

Original article

Margin details matter: The prognostic significance of pseudocapsule invasion at the site of involved margin in prostatectomy specimens

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Abstract

Background: An involved surgical margin at prostatectomy has long been associated with elevated risk of prostate cancer recurrence; however, not all patients with an involved margin will relapse, and thus details of the involved margin may provide an opportunity for risk subset stratification. The present investigation seeks to determine whether a difference exists in recurrence rates when the margin involvement is at a site of prostate pseudocapsule invasion vs. within the prostate parenchyma proper.

Methods: Patients were retrospectively identified for inclusion by clinically localized disease and prostate-specific antigen (PSA) level of <30 ng/ml at diagnosis, managed with prostatectomy alone and identified to have involvement of surgical margin(s). Exclusion criteria were: pT3b or pN1 disease, immediate/nonsalvage postoperative radiation or hormone therapy, or insufficient follow-up (<12 mo). Pathology slides were reviewed by a pathologist blinded to outcome, for determination of pseudocapsule invasion at a site of margin involvement. Disease recurrence was defined as PSA level of ≥ 0.2 ng/ml and rising, per contemporary guidelines. Kaplan-Meier method was used for construction of disease control estimate confidence intervals; Cox Proportional Hazards Model was used to compare disease control across groups.

Results: Between 2003 and 2010, 155 patients were identified for inclusion in the present study. The median age was 61 years, and all had clinical stage T1 and T2 disease (75% T1c). At diagnosis, the Gleason score was 6, 7, and 8–9 for 103 (66%), 42 (27%), and 10 (6%) patients, respectively, with median PSA level of 5.6 ng/ml (85% ≤ 10). For 149 patients with reviewable margin site data, 51 (34%) demonstrated involvement within or beyond the pseudocapsule. At a median follow-up of 68 months (range: 13–137), 62 patients had experienced PSA relapse. The estimated 5-year PSA relapse rates for patients with an involved margin at the site of pseudocapsule invasion vs. prostate parenchyma were 49% vs. 34%, respectively ($P = 0.017$; hazard ratio = 1.853).

Conclusions: Early PSA relapse rates are high for patients with involved surgical margin(s) without seminal vesicle or node involvement at prostatectomy; however, for patients who are followed without immediate adjuvant therapy, presence of tumor cells at the margin in a site of pseudocapsule invasion or penetration confers a higher risk of recurrence. © 2015 Elsevier Inc. All rights reserved.

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1. Introduction

Multiple randomized trials and large single institutional studies have demonstrated that patients who have specific pathologic risk factors have an elevated risk of biochemical

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failure after radical prostatectomy [1–4]. These features, which have been used as eligibility criteria for immediate postoperative (adjuvant) radiotherapy, include invasion of the seminal vesicles, extraprostatic extension (EPE), and involved surgical margin(s) [1–3]. Interestingly, an estimated 40% to 50% of patients randomized to observation or no adjuvant radiotherapy did not manifest clinical or biochemical (prostate-specific antigen [PSA]–defined) recurrence at 10 years [1–3]. Although adjuvant radiation therapy reduced the 10-year failure rates to 25% to 40% [1–3], at present there are no validated substratification criteria to determine which patients within this “high-risk” pathologic subset are at higher or lower risk of recurrence.

Involvement of a surgical margin has long been associated with elevated rates of recurrence [4,5], and subsequent studies have sought to determine whether specific factors within the margin-positive subset may confer higher or lower risk of failure [6,7]. At present, although extraprostatic tumor extension has been validated as a high-risk feature [4], it remains to be determined whether margin involvement in such cases confers a different risk of recurrence from an involved intraparenchymal margin, as may occur when the periprostatic capsule is incompletely excised. We hypothesized that a positive margin located in or through the prostate capsule confers a higher risk of recurrence than a positive margin located in the prostate parenchyma.

2. Methods

Following Institutional Review Board approval at the study institutions, a research database was created with study-specific patient, treatment, and outcome data fields. Eligible cases were identified by review of medical records and quality assurance database. After selection for prostate adenocarcinoma cases, a review of patient records was performed to eliminate patients with advanced or metastatic disease at diagnosis (including preprostatectomy evidence of seminal vesicle or pelvic lymph node involvement) or PSA level of ≥ 30 ng/ml at diagnosis. Preoperative staging studies were performed at the discretion of the managing urologist, with bone scan and computed tomography scans generally performed for patients with Gleason scores of 8 to 10 or PSA level of > 20 ng/ml. All patients underwent radical retropubic prostatectomy (open or laparoscopic, with or without robot assistance) as primary curative-intent therapy. Patients with involved seminal vesicles or lymph nodes, or both, who received immediate adjuvant therapy (radiation or hormone), or who were lost to follow-up within 1 year of prostatectomy (no PSA > 12 mo postoperatively) were excluded from the analysis.

Standard pathologic specimen preparation techniques were used [8], generally consisting of formalin fixation for 4 to 24 hours, followed by inking of the radial margins. The apex and base are excised and submitted entirely, with

a perpendicular sectioning technique, and 3 to 4 mm serial sectioning of the remainder of the gland. Pathology reports were reviewed to identify cases with involvement of one or more surgical margin(s). A margin was considered involved if there was no cell layer or fibrous stroma separating cancer cell(s) from the inked margin. Specimen slides were rereviewed by a pathologist from each participating institution, who was blinded to patient disease control outcome. Additionally, slides from cases with involved or “close” (≤ 1 mm) margin(s) noted on the original pathology report were reviewed again for accuracy. Special attention was paid to the site of margin involvement, specific to the presence of tumor cells at a margin within or beyond the periprostatic fibrous stromal layer (“pseudocapsule”). When the periprostatic pseudocapsule was disrupted or incomplete, and the involved surgical margin was only demonstrated within the prostate parenchyma (without associated pseudocapsule invasion or penetration), this was not recorded as pseudocapsule invasion.

Postoperative evaluations included physical examination and PSA measurement every 3 to 6 months for the first 2 years postprostatectomy, and every 6 to 12 months thereafter. In the setting of PSA or clinical relapse, restaging imaging and subsequent intervention(s) were performed at the discretion of the managing urologist.

The principal outcome measure of this retrospective study was biochemical relapse-free survival (bRFS), specifically postprostatectomy PSA, measured from date of prostatectomy to date of first rising PSA level of ≥ 0.2 ng/ml, or last follow-up or death, if no PSA rise occurred. Patients with stable postoperative PSAs at 0.1 ng/ml were not considered to have had biochemical relapse. Secondary objectives included analysis of factors associated with bRFS, and identification of low- or high-risk subsets based on this.

2.1. Statistical analysis

The Kaplan-Meier method was used to estimate bRFS for the entire population and subsets. Bivariate analyses between the primary parameter of interest and patient- and tumor-specific factors were calculated using the Mann-Whitney *U* test. Cox proportional hazards model was used to identify variable association with bRFS. Cox proportional hazards regression was used to construct a multivariate model of bRFS. Analyses were performed using SPSS Version 21 (SPSS, Inc.; Chicago, IL).

3. Results

Between January 2003 and December 2010, 544 patients diagnosed with prostate cancer underwent radical prostatectomy at the study institutions, of whom 155 had an involved margin and met study eligibility criteria. Patient demographics and preoperative staging information are

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