The Diagnostic Accuracy of Frozen Section Compared to Permanent Section: Single Center Study

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ABSTRACT

Background

Intra-operative consultation by frozen section is a procedure which plays a major role in the surgical management of patients with neoplastic and non neoplastic disease. Therefore it is critical to determine efficiency of frozen section performance periodically.

Objective

To evaluate the accuracy of frozen section tests at different anatomical sites by comparing the frozen section diagnosis with the histological diagnosis.

Method

We conducted a retrospective study in Dhulikhel Hospital, Kathmandu University Hospital, Dhulikhel, and compared the results of 47 cases of frozen section with their final permanent section diagnosis during a period of January 2017 to December 2018.

Result

A total of 47 cases were studied on frozen section while no case was deferred for permanent paraffin section. The indication of frozen section was for presence/typing of neoplasm in 38 cases (80.75%), clearance of margin in eight cases (17%) and diagnosis of Hirschsprung's disease in one case (2.1%). The overall accuracy of frozen section was 91.4% (43 cases) with 8.5% (four cases) discordant with the diagnosis, reported as false negative. None of the cases were reported as false positive. Sensitivity, specificity, positive predictive value and negative predictive value of frozen section in comparison with permanent section (as gold standard) were 85.18%, 100%, 100% and 83.33% respectively.

Conclusion

The accuracy of frozen section diagnosis at our institute was 91.4% which can be interpreted as comparable with most national and international studies. The overall error rate is 8.5% which is higher than previously published studies. Experience and training of the pathologist reduce the error rate.

KEY WORDS

Accuracy, Discordant, Deferred, Frozen section, Intra-operative consultation, Permanent section

INTRODUCTION

Frozen section is a procedure in which the surgeon removes a portion of the tissue mass which is then given to a pathology laboratory where the tissue is frozen in a cryostat machine, cut with a microtome, and then stained with various dyes, after which the tissue is examined under the microscope. The diagnosis made by the pathologist is conveyed to the surgeon.[1] Frozen section technique was first used in John Hopkins Hospital by William H Welch in the year 1891 for intra-operative consultation. It was further developed in Mayo Clinic by Wilson and McCarty in 1905.[2]

Frozen section plays a major role in the surgical management of patients with neoplastic and non neoplastic disease.[3] In this study we reviewed frozen sections performed during a two year period to assess the diagnostic accuracy and determine the rates of discordant results as well as the reason for discrepancy.

METHODS

We retrospectively reviewed the frozen section cases performed in Pathology Laboratory, Dhulikhel Hospital, Kathmandu University Hospital, Dhulikhel, Nepal from 1st January 2017 to 31st December 2018.

Fresh tissue was sent in a clean plastic container without any fixative or saline (to avoid fixation artifacts/degenerative changes) along with requisition form with complete clinical details from the operation theater. Indication of frozen section was recorded. Patient files in the pathology department provided data regarding the frozen section cases. Tissue specimens sent for frozen section were frozen and cut by a cryostat machine:

For frozen section: Gross examination was done, specimen dissected and sections were taken from representative areas. Frozen sectioning was done on SLEE cryostat Mainz. Tissue was kept in the company's tissue embedding medium and placed in object disc inside the cryostat and was frozen. The cryostat was set at a range between -26° C to -38° C depending upon the nature of the tissue. When the medium and tissue were frozen, the chuck was inserted into the clamping lever and was fixed. Clearance angle was set at 12°. Sections were cut at a thickness of 5-8 µ and were immediately fixed in 95% isopropyl alcohol. Rapid hematoxylin and eosin (H&E) staining was performed.

Frozen section diagnosis was made by consensus of at least two pathologists, including one senior pathologist in correlation with appropriate clinical details. In presence of inter observer variation between two pathologist, the section was consulted with the third or even more pathologist. The diagnosis made by the majority is considered the final diagnosis. The final diagnosis was immediately conveyed to the operating surgeon. The turnaround time of entire procedure from receipt of specimen to delivery of report was recorded. The remaining tissues if available were fixed in 10% formalin, grossed and adequate representative sections were taken according to the standard guidelines. The sections were then evaluated in H&E stain.

The frozen section diagnoses were compared to that of the permanent sections, to assess the accuracy of the technique. The frozen section results in comparison to final diagnoses were then categorized into three groups: concordant, discordant and deferred. Diagnosis was considered as concordant if there was agreement and discordant if there was disagreement with permanent section diagnoses. Deferred cases were defined as indeterminate diagnoses at the time of frozen section examination. Deferral rate was not included in the calculation of accuracy. Finally, discordant cases were reviewed and causes of discrepancy were recorded.

RESULTS

In the two year period, 47 frozen section specimens were received. The submitted tissues for frozen section were primarily from gall bladder, gastrointestinal tract, ovary, and oral cavity [Table1].

Table 1. Comparative diagnostic accuracy analysis of frozen with permanent sections

Tissue processed	No. of cases	Concordant	Discordant
Gall bladder/Biliary tract	12	11	1(cystic duct)
GI tract	11	9	2(pyloric mass
Ovary	6	5	1
Oral cavity/ salivary gland	5	5	
Soft tissue	3	3	
Endometrium	2	2	
Mesentry/Omentum	2	2	
Breast	1	1	
Intradural mass	1	1	
Breast	1	1	
Lung	1	1	
Lymph node	1	1	
Skin	1	1	
Total	47	43 (91.4%)	4 (8.51%)

Indications for frozen section were presence/typing of neoplasm including metastatic deposits in 38 (80.75%) cases, clearance of margins in eight (17.0%) cases and to determine presence of ganglion cells in one case of Hirschsprung's disease. Three cases of frozen sections whose permanent sections were not sent were not included in the study.

Total number of concordant and discordant cases were 43(91.4%) and four (8.51%) respectively [Table1]. Four

cases (8.5%) were discordant with false negative diagnoses. None of the cases was reported false positive.

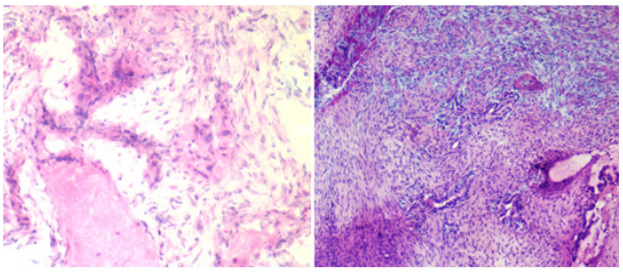

Figure 1. Rapid H&E stained slide of frozen section diagnosed as Positive for malignancy which in Conventional histopathology showed Adenosquamous carcinoma of Gall bladder.

Gall bladder was the commonest tissue received with 17 specimens from 12 cases; all were for presence/typing of neoplasm [fig. 1]. Diagnostic concordance among frozen and conventional histopathology was 91.6 %. Gastrointestinal tract biopsies were sent in 11 cases. Colonic biopsy was the most common followed by rectum and duodenum biopsies [fig. 2, 3]. Diagnostic concordance was seen in nine cases (81.8%) of all GI tract biopsies. Frozen sections from other sites like Oral cavity, Endometrium, Breast, Omentum etc showed 100% diagnostic accuracy [Table 1].

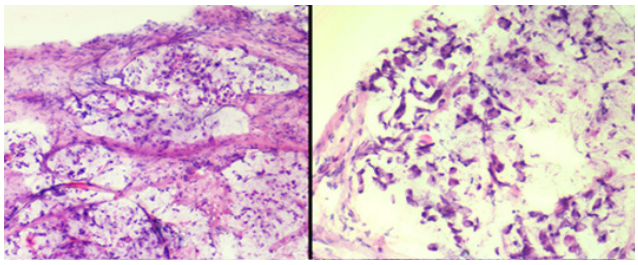

Figure 2. Frozen section slide of Mucinous adenocarcinoma of Colon.

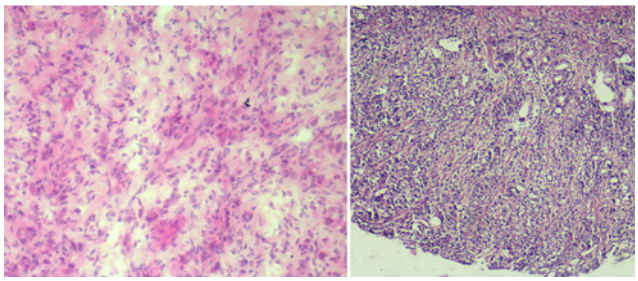

Figure 3. Rapid H&E stained slide of frozen section diagnosed as suspicious of lymphoma which in Conventional histopathology showed poorly differentiated adenocarcinoma of pyloric mass.

The reason for discrepancy was also assessed by reviewing the frozen section slides. Of the four discordant cases, the reason for discrepancy was sampling error in three cases (75%) and misinterpretation in one case (25%). Out of eleven Gastrointestinal tract tissues that were sent for presence/ typing of tissue, frozen section diagnosis showed discordance with paraffin section in two cases which was diagnosed on frozen as Lymphoma and normal colon but final histopathological diagnosis was Poorly differentiated adenocarcinoma and Hirschsprung's disease respectively.

Amongst gall bladder specimens, diagnostic discordance was observed in one case. Part of cystic duct was received. In Frozen section no suspicious or atypical cells were observed. On routine histopathology, remaining tissue from frozen section showed tiny foci suspicious of malignancy however permanent sections of gallbladder showed features consistent with adenocarcinoma. Similarly one of the ovary samples was diagnosed as immature teratoma, whose frozen sections diagnosis was mature cystic teratoma. Those along with the case of Hirschsprung's disease were the cases of sampling error. Additional, limitations observed in these cases was lack of adequate clinical details and technical limitation which resulted mostly from freezing procedure like obscured nuclear details, shrinkage artifacts followed by sectioning.

The diagnosis given at the time of intraoperative consultation was considered as final frozen section diagnosis. Intra observer variability in frozen section diagnosis was not observed when slides were reviewed again during qualitative assessment of morphological features. The frozen section slides are normally preserved for 5 years or more depending upon the availability of space.

Turnaround time was within 20 minutes of receipt of specimen in 40 cases. In 6 cases it was between 20-30 minutes which was due to the large size of the specimen as adequate sampling required thorough inspection of the tissue. In case of Hirschsprung's disease the time exceeded 30 minutes as repeat request was made to process more sections.

Sensitivity, specificity, positive predictive value and negative predictive value of frozen section in comparison with permanent section were 85.18%, 100%, 100% and 83.33% respectively.

DISCUSSION

The most common indication for frozen section in the present study was to determine presence/typing of neoplasm in 38 cases (80.75%) followed by assessment of margins in eight cases (17%) [Table2] which was also seen in other studies of White et al., Roy et al. and Patil et al.[4-6] Presence/typing of neoplasm is important to operating surgeon, as this will decide the type and extent of operative procedure. Also, clearance of margin of a malignant lesion is crucial as tumor recurrence can be aggressive and difficult to treat.[7]

Wendum and Flejou evaluated the accuracy of frozen section in 847 consecutive specimens.[8] Their results showed concordant, discordant and deferred rates of 92.6%, 1.7% and 5.8% respectively that is comparable with our results [Table 3]. Discordant rate in our study is also comparable to other previously published studies reporting discordant rates ranging from 1.4 to 11.8% with a mean of 3.17%.[9]

Table 2. Literature overview of indications of frozen section

Authors	Presence/typing of neoplasm	Margins
Patil et al.[6]	55%	34%
Mishra et al.[10]	84.6%	13.5%
Chbani et al.[12]	85.4%	7.3%
White et al.[13]	41%	26%
Present study	80.7%	17%

Table 3. Literature overview of frozen section diagnostic accuracy

Authors	Study period (years)	No of cases	Concordant (%)	Discordant (%)
Shrestha et al.[2]	5	404	94.6	5.4
Roy et al.[5]	9 month	327	97.6	2.4
Patil et al.[6]	2	100	96.9	3.1
Mishra et al.[10]	2	52	96.2	3.8
Chbani et al.[12]	1	261	95	5
Ahmad et al.[14]	1	342	97.1	2.9
Present study	2	47	91.4	8.51

Concordance and discordance between frozen section and histopathology may differ among lesions and malignant conditions. Mishra et al. showed the concordant rate of 83% in gallbladder, 100% in GI tract tissues, ovarian tissues, and oral cavity tissues.[10] Similarly Patil et al. showed the concordant rates of 100% in GI tract, oral cavity and soft tissue samples, whereas 90.9% concordance in ovarian and 93.75% in Breast tissues.[6] The results are similar to this study.

The reasons for discordant cases were misinterpretation in one (2.12%) and sampling error in three (6.38%) cases. Other previous studies show misinterpretation as the main cause for discrepancy followed by sampling error. However study by Mishra et al. showed equal number of cases of misinterpretation and sampling error.[10] In the present study discordant rate is slightly higher than previously published data [Table 4]. This may be because of the lack of highly experienced or trained pathologist in the institution. Our results show all false negative cases and no false positive cases. This result is comparable to previous studies.

Table 4. Literature overview of limitations of the study

Study	No of cases	Sampling error	Interpretation error
Patil et al.[6]	3/ 100	1.0	2.0
Mahe et al.[15]	17/ 812	0.6	1.5
Evans et al.[16]	3/ 240	0.4	0.8
Present study	4/47	6.38	2.12

Intestinal biopsy from three years old girl with Hirschsprung's disease was sent for identification of ganglion cells to decide the level of resection. Discordant finding was observed on frozen section slides. Diagnosis of Hirschsprung's disease is dependent on correct identification of ganglion cells.[11] However the segment of transverse colon showed paucity of ganglion cell.

This procedure is facilitated if the surgeon gives the pathologist a rectangular piece of the entire muscular wall, so that the tissue can be properly oriented. For reliability of frozen section, the tissue should be at least 4 mm long, and multiple serial sections should be taken. Even under these ideal circumstances it should be understood that the inaccuracy rate is relatively high.[17]

There is a lower deferred and error rate when specimens are interpreted by more experienced pathologists. A study has shown junior residents make higher percentage of inaccurate diagnoses which is improved with additional training.[18] Evaluation of the specimens by two observers or even three, when there is uncertainty, reduces the rate of error.[19] In our study diagnoses on frozen sections made by residents was reviewed by attending two or three pathologists.

As per The *College of American Pathologists (CAP)* cancer protocols the turnaround time in frozen section should be within 20 minutes. Turnaround time does not include transport time prior to receipt of specimen, and also excludes cases where multiple sequential studies are performed.[20] The average turn-around time observed in the present study was 20 minutes, which is comparable with the range reported by other studies.

The frequent limitation observed in present study were technical errors sampling errors, sectioning, inadequate history, staining and labeling. An important technical factor causing difficulty in interpretation is quality of section which limits the evaluation of cellular details. Such limitations are seen in other studies as well.[10]

CONCLUSION

Frozen section is an accurate and reliable test. Out of 47 cases studied the overall accuracy of frozen section was 91.4% (43 cases). Four cases (8.5%) were discordant with the diagnosis, reported as false negative. None of the cases were reported as false positive. Methodological gross/ macroscopic examination, accurate sampling, avoiding technical errors in sectioning and staining, and better communication between pathologist and surgeon along with reevaluation of the interpretations by a second or may be third experienced pathologist is helpful in reducing discordant and deferral rates. This provides rapid, reliable and cost effective details necessary for rapid diagnosis and on table patient management.

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