Cost analysis of thyroid lobectomy and intraoperative frozen section versus total thyroidectomy in patients with a cytologic diagnosis of “suspicious for papillary thyroid cancer”

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Background. The optimal operation for a patient with a thyroid nodule “suspicious for papillary thyroid cancer (PTC)” on fine-needle aspiration (FNA) is unclear. This study examines the incremental cost-utility of thyroid lobectomy with intraoperative frozen section (thyroid lobectomy) versus total thyroidectomy.

Methods. Cost-utility analysis was performed for patients with a cytologic diagnosis of “suspicious for PTC” on FNA. Patients underwent either initial total thyroidectomy or thyroid lobectomy and, if needed, completion thyroidectomy. The incremental cost-utility ratio (ICUR; US$/quality-adjusted-life-year [QALY]), was determined from a societal perspective.

Results. The base-case ICUR of thyroid lobectomy is $90,776/QALY, strongly favoring total thyroidectomy as a more cost-effective modality. On sensitivity analyses, the model is sensitive to the accuracy of frozen section and to the rate of injury to the recurrent laryngeal nerve (RLN). Thyroid lobectomy is more cost-effective only if both frozen section and final pathology are benign in ≥92% of patients (ICUR $47,959/QALY at 92%). With increasing rates of unilateral (>5%) or bilateral (>2%) RLN injury associated with total thyroidectomy, there is a trend toward thyroid lobectomy being more cost effective ($53,127 and $51,325/QALY, respectively).

Conclusion. In our model, initial total thyroidectomy is cost-effective for patients with a single thyroid nodule suspicious for PTC on FNA. Our results strongly support total thyroidectomy for initial treatment; thyroid lobectomy is preferred only when complications reach unacceptable levels. (Surgery 2013;154:1307-14.)

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The risk of malignancy in a solitary thyroid nodule that undergoes fine-needle aspiration (FNA) biopsy and is found to have a cytologic diagnosis of “suspicious for papillary thyroid cancer (PTC)” has been reported to be 57–95% using the Bethesda system.1-3 The 2009 American Thyroid Association Guidelines Taskforce on Thyroid Nodule and Differentiated Thyroid Cancer recommends total thyroidectomy for nodules with this cytologic diagnosis (R25A. Recommendation A); thyroid lobectomy alone is recommended for patients who may prefer a more limited operative procedure (R24. Recommendation C).4 In such patients, thyroid lobectomy with intraoperative frozen section may be performed. If PTC is diagnosed on frozen section, completion thyroidectomy can be performed at the initial procedure. In contrast, if the diagnosis of PTC is made on final pathology, completion thyroidectomy, when performed, is delayed typically for 6–8 weeks.

The operative approach of initial thyroid lobectomy in patients with a nodule suspicious for PTC is contingent on the accuracy of a diagnosis on frozen section diagnosis. Previous studies have examined the role of intraoperative frozen section
on the operative management of nodules interpreted as suspicious for PTC. Haymart et al\(^2\) reported that frozen section diagnosed correctly 13 of 15 patients (87%) with PTC on final pathology, allowing for immediate completion thyroidectomy. In a study of 217 patients with nodules suspicious for PTC, Moon et al\(^3\) also found that the frozen section diagnosis was correct in 189 patients (87%) with PTC. These findings have led some groups to recommend thyroid lobectomy with routine frozen section in patients undergoing surgery for nodules diagnosed as suspicious for PTC on FNA biopsy.\(^2,3\)

The studies supporting initial thyroid lobectomy and intraoperative frozen section do not address several important issues, including patient quality-of-life, additional loss of productivity owing to postoperative recovery from 2 separate operations, and direct costs related to performance of both the frozen section and the delayed completion thyroidectomy. We hypothesize that given the high rate of PTC on final histology in patients with a preoperative FNA biopsy diagnosed as suspicious for PTC, total thyroidectomy would be a more cost-effective strategy from a societal perspective. Therefore, the aim of this study was to determine the incremental cost-utility of total thyroidectomy or thyroid lobectomy with intraoperative frozen section (thyroid lobectomy). All relevant costs and benefits were considered from the societal perspective. Benefits were measured in units of quality-adjusted life-years (QALY). The QALY incorporates the qualitative state of 1 year of life by applying a utility weight for a given state of health, with a range of 0 (death) to 1 (perfect health). Cost-utility is the ratio of the difference in cost between the 2 interventions compared with the difference in QALY. The incremental cost-utility ratio (ICUR) was measured as $/QALY and an ICUR of $50,000/QALY was the threshold for cost-effectiveness.\(^5\) The decision tree model was created and analyzed in TreeAge Pro (2012; Williamstown, Mass).

Each individual in the cohort was assumed to have no previous history of thyroid surgery and a single thyroid nodule with a FNA diagnosis of “suspicious for PTC.” Hypothetic patients were assigned randomly to each treatment arm for analysis (Fig 1). Patients transitioned along the decision tree according to the diagnostic accuracy of frozen section and the probability of endocrine-specific complications (recurrent laryngeal nerve [RLN] injury and hypoparathyroidism). In the thyroid lobectomy arm of the model, patients with PTC on frozen section had completion thyroidectomy at the time of the initial operation. Patients continued in the benign health state until conclusion of the model if both frozen section and final pathology were benign. The patients with a benign diagnosis on frozen section but a subsequent diagnosis of PTC on final pathology (false-negative diagnosis on frozen section) underwent completion thyroidectomy 6 weeks after initial thyroid lobectomy. Patients who underwent immediate

**METHODS**

In a hypothetic cohort of adult patients with a single thyroid nodule and a cytologic diagnosis of “suspicious for PTC” on FNA biopsy, a decision tree model was constructed to determine the cost-utility of 2 treatment strategies—initial total thyroidectomy (total thyroidectomy) or thyroid lobectomy with intraoperative frozen section (thyroid lobectomy).

![Fig 1. Simplified cost-utility analysis decision tree. Patient probability of transition into a given pathologic diagnosis is given as the base-case probability with sensitivity analysis range in parenthesis. Operative complications were factored into each terminal health state. CT, Completion thyroidectomy; FNA, fine-needle aspiration; FS, frozen section.](image-url)
complication with the least utility.

The model also was sensitive to variations in the rates of RLN injury, although all sensitivity analyses performed favored total thyroidectomy. In the base-case, the rate of RLN injury in patients after thyroid lobectomy was 1%; varying the rates of RLN injury from 0% to 4% resulted in ICUR of $71,024/QALY to $550,299/QALY. After initial total thyroidectomy, rates of unilateral and bilateral RLN injury were 2% and 0.5%, respectively, in the base-case analysis (Table). At greater rates of RLN injury after total thyroidectomy, thyroid lobectomy trended toward being cost-effective, with ICURs of $53,125/QALY for a 2% risk of unilateral RLN injury and $51,325/QALY for a 2% risk of bilateral RLN injury, but remained above the cost-effectiveness threshold of $50,000/QALY. Decreasing rates of unilateral RLN injury from 1% to 0% and of bilateral RLN injury from 0.5% to 0% resulted in ICURs of $172,065/QALY and $122,047/QALY, respectively, further supporting initial total thyroidectomy.

RESULTS

In the base-case analysis, thyroid lobectomy was more costly than total thyroidectomy ($6,758 vs $6,457), but slightly more effective (0.980 vs 0.977 QALYs), with a base-case ICUR of $90,776/QALY. Because the base-case ICUR exceeds the $50,000/QALY threshold utilized for this study, initial total thyroidectomy seems to be the more cost-effective algorithm. The difference in cost between the 2 treatment strategies was accounted for almost entirely by the costs of an additional procedure when completion thyroidectomy was performed in the thyroid lobectomy arm. The cost-utility analysis was affected by variations in clinical inputs to the model. Sensitivity analyses demonstrated that the model was most sensitive to changes in accuracy of frozen section in the diagnosis of PTC, rates of RLN injury after thyroid lobectomy and total thyroidectomy, and patient quality of life owing to hypothyroidism (Fig 2).

In the base-case, PTC was diagnosed on final pathology in 15% of cases with a benign diagnosis on frozen section (frozen section had a negative predictive value [NPV] of 85%; Table). Sensitivity analyses were performed for NPV rates of frozen section ranging from 100% (no false negatives on frozen section) to 77% (23% false negatives on frozen section; Fig 3). If the NPV of intraoperative frozen section diagnosis was 100% accurate (no false negatives), thyroid lobectomy was a more cost-effective strategy than total thyroidectomy, with an ICUR of $6,273/QALY. Thyroid lobectomy remained more cost-effective only if both frozen section diagnosis and the final pathologic diagnosis are benign in ≈92% of patients with a preoperative FNA diagnosis of suspicious for PTC (ICUR $47,959/QALY). With a NPV of 77% (23% false negatives on frozen section), thyroid lobectomy was not cost-effective (ICUR of $142,221/QALY).

The model also was sensitive to variations in the rates of RLN injury, although all sensitivity analyses performed favored total thyroidectomy. In the base-case, the rate of RLN injury in patients after thyroid lobectomy was 1%; varying the rates of RLN injury from 0% to 4% resulted in ICUR of $71,024/QALY to $550,299/QALY. After initial total thyroidectomy, rates of unilateral and bilateral RLN injury were 2% and 0.5%, respectively, in the base-case analysis (Table). At greater rates of RLN injury after total thyroidectomy, thyroid lobectomy trended toward being cost-effective, with ICURs of $53,125/QALY for a 2% risk of unilateral RLN injury and $51,325/QALY for a 2% risk of bilateral RLN injury, but remained above the cost-effectiveness threshold of $50,000/QALY. Decreasing rates of unilateral RLN injury from 1% to 0% and of bilateral RLN injury from 0.5% to 0% resulted in ICURs of $172,065/QALY and $122,047/QALY, respectively, further supporting initial total thyroidectomy.
In the base-case, patients were assumed to be euthyroid on thyroid hormone replacement, with a patient utility of 0.99. The model was very sensitive to changes in patient utility associated with hypothyroidism. With minimal change to patient utility (from 0.99 to 0.97), thyroid lobectomy becomes the more cost-effective approach ($49,686/QALY), likely owing to effects on patient quality-of-life when not supplemented to a euthyroid state.

Sensitivity analyses were performed for all other variables listed in the Table. The results of the base-case analysis were robust for all remaining clinical and cost inputs, with thyroid lobectomy with intraoperative frozen section biopsy exceeding the threshold ICUR of $50,000/QALY (Fig 2).

**DISCUSSION**

In a patient with a solitary thyroid nodule that is diagnosed as “suspicious for PTC” on cytology from a FNA biopsy, operative options include initial total thyroidectomy or thyroid lobectomy with or without intraoperative frozen section biopsy. For patients
who undergo initial thyroid lobectomy, completion thyroidectomy may be performed at the initial procedure or at a later date, depending on the accuracy of intraoperative frozen section biopsy in diagnosing the presence of malignancy. Current guidelines from the American Thyroid Association and National Comprehensive Cancer Network favor total thyroidectomy in the majority of patients with nodules interpreted as suspicious for PTC on FNA biopsy, but do not refer to the routine use of intraoperative frozen section in patients who undergo initial thyroid lobectomy.\textsuperscript{4,10} The results of this current study demonstrate that initial total thyroidectomy is a cost-effective approach compared with thyroid lobectomy with intraoperative frozen section biopsy.

For thyroid nodules harboring a diagnosis of “suspicious for PTC” according to the Bethesda classification, published rates of malignancy range from 57\% to 90\%.\textsuperscript{1-3} In a single-institution review of 26 patients with preoperative cytology interpreted as suspicious for PTC who then underwent thyroid

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**Fig 2.** Summary of sensitivity analyses for total thyroidectomy versus thyroid lobectomy with intraoperative frozen section. The solid line represents the cost-effectiveness threshold of $50,000/quality-adjusted life-year (QALY); the dashed gray line represents the base-case incremental cost-effectiveness ratio (ICUR; $90,776/QALY). Minimum and maximum sensitivity analysis inputs are shown.

**Fig 3.** Sensitivity analysis of the negative predictive values of frozen section in diagnosis of papillary thyroid cancer. ICUR, Incremental cost-effectiveness ratio.
lorectomy with intraoperative frozen section, Haymart et al reported 13 patients with a frozen section diagnosis of PTC, and the diagnosis was confirmed on final pathology in all patients (positive predictive value, 100%). In the remaining 13 patients with a benign diagnosis on frozen section, 2 (15%) were found to have PTC on final pathology and required a second operation for completion total thyroidectomy (NPV, 85%). In a study reported by Moon et al, 189 of 217 patients (87%) with PTC were diagnosed correctly on frozen section. Of the remaining 28 patients with benign diagnostis on frozen section, 14 (50%) were found ultimately to have PTC on final pathology. Based on results of institutional frozen section analyses, both of these studies favored thyroid lobectomy with intraoperative frozen section as the initial operative procedure; however, costs of thyroid lobectomy with frozen section versus total thyroidectomy were not evaluated in either study. Based on the results of our cost analysis, total thyroidectomy would be preferred; thyroid lobectomy and intraoperative frozen section become the favored initial procedure only when the concordance rate between frozen section and final pathology is ≥92%, a rate not demonstrated by previous studies and that will likely not be achieved with technology available currently in the pathology suite.

Although the model proposed by the current study was sensitive to rates of RLN injury, total thyroidectomy remained the more cost-effective approach unless rates of unilateral and bilateral RLN injury exceed 5% and 2%, respectively. Thyroid lobectomy also remained less cost-effective (ICUR $71,024/QALY), even if the rate of unilateral RLN injury during thyroid lobectomy was decreased from 1% (base case) to 0%. Therefore, in the hands of experienced thyroid surgeons with low rates of RLN injury, this cost analysis suggests that total thyroidectomy should be the initial procedure in patients with thyroid nodules demonstrated to be suspicious for PTC on preoperative FNA biopsy.11

There are several limitations to this analysis. First, clinical inputs and patient utility were obtained from a review of the current literature and were based on best available data. In particular, patients who may have had multiple complications were assigned utilities derived from individual states of quality of life, which may affect quality-of-life inputs to the model. When tested on sensitivity analyses, however, patient utility had little effect on the model; therefore, any potential discrepancies would likely not affect the analysis. Also, the accuracy of frozen section is variable by institution; knowledge of the accuracy of one’s own institution’s frozen section may influence the decision to perform thyroid lobectomy with frozen section or total thyroidectomy. Second, given the absence of data in the current literature, we assumed equivalent oncologic efficacy when total thyroidectomy was performed as a 1- or 2-stage procedure. Third, the model implemented in this study accumulates QALYs and incurs cost for only 12 months. Long-term costs, such as those for thyroid hormone and calcium supplementation, were not accounted for; however, sensitivity analyses suggest that these costs had little impact on the model. Last, the model did not include performance of a central compartment neck dissection or of molecular analysis for nodules “suspicious for malignancy.” These 2 factors were not included because prophylactic central compartment neck dissection remains controversial even in patients with biopsy-proven PTC and because molecular analysis for the “suspicious for malignancy” cytologic diagnosis is not yet standard of care and data on its use for these nodules are limited.

In conclusion, results of this cost analysis suggest that in patients with no previous history of thyroid surgery and a solitary thyroid nodule diagnosed as “suspicious for PTC” on FNA biopsy, initial total thyroidectomy is a cost-effective approach. This argument is in agreement with the current guidelines published by both the American Thyroid Association and the National Comprehensive Cancer Network.4,10 Thyroid lobectomy should be performed only if complication rates reach unacceptably high levels. Validation of these findings in a prospective, randomized trial would be difficult because of the (1) need for a multi-institutional study with variable institutional rates of accuracy of frozen section for adequate power and clinical relevance and (2) issues of provider bias and lack of clinical equipoise that would negatively influence patient accrual. The complexity of such a study underscores the importance of cost-effectiveness studies, which will likely be reproduced in other areas of specialty cancer/endocrine surgery and are especially important in this current era of healthcare reform where pay-for-performance is being replaced by population management and strategies designed to maximize value—for the patient, society, and the health system.

REFERENCES


DISCUSSION

Dr Christopher R. McHenry (Cleveland, OH): I have a question and a comment for you.

First, one of the things that I think the evaluation of cost effectiveness is also dependent on is the rate of malignancy for a fine-needle aspiration biopsy that’s suspicious for papillary thyroid cancer. So my question is, would your cost-effectiveness model and your conclusions differ if the rate of malignancy in a fine-needle biopsy that was suspicious for papillary thyroid cancer was at the low end of the spectrum, say 40–50%? And I wondered if you accounted for that in your cost-effectiveness model.

Next, I just had a comment. And I’m still not convinced that this will be less costly in everybody’s experience, or of less or more benefit to the patient. I think this is a clinical situation where, in our experience, we have found frozen section examinations to be accurate, and that completion thyroidectomy is uncommon.

So patients in that situation where your frozen section is benign, you can treat the patient with a simple lobectomy. They go home the same day. There’s less operative time. Two thirds don’t require life-long thyroid hormone supplementation. They don’t get temporary hypocalcemia and permanent hypoparathyroidism. And they are less likely to get neck hematoma. And they have half the recurrent laryngeal nerves that are at risk for injury.

So I think there are other factors here other than just cost in deciding how we should treat patients. Will your cost-effectiveness model differ based on the likelihood of malignancy in somebody that has a fine-needle aspiration biopsy that’s suspicious for papillary cancer?

Dr Andrew Leiker (Milwaukee, WI): To address your question, we did not consider the rate of malignancy based on “suspicious for papillary thyroid cancer” on FNA. It is difficult to say whether or not a low malignancy rate on FNA would change our conclusions as it would impact the accuracy of frozen section, for which we do not have the data.
Dr Nancy D. Perrier (Houston, TX): The most important aspect of the cost of thyroidectomy is time in the operating room. Do you have the ability to include that time frame and the change in time for waiting for that frozen section analysis? I think it’s probably different for different institutions, for location, for whether or not the pathologist is immediately available, and whether you are in an ambulatory care building.

Dr Andrew Leiker: Yes, you are correct in recognizing that we did not include the time waiting for frozen section in our analysis.

There are data on the operative time required for a total thyroidectomy as well as a thyroid lobectomy; however, none of this data includes the time waiting for frozen section analysis. We had considered including the operative time, but the data were so sparse and without the time required for frozen section analysis, we would have been required to utilize our institutional time estimates alone, making our results less applicable to other institutions. If more data were available from multiple institutions, it would be possible to include this analysis in future studies and could very well impact our conclusions.

Dr Douglas L. Fraker (Philadelphia, PA): You will be happy to hear that the University of Pennsylvania is aligned with you in the column that does total thyroidectomy for these patients.

My question is, the number you used for the false negative frozen sections—in other words, typically they say follicular neoplasm and then you defer to permanence—seemed very low. I have a very experienced pathologist, Dr LiVolsi, and cytologist, Dr Beloshavic. And I presented at a previous meeting here. They missed 40% of the lesions because the vast majority turn out to be follicular and papillary thyroid cancers, and Virginia will tell you, they just can’t make the call on frozen sections. So where did you get your number, which to me seemed quite low?

Dr Andrew Leiker: You are correct in saying that increasing rates of false-negative frozen section would further augment our conclusion.

To clarify if there is any confusion, we specifically looked at suspicious for papillary thyroid cancer on FNA alone. We did not study any of the other cytologic classifications out of the Bethesda system for reporting thyroid cytopathology. I cannot comment on the rate of false-negative frozen sections at your specific institution. However, we implemented a baseline 85% negative predictive value for frozen section based on data available from a paper published by Haymart et al at the University of Wisconsin and a paper published by Moon et al out of Seoul, South Korea.

Dr Cord Sturgeon (Chicago, IL): First of all, how old did you assume your patient was in this model?

Dr Andrew Leiker: Because our model runs for a time span of 12 months, setting a reference age would not have been applicable. It would have been a necessity if this were a Markov model and rolled out of many years.

Dr Cord Sturgeon: So I was going to say that we did the same study and had the opposite results. But looking for follicular neoplasms assumes a lot lower rate of cancer. And I think that if you were to look at your time horizon over a much longer period of time, you would see that costs accumulate for being on thyroid hormone indefinitely for the rest of your life. And furthermore, people who do sustain those traumatic injuries, like bilateral nerve injury or permanent hypoparathyroidism, the reduction in quality of life accumulates as well.

So I think the most fair analysis would be to roll out those costs over an expected lifetime. And then I think we could come to the strongest conclusions about this.

Dr Andrew Leiker: To address this comment, we thought about rolling the model out over time beyond 12 months, but we performed a sensitivity analysis of all the variables you mentioned, and these variables had little impact on our model over the 12-month period. And we felt, with such low impact, that our conclusions would remain unchanged with the model rolled out over a longer timeframe. However, it is definitely something to take into consideration for future studies.