



# Role of frozen section in evaluating follicular neoplasms of thyroid

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## Keywords:

Follicular neoplasm, frozen section, thyroid

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Received: 16 February 2019;

Accepted: 18 March 2019

Doi: 10.15713/ins.jmrps.158

## Abstract

**Background:** Thyroid lesion diagnosed as follicular neoplasm (FN) on fine-needle aspiration cytology is a challenge to both pathologist and surgeon. To recognize capsular and vascular invasion, histological evaluation is essential. Frozen section (FS) offers intraoperative histological diagnosis, identifies malignant lesions, and thereby guides the extent of surgery.

**Aims and Objectives:** To assess the ability of FS to detect malignancy in cases of cytologically diagnosed as FNs.

**Materials and Methods:** This study was conducted during 2014–2018 at ESIC Model Hospital, Rajajinagar, Bengaluru.

**Results:** FS identified 10 cases of 18 cases reported malignant on FH. Sensitivity, specificity, positive predictive value, and negative predictive value were 56%, 100%, 100%, and 83%, respectively.

**Conclusion:** FS is recommended for intraoperative diagnosis of FNs. It has high specificity and can, therefore, guide the extent of surgery in malignant cases.

## Introduction

Thyroid nodules are common clinical findings, with a reported prevalence of 4%–7% in the general population.<sup>[1]</sup> Fine-needle aspiration cytology (FNAC) is used routinely for evaluation of these nodules. At present, FNAC reporting is based on the Bethesda criteria for reporting thyroid cytopathology, which classifies thyroid lesions into six categories which include non-diagnostic/unsatisfactory, benign, atypia/follicular lesion of undetermined significance, follicular neoplasm (FN)/suspicion for an FN, suspicious for malignancy, and malignant.<sup>[2]</sup>

Although FNAC is a sensitive tool in discriminating benign and malignant lesions, it has limited accuracy in FN. It is not possible to differentiate follicular adenoma from follicular carcinoma (FC) based on FNAC because recognition of capsular and vascular invasion requires histological evaluation.<sup>[3]</sup>

Frozen section (FS) involves rapid freezing and histological evaluation of the surgical tissue fragment, which is usually a thyroid lobectomy specimen. If the nodule is found to be malignant on FS, total thyroidectomy is performed, thereby avoiding a second surgery. If found benign only lobectomy

is performed. FS, therefore, serves to limit overtreatment by eliminating false positives (FPs) and avoids undertreatment in FN cases. The purpose of our study was to assess the ability of intraoperative FS to detect malignancy in patients who were diagnosed as FNs on FNAC.

## Materials and Methods

This study was conducted during 2014–2018 at ESIC Model Hospital, Rajajinagar, Bengaluru. Our inclusion criteria required that FNAC, operative procedure with intraoperative FS, and final histopathology (FH) be performed at our hospital. Complete clinical details were obtained in all cases. A cytological diagnosis of FN (Bethesda 4) was defined by abundant follicular cells arranged in microfollicular aggregates in a background of scanty or absent colloid.

The surgical specimen sent for FS was evaluated macroscopically and suspect regions were frozen in a cryostat and cut into 5  $\mu$  sections. Two to three regions were sampled in each case. Rapid staining was performed using methylene blue or rapid hematoxylin and eosin technique. On FS, lesions were categorized into three types: Benign lesion, malignant lesion, or deferred (diagnosis

pending). Multinodular goiter, hyperplasia, thyroiditis, and adenoma were considered benign. All thyroid cancers including papillary carcinoma, FC, medullary carcinoma, anaplastic, and poorly differentiated carcinomas; lymphoma and metastatic diseases were coded as malignant. Micropapillary carcinomas were included under papillary carcinoma. Reports which were “suspicious” were coded as deferred. The frozen part of the specimen was then thawed and fixed in 10% formaldehyde along with the non-frozen part of the specimen. They were subjected to paraffin embedding for final histopathological assessment.

### Analysis of FS results

FS was considered as positive only in case of malignancy. Benign and deferred cases were counted as negative because in both cases, surgery was suspended awaiting a definitive histological diagnosis. A positive result on FS, subsequently, found to be malignant on FH was regarded as true positive (TP). A negative result on FS found to be benign of FH was regarded as true negative. A positive result on FS eventually diagnosed as benign was regarded as FP. A negative report on FS found to be malignant on FH was considered false negative.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of FS for detecting malignancy were calculated.

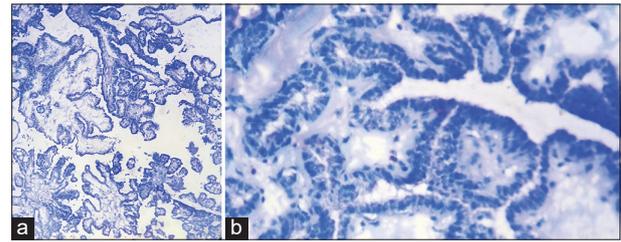
### Results

A total of 56 patients diagnosed with FN on FNAC were included in the study. This included 9 men and 47 women. Of these 56 cases, FS was positive in 10 cases and negative in 46 cases which included 37 benign and 9 deferred cases. Thyroid cancer was diagnosed in 10 cases (17.9%) which included 8 papillary carcinomas (14.3%) and 2 FCs (3.6%). FS appearance of papillary carcinoma and follicular adenoma is displayed in Figures 1 and 2. Of the remaining 46 cases, 37 cases (66.1%) were diagnosed as benign and 9 cases (16.1%) were deferred.

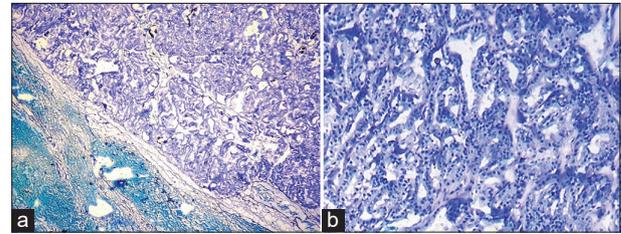
On FH, all 10 cases reported as malignant on FS was confirmed to be malignant. Of the 37 cases reported as benign on FS, four cases turned out to be malignant on FH which included two FC, one papillary carcinoma follicular variant (PCFV), and one lymphoma. Of the nine cases which were deferred on FS, five cases were benign on FH and four cases turned out to be malignant, which included three cases of PCFV and one FC.

Therefore, on FH, malignancy was reported in 18 cases (32.1%) which included 10 cases already reported as malignant on FS, 4 cases which were reported as benign, and 4 cases deferred on FS. Thirty-eight cases (67.9%) were reported as benign on FH which included 21 cases on nodular goiter (37.5%), 12 cases of follicular adenoma (21.4%), and 5 cases of Hashimoto's thyroiditis (8.9%).

Thus of the 18 TPs, FS identified only 10 cases (55.56%). Eight cases were false negative on FS either diagnosed as benign (four cases) or deferred (four cases). The sensitivity, specificity,



**Figure 1:** (a) Papillary carcinoma of thyroid on frozen section, methylene blue stain, ×10. (b) Papillary structures displaying nuclear crowding, ×45



**Figure 2:** (a) Follicular adenoma of thyroid on frozen section, methylene blue stain, ×10. (b) Closer view showing microfollicular pattern, ×45

PPV, and NPV of FS in detecting malignancy were 56%, 100%, 100%, and 83%, respectively, in the present study.

In our study, of 56 cases identified as FN on FNAC, thyroid cancer was diagnosed in 18 cases (32.14%) after FH. Papillary carcinoma was the most common cancer found in 12 cases (21.43%) followed by FC in 5 cases (8.93%).

### Discussion

Cytological diagnosis of FN has continued to be a challenging entity for pathologists and surgeons. Many studies have suggested that FNAC can be used primarily to select patients for surgery and FS can be employed to plan the extent of surgery. Almeida *et al.* stated that FS is particularly indicated when FNAC reports FN.<sup>[4,5]</sup>

In the present study, of 56 cases with FN, thyroid cancer was diagnosed in 18 cases (32.1%) on FH. Malignancy rate reported in literature in the category of FN is 15–30%. Other studies have reported the incidence of malignancy between 18 and 31%. Papillary carcinoma was the most common amounting to 67% (12 cases) of malignancy followed by FC seen in 26% (5 cases) which is in line with other studies. However, Chen *et al.* in their study of 73 cases of FN have reported malignancy in 23 cases (31.5%), of which FC was most commonly seen in 18 cases (78.3%) which included six cases of Hurthle cell carcinoma. We did not come across any Hurthle cell tumors in our study.<sup>[2,6-9]</sup>

In the present study, sensitivity of FS in diagnosing malignant lesions was only 56%, which is less compared to most other studies as shown in Table 1.<sup>[4,10-13]</sup>

**Table 1:** Sensitivity, specificity, PPV, and NPV of frozen section in diagnosing malignancy are elaborated. Findings in our study are compared with similar other studies

Assessment	Guevaraa <i>et al.</i> <sup>[10]</sup>	Kumar <i>et al.</i> <sup>[4]</sup>	Huber <i>et al.</i> <sup>[12]</sup>	Kahmke <i>et al.</i> <sup>[11]</sup>	Callcut <i>et al.</i> <sup>[13]</sup>	Chen <i>et al.</i> <sup>[9]</sup>	Present study
Types of thyroid lesions evaluated	All	All	All	Bethesda 2,3,4,5	Follicular lesions	Follicular neoplasm	Follicular neoplasm (Bethesda 4)
Sensitivity	78.3	71	32.4	76.9	67	25	56
Specificity	100	100	96.5	67.9	100	100	100
PPV	100	100	75	27.8	100	100	100
NPV	94.8	96	81.3	94.8	96	72.46	83

PPV: Positive predictive value, NPV: Negative predictive value

In the analysis of cases cytologically diagnosed as FN s, Chen *et al.* have illustrated their findings on FS and FH from which we have derived the above parameters. Sensitivity of FS in the category of FN was only 25%.<sup>[9]</sup>

The apparently high sensitivity of FS in other studies is possibly due to inclusion of all types of thyroid lesions as opposed to only FN in our study.<sup>[4,10-12]</sup>

In the present study, of the 18 malignancies, 8 cases (44.45%) were missed on FS. These included four cases of PCFV, FC (three cases), and one case of non-Hodgkin's lymphoma.

In our study, none of the four PCFV was identified on FS. PCFV contains fewer nuclear features of papillary carcinoma which is made even more difficult by cellular distortion and loss of nuclear details caused by freezing.<sup>[4,14-17]</sup>

Frequent encapsulation of PCFV thereby resembling follicular adenoma is another source of error. Intraoperative touch imprints or scrapes which preserve the cellular and nuclear details have shown to enhance diagnostic rate of PCFV.<sup>[4,16-18]</sup>

Some studies suggest that gross examination of the thyroid gland at FS gives more relevant information than the microscopic evaluation. The presence of a sclerotic sometimes calcified nodule or a cystic nodule with recognizable papillary structures if seen is very helpful in arriving at the correct diagnosis.<sup>[4,18]</sup>

In the current study, of the three cases of FC s missed on FS, two were microinvasive and one was widely invasive. Most surgical pathologists believe follicular adenoma cannot be confidently distinguished from microinvasive FC on FS because capsular or vascular invasion cannot be adequately assessed. The assessment of capsular and vascular invasion on FS is limited by sampling error, irregularities of the capsule, distortion and collapse of blood vessels, freezing artifacts, and orientation problems with fresh tissue.<sup>[4,9,14,15,17]</sup>

Capsular invasion is best assessed by gross examination and carcinomas often demonstrate a thicker, more irregular capsule than adenomas.<sup>[19]</sup>

Chen *et al.* recommended that routine FS evaluation should be omitted in surgical management of follicular thyroid lesions as it has minimal diagnostic value rendering no additional information 87% of time prolongs operation time and increases costs.<sup>[9]</sup>

Limitation of our study was the small sample size. Diagnostic accuracy of FS could be further enhanced if we had included intraoperative touch imprints in our study.

## Conclusion

FS is recommended in the intraoperative management of FN. Although FS has low sensitivity, it has high specificity and PPV and can, therefore, guide the extent of surgery in malignant cases, thereby avoiding a second surgery. However, a negative result on FS should be interpreted with caution as it does not rule out malignancy.

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**How to cite this article:** Veda P, Rani RU, Lakkanna S. Role of frozen section in evaluating follicular neoplasms of thyroid. *J Med Radiol Pathol Surg* 2019;6:1-4.