

Follicular Lesions of the Thyroid

Does Frozen Section Evaluation Alter Operative Management?

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Objective

The authors determined the usefulness of frozen section (FS) evaluation in the operative management of follicular lesions of the thyroid.

Summary Background Data

Fine-needle aspiration (FNA) cannot reliably discriminate between benign and malignant follicular lesions of the thyroid. Accordingly, FS evaluation is used routinely to guide intraoperative management.

Methods

One hundred twenty-five consecutive patients with follicular thyroid lesions who underwent surgical exploration at the Johns Hopkins Hospital were reviewed.

Results

Frozen sections were categorized in 104 of 120 patients (87%) as “follicular lesion, defer to permanent section,” rendering no useful clinical information. In only 4 of 120 patients (3.3%) did FS evaluation correctly modify the operative procedure. Notably, in six cases (5.0%), an incorrect FS evaluation misled the surgeon, resulting in four misguided operations.

Conclusion

Frozen section evaluation is of minimal diagnostic value for follicular thyroid lesions, rendering no additional information 87% of the time; it prolongs the operation, increases costs, and leads to misguided interventions. Until a more definitive diagnostic tool exists for follicular thyroid lesions, FS evaluation could be omitted, resection of the lobe with the nodule could be performed, and the definitive operative management could be based on the final permanent histology.

The prevalence of thyroid nodules in the general population ranges from 4% to 7%. Although the vast majority of nodules are benign, approximately 5% prove to be malignant.¹ The surgeon's goal is to distinguish which lesions are malignant and perform an appropriate operative procedure. Fine-needle aspiration (FNA) has revolutionized the management of thyroid nodules, providing a safe and convenient preoperative diagnostic tool. Although FNA is very accurate in detecting papillary and

medullary thyroid carcinomas, it is less useful in patients with follicular lesions because the criteria for malignancy—i.e., capsular or vascular invasion—cannot reliably be determined. Accordingly, the FNA diagnosis of a “follicular neoplasm” is commonly made. Because approximately 20% of all follicular lesions ultimately prove to be malignant,¹ patients with indeterminate follicular lesions generally undergo surgical exploration.

Intraoperative frozen section (FS) evaluation has tra-

ditionally been used to assess indeterminate thyroid lesions and guide surgical management. Frozen section evaluation, however, is limited by several variables, including sampling error and freezing artifact. Nonetheless, FS evaluation can reliably diagnose papillary, medullary, and anaplastic thyroid carcinomas.² Its clinical usefulness in follicular thyroid lesions, however, is far less satisfactory. Several studies have addressed this issue, but they are limited by small patient populations, a lack of comparison with preoperative FNAs, and heterogeneous pathologic diagnoses.²⁻¹⁰ The purpose of this study was to determine the accuracy and clinical usefulness of FS evaluation in the operative management of follicular lesions of the thyroid.

MATERIAL AND METHODS

Two hundred ten consecutive patients with follicular thyroid lesions diagnosed by FNA or FS evaluation were identified from the Johns Hopkins Hospital surgical pathology database from May 1984 to January 1994. Of these, 125 underwent surgical resection at the Johns Hopkins Hospital with histologic evaluation, and form the basis for this report. All clinical data were analyzed, and the histology was reviewed.

Of the 125 patients who underwent operations, 118 had undergone preoperative FNAs, 106 of which were performed or reviewed at the Johns Hopkins Hospital. Fine-needle aspirations were categorized as inadequate, indeterminate, benign, follicular neoplasm (cannot distinguish benign from malignant), or suspicious/diagnostic of malignancy. Lesions suspicious for malignancy were categorized with malignant lesions because the effect on surgical management was identical. In patients with multiple FNAs, the most recent diagnostic study was evaluated.

Intraoperative FS evaluations were performed in 120 of these 125 patients. The lesion was grossly identified, measured, and at least one representative section from the area most suspicious for capsular invasion was examined. Frozen section evaluations were categorized as benign, indeterminate, follicular lesion (defer diagnosis to permanent section), or suspicious/diagnostic of malignancy.

Permanent sections were used for definitive pathologic categorization. Sensitivity (true-positives/true-positives + false-negatives), specificity (true-negatives/true-negatives + false-positives), and accuracy (true-positives + true-negatives/total evaluations) for detection of malignancy were calculated for both FNA and FS evaluations.

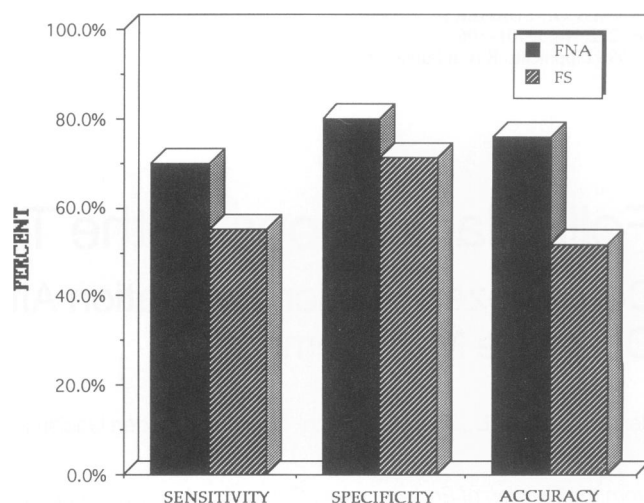


Figure 1. The sensitivity, specificity, and accuracy of fine-needle aspiration (FNA) and frozen section (FS) evaluation in the detection of malignancy with follicular lesions of the thyroid. Sensitivity = true-positives/(true-positives + false-negatives), Specificity = true-negatives/(true-negatives + false-positives), Accuracy = true-positives + true-negatives/total evaluations.

An FNA diagnosis of inadequate, indeterminate, or follicular neoplasm, and a FS diagnosis of indeterminate or follicular lesion were not included in these analyses. Hurthle cell neoplasms were grouped with the follicular lesions.

RESULTS

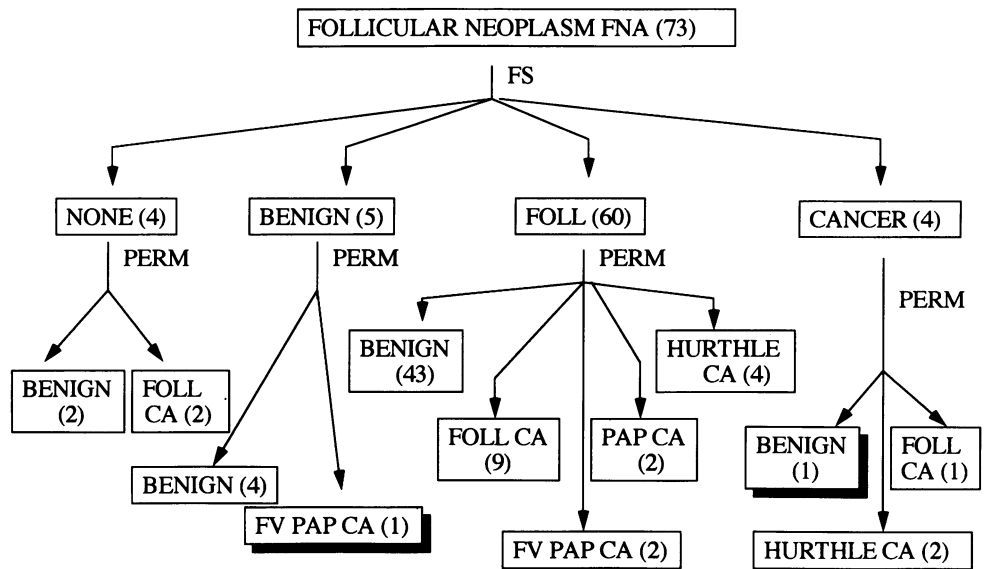
The median age at the time of surgery was 43 years (range 18–82 years). There were 90 women (76%) and 35 men (24%). Figure 1 illustrates the sensitivities, specificities, and accuracies of FNA and FS evaluation in the detection of malignancy. Fine-needle aspiration was superior to FS evaluation in all respects.

The data are stratified according to FNA results in a clinical decision tree format illustrating the subsequent FS and permanent histologic results in Figures 2 through 7. An FNA diagnosis of follicular neoplasm was the most common category, as demonstrated in Figure 2, representing 61% of all FNAs. Of these 73 patients who were explored, 4 had no FS evaluation, 5 had a benign FS evaluation, 60 had a follicular lesion noted on FS evaluation, in which the diagnosis was deferred to permanent histology (82%), and 4 were diagnosed with cancer based on FS evaluation. Of the four patients without an FS evaluation, two ultimately were proven to have cancer. In both cases, the surgeon performed an initial total thyroidectomy based on the clinical impression that the neoplasms were malignant. When the FS evaluation was benign, one of five (20%) patients were proven to have the follicular variant of papillary carcinoma, resulting in a subsequent

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Figure 2. Patients with an FNA diagnosis of "follicular neoplasm" and their subsequent frozen section (FS) evaluation and permanent histology (PERM). The bold background indicates a misguided surgical intervention. FOLL = follicular lesion, defer to permanent histology; FOLL CA = follicular cancer; FV PAP CA = follicular variant of papillary cancer; PAP CA = papillary cancer; HURTHLE CA = Hurthle cell carcinoma.

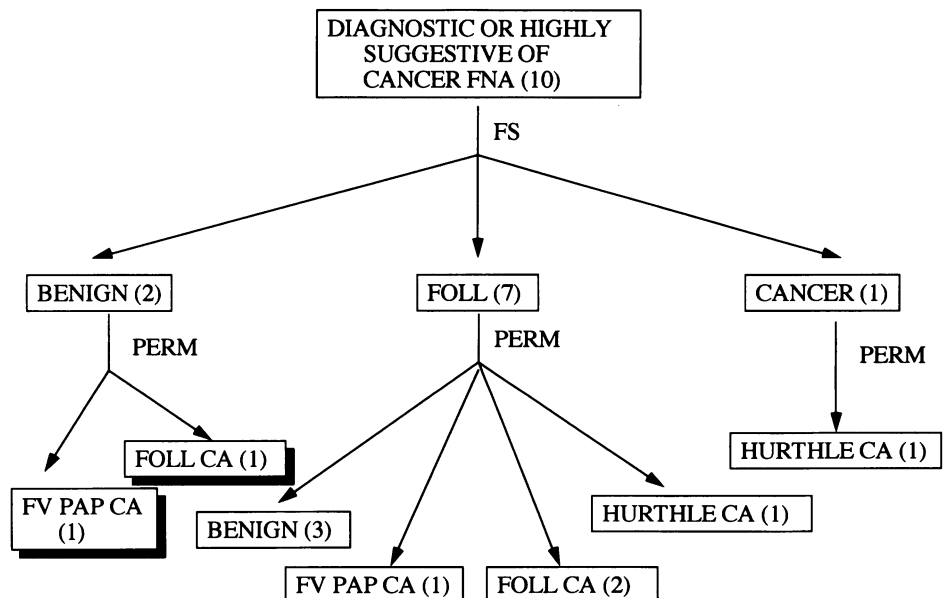


staged completion total thyroidectomy. In the most common group of FS diagnoses, "follicular lesion, defer to permanent," 43 of 60 (72%) were ultimately benign, but 17 of 60 (28%) proved to be malignant. In the four patients who had cancer diagnosed on FS evaluation, one had a benign lesion and underwent an unnecessary total thyroidectomy. The other three patients underwent initial total thyroidectomies. Therefore, for those patients with a follicular neoplasm detected on FNA, the intraoperative FS evaluation was of minimal usefulness because it was rarely diagnostic of malignancy, whereas the permanent section proved to be diagnostic of cancer in 28% of patients. Furthermore, an incorrect FS diagnosis resulted in inadequate

surgery in one case and an overzealous operation in another case (indicated by the bold backgrounds in Fig. 2).

Figure 3 illustrates ten patients who had FNAs suggestive or diagnostic of cancer who also had FS evaluations performed. Frozen section evaluation was considered benign in two patients; however, both patients actually had cancer and underwent staged completion total thyroidectomies. Had the surgical management been based on the preoperative FNA, both patients would have had initial total thyroidectomies, which would have obviated a second operation. In seven of ten cases, FS evaluation yielded a "follicular lesion, diagnosis deferred," which proved to be benign in three cases and malignant in the

Figure 3. Patients with an FNA diagnosis suspicious or diagnostic of cancer, and their subsequent frozen section (FS) evaluation and permanent histology (PERM). The bold background indicates a misguided surgical intervention. FOLL = follicular lesion, defer to permanent histology; FOLL CA = follicular cancer; FV PAP CA = follicular variant of papillary cancer; HURTHLE CA = Hurthle cell carcinoma.



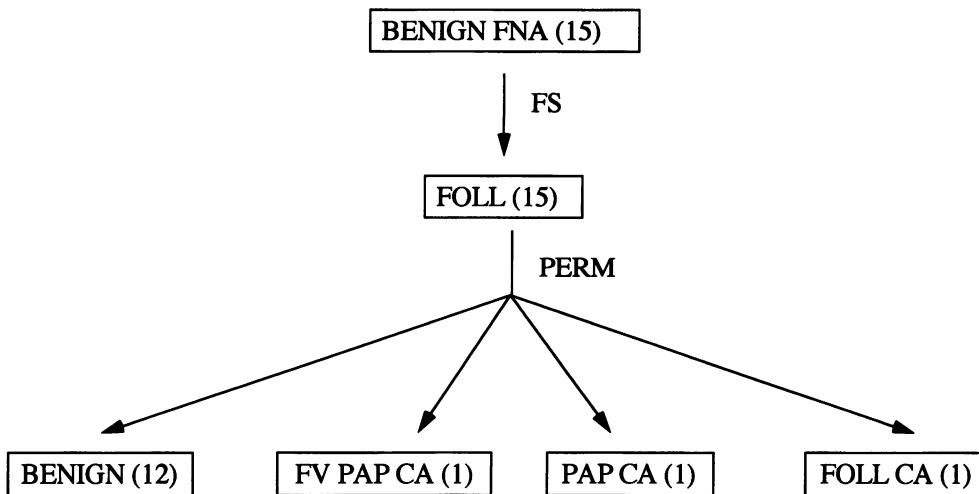


Figure 4. Patients with a benign FNA diagnosis and their subsequent frozen section (FS) evaluation and permanent histology (PERM). FOLL = follicular lesion, defer to permanent histology; FV PAP CA = follicular variant of papillary cancer; PAP CA = papillary cancer; FOLL CA = follicular cancer.

other four. In only one of these ten cases was FS evaluation correctly diagnostic for cancer.

Fifteen patients had benign FNAs, but because of clinical criteria, underwent surgical exploration (Fig. 4). The majority of these cases (12/15) were benign, but three proved to be malignant on final histology. Notably, FS evaluation failed to detect any of these malignant lesions. Ten patients with indeterminate FNAs had surgery (Fig. 5). One of two patients with a benign FS evaluation actually had follicular carcinoma and underwent a subsequent staged completion total thyroidectomy. In eight patients, the FS evaluation was interpreted as a "follicular lesion, defer diagnosis," and one follicular cancer was found among this group. Figure 6 illustrates ten patients with inadequate FNAs who were explored based on clinical symptoms. Nine of these tumors proved to be benign. Frozen section evaluation correctly detected one follicular cancer in this group. Seven patients who did not have an FNA are shown in Figure 7. In six cases, "follicular lesion, defer diagnosis" was the FS diagnosis, one of which (17%) proved to be cancer. One patient had an incorrect FS diagnosis of papillary carcinoma that ul-

timately was shown to be a benign adenoma. This resulted in a misguided total thyroidectomy.

Overall, FS evaluations were classified as "follicular lesion as discussed" in 104 of 120 (87%) patients, rendering no additional information to guide the surgical management. In only 16 of 120 (13%) cases did FS evaluation yield diagnostic information. However, in only 4 of 120 (3.3%) cases did FS evaluation correctly modify the surgical procedure. Notably, in six cases, an incorrect FS actually misled the surgeon and resulted in four misguided interventions.

The surgical procedures performed for lesions that were malignant on permanent histology are shown in Table 1. Twenty-one total thyroidectomies were performed as an initial procedure based on a positive FNA (n = 6), a positive FS evaluation (n = 5), or the surgeon's clinical impression of either bilobar disease or malignancy. Staged completion total thyroidectomies were performed in an additional ten patients who had malignancy detected on permanent histology. Five patients underwent ipsilateral lobectomies/isthmusectomies, and in each case, a completion total thy-

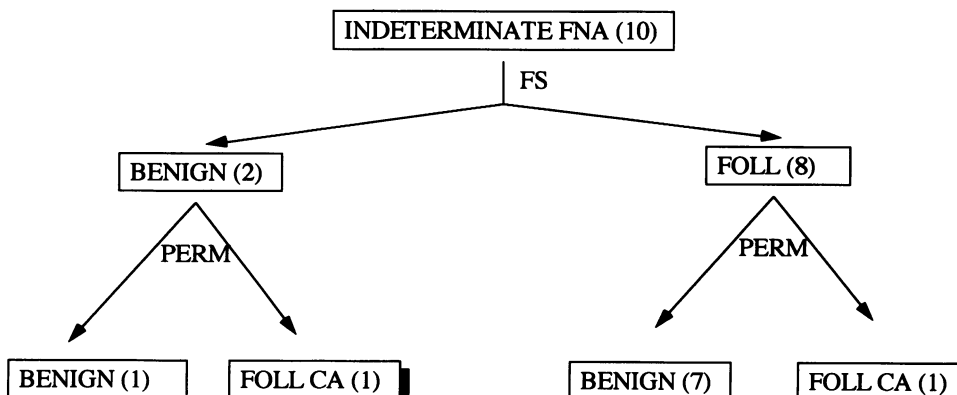
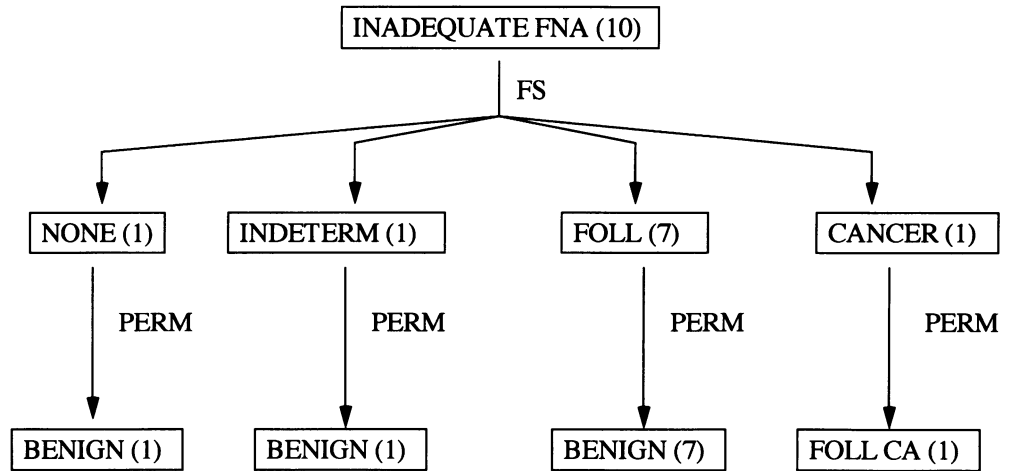


Figure 5. Patients with an indeterminate FNA diagnosis and their subsequent frozen section (FS) and permanent histology (PERM). The bold background indicates a misguided surgical intervention. FOLL = follicular lesion, defer to permanent histology; FOLL CA = follicular cancer.

Figure 6. Patients with an inadequate FNA and their subsequent frozen section (FS) and permanent histology (PERM). INDETERM = indeterminate; FOLL = follicular lesion, defer to permanent histology; FOLL CA = follicular cancer.



roidectomy was declined. Except for one case of post-operative hypocalcemia, there were no complications in these patients.

DISCUSSION

Frozen section evaluation is limited by both technical and interpretative problems.⁴ Capsular invasion is difficult to assess grossly in fresh specimens, and a definitive intraoperative evaluation would require that the entire capsular interface of the nodule be examined microscopically. Although some authors state that three sections are needed to detect capsular or vascular invasion,¹¹ this is time consuming and leaves room for error while not necessarily contributing additional information. In our institution, one or two sections are submitted from each nodule. Furthermore, fresh tissue is soft and pliable, making orientation of the specimen difficult and often leading to distorted architecture. In addition, freezing artifact associated with colloid, edema, blood, and adipose tissue further compromise the quality

of FS evaluation. For these reasons, the most common diagnosis on FS evaluation is “follicular lesion, defer to permanent,” representing 87% of the cases reviewed in this study.

Frozen section evaluation generally costs between \$400 and \$600 per specimen at most institutions. The additional operating room time required varies from 10 to 30 minutes, depending on the number of sections obtained. Therefore, we estimate that the true cost for a FS evaluation ranges from \$500 to \$800 per patient, or based on our data, \$15,000 to \$24,000 per useful FS.

The management for follicular lesions of the thyroid in our division is total thyroidectomy for carcinomas and lobectomy/isthmusectomy for adenomas. Total or near-total thyroidectomy for cancer has been shown to decrease recurrence rates and improve the ability to use ¹³¹I to diagnose and ablate residual neck uptake and metastasis.^{12,13} If a patient had undergone a lobectomy/isthmusectomy for an apparently benign nodule, but the subsequent permanent pathology revealed a cancer, a staged completion total thyroidectomy generally would be performed within 7 to 10 days of the initial surgery.

Many studies address the management of thyroid nodules.^{2-4,6-8,11,14} Several studies advocate FS evaluation for

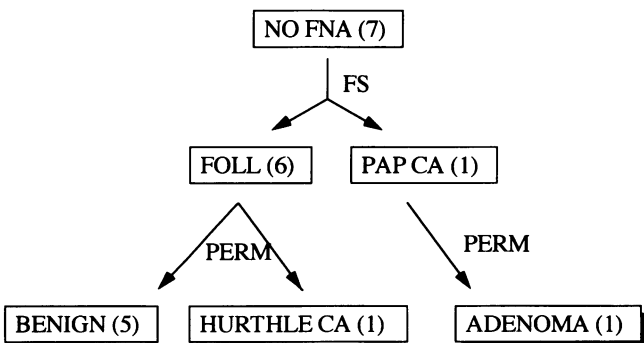


Figure 7. Patients without FNAs and their subsequent frozen section (FS) evaluation and permanent histology (PERM). The bold background indicates a misguided surgical intervention. FOLL = follicular lesion, defer to permanent histology; PAP CA = papillary cancer; HURTHLE CA = Hurthle cell carcinoma.

Table 1. OPERATIONS FOR MALIGNANCY

Procedure	Frozen Section Diagnosis				n
	None	Benign	FOLL	Cancer	
Initial total thyroidectomy	1	2	13	5	21
Staged completion total thyroidectomy	1	1	8	0	10
Lobectomy/isthmusectomy	0	0	5	0	5

FOLL = follicular lesion, defer to permanent histology. n = 36.

all thyroid nodules, including follicular lesions; however, they are limited by high FS deferral rates, numerous FS false-negatives for malignancy, and low numbers of follicular lesions.^{2-4,14} Only two studies were devoted exclusively to follicular lesions.^{5,9} In one of these studies, Kingston et al.⁵ concluded that FS evaluation should be used as a guide because there were no false-positive diagnoses. However, they did not address whether FS evaluation contributed additional information or just confirmed the FNA diagnosis. Furthermore, FNA was not routinely performed during a portion of their study's time frame.

Other authors have argued that FS evaluation offers little in the evaluation of thyroid lesions. Irish et al. stated that "there is no reliable evidence that frozen section analysis is more accurate than FNA,"⁷ and advocate that surgical management be based solely on FNA. Hamburger et al. concluded⁶ that reliance on FNA could eliminate 99% of all thyroid FS evaluations. In their study, FS evaluation contributed useful information less than 1% of the time. In a subsequent study,⁸ Hamburger et al. showed that FS evaluation failed to identify any follicular cancers that FNA had not. In addition, when discussing a study by Kopald et al.,⁴ Dr. Orlo Clark reported only two false-positive FNAs in 500 patients. Moreover, all of his patients with malignant FNAs and benign FS evaluations had cancer on final pathology. Accordingly, Clark does not routinely perform FS evaluation for follicular lesions. Furthermore, in the most recent study,⁹ pathologists with acknowledged expertise in thyroid histology retrospectively reviewed 110 follicular lesions by FS evaluation. They had a deferral rate of 44%, and FS evaluation detected only four of ten cancers, all of which were follicular variants of papillary cancer. In addition, none of the six follicular cancers were identified by FS evaluation.

We recommend that routine FS evaluation be omitted in the surgical management of follicular thyroid lesions. Frozen section evaluation is of minimal diagnostic value, rendering no additional information 87% of the time. It prolongs the operation, increases costs, and leads to misguided interventions. Several investigators have searched for other parameters to guide the management of follicular thyroid lesions, including clinical criteria,¹⁵ DNA ploidy,¹⁶⁻¹⁸ S-phase fraction,¹⁷ stereologic estimates,¹⁷ and immunohistochemistry,¹⁸ with disappointing results. Current research is focused on molecular techniques to detect the presence of oncogenes or point mutations specific to follicular cancers. Until a more definitive diagnostic tool exists for follicular thyroid lesions, FS evaluation could be omitted, resection of the

lobe with the nodule could be performed, and the definitive operative management could be based on the final permanent histology. In cases in which there is obvious tumor extension into contiguous structures or in which there is contralateral nodular disease, proceeding directly to total or near-total thyroidectomy would be appropriate.

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