Tumor volume as a predictor of adverse pathologic features and biochemical recurrence (BCR) in radical prostatectomy specimens: A tale of two methods

Abstract

Purpose
The prognostic value of tumor volume in predicting biochemical recurrence after prostatectomy has been debated. Our aim in this study was to (a) evaluate tumor volume as an independent predictor of adverse pathologic outcomes and BCR and (b) determine the effect of two different methods of tumor volume estimation.

Methods
We reviewed the charts of 3,087 patients who underwent radical prostatectomy at Vanderbilt University Medical Center between 2000 and 2008; of which 1,747 patients had data sufficient for analysis. Prostate specimens were processed as whole mount between 2000 and 2003 and then via systematic sampling from 2003 to 2008, with tumor volume measured by planimetry in the whole-mount group and tumor volume estimated by percent tumor involvement in the systematic sampling group.

Results
Tumor volume estimates were higher with SS than with WM. There were significant associations between larger tumor volume and adverse pathological outcomes, regardless of pathologic method (all with $P < 0.001$). Controlling for other pathologic parameters, tumor volume was an independent predictor of PGS, EPE, and SM in logistic regression models ($P < 0.001$ for TV in all models). Tumor volume was demonstrated to be an independent predictor of BCR in the WM group (1.06, 95% CI 1.01–1.11, $P = 0.013$), though tumor volume was not a significant predictor of BCR in the SS group.

Conclusions
Though the prognostic value of tumor volume is debated, our data demonstrate that tumor volume, when calculated via planimetry on whole-mount pathologic sectioning, is a significant predictor of biochemical recurrence after prostatectomy.
Tumor volume as a predictor of adverse pathologic features and biochemical recurrence (BCR) in radical prostatectomy specimens: A tale of two methods

Ian M. Thompson III · Shady Salem · Sam S. Chang · Peter E. Clark · Rodney Davis · S. Duke Herrell · Yakup Kordan · Roxelyn Baumgartner · Sharon Phillips · Joseph A. Smith Jr. · Michael S. Cookson · Daniel A. Barros

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Keywords Prostate cancer · Tumor volume · Whole mount · Systematic sampling · Biochemical recurrence

Abbreviations

TV Tumor volume

WM Whole mount

EPE Extraprostatic extension

SM Positive surgical margin

LNI Lymph node involvement

SVI Seminal vesicle invasion

PTI Percent tumor involvement

BCR Biochemical recurrence

RALP Robotic assisted laparoscopic prostatectomy

RPP Retropubic radical prostatectomy

Introduction

Prostate cancer is the most common solid tumor, besides non-melanoma skin cancer, affecting males in the United States [1]. Radical prostatectomy has been a preferred treatment for clinically localized disease and the only treatment that has shown a cancer-specific survival benefit compared to conservative management [2]. The risk of biochemical
Tumor volume as a predictor of adverse pathologic features and biochemical recurrence (BCR) is approximately 25% [3], and with growing evidence that adjuvant radiation therapy can delay post-prostatectomy BCR in patients with aggressive disease, there is a need for more accurate prediction of outcome [4].

The prognostic value of pathologic Gleason Score (PGS), extraprostatic extension (EPE), lymph node involvement (LNI), and positive surgical margins (SM) for BCR have been well demonstrated [5-7]. Larger tumor volume (TV) has been associated with worse pathological features, including higher PGS, positive SM, and LNI [8-11]. However, the role of TV as an independent predictor of BCR remains controversial [6, 11-14]. The controversy regarding TV is augmented by different methods of ascertainment (i.e., direct measurement of TV by planimetry vs. visually estimated percent tumor involvement (PTI) of the gland).

In this study, we sought to (a) evaluate TV as a predictor of adverse pathologic outcomes and BCR and (b) determine the effect of two different methods of TV ascertainment.

**Patients and methods**

After obtaining Institutional Review Board approval, we reviewed the files of 3,087 patients with prostate cancer who underwent either open, radical prostatectomy (RRP) or robotic assisted laparoscopic prostatectomy (RALP) between January 2000 and June 2008 at Vanderbilt University Medical Center (VUMC). Patients who had received preoperative radiotherapy (16), neoadjuvant hormonal, or chemotherapy (153), patients with missing tumor volume or a tumor volume of zero (46), patients with no follow-up (276) or follow-up less than 6 months (1,045) were excluded, leaving 1,747 patients for analysis.

**Specimen handling and pathological evaluation**

In all cases, specimens were received fresh, then measured (apex-base, anterior-posterior, and transverse), and weighed. The capsular surface was inked and the prostate was fixed. The apex and bladder neck margin were amputated, serially sectioned on end, and embedded for histological examination. Seminal vesicles were amputated and transversely sectioned.

Between January 2000 and May 2003, prostate tissue was submitted for whole-mount (WM) section per the protocol described by Jack et al. [15]. The total tumor volume in cc was measured by planimetry with areas of outlined tumor foci determined using a digitized graphics tablet and National Institutes of Health Image analysis software (http://www.rsib.info.nih.gov/nih-image/).

Between June 2003 and June 2008, prostate tissue was step-sectioned and systematically sampled (SS) and evaluated according to protocol previously described by Srigley [16]. In this method, tumor volume is determined by estimating percentage of all tissue evaluated that was involved with tumor, then multiplying by the prostate volume to determine the tumor volume.

**Patient follow-up**

Patient follow-up was at the discretion of the treating physician, although in general, patients had the first postoperative PSA 4-6 weeks postoperatively, then every 6 months for 2 years, and yearly thereafter. We used PSA of 0.2 ng/dl or greater, confirmed at least once as the definition of BCR [17].

**Statistical analysis**

Patients were grouped according to pathologic processing method (WM or SS), which corresponds to the method of tumor volume ascertainment (planimetry vs. PTI estimation). For each group, univariate associations between TV and PGS, EPE, SM status, LNI, and seminal vesicle invasion (SVI) were evaluated using Kruskal–Wallis and Wilcoxon tests where appropriate.

In order to further explore the association between TV and other pathologic findings, a series of logistic regression models was developed, using each pathologic parameter (PGS, EPE and SM) as the dependent variable. TV was the main independent variable and the remaining pathologic parameters were covariates. Logistic regression models for SVI and LNI were not done because the small number of events would have resulted in unstable models.

The effect of TV on time to BCR was determined using Cox proportional hazards models. Again, TV was the primary independent variable and PGS, EPE, SM, SVI, LNI were the covariates. The same model was repeated with tumor size expressed as PTI instead of TV and the models were compared.

In order to identify the level of TV concerning for increased risk of BCR, patients were divided into quartiles by TV and Kaplan–Meier curves were constructed. Log-rank tests were used to compare risk of BCR between quartiles. A two-tailed P-value < 0.05 was considered significant and we did not make corrections for multiple comparisons.

**Results**

Table 1 contains clinical and pathological parameters for both groups. The WM group consisted of 476 patients with mean age 59.7, pretreatment PSA median 5.6, and median...
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