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Significance of Lymph Node Ratio in Defining Risk Category in Node-positive Early Stage Cervical Cancer

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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 through December 2011. Univariate and multivariate analysis was used to identify prognostic factors for progression-free (PFS) and overall survival (OS).

Results—Ninety-five patients met 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,

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Conflict of interest

The authors have no conflicts of interest to disclose.

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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 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, 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, 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 cancer. 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 stage 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

M.D. Anderson Cancer Center from January 1990 through December 2011. Patients were included if they had nodal metastases on 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 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 stage 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.

All patients underwent pelvic lymphadenectomy, and 45 patients (47%) underwent para-aortic lymphadenectomy. Median total nodes removed were 19 (range 1–58 nodes), and median number of positive nodes was 1 (range 1–12 nodes). Fifty-eight patients (61%) of patients received radiation with concurrent cisplatin and 27 patients (28%) received radiotherapy alone. A minority of patients either received chemotherapy alone (n=2) or no treatment (n=4). Type of adjuvant therapy was unknown in 4 patients. Twenty-one (22%) patients recurred.

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, Figures 1a and 1b) on multivariate analysis. On univariate analysis for PFS, depth of invasion > 11mm (HR 2.83, 95% CI 1.17–6.80, p=0.03) and positive margins (HR 3.63, 95% CI 1.57–8.35, p=0.002) were identified as prognostic factors for worse PFS (Table 2). However, on multivariate analysis for PFS, only positive margins (HR 3.93, 95% CI 1.70–9.09, p=0.001) and a LNR > 6.6% (HR 2.97, 95% CI 1.26–7.02, p=0.01) were significantly associated with a worse PFS. Type of adjuvant therapy was not significantly associated with PFS on univariate or multivariate analysis. For OS, positive margins (HR 6.08, 95% CI 1.95–18.95, p=0.002) and LNR > 7.6% (HR 3.96, 95% CI 1.31–11.98, p=0.01) were significantly associated with worse OS on multivariate analysis (Table 3). Adjuvant radiation therapy was also associated with improved OS (HR 0.17, 95% CI 0.04–0.69, p=0.01) on multivariate analysis. Age, stage, histology, type of surgery (open or minimally invasive), grade, tumor size, and lymphovascular space invasion (LSVI) were not significantly associated with PFS or OS on univariate or multivariate analysis.

A subset analysis was also performed in patients (n=82) that had 10 lymph nodes removed. Our defined LNR of >6.6% and >7.6% continued to show significantly worse PFS (HR 3.06, 95% CI 1.28–7.34, p=0.01) and OS (HR 3.72, 95% CI 1.32–10.49, p=0.01, Tables 2 and 3). An additional subset analysis was performed examining LNR previously published in the literature of 10% and >10%. [13,14] We did not see a significant association of LNR >10% with PFS (HR 1.20, 95% CI 0.52–2.77, p=NS) or OS (HR 1.17, 95% CI 0.41–3.28, p=NS), even in those patients that had 10 lymph nodes removed.

Discussion

Our study found that a LNR > 6.6% was associated with a significantly worse PFS, and a LNR > 7.6% with a significantly worse OS. This represents one of the largest retrospective series (n=95) evaluating the prognostic value of LNR in patients with stage I-II cervical cancer treated with radical hysterectomy and pelvic and/or para-aortic lymphadenectomy for suspected early-stage disease, with final pathology revealing nodal metastases. We also found other pathologic risk factors such as positive margins were associated with a significantly worse PFS and OS. Consistent with historical data involving use of adjuvant

radiation in node-positive cervical cancer, adjuvant radiotherapy in our node-positive cohort was associated with improved OS.

The presence of lymph node metastases has been shown to be an independent prognostic factor for progression-free and overall survival in early-stage cervical cancer. [1] However, previous retrospective studies have reported variable prognostic significance depending on number of lymph nodes positive, laterality of positive nodes, and metastases to para-aortic nodal chain. This has led to a wide range of reported PFS with positive nodes of 40–85% and OS with positive nodes of 20–90%. [17–22] A prospective Gynecologic Oncology Group (GOG-49) study, however, did not demonstrate an increased risk of recurrence with increasing number of positive nodes. This prospective surgical-pathologic study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix showed a non-significant difference in recurrence risk of 72%, 86%, and 65%, with one, two, and three or more positive nodes, respectively. [23] Because of this discrepancy, there has been recent interest in using LNR as a prognostic tool that allows for assessment of the comprehensive nature of the lymphadenectomy and the burden of nodal disease.

There have been a few previous retrospective studies evaluating the impact of LNR in node-positive cervical cancer, however, across all stage distributions and in the setting of patients receiving neoadjuvant chemotherapy prior to surgery. [13–15] Polterauer et al. reported on a series of 88 consecutive node-positive patients and found that patients with a LNR >10% had a worse disease-free (HR=2.2, 95% CI 1.1–4.7, p=0.01) and overall survival (HR=2.2, 95% CI 1.0–4.8, p=0.05) compared to those patients with a LNR ≤10%. However, this series included all node-positive patients with locally advanced cervical cancer from stage IB1 to IVA treated with primary chemoradiation. [13] Including patients with advanced stages may have affected their reported outcomes. Chen et al. reported on a series of 120 node-positive early-stage (stage IA2–IIA) cervical cancer patients and found a significantly decreased 5-year survival in patients with a LNR >10% compared to LNR ≤10% (12% vs. 43%, p<0.05). The authors state that all patients in this series were treated with postoperative concurrent chemoradiation; however, 75% of these patients also received neoadjuvant chemotherapy prior to surgery. It is unclear how treatment with neoadjuvant chemotherapy may have affected their reported LNR and overall results. [14]

Although our study found significant differences in PFS and OS by higher LNR of >6.7% and >7%, respectively, these patients endured long PFS and OS outcomes of 133 months and 169 months. These prolonged survival outcomes were most likely the result of consistent adjuvant treatment with radiation with/without concurrent cisplatin in the majority of our cohort. Peters et al. reported similar prolonged survival outcomes with pelvic radiation with concurrent cisplatin in high-risk early stage cervical cancer patients after radical hysterectomy and pelvic lymphadenectomy. In this study, high-risk patients, as defined by positive pelvic lymph nodes, surgical margins, or parametria after radical hysterectomy for stage IA2 to IIA cervical cancer, had 4-year PFS and OS rates of 80% after pelvic radiation with concurrent cisplatin. [24]

Our study is limited by its retrospective nature and its inherent bias. However, conducting this study at a large, single institution academic center with centralized pathology review by

gynecologic pathologists helps to limit this bias by assuring consistency of diagnosis. Perioperative data including complications related to lymphadenectomy such as lymphedema or postoperative infection rates was not abstracted from the patients' medical records, which may also be seen as a limitation in our study. However, the focus of our study was more on the association of pathologic variables with survival outcomes and not perioperative morbidity. Our study was also limited by type of adjuvant therapy received. Data were collected for this study during 1990–2011. Although 61% of the node-positive patients were treated with adjuvant chemoradiation, 29% of these patients were treated with adjuvant radiotherapy alone without chemotherapy. This likely reflects the large time span in which the data were collected and the practice changes throughout this time period. A minority of patients received chemotherapy alone, no treatment, or the type of adjuvant therapy they received was unknown. Overall, it is unclear whether these differences in adjuvant therapy would play a significant role in changing survival outcomes with regards to LNR.

The authors also recognize the discrepancy between our retrospective data regarding high LNR compared to previous prospective data [23] showing no difference in recurrence risks with increasing number of positive nodes. Higher LNR will be achieved with higher number of positive lymph nodes detected. Because of this, the value of high LNR as a prognostic factor would need to be evaluated prospectively. The recent interest in sentinel lymph node mapping for cervical cancer [25, 26] may provide the ability for accurate assessment of lymph node metastases to tailor adjuvant therapy, without the associated morbidity of comprehensive lymphadenectomy. With “smarter” detection of positive lymph nodes with sentinel lymph node mapping, comprehensive lymphadenectomy and the use of LNR may become obsolete. However, further prospective, multicenter studies are needed to establish safety and accuracy of sentinel lymph node assessment until our standard of care can be changed.

As we move into an era of personalizing care of patients with metastatic cervical cancer, defining high-risk groups that may benefit from additional therapy is important. Specifically, there is an unmet need to identify candidates for additional adjuvant therapy that may historically have been treated with adjuvant chemoradiation alone. In 2011, Duenas-Gonzalez et al. reported on 515 patients enrolled in a phase III trial comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. The authors found a significant improvement in PFS (HR=0.68, 95% CI 0.49–0.95, $p=0.02$) and OS (HR=0.68, 95% CI 0.49–0.95, $p=0.02$) in the concurrent and adjuvant gemcitabine and cisplatin group, however at the expense of more grade 3 and 4 toxicities (86.5% vs. 46.3%, $p<0.001$). Thus, it is important to determine which high risk subgroups may potentially gain the survival benefit from additional systemic chemotherapy following chemoradiation at the expense of possible increased toxicity.

There is a current Gynecologic Oncology Group study (GOG 274) evaluating patients with stage IB2-IVA cervical cancer with positive nodal metastases and randomizing these patients after primary chemoradiation to no additional adjuvant therapy versus adjuvant carboplatin and paclitaxel for 4 cycles. The outcomes from this study will help us to

determine if systemic chemotherapy after primary chemoradiation offers any survival benefit over standard primary chemoradiation alone, and at what potential toxicity. Using stratified pathologic and nodal risk groups may further help to delineate who may benefit from this additional adjuvant therapy at the expense of potential increased toxicity.

In conclusion, 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. Further prospective trials are needed to stratify patients based on these pathologic factors into risk criteria to determine which patients may benefit from individualized adjuvant therapy.

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Research highlights

In women with node-positive early-stage cervical cancer, a 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.

Figure 1a.

Figure 1b.

Figure 1.

Figure 1a. Kaplan-Meier curves for progression-free survival.

A LNR of >6.7% was associated with significantly worse PFS ($p=0.01$). Those patients with a LNR > 6.7% had a median PFS of 133.2 months. The median PFS for patients with LNR 6.7% was not reached.

Figure 1b. Kaplan-Meier curves for overall survival.

A LNR of >7.6% was associated with significantly worse OS ($p=0.01$). Those patients with a LNR of >7.6% had a median OS of 169.2 months. The median OS for patients with LNR 7.6% was not reached.

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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

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Table 2

Univariate and multivariate analysis for PFS

Variable	No. patients	Median PFS (months)	Univariate			Multivariate		
			HR	95% CI	p-value	HR	95% CI	p-value
Depth of invasion								
11mm	40	NR	Ref	---	---			
>11mm	38	120	2.83	1.17–6.80	0.03			
Margins								
Negative	82	NR	Ref	---	---	Ref	---	---
Positive	13	57.6	3.63	1.57–8.35	0.002	3.93	1.70–9.09	0.001
Radiation								
No	6	79.2	Ref	---	---			
Yes	85	NR	0.56	0.17–1.85	NS			
Chemotherapy								
No	31	NR	Ref	---	---			
Yes	60	134.4	1.16	0.50–2.68	NS			
LNR								
0.066	35	NR	Ref	---	---	Ref	---	---
>0.066	60	133.2	2.79	1.18–6.57	0.06	2.97	1.26–7.02	0.01
Patients with 10 nodes removed								
LNR								
0.066	35	NR	Ref	---	---			
>0.066	47	133.2	3.06	1.28–7.34	0.01			

LNR=lymph node ratio, NR=not reached

Table 3

Univariate and multivariate analysis for OS

Variable	No. patients	Median PFS (months)	Univariate			Multivariate		
			HR	95% CI	p-value	HR	95% CI	p-value
Depth of invasion								
11mm	40	NR	Ref	---	---			
>11mm	38	145.2	2.58	0.90–7.39	NS			
Margins								
Negative	82	NR	Ref	---	---	Ref	---	---
Positive	13	120	3.97	1.40–11.25	0.01	6.08	1.95–18.95	0.002
Radiation								
No	6	79.2	Ref	---	---	Ref	---	---
Yes	85	NR	0.39	0.11–1.35	NS	0.17	0.04–0.69	0.01
Chemotherapy								
No	31	NR	Ref	---	---			
Yes	60	134.4	1.31	0.46–3.73	NS			
LNR								
0.076	39	NR	Ref	---	---	Ref	---	---
>0.076	56	169.2	3.35	1.21–9.27	0.05	3.96	1.31–11.98	0.01
Patients with 10 nodes removed								
LNR								
0.076	39	NR	Ref	---	---			
>0.076	43	145.2	3.72	1.32–10.49	0.01			

LNR=lymph node ratio, NR=not reached