Comparison of Tumor Volume Parameters on Prostate Cancer Biopsies

Esther I. Verhoef, BSc; Charlotte F. Kweldam, MD, PhD; Intan P. Kümmerlin, MD, PhD; Daan Nieboer, MSc; Chris H. Bangma, MD, PhD; Luca Incrocci, MD, PhD; Theodorus H. van der Kwast, MD, PhD; Monique J. Roobol, PhD; Geert J. L. H. van Leenders, MD, PhD

- Context.—Prostate biopsy reports require an indication of prostate cancer volume. No consensus exists on the methodology of tumor volume reporting.

Objective.—To compare the prognostic value of different biopsy prostate cancer volume parameters.

Design.—Prostate biopsies of the European Randomized Study of Screening for Prostate Cancer were reviewed (n = 1031). Tumor volume was quantified in 6 ways: average estimated tumor percentage, measured total tumor length, average calculated tumor percentage, greatest tumor length, greatest tumor percentage, and average tumor percentage of all biopsies. Their prognostic value was determined by using either logistic regression for extra-prostatic expansion (EPE) and surgical margin status after radical prostatectomy (RP), or Cox regression for biochemical recurrence-free survival (BCRFS) and diseasespecific survival (DSS) after RP (n = 406) and radiation therapy (RT) (n = 508).

Men suspected of having prostate cancer undergo biopsies to determine the presence and aggressiveness of a potential tumor. Apart from Gleason score (GS) and number of positive biopsies, an indication of tumor volume should be provided in pathology reports. The College of American Pathologists and the World Health Organization (WHO) state that either linear cancer volume or proportion of prostate tissue involved by cancer should be reported as parameter for biopsy tumor volume. Biopsy tumor volume has been associated with outcome after radical prostatectomy (RP) and radiation therapy (RT); however, tumor volume representation varies amongst studies. In addition, biopsy tumor involvement is a threshold for patient eligibility in some active surveillance protocols, underlining the need for objective and reliable tumor volume quantification. It is yet unknown to what extent tumor volume parameters are mutually related and whether they all have similar prognostic value. The aim of this study was to compare different tumor volume parameters in relation to clinical outcome in a large prostate biopsy cohort.

MATERIALS AND METHODS

Patient Selection

Prostate biopsy cores were taken in the scope of the European Randomized Study of Screening for Prostate Cancer (ERSPC), initial screening round between November 1993 and March 2000, whose trial protocol has been published previously. Participating men underwent sextant prostate biopsies according to the study protocol, with addition of a seventh or eighth biopsy in case of a hypoechoic lesion on transrectal ultrasonography. Each individual biopsy core was embedded in a separate container to enable detailed pathologic evaluation. Three investigators reviewed all prostate biopsies according to the WHO and International Society of Urological Pathology (ISUP) 2014 guidelines. In case no slides were present for review or if metastasis was present at time of diagnosis, cases were excluded. For each patient, GS, grade group, total number of biopsies, number of prostate cancer—

Results.—All tumor volume parameters were significantly mutually correlated ($R^2 > 0.500, P < .001$). None were predictive for EPE, surgical margin, or BCRFS after RP in multivariable analysis, including age, prostate-specific antigen, number of positive biopsies, and grade group. In contrast, all tumor volume parameters were significant predictors for BCRFS (all $P < .05$) and DSS (all $P < .05$) after RT, except greatest tumor length. In multivariable analysis including only all tumor volume parameters as covariates, calculated tumor length was the only predictor for EPE after RP ($P = .02$) and DSS after RT ($P = .02$).

Conclusions.—All tumor volume parameters had comparable prognostic value and could be used in clinical practice. If tumor volume quantification is a threshold for treatment decision, calculated tumor length seems preferential, slightly outperforming the other parameters.

positive biopsies, and tumor volume were recorded. The study was approved by the local Medical Ethics Committee (MEC-2018-1614).

**Tumor Volume Quantification**

Tumor volume was quantified in 6 different ways, as depicted in Figure 1, A through C. First, estimated tumor percentage per core was determined by visual examination. The average estimated tumor percentage for the entire case was calculated by dividing the sum of the estimated percentages per core by the total number of prostate cancer–positive biopsies per patient. Second, measured total tumor length was defined as the sum of the tumor lengths in all biopsies containing cancer as measured in millimeters with a microruler. Third, the average calculated tumor percentage was determined by dividing the sum of the tumor lengths of the entire case by the total length of the prostate cancer–positive biopsies of the entire case as measured in millimeters with a microruler. Fourth, greatest tumor length was defined as the maximum tumor length of an individual biopsy core per patient as measured by a microruler in millimeters. Fifth, greatest tumor percentage was defined as the maximum tumor percentage on an individual core per patient. Sixth, average tumor percentage of all biopsies was determined by dividing the sum of the estimated tumor percentages by the total number of biopsies. Assessment of each tumor volume parameter included intervening nonmalignant tissue in case more than 1 tumor focus was present within a single biopsy.15,16

**Clinical Follow-Up**

Progression was recorded by semiannually monitoring each patient after diagnosis and initial treatment. Biochemical recurrence (BCR) was defined as 2 successive prostate-specific antigen (PSA) levels of 0.2 ng/mL or higher after RP, or any PSA increase greater than 2 ng/mL above the lowest PSA value after RT.18,19 An independent cause-of-death committee reviewed cause of death, including deaths related to screening within the prostate cancer deaths, and determined disease-specific survival (DSS).20

**Statistical Analysis**

Correlations between tumor volume parameters were calculated by using the Pearson’s $R^2$ correlation coefficient. Parameters were log-transformed to normalize data for logistic regression analysis. Crude and adjusted odds ratios were estimated for extraprostatic expansion (EPE), pT stage $\geq 3$ and surgical margin (SM) status by using logistic regression. Hazard ratios for biochemical recurrence-free survival (BCRFS) and DSS were estimated by using Cox regression analysis, in which men lost to follow-up or death from other causes were censored. Multivariable logistic regression analysis with each separate tumor volume parameter was corrected for age, PSA, number of positive biopsies, and grade group. $P$ values less than .05 were considered statistically significant. All statistical analyses were performed in R version 3.2.2 (R, Vienna, Austria).

**RESULTS**

**Patient Characteristics**

At time of diagnosis, the median age of the entire cohort ($n = 1031$) was 67 years (interquartile range [IQR], 62–71 years) and median PSA level was 5.6 ng/mL (IQR, 3.9–8.8 ng/mL). In total 486 men were diagnosed with GS 6 (grade group 1) on biopsy, 370 with GS 3 $\leq 7$ (grade group 2), 71 with GS 4 $\leq 7$ (grade group 3), 55 with GS 8 (grade group 4), and 49 with GS 9–10 (grade group 5) prostate cancer. Four hundred six men (39%) were treated with RP, 508 men (49%) received RT, 8 men (1%) underwent endocrine therapy, and 108 men (11%) were put on watchful waiting, while treatment was unknown for 1 patient. The median follow-up was 13 years (IQR, 8.7–17 years).

**Correlation Between Tumor Volume Parameters**

In total 549 men (53%) underwent 6 biopsies; 460 (45%), 7 biopsies; and 22 (2%), 8 biopsies. The mean total positive biopsy sample length per patient was 26 mm (IQR, 12–36 mm) and the mean total tumor length was 11 mm (IQR, 2.4–16 mm). The median estimated and calculated tumor percentages were 33% (IQR, 15%–55%) and 33% (IQR, 15%–55%), respectively. Average estimated tumor percentage strongly correlated with the average calculated tumor percentage ($R^2 = 0.98, P < .001$). Measured total tumor length moderately correlated with calculated tumor percentage ($R^2 = 0.71, P < .001$). The median greatest tumor length was 4.5 mm (IQR, 2.0–7.8 mm) and the median greatest tumor percentage was 50% (IQR, 20%–80%). Both parameters correlated moderately with calculated tumor percentage ($R^2 = 0.84$ and $R^2 = 0.87$, respectively). Average tumor percentage of all biopsies (median, 12%; IQR, 3.7%–26%) correlated moderately with calculated tumor percentage ($R^2 = 0.74$; Figure 2). Since average estimated tumor percentage and calculated tumor percentage were strongly correlated, and estimated tumor percentage is more easily established in daily practice, we excluded average calculated tumor percentage from further analysis.

**Pathologic Features at Radical Prostatectomy**

Of the 406 patients treated with RP, 98 men (24%) had EPE and 101 men (25%) had positive SM. Since RP specimens were not available for review we did not have information on the contemporary GS or grade group. All tumor volume parameters were strongly associated with EPE (all $P < .001$) and SM status (all $P < .01$) in univariate analysis (Supplemental Table 1; see supplemental digital content, containing 4 tables at www.archivesofpathology.org in the August 2020 table of contents). In multivariable analysis including all tumor volume parameters as covariates, calculated tumor length was the only significant predictive parameter for EPE ($P = .02$), whereas none of the parameters were predictive for SM status (Table 1). Multivariable analysis including age, PSA level, grade group, number of positive biopsies, and each of the tumor volume parameters separately revealed that none of the biopsy tumor volume parameters had independent predictive value for EPE or SM status (Supplemental Table 1). In contrast, PSA and grade group were independently associated with EPE (Supplemental Table 2).

**Outcome After Radical Prostatectomy and Radiation Therapy**

In total 85 of 406 men (20%) experienced BCR and 12 men (3%) died from their disease after RP. All biopsy tumor volume parameters were associated with BCRFS in univariate analysis (all $P < .05$; Supplemental Table 3). None of the parameters was significant in multivariable analysis for BCRFS, including all 5 volume parameters (Table 2). In multivariable analysis including age, PSA level, grade group, number of positive biopsies, and each of the tumor volume parameters separately, tumor volume did not have predictive value for postoperative BCRFS (Supplemental Table 3). The low number of disease-specific deaths ($n = 12$) did not allow statistical analysis for postoperative DSS.

Of the 508 men who received RT, 223 (44%) experienced BCR and 73 (14%) died of prostate cancer. In univariate analysis all tumor volume parameters were significantly
associated with BCRFS (all $P < .001$; Supplemental Table 3).
In multivariable analysis including all tumor volume
parameters as covariates none of the parameters was
significant (Table 2). Multivariable analysis including clin-
icopathologic parameters and each of the tumor volume
parameters separately revealed that all individual biopsy
tumor volume parameters had independent predictive value
for BCRFS after RT (all $P < .05$; Supplemental Table 3), as

![Figure 1. Example of tumor volume quantification methods on prostate cancer biopsies of a single patient. A, Each individual core is reviewed. Total biopsy length is depicted in blue, whereas the red areas represent tumor fields. B, For each core, the tumor percentage was estimated after which the length of the total biopsy specimen, as well as the tumor area, was measured. C, All the tumor volume parameters were calculated for the patient as based on the biopsy measurements.](image)

![Figure 2. Schematic representation of Pearson correlations between 6 different tumor volume parameters. Correlation values can range between 0 and 1, where 1 is the best possible correlation.](image)
well as PSA and grade group (Supplemental Table 4). For DSS after RT, univariate analysis showed that all tumor volume parameters had significant predictive value (all $P < .001$; Supplemental Table 3). In multivariable analysis including all tumor volume parameters as covariates, calculated tumor length was the only positive significant predictive parameter ($P = .02$; Table 2). Multivariable analysis including clinicopathologic parameters and the separate tumor volume parameters showed that all biopsy tumor volume parameters, except greatest tumor length, had independent predictive value for DSS ($P < .05$; Supplemental Table 3) as well as age, PSA, and grade group (all $P < .05$; Supplemental Table 4).

**DISCUSSION**

Biopsy tumor volume is associated with clinical outcome and represents an inclusion parameter in some active surveillance cohorts.21,22 While a measure of tumor volume should be included in prostate biopsy reports, no consensus exists on the method of tumor volume quantification. In this study, we analyzed 6 different methods for tumor volume reporting. We found overall moderate to good correlation between all tumor volume parameters. All had predictive value for EPE, SM status, and BCRFS after RP, as well as BCRFS and DSS after RT in univariate analysis. In multivariable analysis including all tumor volume parameters as covariates, calculated tumor length was the only predictor for EPE after RP and DSS after RT. Since their predictive value is comparable, all tumor volume parameters are acceptable for pathologic reporting, with calculated tumor length being slightly better in predicting some of the endpoints.

The lack of standardization in biopsy tumor volume parameters leads to use of a wide variety of parameters in clinicopathologic studies. While tumor volume measurements are associated with adverse outcome after RP in many studies, results on their independent predictive value in multivariable analysis are inconsistent.23–30 Here, we found that none of the volume parameters was independently predictive for BCRFS after RP. Discordant outcomes between studies can be explained by the application of tumor volume cutoff values in some studies, which might introduce study biases.31 Furthermore, the clinicopathologic parameters included in multivariable analyses are highly variable amongst studies, potentially omitting relevant confounding factors.

The relation between tumor volume and outcome after RT has not been thoroughly studied yet. While greatest percentage tumor involvement was predictive for BCR in univariate analysis in several studies, it was not predictive when other clinicopathologic parameters were included in multivariable analysis.32–34 This is in contrast to our study, in which we show independent predictive value of tumor volume parameters for BCRFS and DSS after RT. This can be explained by inclusion of different clinicopathologic covariates, size of patient cohorts, and use of continuous variables instead of cutoffs.

In this study we found strong mutual correlations between biopsy tumor volume quantification methods and comparable predictive value for clinical outcome. In

### Table 1. Multivariable Analysis of All Tumor Volume Parameters on Outcome After Radical Prostatectomy, Including All Tumor Volume Parameters as Covariates

<table>
<thead>
<tr>
<th></th>
<th>Extraprostatic Expansion</th>
<th>Surgical Margin Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted OR$^a$</td>
<td>95% CI</td>
</tr>
<tr>
<td>Estimated tumor percentage</td>
<td>1.2</td>
<td>0.6–2.4</td>
</tr>
<tr>
<td>Calculated tumor length</td>
<td>2.8</td>
<td>1.1–7.0</td>
</tr>
<tr>
<td>Greatest tumor percentage</td>
<td>1.0</td>
<td>0.4–2.5</td>
</tr>
<tr>
<td>Greatest tumor length</td>
<td>0.5</td>
<td>0.2–1.2</td>
</tr>
<tr>
<td>Average tumor percentage of all biopsies</td>
<td>0.9</td>
<td>0.4–2.1</td>
</tr>
</tbody>
</table>

Abbreviation: OR, odds ratio.

$^a$ Per doubling unit.

### Table 2. Multivariable Analysis of All Tumor Volume Parameters on Survival After Radical Prostatectomy or Radiation Therapy, Including All Tumor Volume Parameters as Covariates

<table>
<thead>
<tr>
<th></th>
<th>Biochemical Recurrence-Free Survival After RP</th>
<th>Biochemical Recurrence-Free Survival After RT</th>
<th>Disease-Specific Survival After RT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted HR$^a$</td>
<td>95% CI</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>Estimated tumor percentage</td>
<td>1.2</td>
<td>0.7–2.2</td>
<td>.47</td>
</tr>
<tr>
<td>Calculated tumor length</td>
<td>0.9</td>
<td>0.4–1.7</td>
<td>.68</td>
</tr>
<tr>
<td>Greatest tumor percentage</td>
<td>0.5</td>
<td>0.3–1.3</td>
<td>.17</td>
</tr>
<tr>
<td>Greatest tumor length</td>
<td>1.5</td>
<td>0.7–3.2</td>
<td>.32</td>
</tr>
<tr>
<td>Average tumor percentage of all biopsies</td>
<td>1.4</td>
<td>0.7–2.7</td>
<td>.34</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; RP, radical prostatectomy; RT, radiation therapy.

$^a$ Per doubling unit.
multivariable analyses including all tumor volume parameters, calculated total tumor volume outperformed the other quantitative parameters for prediction of postoperative EPE and DSS after RT. In their study of multiple tumor measurements, Brimo et al. found total tumor length as best predictive quantifier for postoperative BCRFS. Calculated tumor length is a simple quantitative measurement that can objectively be assessed, as compared to estimated tumor volume measurements, and might be easily comparable between studies. A weakness of total calculated tumor length is that its quantification can be time-consuming when many positive biopsies are present, in which case an estimated tumor percentage or maximal tumor length might be easier to assess. The impact of tumor volume assessment might be strongest on selection of patients for active surveillance. Some surveillance protocols include tumor volume parameters such as 20% or 50% tumor involvement as criteria for eligibility, stressing the importance of reliable tumor volume quantification. Since estimated tumor percentage can be determined by visual examination and is less time-consuming, it is not as objective as measuring tumor length and might result in volume overestimation in small biopsy specimens. A practical solution could be that estimated tumor percentage is given for all patients and that in case of potential surveillance eligibility, objective calculated tumor length is added.

In conclusion, all tumor volume parameters showed moderate to strong mutual correlation, had comparable prognostic value for outcome after RP and RT, and could be used in clinical practice. In case tumor quantification is a prognostic value for outcome after RP and RT, and could be used in clinical practice. In case tumor quantification is a prognostic value for outcome after RP and RT, and could be used in clinical practice.

