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Three Lymphadenectomy Strategies in Low-Risk Endometrial Carcinoma: A Cost-Effectiveness Analysis

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Abstract

Objective—To evaluate the cost-utility of 3 lymphadenectomy strategies in the management of low-risk endometrial carcinoma.

Methods—A decision analysis model compared three lymphadenectomy strategies in women undergoing minimally invasive surgery (MIS) for low-risk endometrial carcinoma: 1) routine lymphadenectomy in all patients; 2) selective lymphadenectomy based on intraoperative frozen section criteria; and 3) sentinel lymph node mapping. Costs and outcomes were obtained from published literature and Medicare reimbursement rates. Costs categories consisted of hospital, physician, operating room, pathology, and lymphedema treatment. Effectiveness was defined as 3-year disease-specific survival adjusted for the impact of lymphedema (utility = 0.8) on quality of life. A cost-utility analysis was performed comparing the different strategies. Multiple deterministic sensitivity analyses were done.

Results—In the base-case scenario, routine lymphadenectomy had a cost of \$18,041 and an effectiveness of 2.79 quality-adjusted life years (QALYs). Selective lymphadenectomy had a cost of \$17,036 and an effectiveness of 2.81 QALYs, while sentinel lymph node mapping had a cost of \$16,401 and an effectiveness of 2.87 QALYs. With a difference of \$1,005 and 0.02 QALYs, selective lymphadenectomy was both less costly and more effective than routine lymphadenectomy, dominating it. However, with the lowest cost and highest effectiveness, sentinel lymph node mapping dominated the other modalities and was the most cost-effective strategy. These findings were robust to multiple sensitivity analyses varying the rates of lymphedema and

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lymphadenectomy, surgical approach (open or MIS), lymphedema utility, and costs. For the estimated 40,000 women undergoing surgery for low-risk endometrial carcinoma each year in the United States, the annual cost of routine lymphadenectomy, selective lymphadenectomy, and sentinel lymph node mapping would be \$722 million, \$681 million, and \$656 million, respectively.

Conclusion—Compared to routine and selective lymphadenectomy, sentinel lymph node mapping had the lowest costs and highest quality-adjusted survival, making it the most cost-effective strategy in the management of low-risk endometrial carcinoma.

Introduction

Historically, the standard surgical management of endometrial cancer included a routine full pelvic lymph node dissection (LND). As two trials have shown no survival advantage for full LND, critics of this approach argue that it increases surgical morbidity without any appreciable diagnostic benefit and no survival gain, especially in 'low-risk' disease'.¹⁻³

Although no consensus exists as to the definition of 'low-risk' patients, some investigators have shown that patients with Grade 1-2 endometrioid histology, tumor size ≤ 2 cm, and 50% myometrial invasion on frozen section have only a 5% chance of nodal metastasis, and have concluded that LND may be omitted in them.^{4,5} Critics of selective LND based on these criteria argue against the accuracy of frozen section, and that some women with advanced cancer will be inadequately staged.⁶ Sentinel lymph node (SLN) mapping is an alternative strategy. Proponents say that it diminishes the risk of lymphedema with routine LND and minimizes the risk of inadequately staging certain patients with selective LND, while critics point out the risk of inaccurate mapping and the possibility of missing disease.^{3,7}

As healthcare costs continue to rise, it is essential to scrutinize not only the benefit of different approaches but also their costs. Prior cost-effectiveness analyses comparing routine and selective LND have had conflicting results, however no studies to date have assessed the cost-effectiveness of a SLN algorithm in comparison to other management strategies.^{8,9} Our objective was to evaluate the cost-utility of SLN mapping, selective LND, and routine LND in the management of low-risk endometrial carcinoma.

Materials and Methods

Low-risk endometrial carcinoma was defined as clinical Stage 1 disease with Grade 1-2 endometrioid histology on preoperative endometrial biopsy. A decision analysis model (Fig. 1) was constructed comparing 3 LND strategies in women undergoing minimally invasive surgery (MIS) for low-risk carcinoma: 1) routine LND in all patients; 2) selective LND based on intraoperative frozen section (Mayo Clinic criteria), in which approximately 60% of patients undergo LND;^{4,10} and 3) SLN mapping based on the Memorial Sloan Kettering algorithm.⁷ The SLN algorithm includes the pathologic ultra-staging of SLN, and the performance of a side-specific pelvic LND if no mapping occurs on a hemi-pelvis. Based on their most recently published data, 80% of patients map to both sides of the pelvis, 15% map unilaterally and require a contralateral side-specific LND, and 5% do not map and require a

bilateral LND.^{7,11} All patients in the 3 arms underwent hysterectomy and bilateral salpingo-oophorectomy. MIS was chosen for the base-case analysis as that is the most common modality used to treat endometrial carcinoma in the United States. The University of Texas MD Anderson Cancer Center Institutional Review Board exempted this study from approval.

The model was constructed using data from the published literature and clinical estimates. Clinical outcomes used are shown in Table 1. The rate of lymphedema after full LND for endometrial cancer varies from 3-38% in the literature, thus 20% was chosen for the base-case scenario.^{3,12-14} There are no published data on the risk of lymphedema with SLN, however studies have shown that patients who had less than 5 lymph nodes (LN) excised had a 0-9% risk of developing it.¹⁴⁻¹⁶ Therefore 5% was chosen as a conservative estimate for the SLN arm. Because not all patients who undergo SLN map bilaterally successfully, 'weighted SLN' adjusts for the fact that 15% of patients require a unilateral LND, and 5% require a bilateral LND. The rate of lymphedema was thus estimated to be slightly higher in the SLN arm, and 'weighted SLN' was used for all our analysis. The utility of lymphedema was considered to be 0.8, based on a large study by Cheville and colleagues assessing the impact of lower extremity lymphedema on quality of life (QOL).¹⁷ Lymphedema was chosen as the main factor affecting QOL as it is often cited as the main complication from full LND, and can have a debilitating effect on patients when significant.^{14,16} Published 3-year disease specific survival (DSS) and overall survival (OS) rates were obtained from the report by Zahl-Eriksson et al, which was a non-randomized study comparing patients who underwent SLN mapping and selective LND at two institutions.¹⁸ In that study, patients in the SLN arm had a significant increase in 3-year DSS (100% vs 98.8%), however a non-significant increase in OS (97.4% vs 95.4%). Additional operating room time needed was estimated for frozen section, LND, and SLN mapping.

The analysis was performed from the perspective of a third-party payer. 2016 Medicare reimbursement rates were used to calculate estimates of costs. Cost categories consisted of hospital, physician, operating room, pathology, and lymphedema treatment (Table 2). The hospital cost of surgery was \$11,697, based on DRG code #740. Surgeon, anesthesia, and pathology fees were obtained from the Medicare Physician Fee Schedule using relevant Current Procedural Terminology (CPT) codes.^{19,20} Pathology costs included the cost of ultra-staging and frozen section, and 'weighted SLN' was used for both surgeon and pathology fees. Additional operating room time was estimated to cost \$30/minute.²¹ Lymphedema treatment costs were estimated at \$2500/year based on a previous study.⁸ Other long-term costs were excluded as they were considered to be equivalent in the 3 arms. Costs were reported in US dollars and were adjusted to 2016 currency values.

A cost-utility analysis was performed comparing the different strategies. A cost-utility analysis is a cost-effectiveness analysis that takes into account cost, survival, and QOL. Effectiveness was defined as 3-year DSS adjusted for the impact of lymphedema on QOL. DSS was used as it was an outcome that was significantly different between LND strategies in the analysis by Zahl-Eriksson et al.¹⁸ The time horizon for our analysis was considered to be 3 years. This was chosen as we based our effectiveness outcome on Zahl-Eriksson et al's study, which is the only one in the literature comparing survival between SLN mapping and selective LND, and which published 3-year survival outcomes. We planned to calculate

incremental cost-effectiveness ratios. Quality-adjusted life years (QALYs) and costs were discounted at an annual 3% rate. Multiple deterministic sensitivity analyses were performed varying the surgical approach (open vs MIS), effectiveness outcome (OS vs DSS), the rates of lymphedema and LND, lymphedema utility, the rate of successful SLN mapping, and costs. Analysis was done using TreeAge Pro 2016 Software (Williamston, MA).

Results

In the base-case scenario, routine LND had a cost of \$18,041/patient and an effectiveness of 2.79 QALYs. The cost was calculated as a summation of the following: hospital (\$11,697), surgeon (\$1,878), anesthesia (\$592), pathology (\$1,517), additional OR time (\$900), and lymphedema treatment (\$1,457). Selective LND had a cost of \$17,036/patient and an effectiveness of 2.81 QALYs, while SLN mapping had a cost of \$16,401/patient and an effectiveness of 2.87 QALYs. When comparing selective to routine LND, the selective LND arm was both less costly (\$1005) and more effective (0.02 QALYs) than routine LND, making it the dominant arm. However, when comparing all 3 strategies, the SLN mapping arm had both the lowest cost and highest effectiveness, dominating the other modalities, and was thus the most cost-effective strategy (Table 3). No incremental cost-effectiveness ratio could be determined because the SLN mapping arm was both less costly and more effective. For the estimated 40,000 women undergoing surgery for low-risk endometrial carcinoma each year in the United States, the annual cost would be \$722 million, \$681 million, and \$656 million, if all underwent routine LND, selective LND, and SLN, respectively (assuming all get MIS).

In order to assess the robustness of these results, we performed several sensitivity analyses adjusting different parameters. In the first sensitivity analysis, we assumed all patients underwent open surgery and used cost estimates for that as opposed to MIS costs (Table 4). In the second analysis, we changed the effectiveness outcome and looked at quality-adjusted 3-year OS instead of DSS (Table 5). SLN mapping remained the most cost-effective strategy in each case.

We also performed multiple other deterministic sensitivity analyses on selected variables in the model across the ranges specified in Tables 1 and 2. We varied the risk of lymphedema in different LN strategies, lymphedema utility, the rate of LND in the selective LND arm, successful SLN mapping rates, survival estimates, additional operating room time needed, and costs. For example, in one analysis, we assumed that the risk of lymphedema was 10%, 0%, and 0% for patients with routine LND, SLN, and no LND, respectively; which impacted the total lymphedema treatment costs in each arm. In this scenario, SLN mapping was still the least costly at \$15,895/patient, compared to \$16,599/patient for selective LND and \$17,312/patient for routine LND. With SLN mapping having the highest effectiveness, it remained the dominant strategy.

In another analysis, we changed several variables simultaneously: we assumed different lymphedema risks (30%, 10%, and 5% for routine LND, SLN, and no LND, respectively), increased the lymphedema utility to 0.95, estimated that 50% of women in the selective LND arm undergo LND, increased additional operating room time needed (60 min for LND,

30 min for SLN, and 25 min for frozen section), and assumed equivalent 3-yr DSS for all 3 arms (95%). Routine LND thus had a cost of \$19,699/patient and an effectiveness of 2.72 QALYs. Selective LND had a cost of \$17,757/patient and an effectiveness of 2.74 QALYs, while SLN mapping had a cost of \$16,998/patient and an effectiveness of 2.75 QALYs. In this analysis and other ones using different estimates for various parameters, SLN mapping remained the most cost-effective approach.

Discussion

In this cost-utility analysis, selective LND was more cost-effective than routine LND in patients undergoing surgery for low-risk endometrial carcinoma. However, compared to routine and selective LND, SLN mapping had the lowest costs and highest quality-adjusted survival, making it the most cost-effective strategy.

There is debate regarding the optimal approach to LND in endometrial cancer. While routine LND was traditionally considered standard of care, some investigators have proposed a selective LND approach, after identifying a cohort of patients for whom LND could be omitted.^{2,22} Others have advocated a SLN mapping strategy, arguing that it decreases the risk of under-staging some patients with selective LND, while minimizing the risk of lymphedema with routine LND.³ A prospective study has suggested that SLN mapping has a high degree of diagnostic accuracy in detecting metastasis, and can safely replace routine LND.²³ Zahl-Eriksson et al concluded that either selective LND or SLN mapping were acceptable for staging, with no apparent detriment to the use of a SLN algorithm.¹⁸

There are several reasons why the SLN mapping strategy was most cost-effective. First, when looking at effectiveness, SLN mapping was associated with improved 3-year DSS when compared to selective LND.¹⁸ When adjusting for the impact of lymphedema on QOL, the difference became even more pronounced, as SLN mapping theoretically leads to less lymphedema than both selective and routine LND.^{17,24} With regards to costs, routine LND had the highest costs due to having the highest surgeon (\$1878), pathology (\$1517), and lymphedema treatment (\$1457) costs. Compared to selective LND, SLN mapping had slightly higher surgeon (\$1621 vs \$1493) and pathology (\$1340 vs \$1240) fees, but significantly less operating room time (\$645 vs \$1140) and lymphedema treatment (\$506 vs \$874) costs, making it the least costly arm. The selective LND arm had the longest operating room time given the need for frozen section on all cases and LND on 60% of the patients. If the time horizon of our study was longer than 3 years, it is possible the cost differences would be even more pronounced when accounting for lymphedema treatment.

Our study has several limitations. Costs were based on Medicare reimbursement rates, which may or may not reflect commercial insurance reimbursement, or the cost of delivering care from a hospital or provider perspective.¹⁹ While published data were used for most parameters, clinical assumptions were made when data was unavailable. Indeed, our biggest assumption was that SLN mapping is associated with a decreased risk of lymphedema compared to LND. While there are no data to support this, we based our assumption on several studies showing that having <5 LNs excised was associated with a much smaller risk of developing lymphedema.¹³⁻¹⁶ Additionally, when looking at effectiveness, the QALY

difference between the different LND arms was small. This can be attributed to the fact that our time horizon was 3 years, and that most patients with low-risk cancer tend to have good clinical outcomes. The 3-year limit was chosen as we based our effectiveness outcome on Zahl-Eriksson et al's study, which was the only one in the literature comparing survival between SLN mapping and selective LND, and which used 3-year survival outcomes.¹⁸ This can also be considered a limitation, as the conclusions regarding effectiveness were based on that study's reported survivals. Future studies that report survival may enhance or diminish our conclusions, therefore they should be interpreted with caution until validated. Additionally, we did not account for the impact of adjuvant pelvic radiation therapy on costs or QOL.

The major strength of our study lies in the fact that we compared all 3 LND strategies currently in practice in this population, and we assessed the cost-effectiveness of SLN mapping in this setting. In addition, our effectiveness outcome was based on published survival data and quality-adjusted for the impact of lymphedema. Indeed, previous analyses comparing routine and selective LND were cost-effectiveness analyses, while ours was a cost-utility study, which is a cost-effectiveness analysis that takes QOL into account.^{8,9} In addition, our findings were robust to multiple sensitivity analyses, which further support our results.

In conclusion, our study showed that SLN mapping was the most cost-effective strategy in the upfront surgical management of low-risk endometrial carcinoma (clinical Stage 1 disease with Grade 1-2 endometrioid histology). This adds to the body of literature evaluating the clinical benefits of this strategy, and may help providers in the decision-making process as they consider which approach to use. Continued research into the costs and effectiveness of different LND strategies is needed.

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Figure 1.
Decision analysis model comparing three lymphadenectomy strategies in women undergoing surgery for low-risk endometrial carcinoma.

Table 1
Clinical parameter estimates and ranges

Parameter	Base-case estimate	Range for sensitivity analysis
Risk of lymphedema ^{3,12-16}		
LND	20%	10 – 30%
SLN	5%	0 – 10%
Weighted SLN *	7%	0 – 13%
No LND	0%	0 – 5%
Lymphedema utility ¹⁷	0.8	0.7 – 0.95
% of pts who undergo LND in selective LND arm ^{4,10}	60%	50 – 75%
SLN mapping rates ^{7,11}		
Bilateral	80%	50 – 90%
Unilateral	15%	10 – 30%
No mapping	5%	0 – 20%
3-year disease-specific survival ¹⁸		
SLN arm	100%	95% – 100%
Selective LND arm	98.8%	95% – 100%
Routine LND arm	100%	95% – 100%
3-year overall survival ¹⁸		
SLN arm	97.4%	95% – 100%
Selective LND arm	95.4%	95% – 100%
Routine LND arm	98.0%	95% – 100%
Operating room time (additional minutes needed)		
Frozen section	20 min	15 – 25 min
LND	30 min	30 – 60 min
SLN	20 min	15 – 30 min
Weighted SLN *	22 min	17 – 34 min

LND: lymphadenectomy; SLN: sentinel lymph node mapping

* Weighted SLN adjusts for the fact that 80% of patients map bilaterally, 15% map unilaterally and require a contralateral side-specific LND, and 5% do not map and require a bilateral LND (base-case estimate)

Table 2
Cost estimates

Cost category	Base-case estimate	Range for sensitivity analysis	CPT codes
Hospital fee	\$11,697		DRG #740
Surgeon fee (minimally invasive surgery) ¹⁹			
Hysterectomy/BSO	\$916		58571, 38572, 38900, 38570
Hysterectomy/BSO + LND	\$1,878		
Hysterectomy/BSO + SLN	\$1,581		
Weighted Hysterectomy/BSO + SLN *	\$1,621		
Surgeon fee (open surgery) ¹⁹			
Hysterectomy/BSO	\$1,033		58150, 58210, 58200, 38900
Hysterectomy/BSO + LND	\$1,896		
Hysterectomy/BSO + SLN	\$1,548		
Weighted Hysterectomy/BSO + SLN *	\$1,639		
Anesthesiologist fee ²⁰	\$592		00846
Pathology fee ¹⁹			
Hysterectomy/BSO + LND	\$1,517		88309, 88307, 88342, 88331
Selective LN Arm			
Hysterectomy/BSO + Frozen section + No LND	\$678		
Hysterectomy/BSO + Frozen section + LND	\$1,614		
Hysterectomy/BSO + SLN (including ultra-staging)	\$1,312		
Weighted Hysterectomy/BSO + SLN *	\$1,340		
Operating room cost/minute ²¹	\$30	\$30 – 60	
Lymphedema treatment cost/year ⁸	\$2,500	\$2,500 – 5,000	

LND: lymphadenectomy;SLN: sentinel lymph node mapping;BSO: bilateral salpingo-oophorectomy;

* Weighted SLN adjusts for the fact that 80% of patients map bilaterally, 15% map unilaterally and require a contralateral side-specific LND, and 5% do not map and require a bilateral LND (base-case estimate)

Table 3

Results of the cost-utility model: Base-case analysis

LND Strategy	Cost	Incremental Cost	Effectiveness (QALY)	Incremental Effectiveness	ICER
SLN	\$16,401		2.87 QALYs		
Selective LND	\$17,036	\$635	2.81 QALYs	- 0.06 QALYs	Dominated
Routine LND	\$18,041	\$1005	2.79 QALYs	- 0.02 QALYs	Dominated

SLN: sentinel lymph node mapping; LND: lymphadenectomy; QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio

Table 4

Sensitivity analysis 1: Open surgery

LND Strategy	Cost	Incremental Cost	Effectiveness (QALY)	Incremental Effectiveness	ICER
SLN	\$16,419		2.87 QALYs		
Selective LND	\$17,093	\$674	2.81 QALYs	- 0.06 QALYs	Dominated
Routine LND	\$18,059	\$966	2.79 QALYs	- 0.02 QALYs	Dominated

SLN: sentinel lymph node mapping; LND: lymphadenectomy; QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio

Table 5

Sensitivity analysis 2: Quality-adjusted 3-year overall survival

LND Strategy	Cost	Incremental Cost	Effectiveness (QALY)	Incremental Effectiveness	ICER
SLN	\$16,401		2.79 QALYs		
Selective LND	\$17,036	\$635	2.71 QALYs	- 0.08 QALYs	Dominated
Routine LND	\$18,041	\$1005	2.74 QALYs	0.03 QALYs	Dominated

SLN: sentinel lymph node mapping; LND: lymphadenectomy; QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio