Economic Impact of Frozen Section for Thyroid Nodules with “Suspicious for Malignancy” Cytology

Craig A. Bollig, MD1, David Gilley2, David Lesko2, Jeffrey B. Jorgensen, MD1, Tabitha L. Galloway, MD1, Robert P. Zitsch III, MD1, and Laura M. Dooley, MD1

No sponsorships or competing interests have been disclosed for this article.

Abstract

Objective. To perform a cost analysis of the routine use of intraoperative frozen section (iFS) among patients undergoing a thyroid lobectomy with “suspicious for malignancy” (SUSP) cytology in the context of the 2015 American Thyroid Association guidelines.

Study Design. Case series with chart review; cost minimization analysis.

Setting. Academic.

Subjects and Methods. Records were reviewed for patients with SUSP cytology who underwent thyroid surgery between 2010 and 2015 in which iFS was utilized. The diagnostic test performance of iFS and the frequency of indicated completion/total thyroidectomies based on the 2015 guidelines were calculated. A cost minimization analysis was performed comparing lobectomy, with and without iFS, and the need for completion thyroidectomy according to costs estimated from 2014 data from Medicare, the Bureau of Labor Statistics, and the Nationwide Inpatient Sample.

Results. Sixty-five patients met inclusion criteria. The malignancy rate was 61.5%, 45% of which was identified intraoperatively. The specificity and positive predictive value were 100%. The negative predictive value and sensitivity were 83% and 95%, respectively. Completion/total thyroidectomy was indicated for 9% of patients; 83% of these individuals had findings on iFS that would have changed management intraoperatively. Application of the new guidelines would have resulted in a significant reduction in the frequency of conversion to a total thyroidectomy when compared with the actual management (26.1% vs 7.7%, \( P = .005 \)). Performing routine iFS was the less costly scenario, resulting in a savings of $474 per case.

Conclusion. For patients with SUSP cytology undergoing lobectomy, routine use of iFS would result in decreased health care utilization.

Keywords

thyroid cancer, frozen section, Bethesda V, suspicious for malignancy, cost analysis

Received May 16, 2017; revised August 30, 2017; accepted October 12, 2017.

The role of intraoperative frozen section (iFS) for the evaluation of thyroid nodules has been a matter of debate for >20 years. Proponents cite the ability of iFS to identify malignant lesions intraoperatively, allowing conversion to a total thyroidectomy (TT) and reducing the need for a future completion thyroidectomy (CT). Opponents argue that it rarely changes management and results in increased costs. Surprisingly, only a few studies have investigated the role of iFS in nodules that are cytologically classified as suspicious for papillary thyroid cancer, and much of these data came prior to the establishment of the Bethesda System for Reporting Thyroid Cytopathology (BSRTC). The limited number of published series since then reported a high specificity and positive predictive value of iFS in nodules classified as Bethesda V–suspicious for malignancy (SUSP) and supported its use.

In 2015, the American Thyroid Association (ATA) released updated guidelines stating that iFS can occasionally confirm malignancy at the time of lobectomy in cytologically indeterminate nodules and allow for conversion to TT if indicated. The guidelines also recommend a risk-based
management strategy, often with less aggressive surgical treatment as compared with prior guidelines, which decreases the frequency of indicated TT/CT.11 No known studies have described the magnitude of this reduction or analyzed the impact of the updated guidelines on the cost-effectiveness of iFS for nodules classified as SUSP.

The aim of this study was to perform a cost analysis of the routine use of iFS among patients with a cytological diagnosis of SUSP in the context of the updated ATA guidelines. Our hypothesis was that it would be less costly to obtain iFS for patients undergoing a diagnostic lobectomy with immediate conversion to a TT when indicated per the iFS results, according to the 2015 ATA guidelines, as compared with diagnostic lobectomy without iFS with a subsequent CT based on the final pathology results if needed.

Methods

Case Series

To further investigate this objective, we performed a retrospective review of patients undergoing thyroid surgery in which iFS was utilized. The study was conducted at the University of Missouri Hospital and Clinics after institutional review board approval was obtained. Current Procedural Terminology codes 60220 and 60240 were used to identify patients who underwent a thyroid lobectomy and TT, respectively, between January 2010 and December 2015. Demographic information, preoperative cytology, iFS, and permanent pathology results were obtained from the patients’ medical records, pathology reports, and operative reports. Exclusion criteria included pediatric patients, patients with a cytologic diagnosis that was not classified according to the BSRTC, patients who underwent thyroidectomy without iFS, and cases where iFS was used to evaluate lymph nodes or parathyroid tissue. Demographic information included sex, age, race, family history of thyroid cancer, history of a thyroid cancer syndrome, and history of radiation exposure. The subset of cases with a cytologic diagnosis of SUSP was analyzed.

Frozen section results were categorized as definitive versus nondefinitive. Definitive iFS subsets included those reported as benign or malignant, while nondefinitive categories included follicular lesion (defer to permanent), probably benign, and suspicious. The sensitivity, specificity, positive predictive value, and negative predictive value for iFS were calculated with permanent pathology results as the histologic gold standard. Only definitive iFS results were considered for these calculations. Malignancies were counted as true positives, and benign lesions were recorded as true negatives. False negatives included lesions that were reported as benign on iFS but malignant on permanent pathology. False positives were considered in our study. For each case, whether or not a TT/CT would have been indicated per the 2015 ATA guidelines was recorded, and the number of cases in which findings on iFS would have resulted in conversion to a TT was calculated. Only the definite indications for conversion that could be discovered intraoperatively were used. The frequency of cases in which iFS altered surgical management according to the operative reports was recorded. The chi-square test was used to explore the association of the hypothetical application of the 2015 ATA guidelines versus the actual operative results with the outcome of conversion to a TT. Statistical significance was set at a $P$ value <.05.

Decision Model

A decision model for the diagnosis and treatment of 2 case scenarios was constructed with Excel 2013:

Scenario 1: Diagnostic thyroid lobectomy without iFS, followed by CT when indicated per the permanent pathology results

Scenario 2: Diagnostic thyroid lobectomy with iFS and conversion to TT when indicated per the iFS results and a CT if needed per the permanent pathology results

Figures 1 and 2 diagram the chance and terminal nodes of the diagnostic strategies of scenario 1 and scenario 2, respectively. The event pathways and treatment outcome probabilities were estimated on the basis of reported rates in the literature, except for the likelihood of converting to a TT and the probability of performing a CT, which were based on the results of our patient cohort due to a lack of comparison data in the literature.

Cost Analysis

All costs were measured in 2014 US dollars. Only costs that differed between the 2 diagnostic strategies were considered.12 Cost estimates for physician-provided services were based on the 2014 mean national Medicare charge limits for surgery, anesthesiology, and pathology services rendered by each strategy.13 Hospital costs were estimated by calculating the weighted average of 2014 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), DRG 627 (thyroid, parathyroid, and thyroglossal procedures without complications and comorbidities).12,14 The computed ratio of 0.126 was then multiplied by the national mean inpatient charge estimates for a partial or total thyroidectomy reported by the Nationwide Inpatient Sample of that year.12,15
Average operating room charges of $62 per minute for 20 minutes spent waiting on iFS were obtained from a 2005 survey of 100 hospitals nationwide. The charges were adjusted for inflation and the cost:charge ratio of 0.126 was applied to generate the estimated cost of $10.52 per minute. The cost of 2 weeks of missed labor for a CT was based on data from mean hourly wages from the US Bureau of Labor Statistics. Finally, because of the equivocal rates of relevant complications and clinical outcomes between the scenarios, a cost minimization analysis was selected as the appropriate method to investigate the study objective, rather than a cost-effectiveness analysis.

Intangible costs such as patient anxiety, pain, and so on were not considered. The costs of scenarios 1 and 2 were calculated in Excel with the probabilities described in the decision models, and the results were compared.

Results

Sixty-five patients met inclusion criteria. Patient characteristics are listed in Table 1. The mean age of patients in our cohort was 49.6 ± 14.9 years, and the majority of patients were female (81.5%). Clinical risk factors for thyroid cancer were present in 8 patients (12.3%), which included 7 with a family history of thyroid cancer and 1 with head and neck radiation exposure during childhood. The mean nodule size was 19 mm (range, 6-47 mm). Table 2 lists the results of iFS and permanent pathology. Overall, a definitive diagnosis was given with iFS in 38.5% of cases, 80% of which were malignant on permanent pathology. An additional 15.4% and 7.7% of cases were SUSP and likely benign on iFS, respectively. A diagnosis was deferred in the remaining 38.5% of cases. On permanent pathology, 61.5% of cases were malignant, and 85% of these were papillary thyroid carcinoma, including variants. The specificity and positive predictive value of iFS were both 100%, while its sensitivity and negative predictive value were 95% and 83%, respectively. We then reviewed how frequently iFS influenced intraoperative decision making, and we found that results on iFS led to conversion to a TT in 17 cases (26%) according to the operative reports. With adherence to the updated ATA guidelines, 6 (9%) patients had a definite indication for a CT/TT, 5 (83%) of whom had findings on iFS supporting conversion to a TT.

Table 3 illustrates a statistically significant reduction in the frequency of conversion to a TT occurring as a result of the hypothetical application of the 2015 ATA guidelines as compared with the actual management, which was largely based on prior guidelines (26.2% vs 7.7%, P = .005).

The costs and probabilities considered in our evaluation are listed in Table 4, along with their sources. Once these were obtained, the cost analysis was performed, as detailed in Table 5. Based on institutional malignancy rates, the
Table 2. Frozen Section and Final Pathology Results.

<table>
<thead>
<tr>
<th>Frozen section results</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive</td>
<td>25</td>
<td>38.5</td>
</tr>
<tr>
<td>Benign</td>
<td>6</td>
<td>9.2</td>
</tr>
<tr>
<td>Malignant</td>
<td>19</td>
<td>29.2</td>
</tr>
<tr>
<td>Nondiagnostic</td>
<td>40</td>
<td>61.5</td>
</tr>
<tr>
<td>Likely benign</td>
<td>5</td>
<td>7.7</td>
</tr>
<tr>
<td>Follicular lesion</td>
<td>25</td>
<td>38.5</td>
</tr>
<tr>
<td>Suspicious</td>
<td>10</td>
<td>15.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Final pathology results</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>25</td>
<td>38.5</td>
</tr>
<tr>
<td>Malignant</td>
<td>40</td>
<td>61.5</td>
</tr>
<tr>
<td>PTC, classical</td>
<td>15</td>
<td>23.1</td>
</tr>
<tr>
<td>Papillary microcarcinoma</td>
<td>10</td>
<td>15.4</td>
</tr>
<tr>
<td>PTC, FV</td>
<td>9</td>
<td>13.8</td>
</tr>
<tr>
<td>Hurthle cell carcinoma</td>
<td>3</td>
<td>4.6</td>
</tr>
<tr>
<td>Follicular carcinoma</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Medullary thyroid carcinoma</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Poorly differentiated carcinoma</td>
<td>1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Abbreviations: FV, follicular variant; PTC, papillary thyroid carcinoma.

Table 3. Frequency of Conversion to Total Thyroidectomy: Hypothetical Application of the 2015 ATA Guidelines vs Actual Operative Management.

<table>
<thead>
<tr>
<th>Actual operative management</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothetical application of 2015 ATA guidelines</td>
<td>17</td>
<td>26.2</td>
</tr>
</tbody>
</table>

Abbreviations: ATA, American Thyroid Association.

Overall cost of scenario 1 was $6698, as opposed to $6224 in scenario 2, leading to the conclusion that use of routine iFS would result in a cost savings of $474 per case. When the rate of malignancy on permanent pathology varied from 60% to 75%, the cost of scenario 1 ranged from $6674 to $6853. When the rate of malignancy identified on iFS varied from 42% to 57%, the cost of scenario 2 ranged from $6223 to $6244. When the rate of false negatives on iFS varied from 15% to 25%, the cost of scenario 2 ranged from $6201 to $6267. Finally, if an additional 20 minutes of operating room costs were included, the cost of scenario 2 ranged from $6411 to $6477 based on the malignancy rates reported in the literature. Overall, the net savings per case based on the malignancy rates obtained from the literature ranged from $407 to $652 if operating room rates were not considered, as opposed to $241 to $399 if they were included.

Discussion

Historically, iFS was the primary means to establish an initial diagnosis in a thyroid nodule and guide surgical management; however, the advent of accurate preoperative fine-needle aspirations resulted in many authors arguing that iFS adds little to intraoperative decision making. Others have asserted that iFS has value, especially with nodules that are SUSP. Prior to publication of the BSRTC, “suspicious” lesions included not only those that were suspicious for papillary thyroid carcinoma but also Hurthle cell lesions, follicular neoplasms, and lymphoma. Lumping such a diverse group into 1 category contributed to the confusion and lack of a consensus regarding the utility of iFS, but widespread adoption of the BSRTC has improved the reporting standards of cytology. Table 6 summarizes recent institutional reviews investigating the utility of iFS in SUSP thyroid lesions, none of which include a cost evaluation.

In 2015 the ATA released updated guidelines advocating a risk-based management strategy with less aggressive surgical treatment as compared with the prior version, which endorsed TT for nearly all high-risk cancers >1 cm. These guidelines mention iFS only once, in recommendation 20, which states that iFS can occasionally confirm malignancy at the time of lobectomy, allowing for conversion to TT if indicated. They note that iFS is most helpful in classic papillary thyroid cancer, whereas its impact is low in follicular variant of papillary thyroid cancer and follicular cell carcinoma.

Following publication of the new guidelines, Abu-Ghanem et al. reported that iFS identified 50% of malignancies with a 100% positive predictive value and specificity among 47 patients with SUSP cytology, concluding that it is a useful adjunctive examination. The only other investigation into the topic following the 2015 ATA guidelines found that iFS altered operative management in 56% of 16 cases with SUSP cytology, with the authors concluding that iFS has some utility in this subset. Neither of these studies included an evaluation of cost-effectiveness or quantified the impact of the updated guidelines.

We present the first study to report on the potential magnitude of the reduction of indicated CT/TT as a result of the 2015 ATA guidelines as well as the economic implications of the new guidelines. We found that while conversion to a TT based on iFS findings occurred in 17 cases (26%), immediate conversion to a TT would have been indicated for only 5 (8%) of these patients if adhering to the new guidelines. One additional patient had findings on final pathology for which a CT would have been recommended. In our cohort, the combined category of definitively malignant and SUSP on frozen section yielded an identification of 45% of malignancies with no false positives, which is comparable to the recent reports detailed in Table 6. If papillary microcarcinomas are excluded, 90% of malignancies were identified as malignant or suspicious on iFS. Interpretation of iFS for thyroid cancer can be difficult and depends on the expertise of the evaluating pathologist. Even in published series at high-volume institutions, the rate of deferred diagnoses on iFS may approach 30% to 40% for SUSP lesions. This number may be disguised by the reported sensitivity, specificity, positive predictive value,
and negative predictive value, which consider only definitive diagnoses in their calculation.

Most prior cost analyses included a diverse group of benign and/or indeterminate lesions or follicular lesions and yielded mixed results on the cost-effectiveness of iFS. In 2013, the only study focusing exclusively on patients with SUSP cytology, Leiker et al found that performing an upfront TT was more cost-effective than a lobectomy with iFS. However, the rates of indicated TT/CT would change significantly from their study given the changes in the 2015 ATA guidelines. Additionally, their model ran for only 12 months, which significantly underestimates the costs of the permanent complications as well as lifelong medication costs associated with an unnecessary TT, given the high survival rate of patients with well-differentiated thyroid cancer. Consequently, another economic evaluation of iFS in this population was indicated.

For our cost analysis, we performed a cost minimization analysis rather than a cost-effectiveness analysis, due to the well-documented comparable clinical outcomes and rates of complications of a TT versus a CT in the literature. Some recent studies reported a higher incidence of temporary hypoparathyroidism among patients undergoing a TT versus a CT, although several other articles cited no significant difference, including a meta-analysis. Most important, no studies in our review demonstrated that patients undergoing a TT have a longer hospital stay versus those undergoing a CT that would lead to higher costs; therefore, this was not factored in to our decision model. Another assumption was that patients undergoing a CT would have similar costs associated with testing/prophylactic treatment of temporary hypocalcemia as those undergoing TT. The issue of time spent waiting in the operating room is a potentially underappreciated cost of iFS; however, in a prospective evaluation, Udelsman et al found that operative times were not significantly longer for patients undergoing iFS, which took an average of 26 minutes. That time waiting could instead be spent establishing hemostasis, closing the incision, and so on. Because of this, we chose to include results of the cost analysis with and without this extra cost. Using rates of malignancy obtained from our patient cohort, we found that the routine use of iFS for SUSP lesions resulted in cost savings of $474 per case. This varied from $241 to $609 if reported ranges from the literature were applied, depending on whether time waiting was considered. Although intangible costs associated with quality of life were not evaluated in this study, when the stress of a second procedure (CT) and recovery were considered, additional benefit would be obtained with the use of iFS. Furthermore, for the majority of the time, iFS gives a nondeferred diagnosis, which allows the patient to receive a diagnosis much quicker, potentially resulting in lessened anxiety. However, the diagnosis may be deferred; false negatives occur; and although the rate of CT is significantly reduced with the use of iFS, it is not eliminated.

Table 4. Decision Tree Inputs Used in Model.

<table>
<thead>
<tr>
<th>Value, US$</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid lobectomy without iFS</td>
<td>5957.99</td>
</tr>
<tr>
<td>Thyroid lobectomy with iFS</td>
<td>5957.99</td>
</tr>
<tr>
<td>Thyroid lobectomy</td>
<td>5957.99</td>
</tr>
<tr>
<td>Intraoperative frozen section</td>
<td>144.93</td>
</tr>
<tr>
<td>Additional 20 min of operating room time</td>
<td>210.45</td>
</tr>
<tr>
<td>Conversion to a total thyroidectomy</td>
<td>345.66</td>
</tr>
<tr>
<td>Completion thyroidectomy</td>
<td>7953.24</td>
</tr>
<tr>
<td>Completion thyroidectomy procedure</td>
<td>6357.24</td>
</tr>
<tr>
<td>Cost of 2 wk lost wages following CT</td>
<td>1596.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Probabilities</th>
<th>Institutional (Rates in Literature)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy on final pathology</td>
<td>0.62 (0.60-0.75)</td>
<td>10</td>
</tr>
<tr>
<td>Malignancy on iFS</td>
<td>0.45 (0.42-0.57)</td>
<td>4, 5, 9, 27</td>
</tr>
<tr>
<td>Malignancies missed on iFS</td>
<td>0.17 (0.15-0.25)</td>
<td>4,5</td>
</tr>
<tr>
<td>CT if iFS was not utilized</td>
<td>0.09 (N/A)</td>
<td>N/A</td>
</tr>
<tr>
<td>Conversion to total thyroidectomy</td>
<td>0.077 (N/A)</td>
<td>N/A</td>
</tr>
<tr>
<td>CT if iFS was utilized</td>
<td>0.012 (N/A)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Abbreviations: CT, completion thyroidectomy; N/A, not available; iFS, intraoperative frozen section.
43 Incorporation of all these variables into a cost analysis would be extremely difficult, if not impossible. For our model, we considered only the definite indications for a TT/CT. The new guidelines allow for some leeway in performing a TT/CT for lesions ≤4 cm without extrathyroidal extension or clinical evidence of lymph node metastasis, to enable radioactive iodine therapy or to enhance follow-up based on patient preferences or clinical high-risk features—although the guidelines also state that lobectomy alone is an oncologically sound operation in these situations as well. Inclusion of these relative indications for a TT/CT would result in additional cost savings.

Our results must be interpreted in the context of their limitations, including the retrospective nature of the review, which has some inherent bias. Additionally, there was a lack of available comparison data on the rates of indicated TT/CT, so these were obtained from our patient population. Although our patient cohort was considerably larger than those in recent studies of this cytologic category, it is still a relatively small study population.

While consideration of performing molecular studies to help suggest surgical management of indeterminate lesions could also be given, none of the patients in this study were evaluated with this testing. Finally, an important assumption in this model is the lack of false-positive iFS, which would potentially lead to unnecessary TT. We felt comfortable with this assumption due to the lack of false-positive iFS in this cytologic group in our study and in all recent studies in our review, although this would be an important consideration in a population where false positives are reported.

## Conclusion

For patients with a cytologic diagnosis of SUSP undergoing diagnostic lobectomy, adherence to the 2015 ATA guidelines would result in a significant reduction in the number of cases in which operative management is changed as a result of iFS. Despite this decrease, use of iFS allows for immediate conversion to a TT, thereby reducing the number of completion thyroidectomies and leading to decreased health care resource utilization.

## Acknowledgments

We thank Chelsea Deroche, PhD, and her assistant Bin Ge, MD, MS, for their assistance with performing the statistical analysis of the data.

## Author Contributions

Craig A. Bollig, design, analysis, interpretation, drafting, final approval, accountability agreement; David Gilley, acquisition, drafting, final approval, accountability agreement; David Lesko, acquisition, drafting, final approval, accountability agreement;
Jeffrey B. Jorgensen, interpretation, critical revision, final approval, accountability agreement; Tabitha L. Galloway, interpretation, critical revision, final approval, accountability agreement; Robert P. Zitsch III, interpretation, critical revision, final approval, accountability agreement; Laura M. Dooley, conception, design, analysis, interpretation, critical revision, final approval, accountability agreement.

Disclosures

Competing interests: None.
Sponsorships: None.
Funding source: None.

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