"Assessment of lymph node status in cases of metastatic malignancy by frozen section and imprint cytology"

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Abstract: Introduction: Dissemination of cancers most commonly occurs by the lymphatic route and is generally favoured by carcinomas. The best achievable goal of any surgical procedure is removal of all the affected tissue and leave behind healthy tissue which is entirely free of any malignant cells. Though histopathological examination is gold standard, it is time consuming and cannot be implemented as an intraoperative diagnostic tool. The present study utilises frozen section analysis and touch imprint cytology as intraoperative tools and analyses their diagnostic accuracy to detect lymph node metastasis in comparison with routine histopathology in epithelial malignancies.

Aim: To evaluate the efficacy of intraoperative diagnosis by touch imprint cytology and frozen section analysis for the assessment of metastatic lymph node deposits.

Materials and methods: Total 76 cases of primary malignancy with suspicious metastatic lymph nodes were investigated. Metastatic nodes were subjected to frozen section and

touch imprint cytology and these findings were compared with routine histopathology and the sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated.

Results: The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of frozen section was found to be 97.30%, 100%, 100%, 97.5% and 98.68%. The values of the same parameters for imprint cytology was found to be 75.68%, 100%, 100%, 81.25% and 67% respectively.

Conclusions: Frozen section analysis proved superior to imprint cytology in detecting lymph node metastasis intraoperatively. Apart from detecting the presence of metastasis, frozen section is able to provide details regarding micro-metastasis, macro-metastasis and perinodal fat invasion. This study predominantly evaluated epithelial malignancies and thus proves the utility of these two intraoperative modalities in them. It also opens new avenues for research pertaining to the utility of these modalities in various malignant mesenchymal tumours.

Keywords: metastasis, touch imprint cytology, frozen sections, intraoperative diagnosis, carcinomas, histopathology.

INTRODUCTION:

The term metastasis is used to imply the migration and spread of cells with malignant potential from the primary tumour to surrounding tissues or distant organs. Initial detachment, intravasation, evading the formidable enforcers of the immune system and extravasation at different sites constitute the metastatic cascade. Cancers, owing to multiple genetic mutations are able to create a fertile soil favouring angiogenesis leading to formation of metastatic tumours [1][2][3]. Dissemination of cancers most commonly takes place through the lymphatic route which is mainly favoured by carcinomas and occasionally by sarcomas. Presence of metastasis greatly influences the staging, treatment and the disease prognosis [4]. Any surgical procedure should focus on removal of all the affected tissue and leaving behind healthy tissue. Affected tissue left behind increases the chances of local recurrence and repeat surgery. Routine histopathological evaluation (HPE) is the gold standard but it is time consuming and can't be implemented as an intraoperative tool. Complete lymph node dissection and negative surgical margins are considered as best curative treatment for cancer. Frozen section analysis (FSA) and touch imprint cytology (TIC) can be used intraoperatively to evaluate metastatic lymph nodes and consult the operating surgeon on which therapeutic modality to opt for. It is vital that the operating surgeon is aware of the neoplastic status of the affected tissue and/ or organ and the extent of it's spread to modulate the surgical treatment [4]. Present day surgical procedures mainly in the rural setup are based on pre-operative investigations. The use of a reliable intraoperative diagnostic tool is almost always lacking. This fact highlights that there is a research gap pertaining to the utility of intraoperative diagnosis in the management of malignant neoplasms. Keeping the above facts in mind, the present study made an attempt to analyse the accuracy of FSA and TIC as compared to routine HPE for assessing the metastatic lymph node deposits.

The rationale behind the present study was to analyse the effectiveness of intraoperative evaluation by FSA and TIC to detect metastatic lymph node deposits in comparison to routine, gold standard HPE. Hence, in the present study, the alternate hypothesis was that the findings obtained on FSA and TIC should directly correlate with those of routine HPE.

The aim of the present study was to evaluate the efficacy of intraoperative diagnosis by touch imprint cytology and frozen section analysis to evaluate metastatic lymph node deposits.

The present study was conducted with the objectives of evaluating metastatic lymph node deposits by FSA and TIC, confirming their presence by routine & gold standard HPE, assessing the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) & diagnostic accuracy of FSA & TIC and comparing these with the gold standard histopathological diagnosis.

MATERIALS AND METHODS:

This cross-sectional study was carried out for a span of seven months. It was conducted in the divisions of Frozen section and Surgical pathology of Department of General Pathology, Jawaharlal Nehru Medical College (JNMC) and Acharya Vinobha Bhave Rural Hospital (AVBRH) in coordination with departments of General Surgery, Obstetrics and Gynaecology, Otorhinolaryngology (ENT) as well as departments of Oral Pathology and Oral and Maxillofacial Surgery, Sharad Pawar Dental College (SPDC), Sawangi (M), Wardha, Maharashtra, INDIA. The study was approved by the institutional ethics committee [DMIMS(DU)/IEC/ Dec 2019/8601] and informed consent was taken from the patients participating in the study.

A total of 76 cases in which metastatic lymph nodes were present were investigated in the present study. The sample size of 76 was calculated by using the formula recommended by Krejcie RV et al. [5]:

$n= (Z\ a/2)^2 \times p \times (1-p)/d^2$ where,

"Z a/2" is the level of significance at 5 % that is 95 % confidence interval.

"p" is the prevalence.

"d" is the desired error of margin.

"n" is the sample size.

Inclusion criteria:

- ✓ All cases of malignancy (all carcinomas, melanomas, germ cell tumours, CNS tumours and sarcomas) which are suspicious of metastatic lymph node deposits.
- ✓ Resected specimens not fixed in formalin.
- ✓ Patients undergoing surgical resections with lymph node dissection for the treatment of above malignancies.
- ✓ Patients of all age groups.
- ✓ Both female and male patients.

Exclusion criteria:

- ✓ All cases with primary lesion in the lymph node itself (Non-Hodgkin lymphoma, Hodgkin lymphoma, Reactive proliferations, inflammatory conditions, primary immune-deficiencies, lymph node inclusions, vascular tumours and tumour like conditions).

- ✓ Cases where lymph node dissection was not done.
- ✓ Formalin fixed resection specimens
- ✓ Benign tumours
- ✓ Cases of recurrence.
- ✓ Cases with previous history of chemotherapy and radiotherapy.

Methodology of interpretation:

The resected specimens were received from the main operation theatre complex in the frozen section room and were grossed according to standard protocol. Lymph nodes received were subjected to touch imprint cytology and frozen section which was performed in accordance with the prescribed guidelines. Sections were subjected to rapid Haematoxylin and Eosin (H& E) staining. After these procedures were completed, the surgical pathologist on duty interpreted the sections and conveyed the findings to the operating team via the intercom. While communicating the findings, the name, age, sex, patient id and the details of the specimen submitted were tallied. Findings were reported either as "positive for infiltration by malignant cells" or "negative for infiltration by malignant cells", whichever was applicable. Confirmation regarding the communication of findings was obtained from the operating team. The average turnaround time (TAT) for the procedure was 20 to 25 minutes.

Method of evaluating lymph node deposits by frozen section analysis (FSA):

All the lymph nodes received were subjected to serial sectioning and were embedded as whole in the freezing mixture. Sections stained with rapid H& E stain were examined under scanner, low-power and high-power objectives. The perinodal fat, node capsule, subcapsular sinus, cortex and the medulla were examined for metastatic deposits. Findings were reported either as "positive for infiltration by malignant cells" or "negative for infiltration by malignant cells", whichever was applicable. Metastatic deposits if present, were further evaluated under the headings of isolated tumour cells (ITCs) [single cells or small clusters of cells not larger than 0.2 millimetres (mm) in the greatest dimension], micro-metastasis (clusters of tumour cells between 0.2 mm and 2 mm) and macro-metastasis (tumour deposits greater than 2 mm). [6]

Method of evaluating lymph node deposits touch imprint cytology (TIC):

The lymph nodes received were bisected and a glass slide was pressed gently on the freshly cut surface avoiding a gliding movement. The touch imprints were immediately fixed in 95% alcohol and then subjected to rapid H& E staining. Findings were reported either as "positive for infiltration by malignant cells" or "negative for infiltration by malignant cells", whichever was applicable. [7]

STATISTICAL ANALYSIS:

The findings obtained on FSA, TIC and HPE were analysed, interpreted and recorded in a well tabulated master chart and graphical representations. Statistical analysis was carried out

by using descriptive and inferential statistics using Chi-square test, sensitivity, specificity, PPV, NPV and diagnostic accuracy. Software used in the interpretation were SPSS ver. 24.0, GraphPad Prism ver. 6.0 and EPI-INFO ver. 6. A p value <0.05 was considered as level of significance.

OBSERVATIONS AND RESULTS:

Observations:

The present study evaluated 76 cases of primary malignancy in which metastatic deposits in the lymph nodes were suspected. The presence or absence of metastatic deposits was evaluated by intraoperative techniques of FSA and TIC and the findings obtained were confirmed on routine HPE. Of all the 76 cases evaluated in the study, 40 (52.63%) cases were males and 36 (47.37%) cases were females. Forty-one (53.95%) cases were under the age group of 41-60 years followed by 21 (27.63%) cases under the age group of 27.63% and 14 (18.42%) cases under the age group of 21-40 years. When histopathological diagnosis was considered, it was observed that oral squamous cell carcinoma (OSCC) occupied the major chunk (60.53%) of the cases. This was followed by infiltrating ductal carcinoma (IDC) of breast with 19 (25%) cases, colorectal adenocarcinoma with 5 (6.58%) cases, transitional cell carcinoma of bladder with 2 (2.63%) cases and 1 (1.32%) case each of non-keratinizing squamous cell carcinoma cervix, endometrial adenocarcinoma, malignant melanoma and papillary thyroid carcinoma (PTC).

Results:

It was observed that the number of positive nodes identified on FSA matched with the number of positive nodes on routine HPE in 71 (93.42%) cases. The findings were discordant in 5 (6.58%) cases [Fig. 1]. On comparing the same findings in case of TIC and routine HPE, concordance was observed in 63 (82.89%) cases while the number of nodes identified did not match in 13 (17.11%) cases. The sensitivity, specificity, PPV, NPV and diagnostic accuracy of FSA was found to be 97.30%, 100%, 100%, 97.50% and 98.68% while the same parameters for TIC were found to be 75.68%, 100%, 100%, 81.25% and 67% respectively [Fig. 2].

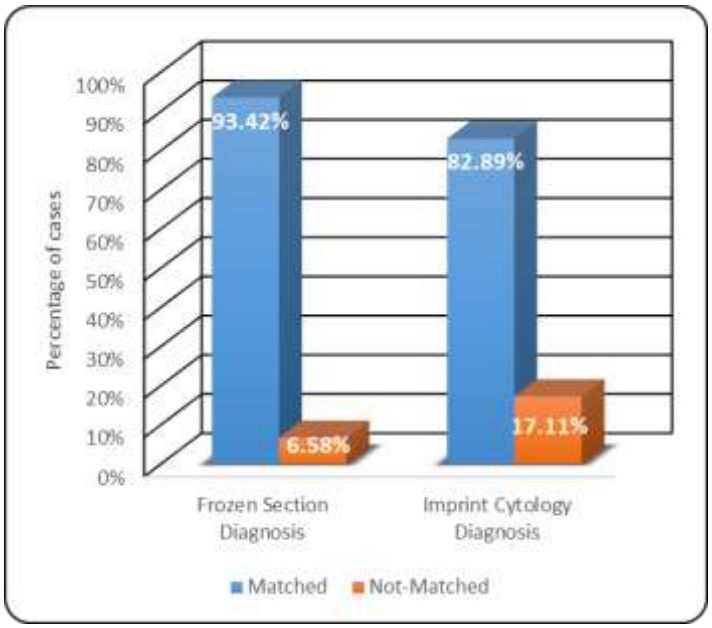

Fig.1: Correlation between number of positive nodes on frozen section and on imprint cytology with number of positive nodes on routine HPE.

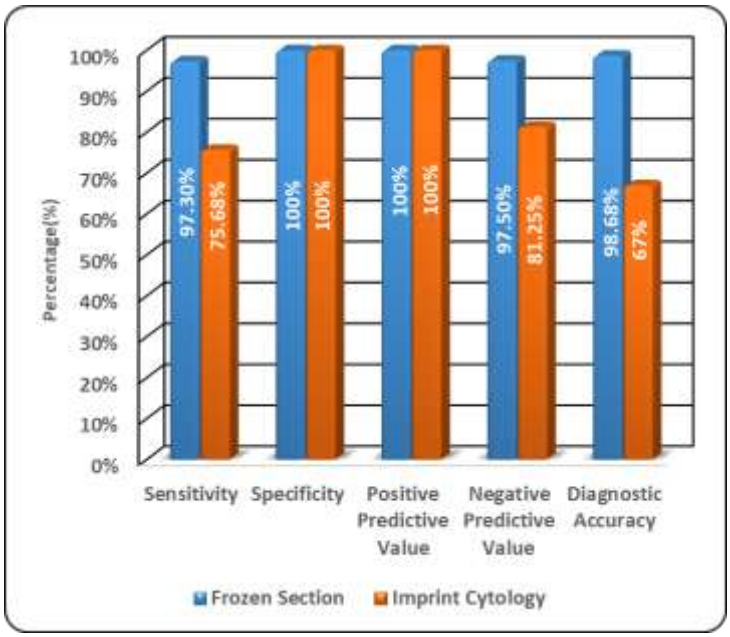

Fig.2: Sensitivity, specificity, PPV, NPV and diagnostic accuracy of frozen section and imprint cytology versus histopathological diagnosis.

DISCUSSION:

The present study made an attempt to evaluate the diagnostic efficacy of intraoperative modalities like FSA and TIC in detecting lymph node metastasis. The findings obtained on these two modalities were compared with the gold standard histopathological examination. The study also made an attempt to explore the research gap pertaining to the utility of intraoperative diagnosis by TIC and FSA in the management of malignant neoplasms. Nodal status on any malignant disease greatly influences the overall TNM staging and the prognosis of the disease [8]. Routine HPE is considered gold standard but it is time consuming and can't be used intraoperatively. The clinical significance of the present study is underlined by the fact that if the nodal status of the disease is known intraoperatively, it can help the operating surgeon modulate the therapeutic modality which can improve postoperative care and overall prognosis and survival in patients with metastatic lymph nodes.

Frozen section analysis (FSA) is an intraoperative diagnostic modality which can be used to differentiate between benign and malignant lesions. It has the capacity to process the specimen in short amount of time and aids the pathologist and the surgeon to evaluate the extent of malignant disease, tissue identification, diagnostic enzyme histochemistry and immunofluorescent methods. FSA also serves as an efficient intraoperative tool to evaluate metastatic lymph node deposits [9]. This technique has high sensitivity, specificity, PPV, NPV and diagnostic accuracy to detect lymph node metastasis. There is a good correlation between the findings obtained on FSA and routine, gold standard HPE. [Table-1].

Table-1: Table depicting the sensitivity, specificity, PPV, NPV and diagnostic accuracy of different studies pertaining to FROZEN SECTION DIAGNOSIS and their comparison with the present study:

STUDIES	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)
Horvath JW et al. [10]	75	100	100	81	92
Ballal DS et al. [11]	89.7	100	97	100	94.1
Lai SK et al. [12]	86.7	91	100	100	97.5
Kim JM et al. [13]	93.5	100	100	96.3	98.5
Lee DH et al. [14]	100	100	100	100	100
Desai DK et al. [15]	91	90	95	96	89
Krishnamurthy A et al. [16]	88.2	85	100	100	94.5
PRESENT STUDY	97.30	100	100	97.50	98.68

Touch imprint cytology is another intraoperative diagnostic modality used to evaluate benign and malignant lesions. It can also be used to evaluate metastatic lymph nodes [17]. It is based on the principle that malignant cells due to their dis-cohesive nature get easily dislodged from the cut surface of the malignant tissue. These dis-cohesive cells can be transferred onto a glass slide like an imprint and further processed [18]. It provides excellent cellular details and facilitates rapid diagnosis. It can be effectively used as an intraoperative tool to evaluate leukaemia, lymphoma, small round cell tumours, astrocytoma and papillary thyroid carcinomas (PTC) [19][20][21][22]. The present study depicted a satisfactory correlation between the findings obtained on TIC and the routine HPE. [Table-2].

Table- 2: Table depicting the sensitivity, specificity, PPV, NPV and diagnostic accuracy of different studies pertaining to TOUCH IMPRINT CYTOLOGY and their comparison with the present study:

STUDIES	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)
Creager AJ et al. [23]	53	98	94	82	84
Asthana MS et al. [24]	87.5	95.4	100	100	93.3
Barranger E et al. [25]	83	100	100	85.5	85.7
Jozaghi Y et al. [26]	68.8	86	100	100	80
PRESENT STUDY	75.68	100	100	81.25	67

Hence, the present study concludes that frozen section analysis has higher sensitivity, specificity, PPV, NPV and diagnostic accuracy as compared to TIC. It can provide detailed architecture of the lesion and is able to impart information regarding the size of secondary tumour and invasion into perinodal fat. In the present study, the frozen section findings in 93.42% cases coincided with routine HPE [Table/Fig: 1]. Dis-coherent findings observed in

6.58% of the cases can be attributed to poor selection of the tissue area, extensive tumour degeneration and necrosis, freezing artefacts, bloated cell morphology and poor processing of the sections. Interobserver and intra-observer variability can also lead to interpretative errors in the form of misdiagnosis, overdiagnosis or underdiagnosis.

Touch imprint cytology (TIC) is a rapid and inexpensive intraoperative modality [27] and can be used as an adjunct to frozen section. It is easy to perform, doesn't require high-tech equipment. Besides the material obtained can be used for ancillary techniques like immunophenotypes, cytogenetics and molecular analysis. In the present study, findings obtained on TIC coincided with routine HPE diagnosis in 82.89% cases [Table/Fig: 1]. The dis-coherent findings obtained in 17.11% cases could have occurred less diagnostic material obtained, presence of cauterized cells, imprint taken from non-representative areas and difficulty in differentiating reactive cells and well differentiated neoplasm. Few more studies on malignancies and associated metastases have been reported [28-33].

LIMITATION (S):

The present study investigated 76 cases of metastatic lymph node malignancy and was conducted for a duration of six months. Such short duration and small sample size are insufficient to assess the effect of implementing FSA and TIC on improving postoperative patient care, overall prognosis and survival in patients with metastatic lymph node deposits. Superior technical expertise is vital for obtaining high quality frozen sections. Otherwise, it can make the interpretation difficult. Similarly, reporting by a beginner surgical pathologist can lead to underdiagnosis or overdiagnosis of a malignant neoplasm. The present study investigated the role of FSA and TIC in epithelial malignancies (carcinomas). It was unable to study utility of these intraoperative modalities in mesenchymal malignancies (sarcomas). The turnaround time (TAT) was also not taken into account while carrying out the study.

CONCLUSION (S):

The present study concludes that frozen section analysis is a formidable intraoperative modality that can be implemented for evaluation of metastatic lymph node deposits in various epithelial malignancies. It is capable of providing a brief overview of the metastatic deposits. Touch imprint cytology can serve as a reliable adjunct to frozen section in remote areas where frozen section facility is not available. It is rapid as compared to frozen section but this comes at the cost of less diagnostic material and loss of tissue architecture. However, cellular details can be evaluated in great detail as compared to frozen section.

It is recommended that frozen section and touch imprint cytology be incorporated intraoperatively in all resections of malignant neoplasms to ensure that no residual disease is left behind. This will greatly reduce the chances of repeat surgery which will further ensure superior postoperative care and positive impact on the overall survival and prognosis in patients with nodal metastasis. Long duration studies with a larger sample size need to be conducted in this regard. Moreover, this study brings forward new avenues for research pertaining to the utility of frozen section and touch imprint cytology in evaluating mesenchymal malignancies (sarcomas). It also motivates surgical pathologists explore areas which can focus on reducing the turnaround time (TAT) of these procedures to increase rapidity of intraoperative diagnosis.

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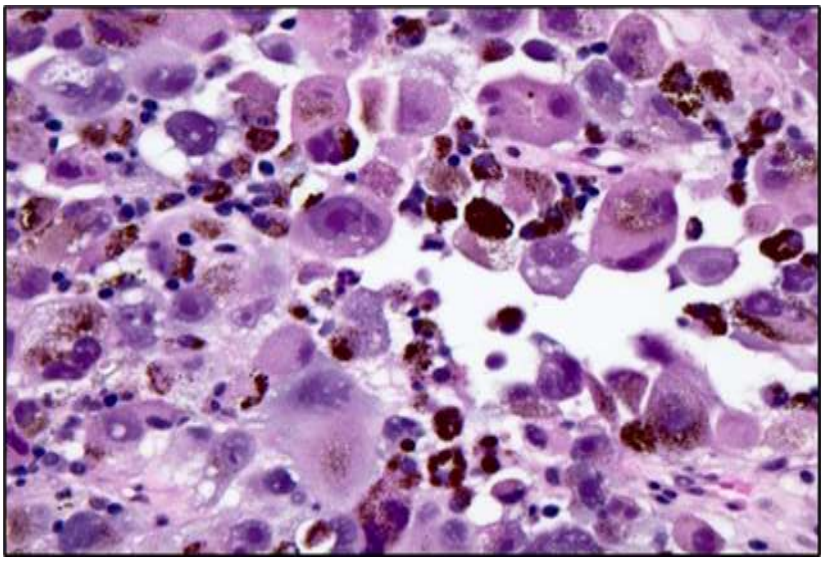
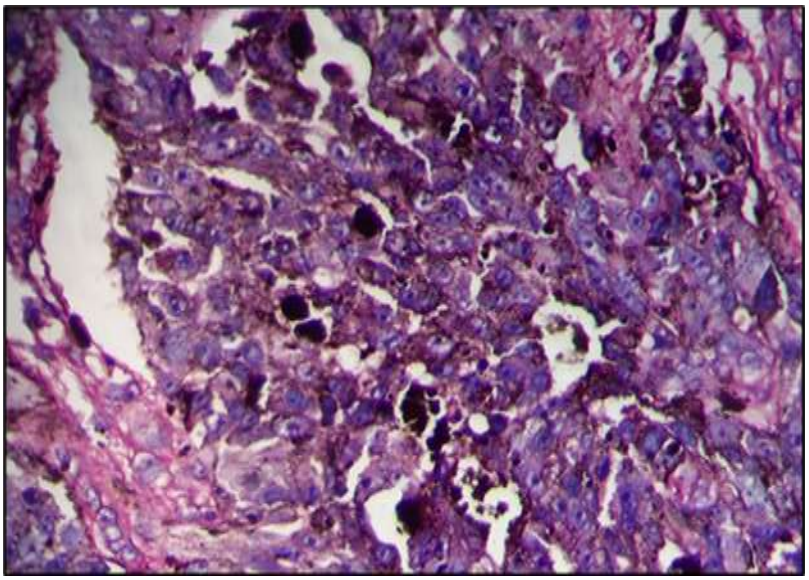
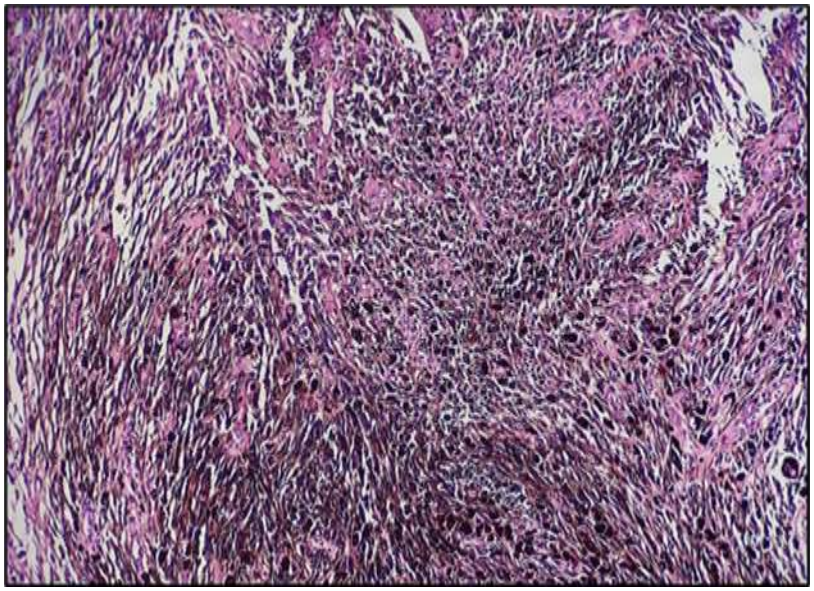


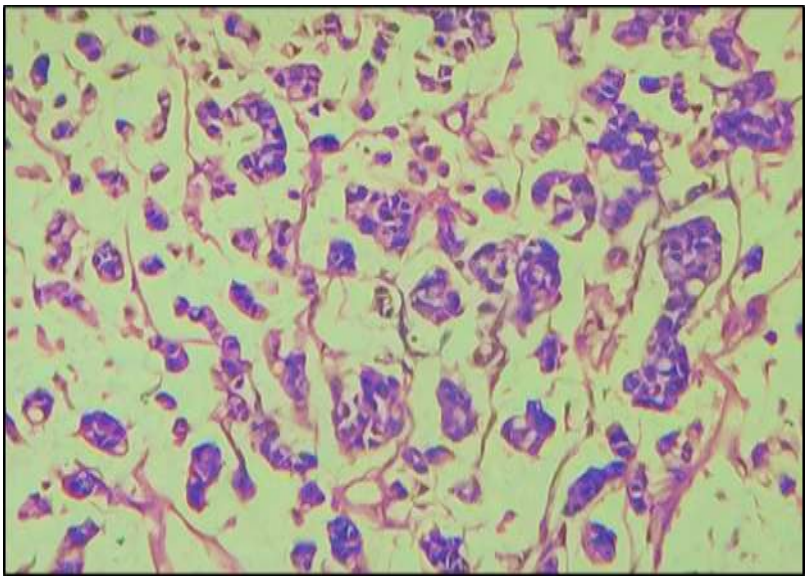
[Fig: 1]: Frozen section stained with rapid H& E stain showing metastatic deposits of Malignant melanoma (high power view: 40x).



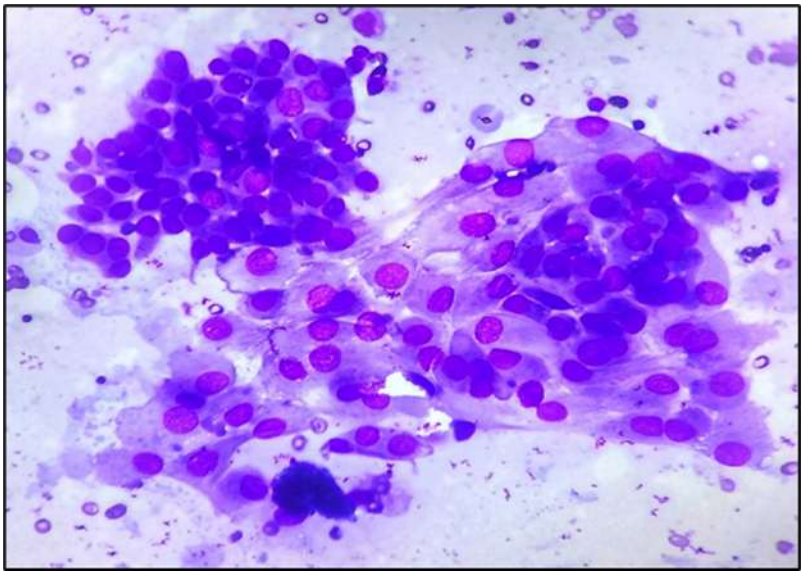
[Fig: 2]: Touch imprint cytology stained with rapid H& E stain showing metastatic deposits of Malignant melanoma (Low power view: 10x).



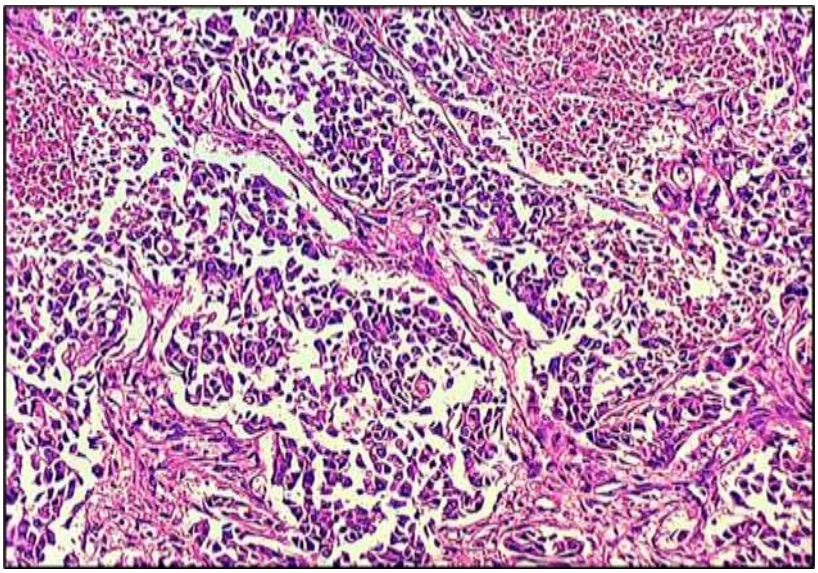
[Fig: 3]: Paraffin embedded section stained with conventional H& E stain showing metastatic deposits of malignant melanoma (low power view: 10x).



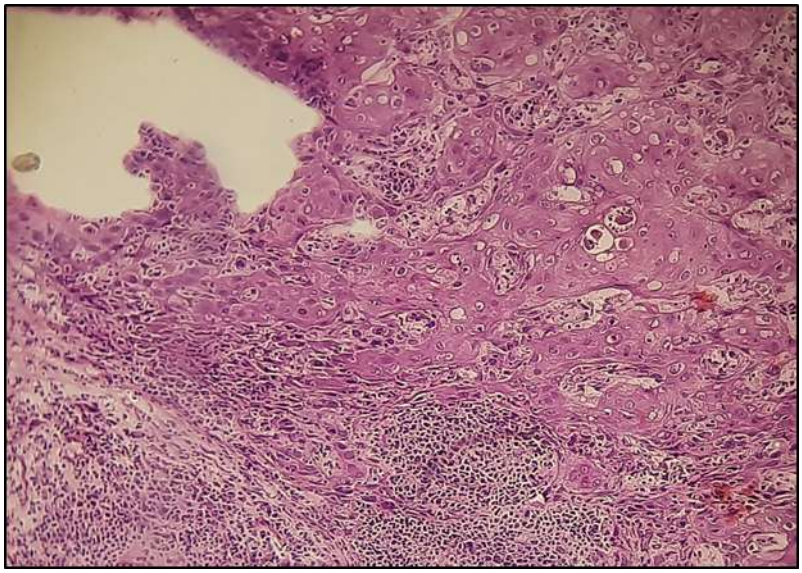
[Fig: 4]: Frozen section stained with rapid H& E stain showing metastatic deposits of Ductal carcinoma (Low power view: 10x).



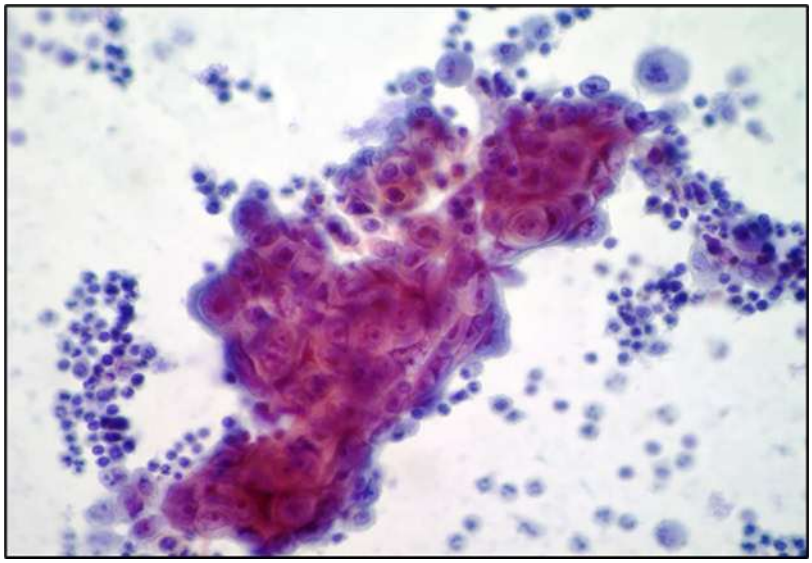
[Fig: 5]: Touch imprint cytology stained with rapid H& E stain showing metastatic deposits of Ductal carcinoma (High power view: 40x).



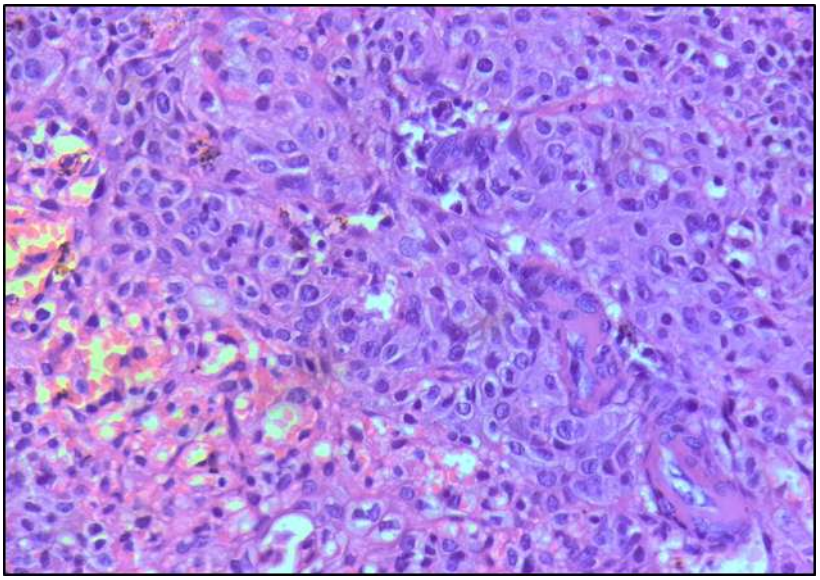
[Fig: 6]: Paraffin embedded section stained with conventional H& E stain showing metastatic deposits of Infiltrating ductal carcinoma (not otherwise specified: NOS type) (low power view: 10x).



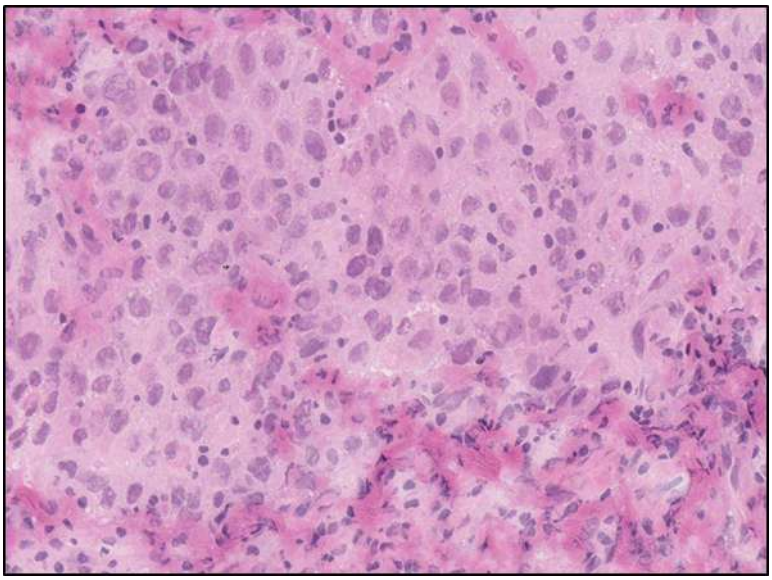
[Fig: 7]: Frozen section stained with rapid H& E stain showing metastatic deposits of Squamous cell carcinoma (Low power view: 10x).



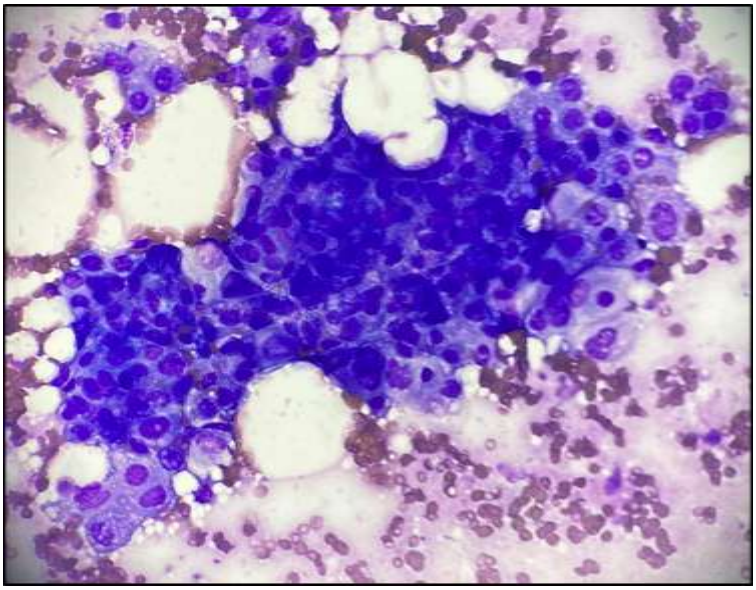
[Fig: 8]: Touch imprint cytology stained with rapid H& E stain showing metastatic deposits of Squamous cell carcinoma (High power view: 40x).



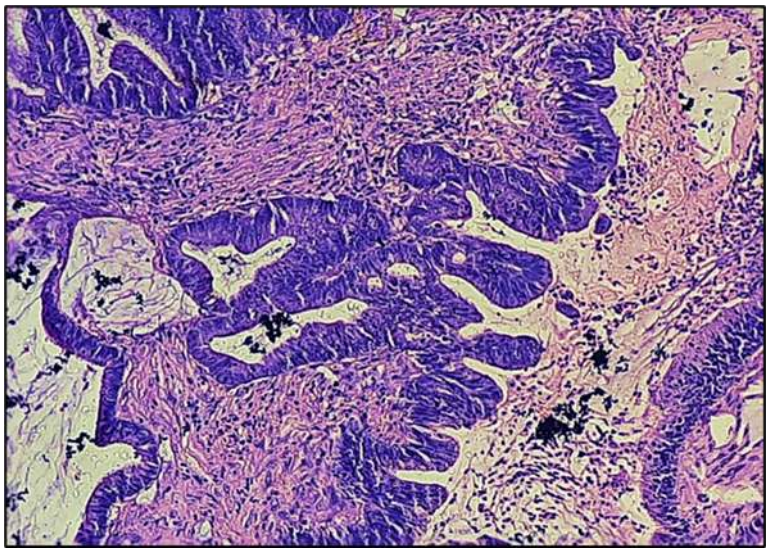
[Fig: 9]: Paraffin embedded section stained with conventional H& E stain showing metastatic deposits of Squamous cell carcinoma (low power view: 10x).



[Fig: 10]: Frozen section stained with rapid H& E stain showing metastatic deposits of colorectal adenocarcinoma (Low power view: 10x).



[Fig: 11]: Touch imprint cytology stained with rapid H& E stain showing metastatic deposits of Colorectal adenocarcinoma (High power view: 40x).



[Fig: 12]: Paraffin embedded section stained with conventional H& E stain showing metastatic deposits of Colorectal adenocarcinoma (Low power view: 10x).