Overall survival after surgical staging by lymph node dissection versus sentinel lymph node biopsy in endometrial cancer: a national cancer database study

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HIGHLIGHTS

- Type of lymph node assessment was not associated with overall survival regardless of the lymphadenectomy extent.
- Type of lymph node assessment was not associated with overall survival even in the presence of lymphatic metastasis.
- Type of lymph node assessment was not associated with overall survival in type 1 and type 2 cancer histology.

ABSTRACT

Objective Substituting lymphadenectomy with sentinel lymph node biopsy for staging purposes in endometrial cancer has raised concerns about incomplete nodal resection and detrimental oncological outcomes. Therefore, this study aimed to investigate the association between the type of lymph node assessment and overall survival in endometrial cancer accounting for node status and histology.

Methods Women with stage I–III endometrial cancer who underwent hysterectomy and lymph node assessment from January 2012 to December 2015 were identified in the National Cancer Database. Patients who underwent neoadjuvant therapy, had previous cancer, and whose follow-up was less than 90 days were excluded. Multivariable Cox proportional hazards regression analyses were performed to assess factors associated with overall survival.

Results Of 68 614 patients, 64 796 (94.4%) underwent lymphadenectomy, 1777 (2.6%) underwent sentinel node biopsy only, and 2041 (3.0%) underwent both procedures. On multivariable analysis, neither sentinel lymph node biopsy alone nor sentinel node biopsy followed by lymphadenectomy was associated with significantly different overall survival compared with lymphadenectomy alone (HR 0.92, 95% CI 0.73 to 1.17, and HR 0.91, 95% CI 0.77 to 1.08, respectively). When stratified by lymph node status, sentinel node biopsy alone or followed by lymphadenectomy was not associated with different overall survival, both in patients with negative (HR 0.95, 95% CI 0.73 to 1.24, and HR 1.04, 95% CI 0.85 to 1.27, respectively) or positive (HR 0.91, 95% CI 0.54 to 1.52, and HR 0.77, 95% CI 0.57 to 1.04, respectively) lymph nodes. These findings held true when sentinel node biopsy alone and sentinel node biopsy plus lymphadenectomy groups were merged, and on stratification by histotype (type one vs type 2) or inclusion of only complete lymphadenectomy (at least 10 pelvic nodes and at least one para-aortic node removed). In all analyses, age, Charlson-Deyo score, black race, AJCC pathological T stage, grade, lymphovascular invasion, brachytherapy, and adjuvant chemotherapy were independently associated with overall survival.

Discussion No difference in overall survival was found in patients with endometrial cancer who underwent sentinel node biopsy alone, sentinel node biopsy followed by lymphadenectomy, or lymphadenectomy alone. This observation remained regardless of node status, histotype, and lymphadenectomy extent.

INTRODUCTION

Endometrial cancer is the most frequent gynecological malignancy in western countries,[1] with minimally invasive total hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment representing the standard of care in clinical early-stage disease.[2] Appropriate nodal assessment is essential to identify lymphatic metastasis, which represents the most critical factor for prognosis and treatment planning.[3]

Pelvic and para-aortic lymphadenectomy was the standard procedure for lymph node assessment until the recent implementation of the sentinel lymph node biopsy technique.[2] Based on its diagnostic accuracy, improved perioperative outcomes, and reduced incidence of lower-extremity lymphedema,[4–6] sentinel lymph node biopsy is replacing lymphadenectomy for staging in apparent early-stage endometrial cancer.[2] However, the impact of sentinel lymph node biopsy on oncological outcomes remains under investigation.

Current evidence shows similar recurrence-free and overall survival in patients who underwent lymph node assessment by sentinel node biopsy instead of lymphadenectomy.[7–18] Nevertheless, the available evidence has limitations, such as a significant proportion of patients undergoing sentinel node biopsy followed by lymphadenectomy.[7–18] Moreover, due to most endometrial cancers being diagnosed

at early stages, patients with lymphatic metastasis are usually a small proportion of the study populations.[19] However, this subpopulation merits particular attention as the possible cytoreductive effect of lymphadenectomy has been hypothesized to provide an advantage primarily to these under-represented patients with node positive disease.[7–18] To further investigate oncological outcomes after sentinel node biopsy versus lymphadenectomy, we queried a multicenter database across the United States to examine the association between the type of nodal assessment and overall survival in women with stage I–III endometrial cancer.

METHODS

Study Population

The study data were derived from the National Cancer Database (NCDB), developed by the American College of Surgeons and the American Cancer Society, who have not verified and are not responsible for the analytical or statistical methodology employed, or drawn conclusions. NCDB and collected data characteristics are described in detail elsewhere.[20] Records in the NCDB are de-identified, exempting the study from Institutional Review Board review.

We identified women with a diagnosis of endometrial cancer who underwent total hysterectomy between January 2012 and December 2015. Women with a previous cancer diagnosis, who had received neoadjuvant therapy, and without treatment completion at the reporting facility were excluded. Additionally, we excluded women with American Joint Committee on Cancer (AJCC) stage IV cancer, non-epithelial histology, missing AJCC staging, and less than 90 days of follow-up. The study population was divided into three groups: sentinel lymph node only group, sentinel lymph node plus lymphadenectomy group, and lymphadenectomy only group using the 'Scope of regional lymph node surgery' variable. Patients without lymph node assessment were excluded. The site-specific variables 'Number of removed pelvic nodes' and 'Number of removed para-aortic nodes' were retrieved to assess consistency with the assigned group and sensitivity analysis. We excluded records with a reported number of removed nodes that was not consistent with the type of lymph node assessment: sentinel lymph node only records with more than 10 pelvic or five para-aortic lymph nodes removed; sentinel lymph node plus lymphadenectomy or lymphadenectomy only records with zero nodes removed or missed values.

Study Variables

Demographic characteristics included in the analysis were age at diagnosis, race, Charlson-Deyo score, insurance status, income, education, and facility type. Income and education levels were estimated using the median household income and the percentage of adults graduating from the high school of the patient's zip code area. The Deyo adaptation of the Charlson's comorbidity score was used to measure comorbidities, grouping patients based on no comorbidities, one or at least two comorbidities.[21] Included endometrial cancer characteristics were AJCC stage, AJCC pathological T and N stage, histology classified as type 1 (endometrioid) or type 2 (serous, clear cell, carcinosarcoma, and mixed), International Federation of Gynecology and Obstetrics (FIGO) grade, and presence of lymphovascular invasion. Notably, the NCDB does not allow distinction between macrometastasis, micrometastasis, and isolated tumor cells. Detailed information about surgical treatment and adjuvant therapy were retrieved, excluding surgical approach (laparoscopy, laparotomy, vaginal, or robotic). The surgical approach is captured at a hospital level, and its inclusion would have excluded a significant proportion of cases, introducing bias. The duration of follow-up was calculated from the date of surgery (hysterectomy) to death or last known vital status. In this regard, the NCDB provides information only on overall survival (death from all causes).

Statistical Analysis

Baseline characteristics were summarized using standard descriptive statistics and compared among the three groups defined by the lymph node assessment. Categorical variables were compared with the χ^2, and continuous variables with the Kruskal-Wallis test. The primary outcome was overall survival, estimated using the Kaplan-Meier method for each group of nodal assessment. Cox proportional hazards regression was used to assess associations between overall survival and each study variable. Variables univariately associated with overall survival were included in multivariable analyses.

Sensitivity analyses were conducted to assess the effect of node status and histology on observed associations (Figure 1). Cox proportional hazards regression models were fitted separately according to the presence of nodal metastasis and histology type (1 vs 2). Moreover, all analyses were repeated restricting the group of patients who underwent lymphadenectomy, with or without sentinel node biopsy, to those with at least 10 pelvic nodes and at least one para-aortic node removed, investigating a possible effect of lymphadenectomy extension.[22 23] Analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC), and tests of statistical significance were conducted with a two-tailed α level of 0.05.

RESULTS

Population Characteristics

A total of 68 614 women represented the study sample: 64 796 (94.4%) patients underwent lymphadenectomy only, 1777 (2.6%) had sentinel node biopsy only, and 2041 (3.0%) underwent both procedures (2014/2041 (98.7%) patients at the same time and 27/2041 (1.3%) in separate procedures) (Online supplemental figure 1). Demographic, clinical, pathological, and treatment characteristics are summarized in Online supplemental table 1. When comparisons were made among the three groups, all characteristics were significantly different. Patients who underwent sentinel node biopsy only reported a higher proportion of AJCC stage IA, type 1 histology, and grade 1–2 endometrial cancer than the other two groups. Consistently, adjuvant therapy was adopted in a lower proportion of these patients.

Overall Survival

For the entire study population, the median follow-up was 34.5 (IQR 22.1–48.2) months. The 5 year overall survival was 82.1% (95% CI 81.6% to 82.6%) for the entire population, 90.9% (95% CI 85.6% to 94.4%) in the sentinel node biopsy only group, 81.9% (95% CI 81.3% to 82.4%) in the lymphadenectomy group, and 88.1% (95% CI 83.5% to 90.3%) in patients who underwent both procedures. Factors associated with overall survival in univariate analyses are shown in Online supplemental table 2. On univariate analysis, both

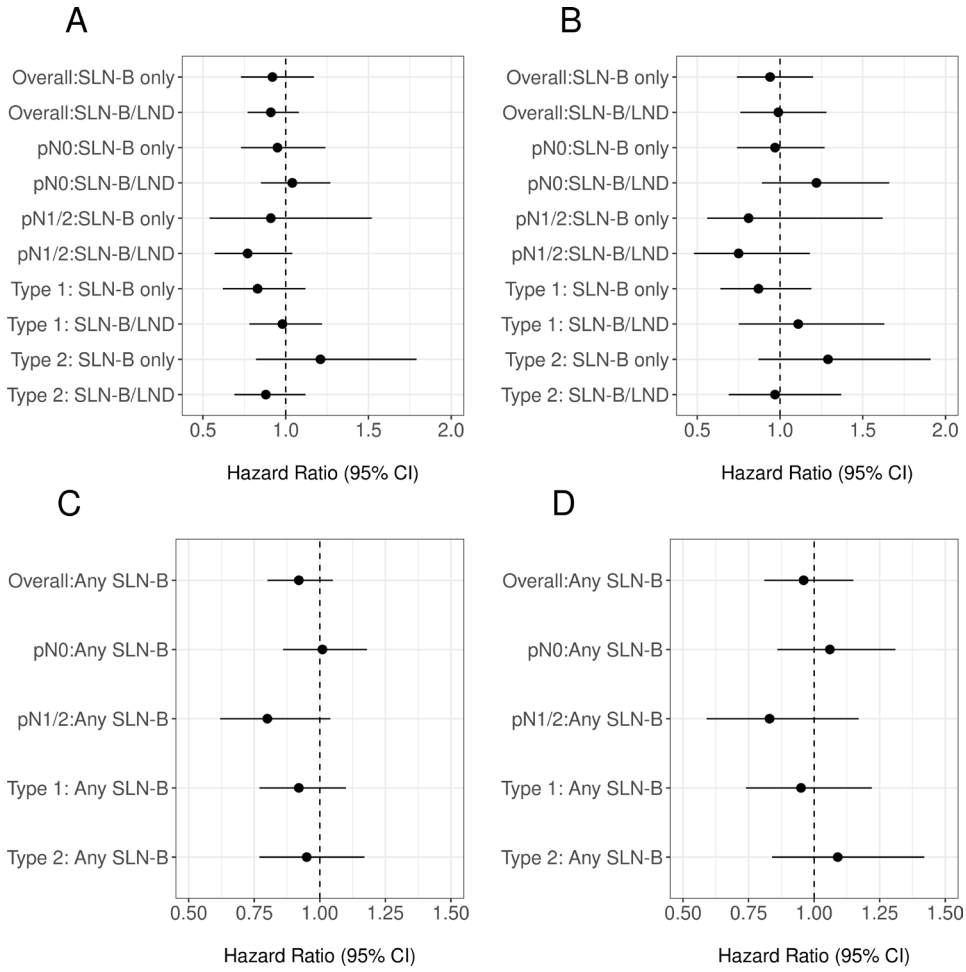

Figure 1 The forest plots show the hazard ratios, and associated 95% CIs, estimating the risk of an event (death from any cause) in each group compared with that of the reference group: lymphadenectomy (LND) only. Hazard ratios lower than one represent a risk of events lower than that of the reference group (left), whereas hazard ratios higher than one represent a higher risk of events (right). Hazard ratios were estimated with multivariable Cox proportional hazard regression models in the entire cohort (A and C) and in the group of patients who underwent LND, with or without previous sentinel lymph node biopsy (SLN-B), with at least 10 pelvic nodes and one para-aortic node removed (B and D). LND, lymphadenectomy; SLN-B, sentinel lymph node biopsy; SLN-B/LND, sentinel lymph node biopsy and lymphadenectomy; any SLN-B, SLN-B merged with SLN-B/LND; type 1, endometrioid histology; type 2, serous, clear cell, carcinosarcoma, and mixed histologies.

sentinel lymph node biopsy only and sentinel node biopsy plus lymphadenectomy were associated with significantly better overall survival than lymphadenectomy only (HR 0.52, 95% CI 0.41 to 0.66, and HR 0.82, 95% CI 0.70 to 0.97, respectively).

Multivariable Analysis Stratified By Lymph Node Status, With And Without Restriction

Multivariable Cox proportional hazards regression models for the entire population and stratified according to the presence or absence of nodal metastasis (Online supplemental figure 2A) are reported in Table 1. Neither sentinel lymph node biopsy alone nor sentinel lymph node biopsy followed by lymphadenectomy was associated with significantly different overall survival compared with lymphadenectomy alone (HR 0.92, 95% CI 0.73 to 1.17, and HR 0.91, 95% CI 0.77 to 1.08, respectively). When stratified by lymph node status, sentinel node biopsy alone and sentinel node biopsy plus lymphadenectomy were not associated with a different overall survival than lymphadenectomy, both in patients with negative (HR 0.95, 95% CI 0.73 to 1.24, and HR 1.04, 95% CI 0.85 to 1.27, respectively) and positive lymph nodes (HR 0.91, 95% CI 0.54 to 1.52, and HR 0.77, 95% CI 0.57 to 1.04, respectively) (Figure 1A).

The analysis was repeated restricting the group of patients who underwent lymphadenectomy to those with at least 10 pelvic nodes and at least one para-aortic node removed (Online supplemental figure 2B), as reported in Table 2. Sentinel node biopsy only and sentinel node biopsy plus lymphadenectomy remained unassociated with overall survival compared with lymphadenectomy alone (HR 0.94, 95% CI 0.74 to 1.20, and HR 0.99, 95% CI 0.76 to 1.28, respectively). This held true both in patients with negative (HR 0.97, 95% CI 0.74 to 1.27, and HR 1.22, 95% CI 0.89 to 1.66, respectively, for sentinel node biopsy alone and sentinel node biopsy plus lymphadenectomy vs lymphadenectomy only) and positive lymph nodes (HR 0.96, 95% CI 0.56 to 1.62, and HR 0.75, 95% CI 0.48 to 1.18, respectively, for sentinel node biopsy alone and sentinel node biopsy plus lymphadenectomy vs lymphadenectomy only) (Figure 1B).

Table 1 Multivariable Cox proportional hazards regression models for overall survival, in the entire group and stratified by lymph node status

		Overall		pN0		pN1/2	
Variable	**Level**	**Multivariable hazard ratio (95% CI)***	**P value**	**Multivariable hazard ratio (95% CI)***	**P value**	**Multivariable hazard ratio (95% CI)***	**P value**
LN surgery	LND only	1.0 reference		1.0 reference		1.0 reference	
	SLN-B only	0.92 (0.73 to 1.17)	0.494	0.95 (0.73 to 1.24)	0.692	0.91 (0.54 to 1.52)	0.710
	SLN-B/LND	0.91 (0.77 to 1.08)	0.271	1.04 (0.85 to 1.27)	0.706	0.77 (0.57 to 1.04)	0.084
Age	Per 10 years	1.61 (1.56 to 1.67)	<0.001	1.70 (1.64 to 1.77)	<0.001	1.38 (1.30 to 1.47)	<0.001
Race	White	1.0 reference		1.0 reference		1.0 reference	
	Black	1.45 (1.36 to 1.56)	<0.001	1.52 (1.40 to 1.66)	<0.001	1.33 (1.19 to 1.49)	<0.001
	Other	0.94 (0.83 to 1.07)	0.368	0.93 (0.79 to 1.10)	0.415	0.92 (0.74 to 1.15)	0.467
	Unknown	0.97 (0.75 to 1.25)	0.821	0.91 (0.66 to 1.27)	0.583	1.07 (0.72 to 1.60)	0.733
Charlson-Deyo score	0	1.0 reference		1.0 reference		1.0 reference	
	1	1.21 (1.14 to 1.28)	<0.001	1.28 (1.20 to 1.37)	<0.001	1.09 (0.99 to 1.21)	0.096
	≥2	1.66 (1.52 to 1.82)	<0.001	1.90 (1.71 to 2.11)	<0.001	1.25 (1.06 to 1.49)	0.010
Insurance status	Private insurance	1.0 reference		1.0 reference		1.0 reference	
	Not insured	1.31 (1.14 to 1.52)	<0.001	1.26 (1.04 to 1.52)	0.019	1.29 (1.03 to 1.62)	0.028
	Medicaid	1.24 (1.10 to 1.39)	<0.001	1.23 (1.06 to 1.43)	0.008	1.13 (0.93 to 1.38)	0.211
	Medicare	1.13 (1.06 to 1.20)	<0.001	1.14 (1.06 to 1.23)	<0.001	1.10 (0.98 to 1.23)	0.109
	Other government	1.0 (0.76 to 1.30)	0.984	0.95 (0.67 to 1.35)	0.782	1.12 (0.74 to 1.71)	0.584
	Unknown	1.19 (0.94 to 1.51)	0.153	1.14 (0.84 to 1.55)	0.400	1.21 (0.82 to 1.78)	0.334
Income	≥$63333	1.0 reference		1.0 reference		1.0 reference	
	$50354–63332	1.04 (0.97 to 1.12)	0.231	1.10 (1.01 to 1.19)	0.030	0.96 (0.85 to 1.09)	0.531
	$40227–50353	1.05 (0.97 to 1.14)	0.200	1.11 (1.01 to 1.22)	0.031	0.94 (0.82 to 1.08)	0.387
	<$40227	1.11 (1.01 to 1.21)	0.025	1.17 (1.05 to 1.30)	0.006	1.01 (0.87 to 1.18)	0.859
	Unknown	0.54 (0.28 to 1.04)	0.065	0.56 (0.21 to 1.51)	0.253	0.56 (0.23 to 1.35)	0.194
Education (% no HSD)	≥17.6%	1.05 (0.95 to 1.15)	0.326	1.01 (0.90 to 1.14)	0.816	1.07 (0.90 to 1.26)	0.441
	10.9%–17.5%	1.07 (0.99 to 1.16)	0.104	1.04 (0.94 to 1.15)	0.451	1.09 (0.94 to 1.26)	0.261
	6.3%–10.8%	1.14 (1.06 to 1.22)	<0.001	1.13 (1.04 to 1.23)	0.006	1.13 (0.99 to 1.28)	0.074
	<6.3%	1.0 reference		1.0 reference		1.0 reference	
	Unknown	2.10 (1.05 to 4.21)	0.037	2.25 (0.81 to 6.25)	0.122	1.74 (0.65 to 4.65)	0.270
Facility type	Community	1.24 (1.09 to 1.42)	0.001	1.29 (1.10 to 1.53)	0.002	1.13 (0.90 to 1.41)	0.287
	Comprehensive community	1.13 (1.07 to 1.19)	<0.001	1.16 (1.08 to 1.23)	<0.001	1.07 (0.98 to 1.18)	0.150
	Academic	1.0 reference		1.0 reference		1.0 reference	
	Integrated network	1.08 (1.00 to 1.16)	0.040	1.13 (1.03 to 1.23)	0.007	1.0 (0.88 to 1.14)	0.968
	Unknown	2.42 (1.84 to 3.18)	<0.001	2.55 (1.81 to 3.59)	<0.001	1.99 (1.27 to 3.14)	0.003

Continued

Table 1 Continued

Variable	Level	Overall		pN0		pN1/2	
		Multivariable hazard ratio (95% CI)*	P value	Multivariable hazard ratio (95% CI)*	P value	Multivariable hazard ratio (95% CI)*	P value
AJCC pathological N stage	pN0	1.0 reference		–		–	
	pN1	1.65 (1.53 to 1.77)	<0.001	–		1.0 reference	
	pN2	1.73 (1.59 to 1.89)	<0.001	–		1.06 (0.97 to 1.15)	0.241
AJCC pathological T stage	pT1	1.18 (0.88 to 1.58)	0.263	1.07 (0.77 to 1.49)	0.691	1.78 (0.97 to 3.27)	0.063
	pT1A	1.0 reference		1.0 reference		1.0 reference	
	pT1B	1.69 (1.58 to 1.80)	<0.001	1.65 (1.53 to 1.78)	<0.001	1.43 (1.21 to 1.68)	<0.001
	pT2	2.30 (2.12 to 2.49)	<0.001	2.13 (1.93 to 2.35)	<0.001	2.10 (1.78 to 2.47)	<0.001
	pT3/3A/3B	3.21 (2.97 to 3.47)	<0.001	3.06 (2.77 to 3.39)	<0.001	2.91 (2.50 to 3.39)	<0.001
Grade	Well/moderately	1.0 reference		1.0 reference		1.0 reference	
	Poorly/undifferentiated	2.08 (1.94 to 2.22)	<0.001	2.03 (1.87 to 2.19)	<0.001	2.10 (1.84 to 2.40)	<0.001
	Unknown	1.55 (1.45 to 1.66)	<0.001	1.44 (1.33 to 1.56)	<0.001	1.81 (1.57 to 2.08)	<0.001
Lymph vascular invasion	Not present	1.0 reference		1.0 reference		1.0 reference	
	Present	1.63 (1.54 to 1.73)	<0.001	1.71 (1.60 to 1.83)	<0.001	1.33 (1.19 to 1.49)	<0.001
	Unknown	1.15 (1.04 to 1.28)	0.009	1.13 (1.0 to 1.27)	0.055	1.04 (0.85 to 1.28)	0.713
Histotype	1	1.0 reference		1.0 reference		1.0 reference	
	2	1.63 (1.54 to 1.73)	<0.001	1.71 (1.59 to 1.84)	<0.001	1.44 (1.31 to 1.60)	<0.001
Adjuvant chemotherapy	No chemotherapy received	1.0 reference		1.0 reference		1.0 reference	
	Chemotherapy received	0.81 (0.76 to 0.86)	<0.001	0.85 (0.79 to 0.92)	<0.001	0.68 (0.61 to 0.75)	<0.001
Adjuvant hormone therapy	No hormone therapy received	1.0 reference		1.0 reference		1.0 reference	
	Hormone therapy received	1.12 (0.84 to 1.49)	0.442	1.01 (0.66 to 1.53)	0.974	1.09 (0.74 to 1.63)	0.658
	Unknown	1.07 (0.91 to 1.25)	0.441	1.12 (0.93 to 1.36)	0.240	1.0 (0.75 to 1.33)	0.997
Adjuvant radiation therapy	No radiation	1.0 reference		1.0 reference		1.0 reference	
	Brachytherapy	0.81 (0.75 to 0.86)	<0.001	0.85 (0.79 to 0.92)	<0.001	0.63 (0.53 to 0.74)	<0.001
	External beam	0.88 (0.83 to 0.94)	<0.001	1.01 (0.92 to 1.10)	0.876	0.73 (0.67 to 0.81)	<0.001
	Other	0.81 (0.57 to 1.14)	0.224	0.90 (0.58 to 1.40)	0.643	0.68 (0.38 to 1.20	0.181

*Hazard ratios estimate the risk of an event (death for any cause) in each group compared with that of the reference group. Hazard ratios lower than one represent a risk of events lower than the reference group, whereas hazard ratios higher than one represent a higher risk of events.
AJCC, American Joint Committee on Cancer; HSD, high-school diploma; LN, lymph node; LND, lymphadenectomy; SLN-B, sentinel lymph node biopsy.

Table 2 Multivariable Cox proportional hazards regression models for overall survival limited to patients who underwent LND with at least 10 pelvic nodes and at least one para-aortic node removed, in the entire group and stratified by lymph node status

		Overall		pN0		pN1/2	
Variable	**Level**	**Multivariable hazard ratio (95% CI)***	**P value**	**Multivariable hazard ratio (95% CI)***	**P value**	**Multivariable hazard ratio (95% CI)***	**P value**
LN surgery	LND only	1.0 reference		1.0 reference		1.0 reference	
	SLN-B only	0.94 (0.74 to 1.20)	0.637	0.97 (0.74 to 1.27)	0.807	0.96 (0.56 to 1.62)	0.864
	SLN-B/LND	0.99 (0.76 to 1.28)	0.918	1.22 (0.89 to 1.66)	0.217	0.75 (0.48 to 1.18)	0.219
Age	Per 10 years	1.59 (1.50 to 1.68)	<0.001	1.67 (1.56 to 1.80)	<0.001	1.42 (1.29 to 1.57)	<0.001
Race	White	1.0 reference		1.0 reference		1.0 reference	
	Black	1.49 (1.33 to 1.68)	<0.001	1.62 (1.39 to 1.89)	<0.001	1.40 (1.16 to 1.68)	<0.001
	Other	0.98 (0.80 to 1.21)	0.879	1.07 (0.83 to 1.39)	0.604	0.86 (0.61 to 1.22)	0.400
	Unknown	0.97 (0.63 to 1.49)	0.873	0.80 (0.44 to 1.45)	0.455	1.40 (0.74 to 2.64)	0.306
Charlson-Deyo score	0	1.0 reference		1.0 reference		1.0 reference	
	1	1.22 (1.11 to 1.35)	<0.001	1.34 (1.19 to 1.51)	<0.001	1.07 (0.91 to 1.25)	0.443
	≥2	1.56 (1.31 to 1.85)	<0.001	1.57 (1.27 to 1.95)	<0.001	1.54 (1.15 to 2.04)	0.003
Insurance status	Private Insurance	1.0 reference		1.0 reference		1.0 reference	
	Not insured	1.35 (1.07 to 1.71)	0.010	1.61 (1.19 to 2.17)	0.002	1.08 (0.75 to 1.57)	0.643
	Medicaid	1.37 (1.13 to 1.66)	0.001	1.28 (0.98 to 1.68)	0.074	1.39 (1.05 to 1.83)	0.021
	Medicare	1.15 (1.03 to 1.28)	0.012	1.23 (1.07 to 1.41)	0.003	1.05 (0.88 to 1.26)	0.596
	Other government	1.12 (0.72 to 1.74)	0.625	0.97 (0.53 to 1.76)	0.907	1.51 (0.77 to 2.95)	0.233
	Unknown	0.98 (0.66 to 1.47)	0.938	0.88 (0.47 to 1.65)	0.690	0.99 (0.59 to 1.68)	0.976
Income	≥$63333	1.0 reference		1.0 reference		1.0 reference	
	$50354–63332	1.0 (0.89 to 1.13)	0.947	1.09 (0.94 to 1.26)	0.264	0.92 (0.75 to 1.12)	0.396
	$40227–50353	1.08 (0.95 to 1.23)	0.226	1.13 (0.96 to 1.32)	0.134	1.0 (0.81 to 1.23)	0.962
	<$40227	1.06 (0.91 to 1.23)	0.490	1.18 (0.97 to 1.43)	0.100	0.93 (0.73 to 1.19)	0.575
	Unknown	0.56 (0.18 to 1.75)	0.318	0.78 (0.11 to 5.54)	0.801	0.58 (0.14 to 2.37)	0.447
Education (% no HSD)	≥17.6%	1.06 (0.91 to 1.25)	0.440	1.01 (0.82 to 1.24)	0.929	1.06 (0.82 to 1.37	0.646
	10.9%–17.5%	1.06 (0.93 to 1.22)	0.400	1.06 (0.89 to 1.26)	0.530	0.99 (0.79 to 1.24)	0.898
	6.3%–10.8%	1.17 (1.04 to 1.32)	0.008	1.23 (1.06 to 1.43)	0.006	1.05 (0.86 to 1.29)	0.620
	<6.3%	1.0 reference		1.0 reference		1.0 reference	
	Unknown	2.71 (0.83 to 8.88)	0.099	2.54 (0.34 to 18.83)	0.362	1.62 (0.34 to 7.72	0.548
Facility type	Community	1.15 (0.93 to 1.43)	0.189	1.28 (0.97 to 1.69)	0.081	1.02 (0.73 to 1.43)	0.914
	Comprehensive community	1.05 (0.95 to 1.15)	0.346	1.10 (0.98 to 1.23)	0.112	0.99 (0.85 to 1.16)	0.926
	Academic	1.0 reference		1.0 reference		1.0 reference	
	Integrated network	0.95 (0.84 to 1.07)	0.356	1.01 (0.87 to 1.17)	0.943	0.86 (0.71 to 1.05)	0.146
	Unknown	2.09 (1.29 to 3.39)	0.003	1.60 (0.77 to 3.30)	0.207	2.50 (1.29 to 4.85)	0.007

Continued

Table 2 Continued

Variable	Level	Overall		pN0		pN1/2	
		Multivariable hazard ratio (95% CI)*	P value	Multivariable hazard ratio (95% CI)*	P value	Multivariable hazard ratio (95% CI)*	P value
AJCC pathological N stage	pN0	1.0 reference		–		–	
	pN1	1.72 (1.52 to 1.94)	<0.001	–		1.0 reference	
	pN2	1.91 (1.69 to 2.17)	<0.001	–		1.14 (0.99 to 1.30)	0.069
AJCC pathological T stage	pT1	1.06 (0.61 to 1.84)	0.824	1.0 (0.54 to 1.88)	0.991	1.34 (0.42 to 4.25)	0.624
	pT1A	1.0 reference		1.0 reference		1.0 reference	
	pT1B	1.62 (1.45 to 1.82)	<0.001	1.58 (1.39 to 1.80)	<0.001	1.53 (1.19 to 1.97)	<0.001
	pT2	2.29 (2.00 to 2.61)	<0.001	2.22 (1.87 to 2.63)	<0.001	2.18 (1.69 to 2.81)	<0.001
	pT3/3A/3B	2.94 (2.58 to 3.33)	<0.001	3.10 (2.61 to 3.70)	<0.001	2.71 (2.14 to 3.44)	<0.001
Grade	Well/moderately	1.0 reference					
	Poorly/undifferentiated	2.0 (1.78 to 2.24)	<0.001	1.93 (1.68 to 2.22)	<0.001	2.13 (1.73 to 2.62)	<0.001
	Unknown	1.66 (1.47 to 1.87)	<0.001	1.58 (1.37 to 1.83)	<0.001	1.83 (1.47 to 2.29)	<0.001
Lymph vascular invasion	Not present	1.0 reference		1.0 reference		1.0 reference	
	Present	1.53 (1.39 to 1.69)	<0.001	1.61 (1.43 to 1.80)	<0.001	1.37 (1.15 to 1.64)	<0.001
	Unknown	1.05 (0.88 to 1.26)	0.567	1.04 (0.84 to 1.29)	0.732	0.99 (0.71 to 1.38)	0.952
Histology	1	1.0 reference		1.0 reference		1.0 reference	
	2	1.62 (1.47 to 1.79)	<0.001	1.62 (1.43 to 1.84)	<0.001	1.59 (1.37 to 1.86)	<0.001
Adjuvant chemotherapy	No chemotherapy received	1.0 reference		1.0 reference		1.0 reference	
	Chemotherapy received	0.87 (0.78 to 0.96)	0.006	0.89 (0.78 to 1.02)	0.082	0.79 (0.65 to 0.94)	0.010
Adjuvant hormone therapy	No hormone therapy received	1.0 reference		1.0 reference		1.0 reference	
	Hormone therapy received	1.22 (0.74 to 2.0)	0.437	0.77 (0.36 to 1.61)	0.482	1.77 (0.90 to 3.46)	0.099
	Unknown	1.02 (0.78 to 1.33)	0.895	1.03 (0.73 to 1.44)	0.882	0.99 (0.65 to 1.51)	0.973
Adjuvant radiation therapy	No radiation	1.0 reference		1.0 reference		1.0 reference	
	Brachytherapy	0.79 (0.71 to 0.88)	<0.001	0.84 (0.74 to 0.95)	0.004	0.67 (0.53 to 0.86)	0.002
	External beam	0.82 (0.74 to 0.91)	<0.001	0.84 (0.72 to 0.99)	0.033	0.78 (0.67 to 0.91)	0.001
	Other	0.78 (0.43 to 1.41)	0.412	0.45 (0.17 to 1.21)	0.114	1.22 (0.57 to 2.60)	0.609

*Hazard ratios estimate the risk of an event (death for any cause) in each group compared with that of the reference group. Hazard ratios lower than one represent a risk of events lower than the reference group, whereas hazard ratios higher than one represent a higher risk of events.
AJCC, American Joint Committee on Cancer; HSD, high-school diploma; LN, lymph node; LND, lymphadenectomy; SLN-B, sentinel lymph node biopsy.

The analyses following merging sentinel node biopsy only and sentinel node biopsy plus lymphadenectomy (Online supplemental figure 2C) into a single group are reported in Online supplemental tables 3 and 4. Any sentinel node biopsy was not associated with different overall survival compared with lymphadenectomy, both in the entire study population (HR 0.92, 95% CI 0.80 to 1.05) (Figure 1C) and after restriction to patients with at least 10 pelvic nodes and at least one para-aortic node removed (HR 0.96, 95% CI 0.81 to 1.15) (Figure 1D). These findings held true both in negative and positive nodes (Figure 1C,D). In multivariable analyses, older age, black race (vs white), Charlson-Deyo score ≥2 (vs 0), higher AJCC pathological T stage (vs pT1A), grade 3 (vs 1–2), presence of lymphovascular invasion (vs absent), and type 2 histology (vs type 1) were independently associated with worse overall survival. Conversely, receipt of adjuvant chemotherapy was independently associated with improved overall survival, but not in patients with negative nodes following removal of at least 10 pelvic nodes and at least one para-aortic node.

Multivariable Analysis Stratified By Histotype, With and Without Restriction

Multivariable Cox proportional hazards regression models stratified by histotype (type 1 vs type 2; Online supplemental figure 2D) are reported in Table 3. On multivariable analysis, neither sentinel node biopsy alone nor sentinel node biopsy plus lymphadenectomy were associated with a different overall survival compared with lymphadenectomy alone both in type 1 (HR 0.83, 95% CI 0.62 to 1.12, and HR 0.98, 95% CI 0.78 to 1.22, respectively) and type 2 endometrial cancer (HR 1.21, 95% CI 0.82 to 1.79, and HR 0.88, 95% CI 0.69 to 1.12, respectively) (Figure 1A). The lack of an association (Table 4 and Figure 1B) remained after restricting the analysis to patients who underwent lymphadenectomy with removal of at least 10 pelvic nodes and at least one para-aortic node (Online supplemental figure 2E).

After merging into a single group patients with sentinel node biopsy only and sentinel node biopsy plus lymphadenectomy (Online supplemental figure 2F), any sentinel node biopsy was not associated with a different overall survival compared with lymphadenectomy both in type 1 (HR 0.92, 95% CI 0.77 to 1.10) and type 2 histology (HR 0.95, 95% CI 0.77 to 1.17) (Online supplemental table 5 and Figure 1C). Lack of associations was observed after restricting the analysis to patients with removal of at least 10 pelvic nodes and at least one para-aortic node both in type 1 (HR 0.95, 95% CI 0.74 to 1.22) and type 2 histology (HR 1.09, 95% CI 0.84 to 1.42) (Online supplemental table 6 and Figure 1D).

In all multivariable analyses, older age, black race (vs white), Charlson-Deyo score ≥1 (vs 0), higher AJCC pathological stage, and the presence of lymphovascular invasion (vs absence) were independently associated with worse overall survival. Conversely, the receipt of adjuvant chemotherapy and any radiotherapy were independently associated with improved overall survival, but not in the subset of patients with removal of at least 10 pelvic nodes and at least one para-aortic node (chemotherapy in type 2 and radiotherapy in type 1). Uninsured status, Medicaid, and Medicare (vs private insurance), low income, and non-academic institutions were significantly associated with worse overall survival only in patients with type 1 histology. This association was absent in the restricted analysis for non-academic institutions and worse overall survival in patients with type 1 histology.

DISCUSSION

Summary of Main Results

An association between the type of nodal assessment and overall survival in endometrial cancer was not observed, even in patients with lymphatic metastases, and regardless of histotype. An improved overall survival with lymphadenectomy was not observed, even including only patients with removal of at least 10 pelvic nodes and at least one para-aortic node. Conversely, factors known to be associated with overall survival were confirmed prognostic factors.

Results in the Context of Published Literature

Prospective studies have confirmed the high diagnostic accuracy of sentinel lymph node algorithms for nodal metastasis, leading to expansion endorsed by the National Comprehensive Cancer Network guidelines.[2 24–26] However, substituting lymphadenectomy with sentinel node biopsy has raised concerns about the risk of incomplete nodal resection with possible detrimental outcomes. To date, available evidence reported similar recurrence-free survival and overall survival in patients staged by sentinel node biopsy alone versus lymphadenectomy, regardless of the risk category.[7–10 12–15] However, important limitations are present, such as retrospective designs, short follow-ups, relatively small numbers of patients, a significant proportion of cases with sentinel node biopsy followed by lymphadenectomy, and the limited power in patients with lymphatic metastasis.[7–18]

Our study aimed to overcome some of these limitations by including a robust number of patients from diverse institutions represented in a national database, accurately representing the proportion of patients with lymphatic metastasis, and accounting for the performance of full lymphadenectomy after sentinel node biopsy. Moreover, we accounted for the extent of lymphadenectomy by restricting the analysis to those patients who underwent removal of at least 10 pelvic nodes and at least one para-aortic node, as this factor is thought to regulate the association between lymphadenectomy and oncological outcomes,[22 23] a factor that was not considered in a recent NCDB analyses.[19] With these methodological advantages, our results are consistent with previous observations and additionally support a similar overall survival between sentinel node biopsy and lymphadenectomy regardless of nodal status, histotype, and the number of removed lymph nodes during lymphadenectomy.

Strengths and Weaknesses

The strengths of our study include the large sample size, the representation of patients with positive nodes, and the account of the extent of lymphadenectomy, and its performance after sentinel lymph node biopsy. Nonetheless, limitations should be considered. Differences between lymph node assessment groups for known risk factors stress the possible presence of unknown confounders associated with both lymph node assessment and overall survival. Notably, limited overlap in population characteristics impeded the adoption of propensity score methodologies. The inverse probability weighting methodology generated

Table 3 Multivariable Cox proportional hazards regression models for overall survival stratified by histotype

		Histology 1		Histology 2	
Variable	**Level**	**Multivariable hazard ratio (95% CI)***	**P value**	**Multivariable hazard ratio (95% CI)***	**P value**
LN surgery	ALND only	1.0 reference		1.0 reference	
	SLN biopsy only	0.83 (0.62 to 1.12)	0.225	1.21 (0.82 to 1.79)	0.330
	SLN and ALND	0.98 (0.78 to 1.22)	0.829	0.88 (0.69 to 1.12)	0.298
Age	Per 10 years	1.74 (1.66 to 1.81)	<0.001	1.44 (1.37 to 1.51)	<0.001
Race	White	1.0 reference		1.0 reference	
	Black	1.52 (1.36 to 1.69)	<0.001	1.41 (1.29 to 1.54)	<0.001
	Other	0.92 (0.77 to 1.10)	0.372	0.96 (0.80 to 1.16)	0.677
	Unknown	1.14 (0.82 to 1.60)	0.433	0.84 (0.57 to 1.24)	0.391
Charlson-Deyo score	0	1.0 reference		1.0 reference	
	1	1.26 (1.17 to 1.37)	<0.001	1.16 (1.07 to 1.26)	<0.001
	≥2	1.97 (1.75 to 2.21)	<0.001	1.40 (1.22 to 1.61)	<0.001
Insurance status	Private insurance	1.0 reference		1.0 reference	
	Not insured	1.54 (1.28 to 1.85)	<0.001	1.02 (0.81 to 1.29)	0.851
	Medicaid	1.36 (1.15 to 1.61)	<0.001	1.09 (0.92 to 1.29)	0.338
	Medicare	1.15 (1.05 to 1.26)	0.002	1.08 (0.99 to 1.19)	0.087
	Other government	0.99 (0.69 to 1.44)	0.967	1.04 (0.71 to 1.53)	0.833
	Unknown	0.95 (0.67 to 1.35)	0.774	1.47 (1.06 to 2.03)	0.022
Income	≥$63 333	1.0 reference		1.0 reference	
	$50 354–63 332	1.08 (0.98 to 1.19)	0.108	1.03 (0.93 to 1.15)	0.516
	$40 227–50 353	1.13 (1.01 to 1.25)	0.027	1.01 (0.90 to 1.13)	0.909
	< $40 227	1.25 (1.11 to 1.42)	<0.001	1.01 (0.89 to 1.15)	0.839
	Unknown	0.79 (0.34 to 1.87)	0.166	0.25 (0.08 to 0.79)	0.017
Education (% no HSD)	17.6% or more	1.0 (0.88 to 1.14)	0.976	1.05 (0.91 to 1.20)	0.531
	10.9%–17.5%	1.07 (0.96 to 1.20)	0.245	1.03 (0.91 to 1.16)	0.654
	6.3%–10.8%	1.15 (1.04 to 1.27)	0.005	1.11 (1.00 to 1.24)	0.049
	Less than 6.3%	1.0 reference		1.0 reference	
	Unknown	0.79 (0.34 to 1.87)	0.597	3.64 (1.10 to 12.03)	0.034
Facility type	Community	1.25 (1.05 to 1.48)	0.013	1.17 (0.95 to 1.44)	0.144
	Comprehensive community	1.11 (1.03 to 1.20)	0.006	1.14 (1.06 to 1.24)	<0.001
	Academic	1.0 reference		1.0 reference	
	Integrated network	1.13 (1.03 to 1.25)	0.013	1.0 (0.90 to 1.10)	0.975
	Unknown	3.38 (2.48 to 4.62)	<0.001	1.18 (0.64 to 2.18)	0.588
AJCC pathological N stage	pN0	1.0 reference		1.0 reference	
	pN1	1.74 (1.56 to 1.94)	<0.001	1.63 (1.49 to 1.80)	<0.001
	pN2	2.11 (1.84 to 2.43)	<0.001	1.62 (1.45 to 1.81)	<0.001
AJCC pathological T stage	pT1	1.27 (0.88 to 1.83)	0.210	0.97 (0.61 to 1.55)	0.890
	pT1A	1.0 reference		1.0 reference	
	pT1B	1.70 (1.55 to 1.85)	<0.001	1.65 (1.49 to 1.83)	<0.001
	pT2	2.54 (2.26 to 2.85)	<0.001	2.06 (1.84 to 2.31)	<0.001
	pT3/3A/3B	3.80 (3.39 to 4.27)	<0.001	2.79 (2.51 to 3.10)	<0.001
Grade	Well/moderately	1.0 reference		1.0 reference	
	Poorly/undifferentiated	2.29 (2.12 to 2.48)	<0.001	2.15 (1.86 to 2.48)	<0.001
	Unknown	1.24 (1.13 to 1.35)	<0.001	2.12 (1.82 to 2.48)	<0.001

Continued

Table 3 Continued

Variable	Level	Histology 1		Histology 2	
		Multivariable hazard ratio (95% CI)*	P value	Multivariable hazard ratio (95% CI)*	P value
Lymph vascular invasion	Not present	1.0 reference		1.0 reference	
	Present	1.67 (1.54 to 1.81)	<0.001	1.55 (1.42 to 1.69)	<0.001
	Unknown	1.11 (0.96 to 1.29)	0.147	1.14 (0.98 to 1.32)	0.099
Adjuvant chemotherapy	No chemotherapy received	1.0 reference		1.0 reference	
	Chemotherapy received	0.78 (0.70 to 0.86)	<0.001	0.77 (0.71 to 0.84)	<0.001
Adjuvant hormone therapy	No hormone therapy received	1.0 reference		1.0 reference	
	Hormone therapy received	1.05 (0.74 to 1.48)	0.784	0.97 (0.57 to 1.63)	0.894
	Unknown	1.07 (0.86 to 1.33)	0.563	1.05 (0.83 to 1.32)	0.709
Adjuvant radiation therapy	No radiation	1.0 reference		1.0 reference	
	Brachytherapy	0.83 (0.76 to 0.91)	<0.001	0.74 (0.67 to 0.82)	<0.001
	External beam	0.87 (0.79 to 0.95)	0.003	0.84 (0.77 to 0.92)	<0.001
	Other	0.93 (0.57 to 1.52)	0.768	0.71 (0.43 to 1.16)	0.171

*Hazard ratios estimate the risk of an event (death for any cause) in each group compared with that of the reference group. Hazard ratios lower than one represent a risk of events lower than the reference group, whereas hazard ratios higher than one represent a higher risk of events.
AJCC, American Joint Committee on Cancer; HSD, high-school diploma; LN, lymph node; LND, lymphadenectomy; SLN-B, sentinel lymph node biopsy.

extreme probabilities and marked covariate imbalance. The propensity score matching would have excluded a significant proportion of unmatched individuals, losing precision and generalizability.[27]

Additionally, the lack of details in the NCDB could have led to bias. This could be first introduced via the omission of details such as type of lymphatic metastasis and surgical approach, as well as pertinent practice demographics during the early adoption period of sentinel node techniques. Next, the number of cases in which the sentinel node biopsy was followed by a second surgery for completing lymphadenectomy was too small to account for these in the analysis. Finally, it was not possible to identify patients who underwent lymphadenectomy for grossly enlarged lymph nodes. These patients are expected to be included in the lymphadenectomy group, potentially representing a subset with a worse prognosis.

Implications for Practice and Future Research

Two randomized controlled trials showed no benefit of full pelvic lymphadenectomy in apparent early-stage endometrial cancer.[28 29] In contrast, retrospective studies have reported improved survival in patients who underwent full (more than 10 pelvic and more than one para-aortic) or extended lymphadenectomy.[23 30 31] All these studies are limited by a staging bias: false-negative cases increase with limited or absent lymphadenectomy. These false-negative patients will receive inadequate adjuvant therapy, leading to worse overall survival.[22 23] In this regard, sentinel node biopsy allows us for the first time to separate the possible therapeutic role from the staging role of lymphadenectomy, focusing on the actual population of patients who may benefit from it, patients with FIGO 2009 IIIC endometrial cancer. This serves to clarify whether completing lymphadenectomy after positive sentinel node biopsy is necessary.

We noted no difference in overall survival based on the type of nodal assessment among patients with positive nodes and type 2 histology, even in those who underwent removal of at least 10 pelvic nodes and at least one para-aortic node. Therefore, our results do not support a therapeutic role of lymphadenectomy in these patients. The omission of 'backup' lymphadenectomy in patients with positive sentinel lymph node or with type 2 histology appears safe.[32] Interestingly, this observation in patients with endometrial cancer and lymphatic metastasis is consistent with the lack of benefit of completion lymphadenectomy reported for melanoma and breast cancer.[33 34]

Regardless of the clinical practice, we found comparable overall survival between sentinel node biopsy and lymphadenectomy, even in patients with lymphatic metastases, type 2 histology, and a high number of removed nodes during lymphadenectomy, showing further research is needed. Future studies focusing on patients who may benefit from a 'cytoreductive effect' of lymphadenectomy should be conducted to exclude a therapeutic role of lymphadenectomy. In this regard, only randomizing patients with positive sentinel nodes or type 2 histology to undergoing additional lymphadenectomy versus no additional surgery and subsequent standardized adjuvant therapy will definitively answer this question.

CONCLUSIONS

The results of our study suggest that the type of lymph node assessment does not affect overall survival in endometrial cancer

Table 4 Multivariable Cox proportional hazards regression models for overall survival limited to patients who underwent LND with at least 10 pelvic nodes and at least one para-aortic node removed stratified by histotype

		Histology 1		Histology 2	
Variable	**Level**	**Multivariable hazard ratio (95% CI)***	**P value**	**Multivariable hazard ratio (95% CI)***	**P value**
LN surgery	ALND only	1.0 reference		1.0 reference	
	SLN biopsy only	0.87 (0.64 to 1.19)	0.386	1.29 (0.87 to 1.91)	0.209
	SLN and ALND	1.11 (0.75 to 1.63)	0.601	0.97 (0.69 to 1.37)	0.858
Age	Per 10 years	1.92 (1.52 to 2.42)	<0.001	1.43 (1.32 to 1.56)	<0.001
Race	White	1.0 reference		1.0 reference	
	Black	1.46 (1.19 to 1.79)	<0.001	1.53 (1.32 to 1.77)	<0.001
	Other	0.97 (0.72 to 1.31)	0.856	1.0 (0.75 to 1.33)	0.976
	Unknown	1.24 (0.68 to 2.26)	0.476	0.81 (0.43 to 1.51)	0.507
Charlson-Deyo score	0	1.0 reference		1.0 reference	
	1	1.26 (1.17 to 1.37)	<0.001	1.15 (1.01 to 1.32)	0.036
	≥2	1.97 (1.75 to 2.21)	<0.001	1.32 (1.02 to 1.70)	0.032
Insurance status	Private insurance	1.0 reference		1.0 reference	
	Not insured	1.76 (1.29 to 2.41)	<0.001	0.97 (0.69 to 1.38)	0.879
	Medicaid	1.62 (1.23 to 2.13)	<0.001	1.18 (0.90 to 1.56)	0.236
	Medicare	1.27 (1.08 to 1.48)	0.003	1.06 (0.92 to 1.24)	0.418
	Other government	1.18 (0.68 to 2.06)	0.562	1.00 (0.47 to 2.11)	0.989
	Unknown	3.93 (1.26 to 12.31)	0.332	1.21 (0.73 to 2.01)	0.465
Income	≥$63 333	1.0 reference		1.0 reference	
	$50 354–63 332	1.05 (0.89 to 1.25)	0.567	0.99 (0.84 to 1.17)	0.922
	$40 227–50 353	1.20 (1.01 to 1.44)	0.042	1.00 (0.84 to 1.20)	0.985
	<$40 227	1.26 (1.02 to 1.57)	0.034	0.95 (0.77 to 1.17)	0.597
	Unknown	0.79 (0.34 to 1.87)	0.019	--	
Education (% no HSD)	≥17.6%	1.02 (0.81 to 1.28)	0.875	1.03 (0.82 to 1.28)	0.806
	10.9%–17.5%	1.07 (0.88 to 1.30)	0.514	1.02 (0.84 to 1.24)	0.843
	6.3%–10.8%	1.21 (1.02 to 1.43)	0.029	1.11 (0.94 to 1.32)	0.211
	< 6.3%	1.0 reference		1.0 reference	
	Unknown	0.44 (0.13 to 1.51)	0.193	--	
Facility type	Community	1.09 (0.81 to 1.47)	0.575	1.18 (0.87 to 1.61)	0.284
	Comprehensive community	1.01 (0.89 to 1.15)	0.897	1.10 (0.97 to 1.26)	0.132
	Academic	1.0 reference		1.0 reference	
	Integrated network	1.01 (0.85 to 1.20)	0.892	0.89 (0.75 to 1.05)	0.154
	Unknown	3.14 (1.85 to 5.35)	<0.001	0.57 (0.14 to 2.33)	0.432
AJCC pathological N stage	pN0	1.0 reference		1.0 reference	
	pN1	1.63 (1.34 to 1.98)	<0.001	1.81 (1.53 to 2.13)	<0.001
	pN2	2.25 (1.84 to 2.75)	<0.001	1.87 (1.59 to 2.20)	<0.001
AJCC pathological T stage	pT1	1.40 (0.69 to 2.83)	0.350	0.72 (0.30 to 1.74)	0.466
	pT1A	1.0 reference		1.0 reference	
	pT1B	1.63 (1.40 to 1.91)	<0.001	1.62 (1.38 to 1.91)	<0.001
	pT2	2.50 (2.06 to 3.05)	<0.001	2.08 (1.73 to 2.49)	<0.001
	pT3/3A/3B	3.43 (2.81 to 4.18)	<0.001	2.69 (2.28 to 3.19)	<0.001
Grade	Well/moderately	1.0 reference		1.0 reference	
	Poorly/undifferentiated	2.30 (2.00 to 2.63)	<0.001	1.87 (1.47 to 2.38)	<0.001
	Unknown	1.34 (1.15 to 1.56)	<0.001	2.03 (1.58 to 2.62)	<0.001

Continued

Table 4 Continued

Variable	Level	Histology 1 Multivariable hazard ratio (95% CI)*	Histology 1 P value	Histology 2 Multivariable hazard ratio (95% CI)*	Histology 2 P value
Lymph vascular invasion	Not present	1.0 reference		1.0 reference	
	Present	1.61 (1.40 to 1.85)	<0.001	1.44 (1.26 to 1.66)	<0.001
	Unknown	0.99 (0.76 to 1.29)	0.924	1.10 (0.87 to 1.40)	0.417
Adjuvant chemotherapy	No chemotherapy received	1.0 reference		1.0 reference	
	Chemotherapy received	0.78 (0.66 to 0.92)	0.003	0.89 (0.78 to 1.03)	0.107
Adjuvant hormone therapy	No hormone therapy received	1.0 reference		1.0 reference	
	Hormone therapy received	0.78 (0.40 to 1.50)	0.451	2.12 (1.00 to 4.48)	0.050
	Unknown	0.95 (0.64 to 1.41)	0.787	1.11 (0.78 to 1.58)	0.565
Adjuvant radiation therapy	No radiation	1.0 reference		1.0 reference	
	Brachytherapy	0.85 (0.73 to 0.98)	0.026	0.71 (0.61 to 0.83)	<0.001
	External beam	0.86 (0.73 to 1.00)	0.054	0.77 (0.67 to 0.89)	<0.001
	Other	0.64 (0.24 to 1.71)	0.374	0.89 (0.42 to 1.88)	0.763

*Hazard ratios estimate the risk of an event (death for any cause) in each group compared with that of the reference group. Hazard ratios lower than one represent a risk of events lower than the reference group, whereas hazard ratios higher than one represent a higher risk of events.
AJCC, American Joint Committee on Cancer; HSD, high-school diploma; LN, lymph node; LND, lymphadenectomy; SLN-B, sentinel lymph node biopsy.

regardless of lymph node status, histotype, and the number of removed nodes during lymphadenectomy. However, considering study limitations and acknowledging that an absence of evidence of effect is not equal to evidence of absence of effect, further research is needed to confirm these observations and to clarify the role of lymphadenectomy in patients with endometrial cancer and positive nodes.

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