Validation of frozen section in intraoperative decision making in malignancies

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CERTIFICATE

This is to certify that the dissertation entitled "**Validation of frozen section in Intraoperative decision making in malignancies"**is a bonafide work done by **Dr. K. Kavitha ,** Department of Surgical Oncology, Centre for Oncology, Government Royapettah hospital and Kilpauk Medical College , Chennai, in partial fulfillment of the University rules and regulations , for the award of **M.Ch.Degree (Branch VII) in Surgical Oncology** , under my guidance and supervision during the academic year**August 2011 to August 2014**.

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DECLARATION

I solemnly declare that the dissertation titled "***Validation of frozen section in intraoperative decision making in malignancies*** was done by me at Department of Surgical Oncology, Kilpauk Medical College andGovernment Royapettah Hospital, Chennai between August 2011 to February 2014 under theguidance and supervision of Prof. Dr. R.Rajaraman. The Dissertation is submitted to The TamilNaduDr.M.G.R. Medical University towards the partial fulfillment for the award of M.Ch.Degree(Branch VII) in Surgical Oncology.

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CONTENTS

INTRODUCTION

The Frozen section procedure is a laboratory procedure to perform rapid microscopic pathological analysis of specimen. The technical name of this procedure is *Cryosection***.**

Frozen section is an important tool in the armamentarium of the surgical oncologist. Intraoperative diagnosis is extremely important and may provide direct evidence and foundation for the extent of the surgery.

Intraoperative cytopathological diagnosis is done for the following reasons

1. Establishing the nature of disease

   When the primary diagnosis of malignancy is uncertain, a frozen section is done for diagnosis which in turn alters the management plan.

2. Assessment of adequacy of margins , nodes or extent of disease

   When the primary diagnosis of malignancy is established, frozen section is valuable in assessing margin status, extent of disease & nodes which help in decision regarding operability & extent of surgery.

3. Representation of biopsy specimen

   In difficult biopsy specimens, frozen section helps to determine the specimen adequacy and to ascertain whether the biopsy is taken from the representative area.

However, frozen section has its own limitations. The frozen section artifacts, suboptimal histology of the frozen section, pressure for an immediate diagnosis, and lack of ancillary studies at the time of intraoperative consult are among the limitations of the frozen section diagnosis. With better quality histology and additional anxillary studies such as immunohistochemistry, flow cytometry, etc., we may be able to make a more thorough diagnosis on the permanent evaluation.

Frozen section is considered unacceptable in the following circumstances

Request done out of curiosity

If the frozen section report will not change the immediate treatment or surgical plan

REVIEW OF LITERATURE

HISTORY OF FROZEN SECTION

Prior to the 19th century , pathological diagnosis was primarily made post mortem. Giovanni Morgagni is considered to be the father of Pathological anatomy. He published his series of clinical and gross pathological correlation of 700 autopies in his book, " The seats and causes of disease ''in the year 1761 . (1)

Pathology as an independent speciality of medicine originated with Karl Rokitansky who putforth the first general classification of diseases between 1842 and 1846. (2)

The first intraoperative frozen section was requested by William Halsted at the John Hopkins Hospital ,for a case of suspected breast cancer , to be done by pathologist Welch in 1891 (3).

Welch prepared the slide using a CO2 freezing microtome. In 1895, Thomas Cullen developed a technique of freezing formalin fixed tissue. The fixation step however took more than an hour prior to frozen section .

The Cryostat method, currently accepted as the standard was first published in JAMA in 1905 by Louis Wilson of the Mayo Clinic.(4). A Dextrin solution was used to embed the tissues and a CO2 microtome was used. Finally Methylene blue was used to stain the slides . Since permanent mounting was not done , this procedure could be completed in a few minutes as against an hour in the Cullens technique. Today, most centres use a brief fixation prior to staining with hematoxylin and eosin, but the technique is similar to the one introduced by Wilson.

QUALITY ASSURANCE INDICATORS IN FROZEN SECTION

The College of American Pathologists have laid down standards for performing frozen section (5, 6)

1. Only one frozen section specimen should be grossed in each grossing area
2. Only labeled slides to be used to avoid switching of specimens
3. The slides , after frozen section must be permanently mounted and retained in the archive along with the permanent sections
4. The cryostat must be periodically cleaned with 70% alcohol.
5. Cryostats used regularly must be thawed every week
6. Frozen section turnaround time should be limited to 20 minutes of the receiving the specimen

Technical Considerations

Frozen section can be produced by using a freezing microtome, Cryostat or a standard microtome modified by the addition of thermomodules. Cryostat is the most common instrument used .

Cryostat:

A cryostat is a refrigerated chamber , that has a means to freeze samples, houses a rotating microtome and a knife holder. The normal working temperatures are between 0 to -30 degrees C . Temperatures below this require the use of cryogens like liquid nitrogen. The section thickness can be adjusted to 5 to 30 microns. The recommended temperature at the start of procedure is – 20 degrees.

Procedure:

1. Grossing the specimen

2. Sampling the most representative area

3. Embedding

4. Freezing

5. Sectioning

6. Fixation

7. Staining and cover slipping

8. Interpretation

Embedding:

After grossing , sampling is done in the representative area with size of specimen block no more than 2 X 2 cm. The specimen block is next embedded with the help of an embedding medium. Embedding is a means of freezing the tissue in a precise position .Commonly used solutions for embedding are polyvinyl alcohol and polyethyleneglycol.

Freezing techniques:

A variety of techniques can be used for freezing.

1. Plunge freezing into cooled isopentane

   A small beaker containing isopentane is placed in another container of dry ice to bring about a working temperature of – 70 degrees. Tissues frozen by this method can be immediately sectioned.

2. Using a cryocompound : Specimens are mounted on a specimen holder with the cryocompound and allowed to freeze in the chamber

   Optimal Cryostat temperatures for un fixed tissues:

-12 to – 16 degrees:	Lymph node
	Liver
	Kidney
	Spleen
	Testis
	Brain
-18 to – 30 degrees:	Breast
	Skin
	Thyroid
	Adrenal
	Muscle

Sectioning:

Sectioning is done with the rotating microtome and using either a brush or anti roll plate to prevent rolling of sections. The sections are retrieved on a glass slide. It is important to cut at the ideal temperature

because further decrease in temperature causes tissue to shatter and curl . Cutting is ideal at – 16 to – 18 degrees.

For best interpretation of morphology, sections must be 5 microns thick.

Fixation:

The slides are immediately fixed with a fixative , which may be 95% ethanol, methanol, formalin or acetone. 95% ethanol is most commonly used. If fixation is delayed for a few seconds, air drying artefacts may occur.

Staining :

Staining is done similar to regular H& E sections or using toluidine blue.

Artefacts:

1.Freezing artefacts:

Slow freezing can cause ice crystal formation that can replace the normal architexture with a swiss cheese pattern. Hence freezing has to be rapid , to avoid crystallization of water to form artefacts.

2.Air drying artifact:

Air drying causes enlargement of cells and nuclei, leaking of cytoplasmic fluid, blurring of cytoplasmic borders and smudging of nuclear details.

FROZEN SECTION ERRORS

The possible reasons for errors in a frozen section analysis are

1. Technical

   Example: Difficulty in mounting, staining or mechanical problems with the cryostat

2. Sampling error
3. Diagnostic error
4. Communication error

Sampling error accounts for two thirds of discrepancies in frozen section . Diagnostic error accounts for less than 0.5 % of errors.(7)

IMPLICATIONS OF A FALSE RESULT ON FROZEN SECTION

The implications of a false positive result on frozen section would be added cost of frozen section in addition to

1. Unnecessary surgery and associated risk and morbidity . Ex: Lymphedema in completion axillary dissection
2. Increased volume of resection
3. Increased operative time and cost

The implications of a false negative result would be

1. Reoperations : Ex: margin positivity on final histopathology requiring reexision
2. Additional morbidity during re operation since this may be technically more difficult than the primary surgery due to post operative fibrosis and inflammation
3. Additional cost
4. Psychological trauma to the patient

INTERPRETATION

INTRAOPERATIVE CONSULTATION OF HEAD AND NECK MALIGNANCIES

Since the preoperative diagnosis is often available, intraoperative consultation for head and neck malignancies is usually for assessment of margin and nodal status. Problems encountered during frozen section are due to mucosal changes such as edema and inflammation with postinflammatory atypical cells secondary to neoadjuvant therapy.It maynot be technically possible at frozen section to differentiate these changes from microscopic nests of residual tumor. Because of this, a frozen section diagnosis of infiltrative cancer should have irregular growth patterns and desmoplasia.

In head and neck cancer there may be foci of in situ changes in the margin , due to field cancerisation. Batsakis (8) reports that involvement of the margin by invasive cancer must be reported as positive margin. The clinical significance of preinvasive dysplasia in terms of overall and disease free survival is debatable(8,9,10,11). Local recurrence can occur in 75% of patients with a positive surgical margin.The most widely accepted close margin is less than 5 mm(12) from the inked margin.

The margin for analysis can be obtained from the specimen side or from the patients side. Spiro et al (13) reported a diagnostic accuracy rate of 89% when the specimen was collected either way . More importantly , it was found that there was difficulty in relocating the frozen section harvest site , for additional clearance.

In general, frozen section for margin status has 96% to 99% correlation with final histopathology.(14, 15)

Frozen section analysis of neck nodes is generally non problematic. Frozen section analysis of sentinel nodes give a sensitivity of 93% and negative predictive value of 94%

Artefacts of previous treatment:

1. Epithelial hyperplasia and ulceration
2. Stromal changes characterized by atypical fibroblasts due to previous radiotherapy (radiation fibroblasts)
3. Delayed vascular changes following radiation. Intimal proliferation with foamy macrophages are seen several weeks post radiation
4. Treatment related sialometaplasia

Frozen section of salivary gland tumors:

The main indications would be to differentiate benign from malignant tumors. The accuracy of a preoperative FNA is as good a frozen section(16) and the results of the FNA must be made available. In a pleomorphic adenoma, the diagnostic difficulty is to differentiate from mucoepidermoid carcinoma and carcinoma ex- pleomorphic adenoma due to the presence of hypercellularity.

Contraindication for frozen section in head and neck malignancies :

1.When the frozen section analysis does not directly affect the management

2. Evaluation of lesions that are suspicious for melanoma

3. Evaluation of heavily calcified or ossified tissue

INTRAOPERATIVE CONSULTATION OF THYROID MALIGNANCIES

Frozen section has historically been used to evaluate thyroid nodules , to aid in immediate completion thyroidectomy if a diagnosis of malignancy is confirmed. Papillary carcinoma of thyroid has nuclear features like overlapping, crowding and nuclear membrane changes like, intranuclear cytoplasmic pseudoinclusions seen as nuclear grooving . Frozen section does not pick up the characteristic nuclear membrane features.The classical " orphan annie eye nuclei''of papillary carcinoma are artifacts due to chromatin clearing on paraffin fixation and are not appreciated on frozen section. A preoperative FNA or an intra operative imprint cytology brings out the nuclear features of papillary carcinoma , better than a frozen section.

Medullary carcinoma cells exhibit a fine granular cytoplasm and salt and pepper chromatin and inconspicuous nucleoli. These features are identifiable by FNA, frozen section and by final paraffin sections.

Thus the advent of FNAC has decreased the need for frozen section, with most of the diagnosis of papillary and medullary carcinoma being done by FNA with reasonable accuracy.

Since the diagnosis of follicular carcinoma requires the presence of invasion, it is not reliably established by FNA. A large meta analysis of comparison of FNA vs frozen section in thyroid malignancies showed that FNA had better sensitivity , but less specificity and positive predictive value when compared to frozen section . (17)

The value of frozen section in follicular neoplasms of thyroid was evaluated by Callcut et al . Of 152 cases frozen section was reported as benign in 32%, indeterminate in 2% and malignant in

4%, further evaluation necessary in 62%.Howeven for those reported as positive, the sensitivity was 67%, specificity and positive predictive value 100% .

Hence, the current major indication for frozen section for thyroid malignancy is to characterize a follicular neoplasm . However, even in these cases, possibility of deferring the diagnosis until permanent sections are obtained can occur in upto 60% of situations. This is due to the need for meticulous sectioning required to identify capsular and vascular invasion , which may be difficult in the limited number of sections done during frozen section(18) .Hence, the clinical utility of frozen section in thyroid malignancies is questionable.

INTRA OPERATIVE EVALUATION IN GYNAECOLOGICAL ONCOLOGY

Major indication for frozen section in gynaecological oncology

1. Characterization of ovarian masses

2. Evaluation of uterus in cancer endometrium

3.Margin assessment for vulvectomy specimens(19)

OVARIAN MASSES

They form one of the major indication for frozen sections, due to the decreased sensitivity of preoperative investigations to clinch a diagnosis of malignancy with certainity. A localized complex ovarian mass on imaging predicts malignancy only in 25% of cases. Only 25% of stage I ovarian masses have elevated tumor markers. (20)

Procedure:

It is imperative to document the intactness of ovarian capsule and ovarian surface involvement before opening the specimen.

Nature of contents , presence of solid & cystic areas to be noted.

Pathologies which do not require frozen

1. Unilocular cyst with smooth lining and no solid areas or papillary excrescence can be reported as benign simple cyst because sampling of the cyst wall would be random and the chance of finding an occult lesion is very minimal .

2.Teratoma

Sebaceous contents , hair or other features of teratoma should direct a search for the Rokitansky tubercle. This is the solid component of a teratoma which has to be evaluated . If no soft, fleshy component is present , a report of benign cystic teratoma may be given without a frozen section.

When evaluating the Rokintansky tubercle, a search for immature neural epithelium must be made. Here the possibility of a mature neuronal differentiation like retina or cerebellar granular layer should be born in mind.

3. A Unilocular chocolate cyst without a solid component is diagnostic of endometriosis and a diagnosis can be given without frozen, if there is no solid component.

Soild components are usually areas of fibrosis, but since clear cell and endometroid carcinomas can be associated, these areas need to be sampled.

Serous tumors

Serous carcinomas present as solid – cystic masses and exhibit obvious cystological atypia on frozen section.

Serous borderline tumors present as unilocular serous cyst with papillary lining.

Mucinous Tumors

They form a great source of discrepancy in gynaecological specimens.

Mucinous tumors may be primary or secondary. In primary lesion, they may be benign, borderline or malignant.

Lesions with a few smooth walled cysts and no solid areas are benign, 95% of the time. They can be reported without a frozen section. (21)

Multilocuted, solid and cystic mucinous tumors require frozen section evaluation.

Adequate sampling requires one section per cm of this tumor which is impractical on frozen section. Hence up to 25% of patients diagnosed as borderline tumor will have evidence of carcinoma on final histopathology.

The predictive value of frozen section is 95% for benign, 65% for borderline and 99% for malignant tumor.(22)

Metastatic lesions to ovary

Ovarian metastasis can arise from any part of the gut.(23)

Gross appearance of metastatic lesions vary from solid lesion to a multiloculated cystic lesion to a unilocular lesion occasionally.

Krukenbergs tumor present as bilateral solid lesions with smooth, lobulated surface with mucin extruding on cut section.

All patients with bilateral tumors and suspicious histology must have the GIT evaluated during surgery. Appendectomy is a part of staging for mucinous tumors. Patients with ovarian mucinous tumor with pseudomyxoma Peritonei, must have an appendectomy performed.(24)

Features to differentiate a metastatic versus primary mucinous tumor[25)

	Primary	Metastasis	P Value
Laterality	Unilateral 95%	Bilateral 60-75%	< 0.000
Microscopic surface involvement	Absent	79%	<0.00
Nodular growth pattern	Absent	42%	<0.000
Infiltrative invasive pattern	16%	91%	<0.000
Small glands	12%	94%	<0.000
Expansile invasive pattern	88%	18%	<0.000
Complex papillae	60%	8%	0.0004
Benign appearing areas	76%	36%	0.008
Borderline with atypia	57%	31%	0.035

Ovarian small blue cell tumor

Differential diagnosis:

- Ovarian lymphoma

- Granulosa cell tumor

- Undifferentiated Carcinoma.

- Desmoplastic round cell tumor.

Ovarian tumors in pregnancy

Adnexal masses in pregnanacy vary in incidence from 1 in 632 (26) to 1 in 1000 (27). Most of these are benign

Mature cystic teratoma	27-50 %
Cysadenomas	20-34%
Functional lesions	13-18%

Malignant, including borderline tumors were around 6% of tumors (28)

Germ cell tumors form the majority	30-40%
Borderline tumors	30-35%
Cysadenocarcinoma	05-10%
Stromal tumors	10-20%

The differential diagnosis of solid lesions with cells with abundant pink cytoplasm are

1.Functional lesions

Luteoma of pregnancy, Corpus luteum of pregnancy , Stromal hyperthecosis

2.Tumors :

Steroid cell tumor

luteinized granulose cell tumor

Leydig cell tumor

Oxyphilic variant of clear cell carcinoma

Metastatic carcinoma with stromal luteinisation.

ENDOMETRIAL CARCINOMA

Intra operative evaluation may be done to detect the depth of myometrial invasion and confirmation of grade, since most patients have a pre operative diagnosis available.

Accuracy of intra operative assessment of grade is between 80-96% and under grading can be done and is usually due to sampling error.(29)

Assessment of myometrial invasion by gross inspection may be wrong in30% of cases , especially with high grade tumors.(30)

In general intra operative assessment in gynaecologic oncology is useful, with the exception of ovarian mucinous tumors.

INTRA OPERATIVE EVALUATION OF SKIN LESIONS

Indications

Frozen section for margin assessment forms the main indication in Skin cancers.

On rare occasions, frozen section may be used for primary diagnosis.

Frozen section for non-melanoma skin cancers

Accurate assessment for margins is important in squamous cell carcinomas and basal cell carcinoma, since local recurrence rates may be as high as 60% with positive margins.(31 ,32)

Margin assessment is more important in recurrent lesions. In primary tumors 90% present with distinct borders. In recurrent tumors, microscopic foci of disease may be present beyond the clinically detected margin in 24% of cases.(33)

Therefore the appropriate indications for frozen section in non-melanoma skin cancers are

- Clinically illdefined lesions
- Recurrent lesions
- Infiltrative growth pattern
- Location in areas like eye, forehead, nose etc were wide resection may not be feasible
- When immediate complex reconstruction is planned after treatment

Frozen section in malignant melanoma.

Frozen section should be discouraged for a suspected melanocytic lesion because

- Freezing causes tissue distortion which precludes assessment of depth of invasion
- Ability to determine cytological atypia is compromised with freezing
- Difficulty in differentiating junctional melanocytic hyperplasia from Melanoma.

Hence frozen section for melanoma is to be restricted to lesions present in cosmetically important areas like the face and as a part of Mohs micrographic surgery.

Moh's micrographic surgery

Moh's micographic surgery is a special surgical technique used for high risk skin cancer, in locations were wide clearance cannot be achieved. This provides high cure rates in addition to maximal preservation of uninvolved tissue.(34)

In Mohs surgery, serial horizontal sectioning of tissue is done unlike the vertical sectioning done for wide local excision. This allows for complete assessment of entire surgical margin. The first specimen is excised with 0.5 - 1cm margin, it is oriented, photographed and horizontally sectioned to 5 to 7 microns thickness ,frozen and processed. In case of positive margins, the exact site of tumor involvement is re-excised and evaluated until a negative margin is achieved. Immunostaining can be used to aid frozen section analysis. Rapid immunostaining for cytokeratin , MART-1 and CD-34 are available, for evaluating squamous cell carcinoma, Melanoma and Dermatofibrosarcoma protruberons respectively.(35)

Indications of Mohs surgery

1.High risk basal cell carcinoma

BCC’s > 6mm

BCC’s located in central face, eyelids, ears, pre and post auricular areas, chin, hands and feet

Recurrent lesions

Tumors >20mm on the trunk with aggressive pathological features

2. Squamous cell carcinoma

Poorly differentiated tumor

Tumors exhibiting perineural invasion

Size >20 mm in high risk locations (ears, lips)

3.DFSP

4. Microcystic adnexal carcinoma and extra –mammary pagets disease

These have a high recurrence risk despite wide excision and negative margins, hence the necessity for frozen section

5.Melanoma.

The use of Moh’s surgery in melanoma is controversial. There are no randomized comparison of wide excision with Moh’s surgery. However, a report of 625 patients with head and neck melanoma treated with Moh’s surgery showed similar DFS and recurrence rates compared to historical control, when followed up for a period of 58months.(36)

Limitations of Moh’s surgery - Frozen section analysis

Cases with skip areas such as superficial basal cell carcinomas can recur despite negative margins.

Cancers with perineural invasion like squamous cell cancers can recur despite negative margins.

Frozen section can be difficult to interpret in dense inflammation .

There may be difficulty in differentiating BCC from basaloid proliferation.

INTRA OPERATIVE EVALUAITON OF BREAST LEISONS

Intra operative assessment of breast lesions has historic relevance because frozen section was primarily developed to evaluate breast lesions which were only clinically detected in the pre-mammographic era.

Currently, most diagnosis of breast cancers are made pre operatively by FNA or core needle biopsy. Hence frozen section is currently indicated

- When previous multiple core needle biopsies are negative, for a suspected malignant lesion.
- Margin assessment following breast cancer conservative surgery.
- Evaluation of sentinal node

Frozen section of sentinel node.

Sentinel node biopsy has become the standard of management of node negative axilla, in cancer breast. The use of frozen section avoids re operation in view of positive sentinel node on final histopathology. The ASCO recommends for an intraoperative assessment of sentinel node by frozen section , in spite of risk of potential loss of diagnostic tissue.(37)

Hence, frozen section is justified if the surgeon is prepared to perform an at the same sitting axillary dissection, in the event of positive sentinel node.

There is a reported 10-30% false negative rate of frozen section, which is due to sampling error, ie failure to freeze the entire node or inadequate sectioning. Frozen section is also less reliable to identify micrometastasis and isolated tumor cells . [38].

However, the false positive rate of frozen section is low, justifying its use in node negative axilla.

Invasive lobular carcinoma requires a special mention due to the increased false negativity associated with it on frozen section. Chan et al have reported a meta analysis of 5298 breast cancers and showed that the false negative rate for ILC was 47.6% vs 37.8% for IDC, p=0.006 . [39]

INTRA OPERATIVE EVALUATION OF THE BILIARY SYSTEM

Frozen section in mass lesions of the liver

Usually indicated for liver lesions detected during abdominal surgery for other malignancies, to rule out metastasis.

Rarely primary liver tumors may be subjected to frozen section for diagnosis and for margin status.

Metastatic tumor

Diagnosis of metastatic tumor is usually straightforward and is achieved by using desmoplasia and cytomorphological features of malignancy like nuclear and architectural changes. However, it is not possible to distinguish between intrahepatic cholangiocarcinoma from metastatic adenocarcinoma, unless an insitu component is identified.

Hepatic adenomas

They occur only in non-cirrhotic livers and never cause elevation of AFP. The key to distinguish an adenoma from normal liver is that, an adenoma lacks portal tracts within the tumor.

Hepatocellular carcinoma

The differential diagnosis of HCC in a non cirrhotic is Focal nodular hyperplasia and hepatic adenoma and in the differential diagnosis in a cirrhotic liver is dysplastic nodule.

The presence of intracytoplasmic bile rulesout a metastatic tumor.

The presence of cirrhosis or macrovesicular steatosis must be reported because this may influence the extent of resection.

Gallbladder and Extra hepatic billiary tree

Frozen section are generally indicated for margin status.

There is a high false negative rate of around 9% for bile duct margins in cholangiocarcinoma. This is because of marked reactive changes produced by mucosal erosion and inflammation, probably secondary to stent placement.(40)

The occurrence of dysplasia at the margin, doesnot affect survival in contrast to invasive carcinoma at the margins. The presence of dysplasia, nevertheless must be reported. (41)

Pancreas

Frozen section of pancreatic malignancies are one of the most difficult to interpret, the reasons being:

The frequent co-existance of chronic pancreatits

Dense inflammatory response to tumors.

Mild cytological atypia displayed by pancreatic adenocarcinomas.

Hence frozen section for a primary diagnosis of pancreatic malignancy is generally discouraged.

INTRA OPERATIVE EVALUATION OF NODES

Indications:

1. To rule out metastasis in known malignancy
2. Evaluation of sentinel node
3. Evaluation of nodes for suspected lymphoma

   The differential diagnosis of enlarged nodes would be infective , including chronic infections like tuberculosis, sarcoidosis, metastasis and lymphoma.

Suspected metastatic nodes

Metastasis to non regional nodes would deem a carcinoma metastatic and render the patient inoperable for curative surgery. Hence , it is important to subject suspicious non regional nodes for frozen section , if encountered during a curative resection. This situation is appropriate in most GI malignancies, cervical cancer and mediastinal lymphadenopathy for non small cell lung cancer. Frozen section can reliably predict metastasis in 97% of cases.

Nodal evaluation in melanoma

Clinically enlarged node or a sentinel node may be subject to frozen section in cases of melanoma. Melanoma has a wide spectrum of cytomorphological features and can mimic lymphoma, sarcoma or metastatic carcinoma. The presence of dusky brown pigment is a clue , but pigmentation may also be associated with melanocytic hyperplasia and pigmentation may be absent in amelanotic melanomas.

Evaluation of sentinel node in a melanoma has very low sensitivity of 29 to 82%. Hence frozen section is currently not recommended for evaluation of melanocytic lesions.

Sentinel node evaluation

Sentinel node biopsy is now considered standard for evaluation of node negative axilla in cancer breast. The reported sensitivity and specificity for sentinel node biopsy is 76% and 99% respectively. Notably, frozen section is more sensitive than touch imprint cytology , which has a sensitivity of 62% but with similar specificity at 99%. The sensitivity of frozen section can be improved with the addition of rapid immunohistochemistry , but the addition of this is not mandatory for evaluation of sentinel nodes.

Intra operative evaluation of suspected lymphomas

The accuracy of diagnosing of lymphoma by frozen section or imprint cytology is relatively poor. The mean diagnostic accuracy is 78%. This is due to the difficulty in differentiating low grade tumors from relative hyperplasia and the diagnosis is confirmed only by final histopathology with the aid of ancillary studies. (42)

Hence frozen section is discouraged, since it uses up diagnostic material and it fails to provide the detailed cellular morphology required for definitive diagnosis.(43)

Artifacts in nodal evaluation:

Artifacts of preparation can make interpretation difficult. Lymph nodes with fatty replacement in particular can cause difficulty in sectioning. Air drying artefacts can limit cytological assessment.

INTRAOPERATIVE EVALUATION OF THE GASTROINTESTINAL TRACT

Indications :

To determine the adequacy of tumor resection by evaluating the margins.

To determine the diagnosis ,when unexpected or unusual findings are encountered.

Contraindications :

Frozen sections are to be avoided on endoscopic biopsies for the following reasons

1. Small amount of tissue available would be exhausted on frozen section and would be unavailable for final study
2. Frozen artefacts may compromise the accuracy of diagnosis.

ESOPHAGUS

Most common indication is margin assessment following resection. Details of preoperative therapy including radiotherapy or chemotherapy should be available to the pathologist to avoid misinterpretation of radiation atypia as neoplasia.

During margin assessment, It is imperative to check for presence of insitu lesions such as Barrett's esophagus, which may be at risk of neoplastic transformation later.

It has to be remembered that occasionally adenocarcinoma may extend proximally in submucous plane, leaving the overlying mucosa to be normal. One report of such extent for 8cm available (44)

STOMACH

Margin assessment

Frozen section of gastric adenocarcinoma is usually straight forward. However signet ring cell gastric adenocarcinoma can pose difficulties. The tumor cell in this case is small, inconspicuous, are non cohesive and may resemble lymphocytes.

Mesenchymal tumors

Diagnosis of gastric mesenchymal tumors are difficult on frozen section since most of them have the appearance of spindle cell lesions. The differential diagnosis would be GIST, leiomyoma, leiomyocarcinoma, nerve sheath tumour and inflammatory polyps .The definitive diagnosis requires the presence of specific immunostaining. There may be difficulty in reporting a benign spindle lesion on frozen section because, further sectioning may show features of aggressive behaviour.

SMALL INTESTINE

Frozen section is commonly done in the small intestine to characterize a mass lesion .High grade lymphoma and adenocarcinomas are diagnosed with reasonable accuracy in frozen section. However the diagnoses of low grade lymphomas are to be deferred until permanent sections are prepared.

Metastatic tumors are more common in the small bowel when compared to a primary. Feature that suggest a primary tumor are, presence of a precursor lesion like adenoma , predominant lesion in the superficial layers or predominant involvement of the outer layer of bowel wall would suggest metastasis.

APPENDIX

The margins for resection are not necessarily evaluated in adenocarcinoma of the appendix since a right hemicolectomy is indicated for appendicular adenocarcinoma regardless of margin status. However, for a carcinoid tumor, margin status is important because , for a negative margin, resection would suffice .

COLON AND RECTUM

Generally margin assesment is done by gross evaluation. Occasionally, a distal resection may be subject to frozen section for an ultra low anterior resection.

FROZEN SECTION OF BONE TUMORS

Intraoperative evaluation is discouraged in bone tumors due to the difficulty in freezing calcified or chondroid tissue and the inherent errors associated with differentiating between neoplastic and reactive processes and between benign and malignant pathologies.

In bone tumors, intraoperative evaluation however can be done for evaluating the biopsy from the soft tissue component, to make sure they represent the tumor and would be adequate for evaluation by paraffin sections.

SUMMARY OF REVIEW OF LITERATURE

Frozen section can be undertaken with reasonable accuracy for evaluating the following

1. Evaluation of margin status and nodes in head and neck squamous cell cancers
2. Diagnosis of most ovarian masses with the exception of ovarian mucinous neoplasms
3. Diagnosis of a breast primary, assessment of margins in breast conservation and sentinel node biopsy

4. Evaluation of margins in squamous and basal cell carcinoma
5. Diagnosis and assessment of margins in carcinoma stomach, esophagus , small intestine and colon.
6. Evaluation of nodes for suspected metastasis

Frozen section has limited value in the following situations:

1.Evaluation of ovarian mucinous neoplasms

2.Evaluation of grade and depth of myometrial invasion in endometrial cancers

3. Mesenchymal lesions of the gastrointestinal tract

4.Margin assessment in cholangiocarcinoma , carcinoma gall bladder and pancreas , due to the associated inflammation

Frozen section is not recommended due to inaccuracy of diagnosis in the following situations:

1.Melanoma : For primary diagnosis, margin status and sentinel node

2. Thyroid malignancies

3. Suspected lymphoma, especially low grade lymphoma

Frozen section is not recommended in the following situations due to high sensitivity of gross assessment:

Ovarian cysts

1.Unilocular simple serous ovarian cyst

2. Teratoma without a Rokitansky nodule of fleshy areas

3. Chocolate cyst with no solid areas

4. Mucinous cyst with few smooth walled cysts and no solid area

The risk of malignancy in these situations is very minimal and frozen section can be safely omitted.

Skin Cancer

In a primary squamous cell carcinoma of the skin with well defined borders and a proliferative type of growth pattern, the gross assessment correlates well with microscopic margins , hence frozen section can be omitted in this situation.

AIM OF STUDY

To validate the efficacy of frozen section in the intraoperative management of various malignancies , by comparing it with the permanent paraffin section.

MATERIALS AND METHODS

STUDY DESIGN

Study Design **:** Prospective study

Place of study **:** Department of Surgical Oncology

Govt. Royapettah hospital, Kilpauk Medical College, Chennai

Duration of study **:** October 2011 – January 2014

Inclusion Criteria:

1. Patients requiring frozen section for primary diagnosis

When preoperative diagnosis/ biopsy not possible

Unexpected intraoperative findings & to assess the presence of synchronous lesions

2. In patients with known malignancy

To assess margin status

To assess the extent of disease

3. For assessment of lymph nodes

For establishing a diagnosis

To assess involvement of the node, in case of known primary

Sentinel node evaluation in selected cases

4. Assessment of specimen adequacy

To assess the adequacy of specimen in difficult biopsies

Exclusion criteria:

1. When intraoperative pathological diagnosis has no immediate surgical implications
2. Technically difficult specimen such as heavily ossified tissue
3. When the primary diagnosis is not known and the primary lesion size < 1 cm, Frozen section is not indicated because enough tissue would not be available for the permanent section

Materials

1. Clinical data of patients
2. Intraoperative tissue samples for frozen section analysis
3. Surgical specimen for permanent paraffin section

Frozen section analysis of 120 patients were performed in the study period. The clinical details of the patients were collected preoperatively and informed consent for frozen section analysis was obtained. The patients were informed of the various management options and the change in the intraoperative management as per the frozen section reports. Tissue samples for frozen section were collected intraoperatively and sent to the laboratory immediately.

In the laboratory, the specimen was initially grossed by the pathologist, the most representative area selected and sampling was done. The sample was then embedded in a gel like medium consisting of polyethylene glycol and polyvinyl alcohol and frozen rapidly in a cryostat machine to - 20 to – 30 ^{0} Celsius. The Cryostat used in our hospital was Leica CM 1510 S. After adequate freezing, the sample was sectioned with the microtome portion of the cryostat . 5 micron section thickness was most commonly used. The section was picked up on a glass slide using the brush technique, fixed with 95% ethanol and stained with hematoxylin & eosin . The slides were interpreted by the pathologist. Time taken for reporting was documented. With the frozen section report, the extent of surgery was confirmed and surgery was completed. The surgical specimen were sent for permanent paraffin section.

A final analysis was done and the frozen section report was compared with the final histopathology report as to whether the frozen section was concordant / discordant / indeterminate.

The sensitivity , specificity , positive and negative predictive value of frozen section were calculated. The accuracy rate , discordance rate and deferral rate of frozen section were calculated and compared with various studies with the aim of validating frozen section evaluation at our centre.

Concordance was defined as an adequate intraoperative frozen section evaluation which had complete diagnostic agreement with the final histopathology examination.

Discordance was defined as an adequate frozen section evaluation with diagnostic disagreement with final histopathology.

The number of cases in which diagnosis were deferred were analyzed and excluded from the calculations of concordant and discordant rates.

RESULTS

Systemwise and disease wise distribution of frozen section samples

1	Head and neck	40
2	Gynaecology	29
3	GIT	18
4	Breast	9
5	Musculoskeletal	7
6	Urology	4
7	Skin	8

8	Others	5

Head and neck and gynecologic tumors were the most common indications for frozen section, accounting for 57% of cases. This reflects the case distribution in our centre where head and neck and gynecologic tumors are the major contributors .

Disease wise distribution

(i)Head and neck malignancies

Squamous cell carcinoma : 30/40

Salivary gland tumors : 7/40

Thyroid : 2/40

Meibomian carcinoma : 1/40

Among head and neck malignancies, squamous cell carcinomas accounted for the majority[75%]of requests, again reflecting on the case distribution in our centre.

(ii) Gynaecological malignancies

Adnexal mass / CA ovary : 19/29

Cervical cancer : 7/29

Endometrial pathology : 2/29

Peritoneal malignancy : 1/29

Among gynaecological tumors, adnexal masses were most commonly sought for frozen section analysis. This can be explained by the fact the preoperative diagnosis is often not available for ovarian masses which necessitates intraoperative evaluation in many of these cases.

(iii) Other tumors

GIT

Pancreatic mass	: 5
CA Esophagus	: 4
CA stomach	: 5
Small intestine	: 1
Colorectal CA	: 2
HCC	: 1

Musculoskeletal

Bone tumors	: 3
Soft tissue sarcoma	: 4
Breast lump / CAbreast	: 9

Skin

Melanoma	: 4
SCC skin	: 4

Urology

CA Bladder : 2

Renal : 1

CA penis : 1

Retroperitoneal mass : 3

Suspected lymphoma : 2

Preoperative diagnosis

Preoperative diagnosis was available in 71/120 patients and not available in 49/120 patients.

Preoperative diagnosis was not available in the following cases

1.Adnexal mass : 17

2.Breast : 8

3.Retroperitoneal mass : 3

4.Pancreatic mass : 2

5.Small intestinal mass : 1

6.Bone tumors : 2

7.Soft lesion tumor : 2

Adnexal masses were the most common specimens sent for primary diagnosis, since preoperative tissue biopsy is contraindicated in operable cases.

Retroperitoneal masses, small intestinal masses, pancreatic masses were also subject to primary diagnosis. This is due to the inefficiency of the available diagnostic modalities for preoperative diagnosis.

In addition, some breast, bone and soft tissue tumors was sent for primary diagnosis. These cases were those with extensive necrosis and multiple preoperative core needle biopsies were reported negative for malignancy.

Number of samples

A total of 179 samples were sent from 120 patients. Multiple samples were sent from 37 patients.

The most common reason for multiple samples to be sent was, to assess suspicious nodes or margins ,to guide the extent of surgery. This was the reason in 27/37 cases. The other reasons were

If the first specimen was negative in a clinically suspicious tumour(6/37 cases)

In sentinel node biopsy, when multiple sentinel nodes were positive (2/37 cases)

When multiple tumors were present (2/37)

Type of samples

The following types of samples was sent for frozen section evaluation

1	Nodes	79	44.13%
2	Tumor (for primary diagnosis)	58	32.40%
3	Margins	19	10.61%
4	Sentinel nodes	13	7.26%
5	Metastatic tumor deposit	10	5.58%
6	Total	179	100%

The most common requisite for frozen section was evaluation of enlarged nodes, accounting for 44 % of the samples, followed by evaluation of tumor for primary diagnosis which accounted for 32% of samples.

Adequacy of samples for evaluation.

Adequate for evaluation	165	92.17%
Inadequacy for evaluation	14	7.8%
Total	179	100%

The samples sent were adequate for frozen section evaluation in 92.17% . However they were inadequate for evaluation in 7.8%.

The reasons for inadequacy were

(i) Tissue too tiny to be processed. This was seen in 8 out of 16 samples (50% of samples)

(ii) Presence of extensive necrotic material which was difficult to freeze. This was seen in 8 out of 16 (50% of cases)

Tiny specimens were either nodal tissue sent for evaluation or a core needle biopsy from a primary tumor.

Time taken for frozen section analysis

1	<20 minutes	0
2	21-30 minutes	1
3	31-40 minutes	2
4	41-50 minutes	14
5	51-60 minutes	43
6	61-70 minutes	39

7	> 70 minutes	21

Time taken for evaluation was 50-70 minutes in 68% cases.The average time taken for evaluation was 62 minutes.

Frozen section report

1	Inadequate for evaluation	14/179
2	Suspicious	2/179
3	Positive for malignancy	51/179
4	Negative for malignancy	112/179

Among the 14 samples which were inadequate for evaluation ,10 were due to small size of the sample (<0.5 cm in greatest dimension) and 4 were due necrotic material. which were technically difficult to freeze.

Hence, 16 /179 samples were deferred for final histopathological analysis, giving a deferral rate of 8.9%.

Concordance of frozen section with final histopathology

1	Concordant	148/163	90.79%
2	Discordant	17/163	10.42%

Of the 163 samples which were technically evaluable and interpretable, 148 were concordant with paraffin sections giving a concordance rate of 90.79%. 17/163 samples were discordant with paraffin sections giving a discordant rate of 10.42%

Analysis of sensitivity ,specificity, false positive and false negative rates of frozen section

163 specimens were adequate for evaluation on frozen section. Frozen section was reported positive for malignancy in 51 samples and out of these 48 were true positive (positive on paraffin section also and 5 were false positive (negative on paraffin section)

Frozen section was reported negative for malignancy in 112 samples and out of these ,

100 were true negatives (negative on paraffin section) and 12 were false negative (positive on paraffin section)

Sensitivity of frozen section

$$\frac{\text{Truepositive}}{\text{True positive + False negative}} \times 100 = \frac{48}{46 + 12} \times 100 = 80\ \%$$

Specificity of frozen section

$$\frac{\text{True Negative}}{\text{True Negative + False positive}} \times 100 = \frac{100}{100 + 5} \times 100 = 95.2\%$$

Positive predictive value of frozen section

Truepositive

_____ x 100 = _48___ x 100 = 90.56%

True positive + False positive 53

Negative predictive value of frozen section

Truenegative

_____ x 100 = _100___ x 100 = 89.2%

True positive + False negative 112

Concordance rate

Truepositive+Truenegative

_____ x 100 = _100 +48__ x 100 = 90.79%

Total evaluation 163

Analysis of discordant cases

Table of discordant cases

False positive cases

	CASE	FROZEN REPORT	HISTOPATHOLOGY	REASON

1	Sentinel node [H&N SCC]	Positive for malignancy	Reactive adenitis	Frozen artifact
2	Neck node [Mucoepidermoid CA Parotid]	Positive for malignancy	Reactive adenitis	Frozen artifact
3	Adnexal masses [2 cases]	Borderline ovarian masses	Inflammatory mass Benign mucinous cystadenoma	Frozen artifact Frozen artifact
4	Follicular neoplasm thyroid	Follicular carcinoma	Follicular adenoma	Frozen artifact

False positive rate : $\frac{\text{False positive}}{\text{Total positive}} \times 100 : 9.4\%$

False negative cases

	CASE	FROZEN REPORT	HISTOPATHOLOGY	REASON
1	Ca Breast [5 samples 2 cases]	Necrotic tissue	Infiltrating Ductal Ca	Sampling error
2	Small bowel lymphoma nodes [2 samples]	Reactive nodes	Diffuse large B cell lymphoma	Interpretation error

3	Melanoma foot, inguinal node	Negative for malignancy	Positive for secondary melanomatous deposit	Inherent interpretation error
4	Ca head of pancreas	Negative for malignancy	Adenocarcinoma	Inherent interpretation error
5	Ca ovary peritoneal deposits [2 samples.]	Negative for malignancy	Serous cystadenocarcinoma deposits	Sampling error
6	Margin status [Head & neck SCC]	Negative for malignancy	Positive . for malignancy	Sampling error

False negative rate : $\frac{\text{False negative}}{\text{Total negative}}$ X 100 : 10.71%

Subset analysis for sensitivity and specificity by type of sample

(i) Sensitivity and specificity for evaluation of nodes by frozen section

True positive :18/72

True Negative :52/72

False positive :1/72

False Negative:1/72

The sensitivity and specificity of frozen section evaluation of nodes was high at 94.1% and 98.1%. The concordance rate for nodal evaluation was 97.2%.

(ii) Sensitivity and specificity for evaluation of margin status

True positive : 3/18

True Negative : 14/18

False positive : 0

False Negative : 1/18

The sensitivity and specificity for evaluation of margin status by frozen section were 75% and 100% respectively.

The Concordance rate for evaluation of margin was 94.4%

(iii) Sensitivity and specificity for primary diagnosis of tumor by frozen section

True positive : 19/52

True Negative : 23/52

False positive : 2/52

False Negative: 8/52

The sensitivity and specificity for primary diagnosis of tumor by frozen section were 70.3% and 92 5% respectively .

The concordance rate for primary diagnosis of tumor was 80.76%

Diagnostic accuracy by anatomic sites evaluated

	Site	No.	Concordance rate	Inconclusive	False positive	False negative
1	Head & Neck	40	89.4%[34/38]	5%[2/40]	7.8%[3/38]	2.6%%[1/38]
2	Gynaecology	29	85.1%[23/27]	6.8%[2/29]	7.4%[2/27]	7.4%[2/27]
3	GIT	18	80%[8/10]	44.4%[8/18]	0	20%[2/10]
4	Breast	9	77.7%[7/9]	0	0	22%[2/9]
5	Skin	8	87.5%[7/8]	0	0	12.5%[1/8]

6	Musculoskeletal	7	85.7%%[6/7]	14.2%[1/7]	0	0

In this study , maximal deferral rate was for GIT specimens. This can be explained by the increased number of small samples [less than 0.5cm largest dimension] sent for frozen section from GIT pathology which were technically difficult to freeze and process.

DISCUSSION

In the present study , 57% of samples [69/120] were from head and neck and gynaecological tumors, reflecting the distribution of case burden at our centre.

A total of 179 samples from 120 cases were analyzed . The most common indication for intraoperative evaluation was to assess suspicious nodes , accounting for 44.13%[79/179] , followed by frozen section of the tumor for primary diagnosis which accounted for 32.40%. [58/179].The other indications were to assess margins , sentinel nodes and metastatic tumor deposits at 10.61%,7.26% and 5.58% respectively.

The concordance and discordance rates of frozen section described in the literature varies between 92 to 98% and 1 to 7 % respectively.[45-50].The college of American Pathologists have reviewed over 90,000 frozen sections from 461 institutions and have showed a concordance rate of 98.52%.[52]. Discordance rates up to 11% have been documented. [51].However, the accuracy of frozen section varies with the site of biopsy , type of specimen and diagnosis [52]

The results of the present study showed an overall concordance rate of 90.79% and an overall discordance rate of 10.42%. On subset analysis, the concordance rate for evaluation of nodes , margins and for evaluation of the primary for diagnosis were 97.2%, 94.4% and 80.76% respectively.

Analysis of false positive cases

A case of follicular adenoma thyroid , two cases of adnexal masses, of which one was a borderline mucinous tumor, a case of sentinel node from head and neck squamous cell carcinoma and a suspected neck node from mucoepidermoid carcinoma Parotid were false positive on frozen section.

Frozen section artifacts cause architectural distortion and alteration in the nuclear cytoplasmic ratio, which resulted in interpretation errors in the evaluation of nodes and adnexal masses.

Follicular neoplasms of thyroid and borderline ovarian tumors have inherent limitations to be diagnosed by frozen section . [53 - 56]

Analysis of false negative cases

A case of suspected inguinal node metastasis from melanoma foot, mesenteric nodes from small bowel lymphoma, core needle biopsies from cancer breast [2 cases] , a core needle biopsy from pancreatic head mass , cancer ovary with peritoneal deposits [2 samples] and a margin from head and neck squamous cell carcinoma were false negative on frozen section.

The most common reason for false negativity was sampling error [8/12 samples]. In addition, there are inherent limitations in the diagnosis of lymphoma, melanoma and head of pancreas mass by frozen section. The diagnosis of melanoma and lymphoma require serial sectioning and use of ancillary studies and hence the diagnosis is deferred for histopathological examination.[57, 58]. Regarding pancreatic masses, a number of studies have confirmed the inaccuracy of frozen section in differentiating between malignancy and chronic pancreatitis. [59, 60,61]

Subset analysis and corrected concordance rates

On subset analysis , it was found that the concordance rate of frozen section in evaluating nodes was 97.2% and margin status was 94.4%. However , the concordance rate of frozen section for primary diagnosis of tumor was only 80.76%. But, after excluding melanoma, lymphoma, follicular neoplasm of thyroid, borderline ovarian cancer and pancreatic mass, which have their own limitations for diagnosis by frozen section, the corrected concordance rate was 89.36%.

The corrected overall concordance and discordant rates were 93.08% and 6.9% respectively.

Deferral rate

In this study, 8.9%(16/179) of samples were deferred for histopathological analysis. 87.5% [14/16] of the samples were deferred due to technical difficulty of performing a frozen section ,

either due to inadequacy in freezing or processing. 12.5% [2/16] samples were deferred due to interpretation difficulty due to frozen artifacts.

Comparison with other studies[62-67]

	Study	Concordance rate	Discordance rate	Deferral rate
1	CAP program, 1990	96.5%	3.5%	3.9%
2	CAP review, Zabro, 1991	98.3%	1.7%	4.2%
3	Mayo Clinic study	97.8%	2.2%	-
4	CAP review, Novis, 1996	98.1%	1.8%	4.6%
5	Wen, China study, 1997	92.6%	3.6%	4.7%
6	Pakistan study, 2008	97.08%	2.92%	3.93%
7	IOSR JDMS, 2013	92%	2%	6%
8	This study	93.08%	6.9%	8.9%

The concordance rate of this study was comparable to other studies as shown in the table. The discordance and deferral rates were higher when compared to other studies. This was mainly due to technical errors which is expected to decrease with increase in experience with frozen sections and with strict adherence to quality control.

Diagnostic accuracy by anatomic sites evaluated

In this study , maximal deferral rate was for GIT specimens. This can be explained by the increased number of small samples [less than 0.5cm largest dimension] sent for frozen section from GIT pathology which were technically difficult to freeze and process.

Diagnostic accuracy by type of tissue processed

	Type	No.	Concordance rate	Inconclusive	False positive	False negative
1	Nodes	79	97.2%[70/72]	[8.8%]7/79	1.38%[1/72]	0
2	Tumor	58	84.6%[44/52]	[10.3%]6/58	5.7%[3/52]	9.6%[5/52]
3	Margin	19	94.4% [17/18]	0	0	1/18[5.5%]
4	Sentinel node	13	91.6%[11/12]	[7.6%]1/13	8.3%[1/12]	0
5	Tumor deposits	10	100%[8/8]	[20%]2/10	0	0

The concordance rate of nodal evaluation, margin assessment, sentinel nodes and tumor deposits were more than 91% and comparable to other studies. The concordance rate of evaluation of primary tumor was 84.6% . This was due to the inclusion of certain pathologies which are difficult to evaluate by frozen section.

Suggestions to improve accuracy and decrease discordance

Strict adherence to quality control measures and periodic audit

Interdisciplinary communication to decrease sampling and interpretation errors

Use of imprint cytology as an adjunct to frozen section to overcome the errors produced by frozen section artifacts

Use of ancillary studies along with frozen section analysis

CONCLUSION

Frozen section is reliable and accurate for intraoperative evaluation of nodes , margin status and for the primary diagnosis of most tumors.

However, it has limited value in the evaluation of certain tumors like melanoma, follicular neoplasms of the thyroid, lymphomas, borderline ovarian tumors and pancreatic mass lesions.

Tumors with a large necrotic component and very small samples pose challenges in evaluation by frozen section due to high sampling errors and technical difficulty respectively.

Frozen section evaluation is an accurate means of intraoperative diagnosis and its efficacy can be validated at our centre

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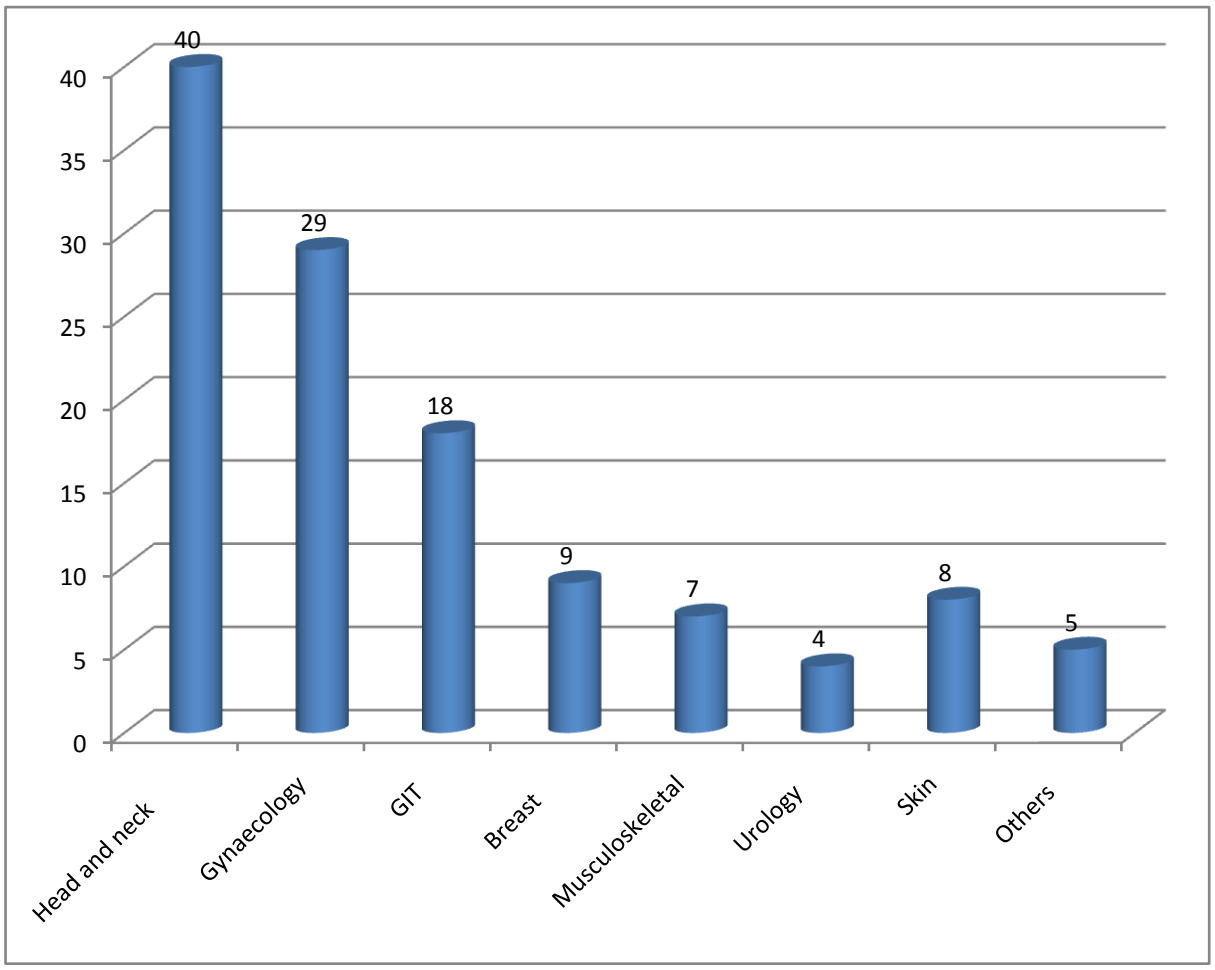
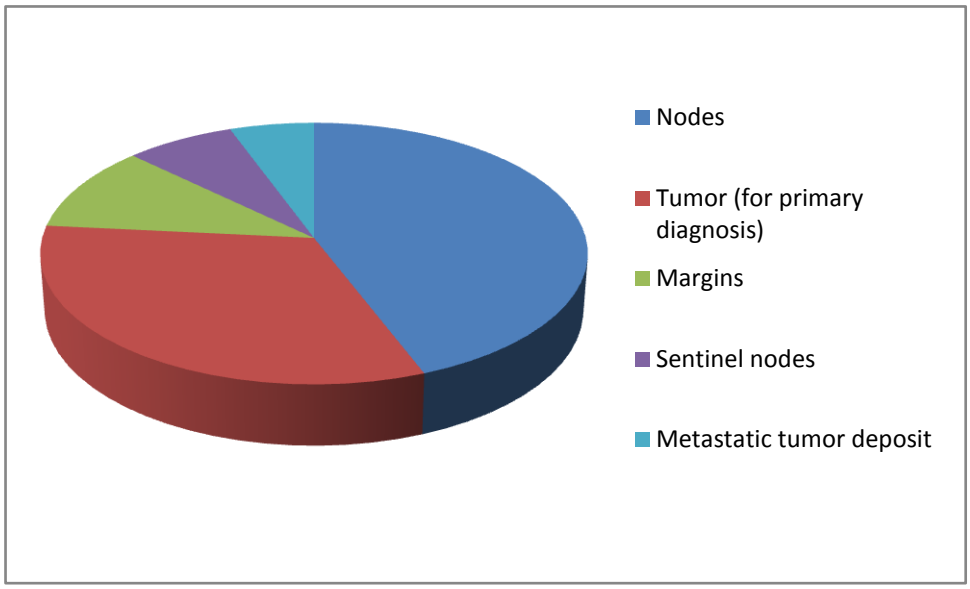
CHARTS

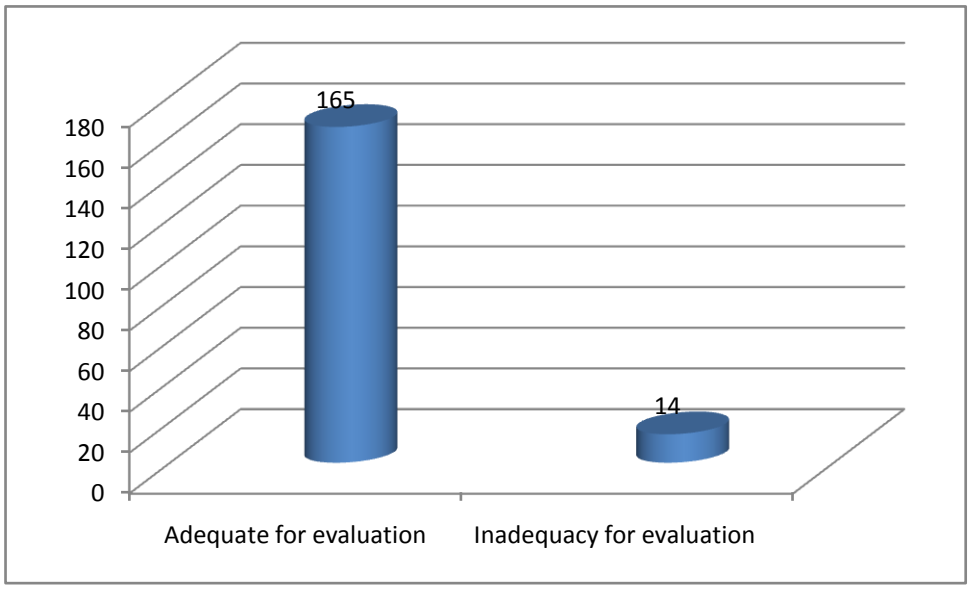
Systemwise and disease wise distribution of frozen sections samples



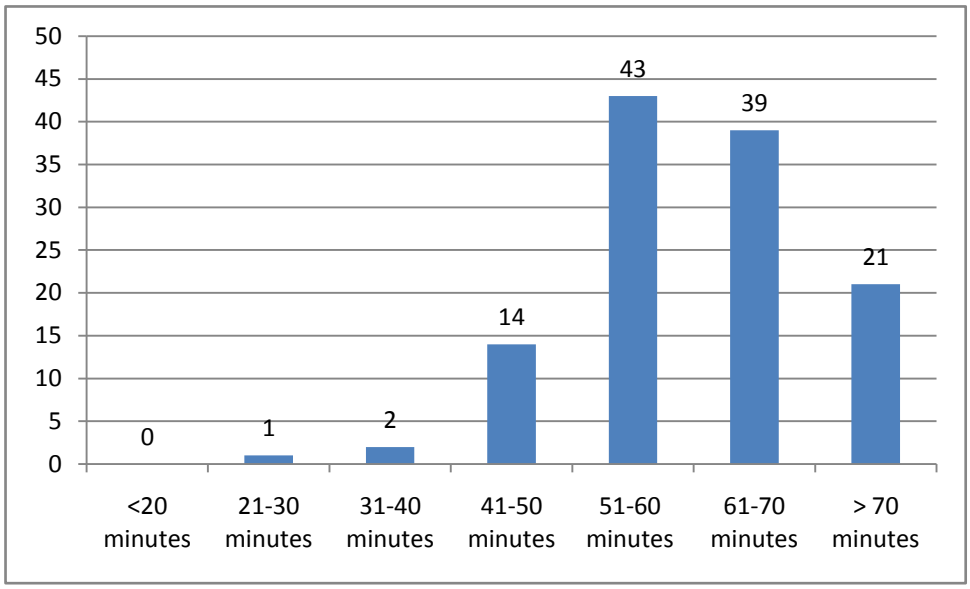
Type of samples



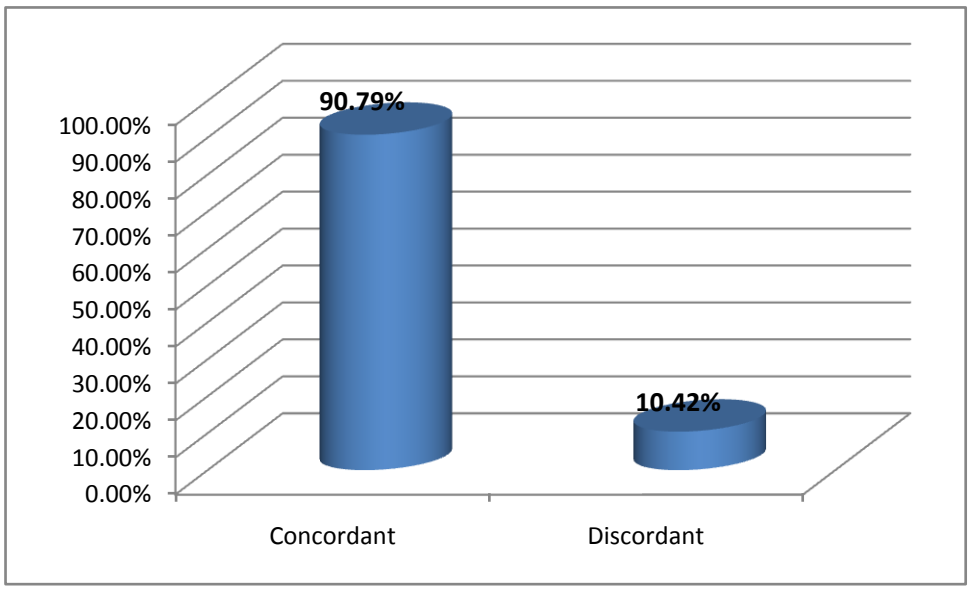
Adequacy of samples for evaluation.



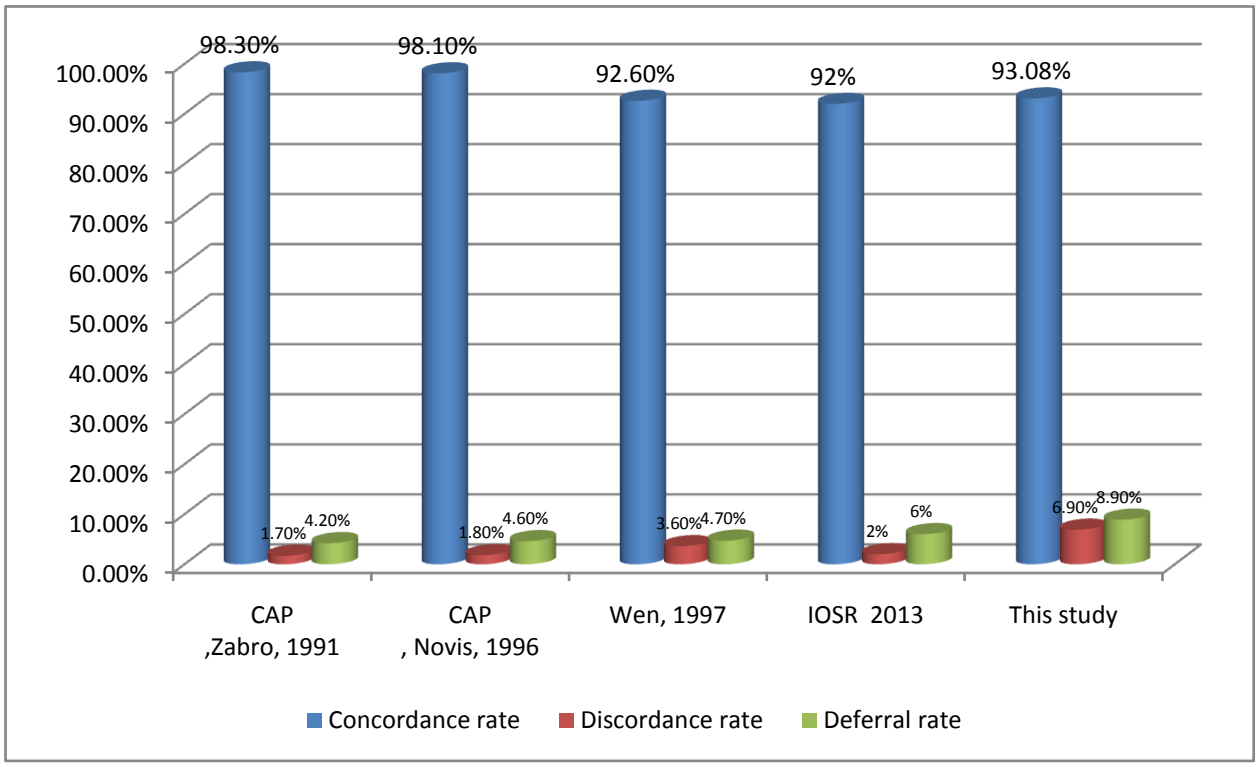
Time taken for frozen section analysis



Concordance of frozen section with final histopathology

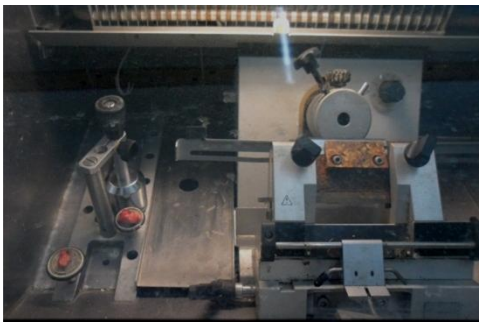


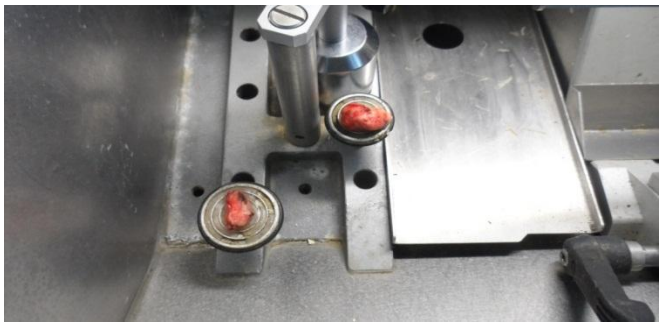
Comparison with other studies



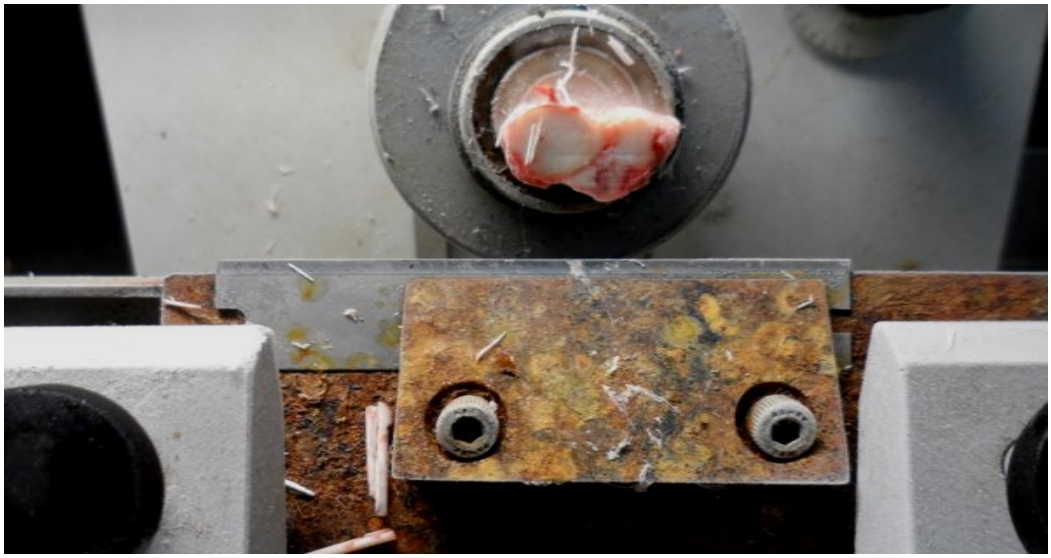
CRYOSTAT

FREEZING THE SAMPLE



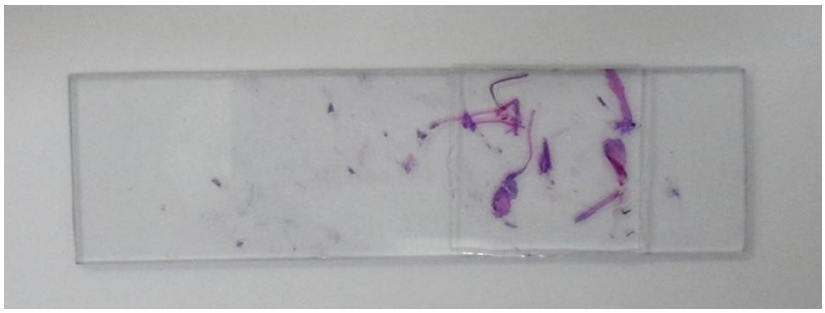


SECTIONING

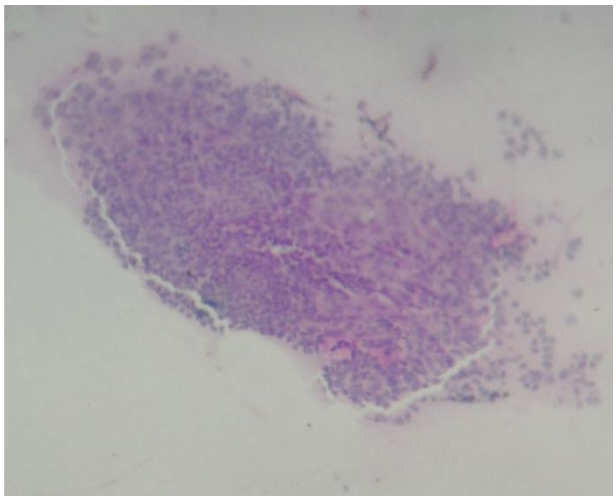


PREPARING THE SLIDES

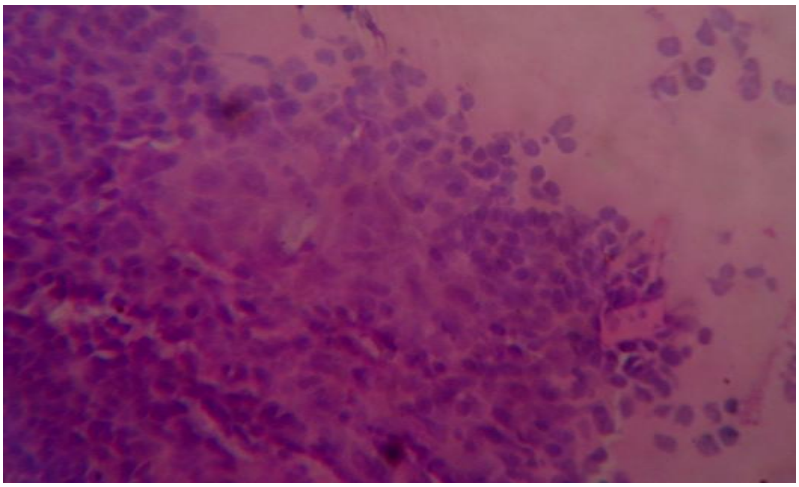
STAINED SLIDE



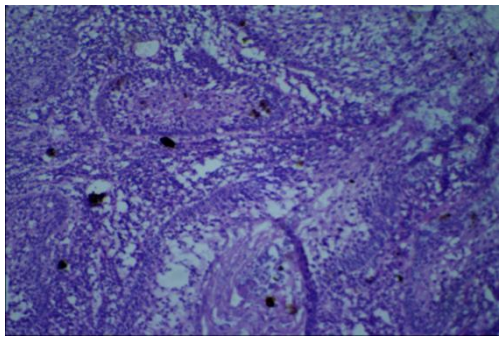
MICROSCOPIC VIEW



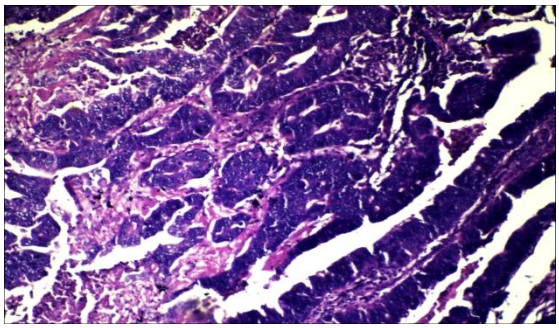
HIGH POWER VIEW



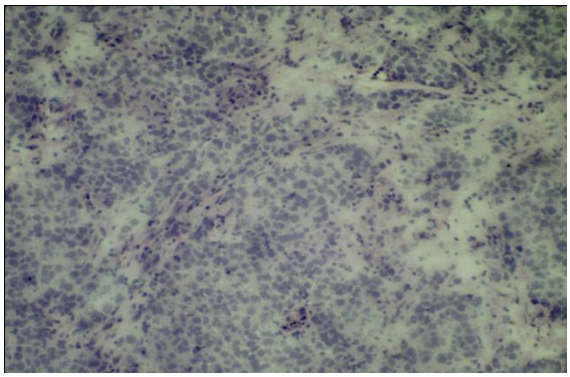
Squamous cell carcinomatous deposit in a node

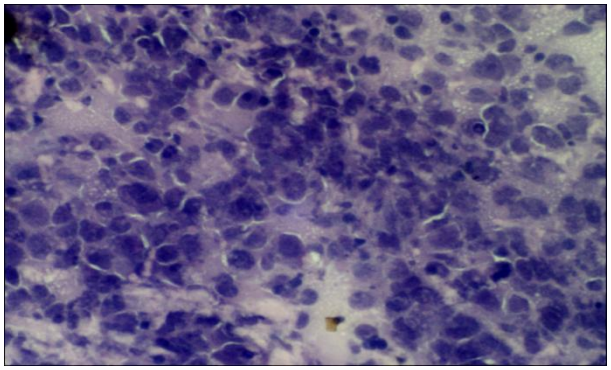


Adenocarcinomatous deposit in a node

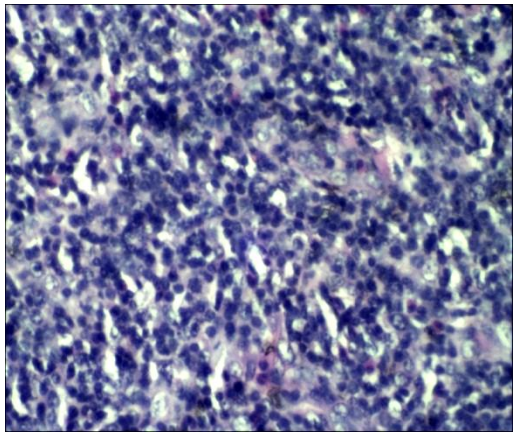


Dysgerminoma Ovary

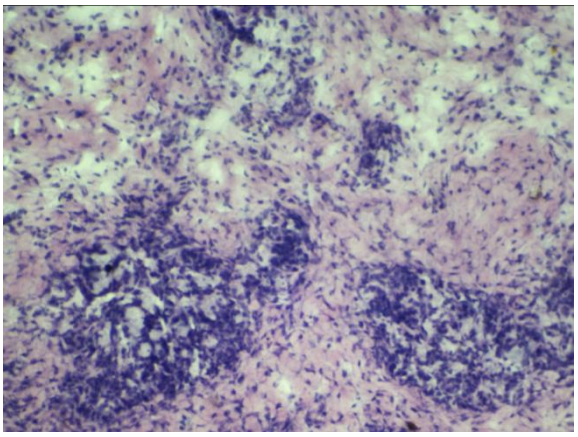




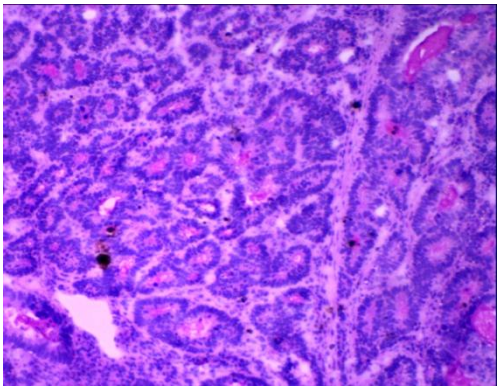
Hodgkins Lymphoma [mixed

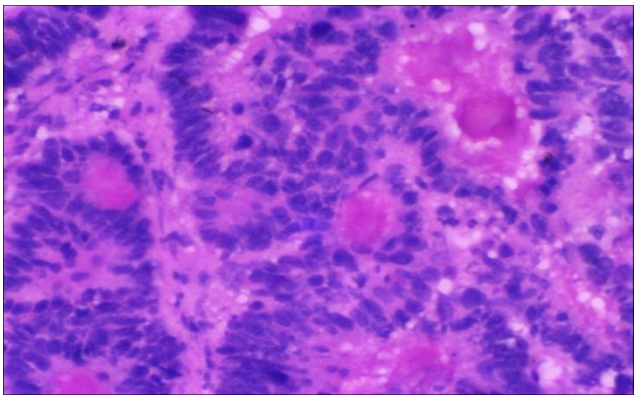


Krukenberg tumor

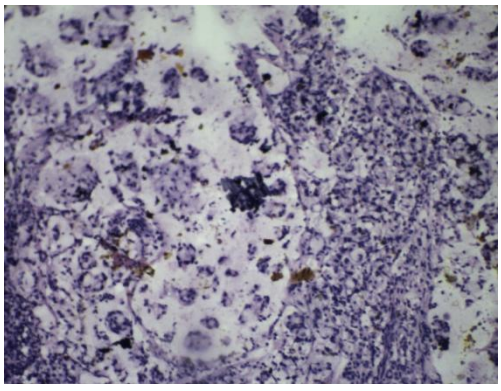


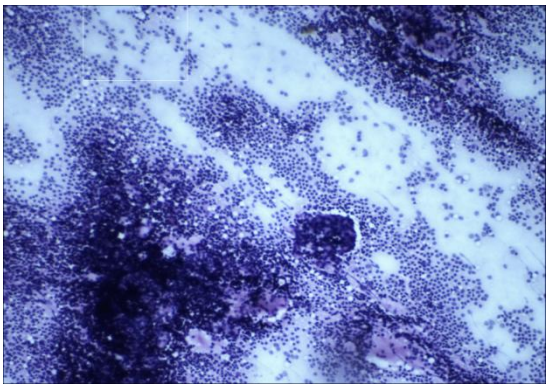
Carcinoma Stomach



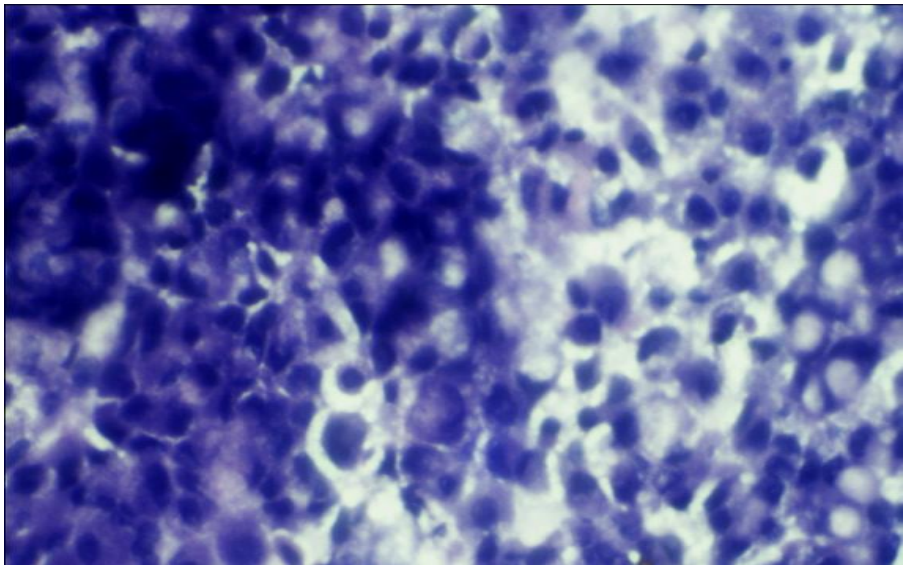


Mucinous tumor

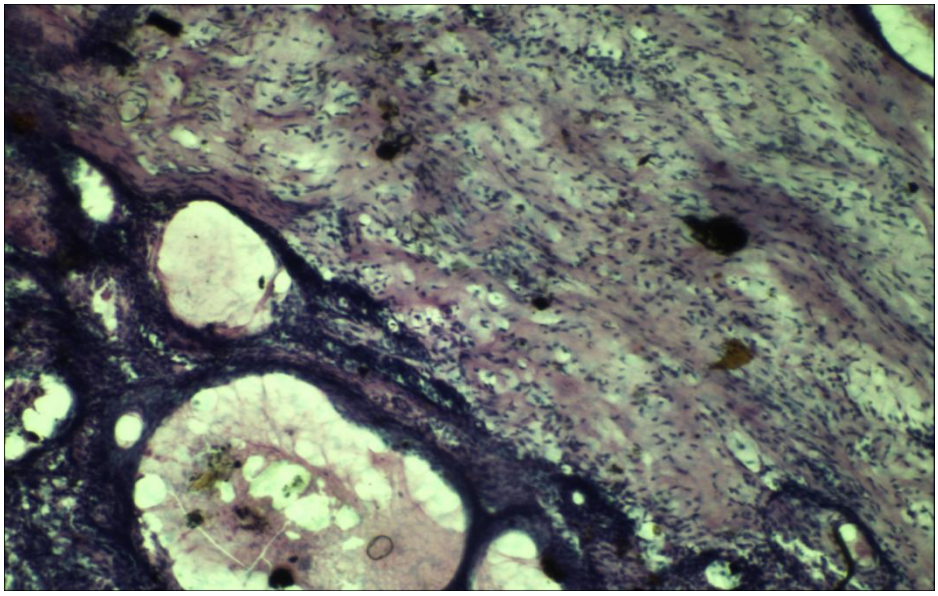




Peritoneal deposit



Pleomorphic adenoma



Validation of frozen section in intraoperative decision making in malignancies

Name: Age: CD NO: IP NO:

Address :

Clinical Diagnosis & Stage :

Primary / Recurrence :

Relevant clinical details :

Relevant investigation :

Pre op pathological diagnosis : Yes / No

If Yes , report :

Neoadjuvant therapy :

Management Plan :

Date of surgery :

Surgery performed :

Intraop analysis type : Cytology / Imprint cytology / Frozen section

Intraop tissue type : Fluid / Tumor tissue / Node/ Sentinel node/ Margin status

Number of specimens sent :

Reported at :

Waiting time :

Intraop report : Fluid cytology (+/ - / indeterminate)

Imprint cytology (+ / - / indeterminate)

Frozen Section (+ / - / indeterminate)

Intra op full report :

Change in management : Yes / No

If Yes, Mention the change :

Other factors which changed management :

Final HPE :

Concordance : Concordant / Discordant

If discordant, FS : False positive / False Negative

If discordant, Imprint : False positive / False Negative

If discordant , Fluid cytology : False positive / False Negative

S. no	Name	Age	CDNO	Category	Clinical diagnosis	preop Diag	Date	BX	FS: Node/ tumor/ Margin/ SN	No. of specimen	Adequacy	Feasibility	Time	Report : Positive /Negative	Final HPE	False +	False -	Concordant
						Y / N							(MTS)	Inadequate/ Suspicious				
1	M	51	63/12	H&N SCC	Ca cheek L	Y	17.9.11	SCC	SN	1	N	N	60	I	N	N	N	
2	G	26	69/12	Salgland	Ca Parotid R	Y	30.1.12	N	N	1	Y	Y	65	N	N	N	N	C
3	V	38	79/12	H&N SCC	Ca tongue	Y	15.2.12	SCC	SN	1	Y	Y	45	P	N	Y	N	D
4	V	65	107/12	H&N SCC	Ca cheek L	Y	22.2.12	SCC	SN	1	Y	Y	60	N	N	N	N	C
5	A	43	151/12	GIT	Rec Ca rectum	Y	8.3.12	SCC	N	1	Y	Y	65	P	P	N	N	C
6	A	34	201/12	Ovary	R adnexal mass	N	9.3.12	N	T	1	Y	Y	70	N	N	N	N	C
7	I	55	176/12	H&N SCC	L Lower alveolu	Y	14.3.12	MD SCC	N	1	Y	Y	45	N	N	N	N	C
8	L	46	479/11	H&N SCC	Ca tongue	Y	16.3.12	SCC	N	1	Y	Y	45	N	N	N	N	C

9	K	21	269/12	Sal gland	Rec Ca L Parotid	Y	27.3.12	Acinic C C	N	1	Y	Y	55	N	N	N	C
10	J	38	223/12	Cervix	Ca Cervix	Y	16.3.12	SCC	N	1	Y	Y	60	P	P	N	C
11	M	48	258/12	Sal gland	L Parotid	N	4.4.12	Nil	N, T	2	Y,Y	Y,Y	75	N, N	N, N	N	C
12	E	51	290/12	Lympho ma	Lymphoma	N	4.4.12	Nil	N	1	Y	Y	60	S	P	N	I
13	J	62	619/11	H&N SCC	Ca tongue	Y	10.4.12	SCC	N	2	Y	Y	75	P, N	P, N	N	C
14	R	53	347/12	Ovary	R adnexal mass	N	12.4.12	Nil	T	1	Y	Y	60	N	N	N	C
15	V	48	331/12	Cervix	Ca Cervix	Y	20.4.12	SCC	M	1	Y	Y	55	N	N	N	C
16	R	71	353/12	Bone	Bone tumor	N	4.5.12	Nil	T	1	Y	Y	75	P	P	N	C
17	M	70	246/12	Lympho ma	Lymphoma	N	24.11.12	Nil	N	1	Y	Y	55	P	P	N	C
18	P	37	460/12	Bone	Bone tumor	N	15.5.12	Nil	T	4	N, N, N, Y	N, N, N, Y	85	N, N, N, P	N, N, N, P	N	C
19	N	65	436/12	SCC Skin	SCC Skin	Y	15.5.12	SCC	N	1	Y	Y	40	N	N	N	C
20	K	37	749/09	Ovary	BL adnexal mass	N	17.5.12	Nil	T	2	Y,Y	Y,Y	60	N, N	N, N	N	C
21	J	56	1024/11	Endometrium	Polyp	N	17.5.12	Nil	T	1	Y	Y	50	N	N	N	C
22	S	35	533/	Ovary	L adne	N	24.5.	Nil	T	1	Y	Y	50	N	N	N	C

			12		xal mass		12											
23	J	46	728/12	H&N SCC	Ca tongue	Y	11.6.12	SCC	N	3	Y,Y,Y	Y,Y,Y	65	N,N,N	N,N,N	N	N	C
24	W	22	572/12	Bone	GCT sacrum	Y	13.6.12	GCT	M	1	Y	Y	45	P	P	N	N	C
25	K	65	637/12	H&N SCC	Ca L Lower alveolus	Y	14.6.12	SCC	SN	3	Y,Y,Y	Y,Y,Y	75	N,N,N	N,N,N	N	N	C
26	G	56	596/12	GIT	Esophagus	Y	22.6.12	SCC	N	2	N,Y	N,Y	60	I,N	I,N	N	N	C
27	P	45	607/12	H&N SCC	Ca tongue	Y	27.6.12	SCC	SN	1	Y	Y	65	N	N	N	N	C
28	A	48	635/12	Breast	Ca Breast	N	28.6.12	Nil	T	1	Y	Y	65	P	P	N	N	C
29	S	47	603/12	Breast	Ca Breast	N	28.6.12	Nil	T	3	N,N,N	Y,Y,Y	75	N	P	N	Y	D
30	J	55	602/12	Salgland	R Parotid	Y	28.6.12	Mucoepi Ca	N	1	Y	Y	55	P	P	N	N	C
31	M	55	1276/12	Ovary	Ca ovary	Y	10.7.12	Papillary CA	T,T,T,T	4	Y,Y,Y,Y	Y,Y,Y,Y	75	P,P,P,P	P,P,P,P	N	N	C
32	T	55	732/12	Breast	Ca Breast	N	19.7.12	Nil	T	2	Y,Y	Y,Y	60	N,N	P,P	N	Y	D
33	J	52	728/12	Thyroid	SNT	N	20.7.12	Nil	T	1	Y	Y	45	P	N	Y	N	D
34	S	43	777/12	STS	STS	N	26.7.12	Nil	T	1	Y	Y	60	N	N	N	N	C
35	R	47	713/12	H&N SCC	Ca R upper alveolus	Y	24.7.12	SCC	SN	3	Y,Y,Y	Y,Y,Y	70	N,N,N	N,N,N	N	N	C

36	A	70	886/12	H&N SCC	Ca tongue	Y	3.9.12	SCC	N	1	Y	Y	60	N	N	N	N	C
37	P	72	965/12	STS	STS	Y	27.9.12	PMFH	N	4	Y,Y,Y,Y	Y,Y,Y,Y	75	N	N	N	N	C
38	R	50	1063/12	Ovary	R Ovarian mass	N	17.10.12	Nil	T, T	2	Y,Y	Y,Y	70	P, N	P, N	N	N	C
39	L	55	1038/12	GIT	Esophagus	Y	26.10.12	SCC	N, N, N	3	N, N, Y	N, N, Y	70	I,I, N	I,I, N	N	N	C
40	J	14	1081/12	URO	R Renal mass	N	1.11.12	Nil	N	1	Y	Y	65	P	P	N	N	C
41	M	52	1100/12	STS	STS	Y	2.11.12	Synovial sarc	N	1	Y	Y	60	N	N	N	N	C
42	K	57	1154/12	H&N SCC	Ca floor of mouth	Y	23.11.12	SCC	SN	1	Y	Y	55	N	N	N	N	C
43	S	30	1225/12	SCC Skin	SCC Skin	Y	29.11.12	SCC	M	2	Y,Y	Y,Y	65	N, N	N, N	N	N	C
44	A	50	1692/12	Cervix	Ca Cervix	Y	10.12.12	SCC	N	1	Y	Y	60	P	P	N	N	C
45	R	60	1857/12	Peritoneum	peritoneum	N	12.12.12	Nil	T	1	Y	Y	75	P	P	N	N	C
46	L	45	669/12	Cervix	Ca Cervix	Y	14.12.12	SCC	N, N	2	Y,Y	Y,Y	70	P, N	P, N	N	N	C
47	M	38	834/12	H&N SCC	CA R Cheek	Y	18.12.12	SCC	M, M,	3	Y,Y,Y	Y,Y,Y	75	N, N, S				

									M									
48	M	62	520/12	H&N SCC	R Pyriform fossa	Y	20.12.12	SCC	N,N	2	Y,Y	Y,Y	65	P,N	P,N	N	N	C
49	I	50	1335/12	Ovary	R adnexal mass	N	11.1.13	Nil	T	1	Y	Y	55	N	N	N	N	C
50	V	66	1270/12	Ovary	R adnexal mass	N	19.1.13	Nil	T,T	2	Y,Y	Y,Y	60	P,N	P,N	N	N	C
51	S	74	012/13	GIT	Esophagus	Y	23.1.13	SCC	N,N	2	Y,Y	Y,Y	60	N,N	N,N	N	N	C
52	R	63	54/13	Melanoma	Melanoma	y	30.1.13	Melanoma	SN	1	Y	Y	50	N	N	N	N	C
53	K	60	40/13	SCC Skin	SCC Skin	Y	1.2.13	SCC	N,N,N	3	Y,Y,Y	Y,Y,Y	75	N,N,N	N,N,N	N	N	C
54	M	39	73/13	Ovary	R adnexal mass	N	5.2.13	Necrotic mass	T	1	N	N	40	I	I	N	N	C
55	A	64	497/12	H&N SCC	larynx	Y	12.2.13	SCC	M	1	Y	Y	55	N	N	N	N	C
56	E	67	77/13	H&N SCC	larynx	Y	13.2.13	SCC	M	1	Y	Y	55	N	N	N	N	C
57	K	56	58/13	RP tumor	RP tumor	N	14.2.13	Nil	T	1	Y	Y	50	P	P	N	N	C
58	P	56	84/13	H&N SCC	Ca cheek L	Y	15.2.13	SCC	N	1	N	N	50	I	I			
59	M	60	187/13	GIT	HCC	N	18.2.13	Nil	T,T,N	3	Y,Y,Y	Y,Y,Y	70	P,P,N	P,P,N	N	N	C
60	D	60	110/13	Melanoma	Melanoma	Y	20.2.12	Melanoma	N	1	Y	Y	65	N	P	N	Y	D
61	K	55	114/	H&N	Ca L Lowe	Y	15.2.	SCC	N,N,	3	Y,Y,Y	Y,Y,Y	70	N,N,	N,N,	N	N	C

			13	SCC	r alveolus		13		N					N	N			
62	R	45	94/13	H&N SCC	Ca tongue	Y	21.2.13	SCC	N	1	Y	Y	80	N	N	N	N	C
63	B	51	131/13	Breast	Ca Breast	N	22.2.13	Nil	T	1	Y	Y	90	P	P	N	N	C
64	M	65	115/13	H&N SCC	Ca tongue	Y	28.2.13	SCC	N	1	Y	Y	65	P	P	N	N	C
65	R	65	218/13	Sal gland	Ca Parotid R	Y	4.3.13	CA pl adenoma	N	1	Y	Y	65	N	N	N	N	C
66	R	42	210/13	GIT	Ca stomach	Y	5.3.13	Adenoca	T, T	2	Y	Y	65	P	P	N	N	C
67	C	45	78/09	URO	Ca Penis	Y	5.3.13	SCC	M	1	Y	Y	60	N	N	N	N	C
68	R	55	897/12	H&N SCC	Ca floor of mouth	Y	6.3.13	SCC	N, N, N	3	Y,Y,Y	Y,Y,Y	70	N, P, N	N, P, N	N	N	C
69	G	65	172/13	GIT	Ca stomach	N	8.3.13	Nil	T	1	Y	Y	75	P	P	N	N	C
70	A	44	256/13	GIT	Ca pancreas	Y	13.3.13	Adenoca	N, N	2	Y,Y	Y,Y	65	N, N	N, N	N	N	C
71	D	65	216/13	H&N SCC	Ca L Lower alveolus	Y	15.3.13	SCC	N, M	2	Y,Y	Y,Y	60	N, N	N, N	N	N	C
72	R	64	302/13	URO	CA Bladder	Y	21.3.12	TCC	T	1	Y	Y	55	P	P	N	N	C
73	S	40	246/13	Breast	Ca Breast	Y	21.3.13	IDC	N	1	Y	Y	50	N	N	N	N	C
74	M	40	254/	STS	STS Lt thigh	N	22.3.	Nil	T	1	Y	Y	45	N	N	N	N	C

			13				12										
75	A	50	254/13	Melanoma	Melanoma	Y	22.3.13	Melanoma	M, M, M	3	Y,Y,Y	Y,Y,Y	70	P,P,N	P, P, N	N	N	C
76	M	49	151/13	Ovary	L adnexal mass	N	25.3.13	Nil	N	1	Y	Y	65	N	N	N	N	C
77	V	32	277/13	Ovary	L adnexal mass	N	26.3.13	Nil	T	1	Y	Y	65	N				
78	C	40	270/13	H&N SCC	CA L Cheek	N	3.4.13	Nil	T	1	Y	Y	75	N	N	N	N	C
79	S	51	125/11	Meibomian	Ca L Eye	Y	9.4.13	Nil	N	1	Y	Y	65	N	N	N	N	C
80	G	63	331/13	SCC Skin	SCC Skin	Y	17.4.13	SCC	N	1	Y	Y	65	N	N	N	N	C
81	K	48	424/13	Melanoma	Melanoma	Y	3.5.13	Melanoma	SN	1	Y	Y	55	N	N	N	N	C
82	R	58	513/13	Breast	Phyllodes	N	3.5.13	Nil	T	1	Y	Y	65	N	N	N	N	C
83	M	59	411/13	H&N SCC	Ca hypopharynx	Y	7.5.13	SCC	N	1	Y	Y	60	N	N	N	N	C
84	S	47	547/13	Breast	Ca Breast	N	15.5.13	Nil	T	T	Y	Y	75	P	P	N	N	C
85	S	30	531/13	Ovary	R adnexal mass	N	22.5.13	Nil	T, T	2	Y,Y	Y,Y	70	P, N	N, N	Y	N	D
89	R	36	565/13	GIT	Ca pancreas	N	28.5.13	Nil	T	1	N	N	55					
90	M	66	564/13	H&N SCC	CA R Cheek	Y	29.5.13	SCC	M	1	Y	Y	65	N	N	N	N	C

91	A	61	575/13	H&N SCC	CA R Cheek	Y	30.5.13	SCC	N	1	Y	Y	65	N	N	N	N	C
92	L	28	517/13	RP tumor	RP tumor	N	5.6.13	Nil	T, N	2	Y,Y	Y,Y	75	P, N				
93	K	33	608/13	RP tumor	RP Cyst	N	6.6.13	Nil	T	1	Y	Y	60	N	N	N	N	C
94	K	53	596/13	GIT	Ca stomach	Y	11.6.13	Adenoca	N	1	Y	Y	65	P	P	N	N	C
95	M	47	1051/12	Cervix	Ca Cervix	Y	12.6.13	SCC	N	1	Y	Y	60	P	P	N	N	C
96	R	45	312/13	GIT	CA esophagus	Y	18.6.13	SCC	N	2	Y, N	Y, N	65	N,I	N, I	N	N	C
97	V	36	646/13	H&N SCC	Ca R Lower alveolus	Y	26.6.13	SCC	N, N, M	3	Y,Y,Y	Y,Y,Y	75	N, N, N	N, N, N	N	N	C
98	C	65	648/13	H&N SCC	Ca L Lower alveolus	Y	27.6.13	SCC	M	1	Y	Y	60	N	N	N	N	C
99	K	45	685/13	Cervix	Ca Cervix	Y	2.7.13	SCC	N	1	Y	Y	65	P	P	N	N	C
100	S	52	684/13	GIT	SI lymphoma	N	9.7.13	Nil	N, N, N, T	4	Y,Y,Y,N	Y,Y,Y,N	90	N, N, N,I	P, P, P, P	Y	N	D
101	M	63	959/13	GIT	Ca pancreas	Y	19.8.13	Adenoca	N, T	2	N.Y	N, Y	60	N, P	N, P	N	N	C
102	G	58	937/13	Sal gland	L Parotid	N	27.8.13	PL adenoma	T	1	Y	Y	60	N	N	N	N	C
103	K	40	943/13	H&N SCC	CA R Cheek	Y	29.8.13	SCC	M, M	2	Y,Y	Y,Y	65	N, N	N, P	N, Y	N, N	C,D
10	J	55	90	Sal	Muco	Y	4.	Mu	N,	2	Y,Y	Y,Y	55	N,	N,	N	N	C

4			9/13	gland	epi CA lip		9.13	co epi Ca	N					N	N			
105	N	65	937/13	GIT	Ca pancreas	N	15.9.13	Nil	N	1	Y	Y	60	N	N	N	N	C
106	M	55	945/13	Endometrium	CA Endometrium	y	19.9.13	Adenoca	T	1	Y	Y	55	N	N	N	N	C
107	R	47	960/13	Breast	Ca Breast	N	20.9.13	IDC	T	1	Y	Y	55	P	P	N	N	C
108	L	45	1023/13	Thyroid	Pap CA thyroid	Y	20.9.13	Papillary CA	N	1	Y	Y	65	P	P	N	N	C
109	S	45	1034/13	H&N SCC	Leukoplakia	N	5.10.13	Leuloplakia	T	1	Y	Y	60	N	N	N	N	C
110	R	56	1038/13	GIT	Ca pancreas	Y	7.10.13	Adenoca	N	2	Y,Y	Y,Y	65	N, N	N, N	N	N	C
111	M	39	1056/13	Breast	Ca Breast	N	8.10.13	Nil	T	1	Y	Y	60	P	P	N	N	C
112	E	38	1067/13	GIT	polyp stomach	N	17.10.13	Nil	T	1	Y	Y	65	N	N	N	N	C
113	D	35	1211/13	Ovary	Ca ovary	Y	5.11.13	N	T, T, T	3	Y,Y,Y	Y,Y,Y	75	N, N, P	P, P, P	N	Y, Y, N	D,D,C
114	G	45	1283/13	Ovary	R adnexal mass	N	8.11.13	Nil	T	1	Y	Y	60	N	N	N	N	C
115	N	35	1301/13	Ovary	R adnexal mass	N	18.11.13	Nil	T	1	Y	Y	60	P				
116	K	22	515/	Ovary	R adne	N	20.1	Nil	T	1	Y	Y	65	P	P	N	N	C

			13		xal mass		1.13										
117	M	55	1343/13	Cervix	Ca Cervix	Y	29.11.13	SCC	N	1	Y	Y	55	P	P	N	N	C
118	T	43	1370/13	Ovary	R adnexal mass	N	4.12.13	Nil	T	1	Y	Y	60	N	N	N	N	C
119	E	39	1405/13	Ovary	BL adnexal mass	N	5.12.13	Nil	T	1	Y	Y	65	P	P	N	N	C
120	A	47	1472/13	GIT	CA R Colon	N	23.12.13	Nil	T	1	Y	Y	55	P	P	N	N	C
121	S	74	1525/13	URO	CA Bladder	Y	9.1.14	SCC	N	1	Y	Y	60	P	P	N	N	C

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Validation of frozen section in intraoperative decision making in malignancies

INTRODUCTION

The Frozen section procedure is a laboratory procedure to perform rapid microscopic pathological analysis of specimen. The technical name of this procedure is Cryosection. Frozen section is an important tool in the armamentarium of the surgical oncologist. Intraoperative diagnosis is extremely important and may provide direct evidence and foundation for the extent of the surgery.

Intraoperative cytopathological diagnosis is done for the following reasons

1. Establishing the nature of disease
   When the primary diagnosis of malignancy is uncertain, a frozen section is done for diagnosis which in turn alters the management plan.
2. Assessment of margins , nodes or extent of disease
   When the primary diagnosis of malignancy is established, frozen section is valuable in assessing margin status, extent of disease & nodes which help in decision regarding operability & extent of surgery.
3. Adequacy of biopsy specimen
   In difficult biopsy specimens, frozen section helps to determine the specimen adequacy and to ascertain whether the biopsy is taken from the representative area.

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