

Role of Fine Needle Aspiration and Frozen Section in the Diagnosis of Thyroid Lesions .

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Citation

C Batra, S Singh, R Katra, N Marwah, S Marwah, A Atreja. *Role of Fine Needle Aspiration and Frozen Section in the Diagnosis of Thyroid Lesions* .. The Internet Journal of Pathology. 2009 Volume 11 Number 1.

Abstract

The study compares fine needle aspiration cytology and frozen section of thyroid to final histopathologic diagnosis and characterizes the pitfalls in their use. Material and Methods : FNAC and FS were evaluated in 50 patients who underwent a thyroid surgery. Accuracy of FNAC and FS were assessed by definitive histological section as reference. Sensitivity, specificity, positive predictive value and negative predictive value were calculated for both FS and FNAC. Results. On frozen section evaluation 9 of the 13 (69.2%) malignancies could be diagnosed . Of the 6 deferred diagnosis only 2 turned out to be malignant on histopathology No false positivity was reported with frozen section while. False negativity was seen in 2 cases. Fine needle aspiration cytology was able to detect only 6 out of 13 malignant cases where as 10 were labelled as suspicious and 2 showed inadequate cellularity. Two of the 4 cases missed on frozen section were papillary microcarcinomas. The other 2 cases were follicular carcinoma where capsular and vascular invasion could not be demonstrated on frozen section. Sensitivity, specificity and accuracy of frozen section was reported to be 81.8%, 100% and 95.4% respectively as compared to 60%, 100%, and 89.4% of that of FNAC. Conclusion. Frozen section evaluation remains a useful tool, complimentary to FNAC. Frozen section can be avoided when the FNAC is consistent with benign or malignant, but could be of value (i) When FNAC result is reported as suspicious or inadequate. (ii) In diagnosis of unsuspected nodule found at surgery.

INTRODUCTION

Diseases of thyroid are of great importance because they are amenable to medical or surgical management.¹

It is estimated that 4% to 10% of the population will have a clinically apparent nodular thyroid disease. Hence, a large number of patients seek medical attention for this problem. The incidence of malignancy in patients with solitary thyroid nodule varies from 5% to 30%.²

The traditional evaluation of patients with thyroid pathology included detailed history and clinical examination, thyroid function tests, radioactive scan and ultrasonography. These measures, however, cannot distinguish with certainty benign from malignant lesions.³

The traditional approach to a clinically suspicious thyroid nodule consisted of ipsilateral lobectomy and intraoperative frozen section (FS) to determine the extent of thyroid resection. False positive diagnosis can lead to more extensive surgical procedures, which may increase the risk of associated complications. False negative or indeterminate diagnosis can lead to incomplete operations which may necessitate reexploration and resection at a later date.³

The approach to thyroid nodules has been modified by preoperative Fine Needle Aspiration Cytology (FNAC). This technique has become the most widely used test to select patients for thyroidectomy. With the increased use and acceptance of FNAC, added benefit of frozen section has been called into question.³ Despite preoperative evaluation there remains a group of nodules where needle aspiration results are either suspicious or indeterminate. In this group of patients intraoperative frozen section may help surgeon to assess the thyroid lesion, to make decision regarding thyroidectomy and to confirm the preoperative diagnosis based on fine needle aspiration cytology.²

This purpose of this study was to compare fine needle aspiration cytology and frozen section of thyroid to final histopathologic diagnosis and to characterize the pitfalls in their use. .

MATERIAL AND METHODS

The present study was conducted on fifty cases of thyroid tissue submitted during thyroid surgery for frozen section evaluation in Department of Pathology, Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak from

2005 to 2007. Only those cases were included in the study in which preoperative FNAC was performed.

Intraoperative frozen section examination was performed on grossly abnormal areas or on representative areas of generalized pathology obtained by serial sectioning of the thyroid tissue. In order to optimize the efficacy of frozen section examination in diagnosis of carcinoma, four to ten frozen section examinations were performed in a patient with suspected follicular neoplasm to evaluate separate quadrants of the nodule capsular interface for capsular or vascular invasion. When the diagnosis was apparent it was reported to the surgeon in the operating room. The average time required to establish frozen section diagnosis ranged from 15-20 minutes and generally required 4 to 10 slides. Further decisions regarding the extent of thyroid surgery were based on frozen section diagnosis.

The rest of the tissue was subjected to routine paraffin sections at 4 μ m thickness. The final histopathological diagnosis was established on routine haematoxylin and eosin staining of sections prepared from paraffin blocks and special histochemical stains, wherever necessary. The results of frozen section were analyzed and compared to final histopathologic diagnosis and with preoperative FNA findings.

The cytological findings for FNA were classified as follows:

- Benign
- Suspicious
- Malignant
- Inadequate for evaluation

An adequate FNAC was defined by the presence of at least six separate groups of 10 or more well preserved follicular epithelial cells. Aspirates that did not meet this criteria were classified as inadequate for evaluation.

The frozen section results were categorized as:

- Benign
- Malignant
- Deferred

Sensitivity, specificity and diagnostic accuracy was assessed for FNAC and frozen section. The results were given as

follows:

- True positive: a result positive for malignancy with subsequent final histopathological confirmation.
- True negative: a result negative for malignancy with definitive histopathological confirmation.
- False positive: a result that was positive for malignancy but with no evidence of carcinoma on histopathological examination.
- False negative: a result that was negative for malignancy but with a diagnosis of malignant disease on histopathological assessment.

Sensitivity was defined on the basis of thyroid cancer detected with FNA or frozen section technique: true positive / [true positive + false negative]. Specificity was defined on the basis of the detection of benign thyroid disease: true negative/ [true negative + false positive]. Diagnostic accuracy represented the combination of sensitivity and specificity: [true positive + true negative]/ [true positive + false positive + true negative + false negative].

For statistical calculations, cases labelled as inadequate and suspicious by FNAC and the cases whose diagnosis was deferred on frozen section examination were not included

RESULTS

In our study group the mean age (and standard deviation) was (40.5 \pm 14.58) with the age ranging from 7 to 70 years. Most of the patients were in the age group of 31-50 years forming 52% of the study group

Most of the patients were females, constituting 41 (82%) of 50 cases. Out of a total of 9 (18%) male patients, 4 (44.4%) had a benign disease and 5 (55.5%) had a malignant disease. While in female patients, 8 out of 41 i.e. 19.5% patients had a malignant disease.

Out of 50 patients who underwent thyroid surgery 37 (74%) patients had a benign disease and 13 (26%) patients had a malignant disease. The most common thyroid lesions were multinodular goiter / adenomatous goiter as diagnosed in 33 (66%) cases. Most common malignant lesion was papillary carcinoma seen in 10 (20%) patients Table 1.

Figure 1

Table 1 Distribution of cases on histopathological evaluation

Histopathological diagnosis	Number of cases (n=50)	Percentage
Benign		
MNG/ Nodular goiter/ adenomatous goiter	33	66
Follicular adenoma	2	4
Hashimoto's thyroiditis	2	4
Total	37	74
Malignant		
Papillary carcinoma	10	20
Follicular carcinoma	2	4
Anaplastic carcinoma	1	2
Total	13	26

Table 2 compares the results of preoperative FNAC, frozen section results and final histopathological diagnosis.

Out of six malignant cases which were correctly diagnosed as malignancy by both FNAC and frozen section, 5 were papillary carcinomas and 1 was anaplastic carcinoma.

Figure 2

Table 2

FNAC result, Number of cases	Frozen section result, number of cases	Final histopathological diagnosis, number of cases
Malignant – 6	Malignant – 6	Malignant – 6
Benign – 32	Malignant – 1	Malignant – 1
	Benign – 28	Benign – 27, Malignant – 1
	Deferred – 3	Benign –1, Malignant – 2
Suspicious – 10	Malignant – 2	Malignant – 2
	Benign – 5	Benign – 4, Malignant – 1
	Deferred – 3	Benign –3
Inadequate – 2	Benign –2	Benign –2

Showing results of Preoperative FNAC and Frozen section biopsy and correlation with final histopathological findings

Of the 4 cases of malignancy missed by both FNAC and frozen section two were papillary carcinoma measuring <1cm in size. Other two of these cases were follicular carcinomas. One of these two cases was reported as suspicious on FNAC and as papillary hyperplasia by frozen section. The second patient with follicular carcinoma was diagnosed as colloid goiter on FNAC but on frozen section, it was reported as follicular neoplasm and was deferred to final histopathology to look for any capsular or vascular invasion.

All the 3 malignancies that were missed by FNAC and diagnosed by frozen section were papillary carcinomas. Two of these were reported to be suspicious on FNAC and one of them was labeled as cystic lesion on FNAC.

For statistical calculations, cases labelled as inadequate and suspicious by FNAC and the cases whose diagnosis was deferred on frozen section examination were not included.

Overall sensitivities of FNAC and frozen section were 60% and 81.8% respectively; specificities were 100% for both and diagnostic accuracy was 89.4% and 95.4% respectively. When the cases labeled as suspicious by FNAC were included as malignant the sensitivity of FNAC increased to 69.2% while its specificity and accuracy dropped to 80% and 77.1%, respectively. Table 3

Figure 3

Table 3

Thyroid disease section result	FNAC		Frozen section
	Excluding suspicious cases	Including suspicious cases	
Sensitivity	60%	69.2%	81.8%
Specificity	100%	80%	100%
Accuracy	89.4%	77.1%	95.4%

A comparative analysis of FNAC & Frozen section examination for diagnosis of benign and malignant thyroid disease

DISCUSSION

Although thyroid disease is very common, the incidence of clinically apparent thyroid nodules varies between 4% to 10% of the population. The incidence of malignancy in patients with solitary thyroid nodule varies from 5% to 30%.²

Distinguishing benign from malignant lesions preoperatively is essential to avoid large number of unnecessary operations and to treat patients with malignancy in one operation to avoid high rate of complications associated with second stage operation. FNAC of thyroid nodules has been shown to be safe, accurate and superior to clinical assessment in cases with malignant disease.⁴

Many surgeons perform lobectomy and isthmusectomy as the minimum standard procedure for operative management of a thyroid nodule and rely on routine frozen section examination of thyroid for intraoperative diagnosis of thyroid cancer before proceeding with more extensive thyroid resection.⁵

In the present study, correlation of frozen section and FNAC results with the final histopathological diagnosis revealed that FNAC and frozen section examination were able to detect 6 and 9 respectively out of 13 malignancies reported in the present study (Table 2).

There were no false positive results in recognition of malignancy. Frozen section evaluation led to detection of malignancy in 1 case reported as benign and 2 cases reported

as suspicious on FNAC and confirmed malignancy in the 6 patients reported as malignant disease on fine needle aspiration.

Out of the four cases missed by both frozen section and FNAC, two were papillary carcinomas measuring 1cm and less than 1cm in dimension. Carcinomas less than 1cm in diameter usually accorded as microcarcinomas, have been vastly implicated as cause of missed carcinomas on frozen section and FNAC. Six out of eight carcinomas missed by frozen section in study conducted by Lin⁶ et al were microcarcinomas and he attributed this to sampling error, a limitation shared by both FNA and frozen section. Both these techniques sample only a small part of whole lesion and may therefore miss a small focus of carcinoma and give a false negative diagnosis. These small carcinomas would not be detected until permanent / paraffin sections are done. Sabel et al⁷ missed 11 papillary carcinomas, six of them were less than 1cm in size and six were found within benign nodules such as follicular adenoma or Hashimoto's thyroiditis. Chang et al⁸ found that 50% of carcinomas missed by frozen section had size less than 1cm.

The other pitfall in the diagnosis of papillary carcinoma is its follicular variant (FVPTC). The FNA and frozen section diagnosis of FVPTC is based on the identification of typical nuclear features of papillary carcinoma including ground glass nuclei, nuclear pseudo-inclusions and nuclear grooves. Intraoperative frozen section evaluation has poor sensitivity for FVPTC probably because of loss of nuclear details caused by freezing the tissue and frequent appearance of tumour encapsulation resembling follicular adenoma.⁹

The cytological diagnosis of FVPTC is difficult because of overlapping of cytomorphological features of benign and neoplastic follicular lesions due to abundance of colloid, monolayered sheets of follicular cells and presence of only a few characteristic nuclear features. However, Rupp and Ehya¹⁰ and Chen et al¹¹ emphasized that nuclear grooving, when seen in abundance, can be considered a reliable criteria on FNA.

Other 2 malignancies missed in this series by both FNAC and frozen section were follicular carcinomas. In fact both the carcinomas included in the present study could not be diagnosed by frozen section. One of them was labelled as follicular neoplasm and deferred to the final histopathology to look for any capsular or vascular invasion. Other one was reported as papillary hyperplasia as a dominant component of adenomatous goiter. This dilemma regarding the presence

or absence of capsular and/or vascular invasion in cases of follicular neoplasm is well recognized in literature. The same was responsible in 2 cases of follicular adenoma whose diagnosis was deferred on frozen section to histopathology. Unless entire capsule is evaluated on permanent section, the possibility of malignancy cannot be totally ruled out. Four to ten frozen sections were examined in patients with follicular neoplasm to evaluate separate quadrants of nodule capsule interface.

According to McHenry et al⁵, the assessment of capsular and/or vascular invasion by frozen section is seldom useful. It is limited by sampling error; variable thickness and irregularity of the capsule as well as blood vessel distortion and collapse. It is also difficult to distinguish simple entrapment of cells in the thyroid capsule from malignant capsular invasion.

There is little debate in the literature regarding the specificity of frozen section in diagnosis of follicular carcinoma if diagnostic criteria of capsular or vascular invasion are fulfilled, however, the sensitivity of technique has been generally reported as poor and is highly variable ranging from 52%¹² to 78%.¹³ Similarly, the diagnostic accuracy has been reported as low as 50%¹⁴ and as high as 98%.¹³

Unlike other thyroid lesions, for which FNAC is helpful adjunct in diagnosing malignancy, FNAC has proven significantly less useful for follicular lesions because of its inability to identify hallmark features of malignancy.

In one case of anaplastic carcinoma which was correctly diagnosed on FNAC, the frozen section was reported as malignant but the type of malignancy was deferred for permanent section. Saha et al¹⁵ have observed that one of the discrepancies between frozen and permanent section in patients with malignant disease is determination of cell type.

The evaluation of nuclear characteristics by frozen section is also limited. In the present series, the optically clear nuclei were not observed on frozen section examination.. McHenry et al⁵ also recorded the absence of this nuclear feature in frozen section examination of papillary carcinoma. Kraemer et al¹⁶ reported that optically clear nuclei could be demonstrated on frozen section examination in 37% of patients with papillary carcinoma.

Overall sensitivity, specificity and accuracy of frozen section in determination of malignancy in thyroid lesions in the present study were 81.8%, 100% and 95.4% respectively.

The sensitivity in literature varied from 50% in a study by Richards et al¹⁷ to 93% in the study by McHenry et al.⁵

Zambudio et al¹⁸ have reported the lowest sensitivity of 19%, but their study was limited to determination of malignancy associated with multinodular goiter. The specificity and accuracy of frozen section in literature was found to vary from 99 to 100% and 71 to 100% respectively.^{3,5,8,17-19}

FNAC of the thyroid lesions was able to correctly diagnose only 6 of 13 malignancies in the current series. Of the 10 cases reported as suspicious by FNAC, 3 cases turned out to be malignant on permanent section. There were no false positive results for malignancy. Of the 34 patients classified to have benign disease, 6 turned out to be malignant. 2 cases were labeled inadequate for any opinion. For the statistical purpose, the cases labeled as inadequate and suspicious on FNAC were left out. The sensitivity, specificity and accuracy of FNAC so calculated turned out to be 60%, 100% and 89.4%. When lesions labelled as suspicious were added as malignant, the sensitivity increased to 69.2% while the specificity and accuracy were reduced to 80% and 77.1%, respectively. In literature, the sensitivity, specificity and accuracy of FNA in diagnosing malignancy varied from 50% to 93%, 89 to 100% and 87 to 98% respectively.^{3,5,8,17-19} In this series, the specificity and accuracy were within the reported range in literature, whereas sensitivity was lower than many reported series. This decreased sensitivity can be attributed to an increased percentage of papillary carcinomas presenting as cystic lesions which were missed by FNAC. This reduction in the sensitivity of FNAC to detect papillary carcinoma in cystic lesions has been reported in literature.²⁰

Frozen section was able to diagnose malignancy in 3 (42.8%) out of 7 cases of malignancy missed by FNAC (Table 2). While FNAC was suspicious in 2 of these cases, 1 case was labeled as benign on FNAC. Thus total thyroidectomy in these 3 patients was contemplated and reoperation was prevented. Both the microcarcinomas were missed by FNAC as well as by frozen section. Frozen

section confirmed malignancy in all the six cases reported as malignant by FNAC.

Two cases with inadequate FNAC were found to have a benign disease and frozen section also reported benign pathology. Most authors recommend frozen section examination if FNA is inadequate.

The results of FNAC and frozen section also differ as a natural consequence of different objectives and concerns of pathologists in the two settings. Pathologists providing needle biopsy diagnosis are primarily concerned with not missing a cancer, for that results in patient not having an operation that is needed. Pathologists perform frozen sections only on patients who are having operations. They are primarily concerned with not making a false positive diagnosis that will lead to an unnecessary cancer operation.

In conclusion, frozen section evaluation remains a useful tool, complimentary to FNAC. Frozen section can be avoided when the FNAC is consistent with benign or malignant, but could be of value (i) When FNAC result is reported as suspicious or inadequate. (ii) In identifying possible metastasis to cervical lymphnodes (iii) In diagnosis of unsuspected nodule found at surgery.

Frozen section was found to be sensitive, specific and accurate diagnostic procedure in evaluating thyroid nodules. Intraoperative frozen section biopsy was most useful for patients with suspicious FNA biopsy findings. Present study also suggests that frozen section biopsy is not necessary when FNA gives a definite benign or malignant diagnosis. However both the techniques have pitfalls in diagnosing microcarcinomas and follicular carcinomas.

FNAC can be used primarily to select patients for surgery. Frozen section can be employed to plan the extent of surgery, a role requiring high specificity. . Kraemer¹⁶ puts it 'As the surgeon drives, pathologists posts the road signs'

References

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