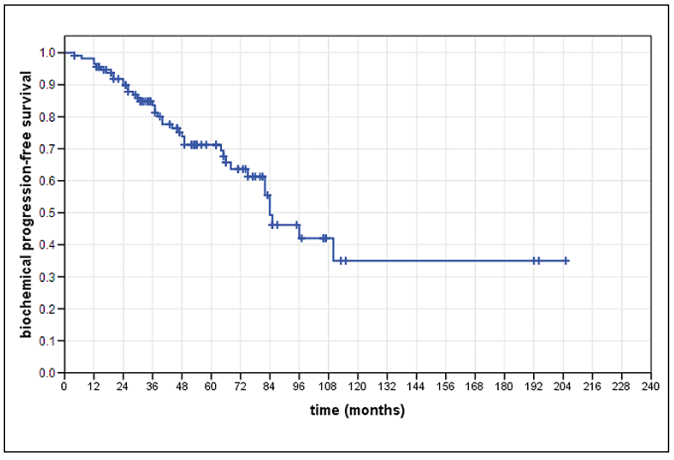

Figure 1. *Biochemical progression-free survival.*

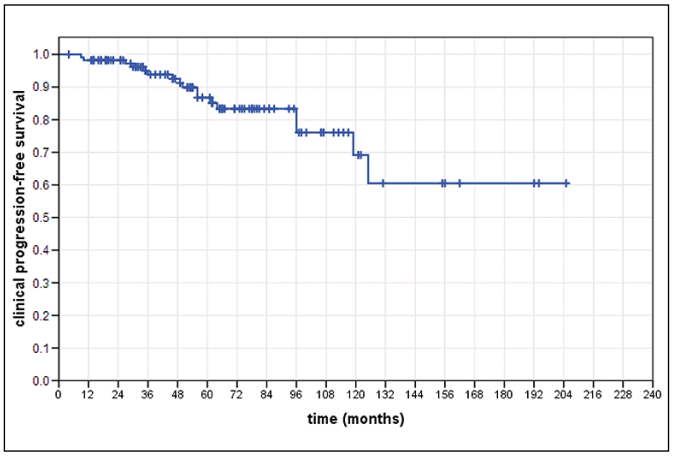

Figure 2. *Clinical progression-free survival.*

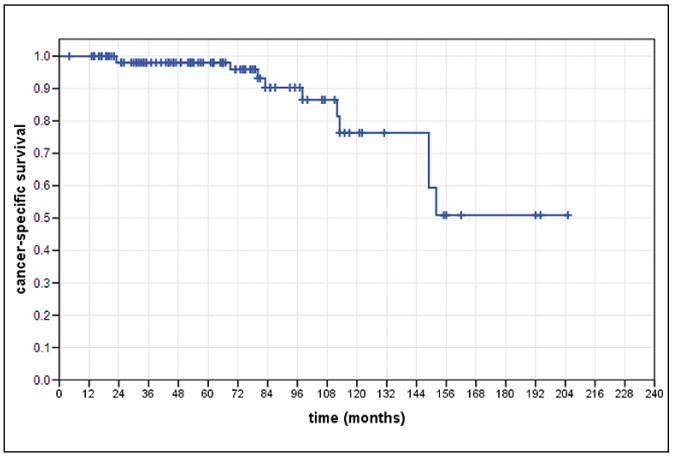

Figure 3. *Cancer-specific survival.*

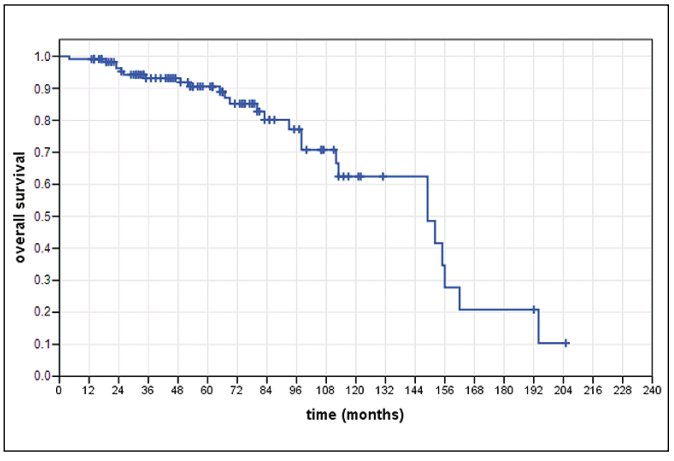

Figure 4. *Overall survival of very high-risk prostate cancer.*

Table 2. *Biochemical progression-free survival*

	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	0.980	(0.927; 1.035)	0.466	0.997	(0.941; 1.056)	0.920
PSA	1.001	(0.983; 1.019)	0.955	1.002	(0.984; 1.020)	0.868
Specimen Gleason score	1.358	(0.966; 1.910)	0.078	1.684	(1.150; 2.468)	0.007
Positive lymph node	0.791	(0.279; 2.240)	0.659	3.246	(0.931; 11.312)	0.065
Positive surgical margin	0.805	(0.427; 1.516)	0.501	1.110	(0.555; 2.219)	0.768
Pathological stage (pT4 *vs.* pT3b)	1.093	(0.261; 4.583)	0.903	0.784	(0.164; 3.750)	0.760
Neoadjuvant ADT	2.771	(1.393; 5.514)	0.004	3.824	(1.726; 8.470)	0.001
Adjuvant ADT	0.368	(0.138; 0.739)	0.005	0.157	(0.065; 0.379)	<0.001

Table 3. *Clinical progression-free survival*

	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	0.959	(0.886; 1.038)	0.296	0.974	(0.899; 1.055)	0.512
PSA	1.002	(0.977; 1.027)	0.882	0.993	(0.962; 1.024)	0.650
Specimen Gleason score	1.603	(0.959; 2.681)	0.072	1.304	(0.737; 2.306)	0.362
Positive lymph node	2.274	(0.738; 7.007)	0.152	3.517	(0.867; 14.273)	0.078
Positive surgical margin	0.622	(0.239; 1.614)	0.329	0.687	(0.229; 2.059)	0.502
Pathological stage (pT4 *vs.* pT3b)	0.045	(0; 279.317)	0.486	0	(0; ∞)	0.986
Neoadjuvant ADT	4.855	(1.864;12.649)	0.001	5.883	(1.837; 18.840)	0.003
Adjuvant ADT	2.763	(0.983; 7.771)	0.054	1.619	(0.481; 5.447)	0.437

In contrast, a recently published study showed significantly longer time to BPFS and hence also potential benefit in conjunction with OS after neoadjuvant ADT in patients with high-risk prostate cancer [27]. It is not apparent why patients in our cohort with neoadjuvant ADT had a higher risk of biochemical and clinical progression, and the reasons may be complex. Higher biological PCa aggressiveness or PCa consisting of abundant ADT-resistant cell populations in the background of ADT-sensitive cells may explain our observations.

This study confirms that very high-risk PCa comprises a heterogeneous group with significantly different times of biochemical and clinical progression and different overall specific treatment results. In our cohort, 26% of patients remained without adjuvant therapy. This points to the need to identify PCa patients at highest risk of developing metastasis and clinical progression with subsequent death, or on the contrary, patients who would receive the highest benefit from radical surgical treatment. Sundi et al. [28] demonstrated that the presence of any primary Gleason grade of 5.5 or more scores with biopsy Gleason sum of 8 to 10 or the presence of multiple high-risk factors present at diagnosis are common in patients with the least favourable prognosis. Joniau et al. [29] suggest stratifying patients into three prognostic subgroups according to the presence of unfavourable risk factors, cT3-4, Gleason score 8–10 and PSA >20 ng/ml. A good prognosis subgroup (a single high-risk factor); an intermediate prognosis subgroup (PSA >20 ng/ml and cT3-4); and a poor prognosis subgroup (Gleason score 8–10 in combination with at least one other high-risk factor). This allows patients to select the most suitable treatment options, for example, monotherapy with RP, multimodal treatment or inclusion into clinical studies. Other options represent the stratification of patients according to age and comorbidity. In a cohort of 266 patients with very high-risk PCa cT3b/4 treated primary with RP and pelvic lymph node dissection with or without adjuvant treatment, Moltzahn et al. [22] evaluated cancer-specific mortality and other causes of mortality by age and the Charlson comorbidity index. They confirmed low cancer-specific mortality in otherwise healthy men, which was not dependent on age, thus favoring RP even in older patients. Conversely, patients with multiple comorbidities had a higher risk of death due to other causes of mortality while sharing the low risk of cancer-specific mortality.

The work has several limitations. First of all, it is presented as retrospective analysis while diagnostic and therapeutic procedures have changed over time. Most of the patients had clinical stage based only on digital rectal examination. ADT and adjuvant radiotherapy were indicated on the individual judgement of a physician. Most of the patients did not undergo extensive pelvic lymph node dissection; therefore the number of affected nodes will probably be higher.

CONCLUSIONS

Treatment of patients with very high-risk PCa in most cases is multimodal with RP as the primary treatment (the first step). Histopathological examination of the removed prostate and lymph nodes provides accurate information about the pathological staging allowing an optimal choice of adjuvant therapy. Our results suggest that neo-adjuvant ADT and Gleason score increase risk of biochemical progression while adjuvant ADT decreases this risk. Neo-adjuvant ADT and positive lymph nodes increases the risk of clinical progression. A significant portion of our patients benefited from the RP alone and remained without the need for adjuvant therapy. Our experience with the surgical treatment of very high-risk PCa supports RP in the treatment of these disease stages.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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