Prognostic Significance of Histology and Positive Lymph Node Involvement Following Radical Hysterectomy in Carcinoma of the Cervix

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Objective: Lymph node (LN) metastasis portends a poor outcome in women with carcinoma of the uterine cervix. We queried a large database to analyze the importance of number of positive LN and histology in relation to survival after radical hysterectomy and lymphadenectomy.

Methods: Data were collected from the Surveillance, Epidemiology, and End Results Program on women who had primary surgery for the years 1988 to 2003 (n = 4559). Statistical analyses were performed using conventional methods.

Results: The median number of LNs examined per patient has significantly declined in recent years ($P = 0.003$). The 5-year rates of cause specific and overall survival were 94% and 91%, 76% and 69%, 62% and 58%, and 41% and 35%, for 0, 1 to 2, 3 to 9 and ≥10 positive LNs, respectively. Pathologic LN involvement was associated with higher grade, higher stage, larger tumor size, and squamous cell histology. Predictors for both cause specific and overall survival on multivariate analysis included number of involved LN, histology, tumor grade, tumor size, disease stage, and pelvis or paraaortic lymphatic involvement.

Conclusions: Adenocarcinoma histology independently predicted for a more aggressive phenotype, particularly in women with LN involvement. The number of LNs examined did not independently predict for survival when adjusted for patient and disease characteristics, providing context for the investigation of sentinel node biopsy or other sampling methods. LN positive disease in carcinoma of the cervix predicts a prognosis that is inversely related to the number of involved nodes. Tumor grade, size, and FIGO stage were associated with increasing risk for lymph node metastases.

Key Words: uterine cervix, carcinoma, lymph node, surgery

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Although carcinoma of the uterine cervix represents one of the most common malignancies among women in the world, in the United States it is the third most common gynecologic malignancy and does not rank among the top 10 new malignancies estimated among women for 2007.[1] Great strides in the management of carcinoma of the uterine cervix have been achieved in this country as the death rate among women affected by this malignancy has significantly declined from the mid 1970s to 2002.[1]

Although the majority of women in the contemporary era present with primary disease that is localized, approximately 34% of women continue to present with regional disease and 9% with distant metastasis.[2] Many of the women with localized disease can be cured after definitive management, and current data suggest that primary surgery or radiation therapy provide equivalent outcomes.[2,3] Women who present with regional or distant disease are at greater risk for death as lymph node metastasis have been shown to significantly reduce 5-year survival.[4,5]

Two institutions have retrospectively evaluated their series of women with early stage disease who have undergone radical hysterectomy with lymphadenectomy in an effort to identify those women who are at greatest risk of relapse and mortality in relation to the presence of lymph node metastasis.[6,7] Although extensive in their analyses, these reports are limited by small patient numbers and by the focus only on women with early stage disease. The Gynecologic Oncology Group examined women with early stage disease in an effort to identify predictors of recurrence.[8] The number of positive lymph nodes was not predictive, whereas lymph-vascular space invasion, depth of tumor invasion, and tumor size were independent prognostic factors.

Using a large population database, we investigated the impact of positive lymph nodes on all-cause and disease-specific mortality among women undergoing definitive primary surgery with lymphadenectomy within the United States. We attempted to identify independent predictors of prognosis and predictors of the anatomic extent and absolute burden of lymph node positive disease in women with primary carcinoma of the uterine cervix. We examined trends in the presentation and management of disease over the time period analyzed.

MATERIALS AND METHODS

Data for these analyses were obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, using the SEER 17-Registries plus Alaska 1973–2003 data set (November 2005 edition).[9] SEER is comprised of a set of geographically defined, population-based, central cancer registries in the United States and is operated by local nonprofit organizations under contract with the National Cancer Institute. Serial registry data are submitted electronically without personal identifiers on a biannual basis.[9]

The analyzed population consisted of women with primary carcinoma of the uterine cervix of adenocarcinoma or squamous cell histologic subtypes (International Classification of Diseases codes 8020, 8070, 8071, 8072, 8140, all with the behavior code of 03) for the years 1988 to 2003. Eligible women were limited to those who had been recorded as having undergone a modified radical hysterectomy or extended hysterectomy with a lymph node examination. The information gathered from the database on the eligible women included year of diagnosis, age at diagnosis, race/ethnicity, marital status, histologic classification, grade, SEER summary stage, extent of disease, tumor size, number of lymph nodes examined, number of lymph nodes positive, site of positive lymph nodes, time from diagnosis to last contact, vital status at last contact, and cause of death. Data on known

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prognostic variables including lymph vascular space invasion, margin status, depth of invasion, and use of chemotherapy are not collected within the SEER program and are not included in the analysis. The positive lymph node ratio was calculated by dividing the number of positive lymph nodes by the total number of lymph nodes evaluated for each woman.

Baseline clinical and pathologic variables were assessed for potential associations with node positive disease by χ^2 and analysis of variance for categorical and continuous variables, respectively. Rates of cause-specific survival (CSS) and overall survival (OS) were estimated using the Kaplan-Meier method and the significance of comparisons was determined using the log-rank test.[10] Initial exploratory analysis revealed significantly divergent outcomes among women with 0, 1 to 2, 3 to 9, ≥10 positive lymph nodes, respectively, lending the analysis of positive lymph nodes to categories in addition to as a continuum. Multivariate Cox proportional hazards regression analyses were conducted to identify predictors of CSS and OS.[11] The time of death was measured from the recorded date of diagnosis to the date of death because of cervix cancer (CSS) or from any cause (OS). Women who were alive were censored at the date of last contact. Statistical significance was declared for $P < 0.05$.

RESULTS

The median age of the 4559 analyzed women was 43 years (range: 19–92). The median follow-up period was 4.4 years (range: 1 month–16 years). Three hundred twenty-eight women (7%) were included for the years 1988 and 1989. For the decade 1990 through 1999, 2494 women (55%) were included. The years comprising 2000 through 2003 contributed an additional 1737 eligible women (38%). Table 1 contains patient, tumor, and survival information for the included women. Adenocarcinoma was diagnosed in 23% of all women and this ratio was consistent throughout the time period analyzed.

The median reported number of lymph nodes evaluated pathologically per woman was 20 (range 1–86). The number of lymph nodes evaluated significantly decreased over the analyzed time period ($P < 0.0001$) with median number of lymph nodes examined in 1988 and 1989 of 21 (range: 1–67) and 23 (range: 1–90), respectively, compared with 20 (range: 1–70) and 19 (range: 1–90) for the most recent 2 years, 2002 and 2003, respectively. For all eras, women who had ≤13 lymph nodes pathologically examined (lowest quartile) experienced significantly worse OS ($P = 0.01$), but not CSS ($P = 0.51$), compared with those who had more lymph nodes evaluated (5-year OS, 89% vs. 91%, respectively).

Eight hundred forty-eight of 4559 women (18.6%) were reported as having lymph node involvement. The median number of positive nodes among these women was 2 (range: 1–43). Of those women with involved nodes, 556 (65%) had 1 to 2 positive lymph nodes, 261 (31%) had 3 to 9 positive nodes, and 31 (4%) had ≥10 involved.

Estimated CSS and OS for women stratified by the number of positive lymph nodes (Fig. 1) and the lymph node positive ratio are provided (Fig. 2).

Age and race/ethnicity were not associated with node positive disease. Forty percent of women with a tumor ≥4 cm had at least 1 nodal metastasis compared with 17% of women with tumors <4 cm. The recorded size of tumors has not changed significantly over the time period analyzed ($P = 0.6$). Women with ≥10 positive lymph nodes significantly were more likely to have grade 3 disease, a tumor ≥4 cm, and to have involvement of the paraaortic lymph nodes. Crude death totals increased among lymph node positive groups, 10%, 27%, 36%, and 58% for 0, 1 to 2, 3 to 9, and ≥10 involved nodes, respectively ($P < 0.0001$). A similar increase in death attributable to cancer of the cervix with increasing number of positive nodes was observed ($P < 0.0001$). Women with a positive lymph node of ratio ≤10% were more likely to have 1 to 2 positive lymph nodes, whereas those with a ratio >25% were significantly more likely to have ≥10 involved nodes ($P < 0.0001$). Seventy-six (1.7%) women had involvement of the paraaortic lymph nodes and the prevalence of paraaortic involvement was directly related to disease stage, increasing from 0.7% to 5% to 19% to 32% for stages I, II, III, and IV, respectively ($P < 0.0001$). Information regarding whether women with paraaortic involvement also had pelvic lymph node involvement is not available in the SEER, and therefore was not analyzed. The estimated 5-year rates of CSS and OS were 45%

TABLE 1. Summary of Demographic, Clinical and Pathologic Characteristics

	n (%)
Median age, yr (range)	43 (19–92)
Ethnicity	
White	3622 (79)
African American	419 (9)
Other	518 (11)
Histology	
Squamous cell	3514 (77)
Adenocarcinoma	1045 (23)
Grade	
Unknown	881 (19)
1	435 (10)
2	1604 (35)
3	1639 (36)
FIGO stage	
I	3909 (86)
II	564 (12)
III	48 (1)
IV	38 (1)
Tumor size	
Median, cm (range)	2.5 (0.1–38)
<4 cm	2054 (73)
≥4 cm	754 (27)
Median no. LN examined (range)	20 (1–90)
Median no. positive LN* (range)	2 (1–43)
0 LN positive	3715 (81)
1–2 LN positive	556 (12)
3–9 LN positive	261 (6)
≥10 LN positive	31 (1)
Positive LN location	
Pelvic LN	773 (17)
Para-aortic LN	75 (2)
Positive LN ratio	
0	3715 (81)
≤10%	435 (10)
11%–25%	257 (6)
>25%	152 (3)
Median follow-up, yr (range)	4.4 (.2–16)
Alive	3929 (86)
Dead	630 (14)
Dead due to disease	391 (9)

*Among women with positive LN.
LN indicates lymph node; other, American Indian, AK native, Asian/Pacific Islander.

and 39% for women with paraaortic involvement compared with 72% and 67% for women with pelvic lymph node involvement ($P < 0.0001$).

Multivariate analysis revealed the significant predictors for improved CSS to include squamous cell histology, lower grade, lower FIGO stage, smaller tumor size, fewer involved LN, lower or zero positive lymph node ratio, and pelvic compared with paraaortic LN involvement (Table 2). Similar analysis for the OS end point revealed younger age, squamous cell histology, lower grade, lower FIGO stage, smaller tumor size, fewer involved LN, lower or zero positive lymph node ratio, and pelvic compared with paraaortic LN involvement to be independent predictors.

Analysis of the impact of histology in relation to lymph node status was performed after those observations. Women with adenocarcinoma had significantly more favorable disease characteristics, including age (women < median 43 years, 52% vs. 48%, $P = 0.04$), grade (poorly differentiated, 19% vs. 41%, $P < 0.0001$), tumor size (≥4 cm, 18% vs. 29%, $P < 0.0001$), stage (stage I, 92% vs. 84%, $P < 0.0001$), and lymph nodes status (positive, 13% vs. 20%, $P < 0.0001$), compared with those with squamous cell carcinoma. Women with adenocarcinoma histology and no lymph node involvement experienced significantly improved OS ($P = 0.005$) with a trend toward improved CSS ($P = 0.07$) compared with women with squamous cell histology and no nodal disease. Conversely, in the setting of positive lymph nodes, women with squamous cell histology faired significantly better than those with adenocarcinoma histology for both the CSS ($P = 0.009$) and OS ($P = 0.02$) endpoints (Fig. 3).

DISCUSSION

Importantly, these data demonstrate potential biologic differences that exist between the 2 most common histologies of cervix carcinoma, squamous cell, and adenocarcinoma. Previously, smaller reports have documented distinct clinical outcomes in women with early stage disease and differing histologies.[12–14] Adenocarcinoma histology was an independent predictor for poorer CSS and OS on multivariate analysis. Terada et al observed significantly poorer survival among female with stage IB cervix carcinoma with lymph node metastasis who had adenocarcinoma or adenosquamous histology compared with squamous cell carcinoma.[12] Likewise, in this large analysis, women with node positive disease and adenocarci-

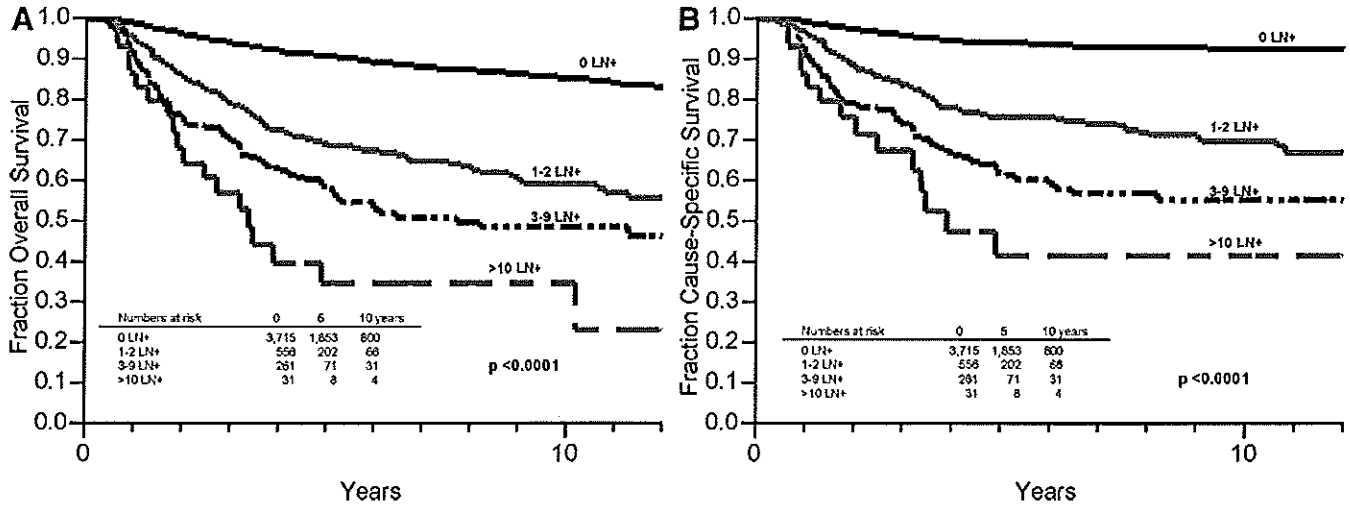

FIGURE 1. Estimated OS (A) and CSS (B) of women stratified by number of positive lymph nodes.

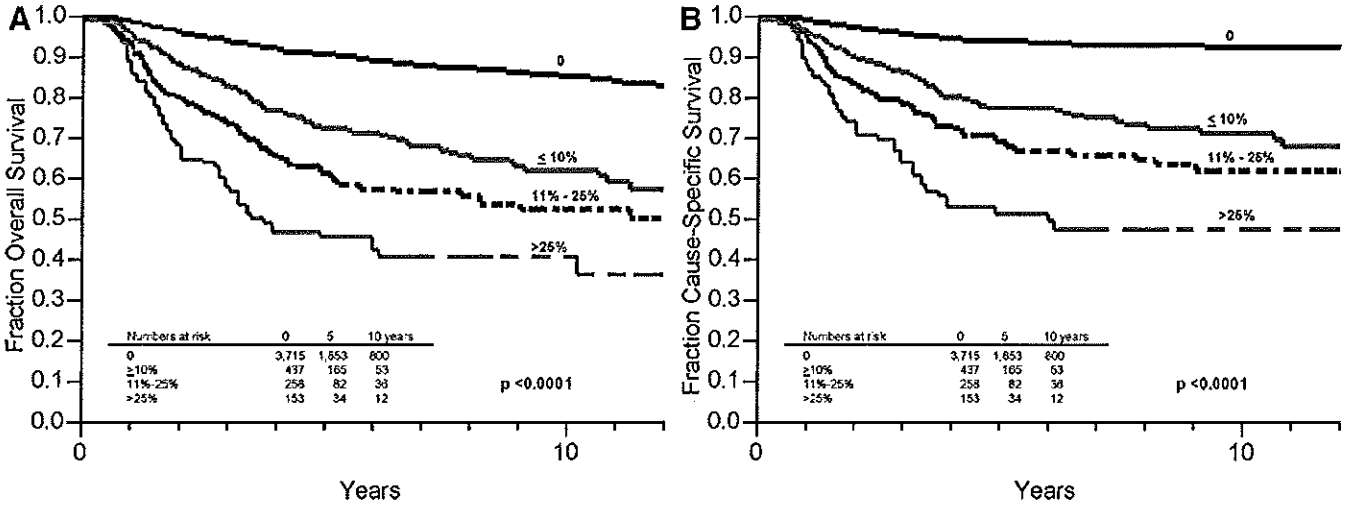

FIGURE 2. Estimated OS (A) and CSS (B) of women stratified by positive lymph node ratio.

TABLE 2. Multivariate Analysis for Predictors of Overall and Cause-Specific Survival

	Cause-Specific Survival HR (95% CI)	P	Overall Survival HR (95% CI)	P
Age at diagnosis*	1.01 (0.99–1.02)	0.46	1.03 (1.02–1.04)	<0.0001
Ethnicity		0.28†		0.06†
White	Reference		Reference	
African American	1.19 (0.92–1.52)		1.29 (1.04–1.56)	
Other	0.94 (0.74–1.19)		0.86 (0.70–1.04)	
Histology		0.005		0.02
Squamous cell	Reference		Reference	
Adenocarcinoma	1.26 (1.07–1.46)		1.18 (1.03–1.34)	
Grade		0.0003†		<0.0001†
1	Reference		Reference	
2	1.03 (0.81–1.33)		0.96 (0.79–1.17)	
3	1.60 (1.29–2.04)		1.47 (1.23–1.77)	
FIGO stage		<0.0001†		<0.0001†
I	Reference		Reference	
II	1.22 (0.93–1.63)		1.18 (0.94–1.52)	
III	0.95 (0.52–1.58)		1.00 (0.60–1.54)	
IV	1.45 (0.85–2.31)		1.31 (0.82–1.99)	
Primary tumor size*	1.11 (1.08–1.14)	<0.0001	1.10 (1.07–1.12)	<0.0001
No. LN examined*	0.99 (0.98–1.00)	0.18	0.99 (0.98–1.00)	0.12
No. positive LN		<0.0001†		<0.0001†
0	Reference		Reference	
1–2	1.14 (0.90–1.45)		1.11 (0.91–1.38)	
3–9	1.54 (1.20–1.99)		1.41 (1.12–1.77)	
>10	1.42 (0.85–2.19)		1.39 (0.88–2.05)	
Positive LN ratio		<0.0001†		<0.0001†
0	Reference		Reference	
<10%	1.14 (0.91–1.42)		1.14 (0.93–1.38)	
11%–25%	1.26 (0.98–1.60)		1.16 (0.93–1.43)	
>25%	1.72 (1.31–2.22)		1.63 (1.28–2.06)	
Positive LN location		<0.0001†		<0.0001†
pN0	Reference		Reference	
Pelvic LN	1.30 (1.07–1.59)		1.23 (1.03–1.47)	
Paraaortic LN	1.80 (1.28–2.46)		1.70 (1.26–2.24)	

*Continuous variable.
†*P* value for trend.
CI indicates confidence interval.

noma histology experienced significantly worse rates of overall and cause-specific survival relative to their squamous cell histology counterparts. The absolute difference in the rate of survivorship at 10 years was >30% for both end points, significantly favoring squamous cell. Uniquely, women with adenocarcinoma had similar if not more favorable disease characteristics relative to women with squamous cell histology, suggesting that adenocarcinomas are biologically more aggressive, more treatment resistant, or both.

Conversely, and somewhat unexplainably, women without nodal involvement but with adenocarcinoma histology experienced significantly improved outcomes compared with women with squamous histology. Perhaps the best explanation of this finding is that women with adenocarcinoma generally harbored disease with much more favorable disease characteristics compared with their squamous-type counterparts. Other biases, including surgical approaches, postoperative treatment regimen and baseline health factors cannot be accounted for within SEER. Further clinical and translational investigation to account for the disparity in outcomes between the 2 most common histologies of cervical carcinoma is warranted and could be considered as a component in future trial design.

Despite not being a component of the internationally accepted criteria for staging cervix cancer, perhaps the greatest predictor for recurrence and death in these women is the presence and anatomic location of positive lymph nodes. Early reports documented significantly inferior survival observed in women with lymph node involvement,[4,5] whereas other studies have reported the more specific factors of anatomic location[12,15,16] and absolute number of involved lymph nodes to be prognostic.[6,17–19] We drew on a wealth of information available through the National Cancer Institute supported SEER database in the United States to comprehensively evaluate these factors as they relate to overall and cause-specific survival with the largest cohort of women in the postradical surgery setting reported to date.

Among the 4559 analyzed women, we observed a median 20 lymph nodes (mean 22) evaluated per woman. This compares

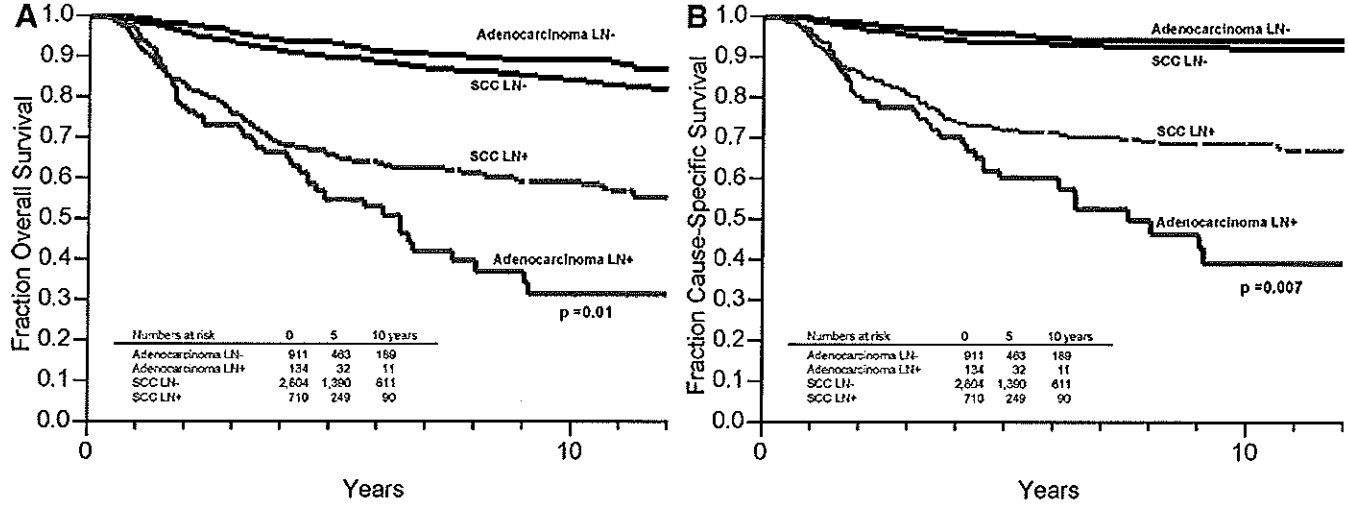

FIGURE 3. Estimated OS (A) and CSS (B) of women stratified by lymph node involvement for squamous cell and adenocarcinoma histologies.

favorably to reports in the literature of lymph nodes evaluated (mean: 16.7–32).[17,20] Further, 19% of women in this series was found to have lymph node metastasis upon pathologic review, comparable to the rates of positive nodal prevalence reported within the literature (range: 15%–52%).[8,18,19,21–23] Paraaortic lymph node metastasis have been reported to range from 4% to 16% within the literature,[22,24] whereas we identified 76 women (1.7%) with paraaortic nodal metastasis at surgery. The lower rate of paraaortic LN involvement documented here may be because of less precise documentation of nodal location within the SEER than on prospective protocols or in single institutional databases. Generally, the composite of our findings compares favorably to that reported from other institutions and series, lending credence to our observations despite the inherent weaknesses of retrospective analysis and serve to validate previous reports that were generally limited to smaller sized cohorts.

In terms of the potential benefit of tumor resection, data from a randomized trial of surgical removal of the uterus and cervix after attenuated radiotherapy compared with definitive radiotherapy revealed that resection offered no significant benefit with regards to pelvic recurrence and survival.[25] No randomized data have been reported regarding the role of primary lymph node removal or "debulking" in women with cervix cancer, although some retrospective reports are available.[26–28] In an earlier report, Hacker et al retrospectively observed that women with macroscopic nodal involvement who received nodal resection experienced similar survival to women with microscopic nodal disease.[27] Cosin et al updated and expanded the former experience, confirming those findings of Hacker.[26] Women in the current series who had a less extensive (by number) lymph node dissection experienced significantly worse OS in actuarial analysis—removal of 13 or fewer LN was detrimental to OS in all time periods among all women analyzed. However, this factor was not found to independently predict for either survival end point in the multivariate analyses. This incongruity is likely explained by the many biases not accounted for within the SEER including what the surgeon encountered at the time of resection, surgical training of the physician (gynecologic oncologist vs. general gynecologist), reasons for sampling versus thorough dissection, presence of matted or very large lymph node metastasis, degree to which the pathologic specimens were evaluated, among others. Our findings do not substantiate those of other authors who conclude that surgical removal of lymph nodes is therapeutic, although this analysis is limited in so far as it does not characterize the positive lymph nodes by size or location. Perhaps these observations can serve to bolster the argument for investigating the more broad application of sentinel lymph node biopsy, particularly in early stage disease, as recent review of the literature observed a sensitivity of 92% with optimal technique.[29]

Unadjusted and adjusted analyses in this series undeniably confirm the importance of lymph node involvement as it relates to prognosis in women with cervix cancer who undergo radical hysterectomy. Women with lymph node positive disease experienced significantly inferior survival compared with women without lymph node involvement. Further, the absolute number of lymph nodes involved was independently predictive of both overall and cause-specific survival. Others have similarly reported that prognosis inversely associated with the number of lymph nodes involved in both locally advanced[18] and early stage disease.[17,19,30,31]

The lymph node positive ratio was also strongly predictive of survival with women who had 25% or greater involvement experiencing the highest risk for any death relative to all other potential predictors on adjusted analysis. The positive lymph node ratio is increasingly being investigated and identified as a putative characteristic that identifies more aggressive disease and predicts poorer outcomes in cancers of the stomach, esophagus, endometrial, pancreas and breast.[32–36] The positive lymph node ratio seems to be a favored target as it would conceivably be quite applicable, accounting for the wide variation that exists in the extent to which lymph nodes are resected and pathologically analyzed, the world over. To our knowledge this is the first analysis to address its potentially application to cervix cancer. Based on its strong predictive value on adjusted analysis in this series, it would be reasonable to further investigate its utility and its potential application for women undergoing primary therapy, particularly in a prospective, controlled mechanism.

The location of lymph node metastases has been evaluated as a putative predictor for survival endpoints. Several series have documented poorer outcomes in women with paraaortic lymph node involvement[12,16,24] and we have observed a similar finding in this group of women—the 76 women with positive paraaortic lymph nodes experienced significantly worse OS and CSS compared with those with pelvic lymph node involvement alone. We were further able to document an association of stage with the prevalence of paraaortic lymph node involvement, as 5% to 32% of women had paraaortic lymph node involvement with stage II to IV disease.

Predictors for a greater burden of nodal metastases identified include higher grade, higher stage, and larger tumor size. Similarly, more women with FIGO stage III or IV disease had lymph nodes involved than not. These findings, particularly as they relate to the postoperative management of these women, require greater investigation. The details of postoperative therapy, be it radiotherapy, chemotherapy, or a combination, are not adequately addressed with SEER data alone and, therefore, the impact of adjuvant treatment on these results are yet to be identified and reported.

CONCLUSION

Among women undergoing radical resection for primary cervical cancer in the SEER, adenocarcinoma histology independently predicted for a more aggressive phenotype and was particularly pronounced in those women with LN involvement. The number of LNs examined did not independently predict for survival for any time period when adjusted for other patient and disease characteristics, questioning the ultimate benefit of extensive LN surgery and providing context for the investigation of sentinel node biopsy or other less extensive sampling methods. LN positive disease in carcinoma of the cervix predicts a prognosis that is inversely related to the number of involved nodes—a greater burden of lymph node involvement significantly decreases both overall and cause-specific survival. Tumor grade, size, and FIGO stage were associated with increasing lymph node metastases.

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