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ORIGINAL RESEARCH

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Pathologic primary tumor factors associated with risk of pelvic and paraaortic lymph node involvement in patients with endometrial adenocarcinoma

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Abstract

The presence of lymph node (LN) positivity in endometrial adenocarcinoma (EAC) patients guides adjuvant treatment, but recommendations regarding LN evaluation at the time of primary surgery remain variable. Primary pathologic tumor characteristics may predict risk of LN involvement in EAC patients with limited LN evaluation. Patients diagnosed between 2004–2016 with pathologic T1–T2 EAC in the National Cancer Database who had at least one lymph node sampled at the time of surgery were included. Pathologic primary tumor predictors of LN involvement were identified using logistic regression. To predict overall, pelvic only, and paraaortic and/or pelvic LN involvement, nomograms were generated. Among 57,810 EAC patients included, 4002 were node positive. On multivariable analysis, increasing pathologic tumor category (pT2 versus pT1a, odds ratio (OR) 5.43, 95% confidence interval (CI) 4.89–6.02, $p < 0.001$), increasing pathologic tumor grade (grade 3 versus grade 1, OR 1.62, 95% CI 1.47–1.79, $p < 0.001$), increase in tumor size per centimeter (OR 1.05, 95% CI 1.04–1.06, $p < 0.001$), and presence of lymphovascular invasion (LVI) (OR 6.33, 95% CI 5.87–6.83, $p < 0.001$) were predictive of overall LN positivity. The presence of LVI was a stronger predictor of paraaortic LN involvement (OR 6.43, 95% CI 5.55–7.47, $p < 0.001$) than pelvic LN involvement (OR 5.42, 95% CI 4.98–5.90, $p < 0.001$) in multivariable analysis. For patients with limited LN evaluation, pathologic tumor features can be used to estimate the risk of pelvic or paraaortic LN involvement. This information may inform adjuvant treatment decisions and guide future studies.

Keywords

Endometrial adenocarcinoma; Pathologic predictors; Lymph node positive; Tumor category; Histologic grade; Lymphovascular invasion

1. Introduction

Endometrial cancer is typically locally confined but can involve regional lymph nodes (LN). Clinically apparent early stage disease is initially managed with surgery with pathologic staging impacting adjuvant treatment decisions. The use of pelvic lymphadenectomy is controversial [1], and either pelvic LN dissection +/− paraaortic LN sampling [2] or sentinel lymph node biopsy [3, 4] can be considered for staging evaluation. Pelvic lymphadenectomy was not associated with survival benefit in two randomized studies [5, 6]. However, among patients found to have nodal involvement, systemic therapy and radiation have been shown to improve patient outcomes showing pathologic nodal information is clinically meaningful [7, 8].

Given these controversies, depending upon institutional practice patterns, the pathologic information available to determine nodal status could range from no lymph nodes evaluated to a full lymphadenectomy. Increasingly, sentinel lymph node biopsy is being performed as an alternative to pelvic lymphadenectomy. Furthermore, a lack of pathologic nodal information could impact treatment recommendations for adjuvant therapy. Accurately estimating lymph node positivity risk from primary tumor pathologic factors may help to personalize adjuvant treatment recommendations.

Previous studies have identified lymphovascular invasion, tumor grade, tumor category, and tumor size as primary tumor risk factors of lymph node positivity. Most of these series included a limited number of patients from single institutions. There is also limited information, from large patient cohorts, regarding how to quantitively calculate the increased risk of nodal involvement from multiple risk factors. In this study, the National Cancer Data Base (NCDB) was queried with the goal of validating previously identified risk factors of nodal involvement in a large national patient sample, assessing for additional predictors, and developing a nomogram to help quantify nodal involvement.

2. Methods

2.1 Patient selection

The NCDB was queried, and 476,104 patients diagnosed in the years 2004–2016 with endometrial cancer were identified (**Supplementary Fig. 1**). Initial exclusion criteria were the absence of known pertinent pathologic data, such as lymphovascular invasion (LVI), tumor grade, or tumor size (n = 354,392). Patients were excluded if they had undifferentiated tumors. Patients without known nodal stage were excluded (n = 29,427). Patients were included if they had T1a, T1b or T2 primary tumor category per the American Joint Committee on Cancer (AJCC). Patients with unclear nodal status or no lymph nodes sampled during surgery were excluded (n = 9565). Non-adenocarcinoma histology was an exclusion criterion (n = 14,018).

2.2 Statistical analysis

Multivariable imputation with fully conditional specification was used to impute missing values. Pathologic lymph node involvement (≥1 positive) was the primary end point of the study. Patients with AJCC N1 involvement corresponded to those with only pelvic LN positivity while AJCC N2 involvement corresponded to paraaortic +/− pelvic LN positivity.

Predictors of any regional LN positivity, only pelvic LN involvement, and paraaortic +/− pelvic LN positivity were identified using logistic regression. Tables 2,3,4 contain covariates in the multivariable model. Variable inflation factor was used to assess for multicollinearity [9]. Internal bootstrap resampling with 1000 replicates for model validation was used to obtain optimism corrected c-index [10]. Model data were used to generate nomograms for predicting the probability of LN positivity. R statistical software (version 3.6.2; R Foundation, Vienna, Austria) was used with statistical significance defined at a level of 0.05 using a 2-sided test.

3. Results

A total of 57,810 patients were included, and 4002 (6.9%) had a pathologically positive lymph node. Tumor pathologic factors are listed in Table 1. Multiple factors were associated with lymph node positivity on univariate analysis, including higher T-classification (pT2 versus pT1a, odds ratio (OR) 11.93, 95% confidence interval (CI) 10.84–13.12, $p < 0.001$; pT1b versus pT1a, OR 6.0, 95% CI 5.54–6.50, $p < 0.001$), presence of LVI (OR 11.14, 95% CI 10.40–11.95, $p < 0.001$), higher tumor grade (grade 3 versus grade 1, OR 4.25, 95% CI 3.89–4.65, $p < 0.001$; grade 2 versus grade 1, OR 2.42, 95% CI 2.23–2.62, $p < 0.001$), and tumor size (OR 1.15, 95% CI 1.13–1.16, $p < 0.001$) (Table 2). Multivariate logistic regression analysis revealed multiple independent factors of lymph node involvement, including LVI (OR 6.33, 95% CI 5.87–6.83, $p < 0.001$), higher primary tumor category (pT2 versus pT1a, OR 5.43, 95% CI 4.89–6.02, $p < 0.001$; pT1b versus pT1a, OR 3.09, 95% CI 2.84–3.37, $p < 0.001$), higher tumor grade (grade 3 versus grade 1, OR 1.62, 95% CI 1.47–1.79, $p < 0.001$; grade 2 versus grade 1, OR 1.50, 95% CI 1.37–1.63, $p < 0.001$), and tumor size (OR 1.05, 95% CI 1.04–1.06, $p < 0.001$) (Table 2).

Multiple significant pelvic only LN predictors included LVI (OR 5.42, 95% CI 4.98–5.90, $p < 0.001$), higher primary tumor category (pT2 versus pT1a, OR 4.91, 95% CI 4.37–5.52, $p < 0.001$; pT1b versus pT1a, OR 2.91, 95% CI 2.64–3.20, $p < 0.001$), higher tumor grade (grade 3 versus grade 1, OR 1.43, 95% CI 1.28–1.60, $p < 0.001$; grade 2 versus grade 1, OR 1.48, 95% CI 1.34–1.62, $p < 0.001$), and tumor size (OR 1.04, 95% CI 1.03–1.05, $p < 0.001$) (Table 3).

Paraaortic LN involvement +/− pelvic LN positivity was predicted by LVI (OR 6.43, 95% CI 5.55–7.47, $p < 0.001$), increasing primary tumor category (pT2 versus pT1a, OR 4.72, 95% CI 3.88–5.74, $p < 0.001$; pT1b versus pT1a, OR 3.21, 95% CI 2.71–3.82, $p < 0.001$), higher tumor grade (grade 3 versus grade 1, OR 1.92, 95% CI 1.61–2.29, $p < 0.001$; grade 2 versus grade 1, OR 1.44, 95% CI 1.22–1.70, $p < 0.001$), and tumor size (OR 1.04, 95% CI 1.03–1.06, $p < 0.001$) (Table 4).

Individual nomograms for predicting regional lymph node positivity (Fig. 1), pelvic only lymph node positivity (**Supplementary Fig. 2**), and paraaortic involvement +/− pelvic LN positivity (**Supplementary Fig. 3**) were generated. Of note, LVI was more strongly associated with paraaortic lymph node positivity relative to only pelvic lymph node positivity.

4. Discussion

Multiple studies have identified risk factors for lymph nodal involvement in endometrial cancer. GOG (Gynecologic Oncology Group) 33 strongly correlated lymph node positivity with higher grade tumors and deeper myometrial invasion [11]. A subsequent study, GOG 210, confirmed the predictive value of primary tumor grade and stage in predicting lymph node involvement, as well as describing additional predictors of nodal positivity, including non-endometrioid histology and the presence of lymphovascular invasion [12]. These prior studies provided tables to show relationships between grade and myometrial invasion with lymph node risk but did not include other variables such as LVI and tumor size. It remains difficult to determine how to summate the risk of each of these variables together to come up with a final estimate of lymph node risk.

4.1 Summary of main results

Our analysis of over 57,000 patients was limited to those with endometrial adenocarcinoma and pathologic tumor category I–II. Significant pathologic predictors of lymph node positivity included LVI, tumor category, grade, and tumor size. These results were generally consistent with previous studies. The impact of individual pathologic risk factors on LN positivity was also compared for only pelvic lymph node positivity versus paraaortic involvement with or without pelvic lymph node positivity.

4.2 Results in the context of published literature

The most significant predictor of lymph node involvement was the presence of LVI (>6-fold increased risk). LVI was

TABLE 1. Distribution of pathologic tumor variables for the full cohort and those with or without any regional LN positivity. LN involvement is associated with other less favorable pathologic factors and with the number of lymph nodes examined.

	Full Cohort N = 57,810	LN negative N = 53,808	LN positive N = 4002	*p*
Pathologic tumor category				
1a	37,851 (65.5%)	36,919 (97.5%)	932 (2.5%)	
1b	15,499 (26.8%)	13,461 (86.9%)	2038 (13.1%)	<0.001
2	4460 (7.71%)	3428 (76.9%)	1032 (23.1%)	
AJCC pathologic nodal stage				
0	53,808 (93.1%)	53,808 (100%)	0 (0.00%)	
IIIC1	2960 (5.12%)	0 (0.00%)	2960 (100%)	-
IIIC2	1042 (1.80%)	0 (0.00%)	1042 (100%)	
Grade				
1	26,837 (46.4%)	25,869 (96.4%)	968 (3.6%)	
2	22,401 (38.7%)	20,544 (91.7%)	1857 (8.3%)	<0.001
3	8572 (14.8%)	7395 (86.3%)	1177 (13.7%)	
LVI				
Absent	47,291 (81.8%)	45,918 (97.1%)	1373 (2.9%)	<0.001
Present	10,519 (18.2%)	7890 (75.0%)	2629 (25.0%)	
Tumor size (cm)				
Median (IQR)	3.50 (2.30; 5.00)	3.50 (2.20; 4.90)	5.00 (3.50; 6.50)	<0.001
Mean (SD)	3.89 (2.90)	3.78 (2.84)	5.35 (3.35)	<0.001

Results shown with mean with standard deviation for continuous and count with column percentage for categorical variables. LN: lymph node; AJCC: American Joint Committee on Cancer; LVI: lymphovascular invasion; IQR: interquartile range; SD: standard deviation.

TABLE 2. Pathologic tumor variables predicting regional lymph node involvement in logistic regression.

Covariates	Univariate		Multivariable	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Pathologic tumor category				
1a	1.000	-	1.000	-
1b	6.00 (5.54 to 6.50)	<0.001	3.09 (2.84 to 3.37)	<0.001
2	11.93 (10.84 to 13.12)	<0.001	5.43 (4.89 to 6.02)	<0.001
Grade				
1	1.000	-	1.000	-
2	2.42 (2.23 to 2.62)	<0.001	1.50 (1.37 to 1.63)	<0.001
3	4.25 (3.89 to 4.65)	<0.001	1.62 (1.47 to 1.79)	<0.001
LVI				
Absent	1.000	-	1.000	-
Present	11.14 (10.40 to 11.95)	<0.001	6.33 (5.87 to 6.83)	<0.001
Tumor size (cm)	1.14 (1.12 to 1.15)	<0.001	1.05 (1.04 to 1.06)	<0.001

OR: odds ratio; CI: confidence interval; LVI: lymphovascular invasion.

TABLE 3. Pathologic tumor variables predicting only pelvic lymph node involvement.

Covariates	Univariate		Multivariable	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Pathologic tumor category				
1a	1.000	-	1.000	-
1b	5.39 (4.93 to 5.91)	<0.001	2.91 (2.64 to 3.20)	<0.001
2	10.42 (9.36 to 11.60)	<0.001	4.91 (4.37 to 5.52)	<0.001
Grade				
1	1.000	-	1.000	-
2	2.34 (2.14 to 2.57)	<0.001	1.48 (1.34 to 1.62)	<0.001
3	3.66 (3.30 to 4.05)	<0.001	1.43 (1.28 to 1.60)	<0.001
LVI				
Absent	1.000	-	1.000	-
Present	9.33 (8.63 to 10.09)	<0.001	5.42 (4.98 to 5.90)	<0.001
Tumor size (cm)	1.09 (1.08 to 1.11)	<0.001	1.04 (1.03 to 1.05)	<0.001

OR: odds ratio; CI: confidence interval; LVI: lymphovascular invasion.

TABLE 4. Pathologic tumor variables predicting paraaortic involvement +/− pelvic LN positivity.

Covariates	Univariate		Multivariable	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Pathologic tumor category				
1a	1.000	-	1.000	-
1b	6.84 (5.83 to 8.05)	<0.001	3.21 (2.71 to 3.82)	<0.001
2	12.10 (10.08 to 14.55)	<0.001	4.72 (3.88 to 5.74)	<0.001
Grade				
1	1.000	-	1.000	-
2	2.46 (2.09 to 2.89)	<0.001	1.44 (1.22 to 1.70)	0.007
3	5.34 (4.52 to 6.32)	<0.001	1.92 (1.61 to 2.29)	<0.001
LVI				
Absent	1.000	-	1.000	-
Present	12.24 (10.69 to 14.05)	<0.001	6.43 (5.55 to 7.47)	<0.001
Tumor size (cm)	1.07 (1.06 to 1.08)	<0.001	1.04 (1.03 to 1.06)	<0.001

OR: odds ratio; CI: confidence interval; LVI: lymphovascular invasion.

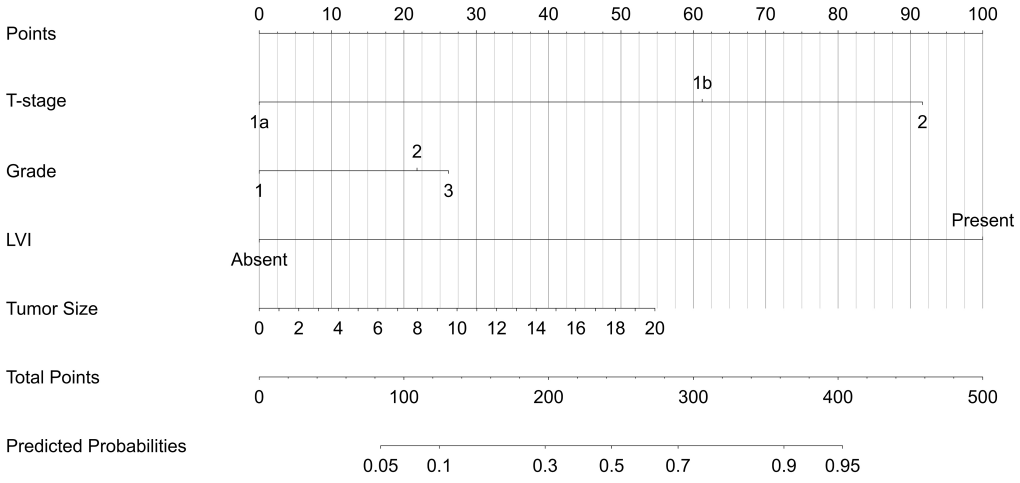

FIGURE 1. Nomogram for predicting regional lymph node positivity risk, size of tumor reported in centimeters. LVI: lymphovascular invasion.

also noted in GOG 210 to be a strong predictor of pelvic LN positivity (4.1% *vs.* 37.5%) and paraaortic LN positivity (2.3% *vs.* 23.8%) [12]. Similarly, multivariable analysis from a study from Stanford University revealed a similar approximate 7.5-fold risk of nodal positivity associated with the presence of LVI [13]. However, a large study from the Mayo Clinic revealed a smaller, approximately 1.5-fold risk of nodal positivity associated with the presence of LVI [14]. Differences in the observed predictive capacity of LVI may be related to variability in pathologic evaluation between institutions.

Primary tumor category and grade also significantly predicted lymph node positivity in the present study. Primary pathologic tumor category T2 (5-fold risk) and T1b (3-fold risk) predicted lymph node positivity at a higher rate compared to T1a disease. Tumor grade was associated with an approximate 1.5-fold risk of nodal positivity for both high and intermediate relative to low tumor grade, consistent with results of GOG 33 and GOG 210 [11, 12]. It is not surprising that higher tumor grade was found to be a strong predictor of lymph node involvement given that both correlate with biologic aggressiveness. A large single institutional study similarly showed in multivariable analysis that pT1b compared to T1a disease was associated with an approximate 3-fold risk of lymph node involvement [13]. Another large single institutional study showed in multivariable analysis that both increasing cervical stromal and myometrial invasion were associated with increased nodal risk, although the increased risk of pT2 disease of approximately two fold was significantly less than observed in our study [14].

We also identified an approximate 5% increase in risk of lymph node involvement for every 1 cm increase in primary tumor size. This was consistent with the multivariable analysis from the Stanford University, which reported an approximate 2.5-fold risk of nodal positivity associated with tumors at least 4 cm in size relative to smaller tumors [13]. However, multivariable analysis from the Mayo Clinic study revealed a larger, approximately 5-fold risk of nodal positivity associated with tumors at least 2 cm in size relative to smaller tumors [14]. Increasing tumor size was also noted to be a predictor of lymph node involvement in GOG 33 and 210 [11, 12].

The relative strength of predictors of pelvic and paraaortic lymph node involvement also differed compared to those of overall lymph node involvement. Of note, LVI was more strongly associated with risk of paraaortic than pelvic only nodal involvement. Our results are consistent with a large single institutional retrospective study that similarly identified the strongest predictor of paraaortic lymph node involvement as LVI with an approximate 5-fold associated risk [15]. LVI may be a surrogate for more aggressive primary tumor biology and as a result be associated with paraaortic lymph node involvement.

This study included nomograms to predict any regional LN positivity, pelvic only LN positivity, and paraaortic LN positivity +/− pelvic LN involvement. LVI, primary pathologic tumor category, grade, and tumor size in centimeters were all significant predictors included in each nomogram. The present study is to our knowledge the largest used to create predictive nomograms for lymph node involvement in uterine cancer patients. In the Stanford and Mayo study nomograms, the most significant predictors of lymph node involvement were LVI and myometrial depth of invasion, respectively [13, 14]. Additional studies indicated that LVI was most significantly associated with lymph node involvement [16, 17]. An additional multicenter retrospective study reported a nomogram showing the strongest predictors of lymph node positivity to be larger primary tumor size and LVI, as well as a strong effect of high tumor grade [18].

4.3 Strengths and weaknesses

The present study is limited by its retrospective nature and use of registry data with the possibility of unmeasured confounding variables unreported by the NCDB, such as myometrial invasion percentage depth and size of regional LN involved, potentially impacting reported results. The NCDB also does not account for variability in scoring systems utilized to define pathologic tumor grade or LVI between reporting institutions, thereby masking potential variability in reporting heterogeneity.

4.4 Implications for practice and future research

This study represents a large study of pathologic risk factors for lymph node involvement in endometrial adenocarcinoma. Our results demonstrated associations between lymph node involvement and multiple established pathologic risk factors, including the presence of LVI, higher tumor pathologic stage, higher pathologic tumor grade, and larger tumor size in a nationally representative multi-institutional cohort. The results of this study confirm established lymph node positivity predictors in clinically apparently node negative endometrial adenocarcinoma and assess the composite impact of these pathologic variables on risk of lymph node involvement by nodal drainage location. This information could be helpful in making adjuvant treatment decisions.

5. Conclusions

For patients with limited LN evaluation, pathologic tumor features can be used to estimate the risk of pelvic or paraaortic LN involvement. Multiple established pathologic risk factors predict the risk of the lymph node involvement, and LVI is the strongest predictor. Nomograms generated in this study may help to account for the composite risk of pathologic lymph node positivity in endometrial cancer patients.

AVAILABILITY OF DATA AND MATERIALS

Data from the National Cancer Database (NCDB) are available from the American College of Surgeons upon requests made by affiliate of member institutions. The NCDB data use agreement prohibits the authors from sharing the data.

AUTHOR CONTRIBUTIONS

EMA—Conceptualization, methodology, writing—original draft, and writing—review and editing. ML—Formal analysis. MK—Conceptualization, methodology, supervision,

writing—original draft, and writing—review and editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Institutional Review Board (IRB) at Cedars-Sinai waived standard approval process given use of de-identified data.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.ejgo.net/files/article/1691339037789306880/attachment/Supplementary%20material.docx.

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