

Frozen Section Analysis in Surgical Pathology: A Comprehensive Review

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Abstract

Background: Frozen section (FS) analysis is an indispensable intraoperative diagnostic tool in surgical pathology, enabling real-time histological assessment to guide surgical decision-making. Despite its widespread use, its diagnostic accuracy varies, and a comprehensive synthesis of its indications, limitations, and organ-specific performance is warranted.

Objective: This comprehensive review aims to evaluate the technical principles, clinical applications, diagnostic accuracy, and inherent limitations of intraoperative frozen section consultation across various surgical specialties.

Methods: A comprehensive narrative review was conducted, recognizing the broad and multidisciplinary scope of the topic. A systematic search of PubMed, Scopus, and Web of Science databases was performed for English-language articles up to October 2025. Keywords included "frozen section," "intraoperative consultation," "surgical pathology," "diagnostic accuracy," and specific organ systems. Studies reporting on FS techniques, accuracy metrics, or diagnostic challenges were included. Given the heterogeneity of study designs and the aim to provide a clinically oriented synthesis, a narrative rather than systematic meta-analytic approach was chosen.

Results: FS demonstrates a variable but generally high diagnostic accuracy, with reported concordance rates with final paraffin histopathology ranging from 84% to 100% (average ~93%). Its utility is paramount for assessing surgical margins, evaluating sentinel lymph nodes, and diagnosing unexpected lesions. However, significant limitations exist, including tissue freezing artifacts, sampling constraints, and diagnostic challenges in specific contexts such as low-grade tumors, post-neoadjuvant therapy specimens, and certain anatomical sites (e.g., central nervous system, ovary, pancreas). Organ-specific analyses reveal distinct patterns of utility and difficulty.

Conclusion: Intraoperative frozen section consultation remains a critical, time-sensitive tool that significantly impacts surgical management. Its optimal use requires technical proficiency, a clear understanding of its capabilities and constraints, and robust interdisciplinary communication. Pathologists and surgeons must recognize it as a preliminary modality, with definitive diagnosis relying on comprehensive paraffin section analysis.

Keywords: Frozen section, Intraoperative consultation, Surgical pathology, Cryostat, Diagnostic accuracy, Margin assessment.

1. Introduction

The frozen section (FS) technique represents a cornerstone of modern surgical pathology, providing a vital bridge between the pathology laboratory and the operating theater. Developed in the late 19th century to obtain rapid histological diagnoses, the

fundamental principle remains unchanged: the rapid freezing of fresh tissue to achieve sufficient hardness for thin sectioning, followed by staining and immediate microscopic evaluation [1]. This process allows pathologists to deliver provisional diagnoses within minutes, directly influencing intraoperative decision-

making, particularly in oncological surgery.

The clinical utility of FS is multifaceted. It is primarily employed to determine the nature of intraoperatively encountered lesions, assess the completeness of tumor excision through surgical margin evaluation, confirm tissue identity and adequacy, and guide the extent of surgical resection. Its value is most pronounced in cancer surgery, where immediate histological information can determine whether additional tissue should be removed, whether lymph node dissection is warranted, or whether the surgical approach should be altered entirely.

However, FS is a diagnostic modality with inherent limitations. The freezing process introduces artifacts that can obscure cytological and architectural detail. The examination is limited to a small sample of the submitted specimen, creating potential for sampling error. Furthermore, the intraoperative timeframe precludes the use of most ancillary studies, such as immunohistochemistry or molecular testing, which are often required for definitive diagnosis in challenging cases. The diagnostic accuracy of FS is therefore variable, influenced by the organ system, tissue type, pathologist expertise, and the specific clinical question.

Despite these limitations, FS remains an essential tool. This comprehensive narrative review aims to synthesize the current evidence on FS analysis. We will examine its technical evolution, detail its clinical applications across surgical specialties, critically analyze its diagnostic performance and limitations, and provide evidence-based recommendations for its optimal use in contemporary practice. Through this analysis, we seek to provide a valuable resource for pathologists and surgeons that underscores the importance of judicious application, technical excellence, and collaborative communication in maximizing the clinical benefit of intraoperative consultation.

2. Methods

This article constitutes a comprehensive narrative review, designed to synthesize and critically evaluate the broad landscape of frozen section practice across surgical specialties. While systematic reviews and meta-analyses are valuable for answering focused questions, the scope of this review—encompassing technical evolution, organ-specific performance, limitations, and future directions—lends itself to a narrative synthesis that integrates diverse evidence and provides practical insights for clinicians.

A systematic search strategy was employed to identify relevant literature. Electronic databases, including PubMed/MEDLINE, Scopus, and Web of Science, were queried for articles published from inception to October 2025. The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and keywords: ("frozen sections"[MeSH] OR "intraoperative period"[MeSH] OR "intraoperative consultation") AND ("pathology, surgical"[MeSH] OR "diagnostic accuracy" OR "sensitivity and specificity") combined with organ-specific terms (e.g., "breast," "central nervous system," "ovary," "sentinel lymph node"). The reference lists of identified key articles were also

manually reviewed for additional relevant sources.

The inclusion criteria comprised: (1) original research articles, reviews, and meta-analyses published in English; (2) studies reporting on the technique, diagnostic accuracy, clinical utility, or limitations of FS; (3) studies involving human tissues. The exclusion criteria included: (1) non-English publications; (2) case reports with fewer than 5 cases; (3) studies focused exclusively on cytological techniques without FS correlation.

The identified literature was screened by title and abstract, with full-text review of potentially relevant articles. Data concerning study design, sample size, organ system, FS indication, concordance rates with final diagnosis, and reported limitations were extracted and synthesized narratively. Given the substantial heterogeneity in study designs, populations, and reported outcomes across the included literature, a formal meta-analysis was deemed inappropriate. The narrative synthesis is structured to provide a critical, clinically relevant overview of technical aspects, organ-specific performance, overarching limitations, and emerging trends.

3. Results

3.1 Technical Aspects and Equipment Evolution

The methodology for FS has evolved significantly from its origins. The first freezing microtome, invented in 1881, was large and relied on ice-salt mixtures. The introduction of ether spray in 1883 reduced freezing times to seconds. Modern portable freezing microtomes are compact devices (approx. 25 x 21 x 10.5 cm) that use carbon dioxide (CO₂) spray or cylinders to freeze tissue mounted on a small metal platform within 1-3 minutes (Figure 1). A thin layer of optimal cutting temperature (OCT) compound is used for adhesion. While portable and cost-effective, these microtomes generally produce sections of inferior quality compared to cryostats, especially for delicate tissues.



Figure 1: Portable freezing microtome. The white arrow indicates the freezing platform where the tissue is mounted.

The cryostat, a temperature-controlled cabinet housing a microtome, represents the current standard in most pathology departments. Maintaining an internal temperature of -20°C to -30°C, it allows for consistent, high-quality sectioning (typically 4-10 µm thick)

and simultaneous processing of multiple fragments with a faster freezing time (approx. 1 minute) (Figures 2 & 3). Its controlled environment minimizes frost and temperature fluctuation artifacts,

enabling finer cuts and more reliable diagnoses, particularly for complex cases.



Figure 2: Cryostat. Standard laboratory cryostat for frozen section processing.



Figure 3: Cryostat with electronic monitor. Modern cryostat featuring digital temperature control and display.

The FS procedure begins with the immediate transport of unfixed, correctly labeled tissue to the pathology laboratory. After gross examination and selection of representative areas, the tissue is mounted, frozen, sectioned, rapidly stained (commonly with

toluidine blue or rapid H&E variants), and coverslipped for microscopic examination (Figure 4). The entire process, from specimen receipt to verbal report, typically targets 15-20 minutes, though complex cases may require longer.

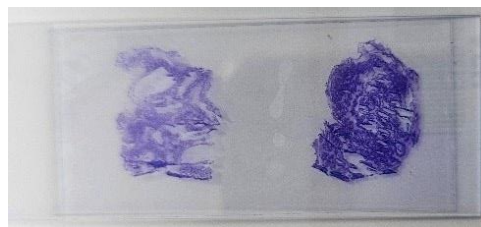


Figure 4: Frozen section slide. Two histological sections stained with toluidine blue, ready for microscopic evaluation.

Complementary cytological techniques, such as touch imprint, scraping, or squash preparation, are valuable adjuncts, particularly for lymph nodes, small biopsies, or when tissue preservation for permanent sections is paramount [27-29]. These methods can provide excellent cellular detail and have reported sensitivity and specificity comparable to FS for specific applications.

3.2 Overall Diagnostic Performance

Large multi-institutional studies report the overall diagnostic accuracy of FS, defined as concordance with the final paraffin-embedded diagnosis, to be between 84% and 100%, with an average of approximately 93.3% [2, 4, 17]. This high aggregate accuracy underscores its reliability as an intraoperative tool. However, discordance rates are significant and merit analysis.

Discordant diagnoses are categorized as deferred (a definitive diagnosis cannot be rendered intraoperatively), false-negative, or false-positive. The reported incidence of FS error varies from 4.1% to 7.5% [16, 18]. A detailed analysis of discrepancies reveals that

sampling error is the most frequent cause (approximately 51.2%), wherein the frozen section sample is not representative of the lesion present in the entirety of the specimen [5, 6]. Interpretive error accounts for approximately 44.2% of discrepancies, reflecting the diagnostic challenges posed by freezing artifacts and morphological mimics. Technical sectioning issues contribute minimally (2.3%) [5, 6].

The clinical impact of false-negative diagnoses (average 67.8% of discordances) is potentially severe, as it may lead to incomplete resection or under-staging [4]. False-positive rates are lower but can result in unnecessarily extensive surgery.

3.3 Organ-Specific Applications and Performance

The utility and diagnostic challenge of FS vary considerably across different organ systems.

Breast Pathology: FS is extensively used for margin assessment during breast-conserving surgery. Reported performance metrics show sensitivity of 75-85%, specificity of 82-95%, and a very high

negative predictive value (98-99%) [10, 11]. This high NPV is clinically valuable, as a negative FS margin strongly predicts final margin negativity. However, the positive predictive value can be modest (21-68%), reflecting sampling limitations. FS for sentinel

lymph node evaluation shows high sensitivity and specificity for macrometastases (>2mm) but poor sensitivity for micrometastases and isolated tumor cells [19, 32]. Table 1 summarizes key performance data.

Application / Organ	Reported Sensitivity	Reported Specificity	Key Challenges	Primary References
Breast - Margins	75-85%	82-95%	Sampling error, multifocality	[10-12]
Breast - Sentinel Node	70-90% (Macro)	~100%	Micrometastases, lobular carcinoma	[19, 32]
Central Nervous System	Varies by tumor type	Varies by tumor type	Severe artifacts, glial vs. mesenchymal tissue	[7, 8]
Ovary	Varies widely	Varies widely	Mucinous/borderline tumors, metastatic vs. primary	[22, 23]
Salivary Glands	98.4% (Benign vs. Malignant)	87% (Benign vs. Malignant)	Specific tumor typing	[26]
Thyroid	High for classic PTC	High for classic PTC	Follicular-patterned lesions	[33]

Table 1: Selected Frozen Section Performance Metrics by Application

Central Nervous System (CNS): FS of neurosurgical specimens is notoriously challenging due to severe freezing artifacts, particularly in neuroglial tissue [7]. Its primary role is often to distinguish neoplastic from non-neoplastic tissue, differentiate high-grade from low-grade gliomas, or confirm lesional sampling, rather than provide precise tumor classification.

Gynecologic Pathology: Ovarian tumors present one of the greatest diagnostic challenges, with discordance rates up to 70% reported, especially for mucinous, borderline, and metastatic tumors [22, 23]. FS is crucial for determining whether to proceed with comprehensive staging surgery. In endometrial cancer, FS can assess myometrial invasion depth (accuracy 75-90%) to guide lymphadenectomy decisions [9].

Head and Neck Pathology: FS for salivary gland tumors shows excellent accuracy (97.1%) in distinguishing benign from malignant lesions, though precise classification is often deferred [26]. For thyroid nodules, FS reliably diagnoses classic papillary carcinoma but is less accurate for follicular-patterned lesions where invasion must be assessed [33].

Thoracic, Hepatopancreatobiliary, and Gastrointestinal Pathology: FS of pulmonary nodules is highly accurate for lesions >1 cm but less so for smaller nodules [3]. In pancreatic surgery, distinguishing well-differentiated adenocarcinoma from chronic pancreatitis remains a classic diagnostic pitfall [25]. For appendiceal mucinous lesions, FS aids in distinguishing low-grade from high-grade neoplasms, impacting surgical approach [15, 21].

3.4 Limitations and Specific Challenges

Beyond organ-specific issues, several overarching limitations

define the appropriate use of FS:

- **Contraindications:** Liquid specimens (e.g., effusions) and bony tissues are not suitable for standard FS.
- **Artifacts:** Ice crystal formation, nuclear distortion, and tissue fragmentation can mimic or obscure pathology.
- **Specimen Depletion:** Freezing consumes tissue, which can be critical for small biopsies needed for definitive diagnosis and ancillary studies.
- **Interpretive Pitfalls:** Common challenges include distinguishing reactive atypia from carcinoma, low-grade lymphoma from reactive hyperplasia, and desmoplasia from sarcoma.
- **Post-Treatment Changes:** Specimens after neoadjuvant therapy often show fibrosis and inflammatory infiltration that can mask residual tumor cells, increasing error rates [20].

4. Discussion

4.1 Factors Affecting Diagnostic Accuracy and Error Mitigation

The diagnostic accuracy of FS is not intrinsic to the technique but is influenced by a complex interplay of factors. Recognizing and managing these factors is key to minimizing errors.

Pre-Analytical Factors: The foundation of an accurate FS is laid before the tissue reaches the microtome. Specimen handling is critical; tissues must be fresh, unfixed, and promptly transported. Clinical information is indispensable; the pathologist must know the specific surgical question, patient history, and relevant imaging findings to contextualize the microscopic findings. Sampling by the pathologist is perhaps the most crucial step; selecting the wrong area or an unrepresentative fragment is the leading cause of error.

Analytical Factors: Pathologist expertise is paramount. Experienced pathologists are familiar with FS artifacts and the morphological "look" of various tissues and tumors in frozen preparations. Technical quality matters; thick, fragmented, or poorly stained sections compromise interpretation. The use of adjunctive cytology can provide additional cellular detail and preserve tissue.

Post-Analytical Factors: Communication between pathologist and surgeon must be clear, timely, and bidirectional. The pathologist should convey not only a diagnosis but also the degree of confidence and any relevant limitations. Crucially, continuity of care—having the same pathologist review both the FS and the subsequent permanent sections—is considered a best practice. It allows for direct correlation, feedback, and learning, reducing future errors [18].

4.2 Clinical Implications and Strategic Use

FS is a powerful tool that alters surgical pathways. Its judicious use requires strategic thinking:

Clear Indications: FS should be requested for questions where the answer will immediately change the surgical procedure (e.g., extend margins, perform lymphadenectomy, confirm lesional tissue).

Managing Expectations: Surgeons must understand that FS is a preliminary consultation with inherent limitations. It is not a shortcut to a final diagnosis, and deferral is sometimes the most responsible course of action.

Economic and Logistical Considerations: The FS service requires significant infrastructure (equipment, skilled personnel, 24/7 availability) and has cost implications. Its use should be justified by a clear clinical benefit.

5. Recommendations for Practice

Based on the synthesized evidence, we propose the following recommendations:

- 1. Establish Institutional Protocols:** Develop clear guidelines for FS requests, specimen handling, and communication pathways between surgery and pathology.
- 2. Invest in Training:** Ensure pathologists and histotechnologists receive dedicated training in FS techniques and interpretation.
- 3. Prioritize Communication:** Implement structured methods (e.g., standardized requisition forms, direct phone calls) to ensure complete clinical information exchange.
- 4. Embrace a Team-Based Approach:** Foster a collaborative environment where pathologists are integrated into surgical decision-making discussions when appropriate.
- 5. Implement Quality Assurance:** Regularly review discordant cases in a non-punitive, educational forum to identify systemic issues and opportunities for improvement.

6. Future Directions

The field of intraoperative diagnosis continues to evolve. Digital pathology and telepathology, including the use of whole slide imaging (WSI) for frozen sections, enable remote consultation, expert second opinions, and telementoring, which is particularly valuable for rare cases or institutions without subspecialty expertise [34]. Artificial intelligence (AI) is emerging as a transformative tool; machine learning algorithms are being developed to assist in the interpretation of frozen sections, showing potential to augment pathologist accuracy, reduce inter-observer variability, and expedite diagnosis, especially in challenging scenarios like low-grade tumors or post-neoadjuvant therapy specimens [35].

Beyond digital tools, advanced imaging techniques such as confocal microscopy or optical coherence tomography are being investigated for real-time, non-destructive margin assessment. Furthermore, the development of rapid immunohistochemistry and molecular techniques adaptable to the intraoperative timeframe could revolutionize FS by allowing for precise subtyping of tumors during surgery.

7. Conclusion

Frozen section analysis remains an essential, high-stakes component of modern surgical pathology. This review confirms its high aggregate diagnostic accuracy but also highlights the significant variability across organ systems and the numerous factors that influence its performance. Its greatest value is realized not as a standalone test, but as a node in a well-orchestrated clinical process. The path to optimal patient outcomes is paved by technical excellence, deep knowledge of limitations, and, above all, seamless collaboration between pathologist and surgeon. As technologies advance, the core principles of judicious indication, expert execution, and clear communication will continue to define the safe and effective use of this indispensable intraoperative tool.

Declarations

Ethical Approval: This narrative review did not involve direct experimentation on human or animal subjects. The use of illustrative images was approved by the Research Ethics Committee of Fluminense Federal University (CAAE: 43900620.8.0000.5243), with informed patient consent obtained. This research standard is defined in Resolution National Health Commission (CNS) n° 466 of 2012 and in Operational Standard n° 001 of 2013 of the CNS. Informed Consent: For any directly contributed case illustrations, informed consent was obtained from all subjects.

Data Availability Statement: No original datasets were generated for this narrative review. All discussed data are available from the cited references.

Credit Authorship Contribution Statement:

- **Angela S. Rezende & Teresa C.F. Gutman:** Conceptualization, Methodology, Investigation, Writing – Original Draft.
- **Karin S.G. Cunha:** Investigation, Visualization, Writing –

Review & Editing.

- **Fabiana R. Rodrigues:** Validation, Supervision, Writing – Review & Editing.
- **Vânia G.S. Lopes:** Supervision, Project administration, Writing – Review & Editing.

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