



CORRELATION OF INTRAOPERATIVE FROZEN SECTION WITH HISTOPATHOLOGICAL DIAGNOSIS IN A TERTIARY CARE CENTER

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KEYWORDS :

Introduction:

Frozen section is a diagnostic procedure used to provide rapid diagnosis to guide intra or perioperative patient management. The indications of frozen section are diagnosis of lymph node metastasis, evaluation of margins, confirmation of presence of representative samples for paraffin section diagnosis and to determine the nature of a lesion that may require ancillary test.

Frozen section is more difficult to interpret than examination of paraffin embedded sections therefore it should be interpreted by a competent pathologist. Good communication between surgeon and pathologist can provide rapid, reliable, cost effective information necessary for optimum patient care and can avoid misinterpretation of frozen section.

It should not be used to merely to satisfy a surgeon's curiosity or to compensate for inadequate preoperative evaluation or a mechanism to communicate information more quickly to the patient or patient's family.

A college of American Pathologist (CAP) sponsored review of over 90,000 frozen sections showed a concordance rate of 98.52%. The main causes for the discrepancies were either misinterpretation of the original frozen section, absence of diagnostic tissue in the frozen material but present in the unsampled tissue or in the corresponding permanent section.¹

The correlation between intraoperative frozen section diagnosis and permanent sections should be an integral part of quality assurance activities in pathology departments. This study aims at correlation of frozen tissue diagnosis and histopathology diagnosis.

Material and methods:

It was a retrospective analysis of 84 cases of frozen section biopsy, reported in the RL Jalappa hospital and Research centre attached to Sri Devaraj URS Medical college, Kolar between January 2014 to December 2017. All the data were retrieved from the register maintained in Department of Pathology.

Representative sections from resected surgical specimens were taken by pathologist. Frozen sections were cut on a Leica1100cryostat machine and evaluated in Hematoxylin and Eosin (H&E) stain. Subsequently, for the permanent section, specimens were fixed in 10% buffered 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 diagnosis were correlated with the final histological diagnosis to assess the accuracy of the frozen section. Case with discrepancies between frozen section and final diagnosis were analyzed and compared with the other studies.

Results: 84 cases were included in the study

The most common indication for frozen section in our hospital was:

- 1) Confirmation of primary diagnosis-benign/malignant(87%)
- 2) Surgical margin involvement (4%)
- 3) Assessing nodal status and skin involvement in malignancies(9%)

The most common organ/tissue sent for frozen section in our hospital was ovary followed by uterus, CNS lymph node, oral cavity, breast, male genital system, nasal cavity. Details shown in Table 1.

Out of 84 cases correlation was seen in 91.6% cases and disagreement was seen in 8.4% cases.

Table 1: Showing site wise distribution of cases

Organ/site	No. of cases	Concordant cases	Discordant cases
Ovary	28	27	1
Uterus	13	12	1
CNS	9	6	3
Lymphnode	8	8	0
Oral cavity	6	6	0
Breast	5	4	1
Male genital system	4	4	0
Nasal cavity	4	3	1
Thyroid	2	2	0
Parotid	1	1	0
Ear	1	1	0
Skin	1	1	0
Spinal	1	1	0
Soft tissue	1	1	0
Total	84	77	7

Ovary –comprised of 28 cases in which the most common diagnosis was Mucinous cystadenoma (29%) followed by serous cystadenoma(14%) and simple cyst (14%). Other specimens sent for frozen section was diagnosed as serous cyst, endometriosis, follicular cyst, granuloma of ovary and serous cystadenocarcinoma. All these cases showed concordance with histopathology. One case which showed discordance was a case of mucinous cystadenocarcinoma on histopathology which on frozen section was diagnosed as mucinous cystadenoma.

Uterus –was subjected to frozen section in 13 cases commonest diagnosis was simple cystic hyperplasia of endometrium(23%) followed by leiomyoma(15.3%). Other cases were of complex hyperplasia of endometrium, adenomatous polyp, adenomyosis, endometrial sarcoma (Figure 1 & 2). One case which showed discordance was a case of endometrial adenocarcinoma which was diagnosed as complex hyperplasia with atypia on frozen section.

CNS –comprised of 9 cases in which the most common diagnosis was Meningioma(22%). Other cases comprised of astrocytoma, craniopharyngioma and tuberculoma. Three cases showed discordance. A case of hemangioblastoma on histopathology was diagnosed as benign spindle cell tumor on frozen section. Another case of vascular hamartoma on histopathology was diagnosed as meningioma with secondary change on frozen section. A case of glioma (possibility of ependymoma and oligodendroglioma) on histopathology was misinterpreted as small round cell tumor on frozen section.

Lymphnode: comprised of 8 cases. In all the cases lymphnodes were sent to assess metastatic deposit. Among them one case was diagnosed as granulomatous lymphadenitis along with sinus histiocytosis and in

the other seven cases no metastatic deposit was identified in the lymphnode . There was 100%concordance between frozen section and histopathology diagnosis.

Oral cavity: comprised of 6 cases. Excision biopsy of oral lesion were sent for frozen section. Four cases were diagnosed as Squamous cell carcinoma and two cases showed moderate dysplasia. The results were in agreement with the histopathological diagnosis.

Breast: comprised 5 cases. Received specimens were diagnosed as ductal carcinoma ,fibroadenoma, papillary carcinoma, ductal papilloma on both frozen section and histopathology. One case of papillary carcinoma in background of phyllodes tumor was misdiagnosed as fibroadenoma on frozen section .

Male genital system: In 3 cases frozen section was done to assess the margin status in Penile Squamous cell carcinoma (75%).There was 100%concordance between frozen section and histopathology

Table 2:Discordant cases

Organ system (specimen)	Frozen section Diagnosis	Permanent diagnosis	Reason for error	Impact on pathology report	Potential intraoperative impact
Female genital tract (Ovary)	Mucinous cystadenoma	Mucinous cystadenocarcinoma	Sampling error	Category change-False negative	Yes
Female genital tract (Uterus)	Complex hyperplasia with atypia	Endometrial adenocarcinoma	Sampling error	Category change-False negative	Yes
CNS	Benign spindle cell tumor	Hemangioblastoma	Interpretation error	Category change-False negative	Yes
CNS	Meningioma with secondary change	Vascular hamartoma	Interpretation error	Category change-False positive	Yes
CNS	Small round cell tumor on frozen section	Glioma (possibility of ependymoma and oligodendroglioma)	Interpretation error	Category change-False negative	Yes
Breast	Fibroadenoma	Papillary carcinoma in background of phyllodes tumor	Sampling error	Category change-False negative	Yes
Nasal cavity	Malignant nasal mass	Nasopharyngeal angiofibroma	Interpretation error	Category change-False negative	Yes

Discussion:

The surgeon's confidence in frozen section results, depends on its diagnostic accuracy. In view of limited amount of tissue that is submitted or sampled during frozen section examination and the quality of frozen sections compared with permanent sections, discrepancies are expected between frozen section diagnoses and final diagnoses. Evaluating discrepancies, identifying deficiencies and resolving the underlying problems helps to improve the accuracy of frozen section. In our study the overall sensitivity was 92.7%, specificity was 98.8%, positive predictive value was 98.7%, negative predictive value was 93.2% and diagnostic accuracy was 95.81%. Chandramouleeswari K. and his colleagues found a accuracy of 92% and in another study by Shrestha and her colleagues a accuracy rate of 94.6% was found.²

In our study the highest deferral rate was found in neuropathological specimens. One case of hemangioblastoma on histopathology was diagnosed as benign spindle cell tumor on frozen section. This was due to selection of peritumour tissue for frozen section.

Another case of vascular hamartoma on histopathology was diagnosed as meningioma with secondary change on frozen section. This was due to misinterpretation of endothelial cells as elongated spindle meningothelial cells on frozen section.

A case of glioma (possibility of Ependymoma or oligodendroglioma)on histopathology was diagnosed as small round cell tumor on frozen section. This is due to misinterpretation of small glial cells.

Similar results were found in another study in Iran where the most common discrepancy was observed in frozen section of neuropathological specimen specially in differentiating spindle cell tumors ,low grade glioma or reactive gliosis.³ In another study discrepancy was seen in spindle cell lesions, astrocytoma versus oligodendroglioma, lymphoma, reactive versus neoplastic process.⁴ In another study done in France most discrepancies were seen in gliomas, hemangioblastomas, and metastatic tumors . Misinterpretation are mainly due to histologic similarities between different lesions, limited sampling, small biopsy samples and inadequate information about tumor location and radiologic findings.⁵

diagnosis in assessment of the margin status .Also received was a case of Yolk sac tumor of testis which showed agreement with HPE diagnosis.(Figure 1)

Nasal cavity: comprised of 4 cases including angiofibroma, polyp, inverted papilloma. One case of nasopharyngeal angiofibroma was misdiagnosed as malignant nasal mass on frozen section.

Thyroid: Comprised of one case which was reported as follicular adenoma both on frozen section and histopathology.

Also received was a unusual cases of Kimura's disease in parotid gland which was diagnosed inflammatory lesion on frozen section .

Also received one specimen each from other sites like ear, soft tissue ,skin, spine .These cases showed correlation between frozen and permanent sections.

The reported diagnostic accuracy of CNS frozen section diagnosis is between 85–90% in previous studies .

In our study a case of mucinous cystadenocarcinoma on histopathology was diagnosed as mucinous cystadenoma on frozen section. Coffey et al states that the accuracy is lower in mucinous tumors and mesenchymal tumors of ovary.⁶ Large tumor size and tumor heterogeneity of mucinous tumors are the main contributing factors of diagnostic difficulty. For this reason generous sampling particularly from the solid areas of ovarian tumor is required to rule out invasion in mucinous tumor. Also by using intraoperative cytological techniques like Fine needle aspiration cytology and touch imprint cytology can provide nuclear and cytoplasmic details without any freezing artifact. The accuracy reported in previous studies for ovarian tumor is around 90–97%.^{7,8}

In our study disagreement was found in a case of endometrial adenocarcinoma which was diagnosed as complex hyperplasia with atypia on frozen section. This is due to non representative section on frozen section. The cellular outline, nuclear details gets obscured due to clearing artifact because of which the overall morphology of frozen section is inferior to that of routine section. Many studies on frozen section analysis were done in endometrial carcinoma to identify patients who are at increased risk for pelvic and para-aortic nodal metastasis .Nodal metastasis incidence increases with grade of tumor, depth of myometrial invasion, cervical or adnexal involvement, lymphovascular invasion, and poor histologic types.⁹

A case of papillary carcinoma in background of phyllodes tumor on histopathology was diagnosed as fibroadenoma on frozen section. This discrepancy could be due to sampling error in frozen section.The foci of papillary carcinoma was missed due to improper sampling. Histopathological diagnosis of phyllodes is based on stromal cellularity rather than individual cells. Frozen section tends to alter the cellular and stromal architecture which tends to amplify the diagnostic dilemma. In a study similar diagnostic dilemma in a case of phyllodes tumor diagnosis was seen.¹⁰ In a study by Rosai J, Ackerman LV accuracy of frozen section in 679 breast specimens diagnosis was 98.5% . Most of the deferred diagnosis and false negative results involved occult/ intraductal/ intralobular lesions.¹¹Recently breast

specimens were sent for frozen sections to assess the margin status especially in breast conservative surgeries.

In our study one case of thyroid was reported with concordance between FS and histopathology. Overall accuracy rate of FS in thyroid lesions is >90% though the rate can drop low for encapsulated follicular carcinoma. Diagnostic challenge in follicular neoplasm and Hurthle cell neoplasm is due to difficulty in identification of capsular and vascular invasion.¹² Entire capsule must be submitted for the microscopic examination which is time consuming and less productive at the time of frozen section. Frozen section distorts and collapses blood vessels making it difficult to identify angioinvasion. Ground glass appearance of the nuclei produced by formalin fixation is not present in frozen section making diagnostic difficulty for pathologist. Other site such as salivary gland, soft tissue, skin, ear, spine, lymph nodes was sent for frozen section for primary diagnosis, margin assessment and nodal metastasis. Benign and malignant lesions were identified correctly but subtyping was a frequent problem. This was due to loss of architectural pattern and freezing artifact. Many authors believe that determining the presence of malignancy without subtyping is the best option to decrease the discrepancies.

Various artifacts are seen in frozen section. Nuclear artifact can be seen as a result of "drying artifact." Cells of an air dried diff quick stained slide have features of smudgy poorly define chromatin. Also nuclei will show varying tendency to form ice crystals. If tissue were damaged by cautery or ischemia because of loss of osmotic homeostasis it can result in more "nuclear edema".¹³ It is observed that vesicular nuclei have greater tendency to show these ice crystals. Edematous tissues freeze with an appearance similar to soap bubbles this is because as the water freezes the expanding water forms rounded ice crystals which compresses the strands of fibrous tissue giving appearance of bubbles. Overfreezing can cause tissue to have holes. Poor staining also hinders frozen section diagnoses, as nuclear detail is compromised. These artifacts should be identified to avoid misinterpretation.

According to studies the average time for frozen section varies from 20 to 25 minutes.¹⁴ In our study the turn around time was 20 minutes. Turn around time depends on- distance of frozen section room from operation theatre, well trained technicians, expertise of pathologists and good interdepartmental communication.

Conclusion:

Good correlation was found between frozen section and histopathology diagnosis. Out of seven discordant cases three cases were discordant due to sampling error and four cases were due to interpretation error. Prior discussion with surgeon and radiologist helps in improving the diagnostic accuracy of frozen section.

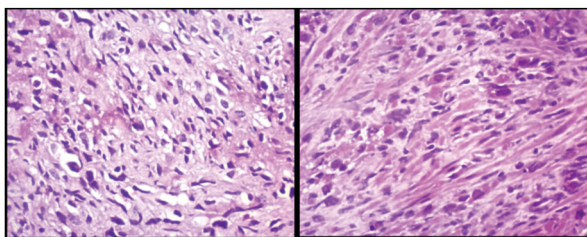


Figure 1: Endometrial sarcoma with necrosis

Figure 2: Endometrial sarcoma on frozen section on paraffin section

References

- Shrestha S, Lee MC, Dhakal H, Pun CB, Pradhan M, Shrestha S, et al. Comparative Study of Frozen Section Diagnoses with Histopathology. *Postgraduate Medical Journal of NAMS*. 2009;3(2):1-5.
- Chandramouleeswari K, Yogambal M, Arunalatha P, Bose JC, Rajendran A. Frozen and paraffin sections- Comparative study highlighting the concordance and discordance rates in a tertiary care centre. *IOSR Journal of Dental and Medical Sciences*. 2013;12(5):26-30.
- Regragui A, Amarti Riffi A, Maher M, El Khamlichi A, Saidi A. Accuracy of Intraoperative diagnosis in central nervous system tumors: report of 1315 cases. *Neurochirurgie*. 2003;49:67-72.
- Savargaonkar P, Farmer PM. Utility of intra-operative consultations for the diagnosis of central nervous system lesions. *Ann Clin Lab Sci*. 2001;31:133-9.
- Plesec TP, Prayson RA. Frozen section discrepancy in the evaluation of central nervous system tumors. *Arch Pathol Lab Med*. 2007;131:1532-40.
- Coffey D, Kaplan AL, Ramzy I. Intraoperative Consultation in Gynecologic Pathology. *Arch Pathol Lab Med* 2005; 129:1544-1557.
- Tangjitgamol S, Jesadapatrakul S, Manusirivithaya S. Accuracy of frozen section in diagnosis of ovarian mass. *Int J Gynecol Cancer*. 2004;14: 212-219.
- Prapaporn S, Surapan K, Anchali P, Jongkolnee S, Sumalee S. Accuracy of intra-

operative frozen sections in the diagnosis of ovarian masses. *Asian Pac J Cancer Prev*. 2008;9: 23-31.

- Kucera E, Kainz C, Reinthaller A, Sliutz G, Leodolter S, Kucera E, et al. Accuracy of intraoperative frozen-section diagnosis in stage I endometrial adenocarcinoma. *Gynecol Obstet Invest*. 2000;49:62-6.
- Laicirica R. Intraoperative assessment of the Breast: Guidelines and Potential Pitfalls. *Arch Pathol Lab Med*. 2005; 129(12):1565-1574.; 129(12): 1575-1578.
- Rosai J, Ackerman LV (1979) The pathology of tumors. Part II: Diagnostic techniques. *CA Cancer J Clin* 29(1): 22-23.
- Anton RC, Wheeler TM. Frozen section of Thyroid and Parathyroid Specimens *Arch Pathol Lab Med* 2005.
- Desciak E. B, Maloney M. E. Artifacts in Frozen Section Preparation. *Dermatologic Surgery*. 2000; 26: 500-504
- Vahini G, Ramakrishna BA, Kaza S, Murthy NR. Intraoperative Frozen Section - A Golden Tool for Diagnosis of Surgical Biopsies. *Int Clin Pathol J* 2017; 4(1): 84-86.