Cost-Effectiveness of Sentinel Node Biopsy and Pathological Ultrastaging in Patients With Early-Stage Cervical Cancer

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BACKGROUND: The objective of this study was to determine the cost-effectiveness of radical hysterectomy (RH) and sentinel lymph node biopsy (SLNB) for the management of early-stage cervical cancer (stage IA2-IB1).

METHODS: A simple decision tree model was developed to follow a simulated cohort of patients with early-stage cervical cancer treated with RH and 1 of 3 lymph node assessment strategies: systematic pelvic lymph node dissection (PLND), SLNB using technetium 99 (Tc99) and blue dye, and SLNB using Tc99 only. SLNB using indocyanine green (ICG) was used as an exploratory strategy. Relevant studies were identified to extract the probability data and utility parameters and to estimate quality-adjusted life-years (QALYs) and absolute life-years (ALYs). Only direct medical costs were modeled, and the time horizon for the study was 5 years. RESULTS: SLNB using Tc99 and blue dye cost $21,089 and yielded 4.54 QALYs and 4.90 ALYs. PLND cost $22,353 and yielded 4.47 QALYs and 4.91 ALYs. SLNB using blue dye and Tc99 was the most cost-effective strategy when ALYs were considered with an incremental cost-effectiveness ratio (ICER) of $144,531. When QALYs were considered, the SLNB technique using Tc99 and blue dye dominated all other strategies. SLNB using ICG cost $20,624 and yielded 4.90 ALYs and 4.54 QALYs. It was clinically superior to and less expensive than all other strategies when QALYs were the outcome of interest and had an ICER of $221,171 per ALY in comparison with RH plus PLND. CONCLUSIONS: SLNB using Tc99 and blue dye with ultrastaging is considered the most cost-effective strategy with respect to 5-year progression-free survival and morbidity-free survival. Although it was included only as an exploratory strategy in this study, SLNB with ICG has the potential to be the most cost-effective strategy.

INTRODUCTION

Cervical carcinoma is the third most common gynecologic malignancy in Canada and the second most common cancer in women worldwide. Forty-six percent of patients have localized/early-stage disease with a 5-year survival rate of approximately 92%. A combination of radical hysterectomy (RH) and pelvic lymphadenectomy is the standard surgical treatment for patients with early-stage cervical cancer (stages IA2 and IB2). Because the reported incidence of lymph node metastases is up to 30% for patients with IB carcinoma and less than 15% for patients with tumors ≤ 2 cm in size,1-3 the majority of patients with early-stage cervical carcinoma ultimately do not benefit from systematic pelvic lymphadenectomy and are exposed to the risks of complications and morbidity.

Over the last decade, sentinel lymph node biopsy (SLNB) has been widely used in patients with melanomas, breast carcinomas, and vulvar carcinomas. The concept of SLNB revolves around mapping the lymphatic drainage from the primary tumor site by means of a tracer and identifying the first set of nodes that receive this lymphatic drainage. The pathological status of sentinel nodes is thought to be reflective of the disease status in other nonsentinel lymph nodes. In patients with positive lymph nodes, sentinel lymph nodes (SLNs) are 3 times more likely to be positive than nonsentinel lymph nodes. Therefore, SLNB can make full regional lymphadenectomy unnecessary in a large number of patients. The clinical benefits of SLNB include a reduced relative risk of lymphedema and sensory loss.4 Theoretical benefits specific to the management of cervical cancer further include decreases in nerve, great vessel, and ureteral injuries, reduced blood loss and operative times, shorter hospital stays, the identification of alternative lymphatic drainage sites, and increased identification of metastatic lymph nodes through pathological ultrastaging.5,6 Pathological ultrastaging is more sensitive in detecting metastatic nodal disease than routine hematoxylin-eosin processing. It is, however, cost- and time-intensive, and this prohibits its application to all nodes removed after a systematic pelvic lymph node dissection (PLND). However, with...
a much smaller number of lymph nodes being removed during SLNB, ultrastaging becomes cost-effective and is now considered a necessary component of SLNB. The feasibility and reliability of SLNB and ultrastaging for the management of early-stage cervical carcinoma have been well documented in several studies.6-12

One of the most disabling long-term morbidities associated with systematic pelvic lymphadenectomy is lower limb lymphedema (LLL). The reported incidence varies with the definition and criteria used to diagnose it. Incidence rates as high as 40% have been reported.13 Most studies, however, suggest that systematic pelvic lymphadenectomy is associated with LLL in 10% to 15% of patients.14 This complication can negatively affect the quality of life of the patients and can result in significant health care expenditures.13 The SLNB procedure, therefore, serves as an attractive alternative to systematic pelvic lymphadenectomy by allowing more selective lymph node dissection and lowering morbidity. In this article, we report the results of a model-based economic evaluation based on evidence from the published literature and examine the relative cost-effectiveness and cost utility of performing SLNB in women with biopsy-proven early-stage cervical cancer (≤2 cm in size) in comparison with traditional surgery (systematic pelvic lymphadenectomy).

MATERIALS AND METHODS

Decision Model

A simple decision tree was developed with commercially available modeling software (TreeAge Pro Suite; TreeAge Software, Williamstown, Mass) so that we could follow a simulated cohort of patients with early-stage cervical carcinoma (International Federation of Gynecology and Obstetrics stage IA2-IB1; Fig. 1). The model compared 3 treatment strategies:

1. RH plus systematic pelvic lymphadenectomy (traditional surgery).
2. RH plus SLNB using blue-dye staining and technetium 99 (Tc99).
3. RH plus SLNB using Tc99 alone.

All patients were assumed to have been evaluated by a gynecological oncologist, and preoperative imaging studies (computed tomography scan of the abdomen and pelvis and pelvic magnetic resonance imaging) had ruled out any radiological evidence of lymph node metastasis or gross parametrial involvement. After surgery, the patients were stratified into 3 categories—low, intermediate, and high risk—on the basis of a histopathological evaluation of the surgical specimens and the risk of recurrence. Patients were stratified as high-risk if the surgical margins or parametria were positive for malignancy or a lymph node metastasis had been identified.15 Intermediate-risk patients included those with lymphovascular space invasion and outer-third cervical stromal invasion.16 All other patients were classified as being at low risk for recurrence. Low-risk patients did not warrant any further treatment and were followed with observation only. Intermediate-risk patients were treated with adjuvant radiation, and high-risk patients received adjuvant chemoradiation. Regardless of the treatment strategy, all patients exited the model through 1 of 4 terminal states: recurrence-free without lymphedema, recurrence-free with lymphedema, recurrence without lymphedema, and recurrence with lymphedema.

Ultrastaging of SLNs can reveal microscopic tumor deposits that otherwise would be missed by routine pathological processing. Approximately 15% to 20% of histologically negative nodes will harbor micrometastases; this frequency closely approximates the recurrence rate in patients with negative nodes.17 Although prospective data are lacking, retrospective studies have suggested that micrometastasis is an independent poor prognostic factor for overall survival.18-21 In our model, the presence of micrometastasis was treated as a high-risk criterion, and these patients were treated with adjuvant chemoradiation. There is little evidence about the prognostic significance and management of isolated tumor cells, and as such, these patients were managed as node-negative in our model.

The time horizon of our decision analysis model was 5 years. Studies examining the natural history of early-stage cervical cancer (tumor ≤2 cm) have shown that, although the disease has a favorable prognosis, of all the patients who are destined to experience recurrence, 50% will do so within 2 years, 75% will do so within 3 years, and 95% will do so within 5 years of surgery.22,23 Lymphedema, which is the primary side effect of systematic lymphadenectomy, usually develops within 2 years of surgery, and in only a small minority will the onset be beyond 5 years.24,25 This makes a 5-year time horizon an optimal approach for our model, with which we were able to capture 95% of recurrences and 95% of cases of lymphedema.

Model Estimates: Clinical Parameters

We performed a systematic search of MEDLINE, the Cochrane Library, EMBASE, and the Cumulative Index to Nursing and Allied Health Literature for studies on SLNB and cervical cancer. References and related articles
were searched to identify further studies. The overall search strategy included the terms cervical cancer, sentinel lymph node biopsy, lymphadenectomy, lymphedema, survival, and outcome as well as phase 3 trials. Transition probabilities for each of the events in the model were extracted from this literature search. For each strategy, we calculated the probability of each of the terminal events described previously. Table 1 lists the baseline probability estimates, their referenced sources, and the ranges and standard deviations used for the sensitivity analysis. All probability estimates were derived from our literature review, and none were arbitrarily assigned by the authors. In the case of multiple reported estimates, the largest and highest quality study that most closely resembled our study population was chosen for the base case analysis. Estimates from the remaining studies were used for the sensitivity analysis. The probability of lymphedema after RH and complete pelvic lymphadenectomy was set at 15% for the base case. The relative risk of lymphedema after SLNB (vs complete pelvic lymphadenectomy) was set at 0.10; that is, in the base case, the model assumes a 90% reduction in the incidence of lymphedema. This estimate of the relative risk of lymphedema is in line with the results of the Groningen International Study on Sentinel Nodes in Vulvar Cancer (GROINS-V), which reported a relative risk of lymphedema of 0.08 with SLNB, and with the results of prospective studies conducted in breast cancer patients, in whom there is much more experience with the procedure. We modeled higher odds of lymphedema in patients receiving adjuvant radiation/chemoradiation in

Figure 1. Simplified representation of the decision analysis model and SLN mapping algorithm used. The RH-SLNB arms (technetium 99m blue dye) use the same decision analysis model as (Top) the RH-PLND arm except that (Bottom) an SLN mapping algorithm is used to identify lymph nodes. The model has 4 terminal states: 1) recurrence without lymphedema, 2) recurrence with lymphedema, 3) recurrence-free state without lymphedema, and 4) recurrence-free state with lymphedema. *If a macroscopically enlarged lymph node is identified, then side-specific lymphadenectomy should be performed. **For patients with false-negative SLNB, the risk of recurrence without adjuvant treatment is modeled as 100%. PLND indicates pelvic lymph node dissection; RH, radical hysterectomy; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy.
each of the treatment strategies according to data from published studies.38,41

The primary components of the quality-of-life assessment in our study were lymphedema and recurrence. The effects of these 2 components on the quality of life were extracted from prior studies assessing treatment-related morbidities in cervical cancer patients via EuroQol-5D, the Global Health Status scale of the Quality of Life Questionnaire Core 30 questionnaires (European Organization for Research and Treatment of Cancer), and time trade-off methods.39,42-44 Being recurrence-free 5 years after the completion of surgery with or without adjuvant therapy was assigned a utility score of 0.94, whereas a recurrence during this period corresponded to a utility score of 0.84 (a utility score of 1 corresponded to perfect health, and a score of 0 corresponded to death). The presence of LLL resulted in an additional absolute disutility of 0.15 according to data from Cheville et al.43

Model Estimates: Costs

Costs in our model were calculated from the perspective of Ontario health care payers (ie, third-party payers) and included direct medical costs only (Table 2). Indirect medical costs (ie, loss of income due to time off work) were not included in the analysis. A gross-costing approach was used, and average treatment costs were calculated. A 25% variation in costs was used for the sensitivity analysis. Costs were estimated from data from the Canadian Institute for Health Information, the Ontario Ministry of Health and Long-Term Care schedule of physician benefits, and hospital payment and administrative databases. All costs are expressed in Canadian dollars.

The cost of lymphedema care after lymphadenectomy for gynecological cancers varies in the literature. Data from the breast literature suggest that patients with lymphedema incur over a 2-year period medical costs $14,000 to $23,000 greater than those incurred by patients without lymphedema.45 On the basis of another

### TABLE 1. Estimates of Clinical Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Standard Deviation (Range)</th>
<th>Model Distribution for Probabilistic Sensitivity Analysis</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral SLN detection rate (ie, at least 1 SLN identified in at least 1 hemipelvis)</td>
<td>0.95</td>
<td>0.025 (0.85-0.95)</td>
<td>β</td>
<td>6, 8, 10, 26</td>
</tr>
<tr>
<td>Bilateral SLN detection rate (ie, at least 1 SLN identified in the contralateral hemipelvis after unilateral SLN detection)</td>
<td>0.9</td>
<td>0.025 (0.85-0.95)</td>
<td>β</td>
<td>6, 8, 10, 26</td>
</tr>
<tr>
<td>Probability of finding macroscopically enlarged node at time of SLNB</td>
<td>0.02</td>
<td>0.0025 (0.01-0.04)</td>
<td>β</td>
<td>12, 26</td>
</tr>
<tr>
<td>Probability of false-negative SLNB</td>
<td>0.05</td>
<td>0.0031 (0.018-0.095)</td>
<td>β</td>
<td>5, 9, 26-28</td>
</tr>
<tr>
<td>Probability of recurrence in patients with false-negative SLNB (without adjuvant therapy)</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>Model assumption</td>
</tr>
<tr>
<td>Probability of meeting intermediate-risk criteria in patients with negative nodes warranting adjuvant radiation therapy</td>
<td>0.25</td>
<td>0.031 (0.19-0.31)</td>
<td>β</td>
<td>16</td>
</tr>
<tr>
<td>Probability of positive nodes (lymphatic metastasis)</td>
<td>0.16</td>
<td>0.02 (0.19-0.21)</td>
<td>β</td>
<td>15, 29, 30</td>
</tr>
<tr>
<td>Probability of presence of micrometastasis</td>
<td>0.22</td>
<td>0.027 (0.17-0.28)</td>
<td>β</td>
<td>17, 31, 32</td>
</tr>
<tr>
<td>Baseline probability of recurrence in patients with localized tumors (low risk)</td>
<td>0.06</td>
<td>0.007 (0.05-0.08)</td>
<td>β</td>
<td>33</td>
</tr>
<tr>
<td>Baseline probability of recurrence in patients with intermediate-risk factors</td>
<td>0.26</td>
<td>0.016 (0.15-0.29)</td>
<td>β</td>
<td>16, 33</td>
</tr>
<tr>
<td>Baseline probability of recurrence in patients with high-risk factors</td>
<td>0.40</td>
<td>0.03 (0.20-0.54)</td>
<td>β</td>
<td>33, 34</td>
</tr>
<tr>
<td>Relative risk of recurrence after chemoradiation in high-risk patients</td>
<td>0.50</td>
<td>0.12 (0.37-0.83)</td>
<td>β</td>
<td>15</td>
</tr>
<tr>
<td>Relative risk of recurrence after radiotherapy in intermediate-risk patients</td>
<td>0.53</td>
<td>0.09 (0.35-0.71)</td>
<td>β</td>
<td>16, 35</td>
</tr>
<tr>
<td>Probability of lymphedema after pelvic lymph node dissection</td>
<td>0.15</td>
<td>0.03 (0.09-0.3)</td>
<td>β</td>
<td>14, 36-40</td>
</tr>
<tr>
<td>Relative risk of lymphedema in SLN strategy (vs traditional surgery)</td>
<td>0.1</td>
<td>0.06 (0.05-0.3)</td>
<td>β</td>
<td>14, 36-40</td>
</tr>
<tr>
<td>Odds ratio of developing lymphedema after adjuvant radiation/chemoradiation</td>
<td>3.47</td>
<td>1.5 (2.08-5.8)</td>
<td>β</td>
<td>38</td>
</tr>
</tbody>
</table>

Abbreviations: SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy. A β distribution was used to model a range of parameter estimates for the probabilistic sensitivity analysis. These are continuous probability distributions defined over the interval [0,1] and parameterized to be centered over the mean value of the parameter.
cost-effectiveness analysis of LLL care after pelvic lymphadenectomy, we used a more conservative estimate of $4000 per patient per year.46–49 This includes physical therapy–related costs and the cost of supplies.

**Cost-Effectiveness Analysis**

Effectiveness in our model was calculated in terms of absolute life-years (ALYs) of progression-free survival and quality-adjusted life-years (QALYs) of progression-free survival at the end of 5 years. Progression-free survival rather than overall survival was used as the endpoint because after progression, treatment for cervical cancer is very individualized, and the costs are quite variable. The primary outcome of interest in our model was the incremental cost-effectiveness ratio (ICER). A strategy was considered cost-effective when the ICER was less than the willingness-to-pay (WTP) threshold of $100,000 per QALY (or ALY depending on the measure of effectiveness). Sensitivity analyses were performed to test the robustness of the model and to account for the uncertainties in the assumptions and model estimates.

**RESULTS**

**Base Case Analysis**

The strategy of RH and pelvic lymph node dissection (PLND; strategy 1) costs $22,353.08 and yields 4.47 QALYs, whereas the strategy of RH and SLNB using Tc99 only (strategy 3) costs $21,462.18 and yields 4.53 QALYs. The strategy of RH and SLNB using Tc99 and blue dye (strategy 2) costs $21,089.56 and yields 4.54 QALYs; this makes it not only the most effective but also the least expensive of the 3 strategies. In health economics, an intervention is considered the dominant strategy if it is both clinically superior and cost-saving.50 As such, the strategy of RH and SLNB using Tc99 and blue dye (strategy 2) dominates all other strategies when quality-adjusted progression-free survival is the outcome of interest (Table 3).

When we focus solely on absolute progression-free survival and ignore the negative quality-of-life impact of lymphedema, systematic PLND yields 4.91 life-years, whereas SLNB using Tc99 and blue dye yields

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**TABLE 2. Cost Estimates**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Costs in 2015 CDN Dollars</th>
</tr>
</thead>
<tbody>
<tr>
<td>RH, SLN mapping, and hospitalization</td>
<td>11,785</td>
</tr>
<tr>
<td>RH, PLND, and hospitalization</td>
<td>11,785</td>
</tr>
<tr>
<td>Routine pathology processing</td>
<td>375</td>
</tr>
<tr>
<td>Pathology processing with SLN ultrastaging</td>
<td>580</td>
</tr>
<tr>
<td>Blue-dye injection (for SLN detection)</td>
<td>30</td>
</tr>
<tr>
<td>Radiosotope (Tc99) plus injection (for SLN detection)</td>
<td>150</td>
</tr>
<tr>
<td>Scintigraphy (for SLN detection)</td>
<td>685</td>
</tr>
<tr>
<td>Adjuvant chemotherapy* plus radiotherapy*</td>
<td>8761</td>
</tr>
<tr>
<td>Adjuvant radiotherapy alone*</td>
<td>6062</td>
</tr>
<tr>
<td>Annual cost of lymphedema care (therapy and supplies)</td>
<td>4000</td>
</tr>
</tbody>
</table>

**Abbreviations:** CDN, Canadian; PLND, pelvic lymph node dissection; RH, radical hysterectomy; SLN, sentinel lymph node; Tc99, technetium 99.

Costs were estimated from data from the Canadian Institute for Health Information, the Ontario Ministry of Health and Long-Term Care schedule of benefits, and hospital payment and administrative databases. For the probabilistic sensitivity analysis, we modeled a 25% variation in costs with a lognormal distribution.

*Chemotherapy costs were calculated for a hypothetical 70-kg woman with a body surface area of 1.75 m², and they include the costs of administration, premedications, outpatient physician visits, and the chemotherapeutic agent (cisplatin administered at 40 mg/m²).

* Radiation therapy costs include the radiation oncologist fees, radiation dosimetry, simulation costs, and professional fees for administering radiation (50.4-Gy total pelvic dose).

**TABLE 3. Baseline Analysis**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Total Cost in CDN Dollars</th>
<th>Incremental Cost in CDN Dollars</th>
<th>Effectiveness</th>
<th>Incremental Effectiveness</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effectiveness = QALYs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RH and PLND</td>
<td>22,353.08</td>
<td>1263.52</td>
<td>4.47</td>
<td>–0.07</td>
<td>Dominated</td>
</tr>
<tr>
<td>RH and SLNB (Tc99 only)</td>
<td>21,462.18</td>
<td>372.62</td>
<td>4.53</td>
<td>–0.01</td>
<td>Dominated</td>
</tr>
<tr>
<td>RH and SLNB (Tc99 and blue dye)</td>
<td>21,089.56</td>
<td>–</td>
<td>4.54</td>
<td>–</td>
<td>Dominated all other strategies</td>
</tr>
<tr>
<td><strong>Effectiveness = ALYs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RH and PLND</td>
<td>22,353.08</td>
<td>1263.52</td>
<td>4.91</td>
<td>0.01</td>
<td>144,531.36</td>
</tr>
<tr>
<td>RH and SLNB (Tc99 only)</td>
<td>21,462.18</td>
<td>372.62</td>
<td>4.90</td>
<td>0.00</td>
<td>224,333.08 (extended domination)</td>
</tr>
<tr>
<td>RH and SLNB (Tc99 and blue dye)</td>
<td>21,089.56</td>
<td>–</td>
<td>4.90</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALY, absolute life-year; CDN, Canadian; ICER, incremental cost-effectiveness ratio; PLND, pelvic lymph node dissection; QALY, quality-adjusted life-year; RH, radical hysterectomy; SLNB, sentinel lymph node biopsy; Tc99, technetium 99.

When QALYs were used as the measure of effectiveness, the strategy of RH and SLNB with Tc99 and blue dye dominated all other strategies. When ALYs were used as the measure of effectiveness, the strategy of RH and SLNB with Tc99 and blue dye was still the most cost-effective.
4.90 life-years. However, the 0.01 life-years (approximately 4 days) of incremental survival with PLND comes at a cost of $1263.52, and this results in an ICER of $144,531.36 for 1 additional life-year. This makes SLNB with Tc99 and blue dye still the most cost-effective strategy at a WTP of $100,000 (Table 3).

Sensitivity Analysis

In our base case analysis, we modeled a 90% reduction in the incidence of LLL with SLNB versus PLND. Although this estimate of risk reduction is similar in magnitude to the results seen in the GROINS-V study and breast cancer literature,36,37 we nonetheless wanted to test the cost-effectiveness of SLNB over various degrees of risk-reduction estimates. Only when the relative risk of lymphedema after SLNB was >68% did the ICER increase above our WTP threshold of $100,000. Importantly, these results remained valid regardless of the baseline risk of lymphedema after PLND. In other words, as long as SLNB reduces the risk of LLL by at least 32% in comparison with PLND, it remains the preferred strategy.

To incorporate the uncertainty in estimation of all our model parameters, a probabilistic sensitivity analysis using a Monte Carlo simulation of 100,000 trials was performed. The acceptability curve (Fig. 2) shows a comparison of the 3 strategies in the model. SLNB using blue dye and Tc99 dominates all other strategies when quality-adjusted life-years are the measure of effectiveness. CE indicates cost-effectiveness; PLND, pelvic lymph node dissection; RH, radical hysterectomy; SLNB, sentinel lymph node biopsy; Tc99, technetium 99; WTP, willingness to pay.

SLN Mapping With Indocyanine Green (ICG)

The fluorescent properties of ICG have been evaluated for the SLN mapping of a number of solid organ tumors, including cervical cancer, and it has emerged as an attractive alternative to the combined Tc99–blue dye technique. However, it has not received Food and Drug Administration or Health Canada approval as an SLN mapping agent, and its use in SLNB remains off-label. Because of the limited number of studies51-54 reporting its use as an SLN mapping agent in cervical cancer, we decided to omit ICG from our primary treatment strategies. Instead, we evaluated its cost-effectiveness as an exploratory arm. ICG has a number of advantages over Tc99-based techniques. It can be administered intraoperatively and does not have the associated costs of preoperative scintigraphy. In a recent multicenter European trial,54 ICG was associated with significantly higher detection and bilateral mapping rates in comparison with the combined Tc99–blue dye technique. Even when utilizing detection rates equivalent to those for the combined Tc99–blue dye technique and with a cost of $195.00 (in Canadian dollars) for a 10-mL
vial of ICG (direct cost from Novadaq Technologies, Bonita Springs, Fla), the strategy of RH and SLNB using ICG cost $20,624 and yielded 4.90 ALYs and 4.54 QALYs. It was clinically superior to and less expensive than all other strategies when QALYs were the outcome of interest and had an ICER of $221,171 per ALY in comparison with RH and PLND. If further studies confirm the superiority of ICG as an SLN mapping agent, SLNB with ICG will undoubtedly be the most cost-effective strategy.

DISCUSSION
The advent of SLNB and pathological ultrastaging has essentially changed the management of early-stage breast cancer and cutaneous melanoma, and in gynecological oncology, it has become the standard of care in the management of vulvar cancer. In recent years, a paradigm shift has been taking place in the management of early-stage cervical cancers as well. Although early studies had suggested unacceptably high false-negative rates, recent studies have shown that with careful patient selection and adherence to strict lymph node mapping algorithms, SLNB combined with pathological ultrastaging can be safely applied to the management of early-stage cervical cancer with acceptably low false-negative rates.\(^{12,26,55}\) An accruing body of evidence suggests that in comparison with systematic PLND, this treatment modality can provide similar if not better diagnostic information, albeit at reduced morbidity levels.\(^{38,43,56,57}\) No study to date has, however, assessed the effectiveness of the 2 procedures in conjunction with the economic impact of the associated morbidities.

The results of our model-based economic evaluation show that in patients with early-stage cervical cancer, SLNB and pathological ultrastaging are more cost-effective than the traditional standard of care (ie, systematic PLND). SLNB with Tc99 and blue dye not only is less expensive but also yields a higher number of QALYs. These results are robust to an extensive probabilistic sensitivity analysis taking into consideration variations in costs and model parameters. Our model is based on strict patient selection criteria and lymph node mapping algorithms. The aim of these selection criteria and mapping algorithms is to reduce the rate of false-negative SLNB. Only when the rate of false-negative SLNB is low does the procedure become clinically and economically preferable. Recent studies have shown that when such criteria and mapping algorithms are followed, the false-negative rate for SLNB is 0.08%.\(^{26}\) In our model, we used a much more conservative estimate of a 5% false-negative rate. Despite this conservative estimate, the SLNB biopsy procedure dominated as the preferred strategy when QALYs were the measure of effectiveness and was the more cost-effective strategy when ALYs were the measure of effectiveness.

Our model also highlights the fact that the false-negative rate of SLNB should be viewed not in isolation but in the context of its impact on guiding adjuvant treatment (ie, no further treatment vs adjuvant radiation vs adjuvant chemoradiation). The decision to provide adjuvant treatment to patients with early-stage cervical cancer is based on both the lymph node status and the histological evaluation of the primary RH specimen. Even in the presence of a false-negative SLNB, a significant proportion of patients will receive adjuvant treatment on the basis of cervical/uterine/parametrial factors. In a study by Niikura et al,\(^{57}\) 40% of patients undergoing SLNB only (tumor size $\leq 2$ cm) received adjuvant radiation or chemoradiation on the basis of the histopathological evaluation of the hysterectomy specimen. More importantly, none of the patients with negative SLNs had a pelvic nodal recurrence at a median follow-up of 4 years. Therefore, the proportion of patients for whom a false-negative SLNB leads to true undertreatment is much smaller than the false-negative rate. In our model, we used a very conservative approach and modeled a 100% risk of recurrence in this undertreated group. Although this conservative approach would bias our model away from SLNB and toward systematic pelvic lymphadenectomy, our results show that the SLNB is still the preferred strategy. In a recent review, Tax et al\(^{26}\) concluded that in comparison with PLND, SLNB reduces the overtreatment rate from 80% to 10% at an acceptable risk of occult metastasis of only 0.08%.

One limitation of our study is that we modeled only lymphedema care and recurrence as the sole determinants of quality of life. Although bowel, bladder, and sexual dysfunction could have been included, these were purposely left out because these morbidities are associated with the radical parametrectomy associated with the procedures and not the lymph node dissections. As such, the incidence and prevalence of these were assumed to be equal in each of the treatment strategies. We eagerly await the results of 3 ongoing clinical trials (the Gynecologic Oncology Group 278 trial, the SHAPE trial, and the ConCerv trial\(^{58}\)) to see whether RH can be replaced by a less radical surgery in patients with early-stage cervical cancer. If this is the case, then simple hysterectomy and SLNB could potentially become the new gold standard for patients with early-stage cervical cancer.
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CONFLICT OF INTEREST DISCLOSURES
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AUTHOR CONTRIBUTIONS
Harinder Brar: Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing—original draft, writing—review and editing, visualization, supervision, project administration, and funding acquisition. Liat Hogen: Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing—original draft, writing—review and editing, visualization, supervision, project administration, and funding acquisition. Al Covens: Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing—original draft, writing—review and editing, visualization, supervision, project administration, and funding acquisition.

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