

Frozen Section: A Review of Accuracy, Trends and Limitations

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Abstract

Frozen section is a procedure wherein a tissue specimen is snap-frozen, sliced by microtome, and stained immediately for rapid diagnosis of probable malignant lesions. This is a relatively crude procedure compared to paraffin-embedded sections, but is effective because it is rapid and gives the surgeon immediate consultation regarding the malignancy of a tissue. With frozen section there is a risk of misdiagnosing malignancy and under-staging or over-staging patients. As it is subject to many limitations in comparison to the block preparation, this review aims to highlight the important concepts regarding frozen section consultation, current trends, accuracy as well as the limitations of this technique.

Keywords: Frozen section, Intra-operative biopsy, Accuracy, Limitations

Introduction

Tissue specimens are usually obtained by doing a biopsy or a surgery and undergo a detailed process including block preparation, fixation, staining, etc., before being assessed by the pathologist. The whole process takes at least 24 to 48 hours. However, sometimes surgeons need histopathological opinion intra-operatively to help in further decision making during the surgery. In such cases, frozen section (FS) biopsy is performed. Though the process of sampling is similar, the processing protocol is designed to reduce the time taken for pathologists' opinion to within a few minutes. It may be considered to be one of the most important procedures performed by a pathologist during her/his practice as it immensely influences the surgical decision and outcome.

Both the pathologist and the operating surgeon should also be aware of the limitations of FS considering the impact on patients' outcome. Hence to decrease the chances of errors, it is imperative for the surgeon to make a prior appointment for FS.

Frozen section is a noteworthy point of intersection between pathologists and surgeons. It is regarded as the most decisive, but not exclusive, form of intra-operative discourse. Its capacity in tissue triage, diagnosis, and intra-operative management should not be misconstrued as a shortcut to an ultimate diagnosis.

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History

Concurrent with its contrivance was the notion of a rapid intra-operative diagnosis, which was first attempted at The Johns Hopkins Hospital more than 100 years ago on a breast biopsy.¹ De Riemer in 1818 made the pioneering effort of using FS technique for histopathological diagnosis. It took two decades for this newly discovered technique to gain popularity, but by the 1920s the use of FS as an intraoperative guide for the surgeon was deemed crucial.² The technique has changed over the years. Now, there are cryostats capable of freezing the specimen rapidly, built-in microtomes which can perform sectioning at 5 µm or less, superior stains, and enhanced light microscope optics. The technical breakthroughs and the variations of implementation among today's institutions notwithstanding, the principles of the preparation and reporting of FS would remain recognizable to our predecessors.

Modern Technique

The development of a cryostat in 1959 has been path-breaking in the advancement of FS technique. The cryostat is a refrigerated container with a rotary microtome. The temperature inside the cryomicrotome is -30°C. The tissue is then processed by freezing it with frozen aerosol sprays followed by putting it onto the cryostat for sectioning. The intra and inter cellular water is frozen resulting in a hard matrix, able to be sliced. The tissue sections are then cut and mounted on glass slides, which are then stained.

The comprehensive effect of the cryomicrotome is twofold. Firstly, it enables sectioning from quick-frozen, unfixed tissue less than 10 µm in thickness and secondly, the use of a modified Haematoxylin & Eosin stain results in permanent preparations.

The whole process to prepare the slides takes about 5–10 min. In addition to this, the pathologist takes time to study the slide and arrive at a diagnosis.³

In a study that included 700 laboratories around the world, it was found that 90% of FS blocks turn-around times were less than 20 min, commencing from the time the pathologists received the FS slides to the time that pathologists returned the diagnoses to surgeons.⁴

Accuracy

Mayo Clinic Rochester, USA, noted a comparative accuracy of 97.7% on reviewing 24,881 cases in a year.⁵ An overall accuracy of 97.56% was reported at Sultanah

Aminah Hospital in Malaysia involving 215 FS specimens over a duration of 4 years.⁶

Other authors report accuracy rate of 98.4% for tumors of the testis,⁷ 91.1% for basal and squamous cell carcinoma of the skin⁸ 99.5% in central nervous lesion⁹ and 97.5% in gynecological malignancy.¹⁰ Ratnavelu et al.¹¹ in their meta-analysis for early stage ovarian tumors and pelvic masses reported an accuracy rate of 99% for malignant tumors and 94% for benign tumors.

However encapsulated follicular carcinoma is an exception. Though, the overall accuracy rate of FS in thyroid lesions is 95%,¹² but the rate can fall to as low as 17% for encapsulated follicular carcinoma.¹³ Consequently, many laboratories are not inclined to perform FS on thyroid lesions, especially while dealing with encapsulated follicular neoplasms. As a matter of fact, many authors do not encourage the routine FS for thyroid lesions.¹⁴ They suggest that FS be performed only when the suspicion of malignancy is remarkable and the FNA cytology results are unsatisfactory or dubious and in cases with unanticipated findings during the course of surgery.

While the accuracy is usually very high, in the head and neck surgeries, margin negativity cannot be ascertained beyond reasonable doubt. A study reported 98.3% accuracy in 81 patients who underwent head and neck surgery with 420 frozen sections carried out. Despite that, 40% (8 of 20) patients with positive margins on the resection specimens, and 100% (15 of 15) with close (<15 mm) margins were not detected by FS analyses.¹⁵ They inferred that patients with early stage lesions and those undergoing resection for recurrence or salvage surgery after radiation therapy failure reaped the maximum potential benefit from FS margins.

In skin tumors such as basal cell carcinoma and squamous cell carcinoma, FS analysis of resection margins proves very helpful for best cosmetic results without compromising with the completeness of resection. An audit of 64 cases of basal cell carcinoma treated from 1988 to 1994 in Hong Kong showed that the rate of complete excision increased after the introduction of FS examination, reaching 89% by 1994.^{3,16}

Trends in Frozen Section

Frozen section has been the forerunner of rapid diagnosis in pathology labs till now, offering valuable information for patient care. Yet, it is believed that advances in other fields like cytopathology has made FS lose some of its appeal.

Since the advent of fine needle aspiration cytology (FNAC) in the latter half of the 20th century, it has been widely accepted for pre-operative diagnosis. Despite its limitations like loss of tissue morphology and architecture, it has replaced the FS biopsy in many surgeries, especially in breast carcinoma.

For minute specimens and sample tissues not capable of being sliced by cryomicrotome, the technique of intra-operative cytology has been a boon, wherein freezing is not required and samples are taken by touch imprint, scraping smear and squash preparation methods.

This has been particularly indicated strongly for CNS, thyroid and lymphoproliferative lesions. Sometimes, this technique forecloses the need for FS entirely.¹⁷ In a study by Wakely PE et al. in reviewing the role of intra-op cytology, it was reported that 49% of 58 cases had the diagnosis furnished by FNAC alone, rendering FNAC as a supplement in FS diagnosis.

In this era of connectivity, pathologist need not be in the hospital to help the surgical team. The use of Internet has given rise to telepathology, whereby surgeons and inexperienced pathologists receive assistance from distant pathology labs where diagnoses are made via digital images. Liang et al.¹⁸ have even devised a low-cost noncommercial method of real-time telepathology for light microscopy that can be used to assist intradepartmental consultation for FS diagnosis. It was reported that the average time duration for telepathology is shorter in comparison to the usual intradepartmental consultation.

Limitations

Limitations of FS need to be considered before requesting for this procedure, to prevent serious mistakes that may be deleterious to the patient's outcome. These shortcomings can be classified into three broad categories, viz., sampling errors, technical problems and interpretative errors.¹⁹

Sampling Errors

1. Poor sampling by the surgeon
2. Poor grossing by the pathologist
3. Difficulty in sampling large tumors to avoid areas of necrosis and edema
4. Incapability of FS to assess capsular or vascular Invasion

Technical Shortcomings

1. Inferior quality section compared to paraffin embedded section. Section is usually thick and air bubbles may easily get into the tissue rendering the visualization of nuclear details cumbersome.
2. Poor staining. Due to fixation by freezing, the quality of staining is affected.

Interpretative Mistakes

1. Heterogeneity of tumors. Tumors like soft tissue sarcoma, hemangiopericytoma-like area of malignant nerve sheath are difficult to diagnose, even on paraffin-embedded samples, let alone FS.
2. Variable tumor differentiation. Tumor grading by FS may not be accurate as the higher grade cells may be missed during sampling, especially for tumors like glioma and chondrosarcoma.
3. Tumors which are difficult to diagnose. It is very tricky to diagnose tumors which mimic normal tissue, like well-differentiated angiosarcoma and signet cells in gastric cancer.
4. Mixed tumors. Tumors with several germ-layer components like teratoma add to the diagnostic predicament of the pathologist.

Conclusion

The pathologist should always be conservative with FS, but accurate. A diagnosis of invasive breast carcinoma should be, in fact, invasive breast carcinoma with no hesitation if that is what the slide shows. Too many surgeons and too many pathologists imply an uncertainty in all frozen sections and take the philosophy of waiting for permanent. If the FS is definite, and many are, a definite diagnosis should be made for the sake of optimum patient care.

Also, suspected cases of infectious diseases such as tuberculosis should best be avoided as handling of the fresh tissue may expose the pathologist and the technician to the infection.

However, though intra-operative dialogue between surgeon and pathologist is very advantageous, one needs to be fully aware of limitations of FS. As long as the above is kept into consideration, the technique of FS is very reliable and serves in the best interest of the patient.

Conflict of Interest: None

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