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Original article

Tumor volume, surgical margin, and the risk of biochemical recurrence in men with organ-confined prostate cancer

Cheryn Song, M.D., Ph.D.[a], Taejin Kang, M.D.[a], Sangjun Yoo, M.D.[a], In Gab Jeong, M.D., Ph.D.[a], Jae Y. Ro, M.D., Ph.D.[b,c], Jun Hyuk Hong, M.D., Ph.D.[a], Choung-Soo Kim, M.D., Ph.D.[a], Hanjong Ahn, M.D., Ph.D.[a,*]

[a] *Department of Urology and Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*
[b] *Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*
[c] *Department of Pathology, The Methodist Hospital, Weill Medical College of Cornell University, Houston, TX 06883, USA*

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Abstract

Objectives: We proposed to investigate predictors of biochemical recurrence (BCR) in pT2 prostate cancer by identifying the interrelationship between the tumor volume and surgical margin status, and their impact on recurrence.

Materials and methods: Clinical, pathologic, and follow-up data of 404 consecutive patients who were treated with radical prostatectomy alone and were diagnosed as pT2 prostate cancer in our institution were reviewed. Percent tumor volume (PTV) was estimated from the cancer distribution map, and the surgical margin status was reviewed by a single pathologist (JYR). Clinicopathologic variables were analyzed with respect to the risk of BCR.

Results and limitations: Recurrence was observed in 39 (9.7%) patients at a mean of 28.9 (5–47) months. Preoperative PSA, biopsy Gleason score, surgical Gleason score, PTV, and surgical margin status were significantly related to BCR in univariate analysis; in multivariate analysis, PTV ($P < 0.001$) and surgical Gleason score ($P = 0.021$) were independent predictors of BCR. PTV was also an independent determinant of positive surgical margin ($P = 0.035$, HR 1.026, 95% CI 1.002–1.050). By combining the 2 predictors 5-year recurrence-free survivals for PTV $\leq$ 14.5% and surgical Gleason score $\leq$ 7, PTV >14.5% or surgical Gleason score > 7, and PTV > 14.5% and surgical Gleason score > 7 were 97.5%, 88.7%, and 44.5%, respectively (log-rank test, $P < 0.01$). Retrospective study nature, use of PTV instead of actual volume, and intermediate follow-up length are the main limitations of the study.

Conclusions: In men with pT2 prostate cancer, percent tumor volume and the surgical Gleason score were independently prognostic of BCR and by combining the 2 factors, risk of BCR could be significantly stratified. Tumor volume further determined surgical margin status undermining its prognostic value as an independent variable.

Keywords: Prostatic carcinoma; Radical prostatectomy; Biochemical recurrence; Tumor volume; Surgical margin

1. Introduction

Disease recurrence in organ-confined prostate cancer is reported to occur in up to 27% of the patients after radical prostatectomy (RP) [1,2]. While it is widely accepted that the positive surgical margin (PSM) in RP specimen is one of the factors associated with disease recurrence, the relationship between a PSM and biochemical recurrence (BCR) in pathologically organ-confined disease is still unclear. In relation to the risk of BCR by iatrogenic capsular incision (CI), several explanations have been proposed; CI may have left tissue containing benign and/or malignant glands distal to the inadvertent incision, which could grow and secrete PSA. Micro-spillage may cause cancer recurrence. Also, there have been suggestions of overdiagnosis of CI for what is really a PSM associated with extraprostatic extension (EPE) and peritumoral desmoplasia [3]. Missing and understaging of overt EPE disease owing to the methods of prostate specimen handling, sectioning intervals, and microscopic examination have also been suggested [4].

Generally, reported incidence of PSM in pT2 prostate cancer ranges from 7% to 29% [5,6]. The margin status is influenced by both surgical technique and tumor character-

* Corresponding author. Tel.: +822-3010-3733; fax: +822-477-8928.
E-mail address: hjahn@amc.seoul.kr (H. Ahn).

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istics such as tumor size, location, and the potential for invasion. Larger tumor should possess greater risk for a margin-positive disease and a subsequent recurrence [7]. Therefore, tumor volume may be a more independent determinant of prognosis after definitive treatment [8–10]. In the same way, Stamey et al. [11] clearly demonstrated that percent Gleason grade 4/5 tumor foci and total cancer volume were highly predictive of disease progression, while capsular penetration and PSM were not. However, contrary reports continue arguing against the significance of tumor volume as an independent prognosticator; similar to the persistent controversy on PSM, no consistent conclusion has been reached regarding the tumor volume, especially in organ-confined prostate cancer. In the present study, we proposed to investigate prognostic factors predictive of BCR in pT2 prostate cancer by identifying the inter-relationship between the tumor volume and surgical margin status, and analyzing the impact on disease recurrence among other clinical and pathologic predictors.

2. Materials and methods

2.1. Patients population

We reviewed 404 consecutive patients who underwent RP and were diagnosed as pathologic T2 prostate cancer in our institution from January 2000 to March 2007 after institutional review board approval was obtained. Clinical (preoperative PSA, biopsy Gleason score, clinical stage) and pathologic (pathologic stage, surgical Gleason score, tumor volume, surgical margin status) data were obtained. All cases were done retropubically and patients with neo-adjuvant or adjuvant therapy, postoperative PSA that did not reach undetectable level within 2 months were excluded. Patients without complete clinical data or lost to follow-up were also excluded. BCR was defined as any increase in PSA $>$ 0.2 ng/ml taken after postoperative 2 months and rising on the subsequent exam. Patients without BCR were censored at last follow-up. Postoperatively, patients were followed at 3- to 4-month intervals during the first 2 years, biannually for the next 3 years, and then yearly thereafter. Mean follow-up was 52.5 (12–101) months after RP.

2.2. Pathologic review and tumor volume estimation

All surgical specimens were examined at 3–5 mm sections from base to apex perpendicular to the major axis after routine fixation. Each slice was prepared for microscopic examination by whole mount slide or divided into bisectional slide. For the present study, all pathology slides were re-reviewed and the PSM was diagnosed by a single uropathologist (JYR). PSM was defined as the tumor extending to the inked surface of the specimen [12], and in areas without definite, identifiable capsule, the definition previously described by Rosen et al. [13] was followed. To determine the tumor volume, the whole prostate outline and areas of cancer distribution were figured into the cancer distribution map. Then the cancer distribution map was scanned to image file for processing using an image-editing

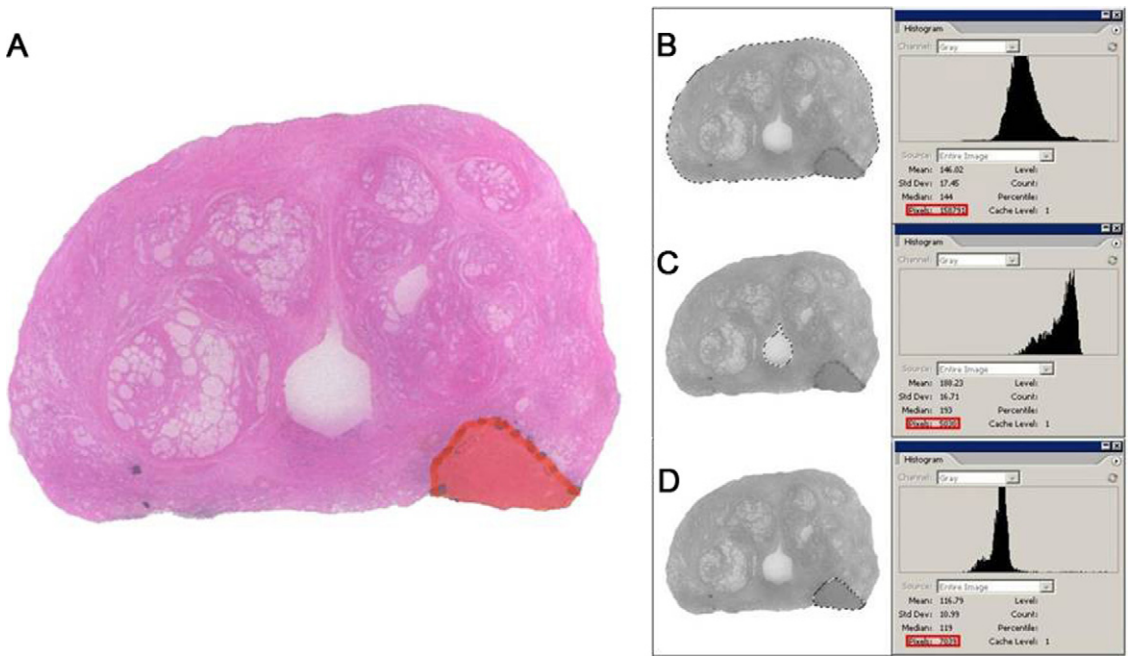

Fig. 1. Calculating the tumor volume using the Photoshop® software. The whole mount slide was scanned to an image file (A) and converted to a grayscale format. Using the selecting tool, the prostate outline (B), urethra (C), and every tumor foci (D) were selected. Pixel sum of the selected area is automatically calculated (red box). (Color version of figure is available online.)