

Comparison of Biochemical Recurrence–Free Survival Between Periprostatic and Pelvic Lymph Node Metastases of Prostate Cancer

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Nilda González-Roibón, MD¹, Jeong S. Han, MD¹, Stephen Lee, MD¹, Zhaoyong Feng, MS¹, Sehbal Arslankoz, MD², Nathaniel Smith, MD¹, Philip M. Pierorazio, MD¹, Elizabeth Humphreys, MS¹, Theodore L. Dewese, MD¹, Alan W. Partin, MD, PhD¹, Trinity J. Bivalacqua, MD, PhD¹, Misop Han, MD¹, Bruce Trock, PhD¹, and Georges J. Netto, MD¹

Abstract

Objective. To assess the pathologic characteristics and prognostic significance of periprostatic lymph node (LN) metastasis of prostate cancer. The latter was performed by comparing biochemical recurrence (BCR)–free survival in cases of periprostatic LN metastasis versus matched patients showing pelvic LN metastasis. **Methods and Materials.** We identified 15 patients who underwent radical prostatectomy in our institution (1984–2011) showing positive periprostatic and negative pelvic LN with available follow-up information (group 1). These patients were matched 1:2 to patients with positive pelvic LN (group 2) for pertinent clinicopathologic parameters. **Results.** Main locations of positive periprostatic LN were posterior base and mid posterolateral. Overall higher rate of positive margins, smaller LN, and metastasis size were encountered in group 1 compared with group 2. At 5 years postprostatectomy, 69% of patients in group 1 were free of BCR, whereas 26% of those in group 2 remained BCR free, suggesting that patients with periprostatic node metastasis appeared to have a lower risk of BCR. However, the difference was not statistically significant ($P = .072$). The same was true when adjusted for the effect of prostate-specific antigen, surgical margin status, size of LNs, size of metastasis, age, and year of surgery. **Conclusion.** Patients with periprostatic node metastasis may have a lower risk of BCR compared with those with metastasis to pelvic LN. Future analysis of larger cohorts will help establish the biologic significance of prostate cancer metastasis to periprostatic LN.

Keywords

prostate cancer, prostatectomy, periprostatic lymph node, metastasis, biochemical recurrence

Introduction

Metastasis to pelvic lymph node (LN) in prostate cancer (PCa) is well known to be associated with poor prognosis.¹

Only few studies have addressed the clinical implications of PCa metastasis to periprostatic LN. The reported incidence of identifying such nodes during pathologic examination of radical prostatectomy specimens ranges from 0.8% to 4.4%.^{2–4} One prior study suggested that the presence of periprostatic LN metastases may have adverse prognosis compared with PCa without any LN metastasis.³ However, the prognostic significance of positive periprostatic LN compared with pelvic LN metastasis is not well

defined. Direct comparison between metastases to pelvic and periprostatic LN has been limited by the relative infrequency of finding periprostatic LN during pathologic examination.

The purpose of our study is to document prognostic significance of metastasis to periprostatic LN, using biochemical recurrence (BCR)–free survival as an end point,

¹Johns Hopkins Medical Institutions, Baltimore, MD, USA

²Hacettepe University School of Medicine, Ankara, Turkey

Corresponding Author:

George J. Netto, Johns Hopkins Hospital, 401 N. Broadway/2242
Weinberg, Baltimore, MD 21231, USA.

Email: gnetto1@jhmi.edu

in comparison with pelvic LN metastasis, in a cohort study in which both groups are matched for age, Gleason score, and pathological stage.

Material and Methods

The study was approved by the Johns Hopkins Hospital Institutional Review Board.

Population and Study Design

Our surgical pathology database was searched for all radical prostatectomy patients with reported identification of any periprostatic LNs between 1984 and 2011. We identified 61 cases of a total of 20 685 radical prostatectomy specimens, 19 of which showed metastatic carcinoma in at least one periprostatic node. Two of these cases also showed positive pelvic LN and were therefore excluded. Fifteen patients had follow-up information available regarding BCR status (group 1). Patients in group 1 were matched 1:2 to patients with positive pelvic LN (group 2) with exact matching on Gleason score, pathological stage, age-group, and race. Three patients in group 1 could only be matched to one patient in group 2 each. This resulted in an analysis cohort of 15 patients with positive periprostatic LN and 27 patients with positive pelvic LN.

All prostatectomy specimens were routinely processed according to our departmental protocol. Briefly, resected specimens were fixed in formalin, sliced at 3-mm intervals, and embedded entirely. All available hematoxylin and eosin slides from the cases were reevaluated. Histopathological characteristics, including Gleason score, margin status, pathological stage, size of periprostatic and pelvic lymph nodes, and their metastatic foci, were assessed by a urologic pathologist on the study. LNs were defined according to the presence of a capsule and other structural elements such as subcapsular sinus and follicles to differentiate from tumor-associated lymphoid infiltrates in perpendicularly transected extraprostatic tumor extension. Clinical information, including age, race, preoperative serum prostate-specific antigen (PSA) and BCR status were also collected.

Statistical Analysis

Comparisons of demographic and clinical characteristics between the 2 groups were performed using the χ^2 test, Fisher's exact test for categorical variables, and the Wilcoxon rank sum test for continuous variables. Survival times were defined from the date of surgery and were represented by integer values. Biochemical recurrence was defined by the occurrence of post-radical prostatectomy serum PSA ≥ 0.2 ng/mL, or the administration

of salvage radiation with a detectable PSA (1 patient). BCR-free survival was estimated using the Kaplan–Meier method and survival curves were compared using the log-rank test. The stratified Cox proportional hazards model was used, with strata defined by the matched triplets. The independent variable was lymph node status (periprostatic vs pelvic LN). A robust sandwich estimator of the covariance matrix was used.⁵ Sample size needed for the Cox proportional hazards model was calculated using the method of George and Desu.⁶ A *P* value $< .05$ indicated statistical significance. Analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC).

Results

The clinicopathological features of patients in both groups are summarized in Table 1. Preoperative serum PSA levels did not differ between the 2 groups. A single periprostatic node harboring metastatic PCa was identified in each of 14 cases. In the remaining case, 2 periprostatic nodes were identified with 1 of the 2 harboring metastasis. The laterality distribution of periprostatic LN was as follows: left (*n* = 3), right (*n* = 7), and unspecified (*n* = 5). Location in relation to the prostate was available for 10 cases; periprostatic LNs were identified in posterior base in 6 cases (1 left and 5 right), mid posterolateral in 3 (2 left and 1 right), and in anterior apex in 1 case.

In group 1, the mean size of periprostatic LN was 1.24 mm with greatest dimension range of 0.9 to 3.2 mm. Average greatest dimension of metastatic foci in periprostatic nodes was 0.7 mm (0.03–2.6 mm). None of these were single cell or isolated tumor cell metastasis. In group 2, pelvic LN and their metastatic foci measured, on average, 6.4 mm (2.5–12 mm) and 2.6 mm (0.5–10 mm) in greatest dimension, respectively. Patients with positive pelvic LN had significantly larger lymph nodes and larger metastases than those with positive periprostatic LN (*P* = .0002 and *P* = .007, respectively).

Surgical margin status was significantly different between the 2 groups (*P* = .024). Fifty-three percent of patients in group 1 showed positive margins. Of these 8 cases, the posterolateral margin was involved in 3 cases and the apical margin in other 3; one case showed involvement of both surgical margins. Only 19% of patients in group 2 showed positive margins.

The median follow-up was 1.0 year (range 1–13 years) for patients with positive periprostatic LN and 2.0 years (range 1–9 years) for patients with positive pelvic LN. The Kaplan–Meier BCR-free survival estimates in both groups are shown in Figure 1. At 5 years after surgery, 26% of patients in group 2 remained free of BCR whereas 69% of those in group 1 were free of BCR at that time. The latter difference did not reach statistical significance (*P* = .072).

Table 1. Characteristics of Patients With Positive Periprostatic Lymph Nodes (Group 1) and Matched Patients With Positive Pelvic Lymph Nodes (Group 2).

Characteristic	Group 1; n (%)	Group 2; n (%)	P
Age in years; median (range)	61 (51-69)	60 (50-69)	.598
Age-group in years			
50-59	6 (40)	11 (41)	.963
60-69	9 (60)	16 (59)	
Race			
White	13 (87)	24 (89)	.765
Non-white	2 (13)	3 (11)	
Preoperative serum PSA (ng/mL); median (range)	6.8 (3.4-24.3)	6.3 (2.9-62.2)	.731
Radical prostatectomy Gleason score			
3 + 4	3 (20)	6 (22)	.997
4 + 3	7 (47)	12 (44)	
8	3 (20)	5 (18)	
9	2 (13)	4 (15)	
Radical prostatectomy stage			
pT2/2X	2 (13)	2 (7)	.882
pT3a	10 (67)	19 (70)	
pT3b	3 (20)	6 (22)	
Positive surgical margins			
Yes	8 (53)	5 (19)	.024
No	7 (47)	22 (81)	
Size of lymph node in mm; median (range)	0.8 (0.1-3.2)	5.5 (2.5-12.0)	.0002
Size of metastasis in mm; median (range)	0.1 (0.03-2.6)	1.0 (0.5-10.0)	.007
Year of surgery			
1992-1999	4 (27)	5 (20)	.782
2000-2005	5 (33)	11 (44)	
2006-2011	6 (40)	9 (36)	
Biochemical recurrence			
Yes	4 (27)	16 (59)	.072 ^a
No	11 (73)	11 (41)	
Adjuvant therapy			
Yes (ADT + XRT)	1 (9)	1 (3)	.454
No	8 (91)	25 (97)	

Abbreviations: PSA, prostate-specific antigen; ADT, adjuvant hormonal therapy; XRT, adjuvant radiation therapy.

^aP value based on log-rank test of Kaplan–Meier biochemical recurrence–free survival curves.

All recurrences in group 1 occurred within 1 year. There was no significant difference in adjuvant therapy between the 2 groups ($P = .454$).

Hazard ratios were estimated using stratified Cox proportional hazards models (Table 2). Model 1 estimated the univariate hazard ratio for both groups. Patients in group 1 had a 38% lower risk of BCR than patients in group 2; however, the finding did not reach statistical significance ($P = .245$). Model 2 adjusted for effect of preoperative serum PSA levels. Patients in group 1 showed a 33% lower risk of BCR than those in group 2 ($P = .349$). Model 3 adjusted for effect of surgical margin status. Although the magnitude of reduced risk in patients with positive periprostatic LN was larger (41% reduction in risk), the findings were not statistically significant ($P = .216$). Models 4

and 5 adjusted for size of lymph nodes and size of metastasis, respectively. Once more, patients with positive periprostatic LN had lower risk of BCR (0.20 and 0.44, respectively). The findings again lacked statistical significance ($P = .677$ and $P = .249$, respectively). Adjustment for residual differences in age or year of surgery led to similar results as in Model 1 (data not shown).

Discussion

The literature on periprostatic LN metastasis is limited, with the few published studies reporting a very low incidence.^{3,4} Periprostatic LNs are relatively small in size, with an average diameter of 1.2 mm found in the present study and therefore not readily identifiable during gross

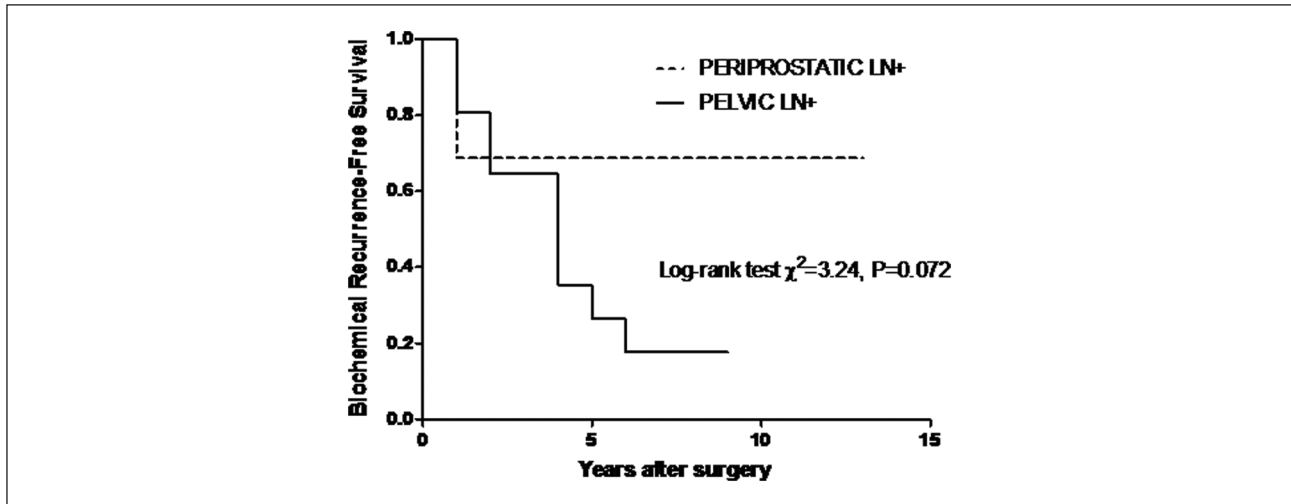


Figure 1. Kaplan–Meier biochemical recurrence (BCR)–free survival estimates in patients with metastasis to periprostatic (group 1) and pelvic (group 2) lymph nodes. All recurrences in group 1 occurred within 1 year. At 5 years after surgery, 69% of patients in group 1 were free of BCR whereas 26% of those in group 2 remained free of BCR at that time.

examination. Extent of sampling during pathological examination of radical prostatectomy could also be a factor in the rate of their identification. As a result, the identification of metastasis to these nodes will be affected by the yield of periprostatic lymph node harvest, which in turn is related to the amount of periprostatic soft tissue removed during surgery.

It has been well documented that the predominant lymphatic drainage of the prostate is to obturator fossa and adjacent external and internal iliac lymph nodes that are most commonly examined after pelvic lymph node dissection in association with radical prostatectomy.

Separate, albeit rare, routes of minor lymphatic drainage to periprostatic LN could explain the phenomenon of metastasis to these nodes. Using a single photon emission computed tomography system after transrectal intraprostatic injection of radioactive tracers, periprostatic LN were identified as sentinel lymph nodes in only 0.3% of patients with high-grade PCa.⁷

Similar to previous reports, most of the positive periprostatic LN in our study were located near the posterior base.^{2,4} This is also in line with previous finding of significantly high lymphatic density in the mid-base region, around the ejaculatory ducts.^{2,4} We also found 1 case with positive periprostatic LN in the anterior apex. A recent study showed that dissection and careful microscopic examination of anterior fibroadipose tissue revealed small lymph nodes in approximately 17% of patients with an overall metastasis rate of 2.5%.⁸ We found periprostatic nodes to be significantly smaller in size in our cases in comparison with pelvic nodes in controls. The same was true for size of metastases in both groups.

In the study by Kothari et al,² all 3 patients with isolated PCa metastasis to periprostatic LN recurred between 4 and 7 months postprostatectomy. Based on such findings, Srigley⁹ suggested that patients with metastatic PCa to periprostatic LN should be staged as pN1. In a more recent study, positive periprostatic LN have been linked to larger tumor volume, higher stage, higher Gleason score, higher recurrence rate, and shorter time to recurrence compared with patients with negative periprostatic nodes.³

Matching for relevant clinicopathological characteristics is a strength in our study that allowed us to minimize the effect of potential confounding parameters on BCR, including age, Gleason score, stage, and year of surgery. Our finding of significantly higher incidence of positive margin in patients with positive periprostatic LN compared with patients with positive pelvic LN is intriguing. However, it remains unclear whether the higher rate of positive margins in our cases is reflective of underlying biological behavior given that margin status did not affect BCR in our cases.

Although our analysis suggested that metastasis to periprostatic LN may be associated with a 30% to 40% BCR risk reduction, the association lacked statistical significance and should be interpreted with caution given the small sample size and the fact that our study remains underpowered. The results, however, warrant further investigation with larger patient cohort and longer follow-up. This is especially true considering the variance of our findings with prior studies and their possible implication on pathological handling of specimens, substaging of tumor, and treatment strategies.

Table 2. Stratified Cox Proportional Hazards Models Comparing Risk of Biochemical Recurrence Between the 2 Matched Groups.^a

	Model 1		Model 2 ^b		Model 3 ^c		Model 4 ^d		Model 5 ^e	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Group 1 versus group 2	0.62 (0.28-1.38)	.245	0.67 (0.30-1.54)	.349	0.59 (0.25-1.37)	.216	0.80 (0.28-2.30)	.677	0.56 (0.21-1.50)	.249
Preoperative PSA	n/a	n/a	1.00 (0.96-1.03)	.946	n/a	n/a	1.07 (0.84-1.37)	.592	n/a	n/a
Surgical margin + versus -	n/a	n/a	n/a	n/a	1.16 (0.43-3.10)	.772	n/a	n/a	0.93 (0.73-1.20)	.593

Abbreviations: HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen; n/a, not applicable.

^aGroup 1 = periprostatic lymph nodes; Group 2 = pelvic lymph nodes.

^bAdjusted for PSA.

^cAdjusted for surgical margin status.

^dAdjusted for size of lymph nodes.

^eAdjusted for size of metastasis.

Authors' Note

Nilda Gonzalez-Roibon and Jeong S. Han contributed equally to this study.

Declaration of Conflicting Interests

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