The Value of Frozen Section Examinations in Determining the Extent of Thyroid Surgery in Patients With Indeterminate Fine-Needle Aspiration Cytology

Jeffrey C. Roach, MD; Keith S. Heller, MD; Sanford Dubner, MD; Laura A. Sznyter, MD

Objectives: To determine the usefulness of intraoperative frozen section (FS) examinations in establishing the diagnosis of thyroid cancer in patients undergoing thyroidectomy for nodules with indeterminate cytological features and to determine the cost-effectiveness of FS examinations in this situation.

Design: Retrospective medical record review. The results of fine-needle aspiration biopsies (FNABs), FS examinations, and final pathologic examinations are compared. A cost-effectiveness analysis of routine FS examinations compared with the cost of additional surgical procedures is performed.

Setting: A private surgical practice in a medical school–affiliated teaching hospital.

Patients: The records of all 480 patients undergoing thyroidectomy between January 1, 1998, and September 30, 2000, were reviewed. All 199 patients with a dominant thyroid nodule and FNAB results either highly suggestive of papillary cancer or indeterminate were studied. In these patients, the definitive operation can be based on the results of the FNAB.

Results: Of the patients with FNAB results highly suggestive of papillary cancer, 95% had cancer according to the final pathologic examination results. The diagnosis of cancer was made by FS examination results in 67% of these patients. Of the remaining 178 patients whose FNAB result was indeterminate, 64 (36%) had thyroid cancer. Malignancy was diagnosed by FS examination results in 30 (47%) of these patients. If FS examinations had not been performed, these 30 patients would have required a second operation to complete a total thyroidectomy. The cost savings of routine FS examinations in patients with indeterminate FNAB results is $1298 per patient.

Conclusions: The routine performance of FS examinations in patients with thyroid nodules with indeterminate cytological features is a cost-effective way of avoiding a second surgical procedure if a total thyroidectomy is indicated. In patients with FNAB results highly suggestive of papillary cancer, FS examinations are not useful. In these patients, the definitive operation can be based on the results of the FNAB.


Since its introduction by Martin and Ellis' more than 70 years ago, fine-needle aspiration biopsy (FNAB) of the thyroid has become the single most useful test for determining the likelihood of malignancy in patients with thyroid nodules. The results of FNAB are generally accurate when interpreted as benign or malignant. In these situations, the results of FNAB can be used to determine whether surgery is required and what the extent of surgery should be. In the 10% to 25% of nodules considered indeterminate by FNAB results, the incidence of malignancy is approximately 30%. Because of this, most surgeons recommend thyroidectomy for patients with nodules with indeterminate cytological features. The extent of thyroidectomy for patients with well-differentiated thyroid cancer (papillary, follicular, and Hurthle cell) is controversial. Some researchers recommend total thyroidectomy for virtually all patients. Others suggest that unilateral thyroid lobectomy is appropriate for patients with low-risk cancers. In patients whose indication for surgery is an indeterminate FNAB result and in whom total thyroidectomy would be recommended if the nodule were a well-differentiated cancer, the intraoperative diagnosis of malignancy by frozen section (FS) examination permits the performance of the definitive operation at the initial surgery, avoiding the need for a second completion thyroidectomy.

Some researchers question the necessity of an intraoperative FS examination because this test is difficult to interpret and can be inaccurate. This article determines the usefulness and cost-


PATIENTS AND METHODS

The medical records of all 480 consecutive patients who underwent thyroid surgery by the members of a single group practice (K.S.H., S.D., and L.A.S.) at a single institution from January 1, 1998, through September 30, 2000, were reviewed. One hundred ninety-nine patients were identified in whom the indication for surgery was a dominant thyroid nodule with indeterminate FNAB cytological features. These patients were selected for further review. Patients in whom the indication for surgery was thyrotoxicosis, local compression due to a benign multinodular goiter, bilateral nodules, or a history of thyroid surgery were excluded from this study. Patients who did not undergo an FNAB or intraoperative FS examination, and those with benign, malignant, or nondiagnostic FNAB cytological features, were also excluded. All patients were either euthyroid or taking replacement doses of thyroid hormone when the FNAB was performed. Serum thyrotropin levels, when available, were either in the normal range or minimally suppressed.

Diagnoses made by FS examination results were categorized as benign, malignant, or deferred for final pathologic examination. Indeterminate FNAB diagnoses were subdivided into 4 categories: indeterminate, not otherwise classified; follicular neoplasm; Hurthle cell neoplasm; and indeterminate with papillary features. Patients whose FNAB result was highly suggestive of papillary cancer, but which did not satisfy all the criteria for the diagnosis of papillary cancer, were considered separately.

The cost-benefit analysis is based on Medicare reimbursement rates for the New York City/suburban/Long Island region of New York. These costs are summarized in Table 1. Statistical significance was calculated using the Fisher exact test (2 × 2 table) or the χ² test (4 × 2 table). effectiveness of intraoperative FS examinations in patients with solitary thyroid nodules with indeterminate FNAB cytological features.

RESULTS

In this group of 199 patients, there were 155 females (78%) and 44 males (22%). The median age of the females was 47 years (range, 13-82 years) and of the males, 49 years (range, 20-71 years).

Twenty-one patients had FNAB results that were considered highly suggestive of papillary cancer, and 20 (95%) of these were cancers (19 papillary and 1 Hurthle cell cancer). In these 21 patients, malignancy was diagnosed by FS examination results in 14 (67%). In 6 patients (29%), the diagnosis was deferred on FS examination. One FS examination result was interpreted as benign. The difference in the incidence of malignancy between this group and the remaining patients with indeterminate FNAB results is highly statistically significant (P<.001).

Of the remaining 178 patients, 64 had well-differentiated thyroid cancers. The details of the incidence and types of malignancy in each FNAB category are summarized in Table 2. There is no significant difference in the incidence of malignancy among the 4 different indeterminate categories (P=.13). An additional 10 patients had microscopic foci of papillary cancer separate from the dominant thyroid nodule.

The diagnosis of cancer was established by intraoperative FS examination results in 30 of these patients. This is 17% of the 178 patients in the 4 indeterminate FNAB categories and 47% of the 64 patients with well-differentiated cancer on final pathologic examination findings. The percentage of patients in whom cancer was diagnosed on FS examination is as follows (data in parentheses indicate the number/total of patients in each category):

<table>
<thead>
<tr>
<th>FNAB Category</th>
<th>% of Cancers Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indeterminate, not otherwise classified</td>
<td>53 (16/30)</td>
</tr>
<tr>
<td>Follicular neoplasm</td>
<td>29 (4/14)</td>
</tr>
<tr>
<td>Hurthle cell neoplasm</td>
<td>25 (3/12)</td>
</tr>
<tr>
<td>Indeterminate with papillary features</td>
<td>88 (7/8)</td>
</tr>
<tr>
<td>Total</td>
<td>47 (30/64)</td>
</tr>
</tbody>
</table>

There was one false-positive result in the FNAB category indeterminate, not otherwise classified. There were no false-negative results. Of the 121 FS examinations that

The medical records of all 480 consecutive patients who underwent thyroid surgery by the members of a single group practice (K.S.H., S.D., and L.A.S.) at a single institution from January 1, 1998, through September 30, 2000, were reviewed. One hundred ninety-nine patients were identified in whom the indication for surgery was a dominant thyroid nodule with indeterminate FNAB cytological features. These patients were selected for further review. Patients in whom the indication for surgery was thyrotoxicosis, local compression due to a benign multinodular goiter, bilateral nodules, or a history of thyroid surgery were excluded from this study. Patients who did not undergo an FNAB or intraoperative FS examination, and those with benign, malignant, or nondiagnostic FNAB cytological features, were also excluded. All patients were either euthyroid or taking replacement doses of thyroid hormone when the FNAB was performed. Serum thyrotropin levels, when available, were either in the normal range or minimally suppressed.

Diagnoses made by FS examination results were categorized as benign, malignant, or deferred for final pathologic examination. Indeterminate FNAB diagnoses were subdivided into 4 categories: indeterminate, not otherwise classified; follicular neoplasm; Hurthle cell neoplasm; and indeterminate with papillary features. Patients whose FNAB result was highly suggestive of papillary cancer, but which did not satisfy all the criteria for the diagnosis of papillary cancer, were considered separately.

The cost-benefit analysis is based on Medicare reimbursement rates for the New York City/suburban/Long Island region of New York. These costs are summarized in Table 1. Statistical significance was calculated using the Fisher exact test (2 × 2 table) or the χ² test (4 × 2 table). effectiveness of intraoperative FS examinations in patients with solitary thyroid nodules with indeterminate FNAB cytological features.

RESULTS

In this group of 199 patients, there were 155 females (78%) and 44 males (22%). The median age of the females was 47 years (range, 13-82 years) and of the males, 49 years (range, 20-71 years).

Twenty-one patients had FNAB results that were considered highly suggestive of papillary cancer, and 20 (95%) of these were cancers (19 papillary and 1 Hurthle cell cancer). In these 21 patients, malignancy was diagnosed by FS examination results in 14 (67%). In 6 patients (29%), the diagnosis was deferred on FS examination. One FS examination result was interpreted as benign. The difference in the incidence of malignancy between this group and the remaining patients with indeterminate FNAB results is highly statistically significant (P<.001).

Of the remaining 178 patients, 64 had well-differentiated thyroid cancers. The details of the incidence and types of malignancy in each FNAB category are summarized in Table 2. There is no significant difference in the incidence of malignancy among the 4 different indeterminate categories (P=.13). An additional 10 patients had microscopic foci of papillary cancer separate from the dominant thyroid nodule.

The diagnosis of cancer was established by intraoperative FS examination results in 30 of these patients. This is 17% of the 178 patients in the 4 indeterminate FNAB categories and 47% of the 64 patients with well-differentiated cancer on final pathologic examination findings. The percentage of patients in whom cancer was diagnosed on FS examination is as follows (data in parentheses indicate the number/total of patients in each category):

<table>
<thead>
<tr>
<th>FNAB Category</th>
<th>% of Cancers Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indeterminate, not otherwise classified</td>
<td>53 (16/30)</td>
</tr>
<tr>
<td>Follicular neoplasm</td>
<td>29 (4/14)</td>
</tr>
<tr>
<td>Hurthle cell neoplasm</td>
<td>25 (3/12)</td>
</tr>
<tr>
<td>Indeterminate with papillary features</td>
<td>88 (7/8)</td>
</tr>
<tr>
<td>Total</td>
<td>47 (30/64)</td>
</tr>
</tbody>
</table>

There was one false-positive result in the FNAB category indeterminate, not otherwise classified. There were no false-negative results. Of the 121 FS examinations that
Nodular thyroid disease is a common clinical condition that affects 4% to 7% of the US population. Only 3% of these nodules are malignant.13 Fine-needle aspiration biopsy has enabled surgeons to be more selective in choosing patients with solitary thyroid nodules that require surgery. Although we recognize that the choice of the definitive operation for well-differentiated thyroid cancer is controversial8-11, it is our practice to perform total thyroidectomy compared with thyroid lobectomy (Table 4). The net savings per patient because of the routine performance of intraoperative FS examinations in all patients with indeterminate cytological features (excluding those highly suggestive of papillary cancer) is $1298.

COMMENT

were deferred, 42 (35%) were cancers. The likelihood of making the diagnosis of well-differentiated thyroid cancer on FS examination is related to the FNAB category and the final pathologic examination results (Table 3).

In the 178 patients previously considered, the FS examination result permitted the performance of the definitive surgical procedure (total thyroidectomy) in 30, avoiding the need for a second surgical procedure (completion thyroidectomy). This cost savings is offset by the additional costs of performing FS examinations in all 178 patients and the additional surgical and anesthesia costs of total thyroidectomy compared with thyroid lobectomy (Table 4). The net savings per patient because of the routine performance of intraoperative FS examinations in all patients with indeterminate cytological features (excluding those highly suggestive of papillary cancer) is $1298.

Table 3. Patients With Cancer in Each FNAB Category in Whom the Correct Diagnosis Was Made on Frozen Section Examination*

<table>
<thead>
<tr>
<th>FNAB Category</th>
<th>Type of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Papillary</td>
</tr>
<tr>
<td>I</td>
<td>60</td>
</tr>
<tr>
<td>FN</td>
<td>27</td>
</tr>
<tr>
<td>H</td>
<td>40</td>
</tr>
<tr>
<td>IP</td>
<td>88</td>
</tr>
</tbody>
</table>

*Data are given as percentage of patients. FNAB indicates fine-needle aspiration biopsy; I, indeterminate, not otherwise classified; FN, follicular neoplasm; H, Hürthle cell neoplasm; and IP, indeterminate with papillary features.

Table 4. Cost Savings

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Cases</th>
<th>Costs, $</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Per Case</td>
<td>Total</td>
</tr>
<tr>
<td>Savings (completion thyroidectomies avoided)</td>
<td>30</td>
<td>8729</td>
</tr>
<tr>
<td>Additional costs of total thyroidectomy*</td>
<td>30</td>
<td>452</td>
</tr>
<tr>
<td>Frozen section examinations</td>
<td>178</td>
<td>97</td>
</tr>
<tr>
<td>Net savings†</td>
<td>. . .</td>
<td>. . .</td>
</tr>
</tbody>
</table>

*Additional surgical and anesthesia charges. †Ellipses indicate data not applicable.

in a study of 504 patients, report that 68% of papillary cancers were diagnosed by FS examination results. No case of follicular cancer was correctly identified by FS examination results. While this study suggests a relatively high sensitivity for the FS examination diagnosis of papillary cancer, studies such as this do not correlate the results of FS examinations with those of FNABs. The ability to make a diagnosis by FS examination results that can be made as accurately by FNAB results preoperatively adds nothing to the management of the patient. A more important study is that of Gibb and Pasieka,20 who identified 71 patients with lesions that were suggestive of cancer by FNAB results, 21 of which were malignant by final pathologic examination results. In 9 (43%) of these patients, malignancy was determined by FS examination results. Similarly, Sabel et al,21 in a series of 561 patients, identified 44 with equivocal FNAB results who subsequently underwent FS examination. In this small group, there were 2 false-negative and 2 false-positive results. Of 7 cancers, 5 were correctly identified by FS examination results.

In the series reported herein, an intraoperative FS examination permitted the performance of a total thyroidectomy at the initial surgery in 17% of the patients with indeterminate cytological features. More important, cancer was diagnosed by FS examination results in 47% of those patients with cancer. It is unclear why our results are different from those previously summarized. The incidence of malignancy in our patients with indeterminate cytological features is 36%, similar to that reported in many other articles.²,5,9 This suggests that our
results with FS examinations are not due to differences in the definition of indeterminate FNAB results. An additional 10 patients had microscopic foci of papillary cancer. These patients were not included in the calculations of the incidence of malignancy or in the cost analysis because we do not consider these occult cancers to be clinically significant and do not perform more extensive surgical procedures when they are discovered.

The results of FS examinations are particularly inaccurate in the evaluation of follicular lesions. Chen et al. include in their study 73 patients with follicular lesions by FNAB results. In only 4 (5%) of the patients did the FS examination result correctly identify a cancer. In another 4 (5%) of the patients, an incorrect FS examination result caused the performance of an inappropriate operation. In these patients, 23 (32%) had cancer (12 follicular, 6 Hürthle cell, 2 papillary, and 3 follicular variant of papillary cancers). Mulcahy et al., while observing that an FS examination result is complementary to an FNAB result, confirm that, for follicular lesions on FNAB, the FS examination result is unlikely to be diagnostic. Even in this group of patients (FNAB category follicular neoplasm), we were able to detect 4 (29%) of 14 cancers by FS examination results. However, only 3 of these cancers were follicular. Of the remaining cancers, 2 were papillary and 9 were follicular variant of papillary. We include in the category follicular neoplasm patients whose FNAB result is described as follicular neoplasm with atypia. This may explain the relatively high percentage of papillary cancers in this group.

In commenting on the accuracy of FNABs, Hamburger and Hamburger note that FNAB results are more accurate than FS examination results in correctly predicting malignancy in patients whose FNAB result is consistent with a high risk of cancer. We make the same observation in our category highly suggestive of papillary cancer. This group has such a high likelihood of malignancy that the patients must be considered separately from other patients with indeterminate cytological features. Because 95% of these patients had cancers and only 67% were diagnosed by FNAB examination results, we recommend that FS examinations not be performed in this group and that the definitive procedure be performed based on the FNAB results alone.

Although there is a trend suggesting a higher incidence of cancer in the category indeterminate with papillary features, this category is not significantly different from the other categories. Because 50% of the nodules in this group are benign, we are reluctant to perform total thyroidectomies unless cancer is confirmed by FS examination results.

Only 1 patient in this series underwent a total thyroidectomy inappropriately based on a false-positive FS examination result. This low rate of false-positive FS examination results is similar to that reported in many other series. The risk of a false-positive FS examination result is so low that it should not be used as an argument against the routine use of an FS examination.

Because we do not recommend FS examinations for nodules in the highly suggestive of papillary cancer category, only the remaining 4 categories were used in the cost analysis. In this analysis, we chose to use reimburse-

Intraoperative FS examination results can accurately establish the diagnosis of cancer in 17% of patients undergoing thyroid lobectomy for thyroid nodules with indeterminate cytological features. If a surgical procedure more extensive than a thyroid lobectomy is recommended for a well-differentiated cancer, the routine performance of FS examinations avoids the need for a second surgical procedure in those patients in whom the diagnosis can be established intraoperatively. Because of the high cost of a second surgical procedure, the routine performance of FS examinations is cost-effective. In those whose FNAB results are highly suggestive of papillary cancer, the likelihood of malignancy is so high that the FS examination adds nothing to the management of these patients and should not be performed.

Accepted for publication October 2, 2001.

This study was presented at the annual meeting of the American Head and Neck Society, Palm Desert, Calif, May 16, 2001.

Corresponding author and reprints: Keith S. Heller, MD, Long Island Surgical Specialists, PC, 410 Lakeville Rd, Suite 310, Lake Success, NY 11042 (e-mail: kheller@lisurg.com).

REFERENCES


