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Significance of number of positive lymph nodes and size as prognostic factors of recurrence and overall survival in cervical cancer patients

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Summary

Objectives: Although not included in the formal staging of cervical cancer, lymph node status is a known prognostic factor that greatly impacts survival. The aim of this study was to investigate the number and size of positive lymph nodes as independent prognostic factors of disease recurrence and overall survival (OS) in cervical cancer patients undergoing definitive chemo-radiation therapy (CRT). *Materials and Methods:* The present authors reviewed the clinical data of eligible women with loco-regionally confined, Stages IB1 through IVA, intact cervical cancer who received definitive CRT at Northwestern Memorial Hospital between January 1997 and September 2009. All women underwent definitive CRT with combined external beam radiation and brachytherapy. Probabilities for risk of recurrence were calculated relative to clinico-pathological variables. OS rates were obtained via the Kaplan-Meier method and differences between groups were analyzed using the log-rank test. *Results:* The authors identified 109 women during the study period with cervical cancer Stages IB1 through IVA treated definitively with CRT who met all inclusion criteria. The incidence of positive lymph nodes in the entire patient population was 42% (46 out of 109 cases). Advanced tumor stage was significantly associated with an increase in number of metastatic nodes ($p = 0.02$) and lymph node size ($p = 0.04$). The number of positive lymph nodes at the time of diagnosis was found to significantly impact risk of recurrence ($p = 0.03$). The present analysis revealed that patients with only one positive lymph node had a significantly lower risk of recurrence than those with >1 nodes, 25% *vs*. 58% ($p = 0.04$). Comparatively, lymph node size had no significant influence on recurrence ($p = 0.45$). *Conclusion:* Incremental increases in metastatic lymph node number at time of diagnosis correlated with worsening loco-regional control and OS. On the contrary, lymph node size was not found to be an independent prognostic factor for recurrence or survival.

Key words: Cervical cancer; Lymph nodes; Prognostic factor; Overall survival.

Introduction

Although lymph node assessment does not fall under the guidelines of the International Federation of Gynecology and Obstetrics (FIGO) staging system [1], the extent of metastatic involvement of the lymph nodes is widely established as critical to disease staging in cervical cancer. Moreover, lymph node status is identified as key to the optimization of adjuvant therapy [2]. Positive pelvic nodes have shown to significantly impact the prognosis of patients in terms of increased recurrence, distant metastases, and worse overall survival (OS) [3]. Recurrence rates in cervical cancer Stages IB-IIA range from 10% to 20% in patients without evidence of lymph node involvement, whereas women with positive nodes experience a rate of relapse up to 70% [4]. Additionally, the five-year survival in women with metastatic nodes is reported to be reduced by 25%-60%, depending on tumor stage [5]. Limited studies have investigated the association between number of metastatic lymph nodes and long-term outcomes in gynecologic malignancies [6-8]. Similarly, the prognostic value of lymph node size in cervical cancer patients has not been fully characterized [9]. The aim of the following study was to evaluate the prognostic impact of metastatic lymph nodes, based on both number and size, in relation to recurrence patterns and survival rates in patients with cervical cancer who have received definitive chemo-radiation therapy (CRT). In doing so, results can be utilized to provide important prognostic predictors and guide individualized treatment planning.

Materials and Methods

The study was approved by the Institutional Review Board at Northwestern Memorial Hospital. Patients were identified using the electronic medical records system. All patients with a diagnosis of intact, FIGO Stages IB1-IVA locally advanced cervical carcinoma treated with definitive CRT from January 1997 through

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Table 1. — *Patients and tumor characteristics.*

		N	%
Age median (range)		48 ± 12 (29-81)	
Race	Caucasian	64	58.7
	African American	24	22.0
	Hispanic	18	16.5
	Other	3	2.8
Smoking	Current smoker	36	33.0
*Characteristics not known where data points are missing not included	Ex-smoker	26	23.9
	Non smoker	44	40.3
	N/A	3	2.8
	< 20 p/y	78	71.5
	20-40 p/y	21	19.3
	> 40 p/y	9	8.3
	N/A	1	0.9
Tumor Stage	IB1	11	10.1
	IB2	19	17.4
	IIA	1	0.9
	IIB	54	49.5
	IIIA	0	0.0
	IIIB	16	14.7
	IVA	8	7.4
Tumor Grade	1	5	4.6
	2	44	40.4
	3	31	28.4
	N/A	29	26.6
Tumor histology	Squamous cell carcinoma	87	79.8
	Adenocarcinoma	18	16.5
	Adenosquamous	4	3.7
Tumor size (cm)	< 4	21	19.3
	≥ 4	82	75.2
	N/A	6	5.5
Parametrial invasion	Unilateral	33	30.3
	Bilateral	73	67.0
	Unknown	3	2.7

September 2009 were included. Time points chosen reflect initiation of electronic medical record and five years prior to date of IRB submission. Demographic, clinical, pathologic, dosimetric, and radiologic data were collected for all patients. Women treated up-front with surgery followed by adjuvant radiation were excluded. Individuals treated with radiotherapy for previous gynecologic or gastrointestinal disease were exclude as were women whom were not treated with curative intent or in whom brachytherapy was omitted.

Patients were treated with definitive cisplatin based chemotherapy and external beam radiation therapy (EBRT) followed by a low dose rate (LDR) brachytherapy (BT over the time period studied). EBRT utilized a four-field technique (anterioposterior/posterioanterior [AP/P] and opposed lateral fields.) Extended field, parametrical boosts, and nodal boost were added at the treating physician's discretion.

Variables were compared using Fisher's exact tests for categorical variables and summarized by frequencies, percentages, and differences between groups. Continuous variables summarized by means, standard deviations medians, and ranges were compared using Wilcoxon rank-sum tests. Survival and treatment outcome analyses were performed via Kaplan-Meier curves and differences between groups were analyzed using the log-rank test. The statistical significance level was set at $p < 0.05$. All statistical analyses were carried out using the SAS software package. All relevant factors were compared in a multivariate Cox regression model via stepwise selection.

Results

Patients and tumor characteristics are presented in Table 1. In this cohort, the majority (78%) of patients were diagnosed as FIGO Stages IB1-IIB. The numbers of patients diagnosed with Stages I, II, III, and IV were 30 (28%), 55 (50%), 16 (15%), and eight (7%), respectively. Table 2 summarizes lymph node characteristics of the study population. The use of imaging tools (CT, PET, PET-CT, MRI, lymphangiography, and/or ultrasound) was applied for clinical evaluation of lymph nodes in all 109 women; 80% (87 out of 109) of the patients underwent multiple scans using two or more imaging modalities. More than half (57%) of the patient cases underwent high sensitivity screening with both CT and PET imaging. Based on the imaging studies, the incidence of positive lymph nodes at time of diagnosis was 42% (46 out of 109 cases). The positive node distribution was 33%, 36%, 62.5%, and 75% for Stages I, II, III

Table 2. — *Lymph node characteristics.*

		N	%
Staging evaluation *Numbers do not add up to total as multiple studies N=109	CT	94	86.2
	PET	54	49.5
	PET-CT	10	9.2
	MRI	42	38.5
	Lymphangiography	39	35.8
	US	5	4.6
Nodal status	Node Negative	63	57.8
	Pelvic	28	25.7
	Para-aortic	1	0.9
	Both (pelvic and PA)	17	15.6
Number of lymph node(s)	0	63	57.8
	1-2	27	24.8
	3-4	16	14.7
	> 4	3	2.8
Lymph node size (cm)	1.0	63	57.8
	1.1-1.9	28	25.7
	2.0-2.9	11	10.1
	3.0-3.9	5	4.6
	≥ 4.0	2	1.8

and IV, respectively. Positive pelvic nodal distribution by stage was five (16.5%), 14 (25%), seven (44%), and two (25%), whereas both pelvic and para-aortic nodal distribution was five (16.5%), five (9%), three (19%), and four (50%). A solitary positive para-aortic node was observed in a single patient with clinical Stage II disease. Tumor stage was significantly correlated with an increased risk of positive nodal involvement and larger size of lymph nodes at p values of 0.02 and 0.04, respectively. On multivariate analysis both tumor size and adenocarcinoma were found to be associated with positive lymph nodes at p values of 0.049 and 0.0006, respectively.

Recurrences were observed in a total of 39 (36%) patients. Loco-regional recurrence (LRR), distant metastasis (DM), and both local and DM accounted for 12, 23, and four cases, respectively. The rates of recurrence in the pelvic nodes, as well as both pelvic and para-aortic nodes were 39% and 53%, respectively. Additionally, although patients with positive nodes had a 43% risk of relapse compared to 30% by the node negative group, nodal status (positive versus negative) did not reach statistical significance for recurrence risk ($p = 0.16$). Out of the 46 node positive patients, observed nodal distribution into one, two, three, four or more nodes were 20 (43%), seven (15%), three (7%), and 16 (35%), respectively. An incremental increase (1-2, 3-4, and > 4) in the number of metastatic lymph nodes at the time of diagnosis significantly impacted risk of recurrence ($p = 0.03$). Patients with only one positive lymph node had a significantly lower risk of recurrence than those with > 1 nodes, 25% *vs*. 58% ($p = 0.04$). Additionally patients with > 2 lymph nodes had an even higher risk of recurrence when compared to those with ≤ 2 lymph nodes, 63% *vs*. 30% ($p = 0.04$). The five-year LRC rates for node counts 0, 1-2, 3-4, and > 4 were 88%, 61%, 73%, and 67%, respectively ($p = 0.051$). The authors analyzed the prognostic value of lymph node size: negative nodes at 1.0 cm compared with positive nodes in the following categories 1.1-1.9, 2.0-2.9, 3.0-3.9, and ≥ 4.0 cm. Lymph node size was not found to have a significant influence on recurrence ($p = 0.45$).

Comparison of OS rates between the node negative and positive groups was not statistically significant ($p = 0.21$). However, a greater number of positive nodes was related to poor survival. OS for patients with one positive lymph nodes compared to > 1 was 57% *vs*. 40% ($p = 0.07$), 1-2 positive nodes compared to > 2 was 50% *vs*. 41% ($p = 0.10$), and 1-3 nodes compared to > 3 was 54% *vs*. 35% ($p = 0.04$), at five years. For the one to three positive lymph nodes group and > 3, there was a trend towards worsened DM and PFS ($p = 0.07$). The five-year OS rates were 56%, 50%, 42%, and 33% for node counts 0, 1-2, 3-4, and >4, respectively. On multivariate analysis, there was a non-significant trend towards worsened OS, and PFS with greater lymph node count at $p = 0.053$ and 0.06, respectively. Comparatively, there was no significant correlation found between the five-year OS, LRR, DM, and PFS rates based on nodal size.

Discussion

Lymph node metastasis is one of the most important prognostic variables in cervical carcinoma [8, 10], hence the need to further investigate clinico-pathological risk factors of lymph node involvement. The present findings of pelvic and para-aortic node involvement at 41% and 17%, respectively, are comparable to previous studies. A report by Grigsby *et al.* using PET imaging evaluated the nodal distribution of 101 cervical cancer patients Stages IA-IVB.

The study reported 67% positive pelvic lymph nodes and 21% para-aortic nodes [11]. Previous studies have reported a close correlation between nodal involvement and tumor stage [12-15]. The present findings revealed that advanced tumor stage was significantly associated with an increase in number of metastatic nodes ($p = 0.02$) and lymph node size ($p = 0.04$). Additionally, the risk of lymph node involvement for lymph node counts 1-4+ was critically associated with tumor stage ($p = 0.0003$). Furthermore, the authors observed a correlation between parametrial invasion and node counts 1-4+ (P=0.08). Alternatively, risk of multiple metastatic nodes or nodal enlargement was not significantly different for any of the other identified clinico-pathological variables.

Several studies have demonstrated worsened overall survival in cervical cancer patients with lymph node involvement [12, 16, 17] The present cohort's five-year OS with lymph node involvement was 47% compared with 56% without involvement. Moreover, overall survival rates by number of metastatic lymph nodes followed a stepwise fashion by which a higher number of positive nodes were associated with worsened OS. The 1-2, 3-4, and > 4 lymph node counts associated with estimated five-year survival rates of 50%, 42% and 33%, respectively. Comparatively, the five-year OS rates by lymph node size were 49%, 40%, 60%, and 50% for the 1.1-1.9, 2.0-2.9, 3.0-3.9, and ≥ 4.0 cm categories, respectively. Consistent with the present results, other researchers have reported a close correlation between increased number of metastatic lymph nodes and poor prognosis in patients with cervical carcinoma [6-8]. The present study did not identify an OS difference between patients with positive *vs*. negative lymph nodes. This finding could possibly be explained by the relatively larger number of single lymph node patients in this cohort compared to those with multiple positive nodes. In effect, the results suggest that a single positive node may not as dramatically worsen survival as compared to the impact of multiple metastatic nodes. Additionally, these findings suggest that the presence of metastasis in itself is more impactful than lymph node size in the prognosis of cervical cancer patients.

There are possible limitations associated with this investigation. The first, is suspected selection bias due to the retrospective nature of the study. Second, considering that almost all of the patients underwent staging by various imaging modalities, there could have been compromised uniformity in the evaluation of lymph node status across the cases. Based on the present literature search, it was apparent to the authors that the combined impact of lymph node number and size on long-term treatment outcomes in cervical cancer has not been previously published. Consequently, this study aimed to investigate the prognostic values for those two lymph node characteristics. The findings from this study could potentially guide in the selection of higher risk patient populations and the design of additional adjuvant therapies, at the same time sparing lower risk patients from the burden of undergoing aggressive treatments.

Conclusion

For the purpose of improved characterization and management of cervical cancer, it is imperative to develop a deeper understanding of the features associated with a worsened prognosis. Additionally, the identification of high-risk patients is of great value in the optimization of treatment. Based on the findings of this study the authors suggest that an increase in number of metastatic lymph nodes at the time of diagnosis is a more valuable factor than nodal size in the prognosis of cervical cancer patients.

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