Intraoperative Frozen-Section Analysis for Thyroid Nodules

A Step Toward Clarity or Confusion?

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Objectives: To determine accuracy and intertest agreement of preoperative fine-needle aspiration cytology (FNAC) and intraoperative frozen-section analysis (FS) findings in thyroid surgery, and to assess the influence of intraoperative FS findings on decision making and the utility of FS in thyroid surgery.

Design: Retrospective analysis. The results of preoperative FNAC, intraoperative FS, and final histopathological analyses were taken from the histopathology reports. We calculated intertest agreement using the $\kappa$ statistic.

Patients: Two-hundred fifteen patients who underwent primary thyroid surgery. All patients were treated by the same surgeon (S.J.W.).

Results: The sensitivity and specificity of FNAC were 57.4% and 91.7%, respectively. The sensitivity and specificity of FS were 32.4% and 96.5%, respectively. The intertest agreement was poor ($\kappa=0.17$). In case of malignant FNAC findings, the FS result did not influence treatment decisions; in case of a malignant FS result on the background of a benign, indeterminate, or nondiagnostic FNAC finding, the FS result influenced treatment decisions in 88% of cases.

Conclusions: Intraoperative FS did not give additional information in cases where a malignant neoplasm was predicted by the FNAC finding. In this setting, it led to conflicting results and did not contribute to correct decision making.

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lated to the accuracy of preoperative and intraoperative diagnostic test results. No test exclusively determines when to operate or to what extent. Rather, tests are available to the clinician as tools that supplement patient history, physical examination, and noninvasive studies. Of importance, even benign disease (eg, gigantic multinodular goiter, Hashimoto disease, thyroid disease–related pain, or dysphagia) can be a reason for total thyroidectomy independent of a cancer diagnosis.

Before FNAC became routine and reliable, intraoperative FS was frequently used to guide the extent of surgery, and its routine use is still recommended by some authors. Nevertheless, the exact role of FS, especially in follicular and Hurthle cell neoplasms, in guiding the extent of thyroidectomy is controversial.

A thorough review by Shaha summarized a considerable number of studies that addressed the accuracy of FNAC and FS and proposed recommendations for the use of FS in thyroid surgery.

It appeared to us that part of the controversy is based on the different test performances found in different institutions. This led us to evaluate our own approach to the use of FS in thyroid surgery. To accomplish this objective, we evaluated the surgical practice of one of the investigators (S.J.W.), a practice that is particularly focused on thyroid surgery with frequent use of the histological findings of intraoperative FS.

Our primary outcome of interest was the influence of FS findings on intraoperative decision making. Secondary outcomes included the agreement between preoperative FNAC and intraoperative FS findings and the determination of when FS is most useful for intraoperative decision making.

It was not our intent to compare different pathologists and different institutions in this study. Rather, our hope was to outline an approach to decision making in thyroid surgery with frequent use of the histological findings of intraoperative FS.

We retrospectively analyzed the medical charts of 215 patients who underwent thyroid surgery. All patients were treated by the same surgeon (S.J.W.) from April 1, 2002, through January 31, 2005.

Ten different pathologists analyzed FNAC and FS specimens at 2 acute care teaching hospitals in the Calgary Health Region. Results of the preoperative FNAC and intraoperative FS were obtained from the cytology and histopathology reports.

Results of FNAC and FS were classified according to the dominant pathological features found in the pathology report. To facilitate analysis, the results were then dichotomized. Group 1 patients had pathological diagnoses that would usually result in a total thyroidectomy. Diagnoses included disorders that were clearly benign (multinodular goiter, Hashimoto disease, and lymphocytic thyroiditis) and disorders with intermediate features that were not worrisome or clear enough to be called a suspected malignant neoplasm or a malignant neoplasm (follicular lesion, follicular nodule, follicular neoplasm, Hurthle cell lesion, Hurthle cell neoplasm, and lesions with atypias).

Group 2 patients were those whose pathological diagnosis would usually result in a total thyroidectomy. Diagnoses were malignant neoplasm (papillary thyroid cancer [PTC] and its follicular variant [PTC FV]) or suspected malignant neoplasm.

Frozen-section analysis was performed on thyroid tissue only because none of the patients in this cohort had lymphadenopathy. To make comparison possible, the results of final histopathological analysis (FH) were also dichotomized as for the FNAC and FS results. Group 1 patients had the following diagnoses on the FH: benign colloid nodule, multinodular goiter, follicular adenoma, Hashimoto thyroiditis, lymphocytic thyroiditis, Grave disease, hyperplastic nodule, adenoma not otherwise specified, microcarcinoma, and lymphoma. Group 1 patients generally underwent a hemithyroidectomy.

Group 2 patients had the following diagnoses on the FH: PTC, PTC FV, follicular thyroid cancer, and Hurthle cell carcinoma. Patients with solitary microcarcinomas of less than 0.5 cm were not included in group 2.

In cases with multiple diagnoses, the one necessitating a total thyroidectomy determined the group that was used for classification. Diagnoses such as follicular carcinoma, medullary thyroid cancer, squamous cell carcinoma, anaplastic carcinoma, and metastasis from other distant primary tumors were not found in this patient cohort.

For diagnosis of well-differentiated PTC, the criteria of Kini et al were used by our pathologists. These include typical papillary architecture, high cellularity, presence of psammoma bodies, and the specific nuclear features of PTC (enlarged, elongated, molded nuclei with nuclear membrane grooves, fine powdery chromatin, micronucleoli, and pseudo-inclusions [Figure 1A]). However, it remains debatable how evident each of these features is (qualitatively) and what proportion of the cells should demonstrate a given feature (quantitatively) to consider it present.

Especially when the term suspected malignant neoplasm was used, the criteria are still not uniformly defined, and a significant interobserver variation that depends on the individual’s experience and thresholds has to be expected. At our institution, this diagnosis was usually rendered when the aspirate demonstrated varying cytologic abnormalities associated with ma-
nostic test results (n=22) were excluded. A test was regarded atypia including pleomorphism, enlarged nuclei, nuclear grooves, coarse or irregular chromatin, prominent or multiple nucleoli, or atypical or numerous mitotic figures.

The incidence should be approximately 15%.

When we assessed agreement between the FNAC and FS findings, we included only patients for whom both tests were performed and the results were diagnostic (n=127). Test agreement was evaluated by the \( \kappa \) statistic.

Median patient age was 44 (range, 19-84) years. One hundred eighty-five patients were women and 30 were men (ratio, 6:1). Fifteen patients had thyroid cancer in their family history and 11 had previous radiation therapy as a risk factor.

Most patients had a solitary, solid, painless nodule of 2 to 4 cm as their only symptom. Only 15 nodules showed signs of calcification, which were malignant in 9 cases. Ultrasonography was the main diagnostic imaging tool and was performed in 84.3% of patients.

### USE OF FNAC AND FS

The cytopathological and histopathological results are given in Table 1. Fine-needle aspiration cytology was performed in 201 patients (Figure 2). Even after undergoing multiple biopsies, 19 patients (9.5%) had nondiagnostic FNAC findings. According to our classification, a total of 50 patients (24.9%, including 33 with PTC, 2 with PTC FV, and 15 with suspected malignant neoplasm) were candidates for total thyroidectomy by FNAC findings. Compared with the FH finding, 32 of the 33 diagnoses of PTC by the FNAC result turned out to be truly malignant, and both of those predicted by the FNAC finding as PTC FV were truly malignant. In contrast, only 5 of the 15 FNAC diagnoses of suspected malignant neoplasm turned out to be truly malignant.

Frozen-section analysis was performed in 150 patients. In 16 patients (10.7%), FS results were clearly malignant neoplasms (n=13) or suspected malignant neoplasm (n=3). Twelve of these 16 specimens were found to be true malignant neoplasms in the FH result.

### TEST PERFORMANCE

Test performance results (sensitivity, specificity, and positive and negative predictive values) are given in Table 2.

### AGREEMENT BETWEEN FNA AND FS FINDINGS

In 127 patients, preoperative FNAC and FS were performed, and the results were diagnostic. The agreement was poor as indicated by a \( \kappa \) of 0.17.

### Table 1. Overview of the FNAC, FS, and FH Results

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Preoperative FNAC</th>
<th>Intraoperative FS</th>
<th>FH</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTC</td>
<td>32 (16.4)</td>
<td>13 (8.7)</td>
<td>41 (19.1)</td>
</tr>
<tr>
<td>PTC FV</td>
<td>2 (1.0)</td>
<td>3 (2.0)</td>
<td>23 (10.7)</td>
</tr>
<tr>
<td>Follicular thyroid cancer</td>
<td>...</td>
<td>...</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>Hürthle cell carcinoma</td>
<td>...</td>
<td>...</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>Microcarcinoma</td>
<td>...</td>
<td>...</td>
<td>10 (4.7)</td>
</tr>
<tr>
<td>Suggestive of malignancy</td>
<td>15 (7.5)</td>
<td>3 (2.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Lesion with atypia</td>
<td>16 (8.0)</td>
<td>3 (2.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Benign lesion (nodule)</td>
<td>19 (9.5)</td>
<td>26 (17.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Multinodular goiter</td>
<td>4 (2.0)</td>
<td>7 (4.7)</td>
<td>29 (13.5)</td>
</tr>
<tr>
<td>Follicular lesion (nodule)</td>
<td>42b (36)</td>
<td>34 (16)</td>
<td>11 (40)</td>
</tr>
<tr>
<td>[nodule] (neoplasm)</td>
<td>(38.8)</td>
<td>(40.7)</td>
<td></td>
</tr>
<tr>
<td>Hürthle cell lesion (neoplasm)</td>
<td>12 (3.7)</td>
<td>16 (4.13)</td>
<td>10 (4.7)</td>
</tr>
<tr>
<td>Hashimoto disease</td>
<td>...</td>
<td>10 (6.7)</td>
<td>9 (4.2)</td>
</tr>
<tr>
<td>Lymphocytic thyroiditis</td>
<td>...</td>
<td>4 (2.7)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Grave disease</td>
<td>...</td>
<td>...</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Hyperplastic (colloid)</td>
<td>...</td>
<td>37 (17.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Adenoma NOS</td>
<td>...</td>
<td>5 (2.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>...</td>
<td>1 (4.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Nondiagnostic result</td>
<td>19 (9.5)</td>
<td>3 (2.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>201 (100)</td>
<td>150 (100)</td>
<td>215 (100)</td>
</tr>
</tbody>
</table>

**Abbreviations:** FH, final histopathological analysis; FNAC, fine-needle aspiration cytology; FS, frozen-section analysis; FV, follicular variant; NA, not available; NOS, not otherwise specified; PTC, papillary thyroid cancer; ellipses, not clearly malignant according to the cytologic grounds alone.

a Because of rounding, percentages may not total 100.

b Preoperative FNAC does not distinguish between a follicular lesion and a follicular nodule.

c In the FH, diagnosis was follicular adenoma.

d In the FH, diagnosis was Hürthle cell adenoma.
According to our classification, the FNAC or the FS finding suggested a total thyroidectomy as appropriate treatment for 61 patients. However, only 45 patients underwent a total thyroidectomy. This apparent discrepancy is explained by the finding that in 17 of these 61 patients, the test results were suspected malignant neoplasm as opposed to being definitive. As a consequence, the surgeon felt confident enough to perform a total thyroidectomy in only 4 of the 17 patients with results of FNAC or FS that constituted suspected malignant neoplasm. On the other hand, in those cases in which the FNAC or the FS finding was clearly malignant neoplasm (n = 44), a total thyroidectomy was performed in most of the cases (n = 41 [93.2%]).

FH FINDING AND ASSESSMENT OF TREATMENT ADEQUACY

After analyzing the FH reports (n = 215), we found that a total thyroidectomy would have been justified in a total of 70 patients (32.6%) owing to malignancy (41 patients [19.1%] with PTC, 23 patients [10.7%] with PTC FV, 3 [1.4%] with follicular cancer not otherwise specified, and 3 [1.4%] with Hurthle cell carcinoma).

However, only 59 of those 70 patients (84.3%) underwent total thyroidectomy; 46 (65.7%) had 1 surgical
procedure and 13 (18.6%) needed a completion thyroidectomy. The completion thyroidectomy rate of the whole cohort was 6.0% (13 of 215). In the remaining 11 patients (15.7%), completion thyroidectomy was not performed owing to age, general health condition, and limited disease.

In addition to these 70 patients, 10 patients were diagnosed as having a solitary microcarcinoma.

**INFLUENCE OF INTRAOPERATIVE FS ON SURGICAL DECISION MAKING**

To address the issue of how FS influenced surgical decision making, we classified the patients into 2 groups. It can be assumed that in case of agreement of both tests (hemithyroidectomy and hemithyroidectomy or total thyroidectomy and total thyroidectomy), suggesting a change of treatment is unlikely. Therefore we were more interested in the groups in which there was a conflict or a discrepancy between the 2 test results (hemithyroidectomy and total thyroidectomy or total thyroidectomy and hemithyroidectomy).

In those groups, the FS finding was more likely to influence the treatment decision. The primary interest was to assess whether the surgical procedure was changed owing to the FS result.

**Group 1: Subjects With Nondiagnostic FNAC Findings or Results That Suggested Hemithyroidectomy**

A total of 151 patients had an FNAC result suggestive of hemithyroidectomy or one that was nondiagnostic (Figure 3A). In 125 of these, an FS was performed. In 11 patients, the FS result was malignant neoplasm or suggested malignant neoplasm, and in 7 of these the surgeon changed the procedure from a hemithyroidectomy to a total thyroidectomy. In 8 cases, the FS result clearly showed a malignant neoplasm; the treatment was changed in 7 of 8 times (88%), whereas it was not changed in the 3 cases with an FS result of suspected malignant neoplasm. In the 8 patients who clearly had malignant disease predicted by the FS finding, 7 findings were truly malignant. In the 3 patients with an FS result of only suspected malignant neoplasm, only 1 finding was truly malignant.

**Group 2: Subjects With FNAC Findings That Suggested Total Thyroidectomy**

Thirty-five patients had a clearly malignant FNAC result, suggesting total thyroidectomy (Figure 3B). In 10 of these (29%), an FS was performed. In 5 patients, the FS finding was benign; in 1, it was nondiagnostic; and in 4, it was malignant. A total thyroidectomy was performed in 9 patients, and therefore a benign result of intraoperative FS was disregarded 4 of 5 times (80%). In the FH report, 9 of these 10 results turned out to be truly malignant.

**COMMENT**

**PRIMARY OUTCOME**

As shown in the "Results" section, the intraoperative FS finding did not influence treatment when the preoperative FNAC finding was suspected malignant neoplasm and the FS finding was benign or indeterminate.

The FS finding influenced treatment in cases of clear malignancy and when preoperative FNAC finding was benign, indeterminate, or nondiagnostic.

These 2 observations reflect the high specificity and low sensitivity of both tests. We infer from these observations that FS can be omitted in the case of a positive FNAC finding. In all cases of malignancy predicted by FNAC, and for those in which FS was not performed, the FH finding also confirmed malignancy.

Because of the rather low sensitivity of FNAC, one is more likely to undertreat patients with malignant disease. If an intraoperative FS result is clearly malignant, this result has been shown to be reliable in most cases, and therefore the risk of overtreatment is low. It is in such situations that FS appears to be most helpful.

**TEST PERFORMANCE**

Compared with other studies, our test sensitivity was low, whereas specificity was high for both tests. Based on these results, we are standardizing our histopathology reports and systematically including cytological features suggesting malignancy that allow a more confident surgical approach as described by Punthakee et al. True-positive findings in the FH results of 33% for specimens termed suggestive of malignant neoplasm by FNAC or FS are on the lower spectrum of the published data and need to be improved.

**EXCLUDING INDETERMINATE LESIONS FROM THE ANALYSIS**

Some authors have suggested that FNAC results of follicular neoplasms, nodules, neoplasms, or Hurthle cell lesions should always be viewed as indeterminate because they may reflect benign or malignant disease. In regard to the utility of FS, some previously published studies found that, in the presence of follicular neoplasms detected by means of FNAC, the FS finding was unlikely to change the diagnosis and treatment.
eight patients in our series had such a diagnosis by FNAC results. When this subgroup was analyzed, 67 had intraoperative FS, and in 4 cases the result predicted malignancy. In 2 of these, the surgeon changed the intraoperative procedure from a hemithyroidectomy to a total thyroidectomy, which, by the FH finding, turned out to be the appropriate treatment. However, the findings in our study confirm that FNAC as well as FS findings were generally unreliable in predicting follicular adenomas, follicular cancer, or PTC FV.

**RISK OF UNDERTREATMENT AND OVERTREATMENT**

On one hand, the patient history and physical examination are the most important factors for determining whether a patient is at risk for malignancy and requires surgery. On the other hand, FNAC and FS are significant additional tools that can help reduce undertreatment and overtreatment.

The high 18.6% rate of completion thyroidectomies may reflect the low sensitivity of both tests and, in addition, the low rate of cancer in the group with suspected malignant neoplasm because a total thyroidectomy was rarely performed in this group. According to the literature, the positive predictive value for malignancy in the case of a suspected malignant neoplasm ranges from 20% to 84%. Although we use the criteria of Kini et al at our institution, our positive predictive value was only approximately 30%, which appears to be average for an institution not specializing in thyroid pathology.

As shown in Figure 2, the FS findings demonstrated malignant or suspected malignant disease in 16 cases, but the lesions were truly malignant in only 12, which leads to a false-positive rate of 25% (75% positive predictive value). Because the sensitivity of the FS finding has been shown to be low, many FS procedures have to be performed to detect malignant neoplasms missed by FNAC. If we used the algorithm that a suspected or clearly malignant FS result would lead to a total thyroidectomy, we would encounter overtreatment in 25% of cases, which is unsatisfying. Therefore, relying on FS when the result is only suspected without taking other indicators of malignancy (family history and radiation exposure) into account is highly likely to lead to overtreatment. Accordingly, it is of major importance that every institution determines its PPV for the group with a suspected malignant neoplasm. If the PPV comes close to 84%, it can be regarded as highly probable for malignancy and sup-

![Figure 3. Influence of intraoperative frozen-section analysis (FS) on surgical decision making. A, Subjects with nondiagnostic fine-needle aspiration cytology (FNAC) findings or a finding suggesting only hemithyroidectomy (hemi). B, Subjects with an FNAC finding suggesting total thyroidectomy (total).](http://archotol.jamanetwork.com/pdfaccess.ashx?url=/data/journals/otol/11932/)
ports a decision to perform a total thyroidectomy. If it is less than 50%, it should be considered indeterminate, and definitive treatment should be deferred to the FH findings; this, of course, increases the rate of undertreatment.

The following were reasons for not performing FS in our patients:

- FNAC clearly favored malignant neoplasm (FS was not performed in 25 of 35 patients).
- Preoperative patient history was highly suggestive of a malignant neoplasm (previous irradiation, fast growing lesion, or positive family history).
- Physical examination findings were highly suggestive of a malignant neoplasm (recurrent laryngeal nerve palsy, airway compression, palpable cervical lymph nodes, or calcification in diagnostic imaging).
- The disease already required a total thyroidectomy (massive multinodular goiter, medically nontreatable Hashimoto disease, diffuse lymphocytic thyroiditis, or severe symptoms such as airway impairment and swallowing problems).

These reasons were found in 43 patients. In 22 patients, however, the reason an intraoperative FS was not performed remained unclear.

REASONS FOR PERFORMING FS IN PATIENTS WITH MALIGNANT NEOPLASMS ALREADY DIAGNOSED BY FNAC FINDINGS

The FNAC finding predicted malignant disease 35 times. Despite these results, intraoperative FS was performed in 10 cases, and, if the FS finding was used to define treatment, it would have led to undertreatment in 5 of 10 cases (50%). The exact reasons why FS was performed despite an FNAC finding already predicting a malignant neoplasm remained unclear, but they appeared to be associated with a lack of other risk factors and young patient age, cases in which overtreatment could be a more difficult problem.

LIMITATIONS OF THIS STUDY

It is clear that the sensitivity of FNAC and FS in our hands is low compared with other published studies. Furthermore, the positive predictive value in cases of suspected malignant neoplasm appeared to be low, which may reflect the reality of a community-based pathological analysis with interobserver variation of pathologists. It was not the intention of this study to analyze this variation; rather, we wanted to elucidate the consequences of an uncertain diagnostic background on surgical decision making. The retrospective nature of this study also obscured the reasons for certain surgical decisions.

COMPARISON WITH OTHER STUDIES

Unlike many published studies, the primary objective of this research was to understand the influence of intraoperative FS on surgical decision making. Furthermore, most published research comes from institutions with a highly specialized focus (surgical and pathological) on the treatment of patients with thyroid disease. This study is more indicative of the performance and outcomes that are to be expected in a busy community-based thyroid surgical practice.

Some authors have concluded that the FS finding rarely affects intraoperative decision making in patients with adequate FNAC results and should not be performed. Poor cost-effectiveness is one of the most important reasons for this recommendation. On the other hand, it was shown by Roach et al that, even when FS was performed on a routine basis in patients with indeterminate FNAC results, it is a cost-effective way of avoiding completion thyroidectomy.

Less frequently, on the other end of the spectrum, some studies have recommended the use of FS independently of FNAC results. Most authors, however, have made their recommendations dependent on different factors. Frozen-section analysis was regarded to be useful in identifying malignancy in patients with an indeterminate or an unsatisfactory cytological diagnosis and dependent on the accuracy of local thyroid cytological findings.

Conclusions similar to those of our study have been stated in previous reports.

Under the circumstances in which the specificity of FNAC and FS is high (>90%) and the sensitivity is low (<70%), we recommend the use of intraoperative FS as follows:

1. In case of clearly malignant FNAC results, intraoperative FS is unlikely to change treatment, is prone to conflicting results, and therefore should be omitted.
2. In case of benign, suspicious, or nondiagnostic FNAC results, we suggest the following algorithm:

   • If clinical signs and/or patient history strongly predict a malignant neoplasm and a total thyroidectomy is planned, a negative FS finding is unlikely to change the surgical procedure and therefore should be omitted.
   • If the disease requires a total thyroidectomy independently of malignancy (eg, compressing multinodular goiter), FS does not add important information and should be omitted.
   • If the patient is unwilling to consent to a total thyroidectomy at the time of the first surgery, FS should be omitted.
   • In the case of planned hemithyroidectomy suggested by the FNAC result, we encourage FS, as long as the surgeon is willing to change the operative procedure from a hemithyroidectomy to a total thyroidectomy if the intraoperative result is consistent with malignancy. Because of the high specificity, the likelihood of overtreatment is low.

Before applying these recommendations, surgeons need to know their local FNAC test performance. For situations in which the sensitivity of the FNAC is high, the role, if any, of FS would be different.

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Author Contributions: Drs Huber, Matthews, Warshawski, and Dort had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Huber, Dziegielewski, Matthews, Khalil, and Dort. Acquisition of data: Huber, Dziegielewski, Warshawski, and Dort. Analysis and interpretation of data: Huber, Dziegielewski, Matthews, Kmet, Faris, and Dort. Drafting of the manuscript: Huber, Kmet, Faris, and Dort. Critical revision of the manuscript for important intellectual content: Huber, Dziegielewski, Matthews, Khalil, and Dort. Statistical analysis: Huber, Kmet, Faris, and Dort. Administrative, technical, and material support: Dziegielewski, Matthews, Khalil, and Dort. Study supervision: Matthews, Warshawski, and Dort.

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REFERENCES