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Original Research Article

Evaluation of Intraoperative Imprint Cytology and Frozen Section in Determination of Tumor and Tumor Margins

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Abstract

Intraoperative pathology consultation is often required for guiding immediate surgical decisions so as to limit the extent of surgery. Accurate intraoperative diagnosis is crucial. The present study evaluates the accuracy of imprint cytology and frozen section in intraoperative consultation for tumor and tumor margins. A total of 157 tissue specimens for type of lesion, tumor margins and lymphnode metastasis were included. Imprint was taken by holding the tissue bit with forceps and touching it onto a clean glass slide without undue pressure or lateral movements. They were stained with Papanicolaou, May-Grunwald Giemsa and Hematoxylin and Eosin [H&E] stains. The tissue bits taken were then embedded and frozen. Section cutting was done using cryostat and were stained using rapid Haematoxylin and Eosin stain, and examined under a light microscope. Later, the tissue was fixed in 10% neutral buffered formalin for routine histopathological processing then stained with H&E stain. Based on the histological diagnosis, the accuracy of intraoperative imprint cytology and frozen section were evaluated. A total of 157 tissue specimens were received during the study period, which were classified into specimens for type of tumor [145 specimens], tumor margins [54 specimens] and lymph node metastasis [7 specimens] for analysis. The overall diagnostic accuracy of imprint cytology in detection of type of tumor was 97.9% and that of frozen section was 98.6%. It can be concluded that imprint cytology typically provides the accurate diagnosis without the need for a sophisticated machine such as cryostat which is required for frozen section analysis.

Keywords: Imprint cytology, Frozen section, Tissue, Tumor, Lymphnode, Metastasis, Histopathology.

INTRODUCTION

Surgeons seek intraoperative consultations for a variety of purposes like diagnosis of an unknown lesion, evaluation of margin status and detection of disease dissemination. In the management of patients with malignancy, a precise, cost-effective and quick intraoperative approach that would assess lesions along with the surgical margin and enable for re-excision if required during the initial surgery is essential. The pathologist's role is to inspect the tissue and its outermost edge under a microscope to determine if the margin has any residual cancer cells.

Touch imprint cytology has been found quite reliable and useful in determination of surgical resection margins. Imprint smears were initially described in the early twentieth century. The proposed ideology is that the cancer cells are more adherent to a glass surface. This histological characteristics of the cell surface of malignant cells enable them to stick to glass surfaces, whereas benign fat tissue does not.

Frozen section analysis has become a widely utilized intra-operative diagnostic technique with a high rate of accuracy. But it has to be kept in mind that frozen sections are inferior to paraffin sections, and errors are possible. Because in a frozen section, only a part of the tissue is examined, it may miss a malignant process that does not affect the entire lesion. Rapid freezing may induce intracellular water crystals to alter the shape of the nucleus and cytoplasm thereby giving an altered appearance. Furthermore, because frozen

sections are generally thicker than paraffin sections, image resolution is lowered.

Using histopathological examination as the gold standard, this study was done to test the accuracy of imprint and frozen section analysis in diagnosing tumour and tumour margins.

MATERIALS AND METHODS

This study was carried out in the Department of Pathology at a Tertiary hospital in Bangalore for a period of 8 years (2015-2022). Tissue specimens were collected from 157 patients, and a cross-sectional, observational study was performed. A detailed history, clinical findings, results of relevant biochemical tests, tumour markers assay and imaging studies were noted.

Macroscopic examination of the tissue was done thoroughly to evaluate the specimens. The specimen was then dissected using a scalpel. Representative areas were selected from the lesion proper and/or surgical margins. Imprint was taken by holding the tissue bit with forceps and touching it onto a clean glass slide without undue pressure or lateral movements. The imprint slides were fixed in isopropyl alcohol and stained with Haematoxylin & Eosin and Papanicoloau stain. Air dried smears were stained with May-Grunwald Giemsa stain.

The tissue bits taken were then embedded in Optimum Cutting Temperature compound and frozen to -25^{o} Celsius. 4 µm thick sectioning was done using LEICA CM 1860 UV cryostat and the sections were picked up on frosted glass slides and were stained using rapid Haematoxylin and Eosin staining and examined under a light microscope. The remaining tissue was fixed in 10% neutral buffered formalin for routine histopathological processing and embedded in paraffin wax. Sections were cut at 3 µm thickness with a LEICA RM2245 microtome and then stained with H&E stain.

The final diagnoses were compared between the Touch Imprint Cytology, Frozen section analysis and the Histopathological examination. For statistical analysis, these three methods were evaluated, analyzed, interpreted and recorded in tabular manner. Inferential and descriptive statistics were done using Chi-square test, sensitivity, specificity, negative predictive value, positive predictive value and diagnostic accuracy. Consent form and ethical clearance were taken during the study.

Inclusion criteria were surgically removed specimens from various organs that were suspected to have neoplastic lesions, surgical margins that had to be assessed for tumor cell clearance, fresh specimens received in clean, sealed, and labelled containers; and cases with advanced notice and appointment.

Exclusion criteria were cases suspected to be inflammatory/infectious conditions, specimens sent in formalin or saline and specimens sent in unlabelled containers.

RESULTS & DISCUSSION

A total of 157 tissue specimens were received during the study period, which were classified into specimens for type of tumor [145 specimens], tumor margins [54 specimens] and lymph node metastasis [7 specimens] for analysis. The kind of tumor was also identified in all tissues sent for tumor margin clearance. A total of 145 surgically resected specimens were received for diagnosis of type of tumor and were broadly classified into non-neoplastic and neoplastic. Non-neoplastic cases included one case of mucormycosis and another case of inflammatory polyp of the nose and paranasal sinus region. Neoplastic lesions were further categorized into benign, borderline and malignant. Majority of the neoplastic lesions were malignant tumors (53.1%). Out of 145 specimens, the majority were breast neoplasms accounting for 57 cases (39.3%), followed by ovarian (36.5%) and uterine neoplasms (6.8%).

A total of 54 cases were sent for analysis of margin status for presence of tumor/malignant cells and 7 lymph nodes were sent for detection of metastatic deposits.

The overall diagnostic accuracy of imprint cytology in detection of type of tumor was 97.9% and that of frozen section was 98.6%. The false-negative and false-positive rate for imprint cytology was 1.2% and 0.68% respectively and the false positive and false negative rate for frozen section was both 0.68%.

Table 1: Distribution of specimens for type of lesions

Category	No. of lesions	Percentage
Non-neoplastic	2	1.3%
Neoplastic:		
Benign	58	40.0%
Borderline	8	5.6%
Malignant	77	53.1%

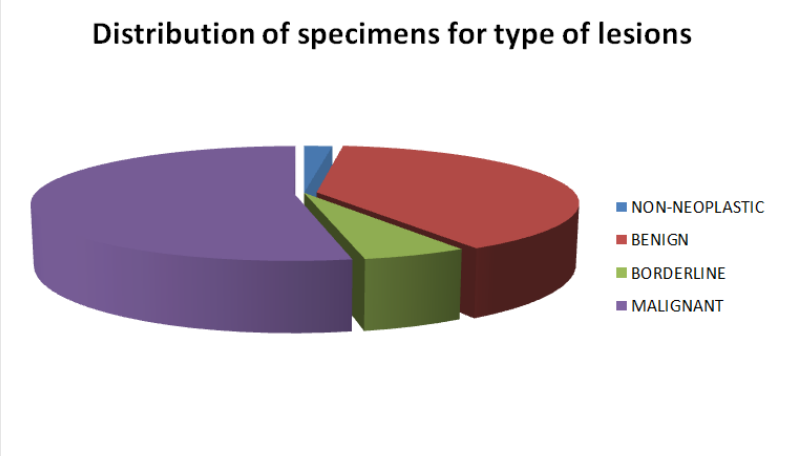


Table 2: Organ-wise distribution of specimens (n=145)

Sl. No	Organ	Histopathological diagnosis	No. Of cases	Organ wise total	Percentage
1.	Ovary	a) Torsion ovarian cyst b) Endometriotic cyst c) Mature teratoma d) Benign serous cystadenoma e) Benign mucinous cystadenoma f) Seromiucinous cystadenoma g) Borderline surface epithelial tumor h) Malignant ovarian tumor	4 2 11 12 4 8 3 9	**53**	**36.5%**
2	Uterus	a) Endometrial polyp b) Endometrial hyperplasia with atypia c) Leiomyoma d) Adenocarcinoma endometrium e) Pleomorphic sarcoma	1 1 3 4 1	**10**	**6.8%**
3	Breast	a) Fibroepithelial lesion b) Fibrocystic disease c) Intraductal papillomatosis d) Papillary neoplasm e) Invasive ductal carcinoma f) Invasive carcinoma with ductal and lobular features	2 3 1 2 47 2	**57**	**39.3%**
4	Salivary gland	Adenoid cystic carcinoma	1	**1**	**0.6%**
5	Gall bladder	Adenocarcinoma	1	**1**	**0.6%**
6	Oral cavity	Squamous cell carcinoma	4	**4**	**2.7%**
7	Thyroid	Colloid goitre Multinodular goitre	3 2	**5**	**3.4%**
8	Nose and PNS	Inflammatory polyp Mucormycosis	1 1	**2**	**1.3%**
9	Testis	Fibrous pseudotumor	1	**1**	**0.6%**
10	Soft tissue	Malignant eccrine tumor	1	**1**	**0.6%**
11	Anorectal	Adenocarcinoma	1	**1**	**0.6%**
12	Tonsils	Poorly differentiated carcinoma	1	**1**	**0.6%**
13	Esophagus	Squamous cell carcinoma	2	**2**	**1.3%**
14	Pancreas	Mucinous adenocarcinoma	1	**1**	**0.6%**
15	Abdominal cavity	Squamous cell carcinoma Benign spindle cell neoplasm Malignant spindle cell neoplasm	1 1 1	**3**	**2%**
16	Cervix	Squamous cell carcinoma	1	**1**	**0.6%**
17	Kidney	Triphasic wilm's tumor	1	**1**	**0.6%**

Table 3: Distribution of specimens sent for margin analysis (n=54)

Sl. No	Organ	Margin involved	Margin uninvolved	Total
1	Breast	8	36	**44**
2	Oral cavity	1	1	**2**
3	Intestine	0	1	**1**
4	Nose and PNS	0	1	**1**
5	Soft tissue	0	1	**1**
6	Skin	0	1	**1**
7	Anorectal	1	0	**1**
8	Esophagus	0	1	**1**
9	Eyelid	0	1	**1**
10	Mandible	1	0	**1**
	Total	**11**	**43**	**54**

Table 4: Status of lymph node metastasis (n=7)

Lymph node Metastasis	
Positive for malignancy	Negative for malignancy
5	2

Table 5: Diagnostic accuracy of Imprint cytology in detecting type of tumor

Sl. no	Organ/organ system	Correct diagnosis		False negative / False positive cases		Diagnostic accuracy
		No. Of cases	Percentage	No. Of cases	Percentage	
1.	Ovary	52	36.3%	**01 [FP]**	**0.6%**	**98.1% (52/53)**
2.	Uterus	10	6.9%	0	0	100% (10/10)
3.	Breast	56	39.1%	**01 [FN]**	**0.6%**	**98.2% (56/57)**
4.	Salivary gland	01	0.6%	0	0	100% (1/1)
5.	Gall bladder	0	0%	**01 [FN]**	**0.6%**	**0% (0/1)**
6.	Oral cavity	04	2.7%	0	0	100% (4/4)
7.	Thyroid	05	3.4%	0	0	100% (5/5)
8.	Testis	01	0.6%	0	0	100% (1/1)
9.	Soft tissue	01	0.6%	0	0	100% (1/1)
10.	Anorectal	01	0.6%	0	0	100% (1/1)
11.	Tonsils	01	0.6%	0	0	100% (1/1)
12.	Esophagus	02	1.3%	0	0	100% (2/2)
13.	Pancreas	01	0.6%	0	0	100% (1/1)
14.	Abdominal cavity	03	2.0%	0	0	100% (3/3)
15.	Cervix	01	0.6%	0	0	100% (1/1)
16.	Kidney	01	0.6%	0	0	100% (1/1)
	Total	**140**	**97.9%**	**3**	**2%**	**97.9% (140/143)**

Key: FP-False Positive, FN-False Negative

Table 6: Diagnostic accuracy of Frozen Section in detecting type of tumor

Sl. No	Organ/organ system	Correct diagnoses		False Negative/ False Positive cases		Diagnostic accuracy
		No. Of cases	Percentage	No. Of cases	Percentage	
1.	Ovary	53	37.0%	0	0	100 (53/53)
2.	Uterus	10	6.9%	0	0	100% (10/10)
3.	Breast	56	39.1%	**01 [FP]**	**0.6**	**98.2% (56/57)**
4.	Salivary gland	01	0.6%	0	0	100% (1/1)
5.	Gall bladder	0	0%	**01 [FN]**	**0.6%**	**0% (0/1)**
6.	Oral cavity	04	2.7%	0	0	100% (4/4)
7.	Thyroid	05	3.4%	0	0	100% (5/5)
8.	Testis	01	0.6%	0	0	100% (1/1)
9.	Soft tissue	01	0.6%	0	0	100% (1/1)
10.	Anorectal	01	0.6%	0	0	100% (1/1)
11.	Tonsils	01	0.6%	0	0	100% (1/1)

12.	Esophagus	02	1.3%	0	0	100% (2/2)
13.	Pancreas	01	0.6%	0	0	100% (1/1)
14.	Abdominal cavity	03	2.0%	0	0	100% (3/3)
15.	Cervix	01	0.6%	0	0	100% (1/1)
16.	Kidney	01	0.6%	0	0	100% (1/1)
	Total	**141**	**98.6%**	**2**	**1.4%**	**98.6% (141/143)**

Key: FP-False Positive, FN-False Negative

Table 7: Diagnostic accuracy of Imprint cytology and Frozen section in the analysis of Surgical margins

Sl. No	**ORGAN/ORGAN SYSTEM**	**CORRECT DIAGNOSES**		**FALSE NEGATIVE / FALSE POSITIVE CASES**		**DIAGNOSTIC ACCURACY**
		No. of cases	**Percentage**	**No. of cases**	**Percentage**	
1.	SURGICAL MARGINS	53	98.1%	**01 [FP]**	**1.8%**	**98.1% (53/54)**

Key: FP-False Positive

Table 8: Diagnostic accuracy of Imprint cytology and Frozen section in the detection of Lymph node metastasis.

Sl. No	**ORGAN/ORGAN SYSTEM**	**CORRECT DIAGNOSES**		**FALSE NEGATIVE / FALSE POSITIVE CASES**		**DIAGNOSTIC ACCURACY**
		No. of cases	**Percentage**	**No. of cases**	**Percentage**	
1.	LYMPH NODE	06	85.7%	**01 [FP]**	**16.6%**	**98.6%(6/7)**

Key: FP-False Positive

Table 9: Proportional Analysis

Parameters	**Imprint smears**			**Frozen section**		
	Tumor diagnosis	**Margin status**	**Lymph node metastasis**	**Tumor diagnosis**	**Margin status**	**Lymph node metastasis**
Sensitivity	97.4%	100%	100%	98.7%	100%	100%
Specificity	98.3%	97.6%	50%	98.3%	97.6%	50%
Positive predictive value	98.7%	91.6%	83.3%	98.7%	91.6%	83.3%
Negative predictive value	96.6%	100%	100%	98.3%	100%	100%

Table 10: Comparison of Imprint cytology with Histopathology for diagnosis of neoplastic lesions

Imprint	**HPE**		
	Malignant	Benign	Total
Malignant	75	1	76
Benign	2	57	59
Total	77	58	135

Uncorrected ChiSquare test: 123.1
Yates Corrected ChiSquare test: 119.2
P value: <0.001

Table 11: Comparison of Frozen section analysis with Histopathology for diagnosis of neoplastic lesions

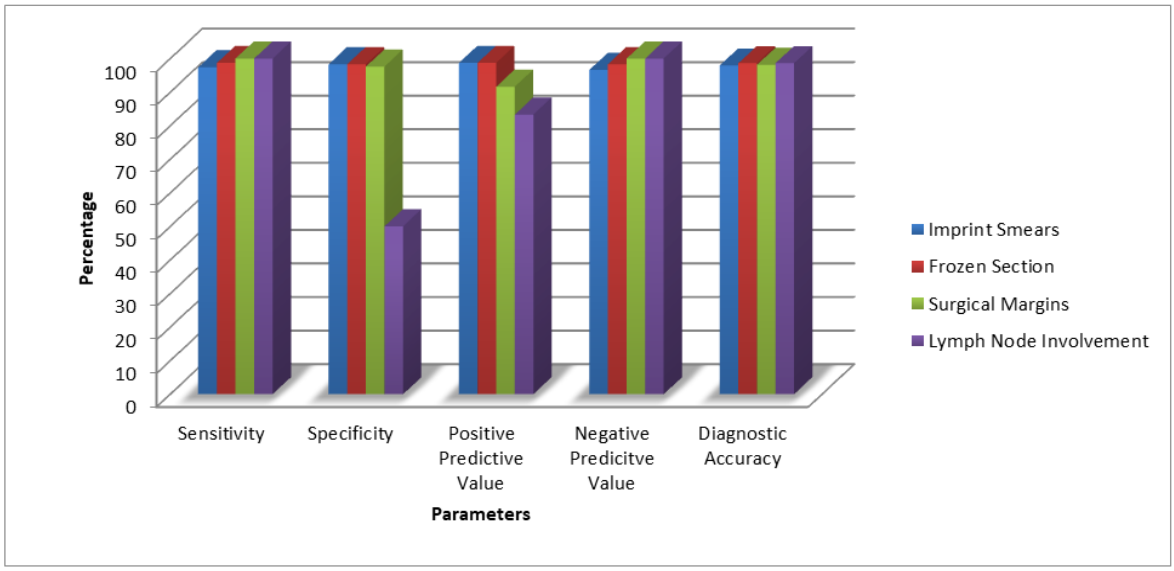
Frozen sections	**HPE**		
	Malignant	Benign	Total
Malignant	76	1	77
Benign	1	57	58
Total	77	58	135

Uncorrected ChiSquare test: 127.0
Yates Corrected ChiSquare test: 123.0
P value: <0.001

Table 12: Comparison of Imprint cytology and Frozen section analysis with Histopathology for evaluation of surgical margins

Imprint and Frozen sections	HPE		
	Positive	Negative	Total
Positive	11	1	12
Negative	0	42	42
Total	11	43	54

Uncorrected ChiSquare test: 48.35
Yates Corrected ChiSquare test: 42.86
P value: <0.001



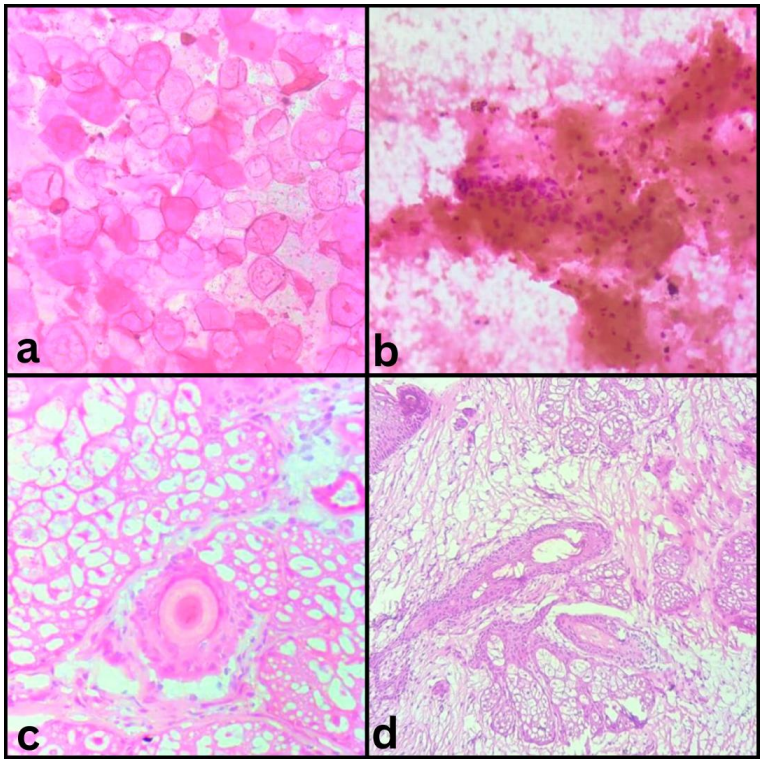


Figure 1: Mature Cystic Teratoma-(a),(b): Imprint cytology of Mature cystic Teratoma, [H&E stain; a, 100x, b, 100x] (c): Frozen section of Mature cystic Teratoma [H&E stain, 40x] (d):Histopathological section of Mature Cystic Teratoma [H&E stain, 100x]

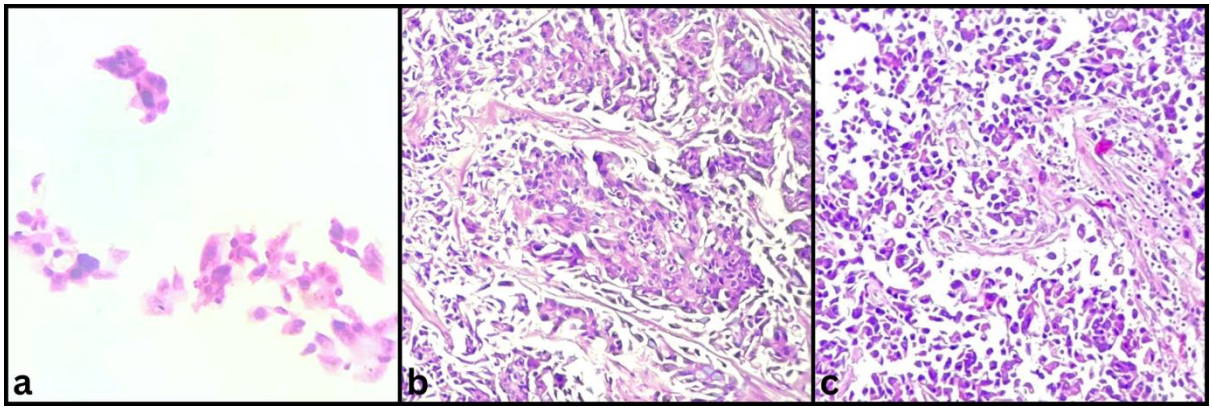


Figure 2: Infiltrating Ductal Carcinoma. (a) Imprint Cytology, (b) Frozen Section, (c) Histopathological section [H&E stain; a, 400x, b, 100x, c 100x]

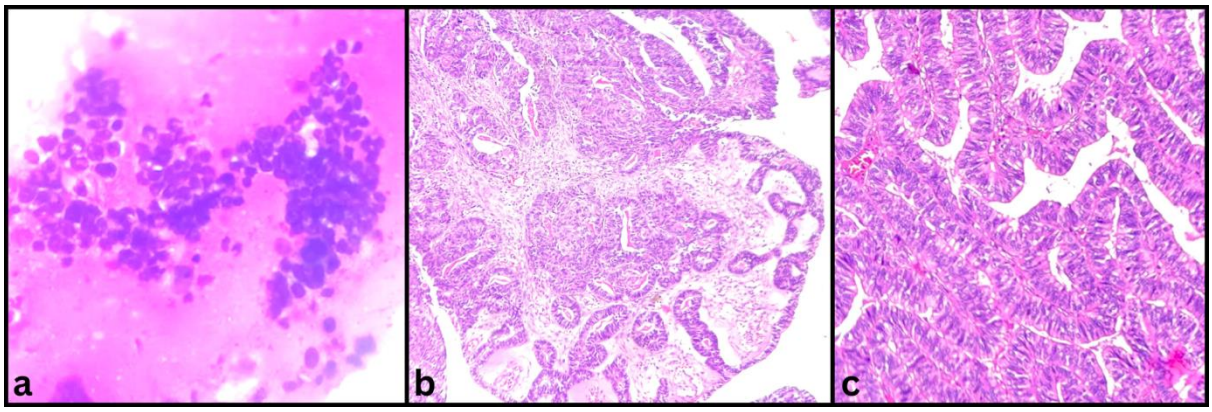


Figure 3: Benign papillary serous cystadenoma. (a) Imprint Cytology, (b) Frozen Section, (c) Histopathological section [MGG stain; a, 400x. H&E stain; b, 40x, c 100x]

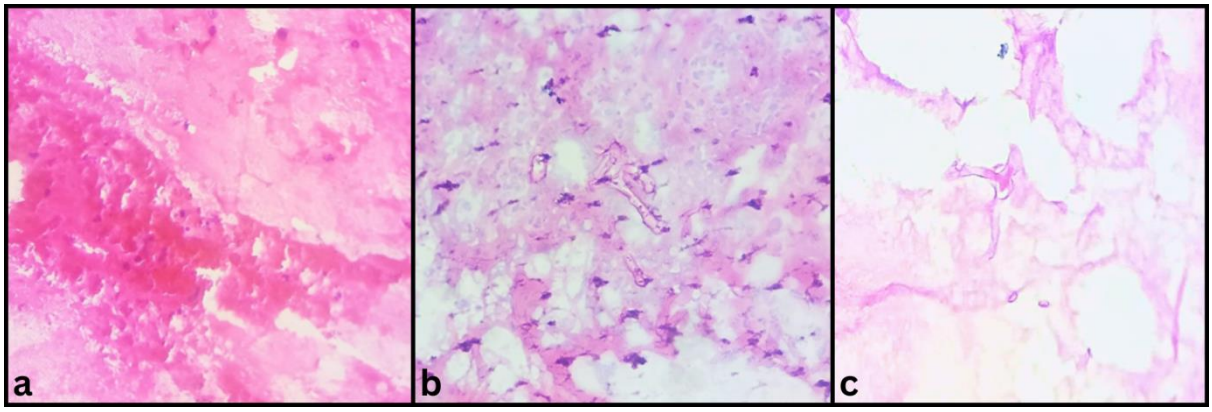


Figure 4: Mucormycosis. (a) Imprint Cytology, (b) Frozen Section, (c) Histopathological section [H&E stain; a, 400x, b, 400x, c 400x]

Frozen sections are a well-established technique for determining the degree of resection and for quick intraoperative diagnosis of lesions. De Riemer attempted for the first time to employ the FS technique for histological diagnosis in 1818. William H. Welch, a renowned pathologist from Johns Hopkins Hospital, used the approach for the first time in 1891 [1].

While the frozen section technique helps to appreciate the necessary tissue architectural details, intraoperative cytological methods such as fine needle aspiration biopsy and touch imprint cytology can clearly demonstrate nuclear and cytoplasmic details without freezing artefacts.

Imprint cytology is an intraoperative tissue assessment technique that was first introduced in 1927 by Dudgeon and Patrick [2].

Of the total 157 specimens studied, 145 cases were sent for the diagnosis of the nature of lesion, 54 cases were sent for the margin status and 7 lymph modes were sent for the detection of presence of malignancy.

The diagnostic accuracy of imprint cytology for the diagnosis of lesions were 97.9% which is similar to the study done by Shubha *et al*., (2018) (94%) and Sharin *et al*., (2019) (98.22%) [3, 4]. The diagnostic accuracy of frozen section for the diagnosis of nature of lesion in our study was 98.6% which is similar to the study done by Shubha et al, (2018) (98%) and Tamhane *et al*., (2020) (99.02%) [3, 5].

Of the three discordant cases in imprint cytology for diagnosis of type of lesion, one was due to interpretation error and the other two were due to gross sampling error.

One case of ovarian serous cystadenoma was misdiagnosed to have few cells which were suspicious for malignancy on imprint smears; however there was no evidence of malignancy on frozen section as well as routine histopathological examination. This false positive diagnosis could be due to the presence of cauterized cells which were misdiagnosed as tumor cells.

A case of Infiltrating ductal carcinoma and another case of adenocarcinoma of gall bladder were misdiagnosed as having no atypical cells on imprint cytology due to gross sampling error. However, it was correctly diagnosed with the help of frozen section and histopathological examination. This false-negative diagnosis could be due to the failure of tumor cells to adhere to the glass slide.

There were two discordant cases in frozen section analysis and both were due to gross sampling error. One was a case of papillary serous cystadenoma which was misdiagnosed as benign teratoma on frozen section. Another was a case of adenocarcinoma of gallbladder which was misdiagnosed as chronic cholecystitis on frozen section. Histopathological examination helped in arriving an accurate diagnosis in both the cases.

In lymph nodes analysis for metastaic deposits, one case was suspected to have tumor cells on imprint as well as frozen section but turned out to be benign on histopathological examination. In surgical margins, one case of breast carcinoma sent for analysis of margin status was falsely reported as positive for malignancy on imprint smears as well as frozen section but was reported as negative for malignancy on paraffin embedded histopathological sections. These false positive diagnosis could be attributed to the probable contamination of tumor cells on imprint smears. Frozen section slides were probably misinterpreted due to the freezing artifact and cellular distortion which is commonly encountered.

In our study, frozen section also played a pivotal role in providing a diagnosis for a clinically unknown lesion. A case of leiomyoma of the uterus was operated and intraoperatively the surgeons found a mass within the abdominal cavity. The mass was excised and sent for frozen section wherein a diagnosis of benign spindle cell neoplasm, possibly a parasitic leiomyoma was given.

In our study, the sensitivity, specificity, PPV and NPV of Imprint cytology for the diagnosis of nature of lesions were 97.4%, 98.3%, 98.7% and 96.6% respectively. And the sensitivity, specificity, PPV, and NPV of Frozen section for the diagnosis of nature of lesions were 98.7%, 98.3%, 98.7% and 98.3% respectively.

In a prospective analytical study of 103 cases sent for margin status conducted by Tamhane *et al*., (2020), the sensitivity, specificity, PPV, NPV, and accuracy of frozen sections was reported as 100%, 98.71%, 100%, 97.08%, and 99.02%, respectively and the sensitivity, specificity, PPV, NPV, and accuracy of TIC for surgical margins was reported as 46.51%, 90.76%, 56.56%, 84.62%, and 86.40%, respectively [5].

In a study conducted by Jaiswal *et al*., (2020) a total of 160 specimens were included and the sensitivity, specificity, PPV, NPV, and diagnostic accuracy of imprint Cytology for diagnosis of lesions were found to be 75%, 89.6%, 82.8%, 84.3% and 83.8% respectively. Out of 104 specimens received for evaluation of margin status, the sensitivity, specificity, PPV, NPV, and diagnostic accuracy of imprint Cytology was found to be 61.5%, 87.7%, 75%, 79.2% and 77.8% respectively [6].

Mondal *et al*., (2018) conducted a study for assessment of surgical margins using Imprint cytology and Frozen sections in 42 cases. The sensitivity, specificity, PPV and NPV of Imprint Cytology was found to be 91.6, 100, 100 and 96.7% respectively and the sensitivity, specificity, PPV and NPV of Frozen sections was found to be 91.6, 100,100 and 96.7%, respectively [7].

Sharin *et al*., (2019), studied 60 cases of head and neck lesions where the sensitivity, specificity, PPV, NPV and diagnostic accuracy of intraoperative diagnosis of the lesion was found to be 92.98%, 100%, 100%, 33.33% and 98.22% respectively. The sensitivity, specificity, PPV, NPV and of the intra-operative marginal status was 80.6%, 90.09%, 83.08%, 88.50% and 86.52% respectively [4].

CONCLUSION

Imprint cytology has many advantages, such as a simple technique, a low learning curve, and a quick procedure. But it also has some drawbacks, such as the

inability to distinguish between carcinoma in situ and invasive lesions, and the inability to provide information on the depth of invasion. Frozen section analysis is frequently used to overcome these constraints. However, it is likely that often hospitals in developing countries do not generally have the appropriate tools for frozen sections. According to the results of the current study, frozen section analysis and imprint smears both have diagnostic accuracy of 97.9% and 98.6% for the diagnosis of neoplastic lesions respectively and a diagnostic accuracy of 98.1% for the determination of surgical margins using both the techniques.

Hence, we can conclude that imprint cytology typically provides the accurate diagnosis without the need for a sophisticated machine such as cryostat which is required for frozen section analysis. As a result, imprint cytology can be well suited for many hospitals where cryostat machines are unavailable and can be used as an adjunct to frozen section analysis to improve intraoperative diagnostic accuracy.

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