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Original article

A single institution experience with biochemical recurrence after radical prostatectomy for tumors that on pathology are of small volume or "insignificant"

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Abstract

Objective: Small volume prostate cancers (<0.5 cc, svPC), and insignificant prostate cancers (<0.5 cc and Gleason scores <7, InsigPC) are considered clinically insignificant by some investigators. The aim of this study is to determine the biochemical recurrence rate (BCR) of svPC and InsigPC in prostatectomy specimens.

Methods: In total, 502 patients with prostate cancer, treated with radical prostatectomy (RP) between 1992 and 2005 and with detailed pathological classification, were included in the present study. Patients were postoperatively followed for a median period of 39.5 months (0.6–150). A total of 82 specimens (16.3%) with svPC including 64 (12.8%) with InsigPC were identified. BCR was defined as 2 consecutive PSA levels >0.10 ng/ml.

Results: In the total group, the median age at the time of surgery was 62.7 years (42.4–73.4) and the median preoperative PSA level was 8.0 ng/ml. Patients with InsigPC had Gleason scores of 4 in 7%, 5 in 37%, and 6 in 56%. Positive surgical margins were identified in 13 (15.9%) svPC and in 8 (12.7%) InsigPC specimens. The 5-year risk of BCR for the svPC group and the insigPC group was 10% (95% CI 2–18%, 7 and 5 patients, respectively) vs. 35% (95% CI 29–41%) in the rest of the cohort (log rank $P = 0.001$).

Conclusion: Patients with svPC and patients with InsigPC have a significantly lower risk of BCR. However, even in this seemingly very favorable patient group, 1 in 10 patients will develop a BCR after RP. Therefore, new studies are needed to examine what the prognostic relevance is of small-volume tumors.

Keywords: Prostate; Prostatectomy; Small volume tumor; Insignificant prostate cancer; Prognosis

1. Introduction

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death in Western men. Unlike other malignancies, not every prostate cancer poses a threat to life and, consequently, need therapy. The wide spread use of prostate specific antigen (PSA) testing has led to a spectacular stage migration to smaller and lower stage prostate cancers. Small-volume cancers (svPC) are those with a volume of 0.5 cc or less. A subset of these tumors are called insignificant prostate cancers (InsigPC). In this case, a volume of 0.5 cc or less is combined with a Gleason score of 6 or less [1,2]. Expectant management is more and more considered to be a reasonable treatment option for these small-volume/insignificant prostate cancers. Therefore, for patients with a relatively long life expectancy, it is important to know what the biological behavior of these small-volume prostate cancers is. However, looking at studies dealing with small-volume prostate cancers, nearly all results and conclusions are based on preoperative classifications, nomograms, or they are comparing preoperative biopsies with postoperative diagnoses [1,3–5].To our knowledge, the only known analysis looking at the outcome of patients with svPC, in this case disease progression, was published by Epstein et al. in 1993 [6]. They analyzed 185 clinical

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stage B adenocarcinomas of the prostate with a follow-up of 5 years and found that no tumor with volume smaller than 0.5 cc (18 patients) was found to have progression following RP.

In the present series of 502 consecutive radical prostatectomy (RP) patients, we characterized and analyzed detailed pathological features of svPC and InsigPC and analyzed the risk of biochemical recurrence (BCR) in this group.

2. Material and methods

2.1. Study population

Between 1992 and 2005, 617 patients were treated with RP for clinically localized prostate cancer at our institute. Of these patients, 115 were excluded from analyses because of preoperative high intensity focused ultrasound (HIFU) treatment, hormonal pretreatment, preoperative irradiation, adjuvant treatment (radiation or hormonal), or preoperative transurethral resection of the prostate. Of the remaining 502 patients, 5 had incomplete follow-up data. Charts were examined retrospectively for clinical follow-up data.

2.2. Assessment of tumor characteristics

All RP specimens were fixed overnight, inked, and cut into serial transverse 4 mm thick slices according to a standard protocol by Ruijter et al. [7]. All slices were macroscopically photographed and subdivided into halves or quadrants to fit routine cassettes for further processing. Apex and base were sagittally sectioned for assessment of surgical margins. Seminal vesicles were sectioned parallel to their junction and embedded in total. After histological staining all specimens were evaluated by one experienced urogenital pathologist (C.A.H.K.), and tumors were outlined on the microscopic slides and subsequently on the macroscopic photographs to allow for reconstruction of tumor extent. Tumor grading was performed according to Gleason. Extraprostatic extension was defined as extension of adenocarcinoma in periprostatic adipose tissue, seminal vesicle invasion as invasion beyond the level of their junction with the prostate. Surgical margins were considered positive if cancer cells were in the inked margin. Tumor volume was calculated as described before [7]. Tumors were initially staged according to the TNM classification that was in general use at the time of surgery, but retrospectively all pT2 tumors were restaged according to the 2002 TNM staging criteria [8].

Small-volume cancers were defined as cancers with a volume $\leq$ 0.5 cc. Insignificant prostate cancers were defined as cancers with a volume $\leq$ 0.5 cc and a Gleason score $<$ 7. PSA values were obtained before surgery and at every follow-up point. BCR after RP was defined as two subsequent PSA levels above 0.10 ng/ml among patients who reached nonmeasurable levels after RP.

Kaplan-Meier curves were used to assess the risk of BCR. Mann-Whitney U-tests, Log rank test and χ^2 test were used for comparisons between groups. The significance level for all analyses was set at $P < 0.05$. SPSS version 14.0 for Windows (SPSS Inc., Chicago, IL) was used for all statistical analyses.

3. Results

In the total group, the median age at the time of surgery was 62.7 years (42.4–73.4). The median preoperative PSA level in this group was 8.0 ng/ml. A total of 82 (16.9%) specimens with total tumor volume 0.5 cc or less, including 64 (12.9%) specimens with a total tumor volume 0.5 cc or less and a Gleason score $<$ 7 were identified. Tables 1 and 2 summarize pathological characteristics of svPC and InsigPC. In the svPC group, Gleason score was 4 in 7%, 5 in 37%, and 6 in 56%. Positive surgical margins were identified in 13 (15.9%) svPC and in 8 (12.9%) InsigPC specimens. None of these patients had lymph node metastasis. There were 7 patients with BCR in the svPC group and in the smaller InsigPC group still 5 patients had BCR (Table 3). The 5-year risk of biochemical progression for the svPC group and the insigPC group was 10% (95% CI 2–18%, 7 and 5 patients, respectively) vs. 35% (95% CI 29–41%) in the rest of the cohort (log rank $P < 0.001$) (Fig. 1).

Table 1
Pathological characteristics for small volume prostate cancers (svPC)

Tumor characteristics	Cancer volume ≤0.5 cc (%)	Cancer volume >0.5 cc (%)	*P*-value
N[a] (%)	82 (16.9%)	404 (83.1%)	
Mean cancer volume (SD)	0.25 (0.14)	4.03 (5.07)	
TNM[b] 2002 (%)			
T2a	37 (45.1%)	34 (8.4%)	
T2b	0	0	
T2c	44 (53.7%)	206 (51.5%)	$P < 0.001$*
T3a	1 (1.2%)	107 (26.6%)	
T3b	0	45 (11.2%)	
T4	0	11 (2.7%)	
Gleason score[c] (%)			
≤6	67 (81.7%)	200 (49.9%)	
7	12 (14.6%)	133 (33.2%)	$P < 0.001$*
≥8	3 (3.7%)	68 (17.6%)	
Positive surgical margins (%)	13 (15.9%)	231 (57.3%)	$P < 0.001$*
Number of tumors (SD)	2.2 (1.4)	2.2 (1.4)	$P = 0.81$†
Unifocal tumor (%)	37 (45.1%)	176 (43.6%)	
Multifocal tumors (%)	45 (54.9%)	228 (56.4%)	$P = 0.80$*
Biochemical recurrence (5-year risk)	7 (10%)	110 (35%)	$P < 0.001$‡

[a] 16 missing.
[b] 1 missing.
[c] 3 missing.
* χ^2 test.
† Mann-Whitney U test.
‡ Log rank test.