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Association of Lymph Node Count and Overall Survival in Node-Negative Endometrial Cancers

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Abstract

Purpose—To estimate whether the number of lymph nodes removed during surgery is associated with overall survival among women with endometrial cancer.

Methods—We performed a retrospective cohort study of women with node-negative, stage I to IIIB endometrial cancer (n = 152,702) identified from the 1998–2011 National Cancer Database. Multivariable Cox proportional hazards regression tested for an association of lymph node count with survival. Restricted mean survival and relative hazard curves were plotted for survival as a function of number of removed lymph nodes.

Results—Among women with node-negative endometrioid endometrial cancer, for each additional five lymph nodes removed, the hazard for death decreased: stage I, the hazard ratio (HR) was 0.95 (95% CI, 0.93 to 0.97; $P < .001$), stage II, HR was 0.90 (95% CI, 0.87 to 0.94; $P < .001$); and stage IIIA-B, HR was 0.92 (95% CI, 0.88 to 0.96; $P < .001$). When grouped by grade,

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each additional five lymph nodes removed was also associated with decreased hazard for death: grade 1, HR was 0.96 (95% CI, 0.93 to 0.99; $P = .009$); grade 2,HR was0.91 (95%CI, 0.89 to0.94; $P < .001$);and grade 3,HR was 0.95 (95%CI, 0.92 to 0.97; $P < .001$). Increased lymph node dissection was also associated with increased survival among women with node-negative stage II (HR, 0.92; 95% CI, 0.86 to 0.98; $P = .01$) or stage IIIA-B (HR, 0.94; 95% CI, 0.89 to 0.99; $P = .025$) uterine serous carcinoma, but not among women with carcinosarcoma or clear cell adenocarcinoma. Five-year survival for women with one to four nodes removed and endometrioid or serous histology was 85% (95% CI, 84% to 85%) and 54% (95% CI, 50% to 59%), respectively. Five-year survival was significantly higher for women with ≥ 20 removed nodes and endometrioid (91%; 95% CI, 90% to 91%) or serous (72%; 95% CI, 68% to 76%) histology ($P < .001$).

Conclusion—Increased lymph node count is associated with a 1% to 14% decreased hazard of death per each additional five lymph nodes removed and a 5% to 20% increased 5-year survival among women with pathologically node-negative endometrioid and serous endometrial cancers.

INTRODUCTION

Lymphadenectomy remains controversial for endometrial cancer.[1] Studies favoring omission of para-aortic lymphadenectomy are GOG 33 and a Memorial Sloan Kettering series that reported 1% to 2% rates of isolated positive para-aortic nodes in clinically uterine-confined disease.[2,3] The prognostic implications of lymph node metastasis merit upstaging from IA-B to stage IIIC. The Benedettei Panici etal[4] and Medical Research Council ASTEC (Efficacy of Systematic Pelvic Lymphadenectomy in Endometrial Cancer)[5] trials of pelvic lymphadenectomy are often quoted as evidence against a therapeutic benefit of lymphadenectomy in endometrial cancer. Both trials evaluated pelvic lymphadenectomy, and 25.2% to 33% of women in the no-lymphadenectomy arms received pelvic radiation.[4,5]

Because the Aalders et al,[6] PORTEC,[7] GOG 99,[8] ASTEC-EN.5,[9] and PORTEC-2[10] trials showed no survival improvement from radiotherapy for early-stage endometrial cancers, using pelvic radiation to sterilize nondissected nodes has decreased.[6-10] Endometrial cancer is now managed with less lymphadenectomy and less pelvic radiation. The critical oncologic question now is: If lymph nodes are less evaluated and treated, how do we know that occult nodal metastasis is not missed and undertreated, and if this leads to decreased survival? We conducted a retrospective cohort study and analyzed pathologically node-negative endometrial cancers from the National Cancer Database to estimate whether the number of removed lymph nodes was associated with survival.

METHODS

Data Source

The 1998–2011 National Cancer Database endometrial cancer data set (n = 441,863) was used to perform a retrospective cohort study. The National Cancer Database is a hospital-based national cancer registry created by the American Cancer Society and American College of Surgeons, and it includes data for approximately 70% of uterine cancers diagnosed nationally.[11] Deidentified, individual-level data are entered by professional cancer

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registrars and are audited.[11] Institutional review board approval for use of this data is not required at Northwestern University Feinberg School of Medicine.

Study Cohorts

Included patients were those with pathologically negative lymph nodes defined by using a combination of the positive node count and the pathologic nodal staging variables. Patients with grade 4 undifferentiated disease were excluded. The International Federation of Gynecologists and Obstetricians staging groups (IA-B, II, or IIIA-B) were determined by using a combination of the staging variables and were 99.8% concordant with the analytic stage group variable. Only patients with node-negative stage IA to IIIB disease (n = 152,702) were included. Patients were further classified by International Classification of Diseases for Oncology, third revision (ICD-O-3) histology codes as follows: endometrioid (8380–8383), serous (8441, 8450, 8460, 8461), carcinosarcoma (8950, 8951, 8980, 8981), and clear cell (8310, 8313). Less common histologies were excluded.

Statistical Analyses

The distribution of count values for the number of removed lymph nodes was evaluated with a histogram. Correlation between the number of removed lymph nodes and age at diagnosis was tested with Spearman's rank correlation test. Survival analyses were performed to test the association of the number of removed lymph nodes with survival separately for each histology and stage. Overall survival (OS) but not disease-specific survival or recurrence is reported by the National Cancer Database. Survival information was available only for patients diagnosed from 1998 to 2006. The majority of patients omitted from survival analyses were those diagnosed from 2007 to 2011 who did not have vital status reported in this data set (n = 77,334). For patients with endometrioid disease, survival analyses were also performed for women grouped by grade to provide specific estimates for each grade group, including grade 1. Adjuvant treatments were coded as dichotomous (yes/no) variables. Counts of the number of removed lymph nodes ranged from one to > 90 and were censored at 90. Charlson-Deyo composite comorbidity scores were not recorded for 36,444 patients diagnosed before 2003. In cohorts for whom comorbidity scores were significantly associated with survival and who were therefore included, this resulted in inclusion of only those patients diagnosed between 2003 and 2006. The comorbidity scores are composites that include 15 common chronic diseases such as diabetes, dementia, and liver disease, among others. Standard variable definitions are available online at the American College of Surgeons.

Multivariable Cox proportional hazards regression models were built by using the Efron approximation for ties. Initial models included the lymph node count as a continuous variable modeled linearly. Covariates of age, comorbidity score, grade, radiation therapy, and chemotherapy were selected because of prior knowledge that these covariates are potential confounders in endometrial cancer survival analyses. The proportional hazards assumption was checked, and model stratification was performed if required. Interactions between significant covariates were tested. Final models were built by stepwise selection; however, the dominant procedure performed by stepwise selection beginning from a full model is removal of variables that do not improve the model (backward selection). The

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analysis of deviance table verified that all terms in each final model significantly improved the model. Goodness of fit was confirmed by examining deviance residuals. Cox models were optimized for each analyzed cohort. Therefore the final model build is not uniform across cohorts. Stratification and nonsignificant covariates were reported explicitly to be transparent regarding the statistical procedures and results. Subset analyses were also performed for cohorts of women treated with pelvic radiation, diagnosed within a narrow age range of 58 to 62 years, or with a composite comorbidity score of zero.

Restricted mean survival curves for women with endometrioid or serous carcinoma were created by plotting survival times as a function of lymph node count for each stage group. Restricted mean survival times were calculated from the univariable Cox proportional hazards regression of overall survival as a function of lymph node count.[12,13] For these calculations, survival was censored at 60 months to match the conventional restriction time of 60 months. Survival curves were displayed with point-wise 95% CIs. All results from the analyses just described model lymph node count as a continuous predictor of survival under an assumption that lymph node count is a linear predictor in the Cox model. To test whether the results are robust to the alternative assumption that allows for nonlinearity of the association of node count with survival, we also plotted the relative hazard of death for women with endometrioid or serous carcinoma derived from multivariable Cox regressions stratified by stage and grade. Possible nonlinearity is allowed by modeling the restricted cubic splines of lymph node count as a continuous variable.

To provide familiar Kaplan-Meier survival estimates, 5-year survival proportions were calculated. Women were grouped by number of removed lymph nodes. Differences in survival were tested for significance with the log-rank test. Two authors (B.L.S. and D.G.S.) independently performed survival analyses with R software using the “survival” and “rms” packages or Stata 14, respectively, and cross-validated the results.

RESULTS

Baseline Characteristics

Among the full National Cancer Database endometrial cancer cohort (n = 441,863), lymph node count was weakly positively correlated with number of pathologically positive lymph nodes (ρ, 0.031; $P < .001$, Spearman’s rank correlation). Patient and disease characteristics are shown in Table 1. Lymph node count was similar between histology groups. A histogram of lymph node count in the node-negative cohort is shown in Appendix Figure A1. Increased age was weakly negatively correlated with decreased lymph node count (ρ, –0.041; $P < .001$, Spearman’s rank correlation). Pelvic radiation with or without brachytherapy was administered to 9.3% (9,885 of 106,054) of women with endometrioid histology and 18.7% (1,258 of 6,720) of women with serous histology. The median follow-up time of the overall cohort was 75.5 months (interquartile range, 51.8 to 104.7 months). Follow-up was shorter for women with nonendometrioid histologies, presumably because of decreased survival (Table 1).

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Survival Analyses

Increased lymph node count was associated with increased survival for all subsets of women with endometrioid histology grouped by stage (Table 2). Similarly, when women with endometrioid histology were grouped by grade, increased node count remained associated with increased survival for all grades, including grade 1 (Table 2).

Increased node count was also associated with increased survival among women with stage II or IIIA-B uterine serous carcinoma. However, node count was not associated with survival among women with stage I serous carcinoma (Table 3; Appendix Table A1). Similarly, node count was not associated with survival among women with carcinosarcoma or clear cell histology (Table 3; Appendix Tables A2 and A3).

The many multivariable regression models reported here confirm that the association of node count with survival is robust to adjustment for confounders and alternative cohort specifications among women with endometrioid or serous histology. Comparing results across the multivariable regression models, as disease stage or grade increased, the significance of patient characteristics often decreased, whereas the significance of disease characteristics (such as stage and grade) and disease modifiers (such as adjuvant radiation therapy or chemotherapy) often developed or increased. This observation suggests the expected increase in the proportion of deaths was disease-specific as disease-specific drivers of mortality such as stage increased. In addition, among women who received pelvic radiation with or without brachytherapy, increased node count was associated with increased survival (Appendix Table A4).

Negative correlation of lymph node count and age at diagnosis does not drive the statistical significance observed for lymph node count. First, some models in which age is highly statistically significant, such as those for carcinosarcoma and clear cell histologies, do not show significance of lymph node count. This is despite the fact that the negative correlation of lymph node count and age is stronger for patients with carcinosarcoma (ρ, −0.126; $P < .001$) and clear cell disease (ρ, −0.108; $P < .001$) than for patients with endometrioid disease, in which the correlation is weak (ρ, −0.039; $P < .001$). Further observations suggesting that age is not confounding the results of lymph node count are that statistical significance (or lack thereof) of the association of lymph node count with survival is consistent within various survival models of each histologic type: significant in endometrioid and serous histologies versus not significant in carcinosarcoma and clear cell histologies. Finally, a sensitivity analysis of only women age 58 to 62 years with endometrioid histology explicitly confirmed a model in which age was not associated with OS, but lymph node count remained associated with decreased hazard for death (hazard ratio [HR], 0.94; 95% CI, 0.90 to 0.99; $P = .013$; Appendix Table A5). Similarly, in a sensitivity analysis of 21,251 women (2,755 deaths) with endometrioid histology and a composite comorbidity score of 0, increased lymph node count remained significantly associated with decreased hazard of death (HR, 0.94; 95% CI, 0.92 to 0.96; $P < .001$ per each five additional nodes removed). These two sensitivity analyses confirm the inference that node count is an important disease-related prognostic factor that is not confounded by measured differences in patient age or comorbidity.

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Restricted mean survival curves of OS by lymph node count for women with endometrioid or serous histology illustrate the association of increased node count with increased survival and provide estimates of the absolute effect size in months (Fig 1). Survival does not trend with the same slope for each cohort (Fig 1). For instance, the effect size on change in survival by change in lymph node count is much larger for patients with serous than for those with endometrioid histology (Fig 1). Increased stage for either histology (serous or endometrioid) is associated with greater effect of increased survival with increased node count (Fig 1). However, there is diminishing return in terms of increased survival with increased number of lymph nodes removed, which is most obvious for the stage IA-B endometrioid cohort (Fig 1). This diminishing return begins between 20 to 30 removed lymph nodes for all cohorts (Fig 1). In other words, the restricted mean survival times are not meaningfully lower at 30 removed nodes than at ≥ 40 removed lymph nodes for these cohorts. An alternative illustration of the association of lymph node count with survival (adjusted for covariates) was generated when lymph node count was modeled nonlinearly as a continuous variable (Fig 2). The relative hazard of death plotted by lymph node count confirmed that most of the potential benefit of lymphadenectomy is achieved after removal of 20 to 30 nodes (Fig 2).

Table 4 shows the proportion of women with node-negative endometrioid or serous endometrial cancer surviving at 5 years of follow-up. Women with one to four removed lymph nodes who may have undergone lymph node sampling or sentinel lymph node biopsy had significantly decreased survival compared with women with more removed lymph nodes ($P < .001$). The proportion of survivors of endometrioid endometrial cancer was 5% to 6% greater when comparing women with 20 or more lymph nodes removed to women with one to four lymph nodes removed ($P < .001$). Among women with serous endometrial cancer, the proportion of surviving women was approximately 20% greater among women with 20 or more lymph nodes removed compared with women with one to four lymph nodes removed ($P < .001$).

DISCUSSION

Increased survival associated with increased lymph node count among women with node-negative endometrial cancers confirmed prognostic importance and suggests that lymph node dissection has therapeutic benefit. The putative therapeutic benefit might be the result of more frequent correct stage assignment with increased lymphadenectomy and subsequent use of adjuvant therapies to treat women with early advanced-stage disease. Some deaths among women with early-stage endometrioid cancer were not disease-specific as reflected by associations of age and comorbidity scores with survival. If patients with node-positive disease were included, we expect that increased lymph node count would also correlate with increased OS of women with carcinosarcoma or clear cell cancer, as previously reported.[14,15]

Increased lymph node dissection, including paraaortic lymphadenectomy, particularly in patients with node-positive disease, is associated with improved survival and decreased nodal recurrence in endometrial cancers.[15-21] Doubling of the lymph node count in a cohort that included patients with advanced-stage and node-positive endometrioid, serous, or

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carcinosarcoma histology was associated with a 28% reduction in risk of death in the first year of follow-up.[14] We analyzed only node-negative carcinosarcomas, and we performed covariate adjustment. Lymph node count is a prognostic factor in node-negative gastric cancer and other malignancies with intraperitoneal and lymphatic spread.[22]

A series of 649 women reported increased survival with multiple-site pelvic lymph node sampling compared with no lymph node sampling ($P < .001$), even among women with stage I disease ($P = .026$) or women who received pelvic radiation ($P = .003$).[16] A Surveillance, Epidemiology, and End Results Program study of 12,333 women with endometrioid histology reported confounder-adjusted increased survival with increased lymph node count among stage IB, grade 3 disease, and all stage IC to IV patients.[17] The SEPAL (Survival Effect of Para-Aortic Lymphadenectomy in Endometrial Cancer) study demonstrated that systematic para-aortic lymphadenectomy was associated with decreased hazard of death (HR, 0.48; 95% CI, 0.29 to 0.83; $P = .005$) among women with high-intermediate risk disease treated with adjuvant radiation or chemotherapy.[18] The SEPAL study results are consistent with a Mayo Clinic series reporting that 67% of all women with any lymph node metastasis after selective lymphadenectomy also had positive para-aortic lymph node metastasis.[19] The Mayo study recommended systematic pelvic and para-aortic lymphadenectomy above the inferior mesenteric artery to the renal vessels and consideration of resection of the gonadal veins in women who did not meet the Mayo criteria.[19]

Strengths of our study include the large number of patients analyzed. Inclusion of only pathologically node-negative patients removes confounding and increases the proportion of surgically staged patients in the analyzed cohorts. Use of restricted mean survival curves to show the association of lymph node count with survival is particularly illustrative (Fig 1). Allowance for nonlinearity of the association between node count and survival association produced consistent results (Fig 2). In multivariable models, the association of node count and survival was robust to alternative covariate selection and was therefore not model dependent. The analyses were performed and reported separately for each stage, for each histology type, and for women with endometrioid histology, grouped by grade 1, 2, or 3. This generates a series of sensitivity analyses demonstrating that the association of lymph node count and survival is also robust to alternative cohort selection criteria. Additional sensitivity analyses included cohort selection by age, comorbidity score, or radiotherapy exposure, all with consistent results. Finally, the association was shown even in unadjusted Kaplan-Meier estimates calculated without any regression model assumptions.

Limitations include the presumption that increased lymph node count suggests increased territory of lymphadenectomy. We cannot adjust for myometrial invasion, tumor size, or lymphovascular space invasion. Effects of errors in data entry are likely limited and minimal with regard to influencing the results. Errors in data entry would not be systematic and histology-specific enough to falsely produce significant and histology-specific associations across large cohorts. Finally, many patients were omitted from each multivariable regression. Omitted patients represent those before 2003 who were missing Charlson-Deyo comorbidity scores or patients missing survival follow-up data. Many of these limitations are overcome in our companion publication, which also provides an independent cohort validation.[23]

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Increased lymph node count could possibly be a surrogate variable for performance of surgery by a gynecologic oncologist more often than a benign gynecologist; however, this idea cannot be tested with the available data. Although variability in node counting among pathologists may be questioned, variation in node counting would eliminate or decrease the observed association of increased node count with increased survival. In addition, normal human anatomic variation in the number of lymph nodes in the body could explain our results only if there were a clear explanation for better endometrioid and serous endometrial cancer prognoses of women born with more lymph nodes.

We infer that comprehensive lymphadenectomy is associated with increased survival among women with endometrioid (all grades) and serous endometrial cancers. We do not believe that the negative results presented here in node-negative carcinosarcoma or clear cell adenocarcinoma should distract from the importance of lymph node evaluation in these histologies, in which increased survival with increased lymphadenectomy was previously reported.[14,15]

The small survival benefit that may be associated with aggressive lymphadenectomy among women with stage I low-grade endometrioid histology should be weighed against the risks of immediate and long-term morbidities associated with performance of systematic pelvic and para-aortic lymphadenectomy. Although the prevalence and quality-of-life impact of lymphadenectomy-related risks such as postoperative lymphedema are still debated, the evidence presented here and by others suggests that reservation is warranted in dismissing the prognostic importance and possible therapeutic benefit of staging lymphadenectomy in apparently uterus-confined endometrioid endometrial cancer. To increase the high cure rate of early-stage endometrioid endometrial cancer, it may be necessary to revisit more aggressive surgical lymphadenectomy. In addition, routine use of a sentinel node protocol can increase detection of clinically occult nodal metastases compared with frequentomission of lymphadenectomy using risk criteria.[24] However, reliance on a sentinel node protocol may result in a stage IIIC1/2 miss rate of 3% compared with systematic lymphadenectomy among women with clinically uterus-confined endometrial cancer.[25] A sentinel node protocol versus routine lymphadenectomy trial is needed to compare morbidity and recurrence after these competing strategies for surgical node evaluation.

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APPENDIX

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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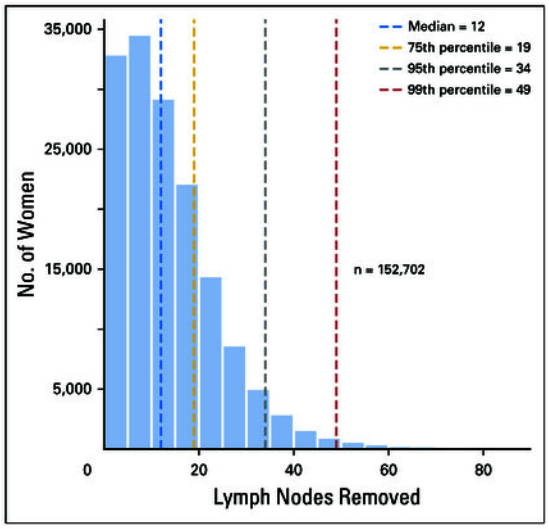

Fig A1.
Histogram of node count.

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Table A1.

Cox Proportional Hazards Models of Overall Survival Among Women With Uterine Serous Carcinoma With Separate Models for Each Stage Group

Serous Histology	HR	95% CI	*P*
	Modeled = 1,103; Events = 302		
Stage IA-B*			
Nodes (per each five removed)	0.98	0.93 to 1.04	.454
Age (per each decade)	1.02	1.00 to 1.03	.021
Charlson-Deyo comorbidity score			
0	1 (reference)		
1	1.44	1.09 to 1.90	.010
2	2.36	1.50 to 3.71	<.001
	Modeled = 638; Events = 303		
Stage II†			
Nodes (per each five removed)	0.92	0.86 to 0.98	.010
Radiation			
No	1 (reference)		
Yes	0.66	0.52 to 0.83	<001
	Modeled = 607; Events = 349		
Stage IIIA-B‡			
Nodes (per each five removed)	0.94	0.89 to 0.99	.025
Age each-decade	1.45	1.30 to 1.63	<.001
Radiation/chemotherapy			
No/no	1 (reference)		
No/yes	0.86	0.65 to 1.14	.307
Yes/no	1.07	0.78 to 1.45	.687
Yes/yes	0.80	0.64 to 0.99	.011

NOTE. All models are statistically significant ($P < .001$, likelihood ratio test).

Abbreviation: HR, hazard ratio.

*Stratification variables: none; nonsignificant variables: grade, radiation, chemotherapy.

†Stratification variables: age categories; nonsignificant variables: grade, comorbidity score, chemotherapy.

‡Stratification variables: none; nonsignificant variables: grade, comorbidity score.

Table A2.

Cox Proportional Hazards Models of Overall Survival Among Women With Uterine Carcinosarcoma With Separate Models for Each Stage Group

Carcinosarcoma Histology	HR	95% CI	*P*
	Modeled = 1,181; Events = 522		
Stage IA-B*			
Nodes (per each five removed)	0.98	0.95 to 1.03	.488

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Carcinosarcoma Histology	HR	95% CI	P
Radiation			
No	1 (reference)		
Yes	0.83	0.69 to 1.00	.044
Chemotherapy			
No	1 (reference)		
Yes	0.62	0.45 to 0.85	.003
	Modeled =318; Events = 211		
Stage II[†]			
Nodes (per each five removed)	0.92	0.82 to 1.02	.100
Chemotherapy			
No	1 (reference)		
Yes	0.55	0.35 to 0.87	.011
	Modeled = 392; Events = 265		
Stage IIIA-B[‡]			
Nodes (per each five removed)	0.96	0.91 to 1.01	.110
Age (per each decade)	1.33	1.18to 1.50	<.001

NOTE. All models are statistically significant (likelihood ratio test).

Abbreviation: HR, hazard ratio.

[*] Stratification variables: age categories; nonsignificant variables: grade, comorbidity score, radiation.

[†] Stratification variables: age categories; nonsignificant variables: grade, comorbidity score, radiation.

[‡] Stratification variables: chemotherapy; nonsignificant variables: grade, comorbidity score, radiation.

Table A3.

Cox Proportional Hazards Models of Overall Survival Among Women With Uterine Clear Cell Carcinoma With Separate Models for Each Stage Group

Clear Cell Histology	HR	95% CI	P
	Modeled = 896; Events = 254		
Stage IA-B[*]			
Nodes (per each five removed)	0.97	0.91 to 1.04	.395
Age (per each decade)	1.99	1.74 to 2.28	<.001
	Modeled = 258; Events = 126		
Stage II[†]			
Nodes (per each five removed)	0.97	0.89 to 1.06	.523
Age (per each decade)	2.07	1.71 to 2.51	<.001
Radiation			
No	1 (reference)		
Yes	0.65	0.46 to 0.93	.019
	Modeled = 172; Events =96		
Stage IIIA-B[‡]			
Nodes (per each five removed)	0.90	0.80 to 1.01	.074

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Clear Cell Histology	HR	95% CI	P
Age (per each decade)	1.58	1.28 to 1.94	<.001

NOTE. All models are statistically significant ($P < .001$, likelihood ratio test).

Abbreviation: HR, hazard ratio.

*Stratification variables: none; nonsignificant variables: grade, comorbidity score, radiation, chemotherapy.

†Stratification variables: none; nonsignificant variables: grade, comorbidity score, chemotherapy.

‡Stratification variables: none; nonsignificant variables: grade, comorbidity score, radiation, chemotherapy.

Table A4.

Cox Proportional Hazards Models of Overall Survival Among Women Who Received Pelvic Radiation

Histology	HR	95% CI	P
	Modeled = 3,377; Events = 887		
Endometrioid and serous*			
Nodes (per each five removed)	0.96	0.93 to 1.00	.028
Age (per each decade)	1.67	1.56 to 1.77	<.001
Charlson-Deyo comorbidity score			
0	1 (reference)		
1	1.21	1.02 to 1.43	.027
2	1.72	1.26 to 2.35	<.001
Chemotherapy			
No	1 (reference)		
Yes	0.77	0.63 to 0.93	.008
	Modeled = 3,150; Events = 772		
Endometrioid only†			
Nodes (per each five removed)	0.95	0.91 to 0.99	.009
Age (per each decade)	1.69	1.58 to 1.80	<001
Charlson-Deyo comorbidity score			
0	1 (reference)		
1	1.27	1.07 to 1.52	.008
2	2.04	1.47 to 2.84	<001

NOTE. Both models are statistically significant ($P < .001$, likelihood ratio test).

Abbreviation: HR, hazard ratio.

*Stratification variables: stage, grade; nonsignificant variables: none.

†Stratification variables: stage, grade; nonsignificant variables: chemotherapy.

Table A5.

Cox Proportional Hazards Regression of Overall Survival of Women Age 58–62 Years With Endometrioid Histology

Histology	HR	95% CI	P
	Modeled = 4,607, Events = 440		

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Histology	HR	95% CI	P
Endometrioid *			
Nodes (per each five removed)	0.94	0.90 to 0.99	.013
Charlson-Deyo comorbidity score			
0	1 (reference)		
1	1.73	1.39 to 2.17	<.001
2	2.66	1.78 to 3.98	<.001
Stage IA-B			
Chemotherapy	1 (reference)		
No			
Yes	2.71	1.54 to 4.76	<.001
Stage II			
Chemotherapy			
No	1.80	1.38 to 2.35	<.001
Yes	1.82	1.41 to 2.35	.627
Stage IIIA-B			
Chemotherapy			
No	3.10	2.19 to 4.38	<.001
Yes	2.34	1.68 to 3.27	.003

NOTE. Model is statistically significant ($P < .001$, likelihood ratio test).

Abbreviation: HR, hazard ratio.

* Stratification variables: grade; nonsignificant variables: age, radiation.

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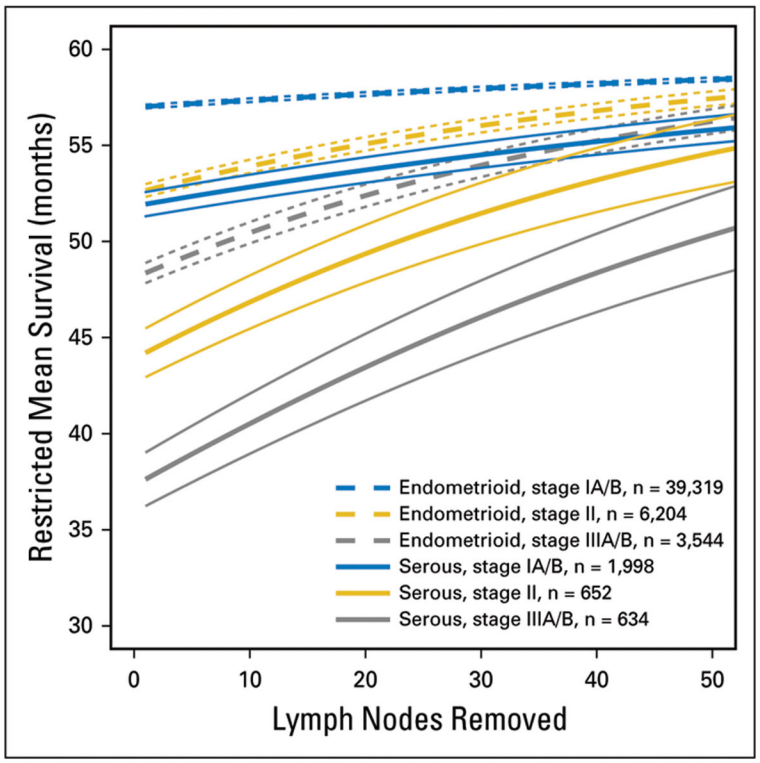

Fig 1.

Restricted mean overall survival curves among women with endometrioid endometrial adenocarcinoma or uterine serous carcinoma. Survival follow-up was censored at 60 months, such that survival to 60 months represents potentially cured women, and the longest calculable mean survival time by lymph node count is 60 months. Lighter weight lines are 95% CIs. $P \leq .002$ for all curves.

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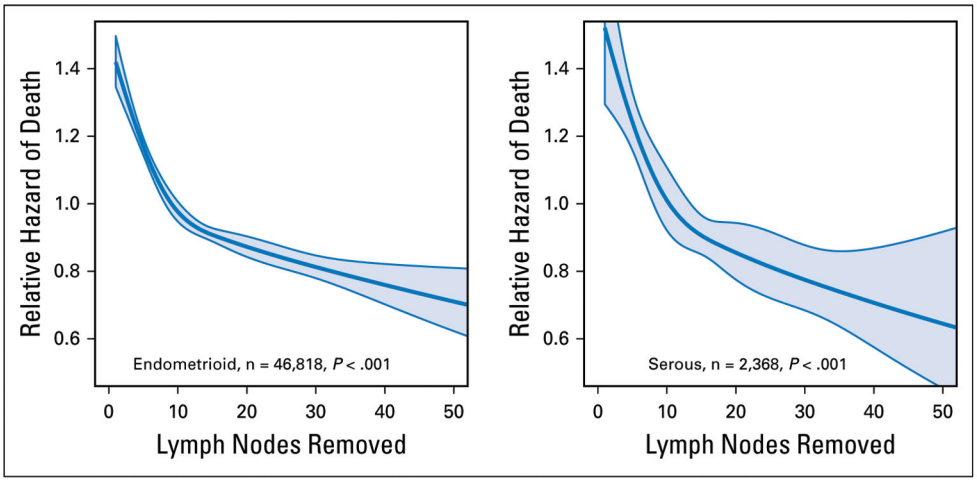

Fig 2.

Relative hazard of death by lymph node count among women with node-negative endometrioid cancer. Shaded areas indicate 95% CI.

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Table 1.

Patient and Disease Characteristics by Histology

	Endometnoid		Serous		Carcmosarcoma		Clear Cell	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
No. of women	106,054		6,720		4,526		2,289	
No. with follow-up	56,988		3,436		2,571		963	
Mean age, years ± SD	61.3 ± 11.4		67.9 ±9.2		67.1 ± 10.9		67.2 ± 10.8	
Charlson-Deyo score								
0	65,974	76.3	3,950	75.2	2,846	75.8	1,197	74.6
1	17,037	19.7	1,070	20.4	753	20.1	337	21.0
2	3,463	4.0	230	4.4	154	4.1	70	4.4
Median clinical follow-up, months (IQR)	76(55–101)		65 (29–92)		49(16–81)		71 (38–102)	
Median No. of lymph nodes examined (IQR)	12 (6–20)		13 (7–21)		13 (7–21)		13 (7–22)	
No. of positive lymph nodes	0		0		0		0	
Stage								
IA-B	88,116	83.1	4,439	66.1	3,017	66.7	1,589	69.4
II	11,224	10.6	1,167	17.4	696	15.4	433	18.9
IIIA-B	6,714	6.3	1,114	16.6	813	18.0	267	11.7
Grade								
1	46,465	46.7	162	3.3	83	3.1	50	2.9
2	38,948	39.1	509	10.4	207	7.7	190	11.1
3	14,162	14.2	4,246	86.4	2,383	89.2	1,473	86.0
Adjuvant radiation								
Yes	24,049	22.9	2,711	40.8	1,961	43.8	963	42.2
No	80,847	77.1	3,938	59.2	2,521	56.2	1,315	57.8
Chemotherapy								
Yes	5,814	5.6	2,858	44.1	1,534	35.0	535	24.1
No	97,179	94.4	3,626	55.9	2,843	65.0	1,683	75.9

Abbreviations: IQR, interquartile range; SD, standard deviation.

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Table 2.

Cox Proportional-Hazards Models of Overall Survival Among Women With Endometrial Endometrioid Adenocarcinoma

Endometnoid Histology	HR	95% CI	*P*
	Modeled = 21,979; Events = 2,670		
Stage IA-B *			
Nodes (per each 5 removed)	0.95	0.93 to 0.97	<.001
Charlson-Deyo score	1 (reference)		
0			
1	1.55	1.42 to 1.70	<.001
2	2.84	2.47 to 3.29	<.001
Chemotherapy	1 (reference)		
No			
Yes	1.68	1.34 to 2.10	<.001
	Modeled = 3,265; Events = 764		
Stage II †			
Nodes (per each 5 removed)	0.90	0.87 to 0.94	<.001
Age (per each decade)	1.78	1.67 to 1.90	<.001
Charlson-Deyo score			
0	1 (reference)		
1	1.33	1.11 to 1.58	.002
2	2.16	1.62 to 2.87	<.001
	Modeled = 1,879; Events = 556		
Stage IIIA-B ‡			
Nodes (per each 5 removed)	0.92	.88 to .96	<.001
Age (per each decade)	1.58	1.47 to 1.70	<.001
Charlson-Deyo score			
0	1 (reference)		
1	1.30	1.05 to 1.60	.016
2	2.26	1.58 to 3.23	<.001
Grade			
1	1 (reference)		
2	1.94	1.48 to 2.54	<.001
3	3.08	2.36 to 4.03	<.001
Radiation: no/chemotherapy: no	1 (reference)		
Radiation: yes/chemotherapy: no	0.93	0.76 to 1.13	.478
Radiation: no/chemotherapy: yes	0.96	0.72 to 1.26	.747
Radiation: yes/chemotherapy: yes	0.59	0.45 to 0.77	<.001
	Modeled = 12,682; Events = 1,256		

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Endometnoid Histology	HR	95% CI	P
Grade 1§			
Nodes (per each 5 removed)	0.96	0.93 to 0.99	.009
Age (per each decade)	2.01	1.91 to 2.12	<.001
Charlson-Deyo score			
0	1 (reference)		
1	1.76	1.55 to 2.00	<.001
2	3.14	2.53 to 3.86	<.001
Stage/chemotherapy interaction			
Stage IA-B: chemotherapy no	1 (reference)		
Stage IA-B: chemotherapy yes	3.01	2.06 to 4.38	<.001
Stage II: chemotherapy no	1.68	1.42 to 1.98	<.001
Stage II: chemotherapy yes	1.65	1.40 to 1.94	.151
Stage IIIA-B: chemotherapy no	1.96	1.49 to 2.59	<.001
Stage IIIA-B: chemotherapy yes	1.54	1.17 to 2.02	<.001
	Modeled 5 10,747; Events 5 1,648		
Grade 2//			
Nodes (per each 5 removed)	0.91	0.89 to 0.94	
Charlson-Deyo score			
0	1 (reference)		
1	1.45	1.29 to 1.63	<.001
2	3.04	2.53 to 3.63	<.001
	Modeled 5 4,110; Events 5 1,142		
Grade 3¶			
Nodes (per each 5 removed)	0.95	0.92 to 0.97	<.001
Charlson-Deyo score			
0	1 (reference)		
1	1.18	1.02 to 1.36	<.001
2	1.69	1.31 to 2.18	<.001

NOTE. All models are statistically significant ($P < .001$, likelihood ratio test). Abbreviation: HR, hazard ratio.

*Stratification variables: age categories, grade; nonsignificant variables: radiation.

†Stratification variables: grade, radiation, chemotherapy; nonsignificant variables: none.

‡Stratification variables: none; nonsignificant variables: none.

§Stratification variables: none; nonsignificant variables: radiation.

//Stratification variables: age categories, stage, radiation; nonsignificant variables: chemotherapy.

¶Stratification variables: age categories, stage; nonsignificant variables: radiation, chemotherapy.

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Table 3.

HRs for Number of Removed Lymph Nodes With OS Among Non-Endometrioid Endometrial Cancers

	Histology								
	Serous			Carcinosarcoma			Clear Cell		
Stage	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
IA-IB	0.98	0.93 to 10.04	.455	0.98	0.95 to 10.03	.488	0.97	0.91 to 10.04	.395
II	0.92	0.86 to 0.98	.010	0.92	0.82 to 10.02	.100	0.97	0.89 to 10.06	.523
IIIA-B	0.94	0.89 to 0.99	.025	0.96	0.91 to 10.01	.110	0.90	0.80 to 10.01	.074

NOTE. All hazard ratios (HRs) are for each additional five lymph nodes removed.

Abbreviation: OS, overall survival.

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Table 4.

Five-Year Survival Proportions by Lymph Node Count Categories for Women With Pathologically Node-Negative Stage I to IIIB Endometrioid or Serous Endometrial Cancer

	Endometnoid				Serous			
Node Count Category	**% Surviving**	**95% CI**	**No. of Patients**	**No. of Deaths**	**% Surviving**	**95% CI**	**No. of Patients**	**No. of Deaths**
1–4	0.85	0.84 to 0.85	9,568	1,344	0.54	0.50 to 0.59	598	248
5–9	0.88	0.87 to 0.88	11,654	1,265	0.65	0.62 to 0.69	691	216
10–14	0.89	0.88 to 0.90	9,561	969	0.67	0.64 to 0.71	683	206
15–19	0.89	0.88 to 0.90	7,200	731	0.73	0.69 to 0.77	508	124
20–24	0.90	0.90 to 0.91	4,627	433	0.76	0.71 to 81	303	65
>25	0.91	0.90 to 0.91	6,447	559	0.72	0.68 to 0.76	501	126
Log rank *P*	<.001				<.001			