

Is Frozen-Section Analysis During Thyroid Operation Useful in the Era of Molecular Testing?

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- BACKGROUND:** With the increased use of molecular testing of thyroid fine-needle biopsies, the frequency and extent of thyroid resection for thyroid nodules has changed. Although the role of frozen-section analysis of the thyroid has been reduced markedly in recent years, many surgeons still routinely use it intraoperatively. We sought to determine the utility of frozen section during thyroidectomy in the era of molecular testing.
- STUDY DESIGN:** We reviewed 236 consecutive patients who had thyroidectomy with intraoperative frozen-section analysis at our institution between November 2015 and October 2017. We re-reviewed the preoperative diagnosis, frozen-section diagnosis, final pathology, and whether operative management changed from the initial plan based on frozen section.
- RESULTS:** Mean age of the patients was 55.6 ± 14.1 years, and 83% were female. Of the 236 patients, frozen section did not change the intraoperative management in 225 (95%). Of the 11 patients whose thyroid operation was modified, the operation was either too much or not enough in 6 patients. In only 5 (2.1%) patients, frozen-section analysis correctly changed the extent of thyroidectomy.
- CONCLUSIONS:** Thyroid frozen-section analysis adds cost and time to thyroid operations without notable benefit. In our cohort, only 2.1% of frozen sections accurately changed intraoperative management. We recommend against its routine use. (J Am Coll Surg 2019;228:474–481. © 2018 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Thyroid nodules are common in the population at large, with greater incidence in women and with advancing age.^{1,2} They are detected most frequently on physical examination or incidentally on diagnostic imaging studies, but despite their prevalence, only 5% to 15% will ultimately harbor a malignancy.³ It is essential for clinicians to be able to differentiate those patients at higher risk who will benefit from surgical biopsy from those for whom surveillance is adequate.

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Ultrasound remains the imaging study of choice for initial assessment and, based on imaging features and clinical context, a subset of thyroid nodules will require additional evaluation with fine-needle aspiration (FNA).⁴⁻⁶ This is a highly sensitive diagnostic tool, however, 15% to 30% of these biopsies will be indeterminate.^{7,8} In addition, in large nodules (>4 cm), there is a higher rate of false-negative results (up to 13%),^{9,10} which can preclude the ability to make decisions based on these biopsy results. Efforts to further stratify risk based on preoperative characteristics have been historically disappointing and, in the past, diagnostic thyroid lobectomy at minimum has been recommended¹¹ to biopsy indeterminate nodules, given malignant risk. Some surgeons have combined operation with routine pathologic frozen-section (FS) assessment as an intraoperative adjunct to determine the extent of operation. The practice is controversial,^{2,12-19} although its advocates promote that it potentially permits a single-stage operation with benefits in terms of cost and quality of life.^{20,21}

During the past decade, however, advances in our understanding of the genetic basis of thyroid malignancy

have emerged, ushering the advent of molecular testing as a way to preoperatively supplement decision-making for these nodules.²² Several commercially available tests are now available,²³ and with their increasing adoption by surgeons and endocrinologists, it has been possible to reduce the number of unnecessary thyroid operation.^{24,25}

Additionally, in 2015, the American Thyroid Association put forth new guidelines with recommendations that, in contrast with traditional thinking,²⁶ for some low-risk papillary thyroid carcinomas (PTC) between 1 and 4 cm without clinical lymph node metastases, thyroid lobectomy alone might be an option for adequate therapy.^{6,27} The reclassification of encapsulated follicular variants of PTC as noncancerous, noninvasive, follicular thyroid neoplasms with papillary-like nuclear features, and the latter's introduction into the lexicon of thyroid pathology²⁸ further modified established treatment algorithms in 2016.

With the many recent changes in thyroid surgery, we sought to determine whether there was a continued role for FS in the modern era.

METHODS

Study design

This was a retrospective review of all patients that underwent FS analysis in the setting of thyroid operation of any extent between November 2015 and October 2017 at an academic tertiary care center. We then used the electronic medical record to review clinical and demographic variables for each patient, preoperative FNA biopsy results and use of molecular testing if available, FS results, and the final pathology. We reviewed the surgeon's preoperative documentation to determine the planned extent of operation, as well as the operative report to determine the ultimate procedure and any intraoperative factors other than FS results that might have modified the course of operation.

Setting and patients

Through a review of all FS reports for thyroidectomy specimens in that time frame, 236 consecutive patients undergoing thyroidectomy were identified by the Department of Pathology. All patients were cared for at the University of Alabama at Birmingham Hospital. Five of the 9 surgeons that perform head and neck endocrine operations at our institution use FS selectively in the conduct of thyroid operations and were the surgeons for all reviewed procedures. The remaining 4 surgeons do not use FS. The FS evaluations were performed by 1 of 20 staff pathologists, although permanent pathologic assessment is performed routinely by a head and neck endocrine pathologist.

Outcomes

Of the 236 patients, 175 (74.1%) underwent preoperative ultrasound-guided FNA biopsy and this information was available. The information was categorized using the standard Bethesda System for Reporting Thyroid Cytopathology,⁷ including inadequate/nondiagnostic (I), benign (II), atypia of undetermined significance/follicular lesion of undetermined significance (III), follicular neoplasm or suspicious for follicular neoplasm (IV), suspicious for malignancy (V), and malignant (VI). Sixty-one (25.9%) patients did not undergo preoperative FNA biopsy; the factors for this were determined for each patient by review of electronic medical record documentation. For those patients with a Bethesda III or IV result, molecular testing was used based on clinical suspicion and patient factors, including, in part, patient preference and insurer coverage. For patients at our institution for whom molecular testing was used, the Afirma (Veracyte) platform was used.

Frozen-section results were classified as negative (benign/indeterminate) or positive for malignancy (suspicious/definitive). Final pathology results were then reviewed to determine the true number of patients with malignant processes, including papillary carcinoma, follicular or Hurthle cell carcinoma, medullary, and poorly differentiated or anaplastic carcinoma. The rate of incidental micro-PTCs (<1 cm) and foci of noninvasive follicular neoplasm with papillary-like nuclear features were tabulated separately.

These were used to determine the false-positive and false-negative rate of FS, as well as its positive predictive value, sensitivity, and specificity. Preoperative documentation was reviewed to establish the planned extent of the operation; these were then correlated with the finalized operative report to determine the ultimate procedure. If there was a change in the extent of operation, the operative documentation was reviewed to determine the prompting factor, either FS results or an intraoperative finding detected by the surgeon (such as tumor invasion into surrounding structures or suspicious lymphadenopathy). Of those for whom FS modified the extent of operation, it was then determined whether this was appropriate on the basis of final pathologic results.

RESULTS

A total of 236 patients undergoing thyroid operations were evaluated with intraoperative FS between November 2015 and October 2017. Of these, 196 (83.1%) were female and 40 (16.9%) were male. Mean age was 55.6 (SD 14.1) years. One hundred and seventy-five (74.1%) patients underwent preoperative ultrasound-guided FNA diagnosis; 16 (6.8%)

were classified as Bethesda I, 70 (29.7%) were Bethesda II, 55 (23.3%) were Bethesda III, 21 (8.9%) were Bethesda IV, 8 (3.4%) were Bethesda V, and 5 (2.1%) were Bethesda VI (Table 1). For those patients that underwent biopsy of more than 1 nodule, the classification schema was used for the nodule of highest surgical concern.

Of the 76 patients classified as Bethesda III and IV, 37 (48.6%) had undergone additional risk stratification with molecular testing; at our institution, this was with Afirma testing and, with this, 33 (89.1%) were further categorized as suspicious. Three of the 37 had benign results (8.1%) but proceeded with the operation due to increased clinical suspicion, and 1 (2.8%) patient had insufficient specimen to complete reliable testing.

Of those 61 patients that did not undergo biopsy, 13 were having operations for compressive symptoms related to thyroid goiter and deferred preoperative FNA; 20 were undergoing procedures for thyroid dysfunction with nodular goiters (18 patients for hyperthyroidism and 2 patients with difficult to manage Hashimoto's thyroiditis); and in 23 patients, suspicious thyroid disease had been detected in the process of preoperative or intraoperative evaluation for hyperparathyroidism. For 1 surgeon, patients undergoing parathyroid exploration were given the option of preoperative thyroid FNA biopsy or intraoperative FS evaluation, given his routine use of FS for confirmation of parathyroid tissue, and this number includes those that had elected the latter option.

Two patients were unable to complete to complete FNA biopsy, 1 due to body habitus and difficulty with atypical anatomy, and 1 with a largely cystic nodule and insufficient solid material for biopsy, per the attempting radiologist. A final group of 3 patients deferred biopsy based on preference, 2 in the setting of growing nodules.

Intraoperatively, 28 patients were determined to have a "positive for malignancy" diagnosis (11.8%) on FS. This included 12 specimens with definitively determined PTC, 1 specimen with definitive medullary thyroid cancer, 12

that were suspicious or concerning for malignancy, and 3 with a possible small focus of invasion or cancer.

Of these FS results, 21 were ultimately correlated with positive malignant findings on final pathology (75% positive predictive value) and 7 (25%) were false positives. Two of the 21 positive malignant findings on FS were ultimately classified as micro-PTC on final pathology.

On review of final pathology, 29 (12.2%) patients were determined to have clinically significant malignancies, of which 19 patients had been identified on FS (sensitivity of 65.5%). These included 21 patients with papillary carcinomas and 5 with follicular carcinomas, of which 4 were Hurthle cell tumors and 3 were medullary tumors. There were no instances of poorly differentiated/anaplastic cancer in this series. In addition to this, there were 26 patients found to have exclusively incidental micro-PTCs ($n = 22$) or foci of follicular thyroid neoplasm with papillary-like nuclear features ($n = 4$). If one excludes these secondary findings, the specificity of FS was 95.6%.

Ultimately, there were 147 partial thyroidectomies and 89 total thyroidectomies performed, 11 of these with central neck dissection. Of these operations, 11 were modified from their original planned extent after receipt of FS diagnosis (4.7%). Five (2.1%) were planned thyroid lobectomies that demonstrated clear evidence of PTC on FS and proceeded to total thyroidectomy with evidence of PTC on final pathology. Of these, 3 of the 5 had a Bethesda V FNA results preoperatively, and 2 were Bethesda III with "suspicious" results on Afirma.

For 6 patients, however, the surgeon was misled by FS results and performed more than or less than necessary operations. In 2 patients, the surgeon performed a total thyroidectomy during a planned lobectomy for worrisome FS findings. In neither of those patients was cancer detected on final pathology. In a third patient, a central neck dissection was added in the course of a total thyroidectomy for suspected PTC on FS; there was no cancer detected on final pathology and lymph nodes were benign. In the fourth

Table 1. Thyroid Fine-Needle Aspiration Results Correlated with Postoperative Findings

Preoperative FNA diagnosis (Bethesda class)	Total patients, n	Malignant on final pathology		Including mPTC and NIFTP	
		n	%	n	%
I. Inadequate/nondiagnostic	16	1	6.3	4	25
II. Benign	70	0	0	10	14.3
III. AUS/FLUS	55	8	14.6	23	41.8
IV. Follicular neoplasm/suspicious for follicular neoplasm	21	3	14.3	8	38.1
V. Suspicious for malignancy	8	5	62.5	5	62.5
VI. Malignant	5	5	100	5	100
None	61	7	11.5	20	32.8

AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FNA, fine-needle aspiration; mPTC, micropapillary thyroid carcinoma; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear feature.

patient, the surgeon performed a total thyroidectomy rather than lobectomy based on the presence of PTC on FS; postoperatively on final pathology, that tumor had been determined to be a micro-PTC. For the 2 additional patients with misleading FSs, the surgeons had proposed total thyroidectomy for preoperatively suspected malignancies, though after negative FS, scaled the operation down to thyroid lobectomy alone, requiring additional evaluation and operation.

DISCUSSION

Frozen section as an intraoperative adjunct continues to be a debated strategy in the surgical management of thyroid nodules. To date, there is conflicting evidence as to the merits of its use in indeterminate nodules,²⁹⁻³² with most studies suggesting that it might have an exclusive role in Bethesda V FNA diagnoses to increase single-stage definitive management.^{15,31,33,34}

We noted this limited area of utility in our series as well, for the 8 specimens with “suspicious for malignancy” FNA diagnoses. We observed FS and permanent pathologic concordance in 6 of 8 specimens, with 1 false-negative diagnosis and 1 false-positive diagnosis on FS. This correctly changed the management for 3 of the lesions, but also led to 1 overtreatment, and for 4 other lesions, the planned extent of operation did not change at the index operation. In addition, recent changes to the recommended extent of operation for smaller, low-risk papillary thyroid tumors in the most recent iteration of the American Thyroid Association guidelines⁶ might even challenge this historic paradigm.

Despite this, multiple investigations have unequivocally demonstrated limited or no benefit in preoperatively determined benign or malignant diagnoses.^{2,16,35} In our study, with respect to benign FNA diagnoses, the rate of final malignancy in our series was 0%. Of the false-positive results on FS, 2 were noted in the setting of Bethesda II FNA diagnoses. All 5 Bethesda VI specimens were positive for malignancy on final pathology in our series, though 1 was misclassified on FS. In fact, it was the result of a false-negative result on FS for a Bethesda VI tumor that led 1 surgeon to erroneously undertreat a process preoperatively defined as malignant by FNA.

A major limitation of FS analysis is difficulty with assessment of capsular and vascular invasion with limited ability to immediately assess the entire capsular interface, which for follicular tumors is a hallmark to differentiate benign from malignant disease.^{17,36} Taking sections in the fresh, non-fixed state at the time of FS can render the thyroid specimen more fragmented and difficult to orient and section by the grossing pathologist, ultimately making evaluation of

capsular invasion more difficult for the pathologist on the subsequent formalin-fixed, paraffin-embedded tissue, which can lead to an equivocal final diagnosis in some cases. Alternatively, placing the specimen immediately in formalin, rather than submitting fresh for FS with subsequent specimen manipulation in the FS laboratory, generally leads to better final, permanent section pathology, which greatly aides the pathologist in evaluating for signs of capsular invasion. In addition, permanent sections processed after FS characteristically show artefactual loss of nuclear features of PTC, which can also lead to inaccurate diagnosis, particularly for small tumors where the entire tumor might have been sampled for FS. For malignancies with more distinctive cytologic and nuclear features, such as papillary, medullary, and anaplastic thyroid carcinomas, FS tends to fare better.³⁷

Even with this, in our series, the overall rate of appropriate modification in the planned extent of the operation was a meager 2.1%, suggesting that even when correct, FS is not beneficial to patients, even with a segment of the patient cohort that has been risk-stratified by molecular testing. It reinforces the concept that for most patients routine FS continues to be unnecessary and can be deceptive.

In this study, FS was used routinely by only a select group of surgeons. When looking exclusively at the 4 surgeons whose practice is focused predominantly on endocrine surgery, 2 routinely use FS and 2 do not.³⁸ Part of the impetus for this study was to determine the use of FS at our institution. Because the results of this study have been discussed, one of the surgeons who previously used routine intraoperative thyroid FS has abandoned this practice.

We recognize that our study is not without some limitations. In our experience, FS evaluation was not performed consistently by pathologists with head and neck expertise. Given 20 different pathologists, there might have been considerable variability in interpretation that might have reduced accuracy of FS by inconsistency in expertise and approach.

However, the non-thyroid subspecialty pathologists that read many of the FS likely have thyroid pathology experience similar to that of most community general pathologists, so these results likely translate to the community practice setting. It is also notable that in 82 patients, initial total thyroidectomy was planned in advance of FS analysis. This was generally for reasons of thyroid dysfunction, bilateral dominant nodules, family history, compressive goiter, Bethesda VI FNA results, or patient preference in the setting of suspicious results. In these settings, the argument for FS was detection of malignancy intraoperatively for facilitation of prophylactic central neck dissection or confirmation of FNA findings. However, in the context of current American

Thyroid Association guidelines, prophylactic central neck dissection is not recommended for cancers <4 cm in size,⁶ and excision of central lymphadenopathy should generally be guided by preoperative imaging or intraoperative findings. Certainly, the definitive determination of malignancy to allow exploration of clinically occult central lymphadenopathy, particularly given the frequently indolent nature of these lymph nodes,³⁹ does not seem to be justified by the additional time and expense involved in FS analysis.

Our study population was heterogeneous and composed of larger proportions of benign (30.0%), inadequate (6.7%), and no FNA (25.8%) biopsies, which might have skewed our results, given the low rate of malignancy in benign specimens or thyroid nodules generally. However, those that were selected for surgical resection typically had additional clinical indications, which promoted concern such as large size for which FNA biopsy might be less reliable,^{9,10} interval growth, obstructive symptoms, evidence of concomitant thyroid dysfunction, or worrisome clinical or ultrasonographic features that would ultimately necessitate operation.⁴⁰ We posit that this cohort is fairly representative of patients undergoing thyroid operations in a typical practice and that our results should be fairly generalizable.

Finally, of those nodules that were indeterminate, Bethesda III and IV, 48.6% underwent additional molecular testing. Two of the 33 patients with high-risk molecular results ultimately had a meaningful modification in surgical extent in the setting of FS diagnosis. Interestingly, of the 33 patients with a suspicious molecular testing result, we observed a clinically significant malignancy rate of only 15%.

CONCLUSIONS

The addition of FS biopsy does not curtail the need for cervical reoperation, and our study demonstrates that it is, in fact, more likely to lead to over- or undertreatment of thyroid disease rather than complement preoperative and intraoperative surgical decision-making. We cannot advocate for its routine use in thyroid operations.

Author Contributions

Study conception and design: Mallick, Lindeman, Chen
 Acquisition of data: Mallick, Stevens, Winokur
 Analysis and interpretation of data: Mallick, Chen
 Drafting of manuscript: Mallick, Chen
 Critical revision: Stevens, Winokur, Asban, Wang, Lindeman, Porterfield

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Discussion



DR CARMEN SOLÓRZANO (Nashville, TN): This expert endocrine surgery group led by Dr Chen, who, by the way, is the president of the American Association of Endocrine Surgeons, examined the use of frozen section during thyroidectomy in the contemporary era of molecular testing and in the era when we are using risk stratification to better design treatment, or punishment, if you will, that fits the crime.

When molecular testing was available, the Afirma platform was used. This was a retrospective study of 236 patients. Among these, only 74% underwent preoperative fine needle aspiration (FNA) biopsy of the nodule and the rest did not. The authors found that in only 5% of the cases, the frozen section changed the intended operative plan. In those cases in which it changed the plan, it changed in more than half to the wrong plan—too much or too little. Overall, only 2% benefited from frozen section. The authors concluded that frozen section is unhelpful and may be deleterious.

Personally, I stopped using frozen section about 8 to 10 years ago for follicular neoplasms, Hurthle cell neoplasms, suspicious for cancer fine needle aspirations (FNAs), and now Bethesda III/IV/V. It does not seem to be helpful. I now use frozen section for lymph nodes that appear suspicious as well as maybe to determine whether something is a parathyroid or a lymph node because you do not want to transplant that into the muscle. First, I do not think you examined the use of frozen section to evaluate lymph nodes in this study. Do you recommend routine use of frozen section to evaluate lymph nodes or to evaluate the extent of extrathyroidal extension of thyroid nodules to see if it changes the intended operation? Second, should patients undergo frozen section of a thyroid nodule if they did not have a preoperative FNA biopsy, and will this change what you do? Many patients did not have FNAs of nodules in this study.

Third, in your study, I believe you classified noninvasive follicular neoplasms with papillary-like nuclear features (NIFTP) as benign. This is controversial. Can you comment on how that would look on frozen section as it has nuclear features of papillary thyroid cancer? Fourth, should patients with suspicious for cancer FNA biopsy, Bethesda V and with suspicious molecular features, undergo a frozen section during the operation to change what you're doing?

Fifth, what did you consider an appropriate operation for cancer in this study, as now we are trying to tailor the operation to less rather than more?