

The impact of sentinel lymph node sampling versus traditional lymphadenectomy on the survival of patients with stage IIIc endometrial cancer

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HIGHLIGHTS

- For patients with stage IIIc endometrial cancer, overall survival was comparable between sentinel lymph node biopsy alone and systematic lymphadenectomy.
- Patterns of adjuvant treatment differed between sentinel lymph node biopsy alone and systematic lymphadenectomy.
- Patients who had sentinel lymph node biopsy alone were less likely to receive chemotherapy alone.

ABSTRACT

Objective To investigate the survival of patients with lymph node positive endometrial carcinoma by type of surgical lymph node assessment.

Methods Patients diagnosed between January 2012 and December 2015 with endometrial carcinoma and uterine confined disease and nodal metastases on final pathology who underwent minimally invasive hysterectomy were identified in the National Cancer Database. Patients who had sentinel lymph node biopsy alone or underwent systematic lymphadenectomy were selected. Overall survival was evaluated following generation of Kaplan–Meier curves and compared with the log rank test. A Cox model was constructed to evaluate survival after controlling for confounders.

Results A total of 1432 patients were identified: 1323 (92.4%) and 109 (7.6%) underwent systematic lymphadenectomy and sentinel lymph node biopsy only, respectively. The rate of adjuvant treatment was comparable between patients who had sentinel lymph node biopsy alone and systematic lymphadenectomy (83.5% vs 86.6%, $p=0.39$). However, patients who had sentinel lymph node biopsy were less likely to receive chemotherapy alone (13.6% vs 36.6%, $p<0.001$) and more likely to receive radiation therapy alone (19.8% vs 5.4%, $p<0.001$) compared with patients who had systematic lymphadenectomy. There was no difference in overall survival between patients who had sentinel lymph node biopsy alone and systematic lymphadenectomy ($p=0.27$ from log rank test), and 3 year overall survival rates were 82.2% and 79.4%, respectively ($p>0.05$). After controlling for confounders, there was no difference in survival between the systematic lymphadenectomy and sentinel lymph node biopsy alone groups (hazard ratio 0.82, 95% confidence interval 0.46 to 1.45).

Conclusions Performance of sentinel lymph node biopsy alone was not associated with an adverse impact on survival in patients with lymph node positive endometrial cancer.

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in the USA, with an increasing incidence.^{1 2} Traditionally, staging of endometrial cancer involved hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy to the level of the renal vessels.^{2 3} While a randomized trial failed to demonstrate a survival benefit among patients with early stage endometrial carcinoma undergoing lymphadenectomy, identification of occult lymph node metastases can guide adjuvant treatment planning, with administration of adjuvant chemotherapy for patients harboring lymph node metastases.^{4 5} However, systematic lymphadenectomy can be associated with significant morbidity, increased blood loss, longer operative time, and higher incidence of postoperative lymphedema.⁶ Two prospective studies established the sentinel lymph node biopsy technique as an alternative to complete lymphadenectomy for the staging of endometrial cancer, demonstrating excellent sensitivity and negative predictive value.^{7 8} Several retrospective studies have further validated these results and the sentinel lymph node biopsy technique has gained widespread acceptance and has been incorporated into the National Comprehensive Cancer Network guidelines.^{6 9} Nevertheless, to date there is limited evidence demonstrating how sentinel lymph node biopsy has impacted survival outcomes and need for postoperative adjuvant treatment.¹⁰

The aim of the present study was to compare survival outcomes between patients with stage IIIc endometrial carcinoma who underwent sentinel lymph node biopsy only versus comprehensive lymphadenectomy using a large multi-institutional hospital based database.

METHODS

Patients diagnosed with a pathologically confirmed endometrial carcinoma between January 2012 and December 2015 were identified in the National Cancer Database, a hospital based database capturing approximately 70% of all malignancies diagnosed in the USA.¹¹ The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytical or statistical methodology employed, or the conclusions drawn from these data. The present study was deemed exempt from institutional board review from Penn Medicine (protocol No 829268).

Patients with disease apparently confined to the uterus who underwent robotic assisted or laparoscopic hysterectomy, had positive lymph nodes according to the pathology report, did not receive radiation therapy or chemotherapy before surgery, and had at least 1 month of follow-up were selected. Similar to a prior analysis, based on the Facility Oncology Registry Data Standards regional lymph node surgery variable that captures the utilization of sentinel lymph node biopsy, we identified patients who underwent sentinel lymph node biopsy alone (without concurrent lymphadenectomy).^{12–13} Patients who did not have sentinel lymph node biopsy and had at least 20 lymph nodes removed served as the comparison group. We selected a cut-off of 20 lymph nodes because it represents a more comprehensive lymph node assessment based on prior publications.¹⁴

Demographic, clinicopathological, and treatment variables were extracted from the deidentified dataset. Patient race was recoded as white, black, and other/unknown, and insurance status as private, government (including Medicaid and Medicare), and uninsured/unknown. Based on prior studies that have used the same cut-off, age was grouped as <65 and ≥65 years to define an older population.^{15–16} The presence of comorbidities was assessed from the Charlson–Deyo Comorbidity index and classified as absent (score 0) or present (score ≥1). The type of treatment facility was categorized into academic/research and other, that included community cancer program, comprehensive community cancer program, and integrated network cancer program. Histology was recoded as endometrioid, non-endometrioid (that included serous, clear cell, and carcinosarcoma), and other/mixed. We defined adjuvant treatment as receipt of chemotherapy and/or radiation therapy within 6 months of surgery. Patients with an unknown interval between surgery and radiotherapy and/or chemotherapy as well as those who received treatment >6 months after surgery were excluded from the adjuvant therapy analysis.

The frequency of distribution of categorical variables was compared with the χ^2 test or Fisher's exact test, and continuous variables with the Mann–Whitney U test. Overall survival was assessed following generation of Kaplan–Meier curves and compared with the log rank test. A Cox multivariate model was constructed to control for confounders found to be associated with overall survival based on univariate analysis. Statistical analyses were performed with the Statistical Package for the Social Sciences V.27 (International Business Machines Corporation Corporation, Armonk, New York, USA), and the alpha level of statistical significance was set at 0.05.

RESULTS

We identified a total of 1432 patients with apparent early stage endometrial carcinoma and positive lymph nodes on final pathology who met the inclusion criteria. Median patient age was 63 years (range 27–89) and the majority were white (84.4%) without comorbidities (76%) and underwent robotic-assisted hysterectomy (78.7%).

A total of 1323 (92.4%) and 109 (7.6%) patients underwent systematic lymphadenectomy and sentinel lymph node biopsy only, respectively. Rate of sentinel lymph node biopsy only for patients with positive lymph nodes was 1.9% in 2012, 5% in 2013, 5.5% in 2014, and 15.4% in 2015. Among patients who had systematic lymphadenectomy, the majority (81.9%) underwent para-aortic lymphadenectomy. Patients who had sentinel lymph node biopsy only had a lower number of lymph nodes removed (median 4 vs 27, $p<0.001$) and a lower number of positive lymph nodes (median 1 vs 2, $p<0.001$) compared with those who had systematic lymphadenectomy. There was no difference between the systematic lymphadenectomy and sentinel lymph node biopsy only groups in terms of race ($p=0.22$), insurance status ($p=0.17$), comorbidities ($p=0.15$), and histology ($p=0.15$). Patients who underwent sentinel lymph node biopsy only were more likely to be managed at academic institutions (74.5% vs 49.9%, $p<0.001$) and be older than 65 years (57.8% vs 44.6%, $p=0.008$). Table 1 depicts the clinicopathological characteristics of patients who had systematic lymphadenectomy and sentinel lymph node biopsy only.

When investigating patterns of adjuvant treatment, we excluded from the analysis 253 cases (190 patients received chemotherapy or radiotherapy more than 6 months after surgery and 63 had an unknown surgery–chemotherapy/radiotherapy interval). Based on 1179 patients, 83.5% and 86.6% who had sentinel lymph node biopsy only and systematic lymphadenectomy received adjuvant treatment ($p=0.39$). However, the type of adjuvant treatment differed between the two groups. Patients who had sentinel lymph node biopsy only were less likely to receive chemotherapy alone (13.6% vs 36.6%) and more likely to receive radiation therapy alone (19.8% vs 5.4%) ($p<0.001$), while rates of chemoradiation (66.7% vs 58%) were comparable. Following stratification by type of adjuvant treatment for patients who received radiation alone, the rate of external beam radiotherapy use (with or without vaginal brachytherapy) was 89.7% and 62.5% in the systematic lymphadenectomy and sentinel lymph node biopsy only groups, respectively ($p=0.011$). Similarly, for patients who received chemoradiation, the rate of external beam radiotherapy (with or without vaginal brachytherapy) was 83.4% and 64.8% in the systematic lymphadenectomy and sentinel lymph node biopsy only groups ($p<0.001$). The aforementioned adjuvant treatment differences were present even after stratification by number of positive lymph nodes (1 positive lymph node, 2 positive lymph nodes, and >3 positive lymph nodes).

Based on the reverse Kaplan–Meier methods, median follow-up of the sentinel lymph node biopsy only and systematic lymphadenectomy groups was 28.3 and 36.0 months, respectively. There was no difference in overall survival between patients who had sentinel lymph node biopsy and systematic lymphadenectomy ($p=0.27$ from log rank test), and 3 year overall survival rates were 82.2% and 79.4%, respectively (Figure 1). After controlling

Table 1 Clinicopathological characteristics of patients with lymph node positive endometrial carcinoma who underwent minimally invasive hysterectomy and systematic lymphadenectomy or sentinel lymph node biopsy only

	LND (n=1323) (n (%))	SLNBx only (n=109) (n (%))	P value
Age (years)			0.008
<65	733 (55.4)	46 (42.2)	
≥65	590 (44.6)	63 (57.8)	
Race			0.77
White	1115 (84.3)	93 (85.3)	
Other/unknown	208 (15.7)	16 (14.7)	
Comorbidities			0.15
No	1000 (75.6)	89 (81.7)	
Yes	323 (24.4)	20 (18.3)	
Insurance			0.17
Private	647 (48.9)	53 (48.6)	
Government	615 (46.5)	55 (50.5)	
Uninsured/unknown	61 (4.6)	*	
Reporting facility			<0.001
Academic	652 (49.9)	79 (74.5)	
Non-academic	655 (50.1)	27 (25.5)	
Histology			0.15
Endometrioid	785 (59.3)	75 (68.8)	
Serous/clear cell/carcinosarcoma	317 (24)	19 (17.4)	
Mixed/other	221 (16.7)	15 (13.8)	
Approach			0.13
Laparoscopic	288 (21.8)	17 (15.6)	
Robotic assisted	1035 (78.2)	92 (84.4)	
Lymph-vascular invasion			0.95
Present	840 (68.2)	74 (68.5)	
Absent	391 (31.8)	34 (31.5)	
Tumor size (cm)			0.06
<2	85 (7.1)	*	
2–4	330 (27.5)	25 (39.7)	
≥4	785 (65.4)	32 (50.8)	
Adjuvant therapy†			<0.001
None	145 (13.4)	16 (16.5)	
Radiation therapy only	51 (4.7)	16 (16.5)	
Chemotherapy only	343 (31.7)	11 (11.3)	
Chemoradiation	543 (50.2)	54 (55.7)	
No of positive lymph nodes			<0.001
1	529 (40)	72 (66.1)	
2	238 (18)	19 (17.4)	
≥3	556 (42)	18 (16.7)	

Missing values: type of treatment facility, 19 cases; tumor size, 169 cases; lymph-vascular invasion, 93 cases.

*Suppressed, n<10 per agreement with National Cancer Database.

†Adjuvant treatment: excluded 253 cases (187 patients received chemotherapy >6 months after surgery, 63 had an unknown surgery-chemotherapy/radiotherapy interval, and 3 patients received radiation therapy >6 months after surgery).

LND, lymphadenectomy; SLNBx, sentinel lymph node biopsy.

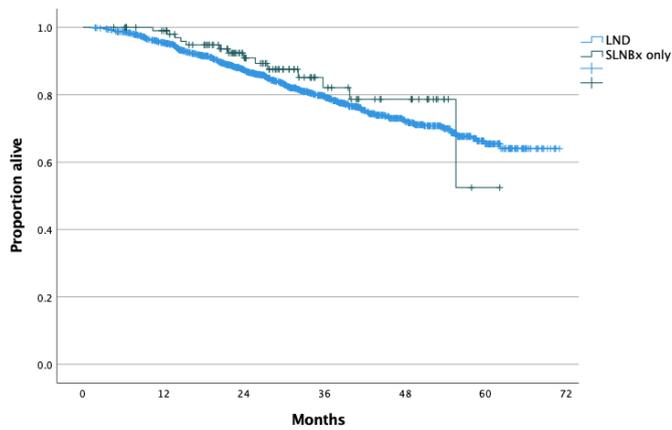


Figure 1 Overall survival of patients with lymph node positive endometrial carcinoma who underwent minimally invasive hysterectomy and sentinel lymph node biopsy (SLNBx) alone or comprehensive lymphadenectomy (LND).

for patient age, race, insurance status, tumor histology, extent of disease, presence of lymph–vascular invasion, and type of adjuvant treatment, there was no difference in survival between the systematic lymphadenectomy and sentinel lymph node biopsy groups (hazard ratio 0.82, 95% confidence interval 0.46 to 1.45) (Table 2).

Following stratification by tumor histology, there was no difference between the sentinel lymph node biopsy only and the systematic lymphadenectomy groups for patients with grade 1/2 endometrioid ($p=0.62$; 3 year overall survival rate 90.5% vs 93.9%) or high grade (grade 3 endometrioid, serous, clear cell, carcinosarcoma) tumors ($p=0.79$; 3 year overall survival rate 64.8% vs 65.2%) (online supplemental Figures 1 and 2). Following stratification by type of adjuvant treatment received, there was no difference in overall survival between the sentinel lymph node biopsy and systematic lymphadenectomy groups for patients who received chemotherapy only ($p=0.21$; 3 year overall survival rate 100% vs 73%), chemoradiation ($p=0.94$; 3 year overall survival rate 84.8% vs 86%), or radiotherapy alone ($p=0.43$; 3 year overall survival rate 78.6% vs 78.6%). Lastly, there was no difference in overall survival between the sentinel lymph node biopsy and systematic lymphadenectomy groups for patients who had one positive lymph node ($p=0.75$; 3 year overall survival rate 76% vs 84.2%) or those who had more than one positive lymph node ($p=0.16$; 3 year overall survival rate 93.9% vs 76.5%).

DISCUSSION

Summary of Main Results

In a large cohort of patients with stage IIIC endometrial carcinoma, performance of sentinel lymph node biopsy only was not associated with worse survival compared with systematic lymphadenectomy. Interestingly, while the majority of patients in both groups received adjuvant treatment, the patterns of adjuvant treatment differed between the sentinel lymph node biopsy only and systematic lymphadenectomy groups. However, stratified analyses based on the type of adjuvant treatment received did not reveal any survival difference. Lastly, we noted an increase in the utilization of sentinel lymph node biopsy only per year of diagnosis, while patients who had sentinel lymph node biopsy only were more likely to be

Table 2 Results of Cox multivariate analysis

Age (years)	
<65	Ref
≥65	1.47 (1.05 to 2.04)
Race	
White	Ref
Black	1.27 (0.87 to 1.85)
Other/unknown	1.42 (0.78 to 2.55)
Insurance	
Private	Ref
Government	1.13 (0.81 to 1.58)
Uninsured/unknown	1.17 (0.60 to 2.26)
Histology	
Endometrioid	Ref
Serous/clear cell/ carcinosarcoma	3.08 (2.25 to 4.21)
Mixed/other	2.16 (1.52 to 3.08)
Lymph–vascular invasion	
Absent	Ref
Present	1.50 (1.11 to 2.04)
Adjuvant therapy	
None	Ref
Chemotherapy only	0.56 (0.39 to 0.80)
Chemoradiation	0.35 (0.24 to 0.50)
Radiation therapy only	0.50 (0.27 to 0.96)
Type of lymph node assessment	
LND	Ref
SLNBx	0.82 (0.46 to 1.45)

LND, lymphadenectomy; SLNBx, sentinel lymph node biopsy.

managed at academic institutions, demonstrating a more rapid adoption of novel techniques in the academic setting.

Results in the Context of Published Literature

While the survival benefit of systematic lymphadenectomy has not been proven in two previously published studies,^{3,4} the performance of lymphadenectomy as part of staging aims in identifying occult lymph node metastases and guiding adjuvant treatment.^{3,4} The sentinel lymph node biopsy technique has emerged as a less invasive alternative approach to endometrial cancer staging, sparing patients from the significant morbidity associated with systematic lymphadenectomy.^{17,18} Studies have demonstrated that systematic lymphadenectomy results in prolonged operative time, increased blood loss and risk of operative injuries, and especially increased prevalence of postoperative lower extremity lymphedema, a complication with a detrimental effect on the quality of life of cancer survivors.^{17,18} A recent analysis of the National Cancer Database also demonstrated better perioperative outcomes and a lower risk of conversion to open surgery for patients undergoing sentinel lymph node biopsy.¹⁹

Evidence on the survival outcomes of patients undergoing sentinel lymph node biopsy is currently emerging. A recent

Original research

systematic review and meta-analysis identified only six studies comparing relapse rates of patients undergoing sentinel lymph node biopsy versus systematic lymphadenectomy²⁰; overall relapse (4.3% vs 7.3%, $p=0.29$) and nodal relapse (1.2% vs 1.7%, $p=0.29$) rates were comparable between the sentinel lymph node biopsy and systematic lymphadenectomy groups ($p=0.63$). However, the majority of studies included a very small number of patients with positive lymph nodes.²⁰ In the largest study to date, outcomes of 104 patients with non-bulky stage IIIc endometrial carcinoma drawn from two large institutions were examined; 48 and 56 patients had systematic lymphadenectomy or sentinel lymph node biopsy algorithm, respectively.²¹ Similar to our study, the median number of lymph nodes removed was higher in the systematic lymphadenectomy group (median 33 vs 12, $p<0.001$). Similar to our study, 13.5% ($n=14$) of patients did not receive any adjuvant treatment. Patterns of adjuvant treatment differed between the two groups. Contrary to our study, the rate of radiation therapy alone was higher in the systematic lymphadenectomy groups (15% vs 2%, $p=0.02$), while rates of chemoradiation (46% vs 50%) were comparable. Similar to our results, risk of progression was comparable between the two groups (hazard ratio 1.27, 95% confidence interval 0.60 to 2.67; $p=0.53$). The authors concluded that the biology of the tumor and type of postoperative treatment were the strongest predictors of prognosis. It should be mentioned that in the aforementioned study, the sentinel lymph node biopsy algorithm group included patients who had ipsilateral or bilateral lymphadenectomy due to mapping failures or surgeon learning curve.

In a recent multi-institutional study that used propensity score matching, Bogani et al compared the long term survival of 180 patients with apparent early stage endometrial cancer who underwent systematic lymphadenectomy, with 90 patients who had sentinel lymph node biopsy alone and 90 patients who had sentinel lymph node biopsy followed by systematic lymphadenectomy.²² In that study, the incidence of lymph node metastasis was 10%. After a median follow-up of 69 months, there was no difference between the three groups in terms of disease free survival and overall survival.²² For patients who had positive sentinel lymph nodes ($n=24$), performance of back-up lymphadenectomy had no impact on disease free survival or overall survival.²² Similarly, another retrospective study examined the oncologic outcomes of patients with deeply invasive endometrioid endometrial carcinoma based on type of lymph node assessment.²³ A total of 94 patients who had systematic lymphadenectomy and 82 patients who had sentinel lymph node biopsy were identified. After controlling for confounders, type of lymph node assessment was not associated with overall or recurrence free survival.²³ Comparable results were also reported for patients with endometrioid endometrial carcinoma and limited myoinvasion.²⁴

In our study, we observed differences in the pattern of adjuvant treatment between patients who underwent systematic lymphadenectomy and sentinel lymph node biopsy only. These differences could be related to patient age (those who had sentinel lymph node biopsy were older), type of treatment facility (patients who underwent sentinel lymph node biopsy were more likely to be treated in academic/research facilities), or year of diagnosis. Unfortunately, the National Cancer Database does not collect data on individual comorbidities or physician preferences that could additionally explain differences in adjuvant treatment patterns. Whether

these differences are also related to the inclusion of patients with isolated tumor cells or micrometastases was not verified because the National Cancer Database does not collect data on the type of metastatic disease. However, we expect the overall percentage of patients with isolated tumor cells or micrometastases classified as lymph node positive in our study to be small. Ultrastaging is recommended when evaluating sentinel lymph nodes and small tumor deposits, such as isolated tumor cells (isolated tumor cells, size ≤ 0.2 mm), micrometastases (size 0.2–2 mm) can be detected compared with standard pathological techniques.²⁵ The prognostic significance of low volume lymph node metastases and optimal management of patients with isolated tumor cells or micrometastases is not well defined and is an area of ongoing research.^{25 26} Several studies suggest that uterine factors should drive the decision to administer adjuvant treatment for patients with isolated tumor cells.^{25 26} A recent systematic review of the literature and meta-analysis identified eight studies reporting a total of 187 patients with micrometastases and 99 patients with isolated tumor cells.²⁶ The majority (72%) did receive adjuvant treatment but they had an increased risk of relapse (odds ratio 1.34, 95% confidence interval 1.07 to 1.67) compared with patients with negative sentinel lymph nodes.²⁶

Strengths and Weaknesses

Several limitations of the present study should be noted. First, while we queried a large hospital database, one could argue that the number of patients who underwent sentinel lymph node alone was relatively small. While during the study enrollment years (2012–2015) the sentinel lymph node technique was not widely adopted, as demonstrated by the increasing percentage, we suspect that a number of cases may have been missed secondary to coding misclassifications. Moreover, given the lack of central pathology review, tumor and stage misclassifications cannot be excluded. In addition, we could not verify if ultrastaging was performed for all sentinel lymph nodes and we could not analyze the volume of metastatic disease (isolated tumor cells, micrometastases, macrometastases). Also, the National Cancer Database does not collect data on tumor relapse, location of relapse, or cause of death, precluding us from analyzing progression free, cause specific survival and patterns of recurrence. No data on the preoperative imaging and intraoperative appearance of lymph nodes were available and thus our population (especially systematic lymphadenectomy group) may have included patients with bulky lymph nodes. In our study, a small percentage of patients (~14%) did not receive adjuvant treatment for unclear reasons (patient refusal, poor functional status). The National Cancer Database does not collect exact surgical details related to the surgeon's choice, failure of sentinel lymph nodes to map, location of resected lymph nodes, location of positive lymph nodes, and whether excision of any grossly enlarged lymph nodes was performed. Lastly, while 82% of patients who underwent systematic lymphadenectomy had para-aortic lymphadenectomy, we could not verify the upper borders of lymph node dissection (inferior mesenteric or renal vessels).

Implications for Practice and Future Research

The results of our study support the utilization of sentinel lymph node biopsy for patients with endometrial carcinoma and refute a therapeutic impact of systematic lymphadenectomy for patients

with positive lymph nodes. However, additional prospective studies with adequate follow-up are needed to further validate the oncologic safety of sentinel lymph node biopsy.

CONCLUSIONS

In a large cohort of patients with lymph node positive endometrial carcinoma who underwent minimally invasive hysterectomy, performance of sentinel lymph node biopsy alone was not associated with a detrimental effect on overall survival compared with systematic lymphadenectomy.

Contributors DN: conception, data acquisition, data management, statistical analysis, critical analysis, and drafting/final editing. MB: conception, critical analysis, and drafting/final editing. EMK, AFH, LC, SK, MM, and RLG: critical analysis and drafting/final editing. NL: supervision, critical analysis, and drafting/final editing.

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