IJSCIA

International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 6 | Issue: 6 | Nov – Dec 2025 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v6i6.1

Is the Frozen Section Still Effective for Identifying Thyroid Lesions? A 6-Year Retrospective Study in a Tertiary Hospital

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ABSTRACT

Background: Thyroid nodules are highly prevalent, with malignancy risk increasing in nodules >4 cm. Intraoperative Frozen Section (FS) is crucial for real-time surgical management. This study evaluated FS diagnostic accuracy and discrepancies in thyroid specimens. ***Method:*** A single-center, retrospective study was conducted using 30 eligible thyroid specimens from Dr. Soetomo General Academic Hospital (2019–2024). Diagnostic performance (accuracy, sensitivity, specificity, PPV, NPV) was calculated, excluding 8 cases with an indeterminate FS diagnosis (follicular neoplasm) from the benign/malignant categorization. ***Result:*** FS achieved a high overall diagnostic accuracy of 95.45%. Specificity and PPV were both 100%, confirming high reliability for positive diagnoses. However, sensitivity was 75% and NPV was 94.74%. A single false-negative case of Papillary Thyroid Carcinoma (PTC) and the high deferral rate for follicular neoplasm (8/30 cases) were the main sources of error. ***Discussion:*** The high specificity (100%) and PPV (100%) confirm that FS is excellent at ruling in malignancies. However, the 25% false-negative rate and the high proportion of deferred diagnoses highlight the FS's major limitations: difficulty in recognizing subtle PTC nuclear features in frozen tissue and the impossibility of assessing capsular or vascular invasion in follicular lesions intraoperatively. These limitations necessitate confirmation by a permanent section in ambiguous cases, restricting FS's role in definitive one-stage surgery for indeterminate nodules. ***Conclusion:*** FS is a highly specific and accurate tool, effectively guiding surgical management. Yet, its use must be cautious for follicular patterned lesions due to the risk of deferred diagnosis and potential for false-negative results.

Keywords: thyroid nodule; frozen section; diagnostic accuracy; follicular neoplasm; papillary thyroid carcinoma.

INTRODUCTION

Thyroid lesions presenting as nodules are a common finding and a primary reason for patients seeking medical attention. The incidence of thyroid nodules has been rising annually. While the malignancy rate in thyroid nodules remains relatively low, generally reported as <5%, this risk increases with the size of the nodule. Specifically, the occurrence of thyroid carcinoma is observed to rise in nodules exceeding 4 cm.[1,2] The clinical prevalence of thyroid nodules is 3–7% in the general population, although the advent of high-resolution ultrasonography (USG) has enhanced the capability to detect clinically occult nodules. USG can now identify thyroid nodules in 50–60% of adult patients.[3,4] Accurate diagnosis and triage of suspicious thyroid nodules are crucial, as only about 5% of USG-detected nodules are confirmed as malignant. Intraoperative Frozen Section (FS) is a valuable tool, particularly in unilateral lobectomy and for patients presenting with suspicious thyroid nodules. The ability to diagnose thyroid malignancy intraoperatively guides appropriate one-stage surgical management. The primary goal of FS is to assist the surgeon in determining if a thyroid lesion is benign or malignant in real-time, thereby informing the extent of the necessary operation. However, inconsistencies exist; FS for thyroid specimens has been reported to have a Positive Predictive Value (PPV) of 76.1% and a Negative Predictive Value (NPV) of 85.7%. A significant number of discrepancies between FS results and postoperative histopathology have been noted, potentially leading to unnecessary thyroidectomy.[4] In fact, the thyroid gland is the fifth most frequent anatomical site experiencing diagnostic discordance between FS and paraffin coupe examination.[5] Given these limitations, the current study aims to evaluate the diagnostic accuracy between intraoperative frozen section (vries coupe) and postoperative histopathology (paraffin coupe) on thyroid tissue specimens, along with investigating the underlying reasons contributing to these observed discrepancies.

METHODS

This study was a single-center, analytical observational investigation employing a retrospective design, utilizing secondary data from the Anatomic Pathology Laboratory of Dr. Soetomo General Academic Hospital, Surabaya, spanning the period of 2019–2024.

The study population comprised thyroid specimens that had undergone both intraoperative frozen section (FS) (vries coupe) and subsequent post-operative histopathology (paraffin section), with full demographic and pathological data available for both reports. Post-operative histopathology was considered the gold standard for definitive diagnosis. Diagnostic performance of the FS was assessed by calculating accuracy, sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV). Importantly, for the calculation of these metrics, cases with an intraoperative FS diagnosis of 'uncertain' or 'indeterminate' (specifically follicular neoplasm), which required definitive classification based on capsular or vascular invasion in the final paraffin section, were excluded from the 2×2 contingency table analysis for benign/malignant categorization. Data collection involved the retrieval of specimen records and a review of corresponding slides, followed by descriptive statistical analysis to report the distribution of diagnoses and the calculated performance metrics.

RESULTS

A total of 39 FS examinations were conducted at the Anatomic Pathology Laboratory of Dr. Soetomo General Academic Hospital, Surabaya, during the period of 2019–2024. Of these, 30 samples met the inclusion criteria for this study. The patient distribution showed a female predominance, with 26 female patients and 4 male patients, resulting in a male-to-female ratio of 1:6.5. The youngest patient in this study was 8 years old, and the oldest was 74 years old. The highest frequency of cases was observed in the 41-50 years age group, with a mean age of 43.17 years.

Lobectomy was the most common type of surgical procedure performed, accounting for 16 patients, followed by isthmulobectomy in 11 patients, and total thyroidectomy in 3 patients. Adenomatous goiter (18 patients) was the most common diagnosis from the FS study. Follicular neoplasm (8 patients), follicular adenoma (1 patient), papillary thyroid cancer (1 patient), poorly differentiated carcinoma (1 patient), and non-Hodgkin lymphoma (1 patient) were the next most common diagnoses.

Adenomatous goiter was the most common diagnosis, with 19 patients, according to the corresponding final diagnosis from the post-frozen section histopathology (paraffin section). Follicular adenoma came in second with 7 patients, papillary thyroid carcinoma with 2, anaplastic thyroid carcinoma with 1, and non-Hodgkin lymphoma with 1.

The calculation of accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) was performed on benign and malignant cases, excluding 8 cases with an uncertain result on FS examination (specifically, follicular neoplasm).

TABLE 1: Patient Characteristics.

Variable		N (%)
Gender	Male	4 (13.33)
	Female	26 (86.67)
Age (Years)	≤10	1 (3.33)
	11-20	1 (3.33)
	21-30	5 (16.67)
	31-40	5 (16.67)
	41-50	8 (26.67)
	51-60	6 (13.33)
	61-70	3 (10)
	>70	1 (3.33)
Type of Surgery	Total Thyroidectomy	3 (10)
	Isthmulobectomy	11 (36.67)
	Lobectomy	16 (53.33)
Frozen Section Diagnosis	Adenomatous Goiter	18 (60)
	Follicular Neoplasm	8 (26.66)
	Follicular Adenoma	1 (3.33)
	Papillary Thyroid Carcinoma	1 (3.33)
	Poorly Differentiated Carcinoma	1 (3.33)
	Non-Hodgkin Lymphoma	1 (3.33)
Postoperative Histopathology Diagnosis	Adenomatous Goiter	19 (63.3)
	Follicular Adenoma	7 (23.33)
	Papillary Thyroid Carcinoma	2 (6.67)
	Anaplastic Thyroid Carcinoma	1 (3.33)
	Non-Hodgkin Lymphoma	1 (3.33)
Total		30

The diagnostic accuracy of the FS examination compared to the paraffin section histopathology (gold standard) was 95.45%. The sensitivity was 75%, the specificity was 100%, the positive predictive value (PPV) was 100%, and the negative predictive value (NPV) was 94.74%.

A case initially diagnosed as adenomatous goiter on FS (a false negative result) demonstrated less distinctive papillary structures (short papilla) and inconspicuous fibrovascular stalks at 40× magnification (Figure 1A). At 400× magnification, the characteristic nuclear features of papillary thyroid carcinoma (PTC) were not evident (Figure 1B). Subsequent post-operative histopathology (paraffin section) of the same specimen, however, revealed a mass composed of characteristic papillary structures at 40× magnification (Figure 1C) and distinct PTC nuclear features, including enlarged and overlapping nuclei, irregular nuclear membranes with pseudoinclusions, and characteristic chromatin described as glassy nuclei (Figure 1D). The final diagnosis for this case was papillary thyroid carcinoma.

The eight cases diagnosed as follicular neoplasm on FS were categorized as indeterminate and excluded from the accuracy calculation for benign/malignant lesions. Upon paraffin section examination, 7 cases of follicular neoplasm were finalized as follicular adenoma, and 1 case was diagnosed as an infiltrative follicular variant of papillary thyroid carcinoma. Follicular neoplasm is considered an indeterminate category because it encompasses follicular adenoma, follicular carcinoma, and infiltrative follicular variant of papillary thyroid carcinoma, which cannot be reliably distinguished based on a frozen section.

One example of a case that showed concordance between FS and post-operative histopathology (paraffin section) was a case of papillary thyroid carcinoma, which exhibited similar complex papillary structures and typical PTC nuclear characteristics in both preparations: nuclear enlargement and overlap, irregular nuclear membranes with pseudoinclusions and nuclear grooves, and chromatin margination (Figure 3).

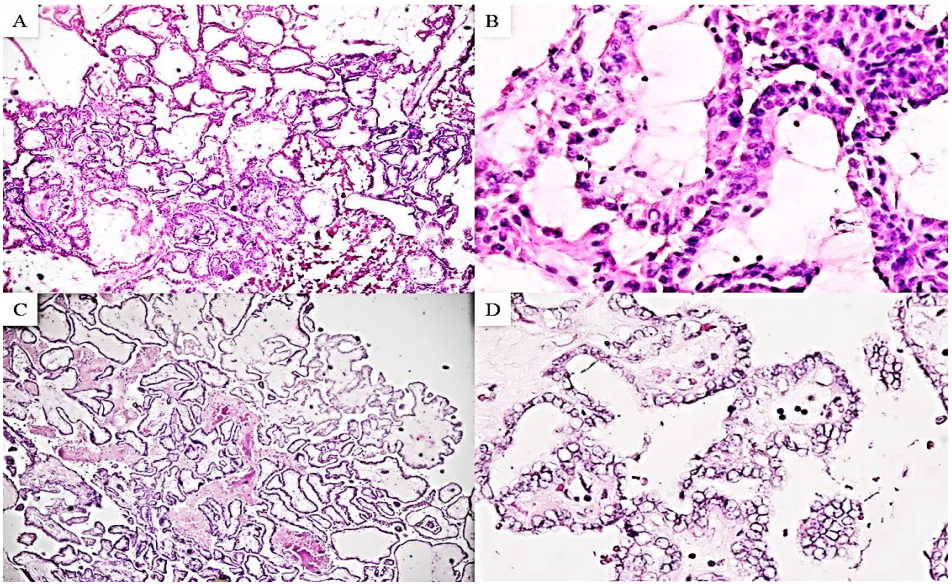

FIGURE 1: A comparison is made between the microscopic features of FS and the post-operative histology (paraffin section). FS was examined and found to have an Adenomatous goiter (A and B). Histopathology analysis revealed Classic PTC (C and D).

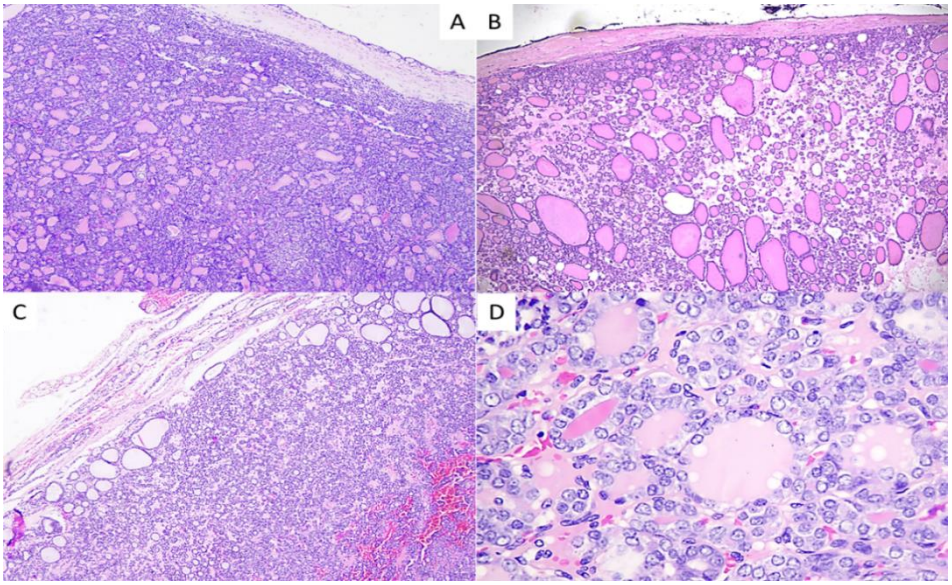

FIGURE 2: A comparison is made between the microscopic characteristics of follicular neoplasm on FS frozen section and post-operative histology (paraffin section). On FS (A), the thyroid nodule was identified as a follicular neoplasm, and and paraffin section (B) showed a follicular adenoma, respectively. Another thyroid nodule that was identified as a follicular neoplasm on FS (C) revealed an infiltrative follicular variant of papillary thyroid carcinoma (D).

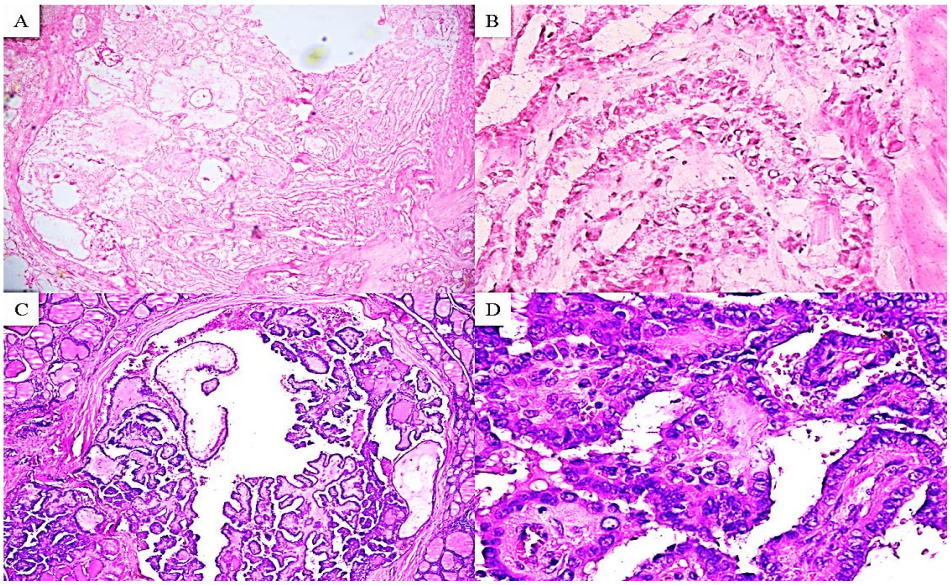

FIGURE 3: Microscopic features of Classic PTC. A and B: on FS examination (40× and 400×). C and D: histopathology (40× and 400×).

DISCUSSION

Frozen section (FS) has long been utilized as a rapid intraoperative diagnostic tool for evaluating thyroid lesions during surgery. The primary goal of FS is to assist the surgeon in determining whether a thyroid lesion is benign or malignant, allowing for real-time decisions regarding the extent of the operation, guiding potential lymph node dissection in cases of suspected malignancy, and potentially avoiding reoperation. However, technical and interpretive limitations remain a subject of debate. Post-operative histopathology (paraffin section) remains the gold standard for diagnosis, as it permits a comprehensive evaluation of the entire tumor structure, including the capsule. Consequently, FS functions more as an intraoperative aid than as a definitive method for establishing thyroid diagnosis.[5]

The present study yielded a high diagnostic accuracy of 95.45% for frozen section compared to paraffin section. The high specificity (100% and PPV of 100%) observed in our findings aligns with other studies, indicating that when an FS suggests malignancy, the diagnosis is highly reliable. Conversely, the sensitivity of 75% and NPV of 94.74% reflect a tendency toward underdiagnosis of malignancy, a pattern also reported in the literature. This lower sensitivity is often observed in cases of follicular neoplasm, where the determination of malignancy hinges on the presence of invasion (capsular or vascular). Such conditions are often difficult to assess rapidly via FS, leading to "deferred" or uncertain diagnoses.

Our findings illustrate this challenge: of the cases diagnosed as follicular neoplasm on frozen section, 7 cases were finalized as follicular adenoma, and 1 case as infiltrative follicular variant of papillary thyroid carcinoma on paraffin section. In the seven benign cases, the final diagnosis was confirmed by the absence of capsular or angioinvasion on comprehensive histopathological review.

A key discordant result was a case of adenomatous goiter on frozen section that was confirmed as papillary thyroid carcinoma (PTC) on paraffin section, and one follicular neoplasm case that became an infiltrative follicular variant of papillary thyroid carcinoma on final section. This highlights the difficulty in identifying the characteristic nuclear features of PTC on frozen section specimens. While architectural patterns, such as complex papillae with fibrovascular stalks, can aid in the diagnosis of PTC, the subtle nuclear changes are often obscured. This is consistent with the observation by Anton & Wheeler (2005) that the characteristic "clear nuclei" seen in formalin-fixed paraffin sections are often not visible in alcohol-fixed or frozen section slides.[5]

The poor sensitivity of intraoperative frozen section for infiltrative follicular variant of papillary thyroid carcinoma is attributed to the loss of nuclear morphological detail due to tissue freezing and the frequent encapsulation of the tumor, which mimics a follicular adenoma.6 Lin (2009) suggested that touch imprint preparations from the cut surface of the nodule could enhance diagnostic capability by preserving cellular and nuclear details, an approach that has been shown to correctly identify more cases of this variant than routine FS.[6]

The debate surrounding the utility of FS is ongoing. Mallick et al. (2019) proposed that FS results influence the surgical plan in only 2.1% of cases, suggesting a need for selective use.[7] The limited sensitivity of FS (25%) for Bethesda Category III and

IV (indeterminate) lesions on pre-operative fine needle aspiration biopsy (FNAB), despite a 100% specificity, further indicate that FS frequently fails to detect malignancy in the very group that requires intraoperative clarification.3,4 Conversely, FS shows high accuracy (≈97%) for lesions with clearer FNAB diagnoses (Bethesda II, V, and VI). These studies reinforce the notion that FS is reliable in ruling out malignancy (high specificity) but is not sensitive enough to detect all cancers, particularly in indeterminate cases.

Discrepancies between FS and paraffin section, which were reported to be up to 9.8% by Adhikari et al. (2018), often stem from sampling and interpretation errors. The inherent limitation of FS is the inability to fully assess the tumor capsule, leading to diagnostic errors that are only rectified upon comprehensive review of the paraffin section.8 This underscores the critical role of high-quality technique and the experience of the pathologist in FS success. Furthermore, the reliability of FS is particularly challenged in large thyroid nodules (>4 cm), where up to 38.8% of FNAB-benign cases may conceal malignancy, typically the follicular variant of papillary thyroid carcinoma and follicular carcinoma.[2]

Our practice, consistent with the literature, attempts to mitigate the risk of misdiagnosis in follicular lesions by taking a higher number of tissue sections (2–4 initial coupes on average) to maximize the chance of assessing the capsule. However, as Anton & Wheeler (2005) note, definitively assessing angioinvasion and capsular penetration requires a full evaluation of the tumor capsule, which is impractical during the time constraints of intraoperative consultation. The freezing process itself distorts and destroys blood vessels, making angioinvasion difficult to ascertain. Therefore, deferring the definitive diagnosis for follicular lesions to post-operative histopathology remains the most appropriate approach, making lobectomy a sufficient initial surgical procedure in these ambiguous cases.[5]

In summary, while it is a valuable and accurate procedure for guiding patient management by reliably identifying clear malignancies intraoperatively, its effectiveness is limited in the indeterminate follicular neoplasm group. The procedure cannot replace the definitive role of post-operative histopathology (paraffin section), which offers superior detail and allows for the critical assessment of invasion required to distinguish between benign and malignant follicular tumors.3,4,8 Moving forward, the integration of digital technology and deep learning has the potential to enhance FS accuracy, even for microcarcinomas, suggesting a continuing, albeit evolving, role for frozen section in thyroid surgery.[9]

CONCLUSION

In thyroid specimens examined at Dr. Soetomo General Academic Hospital from 2019 to 2024, the intra-operative frozen section (FS) analysis demonstrated a high diagnostic reliability compared to the final paraffin section histopathology. Out of 30 eligible cases, and excluding 8 indeterminate follicular neoplasm cases, the frozen section technique achieved an overall accuracy of 95.45%, a high specificity of 100%, and a Positive Predictive Value (PPV) of 100%. Although the sensitivity was 75% and the Negative Predictive Value (NPV) was 94.74%, suggesting a low risk of over-diagnosis of malignancy, the main diagnostic pitfall was the potential for false-negative results, as seen in a case of papillary thyroid carcinoma initially missed on FS due to subtle nuclear and papillary changes. Furthermore, the high rate of deferred diagnosis for follicular neoplasm (8/30 cases) confirms the recognized limitation of frozen section in accurately classifying follicular lesions, which necessitates confirmation by permanent section to distinguish between benign follicular adenoma and malignant follicular carcinoma or follicular variant of papillary thyroid carcinoma. In conclusion, frozen section is a highly specific and accurate tool for intra-operative diagnosis of most thyroid lesions, effectively guiding surgical management, but should be used cautiously for follicular-patterned lesions.

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