ELSEVIER

Urologic Oncology: Seminars and Original Investigations 32 (2014) 26.e1–26.e7

UROLOGIC ONCOLOGY

Original article

# The presence of extracapsular extension is associated with an increased risk of death from prostate cancer after radical prostatectomy for patients with seminal vesicle invasion and negative lymph nodes

J. Mikel Hubanks, M.D.[a], Stephen A. Boorjian, M.D.[a,*], Igor Frank, M.D.[a], Matthew T. Gettman, M.D.[a], R. Houston Thompson, M.D.[a], Laureano J. Rangel, M.S.[b], Eric J. Bergstralh, M.S.[b], R. Jeffrey Karnes, M.D.[a]

[a] *Department of Urology, Mayo Clinic, Rochester, MN*
[b] *Department of Health Sciences Research, Mayo Clinic, Rochester, MN*

Received 18 July 2012; received in revised form 21 August 2012; accepted 4 September 2012

**Abstract**

**Objectives:** Determining clinicopathologic features that stratify the risk of disease progression in patients with seminal vesicle invasion at radical prostatectomy remains critical for patient counseling, clinical trial enrollment, and the judicious application of secondary therapies. Then, we evaluated the prognostic significance of concomitant extracapsular extension (ECE) in patients with seminal vesicle invasion and negative lymph nodes at radical prostatectomy.

**Methods:** We identified 1,132 patients who underwent prostatectomy between 1987 and 2009 and were found to have pT3bN0 disease. Median postoperative follow-up was 10.6 years (interquartile range, 5.9–15.3). Survival was estimated using the Kaplan-Meier method and compared for patients with and without ECE with the log-rank test. The association of ECE with outcome was evaluated using Cox proportional hazards regression models.

**Results:** A total of 693 (61%) patients were noted to have ECE. Compared with pT3bN0 patients without ECE, patients with pT3bN0 tumors and ECE had a significantly worse 15-year biochemical recurrence-free survival (29% vs. 39%; $P < 0.001$), systemic progression-free survival (71% vs. 81%; $P < 0.001$), cancer-specific survival (80% vs. 89%; $P < 0.001$), and overall survival (50% vs. 63%; $P < 0.001$). On multivariate analysis, the presence of ECE was associated with significantly increased risks of systemic progression (hazard ratio [HR], 1.56; $P = 0.006$), death from prostate cancer (HR, 1.71; $P = 0.01$), and all-cause mortality (HR, 1.35; $P = 0.007$). Meanwhile, adjuvant hormonal therapy, which was received by 334 patients (29.5%), was associated with significantly decreased risks of systemic progression (HR, 0.50; $P = 0.0004$) and cancer death (HR, 0.57; $P = 0.03$), but not all-cause mortality (HR, 0.81; $P = 0.09$). Limitations included retrospective design and nonstandardized application of secondary treatments.

**Conclusions:** The presence of ECE in patients with pT3bN0 prostate cancer is associated with increased risks of systemic progression and cancer death. Pending validation, ECE may be incorporated into risk stratification or staging classification or both. Meanwhile, these patients continue to represent ideal candidates for adjuvant therapy trials. 

*Keywords:* Extracapsular extension; Prostate cancer; Radical prostatectomy; Seminal vesicle

## 1. Introduction

Despite the downward risk and stage migration in prostate cancer, which has been noted over the course of the prostate-specific antigen (PSA) era, locally advanced disease, including invasion of the seminal vesicles, continues to be encountered in up to 10% of patients undergoing radical prostatectomy (RP) [1–14]. Although these tumors have been associated with adverse outcomes relative to pathologically organ-confined disease [2–15], patients with seminal vesicle invasion (SVI) have demonstrated a relatively heterogeneous natural history following prostatectomy [2,3]. As such, various efforts to establish the optimal multimodal approach in this setting have been evaluated. Indeed, multiple randomized clinical trials have reported a benefit to adjuvant radiotherapy in men with pT3b tumors [15–19], whereas retrospective data have

* Corresponding author. Tel.: +1-507-284-3982; fax: +1-507-284-4951
*E-mail address:* boorjian.stephen@mayo.edu (S.A. Boorjian).

1078-1439/$ – see front matter 
http://dx.doi.org/10.1016/j.urolonc.2012.09.002

suggested a benefit to adjuvant androgen deprivation therapy as well [7].

Determining clinicopathologic features that stratify the risk of postoperative disease progression in patients with SVI remains critical for patient counseling, clinical trial enrollment, and the judicious application of secondary therapies. Although several previous series have investigated predictors of outcome among men with pT3b tumors [2–6], these studies have involved relatively small numbers of patients with relatively short-term follow-up. Notably, although "classic" prostate cancer prognostic variables of PSA, Gleason score, and surgical margin status have been associated with progression following surgery for men with SVI [2,3,5], an importance of concurrent pathologic extracapsular extension (ECE) in this setting has not been established [2,4,8,15]. Additionally, studies to date have primarily reported the association of tumor variables with postoperative biochemical recurrence. However, the clinical course of biochemical recurrence is frequently prolonged and does not universally predict death from prostate cancer [20–23]. Thus, assessing the association of prognostic variables with the outcomes of systemic progression and mortality remains important to determine the clinical relevance of these features.

Herein, we investigated comparative clinicopathologic outcomes for pT3bN0 prostate cancer patients with and without concurrent ECE. We further evaluated the association of ECE with postoperative survival, controlling for tumor features and receipt of adjuvant therapy.

## 2. Materials and methods

After Institutional Review Board approval was obtained, we reviewed our Prostatectomy Registry of 18,916 patients who underwent RP at Mayo Clinic between 1987 and 2009. Surgical procedures were performed by different surgeons using standard techniques. The extent of pelvic lymph node dissection varied with individual surgeon and over the time period of study. Tumor grade and stage were assigned using the Gleason grading system and the 1997 American Joint Cancer Committee tumor-nodes-metastasis classification system, respectively.

Men who received neoadjuvant therapy ($n$=1,922), as well as those with positive lymph nodes at RP ($n$=819), were excluded from study, as were men who refused release of their records ($n$=218) and 753 foreign patients without known follow-up. From the remaining cohort, we identified 1,132 patients who were found to have SVI at RP (pT3bN0). The presence or absence of concomitant ECE, which may occur either at the site of SVI or separately, was recorded in these men. Nearly, all patients (1,079/1,132; 95.3%) were treated with open RP, whereas 53 (4.7%) underwent robotic-assisted prostatectomy. Adjuvant therapy was defined as treatment received within 90 days of RP and was administered at the discretion of the treating physician. Salvage therapy, defined as secondary treatment beyond 90 days from RP, was likewise recommended according to individual physician discretion. It is noteworthy that, given the retrospective nature of this study, the duration of postoperative androgen deprivation therapy could not be determined.

Postoperative assessments were conducted quarterly to semiannually for the first 2 years, semiannually to annually for the next 3 years, and annually thereafter. Biochemical recurrence was defined as PSA $\geq$0.4 ng/ml [24,25]. Local recurrence was defined as cancer demonstrated on biopsy of the prostatic bed or receipt of salvage radiation therapy to the prostatic bed without evidence of systemic recurrence. Systemic progression involved demonstrable metastatic deposits on imaging or pathologic confirmation of prostate cancer on biopsy of tissue outside the prostatic fossa. Vital status was identified from death certificates or physician correspondence.

Postoperative survival, stratified by the presence or absence of ECE, was estimated using the Kaplan-Meier method and compared with the log-rank test. Patients were censored at the last follow-up or at death if the end point of interest had not been attained. Cox proportional hazard regression models were used to analyze clinicopathologic variables associated with the outcome following RP for patients with pT3bN0 tumors, including the importance of ECE.

Demographic comparisons between patients with and without ECE were performed using the chi-square and rank sum tests as appropriate. All tests were 2-sided, with a $P$ value $\leq$0.05 considered significant. Statistical analyses were performed using the Statistical Analysis System software package, version 8.2 (SAS Institute, Cary, NC, USA).

## 3. Results

Of 1,132 men with pT3bN0 disease, 693 (61%) were found to have concurrent pathologic ECE, whereas the remaining 439 were without evidence of ECE. Patient clinicopathologic demographics, stratified by the presence or the absence of ECE, are outlined in Table 1. As can be seen, patients with ECE were older, with a more advanced clinical stage, have greater preoperative PSA, have higher pathologic Gleason score, and were more likely to have positive surgical margins. Not surprisingly, patients with ECE were also significantly more likely to have received adjuvant therapies.

Median postoperative follow-up was 10.6 years (interquartile range, 5.9,15.3) and was not significantly different for patients with and without ECE (10.0 years vs. 11.2 years, respectively; $P$ = 0.12). During this time, 664 (58.7%) patients from the overall cohort experienced biochemical recurrence, with 179 (15.8%) developing local recurrence, 213 (18.8%) experiencing systemic progression, and 467 (41.3%) having died, with 129 (11.4%) dying from