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Cost-effectiveness analysis of sentinel lymph node biopsy in the treatment of early-stage vulvar cancer

Britt K. Erickson, MD¹, Laura M. Divine, MD², Charles A. Leath III, MD¹, J. Michael Straughn Jr., MD¹

¹Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, Alabama

²Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, Alabama

Abstract

Objective—The objective of this study was to determine the costs and outcomes of inguinal-femoral lymph node dissection (IF-LND) versus sentinel lymph node biopsy (SLNB) for the management of early-stage vulvar cancer.

Methods—A cost-effectiveness model compared two different strategies for the management of early-stage vulvar cancer: 1) vulvectomy and SLNB; 2) vulvectomy and IF-LND. Probabilities of inguinal-femoral node metastases and recurrence rates associated with each strategy were estimated from published data. Actual payer costs of surgery and radiation therapy were obtained using 2012 CPT codes and Medicare payment information. Rates and costs of postoperative complications including lymphedema, lymphocyst formation, and infection were estimated and included in a separate model. Cost-effectiveness ratios were determined for each strategy. Sensitivity analyses were performed to evaluate pertinent uncertainties in the models.

Results—For the estimated 3,000 women diagnosed annually with early-stage vulvar cancer in the United States, the annual cost of the SLNB strategy is \$65.2 million (M) compared with \$76.8M for the IF-LND strategy. 3-year inguinal-femoral recurrence free survival was similar between groups (96.9% vs. 97.3%). This translates into a lower C/E ratio for the SLNB strategy, (\$22,416), compared with the IF-LND strategy (\$26,344). When adding complication costs to the model, C/E ratios further favor the SLNB strategy (\$23,711 vs. \$31,198). Sensitivity analysis revealed that the SLNB strategy remained cost-effective until the recurrence rate after a negative sentinel lymph node approaches 9%.

Conclusions—SLNB is the most cost-effective strategy for the management of patients with early-stage vulvar cancer due to lower treatment costs and lower costs due to complications.

Corresponding Author: Britt K. Erickson, M.D., University of Alabama at Birmingham, 176F Room 5329, 619 19th Street South, Birmingham AL, 35294 britte@uab.edu Phone: 205-317-8019 or 205-934-5631 Fax: 205-975-6411.

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Keywords

Cost-effectiveness analysis; Vulvar cancer; Sentinel lymph node biopsy; Inguinal-femoral lymph node dissection; Postoperative Complications

BACKGROUND

Vulvar cancer is a relatively uncommon malignancy that may be treated with surgery for early stage disease or multi-modality therapy for advanced stage disease. Although patients with lateralized lesions less than 2 cm in dimension with less than 1 mm of invasion may be treated with a simple vulvectomy, the standard treatment for most patients with early-stage vulvar cancer includes radical vulvectomy with inguinal-femoral lymph node dissection (IF-LND). Complications from this procedure include wound infection or breakdown in 20–40% of patients, and lower extremity lymphedema in 30–70% of patients^{1–3}. Moreover, less than one-third of patients have positive nodes thus exposing a large number of women to potentially avoidable surgical morbidity².

The sentinel lymph node biopsy (SLNB) procedure was first introduced as a surgical technique in the treatment of cutaneous melanoma and is now the standard of care for the surgical management of both melanoma and breast cancer^{4,5}. SLNB is based on the principle that metastases spread via lymphatic drainage from a primary tumor to the regional nodes in a direct and predictable pathway. Pathologic assessment of the first or “sentinel” lymph node can predict whether the remaining lymph nodes are negative or positive for metastatic disease. The sentinel node can be identified intraoperatively after injection with either blue dye or radiocolloid or both into the vulvar lesion. This sentinel node is excised and assessed for malignancy; if the node is negative, then no further lymph node dissection is performed.

In an effort to reduce the morbidity associated with IF-LND, SLNB has been evaluated in the treatment of early-stage vulvar disease. Van der Zee first reported on the clinical utility of SLNB in vulvar cancer in a large observational trial from the Netherlands². In a study that included 259 patients with unifocal vulvar disease and negative sentinel nodes, SLNB was feasible and associated with a 2.3% groin recurrence rate and a 97% 3-year survival. Several trials and a recent meta-analysis have evaluated the safety and negative predictive value of SLNB in patients with early-stage vulvar cancer^{1,2,6,7}. Clinical trial results support the integration of SLNB in the primary management of early-stage vulvar cancer^{1,2}. The objective of our study was to determine if SLNB is a cost-effective strategy to manage patients with early-stage vulvar cancer.

METHODS

Of the estimated 4,500 patients diagnosed with vulvar cancer in the United States annually, approximately 65% will be early-stage (confined to the vulva)⁸. A cost-effectiveness analysis was performed to evaluate a hypothetical cohort of 3,000 patients with Stage I (FIGO 2009) vulvar cancer requiring surgery. This model evaluated the costs and outcomes of two strategies: (1) radical vulvectomy with SLNB and (2) radical vulvectomy with IF-

LND (Figure 1). In order to assess the true difference in direct costs associated with these two strategies, our first model considered only those costs related to initial treatment of disease and did not include costs associated with surgical complications or morbidities. Our second model included the rates and costs of complications after surgery.

Patients in strategy 1 underwent a radical vulvectomy and SLNB. Based on rates reported in clinical trials, we assumed a success rate (the ability to identify a sentinel lymph node) of 92%¹. Similar to the currently open clinical protocol GOG 270/GROINSS-V II (), if the sentinel lymph node was positive but less than 2 mm, the patient received adjuvant radiation therapy without further surgical intervention. If the sentinel lymph node was positive and greater than 2 mm, a completion IF-LND was performed followed by adjuvant radiation therapy. In patients in whom a sentinel lymph node was not identified, a full lymphadenectomy was performed. Patients with a negative sentinel lymph node received no further treatment. Because the majority of women with stage I vulvar carcinoma will have midline lesions and require bilateral lymphadenectomy, we assumed that patients in both strategies underwent bilateral lymph node assessment and, if necessary, bilateral inguinal radiation^{1,6}.

In strategy 2, patients underwent radical vulvectomy and IF-LND. Patients with a positive lymph node received adjuvant radiation therapy while patients with negative lymph nodes received no further treatment. Patients in both strategies were followed for 3 years after surgery for recurrence in the lymph nodes. Local recurrences on the vulva were not evaluated in this model.

Rates of lymph node metastases and inguinal-femoral recurrence rates were estimated using published data from clinical trials and observational studies (Table 1). Inguinal-femoral 3-year recurrence free survival was used as a survival outcome to compare strategies. Because ultrastaging was used in the SLNB strategy, we did model a higher rate of lymph node positivity in the SLNB arm (33% vs. 25%)⁶. However, per the GROINSS-V2 protocol as well as pathologic data from the GROINSS-V trial, only those who had lymph nodes metastases greater than 2 mm (estimated at 34% of the sentinel lymph node cohort) went on to have a full lymphadenectomy⁶. We assumed similar inguinal-femoral recurrence rates for patients who underwent a full IF-LND in the SLND group compared to those who underwent IF-LND in strategy 2. Although rates of recurrence vary slightly in the literature⁹, these differences are likely due to differences in patient selection and therefore to ensure model integrity, we utilized the same recurrence rate of 5% in both the SLNB and IF-LND strategy (Figure 1). Cost-effectiveness (C/E) ratios were defined as cost per disease-free survivor. Incremental cost-effectiveness ratio (ICER) was defined as the cost per each additional disease-free survivor.

The actual payer costs of surgery and radiation therapy were obtained using 2012 CPT codes and Medicare payment information (Table 2). We did not use charges billed or indirect costs such as travel or lost time from work. Costs associated with the initial evaluation and work-up were not included in the model. Complications and costs associated with these complications (lymphocyst, lymphedema, and infection) were not included in the primary model; however, they were included in a separate model (Table 3).

The cost of the IF-LND procedure is estimated to be \$24,602 and includes the surgeon's fees, pathology, and hospitalization. The cost of the SLNB is \$18,183 and includes the surgeon's fees, the cost of the SLNB (filtered technetium sulfur colloid, injection, intraoperative mapping, lymphoscintigraphy, and radiologist's interpretation fee), pathology, and hospitalization. Patients with IF-LND had longer hospitalizations compared to those undergoing SLNB². Although this varies widely based on differences in national health care systems, for the United States we estimated a difference in hospitalization of 1 vs 2 days. For patients in the SLNB strategy with metastases greater than 2 mm, costs for a completion IF-LND (including surgeon's fees, pathology, and hospital costs) were \$16,698. The cost of six weeks of external beam radiation included the radiation oncologist's fees, radiation dosimetry, simulation costs, professional fees for administering radiation, and facility fees. A conservative estimate of \$4,070 was used.

Because there is no long-term data on the rate of recurrence for patients with a negative SLNB, a one-way sensitivity analyses was performed to evaluate recurrence rates between 1–10%. All modeling and calculations were performed using a decision analysis program (DATA Version 3.5, TreeAge Pro Software, Williamston, MA).

RESULTS

Using 3,000 hypothetical patients diagnosed annually with early-stage vulvar cancer, the estimated annual cost of the SLNB strategy was \$65.2 million (M); this did not include any costs associated with complications. The cost of with the IF-LND strategy was \$76.8 M (Table 4). Estimated 3-year inguinal-femoral recurrence free survival was similar between groups: 96.9% for SLNB compared to 97.3% for IF-LND. There were 8 additional disease-free survivors in the IF-LND strategy. The C/E ratio was lower in the SLNB strategy, \$22,416 compared with the \$26,344 in the IF-LND strategy. The ICER was \$1.4 M for each additional disease-free survivor.

A one-way sensitivity analysis evaluated the impact of recurrence rates (1% to 10%) in patients with a negative SLNB. As the recurrence rates increases, the ICER decreases from \$1.4 M with a rate of 3% to less than \$100,000 with a rate of 9%. This suggests that SLNB is cost-effective as long as the recurrence risk after a negative sentinel lymph node is less than 9%.

The second model included the treatment costs and costs of complications associated with each strategy. Using conservative estimates of costs associated with complications, the estimated annual cost of the SLNB strategy was \$69.0 M compared to \$91.0 M for the IF-LND (Table 5). The addition of costs associated with complications further favored the C/E ratio in the SLNB strategy (\$23,711) compared to the IF-LND strategy (\$31,198). The ICER was significantly increased to \$2.7 M for each additional disease-free survivor.

CONCLUSIONS

This cost-effectiveness analysis demonstrates that radical vulvectomy with SLNB is more cost-effective than radical vulvectomy with IF-LND in the management of patients with early-stage vulvar cancer. While both management strategies have similar disease-free

survival estimates, SLNB is associated with lower total costs secondary to savings in both upfront treatment as well as fewer complications. Although there are additional costs associated with SLNB including injection, intraoperative mapping, and imaging, these costs are offset by a shorter hospitalization. The difference in treatment costs is approximately \$4,000 more for the IF-LND strategy per patient which results in an additional \$11.6 M costs annually and an ICER of \$1.4 M. Since there is no improvement in disease-free survival, these additional costs with IF-LND are unacceptable.

In addition to initial savings at the time of surgery, SLNB is associated with fewer postoperative complications and lower costs associated with these complications. Specifically, rates of lymphedema following a full inguinal lymphadenectomy are reported to be as high as 67% in prospective studies¹⁰. In women undergoing only a sentinel lymph node biopsy, this rate may be as low as 2%². Although the impact of SLNB on quality of life is difficult to measure, SLNB should be associated with an improved quality of life due to less morbidity.

Several recent studies have evaluated the safety of SLNB as an alternative to IF-LND in women with Stage I vulvar cancer. The Gynecologic Oncology Group (GOG) protocol 173 was a multi-institutional observational trial of 452 women with early stage vulvar cancer¹. All patients underwent a SLNB followed by a complete IF-LND, which yielded a false-negative predictive value of 3.7%. To date, no long-term survival has been reported with this study. The GROINSS-V (GRONigen International Study on Sentinel Nodes in Vulvar cancer) was an observational study of 403 women with early-stage vulvar cancer who underwent a negative SLNB². Of the 403 women enrolled, 8 women had groin recurrences. These cases were thought to be false-negative findings on SLNB representing a false-negative predictive value of 2.9%. Because no prospective data is available to estimate long-term recurrence rates following SLNB, we used data from these studies to determine recurrence rates for the SLNB strategy.

Although SLNB is favored in our model, issues remain concerning the learning curve with SLNB and the relative rarity of vulvar cancer. While surgical experience in SLNB was not taken into account for inclusion in GOG protocol 173¹, GOG 270/GROINSS-V II requires that the surgeon have experience in performing SLNB. To minimize the false-negative rate of SLNB in breast cancer, data suggest that surgeons should perform 20 to 40 cases with acceptable results before abandoning routine axillary dissection^{11,12}. Given the relative rarity of vulvar cancer, the number required of the GROINSS-V II study is less than that reported in the breast cancer literature (0 if the surgeon is experienced with SLNB in other anatomic locations and up to 10 SLNB for vulvar cancer).

There are potential weaknesses with this cost-effectiveness model including our estimates of recurrence after SLNB. Estimated proportions are obtained from observations previously reported and may not reflect the true study population. We attempted to alleviate variability in these estimates by performing a sensitivity analysis using variable rates of recurrence after sentinel lymph node dissection. Given that recurrence rate must approach 9% before the ICER supports the IF-LND, these analyses suggest that the model is robust. Furthermore, we

did not calculate QALYs in our model since we do not have accurate estimates of progression-free survival or accurate estimates of the impact on quality of life.

No model can capture all variability and extra costs, and this model is no exception. We assumed that all patients underwent bilateral lymphadenectomy, which may have overestimated the pathology and surgical costs in both strategies, although hospitalization rates would remain the same. Additionally, we did not account for the costs incurred during the treatment of recurrence. We created two separate models because all the data suggests that SLNB is associated with fewer postoperative complications. Since the reported rates of complications vary drastically in the literature, and the costs associated with these complications are difficult to estimate, we wanted to keep these potential biases separate from the original model.

These data suggest that SLNB is less costly than IF-LND and is associated with fewer postoperative complications. Ongoing research will further define both the safety and morbidity of the SLNB strategy. While it is unlikely that randomized controlled trials of IF-LND versus SLND will be performed, encouraging clinical data combined with the results of our model support radical vulvectomy with SLNB as the preferred treatment in patients with early stage vulvar cancer.

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Figure 1.
Decision Analysis Model

Table 1:

Model Estimates

Clinical Scenario	Rate
Successful IF-LND	92% ¹
IF-LND detected positive nodes	25% ^{3,5}
SLNB detected positive nodes	33% ^{1,2}
SLNB metastasis > 2 mm	34% ⁶
Recurrence rate if SLNB metastasis > 2 mm	5% ⁶
Recurrence rate if SLNB metastasis < 2 mm	2.2% ²
Recurrence rate if IF-LND positive nodes	5% ^{13,14}
Recurrence rate if IF-LND negative nodes	2% ^{13,14}

IF-LND - inguinal-femoral lymph node dissection; SLNB - sentinel lymph node biopsy

Table 2.

Cost Estimates

Intervention		Cost
IF-LND		
	Physician fee (surgeon)	\$1,207
	Pathology	\$418
	Hospitalization	\$22,977
	Total	\$24,602
SLNB		
	Physician fee (surgeon)	\$818
	Filtered technetium sulfur colloid	\$72
	Injection	\$37
	Intraoperative mapping	\$122
	Lymphoscintigraphy	\$420
	Physician fee (injection)	\$227
	Physician fee (radiologists interpretation)	\$125
	Pathology	\$534
	Hospitalization	\$15,829
	Total	\$18,183
Completion IF-LND		
	Physician fee	\$755
	Pathology	\$96
	Hospitalization	\$15,829
	Total	\$16,698
Groin Radiation	Total	\$4,070
Management of Groin Infection ^{13,14}		
	Outpatient management (2 office visits plus oral antibiotics)	\$300
	Inpatient management	\$6,100
	Total	\$6,400
Management of Lymphocyst		
	Office visits (x3)	\$420
	I&D with supplies	\$114
	Total	\$534
Management of Lymphedema ¹⁵		
	Physical therapy (x12)	\$1,200
	Supplies/Lymphedema pump	\$5,825
	Total	\$7,025

IF-LND - inguinal-femoral lymph node dissection; SLNB - sentinel lymph node biopsy

Table 3.

Complication rates

Treatment Strategy	Node Metastases	Complication	Rate (%)	Reference(s)
SLNB	Positive > 2 mm	Lymphedema	67	17
		Lymphocyst	20	18
		Infection	15	17-21
	Positive < 2 mm	Lymphedema	5	2
		Lymphocyst	0	None Reported
		Infection	3	2
	Negative	Lymphedema	2	2
		Lymphocyst	0	None Reported
		Infection	2	2
IF-LND	Positive	Lymphedema	67	17
		Lymphocyst	20	18,20,21
		Infection	15	17-21
	Negative	Lymphedema	45	14,17,18
		Lymphocyst	20	18,20,21
		Infection	15	17-21

IF-LND - inguinal-femoral lymph node dissection; SLNB - sentinel lymph node biopsy

Table 4.

Results of Cost-Effectiveness Model Without Costs of Complications

Strategies	Treatment Costs	Recurrence-free Survival	C/E Ratio
SLNB	\$65.2 M	96.9%	\$22,416
IF-LND	\$76.8 M	97.3%	\$26,344

IF-LND - inguinal-femoral lymph node dissection; SLNB - sentinel lymph node biopsy; M – Million; C/E – cost-effectiveness

Table 5.

Results of Cost-Effectiveness Model Including Costs of Complications

Strategies	Treatment Costs	Recurrence-free Survival	C/E Ratio
SLNB	\$69.0 M	96.9%	\$23,711
IF-LND	\$91.0 M	97.3%	\$31,198

IF-LND - inguinal-femoral lymph node dissection; SLNB - sentinel lymph node biopsy; M – Million; C/E – cost-effectiveness