# Extranodal Extension in Lymph Node–Positive Prostate Cancer

Liang Cheng, M.D., Thomas M. Pisansky, M.D., Dharamdas M. Ramnani, M.D., Bradley C. Leibovich, M.D., John C. Cheville, M.D., Jeff Slezak, B.S., Erik J. Bergstralh, M.S., Horst Zincke, M.D., Ph.D, David G. Bostwick, M.D.

*Departments of Pathology and Urology, Indiana University School of Medicine (LC), Indianapolis, Indiana; the Division of Radiation Oncology (TMP), the Department of Pathology (JCC), the Department of Urology (BCL, HZ), and the Section of Biostatistics (JS, EJB), Mayo Clinic and Mayo Foundation, Rochester, Minnesota; and Bostwick Laboratories (DMR, DGB), Richmond, and University of Virginia Health Sciences Center (DGB), Charlottesville, Virginia*

**Evaluation of extranodal tumor extension may provide prognostic information for patients with epithelial malignancies. However, its importance for the patient who has prostate cancer with regional lymph node metastasis requires further investigation and clarification. This study was performed to evaluate the prognostic significance of extranodal extension (ENE) in a large series of node-positive patients. The study group included 212 node-positive patients who were treated by bilateral pelvic lymphadenectomy, radical retropubic prostatectomy, and androgen deprivation between 1987 and 1992 at the Mayo Clinic. ENE was defined as cancer perforating through the lymph node capsule into perinodal tissue. Nodal cancer volume was measured by the grid method. Univariate and multivariate risk ratios (RR) for distant metastasis-free and cancer-specific survival were estimated using the Cox proportional model. The mean follow-up was 6.3 years (median, 6.1 years). Distant metastasis-free and cancer-specific survival at 5 years for all patients was 91% and 95%, respectively. ENE was found in 126 of 212 patients (59%). The presence of ENE was not significantly associated with distant metastasis-free (RR = 1.6; 95% confidence interval [CI], 0.7 to 3.9) or cancer-specific survival (RR = 2.2; 95% CI, 0.7 to 6.8). Among 98 patients with a single positive node, there was no significant difference in distant metastasis or cancer-specific survival according to the presence of ENE ($P = .88$ and $P = .36$, respectively). After adjusting for Gleason score, DNA ploidy, and ENE, only nodal cancer volume was significantly associated with adverse distant metastasis-free (RR = 1.9; 95% CI, 1.5 to 2.8) and cancer-specific survival (RR = 1.4; 95% CI, 1.1 to 1.9). Our data indicate that the presence of ENE is not associated with unfavorable survival in patients with node-positive prostate cancer treated by radical retropubic prostatectomy, bilateral pelvic lymphadenectomy, and androgen deprivation therapy. In contrast, nodal cancer volume was predictive of distant metastasis-free survival and cancer-specific survival.**

**KEY WORDS: Extranodal extension, Metastasis, Neoplasm, Prognosis, Prostate, Staging, Survival.**

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The treatment of patients who have prostate cancer with regional lymph node metastasis is controversial (1–7). Although treatment may not cure such patients, regional lymph node metastasis may be the only manifestation of cancer progression in some patients (8, 9). Identification of those who are at greatest risk for developing distant metastasis and mortality from prostate cancer will help stratify patients into prognostically distinct groups. Previous studies demonstrated that assessment of extranodal extension (ENE) in patients who are node positive may provide prognostic information in certain human epithelial malignancies, including breast cancer (10, 11), squamous cell carcinoma of the vulva (12, 13), gastric carcinoma (14), and squamous carcinoma of the head and neck (15–21). Others refuted the significance of ENE (22–26). ENE is a frequent histologic finding in lymph nodes with prostate cancer, but its prognostic significance has not been established. We previously demonstrated that nodal cancer volume is the single most important predictor of systemic progression-free survival


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Address reprint requests to: Liang Cheng, M.D., Department of Pathology, UH 3465, Indiana University School of Medicine, 550 North University Boulevard, Indianapolis, IN 46202; e-mail: lcheng@iupui.edu; fax: 317-274-5346.

in patients who are node positive and treated by radical retropubic prostatectomy, bilateral pelvic lymphadenectomy, and androgen deprivation (8). In this study, we evaluated the impact of ENE on survival and its association with other clinical and pathologic characteristics in a large number of patients who were node positive.

## PATIENTS AND METHODS

### Patients

The study population consisted of the Mayo Clinic patients who underwent radical retropubic prostatectomy and bilateral pelvic lymphadenectomy between January 1987 and December 1992. All patients had regional lymph node metastasis at the time of surgery and were treated with androgen deprivation therapy within 90 days of radical prostatectomy. Exclusion criteria from the study were 1) preoperative treatment with androgen deprivation, 2) no androgen deprivation therapy within 90 days of radical prostatectomy, 3) cancer volume of primary tumors not available, 4) DNA ploidy analysis not performed, or 5) histologic slides of lymph node metastasis not available for evaluation. The final study group consisted of 212 patients.

Patients were evaluated quarterly for the first 2 years, semiannually for 2 more years, and then annually. Follow-up examinations after surgery included physical examination, serum prostate-specific antigen (PSA) measurements, chest radiography, and computerized tomography of the abdomen and pelvis, as clinically indicated (8, 9). Radionuclide bone scanning was performed at least annually or as clinically indicated. Serum PSA was measured using the Hybritech Tandem-R PSA assay (Hybritech, Inc., San Diego, CA) in all patients. In patients who underwent follow-up at another institution, PSA concentration was determined at the Mayo Clinic by means of a mailed blood specimen, or the patients were contacted annually and additional medical information was obtained from the local physician, if necessary.

### Specimens

The radical prostatectomy and bilateral pelvic lymphadenectomy specimens were examined by frozen section at operation and subsequently by permanent sections, as previously described (8). Briefly, the apex and base of the prostate were amputated or submitted as *en face* (shave) margins, and the prostate was serially sectioned perpendicular to the long axis of the gland from the apex to the tip of the seminal vesicles. After gross examination of the whole prostate slices, frozen sections were selected to encompass the cancer; the length, width, and height were determined by microscopic examination of frozen sections. The number of cancer sections submitted for frozen examinations from the radical prostatectomy specimens varied from 8 to 20 in this series, depending on cancer volume, prostate volume, and the preference of the pathologist. Approximately 14 prostate blocks were examined per case, and the method of sampling remained constant during the study period (8). All histologic evaluations were performed without knowledge of the clinical outcome. The 1997 TNM (tumor, lymph nodes, metastasis) system was used for pathologic staging (27, 28). Pathologic stages were pT2a (8 patients), pT2b (14 patients), pT3a (35 patients), and pT3b (155 patients). Grading of the primary cancer was performed according to the Gleason system (29) and was based on retrospective review of all available histologic slides by authors (LC, JCC, and DGB). All tumors were examined. Tumor heterogeneity is accounted for by assigning a primary pattern of the dominant grade and a secondary pattern for the nondominant grade; Gleason score was obtained by the summation of these two histologic pattern. Gleason score was 6 (13 patients), 7 (118 patients), 8 (17 patients), 9 (54 patients), and 10 (1 patient). Prostatectomy specimens were examined for deoxyribonucleic acid (DNA) ploidy by flow cytometry with the Hedley technique. DNA ploidy analysis was performed in all patients, and DNA histograms were classified as diploid (101 patients), tetraploid (84 patients), and aneuploid (27 patients).

Bilateral pelvic lymph node dissection was performed using the modified approach, including excision of inferior chain of the external iliac lymphatics and the obturator and hypogastric nodes. The lymph nodes were totally embedded for histologic evaluation. The median number of lymph nodes sampled during bilateral open pelvic lymph node dissection was 14 (range, 4 to 33). The number of positive nodes were one (98 patients), two (55 patients), three (27 patients), four (10 patients), and five or more (22 patients). ENE was defined as cancer perforating the capsule into the perinodal tissue (Fig. 1). The presence of cancer cells within the capsule was not considered ENE. The authors recognized the difficulty in distinguishing whether metastatic cancer is within the lymph node or extends into surrounding adipose tissue because pelvic lymph nodes are extremely fatty. Metastatic deposits within fats were counted as ENE. Nodal cancer volume (size) was determined in permanent sections by the grid method (30), and the total cancer volume of all positive nodes (nodal cancer volume) was used for analysis (8). Nodal cancer volume ranged from 0.01 to 3.05 $cm^3$ (mean, 0.23 $cm^3$; median, 0.06 $cm^3$).

### Statistical Analysis

Survival was estimated using the Kaplan-Meier method. The Cox proportional hazards model was

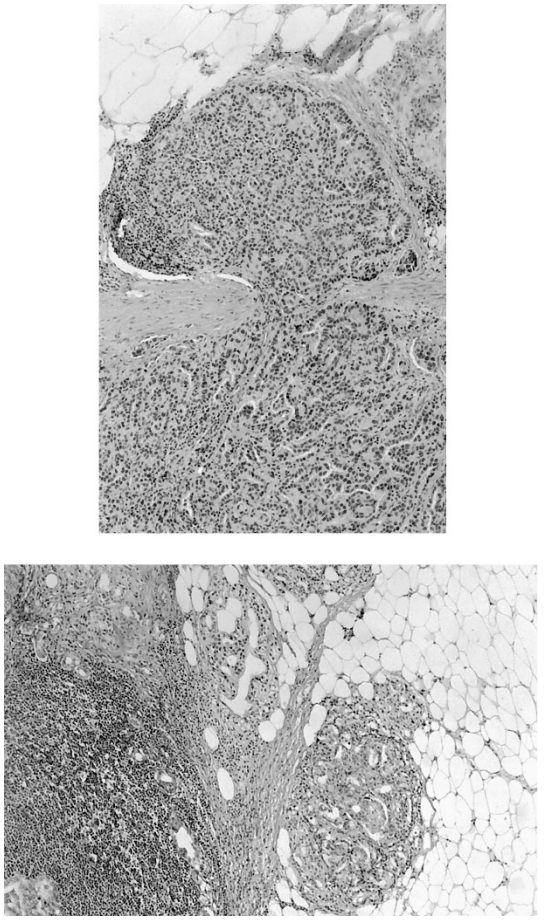

**FIGURE 1.** Extranodal extension in lymph node metastasis from prostate cancer.

used to test for univariate associations of ENE with survival. The influence of ENE on survival was tested after controlling for known risk factors in patients who were node positive (Gleason score, DNA ploidy, and lymph node cancer volume). Analysis of association of continuous variables with survival were performed using single degree of freedom (linear) terms in the Cox model. Comparison of clinicopathologic characteristics between patients with ENE and patients without ENE was assessed using rank sum tests. A $P$ value of less than 0.05 was considered significant, and all $P$ values were two tailed.

## RESULTS

Patients ranged in age from 47 to 79 years (mean, 66 years). During the mean follow-up interval of 6.3 years (median, 6.1 years; range 0.03 to 10.5 years), 23 patients developed systemic progression (distant metastasis), 18 died of prostate cancer, and 17 patients died of other causes. Five-year systemic progression-free and cancer-specific survivals were 91% (±2%) and 95% (±5%), respectively.

ENE was observed in 126 of 212 patients (59%). Fifty patients (23%) had two or more positive nodes that showed ENE. The presence of ENE was not predictive of distant metastasis-free survival or cancer-specific survival (Fig. 2). Patients with ENE involving one node had similar prognosis as those with ENE in more than one node. Five-year actuarial distant metastasis-free and cancer-specific survivals were 94% and 95%, respectively, for patients without ENE, compared with 89% and 95% for those with ENE ($P$ = .29 and $P$ = .15, respectively). For 98 patients with only one positive lymph node, there was no difference in terms of distant metastasis-free or cancer-specific survivals among patients with or without ENE (Fig. 3). Among patients with only one positive node, 5-year actuarial distant metastasis-free and cancer-specific survivals were 96% and 98%, respectively, for patients

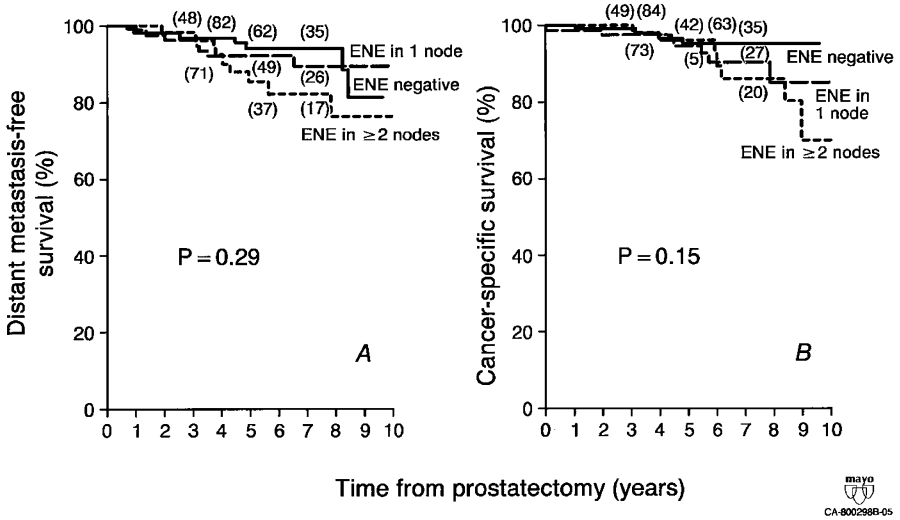


**FIGURE 2.** Kaplan-Meier curves (distant metastasis-free and cancer-specific survival) for 212 patients who were lymph node positive according to the number of nodes with extranodal extension. Numbers within parentheses represent number of patients still under observation at 3, 5, and 7 years.

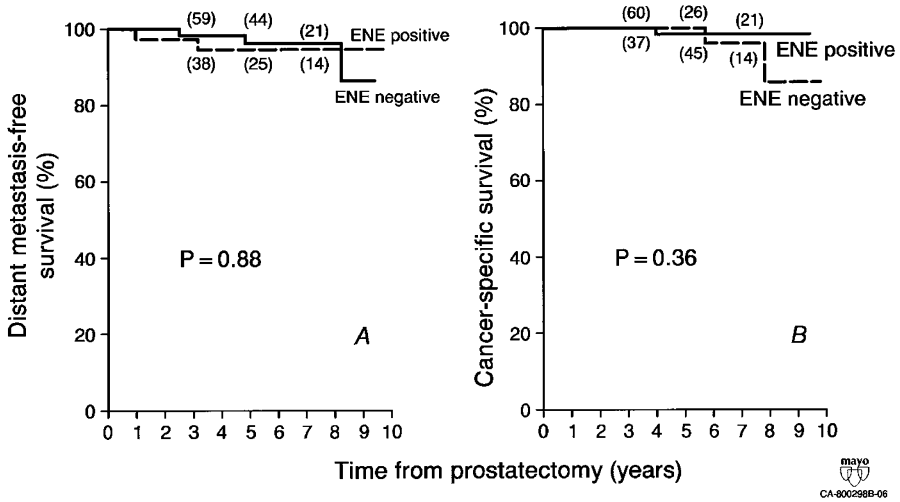


**FIGURE 3.** Kaplan-Meier curves (distant metastasis-free and cancer-specific survival) for 98 patients with single positive lymph node. Numbers within parentheses represent number of patients still under observation at 3, 5, and 7 years.

without ENE, compared with 95% and 100% for those with ENE ($P = .88$ and $P = .36$, respectively).

ENE was associated with higher preoperative PSA concentration, pathologic stage, Gleason score, the number of positive nodes, the largest dimension of nodal metastasis, and nodal cancer volume (Table 1). In a multivariate analysis, ENE was not significantly associated with adverse survival, after adjusting for Gleason score, DNA ploidy, and nodal cancer volume (Table 2). Only nodal cancer volume was associated with poor survival ($P < .001$, Table 2)

## DISCUSSION

We found that more than half of the patients who had prostate cancer with regional lymph node metastasis had ENE. Although the presence of ENE was correlated with preoperative PSA concentration, Gleason score, pathologic stage, and nodal cancer volume, ENE was not associated with worse patient outcome in terms of distant metastasis-free or cancer-specific survival. Conversely, nodal cancer volume provided significant prognostic information, and we recommend that nodal cancer volume (or, as a surrogate, the diameter of largest metastasis) be evaluated in patients with lymph node metastasis.

**TABLE 1. Comparison of Clinical and Pathologic Findings Between Patients with Extranodal Extension and without Extranodal Extension**

| Variables | Median Value | | *P* Value[a] |
|---|---|---|---|
| | Negative ENE ($N = 126$) | Positive ENE ($N = 86$) | |
| Age | 67 | 66 | .66 |
| Preoperative PSA levels (ng/ml) | 17.1 | 27.1 | <.001 |
| Pathologic stage | | | .005 |
| T2 | 68 | 32 | |
| T3 | 37 | 63 | |
| Gleason score | | | .047 |
| 4–6 | 69 | 31 | |
| 7 | 42 | 58 | |
| 8–10 | 35 | 65 | |
| DNA ploidy | | | .10 |
| Diploid | 52% | 43% | |
| Teteraploid | 40% | 42% | |
| Aneuploid | 8% | 15% | |
| The number of lymph nodes sampled | 14 | 14 | .65 |
| The number of positive nodes | 1 | 2 | <.001 |
| The largest dimension of nodal metastasis (cm) | 0.2 | 0.6 | <.001 |
| Nodal cancer volume (cc) | .03 | .18 | <.001 |

ENE, extranodal extension; PSA, prostate-specific antigen.
[a] *P*-value was obtained from the rank sum tests.

In a study of 69 patients who were node positive, Griebling *et al.* (31) found that 55% of patients had evidence of ENE, similar to our findings (59%). With a mean follow-up of 2.9 years, 19 patients (28%) died of prostate cancer. They found that Gleason score and ENE were independent predictors of cancer-specific survival in patients with node-positive prostate cancer. However, the presence of ENE was not associated with reduced survival duration in the present study. The inconsistencies with respect to the prognostic significance of ENE may be related to differences in the size of the study population, duration of follow-up, statistical methods, patient factors, primary cancer characteristics, and the possible influence of therapeutic differences. In Griebling et al.'s (31) study, only 11 patients underwent radical prostatectomy. In the present case series, all patients were treated with radical retropubic prostatectomy, bilateral pelvic lymphadenectomy, and androgen deprivation. Furthermore, only 18 patients (8%) died of prostate cancer (mean follow-up, 6.3 years) in this study.

We previously demonstrated that nodal cancer volume could accurately predict the biologic aggressiveness of node-positive prostate cancer (8). The risk of distant metastases in patients with tumor involvement of regional lymph nodes increased proportionally with increasing nodal can-

**TABLE 2. Risk Ratios (±95% Confidence Intervals) for Risk Factors in Node-Positive Prostate Cancer**

| Characteristics | Univariate Analysis | | | | Multivariate Analysis | | | |
|---|---|---|---|---|---|---|---|---|
| | Distant metastasis | | Cancer-specific death | | Distant metastasis | | Cancer-specific death | |
| | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI |
| Gleason grade | 1.6 | 1.1–2.4 | 1.6 | 1.1–2.5 | 1.1 | 0.7–1.7 | 1.2 | 0.8–2.0 |
| DNA ploidy[a] | 1.6 | 0.7–3.8 | 1.3 | 0.5–3.4 | 0.9 | 0.4–2.2 | 0.9 | 0.3–2.4 |
| Nodal cancer volume[b] | 1.7 | 1.4–2.0 | 1.4 | 1.2–1.8 | 1.9 | 1.5–2.6 | 1.4 | 1.1–1.9 |
| Extranodal extension | 1.6 | 0.7–3.9 | 2.2 | 0.7–6.8 | 0.3 | 0.1–0.9 | 0.8 | 0.2–3.0 |

RR, risk ratio; CI, confidence interval.
[a] Diploid = 0, nondiploid = 1.
[b] Log-2 scale, RR represents risk increase associated with a doubling in cancer volume.

cer volume. Nodal cancer volume was the best predictor of 5-year distant progression-free survival among various clinical and pathologic factors. It correlated with the established prognostic factors of the primary cancer, including Gleason score, DNA ploidy, and size of primary cancer. In that study, all patients with a nodal cancer volume of less than 0.02 cc were free of distant disease progression (8). These findings suggest that nodal cancer volume was closely linked to the biologic behavior of metastatic prostate cancer. On the basis of these findings, we recommend that the nodal cancer volume (or, as a surrogate, the largest dimension of nodal metastases) be reported in patients with regional lymph node metastasis.

The present study may have several potential limitations. Patient follow-up was relatively short, and the sample size and the number of outcome events were limited. Some variables that were inconclusive as a result of the limited statistical power may attain statistical significance if the sample size is increased. For example, Gleason grade was significantly associated with distant metastasis-free survival (risk ratio, 1.6; 95% confidence interval, 1.1 to 2.4) and cancer-specific survival (risk ratio, 1.6; 95% confidence interval, 1.1 to 2.5) in univariate analysis but was not significant after adjusting for nodal cancer volume (Table 1). The significance of Gleason grade on survival needs to be evaluated in the context of limited outcome events (18) and sample size in multivariate analysis. At the Mayo Clinic, most patients who were lymph node positive and treated with radical prostatectomy also underwent immediate adjuvant hormonal therapy. The significance of ENE may differ in patients who are treated with other approaches. Although we did not find an association between ENE and reduced survival, ENE correlated with several known predictive factors, such as preoperative PSA level, pathologic stage, Gleason score, the number of positive nodes, the largest dimension of nodal metastasis, and nodal cancer volume. Further investigation of ENE is indicated to clarify its role in cancer progression.

In summary, the presence of ENE does not seem to be associated with adverse outcome in patients who have prostate cancer with regional lymph node metastasis and who are treated by radical retropubic prostatectomy, bilateral pelvic lymphadenectomy, and androgen deprivation therapy. Conversely, nodal cancer volume (or, as a surrogate, the diameter of largest metastasis) provided useful predictive information and should be reported.

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## Book Review

***Spector TD, Axford JS: An Introduction to General Pathology, 4th Edition, Edinburgh, Churchill Livingstone, 391 pp, 1999 ($39).***

This book was dedicated to the late Professor W.G. Spector, who wrote the first two editions and is remembered by the present authors as "one of the first teachers to believe that understanding rather memorizing the key disease processes is the best way to learn pathology." Written in the same spirit, this fourth edition is a worthy descendant of its predecessors, continuing the time-honored tradition of British teaching at its best.

This slim volume, published in a pocket-size format, was prepared for medical students entering pathology. It covers the classic topics of general pathology, and, so far as I am concerned, it could serve as an ideal text for those 3- to 4-week-long introductory courses that were once called "Mechanism of Disease" or "Pathobiology." In the "modern" curricula dominating the U.S. medical school teaching, unfortunately, few medical students will find time to read it. I hope, however, that the book will not be unnoticed by their professors, especially those who subscribe to Professor Spector's credo.

**Ivan Damjanov**
*University of Kansas School of Medicine*
*Kansas City, Kansas*