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# Significance of lymph node ratio in defining risk category in node-positive early stage cervical cancer☆

Nicole D. Fleming [a,*], Michael Frumovitz [a], Kathleen M. Schmeler [a], Ricardo dos Reis [b], Mark F. Munsell [c], Patricia J. Eifel [d], Pamela T. Soliman [a], Alpa M. Nick [a], Shannon N. Westin [a], Pedro T. Ramirez [a]

[a] Department of Gynecologic Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, United States
[b] Department of Gynecologic Oncology, Hospital de Cancer de Barretos, Sao Paulo, Brazil
[c] Department of Biostatistics, The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, United States
[d] Department of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, United States

## HIGHLIGHTS

- Lymph node ratio can be used to identify patients with worse prognosis.
- Positive margins after radical hysterectomy are a poor prognostic factor irrespective of positive nodal status.
- Lymph node ratio and pathologic risk factors may help to tailor adjuvant therapy in this high-risk population.

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## ABSTRACT

*Objective.* The ratio of positive to negative lymph nodes, or lymph node ratio (LNR), is an important prognostic factor in several solid tumors. The objective of this study was to determine if LNR can be used to define a high-risk category of patients with node-positive early stage cervical cancer.

*Methods.* We performed a retrospective review of patients diagnosed with node-positive stage I or II cervical cancer who underwent radical hysterectomy and pelvic +/− para-aortic lymphadenectomy at MD Anderson from January 1990 to December 2011. Univariate and multivariate analyses were used to identify prognostic factors for progression-free (PFS) and overall survival (OS).

*Results.* Ninety-five patients met the inclusion criteria and were included in the analysis. Median total nodes removed were 19 (range 1–58), and median number of positive nodes was 1 (range 1–12). Fifty-eight patients (61%) received radiation with concurrent cisplatin and 27 patients (28%) received radiotherapy alone. Twenty-one (22%) patients recurred. On multivariate analysis, a LNR > 6.6% was associated with a worse PFS (HR = 2.97, 95% CI 1.26–7.02, p = 0.01), and a LNR > 7.6% with a worse OS (HR = 3.96, 95% CI 1.31–11.98, p = 0.01). On multivariate analysis, positive margins were associated with worse PFS (p = 0.001) and OS (p = 0.002), and adjuvant radiotherapy (p = 0.01) with improved OS.

*Conclusions.* LNR appears to be a useful tool to identify patients with worse prognosis in node-positive early stage cervical cancer. LNR may be used in addition to pathologic risk factors to tailor adjuvant treatment in this population.



## Introduction

Stage I cervical cancer has a relatively favorable prognosis with a cure rate of 80% when treated with radical hysterectomy or primary chemoradiation. However, certain pathologic and clinical risk factors have been identified that place patients with stage I disease at increased risk for recurrence. These include positive lymph node metastases, large tumor diameter, deep stromal invasion, lymphovascular space invasion, close or positive margins, and parametrial involvement. The presence of lymph node metastases is an independent prognostic factor for progression-free and overall survival [1]. Several other factors related to nodal status have been shown to affect prognosis in early stage cervical cancer. These factors include the number of involved metastatic nodes, size of the metastatic deposits, and localization of the metastatic nodes in the pelvis [2,3]. Despite these important prognostic variables,

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* Corresponding author at: 1155 Pressler Drive, Unit 1362, Houston, TX 77030, United States. Fax: +1 713 745 1541.
*E-mail address:* nfleming@mdanderson.org (N.D. Fleming).

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cervical cancer remains a clinically staged disease and lymph node status is not included in the International Federation of Gynecology and Obstetrics (FIGO) staging. However, because nodal metastases are such an important risk factor for recurrence, an accurate knowledge of lymph node status is essential to tailor adjuvant therapy.

The extent of lymph node involvement is an important prognostic factor in most solid tumors including lung, breast, colorectal, cervical, and vulvar cancers. The ratio of positive nodes to the total number of nodes harvested, the lymph node ratio (LNR), has been found to be an independent predictor of survival in pancreatic [4], esophageal [5], gastric [6], colorectal [7,8] and breast cancers [9,10]. There has been recent interest in using LNR as a prognostic tool in gynecologic malignancies, including cervical and endometrial cancers. This allows assessment of the comprehensive nature of lymphadenectomy and burden of nodal disease. Previous multi-center retrospective studies in endometrial cancer have found LNR to be associated with worse progression-free and overall survival [11,12]. A significant correlation between LNR and survival has also been seen in cervical cancer in single-institution retrospective studies, however, across all stage distributions and in patients receiving neoadjuvant chemotherapy prior to surgery [13–15].

The purpose of this study was to examine the relationship between LNR and progression-free and overall survival in early stage cervical cancer patients from a large academic institution with central pathology review. The relationship between LNR and other important clinicopathologic factors was also assessed.

## Methods

After Institutional Review Board approval, women with stages I to II cervical cancer who underwent radical hysterectomy with or without bilateral salpingoophorectomy, and pelvic and/or para-aortic lymphadenectomy were identified from our institutional tumor registry at the M.D. Anderson Cancer Center from January 1990 to December 2011. Patients were included if they had nodal metastases on the final pathology confirmed by M.D. Anderson pathologists. Patients were excluded if radical hysterectomy was aborted due to intraoperative identification of gross involvement of the parametria and/or pelvic lymph nodes, or if positive nodes were detected by intraoperative frozen section. Demographic, clinicopathologic, and adjuvant treatment data were also abstracted from the patient's medical record. Final pathology was used to determine the patient's histologic stage. The total number and the rate of metastatic pelvic and para-aortic lymph nodes were assessed by the M.D. Anderson gynecologic pathology specialists. The LNR was defined as the ratio of positive nodes to the total number of nodes harvested.

Descriptive statistics were used to summarize the demographic and clinical characteristics of the patients. The product-limit method of Kaplan and Meier was used to estimate progression-free (PFS) and overall survival (OS). For PFS, an event was defined as disease progression, recurrence, or death. Cox proportional hazards regression was used to model PFS and OS as functions of potential prognostic factors, including age, stage, grade, chemotherapy, radiation therapy, number of lymph nodes removed, number of positive lymph nodes, and lymph node ratio. Methods previously described by Williams et al. were used to identify the optimal cutpoint for lymph node ratio for PFS and OS. This method considers every possible value of LNR and identifies the value that gives the greatest separation between the 2 survival curves obtained with the survival estimate stratified by that value of LNR. The greatest separation is determined by the smallest p-value. This method also takes into account the fact that multiple testing is being done in the search for the cutpoint, so the p-value reported from the method is adjusted for the multiple testing in order to avoid inflating the Type I Error [16]. A subset analysis was performed using previously published lymph node ratio cutoffs in cervical cancer of ≤10% and >10% [13,14] and in those patients who had at least 10 lymph nodes removed. $p < 0.05$ was considered statistically significant. All analyses were performed with SAS 9.3 for Windows (SAS Institute Inc, Cary, NC).

## Results

Ninety-five patients with stages I to II cervical cancer were found to have nodal metastases at the time of radical hysterectomy and were included in the analysis. Clinicopathologic data are listed in Table 1. Median age was 39.7 years (range 24.5–78.2), median body mass index (BMI) was 27.2 (range 14.4–46.4), and median follow-up was 64.8 months (range 2.4–249.6). Eighty-four patients (88%) underwent radical hysterectomy by open laparotomy, and 11 patients (12%) by minimally invasive surgery. At final pathology, 1 patient (1%) had stage IA1 disease, 2 patients (2%) stage IA2, 84 patients (88%) stage IB1, 5 patients (5%) stage IB2, 2 patients (2%) stage IIA, and 1 patient (1%) had stage IIB disease. On histology, 61 patients (64%) were diagnosed with squamous cell carcinoma and 16 patients (17%) with adenocarcinoma. The remaining patients had either adenosquamous histology (n = 9, 10%) or other histology (n = 9, 10%) including small cell neuroendocrine, sarcomatoid squamous, and clear cell tumors. Twenty-six patients (27%) had grade 2 histology and 62 patients (65%) grade 3 histology. Median tumor size was 30 mm (range 2–80 mm) and median depth of invasion was 11 mm (range 1–25 mm). Thirteen patients (14%) had positive margins at the time of radical hysterectomy, 37 (39%) patients had parametrial involvement, and 77 patients (81%) had lymphovascular space invasion. Only 8 (8%) procedure notes had reported suspicious nodes at the time of radical hysterectomy in the operative findings.

**Table 1**
Clinicopathologic characteristics.

| Characteristic | N (range, %) |
|---|---|
| Median age, years (range) | 39.7 (24.5–78.2) |
| Median BMI (range) | 27.2 (14.4–46.4) |
| Stage | |
| IA1 | 1 (1%) |
| IA2 | 2 (2%) |
| IB1 | 84 (88%) |
| IB2 | 5 (5%) |
| IIA | 2 (2%) |
| IIB | 1 (1%) |
| Histology | |
| Squamous | 61 (64%) |
| Adenocarcinoma | 16 (17%) |
| Adenosquamous | 9 (10%) |
| Other | 9 (10%) |
| Grade | |
| 1 | 2 (2%) |
| 2 | 26 (27%) |
| 3 | 62 (65%) |
| Unknown | 5 (5%) |
| Lymphovascular space invasion | |
| No | 7 (7%) |
| Yes | 77 (81%) |
| Unknown | 11 (12%) |
| Median tumor size (mm) | 30 (2–80) |
| Median depth of invasion (mm) | 11 (1–25) |
| Margin status | |
| Negative | 82 (86%) |
| Positive | 13 (14%) |
| Parametrial spread | |
| No | 58 (61%) |
| Yes | 37 (39%) |
| Adjuvant therapy | |
| Chemoradiation | 58 (61%) |
| Radiation alone | 27 (29%) |
| Chemotherapy alone | 2 (2%) |
| No therapy | 4 (4%) |
| Unknown | 4 (4%) |

BMI = body mass index.