Cost Effectiveness of Intraoperative Pathology Examination during Diagnostic Hemithyroidectomy for Unilateral Follicular Thyroid Neoplasms

Kyle Zanocco, MD, Michael Heller, BA, Dina Elaraj, MD, FACS, Cord Sturgeon, MD, MS, FACS

BACKGROUND: The use of intraoperative pathology examination (IPE) during diagnostic hemithyroidectomy for a follicular neoplasm is controversial. Although this service rarely alters intraoperative decision making, it does provide patients with the possibility of avoiding reoperation for completion thyroidectomy if malignancy is detected. We hypothesized diagnostic hemithyroidectomy with IPE for a unilateral follicular thyroid neoplasm diagnosed on fine-needle aspiration is not cost effective compared with diagnostic hemithyroidectomy alone.

STUDY DESIGN: Cost-effectiveness analysis with a Markov decision model was performed comparing diagnostic hemithyroidectomy without IPE, diagnostic hemithyroidectomy with IPE, and total thyroidectomy. Treatment outcomes and their probabilities were identified based on literature review. Costs were estimated using data from Medicare, the US Bureau of Labor Statistics, and the Nationwide Inpatient Sample. Sensitivity analysis and a 1,000-iteration Monte Carlo simulation were used to examine the uncertainty of cost, probability, and utility estimates in the model.

RESULTS: Diagnostic hemithyroidectomy without IPE had an expected cost of US$7,665 and an effectiveness of 23.95 quality-adjusted life years and dominated both the IPE and total thyroidectomy strategies. Intraoperative pathology examination became cost effective during one-way sensitivity analysis if the sensitivity of IPE increased from 14.3% to 34.4%, the specificity increased from 98.6% to 99.8%, or the pretest probability of malignancy increased from 25% to 43%. Monte Carlo simulation demonstrated that the intraoperative pathology strategy was not cost effective in 92.7% of iterations.

CONCLUSIONS: Intraoperative pathology examination is not cost effective in the diagnosis of follicular thyroid neoplasms during diagnostic hemithyroidectomy. Improvements in both the sensitivity and specificity of this service would be needed to justify its use. (J Am Coll Surg 2013;217:702–710. © 2013 by the American College of Surgeons)
Abbreviations and Acronyms

- FNA = fine-needle aspiration
- FS = frozen section
- IPE = intraoperative pathology examination
- QALY = quality-adjusted life year
- RLN = recurrent laryngeal nerve

rarely changes operative management; it also adds to costs and increases operative time. In addition, intraoperative pathology examination introduces the possibility of false positives, which can lead to the unnecessary removal of the contralateral thyroid lobe in cases of benign follicular neoplasms.

Total thyroidectomy has been proposed as an alternative to diagnostic hemithyroidectomy in patients with follicular neoplasms. Total thyroidectomy eliminates the need for IPE or the possibility of reoperation, but costs more than diagnostic hemithyroidectomy. This procedure also obligates all patients to receive lifelong thyroid hormone replacement and places the contralateral recurrent laryngeal nerve (RLN) and parathyroid glands at risk for injury.

Formal cost-effectiveness analysis has never been performed to compare the following treatment strategies for follicular thyroid neoplasms: diagnostic hemithyroidectomy alone followed by possible completion thyroidectomy, hemithyroidectomy with FS, and total thyroidectomy. We hypothesized that the addition of IPE to diagnostic hemithyroidectomy for a unilateral follicular thyroid neoplasm is not cost effective. In addition, we hypothesized that total thyroidectomy would not be cost effective compared with diagnostic hemithyroidectomy with or without IPE.

METHODS

Reference case scenario

A reference case was defined based on recommendations of the Panel on Cost-Effectiveness in Health and Medicine. The reference case was a patient with a unilateral follicular thyroid neoplasm identified on FNA. This patient was assumed to be an appropriate candidate for thyroidectomy via a cervical incision and without previous neck surgery or intraoperative findings necessitating the use of FS (eg, suspicious lymphadenopathy or the need to query parathyroid tissue). The time horizon for the analysis was the life expectancy of the reference case patient, which was set at 40 years based on the age of patients diagnosed with follicular thyroid neoplasms.

Decision model

A Markov decision model of the diagnosis and treatment of the reference case was constructed using decision software (TreeAge Pro, TreeAge Software, Inc., 2012). The following diagnostic decision alternatives were created: diagnostic hemithyroidectomy without IPE, diagnostic hemithyroidectomy with IPE, and total thyroidectomy without IPE. Figures 1, 2 and 3 diagram the chance and terminal nodes of the three diagnostic strategies. The event pathways and treatment outcomes probabilities resulting from each decision were estimated based on literature review and are shown in Table 1. The pretest probability that an FNA-identified follicular neoplasm was malignant on a definitive pathology examination after surgical excision was assumed to be 25%. The model was given a cycle length of 1 year and was terminated when the number of completed cycles was greater than life expectancy. The optimal decision was defined as the strategy producing the greatest quality-adjusted life expectancy that did not exceed an incremental cost-effectiveness ratio of US$100,000 per quality-adjusted life year (QALY).

Costs

The societal costs of resources consumed for each strategy were estimated using a combination of micro and gross costing techniques. Only costs that differed between the 3 diagnostic strategies were included. All costs in the model were measured in 2010 US dollars. An inflation rate of 4.1% was used to adjust older costs to their 2010 amount when necessary. This rate was calculated from the mean annual changes in the Consumer Price Index for Medical Care from 2000 to 2010. All future costs in the model were subjected to a standard discount rate of 3%.

Cost estimates for physician-provided services were based on 2010 national Medicare charge limits for the surgery, anesthesiology, and pathology services rendered by each strategy. Hospital costs were estimated by calculating an average of 2009 Medicare cost-to-charge ratios for DRG 625 (Thyroid, Parathyroid, and Thyroglossal Procedures with Major Complications and Comorbidities), DRG 626 (Thyroid, Parathyroid, and Thyroglossal Procedures with Complications and Comorbidities), and DRG 627 (Thyroid, Parathyroid, and Thyroglossal Procedures without Complications and Comorbidities) weighted by total amount reimbursed. The computed ratio of 0.189 was then multiplied by the national median inpatient charge estimates for hemi- and total thyroidectomy reported by the 2009 Nationwide Inpatient Sample. Thyroid hormone medication costs were based on average US wholesale prices. The costs for the thyroidectomy-related complications of permanent RLN injury and permanent hypoparathyroidism have been estimated elsewhere and were adjusted to 2010 costs.
cost of missed patient labor due to surgery was based on 2010 annual US hourly earnings. All of the costs used in the model are shown in Table 1.

Effectiveness
Effectiveness was measured as the quality-adjusted life expectancy produced by each strategy. All of the model’s outcomes were assigned a corresponding quality-adjustment factor based on literature review. The time spent by a patient with a particular result was multiplied by that result’s quality-adjustment factor to yield QALYs. Patients requiring reoperation for completion thyroidectomy were assigned a one-time reduction in quality-adjusted life expectancy. A 3% discount rate was applied to all QALYs that were realized in the future. The quality-adjustment factors used in the model are displayed in Table 1.

Sensitivity analysis
Threshold analysis was performed on each reference case variable to identify values where the incremental cost-effectiveness ratio exceeded US$100,000/QALY during one-way sensitivity analysis. Two-way sensitivity analysis was performed on the sensitivity and specificity of intraoperative pathologic examination for malignancy in a follicular neoplasm. A Monte Carlo simulation was performed, where triangular frequency distributions for each variable were simultaneously sampled during 1,000 consecutive iterations. In this probabilistic sensitivity analysis, all variables were allowed to vary ±50% of the reference case estimate or, if not possible in the case of probability and utility estimates, to the greatest extent that allowed the reference case value to remain at the center of a range containing the boundary 0 or 1.

RESULTS
Reference case
The diagnostic hemithyroidectomy without IPE was the least costly, with an expected cost of US$7,665 and an effectiveness of 23.95173 QALYs. The addition of an IPE to this procedure resulted in a loss of 0.00152
QALYs at an additional cost of US$72.17. The IPE strategy was dominated because it was both more costly and less effective than diagnostic hemithyroidectomy alone. The total thyroidectomy strategy was more costly and less effective than the other strategies and was therefore also dominated by diagnostic hemithyroidectomy alone. The reference case results are summarized in Table 2.

**Sensitivity analysis**

The threshold values necessary to achieve a cost effectiveness of US$100,000/QALY for adding intraoperative pathology to diagnostic hemithyroidectomy are listed.
in Table 3. The optimal decision was most sensitive to the sensitivity and specificity of IPE, pretest probability of malignancy in the reference case, and the costs of surgery. If the IPE specificity increased from 98.6% to 99.8%, or if the sensitivity increased from 14.3% to 34.4%, IPE became cost effective. The IPE strategy also became cost effective if the probability of malignancy increased from 25% to 43%, or if the cost of completion thyroidectomy doubled. The model was not sensitive to the rate of hypothyroidism after hemithyroidectomy or the treatment costs or quality-adjustment factors for hypoparathyroidism or RLN injury.

Two-way sensitivity analysis demonstrated that the decision model was sensitive to simultaneous variation of the test characteristics (ie, sensitivity and specificity) of IPE. Figure 4 demonstrates that intraoperative pathology became cost effective for combinations of sensitivity and specificity that were sufficiently high, but the reference case values for these parameters did not produce an incremental cost-effectiveness ratio <US$100,000/QALY.

Monte Carlo simulation demonstrated that the intraoperative pathology strategy was not cost effective when compared with diagnostic hemithyroidectomy without

**Table 1. Model Assumptions**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Reference case value</th>
<th>Range of values in Monte Carlo distribution</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probabilities, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy in follicular neoplasm identified on fine-needle aspiration</td>
<td>25.0</td>
<td>12.5–37.5</td>
<td>5,20</td>
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<tr>
<td>True-positive identification of malignancy on intraoperative pathology examination (sensitivity)</td>
<td>14.3</td>
<td>7.2–21.5</td>
<td>8,15</td>
</tr>
<tr>
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<td>98.6</td>
<td>97.2–100</td>
<td>8,15</td>
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<tr>
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<td>35.0</td>
<td>17.5–52.5</td>
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<tr>
<td>Hypoparathyroidism after completion or total thyroidectomy</td>
<td>1.0</td>
<td>0.5–1.5</td>
<td>21,23-25</td>
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<tr>
<td>Recurrent laryngeal nerve injury (per lobe dissected)</td>
<td>1.0</td>
<td>0.5–1.5</td>
<td>26</td>
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<td>Costs in US$</td>
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<tr>
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<td>4,141.26</td>
<td>2,071–6,212</td>
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<td>Completion thyroidectomy</td>
<td>5,513.61</td>
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<td>Total thyroidectomy</td>
<td>5,500.05</td>
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<tr>
<td>Additional 15 min of anesthesiologist work time</td>
<td>23.57</td>
<td>11.79–35.36</td>
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<td>Intraoperative pathology examination</td>
<td>159.52</td>
<td>79.76–239.28</td>
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<td>Treatment of recurrent laryngeal nerve injury</td>
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<td>Annual cost of permanent hypoparathyroidism, US$</td>
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<tr>
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<td>75.76–227.27</td>
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<tr>
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<td>Quality-of-life adjustment factors</td>
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<td>Euthyroid</td>
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<td>Hypothyroid with hypoparathyroidism</td>
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<tr>
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<td>1-time reduction in quality-adjusted life expectancy for undergoing reoperation for completion thyroidectomy, d</td>
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<td>0.5–1.5</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Time</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Additional anesthesia time due to intraoperative pathology examination, min</td>
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<td>10–30</td>
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<tr>
<td>Additional work missed to undergo completion thyroidectomy, h</td>
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<td>8–24</td>
<td>Expert opinion</td>
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<td>Life expectancy, y</td>
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<td>20–60</td>
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<td>Discount rate, %</td>
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<td>1.5–4.5</td>
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</table>

*Euthyroidism was assigned a quality adjustment factor of 1 and was not varied on probabilistic sensitivity analysis to serve as a baseline for comparison by all other quality adjustment factors.
intraoperative pathology in 92.7% of the iterations. Intraoperative pathology examination was dominant in 1.8% of iterations compared with 82.1% in which hemithyroidectomy without IPE was dominant (Fig. 5).

**DISCUSSION**

This study demonstrates that diagnostic hemithyroidectomy with IPE for unilateral follicular neoplasms diagnosed on FNA produces decreased effectiveness at an increased cost and operative time compared with diagnostic hemithyroidectomy without IPE. However, increases in the pretest probability of malignancy in follicular neoplasms or improvement of the sensitivity or specificity of IPE would make the use of this service cost effective. Total thyroidectomy for follicular neoplasms is more costly and less effective than diagnostic hemithyroidectomy with or without IPE.

<table>
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<tr>
<th>Table 3. The US$100,000/Quality-Adjusted Life-Years Threshold Values for Model Variables That Make Intraoperative Pathology Cost Effective</th>
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This is the first formal cost-effectiveness analysis of IPE for follicular thyroid neoplasms that uses a decision model. Several previous studies using different methodology have arrived at opposing conclusions about whether IPE is a cost-saving or cost-losing service. In a randomized prospective evaluation of FS analysis for follicular thyroid neoplasms, the charge per informative FS was estimated at US$12,470.15 The cost per useful operation-altering FS has been estimated elsewhere on retrospective review to range from US$6,000 to US$26,040.7,8,11 Although these studies argue that FS is not worthwhile because the cost of FS exceeded the cost of reoperation for a completion thyroidectomy, it is difficult to interpret the cost effectiveness of FS because there was no

**Figure 4.** Two-way sensitivity analysis demonstrates the combined effects of changes in the sensitivity and specificity of intraoperative pathology examination for follicular neoplasms on the overall cost effectiveness of this service during diagnostic hemithyroidectomy. The threshold line represents combinations of these test characteristics that produce an incremental cost-effectiveness ratio (ICER) of US$100,000 per quality-adjusted life year (QALY). The area above the threshold line represents values that produce an ICER of <US$100,000 per QALY and would make intraoperative pathology a cost-effective strategy. The reference case test characteristics intersect below the threshold line in the area representing values that exceed the threshold for cost effectiveness.

**Figure 5.** A 1,000-iteration Monte Carlo simulation where all model assumptions were simultaneously varied across their frequency distributions. The incremental cost and incremental effectiveness of intraoperative pathology examination strategy compared with the diagnostic hemithyroidectomy alone are plotted for each iteration. Of 1,000 iterations, 927 (92.7%) exceeded the US$100,000/quality-adjusted life-year threshold for cost effectiveness. ICER, incremental cost-effectiveness ratio.
consideration given to possible improvement in quality of life by avoiding a second procedure.

A cost-minimization analysis of FS for all benign and indeterminate thyroid lesions in the Canadian health care system calculated a cost savings of C$22.01 per patient. However, the sensitivity and specificity of FS (30.2% and 100%, respectively) were higher in that study’s population of patients when compared with the test characteristics of FS in subsets of patients with follicular lesions (14% and 99%, respectively). A retrospective review of patients at the Mayo Clinic undergoing thyroidectomy for suspected follicular and Hürthle cell neoplasms reported FS sensitivity and specificity of 78.3% and 99.3% and savings of >US$400,000 in charges during a 10-year time period due to avoidance of a second operation. Although this study population is also not directly comparable with a subset limited to patients with follicular lesions, it is important to note that the relatively high sensitivity and specificity reported at Mayo is attributed by the authors to an abundance of surgical pathology resources available in the performance of intraoperative examination. A tradeoff is evident between the cost of increased availability of pathology resources and the improvement in test characteristics of IPE. Measuring the impact on saved patient charges alone does not capture the costs of operating a surgical pathology laboratory with the extra equipment and personnel necessary to achieve these results.

Cost-effectiveness analysis with decision modeling enables a more complete economic evaluation of the addition of IPE to diagnostic lobectomy than has previously been studied. This technique allows the value of the increased costs for IPE to be examined in the context of potential effects on quality of life. In addition, sensitivity analysis identifies thresholds for cost effectiveness in outcomes probabilities, utility measurements, and costs that can be applied to unique diagnostic situations with different values than those that appear in the reference case scenario.

Several limitations are evident in this study. The decision model omitted several possible complications, including wound infection, hematoma formation, and operative mortality. Because all diagnostic strategies included surgery, these omissions probably have little impact on the results. However, some of these events might be more likely during reoperation and would make completion thyroidectomy less favorable, therefore improving the cost effectiveness of the IPE strategy. The extra cost of transportation to undergo completion thyroidectomy was also omitted, which would have added to the overall cost of the diagnostic hemithyroidectomy without IPE strategy, although by only a small amount.

The overall cost of completion thyroidectomy could have increased by US$6,273 before IPE became cost effective, so it is unlikely that this omission would change the model’s conclusion. The model assumed that all patients who became hypothyroid after thyroid lobectomy required full-dose thyroid hormone replacement. The outcomes of partial hypothyroidism, which would have required a lower level of thyroid hormone replacement, were not considered. This omission did not alter the conclusions of this study because the model was not sensitive to lower costs of thyroid hormone replacement or the quality-adjustment factor for treated hypothyroidism. The surgical complication of RLN injury has a wide spectrum of severity and treatment costs, including the need for temporary voice therapy, vocal cord medialization, and, at worst, permanent tracheostomy, but this array of possibilities was simplified into a single gross cost and quality of life estimates. We believe our sensitivity analysis adequately addresses the possible impact of these simplifications. The option of outpatient thyroidectomy was not directly considered in this model. Diagnostic hemithyroidectomy and completion thyroidectomy in the outpatient setting would have lowered the costs of these procedures, and sensitivity analysis demonstrates that this effect would diminish the cost effectiveness of IPE.

CONCLUSIONS

This study demonstrates that IPE is not cost effective in the diagnosis of follicular thyroid neoplasms during diagnostic hemithyroidectomy. Improvements in both the sensitivity and specificity of this service would be needed to justify its use.

Author Contributions

Study conception and design: Zanocco, Elaraj, Sturgeon
Acquisition of data: Zanocco, Heller
Analysis and interpretation of data: Zanocco, Sturgeon
Drafting of manuscript: Zanocco, Heller
Critical revision: Zanocco, Heller, Elaraj, Sturgeon

REFERENCES


