ORIGINAL ARTICLE

Maximum tumor diameter adjusted to the risk profile predicts biochemical recurrence after radical prostatectomy

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Abstract Currently, no consensus exists on the best method for tumor quantification in prostate cancer (PCA), and its prognostic value remains controversial. We evaluated how a newly defined maximum tumor diameter (MTD) might contribute to the prediction of biochemical recurrence (BCR) in a consecutive series of PCA patients treated with radical prostatectomy (RP). Patients with PCA who underwent RP without neoadjuvant therapy at a single center were included for analysis. MTD was defined as the largest diameter of all identified tumors in all three dimensions (i.e., length, width, or depth) of the prostate ("Basel technique"). Cox regression models addressed the association of MTD with BCR in three risk groups (low risk—prostate-specific antigen (PSA)< 10 ng/ml, pT2, and Gleason score (GS)≤6; intermediate risk—PSA≥10 and <20 ng/ml and/or pT2 and GS=7; high risk—PSA>20 ng/ml or pT3 or GS≥8) and whole cohort. Within a median follow-up of 44 months (interquartile range (IQR) 23–66), 48 patients (9.4 %) in the intermediate-risk and high-risk groups experienced BCR. In multivariate Cox regression analysis, PSA, pathological stage (pT stage), GS, positive surgical margins (PSMs), and MTD>19.5 mm were independent predictors for BCR ($p<0.05$). In subgroup analysis, MTD as a nominal variable (<24.5 and >24.5 mm) was the only independent predictor of BCR in the intermediate-risk group (hazard ratio (HR) 9.933, 95 % confidence interval (CI) 2.070–47.665; $p<0.05$). MTD is an independent risk factor of BCR in PC patients after RP. The combination of the MTD with other well-known prognostic factors after RP may improve decision-making concerning follow-up intensity or adjuvant treatment.

Introduction

The value of tumor quantitation for prostate cancer (PCA) remains controversial. Despite a current lack of consensus on the appropriate method for tumor volume (TV)/size assessment, reporting of this variable has been suggested by the International Society of Urological Pathology (ISUP) [1]. The association of TV/size with prostate-specific antigen (PSA), Gleason score (GS), pathological stage (pT stage), positive surgical margins (PSMs), and clinical outcomes was shown in several previous studies [2–6]. However, the prognostic value of TV, independent of well-characterized standard clinicopathologic features, on biochemical recurrence (BCR) is weak [7]. Taking into account that higher GS, advanced pT stage with or without PSMs, and positive lymph node status (LN+) are powerful predictors of BCR, some studies provide evidence of the independent prognostic value of tumor quantitation on BCR [3–6, 8–10]. The correct prediction of the probability of BCR is crucial to identify proper timing for adjuvant treatment [11]. This is even more important in patients with intermediate risk constellation where oncologic benefits and adverse events of adjuvant treatment need to be balanced [12].

There is no general consensus on how to best quantify tumor in radical prostatectomy specimens, as shown in a survey across 321 pathology laboratories from 15 west European countries [13]. Several methods for tumor quantification such as TV, maximum tumor diameter (MTD) of the index

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tumor, positive-block ratio estimation, visual estimation, and others have been described showing association with BCR or not [1]. The commonly used methods are visual estimation of TV or MTD of the index tumor. Although estimation of the MTD is less time consuming and inexpensive, there is no consensus on how the index tumor should be designated [1]. In a previous, unpublished study, we developed a new method of assessment of tumor diameter by adding the MTD of all tumor areas along one line after deduction of the diameter of tumor tissue overlapping along this line. Review of over 240 radical prostatectomy showed that modified MTD but not the diameter of the index tumor was a strong independent prognostic marker. Therefore, this method was introduced in our daily practice. Here, we tested the predictive value of this newly defined MTD on biochemical recurrence (BCR) in patients treated with radical prostatectomy (RP). Moreover, we assessed how this variable might optimally contribute to BCR prediction together with other pathological features.

Patients and methods

This study was approved by the institutional ethics review board. All patients ($n=661$) who were treated with either transperitoneal or extraperitoneal laparoscopic RP for PCA between April 2001 and December 2011 at the Department of Urology, University Hospital Basel, Switzerland, were included for analysis. Patients with incomplete clinical data, lost to follow-up ($n=119$), or who received neoadjuvant treatment ($n=7$) were excluded. Patients with LN+ ($n=24$), those who did not reach undetectable PSA level after surgery, or patients who received immediate androgen deprivation treatment after RP were excluded as well. The final study population consisted of 511 patients. PCA was diagnosed by transrectal ultrasound-guided biopsies.

All specimens were processed at the Institute for Pathology, University Hospital Basel, Switzerland. Apical and dorsolateral margins were examined by frozen section analysis according to current guidelines of the International Society of Urological Pathology (ISUP) [14]. Briefly, we used the cone method for cutting the apex and the base and then performed sagittal slicing of the cones. After overnight fixation in 10 % buffered formalin solution, what remained of the prostate gland was sectioned at 3–4-mm intervals along a transverse plane from apex to the base. The external surface had been previously inked. Whole mount tissue slices were embedded and further processed according to routine procedures. Formalin-fixed and paraffin-embedded (FFPE) whole mount sections were stained with hematoxylin and eosin (H&E) and prospectively evaluated by two pathologists independently. The principles of how the greatest diameter was measured are illustrated in Fig. 1. The maximum diameter was calculated as the sum of the largest diameter of all tumor areas

along one line, after deducing the length of overlap of tumor areas along this line. By this method, the maximum tumor diameter never exceeds the size of the whole prostate. If tumors were present in consecutive sections at the same location and orientation, the measurement was performed in the same manner as described above. The largest measure estimated in three dimensions (length, width, and depth) was considered as the MTD. All distances were measured on FFPE sections with a ruler marked with millimeters (Fig. 1).

The predictive value of the MTD for BCR was tested for the whole cohort and for risk groups based on clinicopathological features such as preoperative PSA, pT, and final GS. Low-risk (PSA<10 ng/ml, pT2 and GS≤6), intermediate-risk (PSA≥10 and <20 ng/ml and/or pT2 and GS 7), and high-risk (PSA>20 ng/ml or pT3 or GS≥8) groups were composed. BCR was defined as a serum PSA concentration of >0.2 ng/ml in two independent measurements. The date of the first measurement was defined as the date of BCR. Follow-up for patients who received adjuvant treatment at the time of PSA≤0.2 ng/ml ended with the day the treatment started.

The cutoff value for MTD that best discriminated low and high risk for BCR was designated by computing the receiver operating curves (ROC) and calculating the Youden index. Due to different clinicopathological features and different MTD values in each group, this was done for the whole cohort and the intermediate-risk and high-risk groups.

The comparison of categorical data and continuous variables was performed using chi-square tests and Mann-Whitney U tests, respectively. Cox regression multivariate models were used to identify factors predictive for BCR. Biochemical recurrence-free survival (BFS) was analyzed by the Kaplan-Meier method, and survival of different groups was compared using log-rank tests. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 21.0; Chicago, IL, USA) for Windows. A two-sided p value <0.05 was considered significant.

Results

Clinicopathologic features

At the time of operation, patients were on the average 63 years old (interquartile range (IQR) 59–68) and median PSA was 6.68 ng/ml (IQR 4.9–10.3). The most common clinical stage and Gleason score were T1 (62.4 %) and ≤6 (54.7 %), respectively. Only 37/511 patients (7.3 %) had biopsy GS ≥8 and 3/511 (0.4 %) patients had clinical stage T3. Palpable disease or biopsy GS 7 was present in 190/511 (37.2 %) and 194/511 (38 %) cases, respectively. According to final pathological assessment, 79.6 % of the patients ($n=407$) had organ confined disease. In 67/511 cases (13.1 %), extracapsular extension (ECE) was diagnosed and 37/511 patients (7.2 %) had seminal
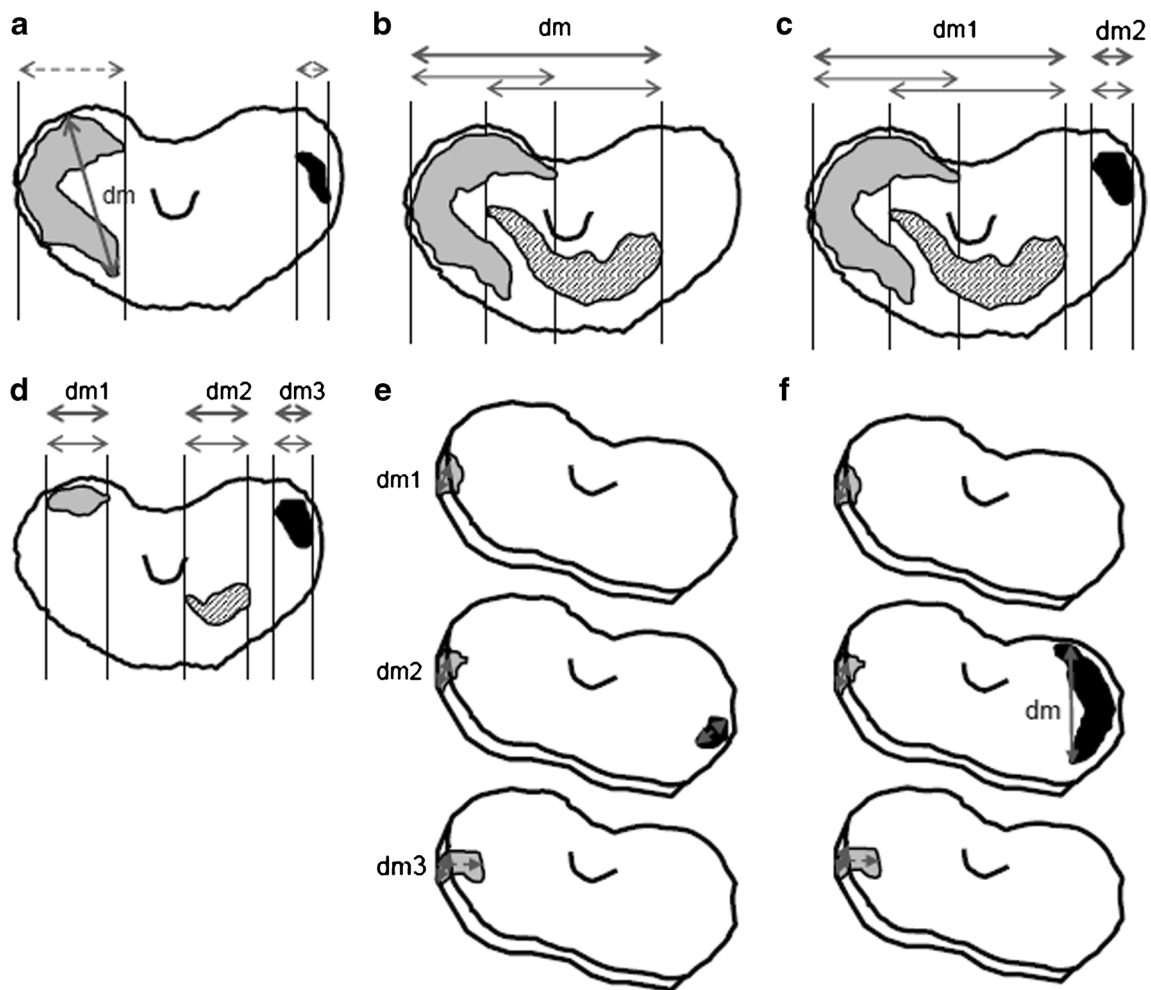
Fig. 1 Largest diameter (*dm*) measured in the horizontal and vertical planes. **a** Largest dm in the horizontal plane including two non-overlapping tumors. **b** Largest dm in the horizontal plane including two partly overlapping tumors. **c** Largest dm in the horizontal plane including several partly overlapping tumors (largest dm=dm1+dm2). **d** Largest dm in the horizontal plane including several non-overlapping tumors (largest dm=dm1+dm2+dm3). **e** Largest dm in the vertical plane including two non-overlapping tumors (largest dm=dm1+dm2+dm3). **f** Largest diameter in the horizontal plane including two non-overlapping tumors. *Thick gray double arrows*=diameters that define the largest diameter; *thin gray double arrows*=tumor diameters including overlap of individual tumors in one axis; *dashed gray arrows*=diameters that are irrelevant for the largest diameter

vesicle infiltration (SVI). Final GS ≤6, 7, and ≥8 was found in 173/511 (33.8 %), 278/511 (54.3 %), and 60/511 (11.9 %) specimens, respectively. PSMs were found in 122/511 patients (23.9 %). The median MTD was 20 mm (IQR 12–26 mm) (Table 1). After median follow-up of 44 months (IQR 24–67), 48 (9.4 %) patients had BCR. Most of BCR (*n*=38) occurred in the high-risk group followed by intermediate-risk (*n*=10) group. In the lower-risk group, none of patients had BCR.

Association of MTD with biochemical recurrence

The estimated cutoff values for MTD were 19.5 mm (area under the curve (AUC) 0.763, 95 % confidence interval (CI) 0.702–0.825; *p*<0.001), 24.5 mm (AUC 0.794, 95 % CI 0.658–0.931; *p*=0.002), and 27.5 mm (AUC 0.590, 95 % CI 0.486–0.694; *p*=0.053) for the whole cohort, intermediate-risk, and high-risk groups, respectively. Patients with higher MTD than the estimated cutoff value showed a significantly worse BFS than patients with smaller MTD in the entire cohort, intermediate-risk, and high-risk groups, respectively (*p*<0.05) (Fig. 2).

In multivariate Cox regression analyses, PSA (hazard ratio (HR) 1.565, 95 % CI 1.090–2.247; *p*=0.015), pT stage (HR 1.728, 95 % CI 1.183–2.523; *p*=0.005), final GS (HR 2.294, 95 % CI 1.631–3.226; *p*<0.001), PSM (HR 2.421, 95 % CI 1.285–4.562; *p*=0.006), and MTD>19.5 mm (HR 2.850, 95 % CI 1.129–7.195; *p*=0.027) were independent predictors for BCR for the whole cohort. In subgroup analysis, MTD> 24.5 mm was the only independent prognostic factor for BCR in the intermediate-risk group (HR 9.933, 95 % CI 2.070–47.665; *p*=0.004), whereas PSA, pT stage, final GS, and PSM were not associated with BCR (Table 2).

Table 1 Clinicopathologic characteristics and oncologic outcome

|	
Age (years)	
Mean	63
Median	63
IQR	59–68
PSA (ng/ml)	
Mean	9.2
Median	6.68
IQR	4.9–10
Clinical stage	
T1	319 (62.4 %)
T2	190 (37.2 %)
T3	3 (0.4 %)
Gleason score (biopsy)	
≤6	280 (54.7 %)
3+4	152 (29.7)
4+3	42 (8.3 %)
≥8	37 (7.3 %)
Pathological stage	
pT2 (organ confined)	407 (79.6 %)
pT3a (extracapsular extension)	67 (13.1 %)
pT3b (seminal vesicle infiltration)	37 (7.2 %)
Gleason score (final)	
≤6	173 (33.8 %)
3+4	197 (38.5 %)
4+3	81 (15.8 %)
≥8	60 (11.9 %)
Maximum tumor diameter (mm)	
Mean	19.8
Median	20
IQR	12–26
Surgical margins	
Negative	389 (76.1 %)
Positive	122 (23.9 %)
Follow-up (months)	
Mean	46.7
Median	44
IQR	23–66
Biochemical recurrence (PSA>0.2 ng/ml)	
No	463 (90.6 %)
Yes	48 (9.4 %)

IQR interquartile range

Discussion

In this consecutive series of PCA patients treated with RP, we found that MTD using a novel method of assessment contributes to the prediction of BCR. For the whole cohort, MTD> 19.5 mm was significantly predictive, and for patients with intermediate risk constellation, MTD>24.5 mm was the only independent predictor of BFS.

Fig. 2 a–c Kaplan-Meier curves depicting biochemical recurrence-free ▶ survival in 511 patients with prostate cancer treated with radical prostatectomy according to maximum tumor diameter: **a** all patients (*p<0.001), **b** intermediate-risk PCA patients (*p<0.001), and **c** high-risk PCA patients (*p=0.025). **d, e** Corresponding receiver operating curves depicting predictive value of biochemical recurrence-free survival: **d** all patients (AUC 0.763, 95 % CI 0.702–0.825; p<0.001), **e** intermediate-risk PCA patients (AUC 0.794, 95 % CI 0.658–0.931; p= 0.002), and **f** high-risk PCA patients (AUC 0.590, 95 % CI 0.486–0.694; p=0.053). *log-rank test

The most common approach for MTD estimation is to measure only the largest (index) tumor [8], as it might have a major impact on BCR [15]. However, the data on measures of tumor extent in RP remain controversial, as summarized in Table 3. Recent studies highlighted the frequent PCA multifocality with the dominant tumor not always representing all poorly differentiated elements [16]. Thus, there is no consensus about the final definition of the index or dominant tumor and, as a consequence, the correct estimation of the MTD [1]. Our method includes measurement of extension of all identified tumors in three dimensions. Initial evaluation of the prognostic ability of MTD in terms of BCR in a series of 464 men showed that tumors <1 cm have longer BFS (two consecutive detectable PSA values) than tumors >2 cm [4]. Multivariate analyses revealed that MTD, PSA, ECE, or LN+ are independent predictors of BCR. This was confirmed by a study in which the authors found MTD (HR 1.7, p=0.011) and GS to be independent determinants for BCR (PSA>0.2 ng/ml), although LN+ and PSA were not included in the multivariate analysis [9]. The most recent study included 364 patients treated with RP and showed a strong independent prognostic value of MTD>20 mm for BCR (HR 3.07, p<0.001) [3]. PSA was omitted in the analysis. In all referred studies, MTD was defined as a largest diameter of the largest tumor.

In contrast, in the most recent series consisting of 781 patients, MTD was not significantly associated with BCR when adjusted for PSM [17]. In contrast, PCA with a MTD >13 mm (median MTD value) in patients with a preoperative PSA <10 ng/ml, pT stage ≤pT3a, and GS 3+4=7 and without PSM was associated with poor BFS. Dvorak et al. concluded that a larger MTD in these cases might serve as trigger for adjuvant treatment [17]. Our results confirm this notion, even though the risk stratification and cutoff value for MTD were different. Another European study investigated the prognostic value of MTD for BCR (PSA>0.1 ng/ml) in 542 PCA patients treated with RP [18]. Patients were stratified in three risk groups according to the D'Amico criteria [19]. Univariate analysis of MTD (continuous variable) revealed a weak association with risk of BCR (HR 1.02) which could not be detected in the high-risk group. PSM, GS, pT stage, and multiple tumors were independent prognostic factors in multivariate analysis. Interestingly, tumor quantity parameters
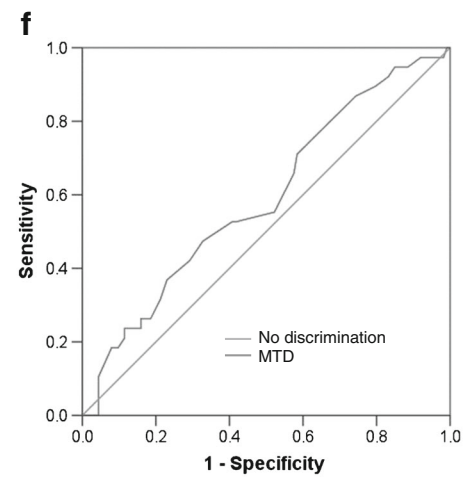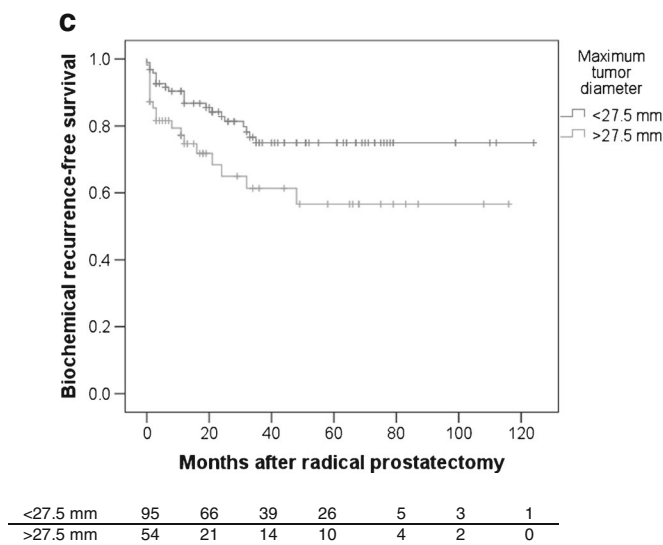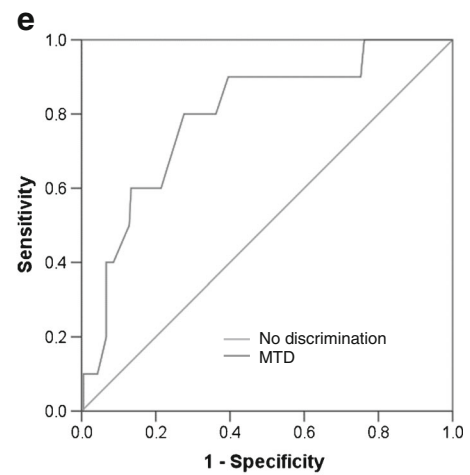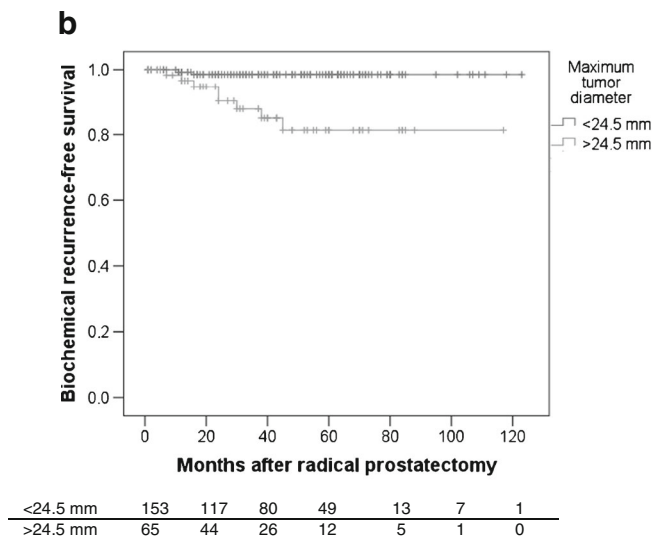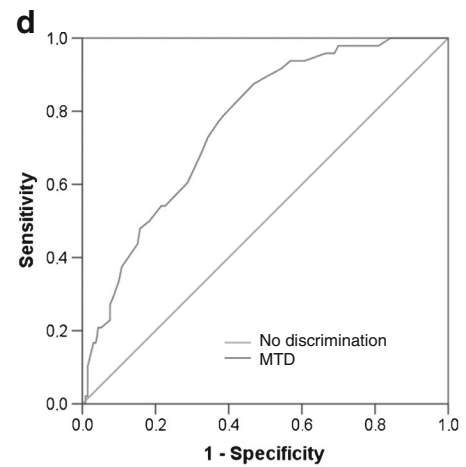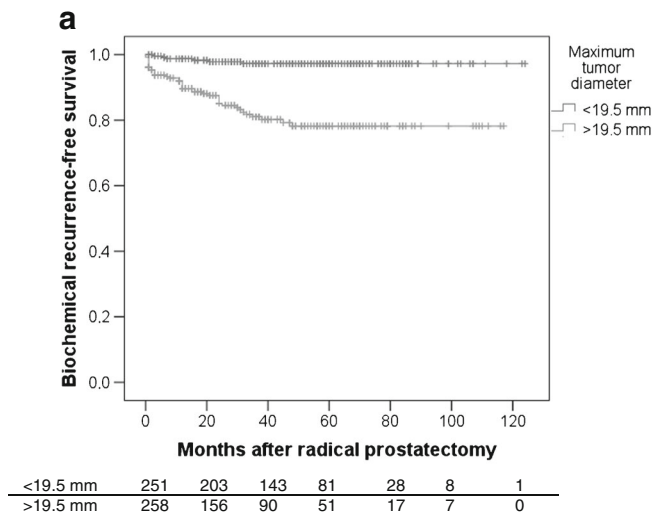
Table 2 Multivariate Cox regression analysis for determinants predicting biochemical recurrence in a whole cohort and patients with intermediate-risk and high-risk prostate cancer

	p value	HR	95 % CI
Whole cohort			
PSA	0.015	1.565	1.090–2.247
pT stage	0.005	1.728	1.183–2.523
Gleason score	<0.001	2.294	1.631–3.226
Surgical margins	0.006	2.421	1.285–4.562
Maximum tumor diameter (<19.5 vs. >19.5 mm)	0.027	2.850	1.129–7.195
Patients with intermediate-risk prostate cancer			
PSA	0.149	1.131	0.957–1.337
pT stage	0.629	1.347	0.402–4.506
Gleason score	0.867	1.099	0.364–3.313
Surgical margins	0.204	0.248	0.029–2.126
Maximum tumor diameter (<24.5 vs. >24.5 mm)	0.004	9.933	2.070–47.665
Patients with high-risk prostate cancer			
PSA	0.110	1.014	0.997–1.031
pT stage	0.098	1.333	0.948–1.873
Gleason score	<0.001	2.066	1.422–3.002
Surgical margins	0.001	3.916	1.793–8.549
Maximum tumor diameter (<27.5 vs. >27.5 mm)	0.533	1.253	0.617–2.542

(MTD and TV) did not provide any additional information regardless of risk stratification. For high-risk PCA, MTD did not provide any further information on BCR prediction, as we found in our study. Although in our study median value in the whole cohort was smaller (19.5 mm vs. 24 mm), MTD was an independent predictor of the BCR.

Another yet less commonly used parameter for tumor quantitation is TV [13]. The initial evaluation of the predictive ability of TV on BCR was discouraging. Epstein at al. found that only GS and PSM are independent predictors for cancer progression (increase in postoperative PSA, local recurrence, and/or presence of distant metastases) in patients with organ-confined disease after RP [20]. Ohori et al. included in the analysis 478 patients with clinically localized PCA treated with RP and found ECE and SVI among with GS to be independent prognostic factors for cancer progression [21]. TV did not have any prognostic value in either study. While Salomon et al. had similar results in their study, progression was defined as BCR (PSA>0.2 ng/ml) [22]. In our analysis LN+ patients were omitted for the multivariate analysis, as its strong prognostic value on progression and cancer-specific survival is well established [23]. Also in a recent study on 344 patients from ERSPC (Rotterdam section) with a long follow-up (mean 96.2 months), the prognostic value of TV was assessed. Age at RP, GS 4+3=7, and PSMs were predictive for BCR but none of the reported TV-related variables (TV, relative TV, and TV>0.5 ml) [24].

Another study provided confusing results by analyzing predictive determinants for PSA failure (≥0.07 ng/ml) in 379 cases after RP [25]. TV was a highly significant and independent predictor of BCR tested in a multivariate model with the percentage of Gleason grade 4/5, LN+, and vascular invasion. Only the largest tumor detected in the specimens was used for further investigation. Chun et al. published corresponding data in which PSA, ECE, TV, and percentage of high-grade Gleason TV (%HGTV) were predictors of BCR (PSA>0.1 ng/ml) [10]. LN+, SVI, and PSM were included in the model, but showed no significant association with risk of BCR. The authors concluded that %HGTV is a powerful predictor of BCR after RP, confirming previous publications [25–28]. Yet another study tested the prognostic value of the percentage of TV (sum of all visually estimated tumor foci in relation to the specimen on every section) in terms of BCR (PSA>0.2 ng/ml) [29]. In multivariate analysis, PSA, final GS, and percent TV were independent predictors of BCR, whereas PSM, pT stage, and LN+ failed to reach significance.

Our study is limited by its retrospective nature and short follow-up time. The low number of BCR is at least in part caused by patients with a high-risk constellation (PSA< 0.2 ng/ml) who already received or rapidly entered into adjuvant treatment. Furthermore, clinical outcome data on local recurrence, metastasis, and mortality were not available. Finally, our cohort contained a high number of organ confined PCAs (79.6 %), a main prognostic factor even though most of them had Gleason score ≥7 (72.2 %).

We conclude that MTD assessed by our novel method might be a useful additional prognostic factor for the prediction of BFS in patients after RP. Especially in patients with intermediate-risk constellation, MTD may influence decision making regarding adjuvant treatment.

Table 3 Overview of publications on tumor quantification for prostate cancer

Author	Year	Quantification method	Median follow-up	Number of patients	End points	Multivariate analyses	Conclusions
Renshaw et al. [8]	1998	Greatest dimension of the largest single focus	27.2	57	Two consecutive detectable PSA values	PSA (RR 1.066; $p=0.017$) Stage T3c/LN+ (RR 3.389; $p=0.015$) MTD (RR 1.117; $p=0.057$)	"…greatest tumor dimension… is a predictor of PSA failure…"
Eichelberger al. [9]	2005	Greatest diameter of the largest single focus	12	364	PSA≥0.1 ng/ml	PSMs (HR 1.78; $p=0.084$) GS (HR 1.9; $p<0.0001$) MTD (HR 1.7; $p=0.011$)	"MTD is a significant predictor of BCR"
Fukuhara et al. [3]	2010	Largest diameter of the largest tumor	33	364	PSA>0.2 ng/ml	Stage>pT2 (HR 2.53; $p=0.003$) GS>6 (HR 1.99; $p=0.037$) PSMs (HR 3.87; $p<0.001$) MTD>20 (HR 3.07; $p=0.037$)	"…MTD is independent prognostic factor for BCR"
Dvorak et al. [17]	2005	Maximal dimension of the largest single focus	65	781	PSA>0.2 ng/ml	PSA (HR 1.02; $p<0.0001$) GS>6 (HR 2.96; $p=0.0002$) Stage pT3b (HR 9.38; $p<0.0001$) PSMs (HR 1.71; $p=0.0004$) MTD (HR 1.03; $p=0.07$)	"…the MTRD value may serve as a proxy for surgical margin status…"
van Oort et al. [18]	2008	Largest diameter of the largest tumor considered in two dimensions; total tumor volume; volume of the largest tumor	39.5	542	PSA>0.1 ng/ml	Stage pT3b (HR 1.79; $p<0.05$) GS>6 (HR 1.97; $p<0.05$) PSMs (HR 3.75; $p<0.05$) NT (1.18; $p<0.05$)	"…MTD is not an independent predictor for BCR"
Ohori et al. [21]	1995	Total tumor volume	32	478	PSA progression or local recurrence or distant metastases	SMI (HR 4.38; $p=0.0001$) GS (HR 1.97; $p=0.0001$) ECE (HR 3.3; $p=0.0015$) TTV ($p=0.25$) PSMs (0.321)	"TV and PSM failed to provide significant contribution on prognosis of BCR"
Salomon et al. [22]	2003	Total tumor volume	63.6	200	BCR	Stage ($p=0.0002$) GS>6 ($p=0.04$) PSMs ($p=0.12$) TTV ($p=0.35$)	"TV does not provide additional prognostic information"
Wolters et al. [24]	2010	Total tumor volume, relative tumor volume	96.2	344	PSA>0.2 ng/ml	Age (HR 1.1; $p=0.008$) SVI (HR 2.32; $p=0.327$) GS 4+3 (HR 5.95; $p<0.0001$) PSM (HR 3.84; $p<0.0001$) TTV (HR 0.95; $p=0.517$)	"TTV did not add prognostic value to routinely assessed pathologic parameters."
Stamey et al. [25]	1999	Index tumor volume	68.7	379	PSA>0.07 ng/ml	ITV (HR 1.68; $p<0.001$) GG 4/5 % (HR 1.49; $p<0.001$) LN+ (HR 1.004; $p<0.001$)	"ITV, GS 4/5 %, LN + and VI were independently associated with PSA increasing"

Table 3 (continued)

Author	Year	Quantification method	Median follow-up	Number of patients	End points	Multivariate analyses	Conclusions
Chun et al. [10]		Total tumor volume, high-grade tumor volume	43.4	780	PSA≥0.1 ng/ml	VI (HR 0.793; $p<0.001$) PSA (RR 1.01; $p=0.013$) ECE (RR 2.43; $p<0.001$) TV (RR 1.03; $p=0.005$) %HGTV (RR 1.03; $p<0.001$)	"TV determines the rate of PSM and %HGTV determines the rate of BCR"
Song et al. [29]	2012	Percent tumor volume	42	1,567	PSA>0.2 ng/ml	PSA (HR 1.006; $p=0.012$) GS (HR 2.183; $p<0.0001$) PTV (HR 1.393; $p<0.0001$)	"…GS, PTV and PSA are independent predictors of BCR…"

RR risk ratio, *HR* hazard ratio, *PSA* prostate-specific antigen, *LN+* positive lymph node status, *MTD* maximum tumor diameter, *GS* Gleason score, *BCR* biochemical recurrence, *PSMs* positive surgical margins, *NT* number of tumors, *TTV* total tumor volume, *RTV* relative tumor volume, *ITV* index tumor volume, *GGS 4/5* the percent of Gleason grade 4/5, *SVI* seminal vesicle invasion, *VI* intraprostatic vascular invasion, *ECE* extracapsular extension, *%HGTV* the percent high-grade Gleason volume, *PTV* percent tumor volume

Conflict of interest We declare that we have no conflict of interest.

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