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COMPARATIVE STUDY OF INTRAOPERATIVE FROZEN SECTION AND HISTOPATHOLOGICAL EXAMINATION IN SURFACE EPITHELIAL OVARIAN TUMORS : RETROSPECTIVE STUDY OF 2 YEARS AT TERTIARY CANCER CARE CENTRE.

Pathology

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ABSTRACT

Ovarian cancer is the third leading site of cancer among women, trailing behind cervix and breast cancer. Surface epithelial ovarian tumors account for approximately two thirds of all ovarian neoplasm. Ovarian tumors represent the most common request site for Frozen Section in gynaecological surgery to determine status of malignancy. Thus extent of surgery is influenced by frozen section.

Frozen Section has a reasonably high sensitivity and specificity in reliable hands. However, studies have demonstrated limited accuracy of Frozen section diagnosis in borderline malignancies. Hence it is important for the pathologist as well as the surgeons to be aware of its limitations along with its advantages.

The present Study aimed to compare the Frozen Section diagnoses with Paraffin Section diagnoses in Surface Epithelial Ovarian Tumors and evaluate the Accuracy of Frozen Section diagnosis. The overall "concordance" between frozen section diagnosis and permanent histopathology report was determined. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of frozen section analysis for benign, borderline and malignant surface epithelial ovarian tumors were evaluated by 2×2 contingency tables.

Our study confirms that the accuracy, sensitivity and specificity of frozen-section diagnosis are high for benign and malignant surface epithelial ovarian tumors whereas it is low for borderline tumors. Borderline tumors remain difficult to be accurately diagnosed at frozen section and requires extensive sampling. The main causes of under-diagnosis in our study are limitation in sampling, tumour heterogeneity and mucinous histology. Frozen section will remain a time tested diagnostic tool so long as surgeries are performed. However, this tool must be judiciously utilized and is most effective when the pathologist and the surgeon are aware of its advantages and limitations.

KEYWORDS

Frozen Section, Surface Epithelial Tumors, Ovarian Tumors

INTRODUCTION

Ovarian Cancer is one of the leading cancers in Indian women.[1] In most of the population-based cancer registries in India, ovarian cancer is the third leading site of cancer among women, trailing behind cervix and breast cancer.[2] The overall 5-year survival is approximately 45%, primarily due to the late stage at diagnosis of the disease.[3]

Ovarian tumors ordinarily produces no distinctive symptoms, as a result most tumors metastasize or spread to other abdominal organs before they are diagnosed.[4] A detailed clinical history, abdomen and pelvic examinations, determination of CA-125 levels and ultrasonography are necessary steps in making diagnosis.

Ovarian tumors represent the most common request site for Frozen Section in gynaecological surgery.[5] Frozen section is used mainly to determine status of malignancy. If the mass is malignant, complete surgical staging with optimal debulking is of utmost importance. In case of benign pathology, conservative surgery can be performed. This is of special importance in young patients where fertility preservation is an important issue. Apart from status of malignancy, type of histology on frozen section guides a surgeon as to how aggressive cytoreduction should be. Thus extent of surgery is influenced by frozen section.

Surface epithelial ovarian tumors account for approximately two thirds of all ovarian neoplasms, and their malignant forms represent about 90% of ovarian cancers in the western world.[6] Frozen Section has a reasonably high sensitivity and specificity in reliable hands. However, studies have demonstrated limited accuracy of Frozen section diagnosis in borderline malignancies. Hence it is important for the pathologist as well as the surgeons to be aware of its limitations along with its advantages.

The present study aimed

- To study and compare the Frozen Section diagnoses with Paraffin Section diagnoses in Surface Epithelial Ovarian Tumors.
- To evaluate the Accuracy of Frozen Section in Surface Epithelial Ovarian Tumors.

MATERIALS & METHOD

The study was conducted in the department of pathology over a period of 2 years. A total of 100 cases histopathologically diagnosed as surface epithelial ovarian tumors on paraffin section were included in the study.

Cases of Primary surface epithelial ovarian tumors in which frozen section examination is done were included. Ovarian tumors other than Surface Epithelial Tumors; like Germ Cell Tumors, Sex Cord Stromal Tumors and Metastatic Ovarian Tumors were excluded from the study. Primary Surface Epithelial Ovarian tumors in which frozen section examination is not done were also excluded.

INTRAOPERATIVE CYTOLOGY

Intraoperative cytology was done by taking imprints from the representative solid/papillary areas of the ovarian mass on cut section as soon as the specimen is received for frozen section. Similarly, scrape and crush smears were prepared. Scrape smears were taken by the knife and subsequently the cytological material so obtained was smeared onto another slide. Crush preparations were done by compressing the tissue between two slides, the material obtained was smeared by another slide. The smears so prepared were stained with Hematoxylin & Eosin stain.

FROZEN SECTION

Intraoperatively, the ovarian mass was excised and sent fresh without delay to the surgical pathology laboratory. Gross inspection was done regarding any areas of capsular breach or tumor deposit on the external surface, colour, consistency and areas of haemorrhage and necrosis. Representative sections were taken. The unfixed tissue sections were then laid on tissue holders after forming a bed of liquid freezing medium. The tissue is then covered with the freezing medium and put inside the cryostat set between -25 to -30 'C. After 1-2 minutes when the tissue is completely frozen, the holder is set inside the cryostat microtome. The tissue is trimmed and when proper exposure of the tissue has taken place, 5µm thin sections are taken on a clean slide. The smears are then stained with Hematoxylin & Eosin stain. The frozen section slides were studied and characterized as benign, borderline or malignant based on morphology. Tumor typing and grading was done wherever possible.

FINAL HISTOPATHOLOGY

All specimens were fixed in 10% buffered formalin. Complete gross examination was done with special emphasis on Weight of the specimen, Ovarian size, Capsule status in details, Tumor size; External appearance - solid/cystic, smooth/papillary; Content of cystic masses-mucinous, serous and Presence of haemorrhage/necrosis/calcification. Representative sections are taken, processed in a tissue processor and then embedded in paraffin wax. Multiple 4-5 micron sections were cut using rotary microtome and are mounted on the glass slide for hematoxylin and eosin stain. The slides are mounted with DPX and then examined under microscope.

The distribution of cases was done according to Morphology on Frozen section and Paraffin section. The frozen section diagnoses and the paraffin section diagnoses were categorized as benign, borderline, and malignant. The overall "concordance" between frozen section diagnosis and permanent histopathology report was determined. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of frozen section analysis for benign, borderline and malignant surface epithelial ovarian tumors were evaluated by 2×2 contingency tables.

Malignant tumors reported as borderline and borderline tumors reported as benign by frozen section were defined as "underdiagnosis" and benign tumor diagnosed as borderline or malignant and borderline tumor diagnosed as malignant by frozen section were defined as "overdiagnosis". Both underdiagnoses and overdiagnoses were interpreted as "Discordant" cases. Pathological slides and clinical data were reviewed to assess the factors leading to discordance.

The association between discordance (overdiagnosis or underdiagnosis) and each clinicopathological factor was determined with univariate analysis via Fischer's exact test. A p value of less than 0.05 was set for statistical significance. SPSS 17.0 was used for the data management and statistical analysis.

OBSERVATION & RESULTS

This study was conducted in the department of pathology for the period of two years. A total of 204 consecutive patients of adnexal mass underwent laparotomy and intra-op frozen section evaluation was requested. Out of 204 cases, 104 cases were excluded from the study, of which 15 were metastatic ovarian tumors, 40 were non-neoplastic masses, 24 were sex cord stromal tumour and 25 cases were germ cell tumours. Thus 100 cases were included in the study and statistical analysis of the data was done as below:

Of the 100 patients with surface epithelial ovarian tumors in the study 34% had benign, 10% had borderline and 56% had malignant histology at the paraffin section. Similarly on frozen section 37% had benign, 11% had borderline and 52% had malignant histology.

Most of the tumours on frozen section with mucinous histological picture were benign (67.4%) however most tumours with serous histology were malignant (56.7%). Similarly, maximum tumours with serous histology on paraffin section were malignant (60.5%) however most of the tumours with mucinous histology were benign (69%). The tumours were further subtyped histopathologically. (Table1 & 2).

Table-1 Distribution of cases according to Histological Type

Histology of Tumor	Frozen Section	Paraffin Section
Serous	30	42
Mucinous	43	43
Endometrioid	1	8
Brenner	1	1
Seromucinous	1	4
Adenocarcinoma, Unspecified	19	1
Adenocarcinoma, Non mucinous	5	1

Table 2: Distribution of cases according to tumor histology and status of malignancy

Table 2A : According to frozen section				
Histology of Tumor	Benign	Borderline	Malignant	Total
Serous	6	7	17	30
Mucinous	29	4	10	43
Endometrioid	-	-	1	1
Brenner	1	-	-	1
Seromucinous	1	-	-	1
Adenocarcinoma, Unspecified	-	-	19	19
Adenocarcinoma, Non mucinous	-	-	5	5
Total	37	11	52	100

Table 2B: According to paraffin section				
Histology of Tumor	Benign	Borderline	Malignant	Total
Serous	6	7	29	42
Mucinous	26	3	14	43
Endometrioid	-	-	8	8
Brenner	1	-	-	1
Seromucinous	-	-	4	4
Adenocarcinoma, Unspecified	1	-	-	1
Adenocarcinoma, Non mucinous	-	-	1	1
Total	34	10	56	100

Of the 100 cases included in the study frozen section was concordant with the paraffin section in 94% of cases with only 6% of discordance. Thus, the overall agreement between frozen section and histopathology was 94% (Table 3).

Table 3: Comparison of frozen section diagnosis with final paraffin section diagnosis according to status of malignancy

Frozen section Diagnosis	Final Histopathology Diagnosis			
	Benign	Borderline	Malignant	Total
Benign	34	2	1	37
Borderline	-	8	3	11
Malignant	-	-	52	52
Total	34	10	56	100

All the 6 cases of discordance were due to under-diagnosis Of the 6 discordant cases, three cases with borderline mucinous tumour on frozen section were diagnosed as mucinous cystadenocarcinoma on paraffin section. Two cases of benign mucinous cystadenoma on frozen section were subsequently reported as borderline mucinous tumour on paraffin section. 1 case of mucinous cystadenocarcinoma was under-diagnosed as benign mucinous cystadenoma on intra-op frozen section evaluation.(Figure 1-5)

The accuracy rates for benign, borderline and malignant tumours were 97%, 95% and 96%, respectively. Thus the overall accuracy for the frozen section was lower for the borderline tumours as compared to benign and malignant tumours. Accuracy was calculated using the formula (True positive + true negative / True positive + true negative + false positive + false negative). (Table 4)

Sensitivity is calculated as true positive/ true positive +false negative. The overall sensitivity of the frozen section diagnosis was highest for the benign tumours (100%). However the ability of the frozen section to detect true positive borderline tumours was least (80%). (Table 4)
Specificity is calculated as: true negatives/ (true negatives + false positives). The sensitivity of frozen section for benign, borderline and malignant tumours was 95.5%, 96.6% and 100% respectively. Thus the ability of frozen section to rule out a malignant tumour was 100%. (Table 4)

Table-4 Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the frozen section for ovarian neoplasms

	Benign	Borderline	Malignant
Sensitivity	100	80	92.8
Specificity	95.5	96.7	100
Positive predictive value	91.9	72.7	100
Negative predictive value	100	97.7	91.7
Accuracy	97	95	96

Positive predictive value (PPV) is calculated as true positive/ true positive+ false positive. The positive predictive value for borderline tumours was least (72.7%) as compared to benign (91.9%) and malignant tumours (100%). (Table 4)

The negative predictive value was highest with benign tumours (100%) followed by borderline (97.8%) and malignant tumours

(91.7%). The negative predictive value was calculated with formula true negatives/ (true negatives + false negatives). (Table 4)

Univariate analysis showed that borderline histology (p=0.017) and mucinous tumours on frozen section (p=0.005) were associated with underdiagnosis of ovarian tumors by frozen section analysis. (Table 5)

Table-5 Univariate analyses of factors influencing frozen section diagnosis in discordant cases

Variable		Accurate diagnosis n(%)	Discordance n(%)	p value
Age (yrs)	<60	71(75.6%)	4(66.7%)	0.638
	>/= 60	23(24.4%)	2(33.3%)	
Preoperative CA 125 (U/ml)	<35	28(35.4%)	1(20%)	0.655
	>/= 35	51(64.6%)	4(80%)	
Epithelial Tumors	Mucinous	37(39.4%)	6(100%)	0.005
	Non-mucinous	57(60.6%)	-	
Tumor Histology	Borderline Tumors	8(8.5%)	3(50%)	0.017
	Others	86(91.5%)	3(50%)	
Ascitic Fluid	Positive	8(9.3%)	-	1.000
	Negative	78(90.7%)	6(100%)	
Tumor size (cm)	<10	17(18%)	-	0.586
	>/= 10	77(82%)	6(100%)	

DISCUSSION

Accurate intra-operative frozen section reporting is important to decide the extent of the surgery required for the management of the adnexal mass and these decisions have direct impact on the prognosis of the disease and future quality of life of the patient. Thus, it becomes necessary that the diagnosis obtained through intra-op frozen section analysis be accurate enough to guide for the necessary surgery and be sensitive enough not to miss the malignant tumours.

According to the literature, frozen section analysis of ovarian neoplasms has a high accuracy rate which was reported to be more than 90% in many studies. In the current series, the overall accuracy of frozen section was 95%. The sensitivity for benign and malignant ovarian tumors was 100% and 92.8 %, respectively and these results were similar to the other published series. However, in case of borderline ovarian tumors the sensitivity of frozen section was only 80 %. In the related literature, the sensitivity of intra-operative frozen section for Borderline ovarian tumors was also presented to be low between 64.6-88.5%.[7-14]

Although our results show that frozen section consultation is a reliable tool for intra operative decision making, there were 6 discordant cases (6 %) which significantly differed from permanent histological diagnoses.

Houck et al. found that mucinous histology was the only significant predictor for under-diagnosis by frozen section.[15] Tempfer et al. reported that a tumor size greater than 3 cm was the only independent factor related to under-diagnosis by frozen section.[16] Also, Brun et al. reported that in addition to tumor characteristics, the experience of the pathologist influences the accuracy of frozen section diagnosis.[8] But, the number of patients was small and the number of clinico-pathologic factors to evaluate was limited. Also, they did not show the clinical impact of misdiagnosis. Thus, a need arises to analyse these statistical parameters of frozen section diagnosis as well to evaluate the factors that potentially influence the accuracy of frozen section.

We analysed the clinical and pathological factors which could potentially influence the accuracy of intra-operative frozen section and found that the significant predictors of discordance in univariate analyses were mucinous tumours (p=0.005) and borderline histology (p=0.017).

The mean tumour size (20 cm) was higher in patients with benign adnexal masses.

It is obvious that compared to permanent pathologic evaluation, there is not enough time to take too many slices during frozen section procedure and large tumors may require multiple slices which is not always feasible in limited time settings. In addition, most of the published studies demonstrated that accuracy of frozen section diagnosis is negatively influenced by large tumor size.[7,17-19]In our view, tumor size is not an independent factor for misdiagnosis per se but it is dependent on the histopathological features of the tumors. Therefore, we think that discordant cases due to larger size tumors are reflections of the diagnostic errors that result from the intrinsic histological features of the tumors. In our study all the under-diagnosed tumours were >10 cm size however univariate analysis did not show any significant influence of tumour size on the misdiagnosis observed on frozen section.(p=0.586)

The distributions of histological pattern in benign, malignant and borderline tumours were comparable with the present available literature. Most of the tumours of mucinous pattern were benign in nature however most of the tumours of the serous type were malignant in nature. Similarly, most of the tumours of clear cell and endometrioid patterns were malignant in nature. There was a single case of mixed pattern (serous + mucinous) of tumour histology which was malignant in nature. (Figure 6)

Mucinous tumors form the largest ovarian masses and are notoriously heterogeneous in their histology with benign, borderline and malignant areas being present in the same tumor. It is nearly impossible to sample large masses extensively at the time of frozen section. Thus, based on the few frozen sections studied, the impression created could be of a benign or borderline sub-type while more extensive sampling on paraffin may disclose that the benign tumor is actually borderline or that the borderline tumor actually has frankly malignant areas. Borderline serous tumour are relatively more consistent in their histology as compared to borderline mucinous tumour. Yet 20% of Borderline Serous Tumors may harbour invasive, low grade serous carcinoma foci that could escape sampling at frozen.

In a retrospective cohort study by Song et al. the overall accuracy, i.e., agreement between frozen section and permanent histology diagnoses, was observed in 228 of 354 (64.4%) cases, yielding a sensitivity of 72.6%, a positive predictive value of 85.1%, underdiagnosis in 108 cases (30.5%), and overdiagnosis in 18 cases (5.1%). Based on multivariate analysis, mucinous histology (OR, 1.48; P=0.022) was the only significant predictor for underdiagnosis by frozen section.[20]

Histopathological feature of the ovarian tumor is important parameter for the success of frozen section diagnosis as well. In the current study, we found that frozen section diagnosis has a lower sensitivity for Borderline tumours (80%) compared to benign lesions (100%) and malignant tumors (92.8%). Univariate analysis showed that borderline histology was significantly associated with misdiagnosis (p=0.017). In a recent pooled analysis of 1,104 patients, Song et al. showed that frozen section diagnosis was correlated with permanent pathology in only 741 of 1,104 patients (67.1 %).[20]

The problems presented by Borderline ovarian tumours are said to be mainly related to limitation in sampling and histopathological heterogeneity. While some authors suggested examination of multiple frozen sections to overcome sampling problems, others resisted this approach and stated that it could impair the permanent section results. Thus the main causes of under-diagnosis in our study are sampling error in borderline tumours due to tumour heterogeneity and mucinous histology. Future studies should aim to increase the accuracy of frozen for Borderline Ovarian Tumors without altering paraffin section results.

CONCLUSION

- Our study confirms that the accuracy, sensitivity and specificity of frozen-section diagnosis are high for benign and malignant surface epithelial ovarian tumors whereas it is low for borderline tumors.
- Borderline tumors remain difficult to be accurately diagnosed at frozen section and requires extensive sampling.
- The main causes of under-diagnosis in our study are limitation in sampling, tumour heterogeneity and mucinous histology.
- Mucinous and borderline histology adversely influence the accuracy and sensitivity of frozen section diagnosis.
- Considering the importance of frozen section analysis in the intraop evaluation and in deciding the surgical management of the adnexal mass and its subsequent prognosis, post-op management and quality of life of patient, it requires continuous evaluation in terms of accuracy and factors that potentially influence the

discordance in the diagnosis. This would further add on to strengthening of frozen section as sole emergency diagnostic test which would translate into long term benefits to the operating surgeon and the patients at large.

- Frozen section will remain a time tested diagnostic tool so long as surgeries are performed. However, this tool must be judiciously utilized and is most effective when the pathologist and the surgeon are aware of its advantages and limitations.

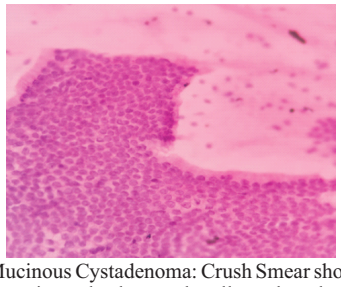

Fig 1- Benign Mucinous Cystadenoma: Crush Smear showing sheet of tumor cells on mucinous background, cells at the edge demonstrate basally located nucleus with abundant cytoplasm and abundant mucin. (H&E, 40x)

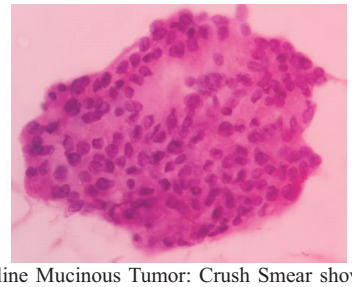

Fig 2- Borderline Mucinous Tumor: Crush Smear showing mild to moderate nuclear pleomorphism along with mitotic figures. (H&E, 40x)

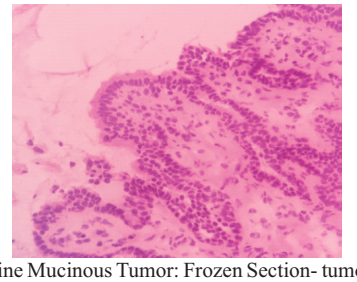

Fig 3- Borderline Mucinous Tumor: Frozen Section- tumor cells show nuclear stratification, crowding and mild to moderate atypia. (H&E, 40x)

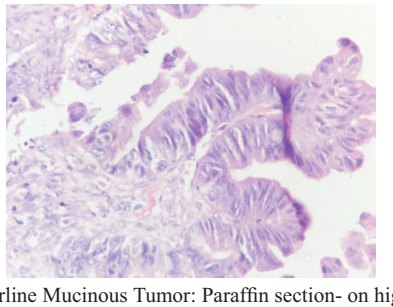

Fig 4- Borderline Mucinous Tumor: Paraffin section- on high power, the lining epithelium shows nuclear crowding and overlapping with moderate atypia. (H&E, 40x)

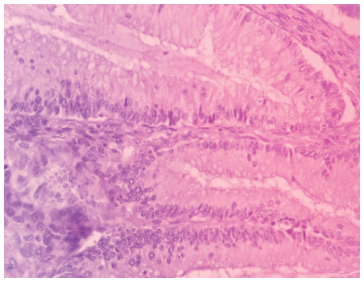

Fig 5- Mucinous Cystadenocarcinoma: Paraffin section- on further magnification, tumor cells have basally located nucleus showing mild to moderate atypia and abundant amount of cytoplasm and apical mucin. (H&E, 40x)

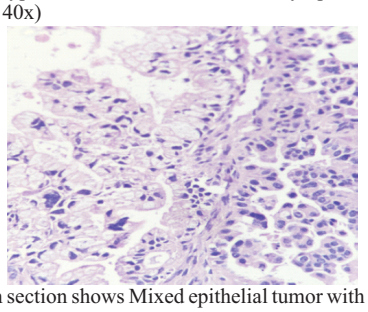

Fig 6: Paraffin section shows Mixed epithelial tumor with area of both Serous papillary adenocarcinoma (on right) and Mucinous adenocarcinoma (on left). (H&E, 40x)

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