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Original Article

Pathology Section

Role of Intraoperative Frozen Section in the Diagnosis of Ovarian Neoplasms- A Retrospective Study in an Oncology Centre

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ABSTRACT

Introduction: Ovarian malignancy is the sixth most common cancer in women and the seventh most common cause of cancer death. Intraoperative frozen section evaluation plays a critical role in guiding the type and extent of surgery. The overall accuracy of the intraoperative frozen section diagnosis for ovarian tumours was reported to be ranging from 85% to 95%.

Aim: To determine frozen section accuracy in the diagnosis of ovarian neoplasms.

Materials and Methods: The present study was a retrospective study taken up in the Department of Pathology, Sri Venkateswara Institute of Medical Sciences, Tirupati, from January 2011 to December 2018 during which all the ovarian masses which were sent for frozen section and later for regular Histopathological Examination (HPE) were included in the study. All the slides of these cases were reviewed by two senior pathologists in a double blind study. The frozen section and the permanent section reports of each patient were compared. The overall accuracy, sensitivity, specificity, positive and negative predictive values of the frozen section diagnoses were studied for benign, borderline and malignant cases by using 2×2 tables. The final histopathological diagnosis was considered as gold standard. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 22.0 for windows.

Results: The study included 289 cases and the overall accuracy of frozen section was 87.89%. Thirty five cases were incorrectly diagnosed, of which 24 cases were underdiagnosed and 11 were overdiagnosed. With respect to malignant potential, the sensitivity for malignant tumours was 81.4% with specificity of 96.8%. For benign tumours, the sensitivity and specificity were 93% and 91.4%, respectively. Borderline tumours had the lowest sensitivity of 68.7% with specificity of 91.8%.

Conclusion: Gross examination is to be done carefully for tumour tissue selection for frozen section diagnosis intraoperatively. The results help to decide the type and extent of surgical management.

Keywords: Accuracy, Malignancy, Serous tumours

INTRODUCTION

Rapid frozen section technique was first introduced by Welsh WM in 1891 [1], a diagnostic tool helps in identifying various ovarian lesions with high degree of accuracy and thus helps the surgeon to choose appropriate surgical procedure [2,3]. Ovarian malignancy is the sixth most common cancer in women and seventh most common cause of cancer death [4]. Most cases are diagnosed in late stages and require aggressive surgical management [5]. Ovarian tumours are a heterogeneous group of lesions which may be benign, borderline and malignant tumours. According to World Health Organisation (WHO), they are classified into epithelial tumours, mesothelial tumours, germ cell neoplasms, sex cord-stromal tumours and secondary malignancies.

The preoperative diagnostic modalities include serum tumour marker level (CA 125) estimation and imaging. CA 125 levels are not specific in some cases, which can be normal in early stages of ovarian carcinoma or can be raised in non neoplastic conditions like endometriosis and pelvic inflammatory disease [6]. In large heterogeneous ovarian masses imaging has limitations in the accurate diagnosis, resulting in limited value. For rapid histological diagnosis, intraoperative frozen section examination plays an important role, thus helping in surgical approach [7]. Malignant germ cell tumours and surface epithelial neoplasms differ in conservative surgical management and preservation of fertility [8]. The overall accuracy of the intraoperative frozen section diagnosis for ovarian tumours was reported to be ranging from 85% to 95% [5,8-10]. The present study was intended to determine the accuracy of frozen section in ovarian tumours. Objectives of the study were to categorise ovarian neoplasms into benign, borderline and malignant on frozen sections. Frozen section diagnosis of ovarian neoplasms was compared with that of the paraffin embeded haematoxylin and eosin stained sections.

MATERIALS AND METHODS

It was a retrospective study conducted from January 2011 to December 2018 in the Department of Pathology, Sri Venkateswara Institute of Medical Sciences, Tirupati. The data was analysed from January 2019 to September 2019. Ethical approval was obtained from Institutional Ethics Committee (IEC No. 1044).

Inclusion criteria: All histopathologically diagnosed ovarian masses for which intraoperative frozen section was performed were included in the study.

Exclusion criteria: Ovarian masses for which frozen section was not performed were excluded from the study.

A total of 289 cases of suspected ovarian masses for which frozen sections were requested within the study period included in the study. All the specimens which were received for frozen were thoroughly examined for tumour size, capsule integrity, consistency and cut section showing solid, cystic and variegated appearance were noted. Later, on an average three to five tissue sections were submitted for frozen from appropriate areas of the tumour. Frozen sections of 5-6 µ thickness were cut using cryostat and stained with Haematoxylin and Eosin (H&E). Reports were given by a senior pathologist with 10 years experience. The tissue remains

and reminder of ovarian mass was later subjected for grossing extensively after formalin fixation, tissue processed, paraffin blocks prepared, sections cut, deparaffinised, H&E sections prepared and reported by a different senior pathologist. The histopathology report includes histological cell type and potential of malignancy, which were divided into benign, borderline and malignant. For each case, histopathological diagnosis of both frozen section and paraffin embedded sections were compared. Overall accuracy, sensitivity, specificity, positive and negative predictive values of the frozen section diagnoses was determined. These were calculated for the three (benign, borderline and malignant) categories using 2×2 tables. Histopathological diagnosis is considered as gold standard.

STATISTICAL ANALYSIS

All the details were recorded in the study proforma and double-checked for accuracy. Frozen and paraffin embedded histopathological section reports of each patient were compared. The overall accuracy, sensitivity, specificity, positive and negative predictive values of the frozen section diagnoses were calculated separately for all the three categories (benign, borderline, and malignant) by 2×2 tables considering histopathological section diagnosis as gold standard. Statistical analyses were all performed using Statistical Package for the Social Sciences (SPSS) software version 22.0 for windows.

RESULTS

A total of 289 cases were subjected for frozen section and diagnosed as ovarian neoplasms. The study age group ranged from 15 to 80 years with a mean age of 47.5 years. The most common age group affected belongs to 5th decade followed by 6th and 4th decades.

Of total 289 cases, 160 were benign on histopathological examination, whereas 32 diagnosed as borderline and 97 as malignant tumours. Out of 160 benign cases, 26 were cystic lesions which include endometriotic, haemorrhagic, follicular and corpus luteal cysts. Serous cystadenoma is the most common benign lesion (62 cases), second common is mucinous cystadenoma (27 cases), followed by sex cord-stromal tumours (fibrothecoma-16 cases, fibroma-1 case), mature cystic teratoma (15 cases), mixed epithelial tumours (6 cases), and benign Brenner tumours (2 cases). Five benign cases were reported as Leiomyomas [Table/Fig-1]. Among borderline neoplasms, 18 cases were borderline mucinous, 12 cases were borderline serous and two cases were borderline seromucinous category. The most common malignant tumours were serous carcinomas (48 cases) followed by mucinous carcinomas (21 cases), adult granulosa cell tumours (9 cases), Metastatic carcinomas (5 cases), dysgerminoma (3 cases) [Table/Fig-1], endometrioid carcinomas (3 cases), immature teratomas (2 cases), one case each of yolk sac tumour, malignant mixed epithelial tumour, malignant melanoma, fibrosarcoma, squamous cell carcinoma arising from teratoma and poorly differentiated malignancy. [Table/Fig-1] explains distribution of ovarian tumours. Total teratoma cases in the present study were 18, out of which 15 are mature cystic teratoma, 2 comes under malignant category, one case of SCC arising from mature cystic teratoma (which is also included under malignancy).

Out of the 289 ovarian tumours, 254 cases (87.89%) of frozen section diagnosis were compatible with paraffin section studies whereas 35 cases (12.11%) were incompatible with the paraffin sections [Table/Fig-2]. Out of 35 cases, 24 (8.3%) were underdiagnosed on frozen section. Of these 24 underdiagnosed cases, 13 were reported as borderline tumours on frozen section and as malignant on paraffin sections. These include six mucinous tumours, six serous tumours and one seromucinous tumour. Of 24 underdiagnosed cases, eight were reported as benign on frozen section and as borderline tumours on paraffin sections. Among these majority were mucinous tumours (4 cases), followed by serous tumours (3 cases) and endometrioid tumour (1 case). One case was diagnosed as benign ovarian lesion, which turned out to malignant on histopathology. Two cases of immature teratoma on histopathology were underdiagnosed as mature teratoma.

Tumour type	Benign (n)	Borderline (n)	Malignant (n)	Total n (%)
Epithelial				202 (69.8)
Serous	62	12	48	122 (42.3)
Mucinous	27	18	21	66 (22.8)
Seromucinous	06	02	01	09 (3.2)
Endometrioid	-	-	03	03 (1.0)
Brenner	02	-	-	02 (0.7)
Germ cell				22 (7.7)
Mature cystic teratoma	15	-	03	18 (6.3)
Dysgerminoma	-	-	03	03 (1.0)
Yolk sac tumour	-	-	01	01 (0.3)
Sex cord-stromal tumour				26 (8.9)
Adult granulosa cell tumour	-	-	09	09 (3.2)
Fibrothecoma	16	-	-	17 (5.8)
Fibroma	1	-	-	-
Others				39 (13.5)
Leiomyoma	05	-	-	05 (1.7)
Haemorrhagic cyst	04	-	-	04 (1.4)
Twisted ovarian cyst	04	-	-	04 (1.4)
Endometriotic cyst	04	-	-	04 (1.4)
Follicular cyst	01	-	-	01 (0.3)
Corpus haemorrhagicum	05	-	-	05 (1.7)
Simple cyst	08	-	-	08 (2.8)
Malignant melanoma	-	-	01	01 (0.3)
Metastasis	-	-	05	05 (1.7)
Undifferentiated carcinoma	-	-	01	01 (0.3)
Fibrosarcoma	-	-	01	01 (0.3)
Total	160	32	97	289

[Table/Fig-1]: Distribution of ovarian tumours.

Frozen section diagnosis	Type of tumour diagnosed			Paraffin section diagnosis
Underdiagnosed (n=24)				
Borderline (n=13)	Mucinous (n=6)	Serous (n=6)	Seromucinous (n=1)	Malignant
Benign (n=8)	Mucinous (n=4)	Serous (n=3)	Endometroid (n=1)	Borderline
Benign (n=1)	-	-	-	Malignant
Mature teratoma (n=2)	-	-	-	Immature teratoma
Overdiagnosed (n=11)				
Borderline (n=6)	Serous (n=4)	Mucinous (n=2)	-	Benign
Malignant (n=3)	Serous (n=2)	Mucinous (n=1)	-	Malignant
High grade carcinoma (n=1)	-	-	-	Sex cord stromal tumour
Spindle cell neoplasm (n=1)	-	-	-	Leiomyoma

[Table/Fig-2]: Incompatible cases between frozen and paraffin sections.

Out of 35 incompatible cases, 11 (3.8%) were overdiagnosed on frozen sections. Of these 11 cases, six were reported as borderline on frozen sections, which turned out to be benign on paraffin sections. These include four serous tumours and two mucinous tumours. Three borderline cases were diagnosed as malignant on frozen section, of which two were serous tumours and one was

mucinous tumour. One sex cord-stromal tumour was diagnosed as high grade carcinoma on frozen section. One spindle cell neoplasm of intermediate grade on frozen section turned out into leiomyoma on paraffin sections. [Table/Fig-3] shows the comparison between the frozen section assessment and the permanent pathological diagnoses for all cases.

Frozen diagnosis	Histopathological diagnosis			
	Benign	Boderline	Malignant	Total
Benign	150	07	04	161
Borderline	07	22	14	43
Malignant	03	03	79	85
Total	160	32	97	289

[Table/Fig-3]: Comparison between the frozen section and the permanent pathological diagnoses.

The statistical analysis in terms of sensitivity, specificity, positive predictive value and negative predictive value of frozen section diagnosis is represented in [Table/Fig-4].

Statistical value (%)	Benign	Borderline	Malignant
Sensitivity	93	68.7	81.4
Specificity	91.4	91.8	96.8
Positive Predictive Value	93.1	51.1	93
Negative Predictive Value	92.1	95.9	91.1

[Table/Fig-4]: Statistical analysis of frozen/histopathological diagnosis.
Statistical analysis tests- sensitivity, specificity, positive predictive value, negative predictive values are calculated using statistical formulas by 2×2 table

The specificity (true negative rate) of frozen section was 96.8%. The sensitivity (true positive rate) of frozen section diagnosis was 81.4%. Overall accuracy for benign, borderline, and malignant tumours is 87.89%. High sensitivity (93%) and positive predictive value (93.1%) are seen in benign tumours. High specificity (96.8%) is seen in malignant tumours. High negative predictive value (95.9%) is seen in borderline tumours.

DISCUSSION

The present study showed 254 compatible cases between frozen diagnosis and histopathological diagnosis, 35 cases showed incompatibility. Overall accuracy of frozen section diagnosis was 87.89%. Surgical treatment plan of ovarian tumours requires accurate histological diagnosis. Conservative management is the modality for benign lesions and for few borderline tumours to preserve fertility. However, the treatment plan for borderline or malignant tumour patients is complete pelvic clearance, omental biopsy or omentectomy and appropriate staging procedures [11]. Although the term frozen section diagnosis is widely used, some authors suggested that the term "intraoperative consultation", because not all diagnoses require a frozen section [12]. The goal of frozen section of ovarian tumours is to discriminate benign, borderline and malignant tumours for appropriate surgical management. Frozen section accuracy varies among different institutions for ovarian tumours. The present study institution had an overall accuracy rate of 87.89% for benign, borderline and malignant ovarian tumours on frozen sections. This is comparable with various studies which range from 85 to 99% [Table/Fig-5] [5,8-10,11,13-15].

In the present study, 35 cases gave incompatible results between frozen and paraffin sections, of which 24 were underdiagnosed and 11 were overdiagnosed. Among the underdiagnosed cases majority were mucinous tumours followed by serous tumours. Most of these tumours are underdiagnosed as borderline tumours which turned out to be malignant on paraffin sections. Careful gross examination for tumour tissue selection is required for accurate intraoperative frozen section diagnosis. Scrupulous examination for solid areas and wall thickening should be made, because of time constraints, this becomes difficult during frozen sectioning for large size mucinous tumours with multiloculations, results in underdiagnosis. Another reason for underdiagnosis is, mixed benign, borderline and malignant components in different areas within the same mucinous tumour, unlike uniform serous tumours [16]. Under sampling is the reason for underdiagnosis in borderline ovarian tumours. A meta-analysis done by Huang Z et al., validates that mucinous histology and unilateral tumours are associated with misdiagnosis of borderline ovarian tumours using frozen section [17]. Germ cell tumours and sex cord-stromal tumours can show similar morphology with surface epithelial tumours [8], which will be sometimes difficult for diagnosis on the frozen section. Present study reported two cases of mature cystic teratoma on frozen which on final paraffin sections turned out to be immature teratomas, due to presence of foci of immature neural tissue in the additional tissue bits given for paraffin section study.

The causes of discordance and deferred cases in the present study were due to sampling error, misinterpretation, lack of communication with the surgeons and technical problems [18,19]. For the reproductive age women who want to preserve the fertility, misdiagnosis of frozen section may lead to improper treatment [17]. Among the overdiagnosed cases, majority were serous tumours (4 cases) followed by mucinous tumours (2 cases) which were diagnosed as borderline on frozen, and proved to be benign on histopathology. The overdiagnosis rate was 3.8%, whereas underdiagnosis rate was 8.3%. In comparison with other studies [8,15,20], present study showed low rates of underdiagnosis than overdiagnosis. Reason behind the overdiagnosis is due to interpretational errors.

Studies	Place of study	No. of cases studied	Overall accuracy of frozen section diagnosis (%)	Sensitivity of frozen section		
				Benign (%)	Borderline (%)	Malignant (%)
Subbian A et al., 2013 [5]	Kidwai Institute, Banglore, India	135	85.18	90.4	31.2	91.5
Yazdani S et al., 2015 [13]	Babol University of Medical Sciences, Iran	126	94.4	99.1	80	66.7
Hashmi A et al., 2016 [8]	Dhaka Medical College, Bangladesh	141	99	100	83	96
Jena M and Burela S- 2017 [14]	MVJ Medical college, Banglore, India.	49	89.7	100	100	58.5
Rose PG et al., 1994 [9]	University of Massachusetts Medical Center, United States	383	92.7	98.7	44.8	92.5
Yeo EL et al., 1998 [10]	Kwong Wah Hospital, Hong Kong	316	95.2	99.6	60	87
Yarandi F et al., 2008 [11]	University of Tehran, Iran	106	93.4	97.4	25	91.6
Sukumaran R et al., 2014 [15]	Regional Cancer Centre, Kerala, India	233	91.8	99.2	88.4	82.95
Present study	Sri Venkateswara Institute of Medical Sciences, Andhra pradesh, India	289	87.89	93	68.7	81.4

[Table/Fig-5]: Comparison of present study with various studies.

Various studies showed sensitivity of frozen diagnosis in ovarian tumours in the range of 90% to 100% and 82.9% to 96% for benign and malignant tumours [5,8-11,15]. Present study showed 93% sensitivity for benign tumours, within the range of previous studies [5,8-11,15] whereas malignant tumours showed low sensitivity of 81.4% in comparison of previous studies [5,8-11,15]. The low sensitivity for malignant tumours in the present study is due to high false negative values observed in borderline tumours, which showed foci of invasion with extensive sampling on paraffin sections.

Low sensitivity for malignant tumours is also observed in some studies like Yazdani S et al., and Jena M and Burela S [13,14]. Sensitivity for borderline tumours was 68.7% is within the range of other studies 44.8% to 83%. Two studies done by Subbian A et al., and Yarandi F et al., showed low sensitivity for borderline tumours which were because of large size mucinous tumours showing tumour heterogeneity [5,11]. For borderline ovarian tumours the accurate diagnosis is important to avoid over treatment or under treatment. In older age group, the treatment for borderline ovarian tumours is hysterectomy with bilateral salpingo-opherectomy and surgical staging. Whereas for reproductive age group, either unilateral salpingo-oopherectomy or cystectomy with surgical staging is the management plan [21]. Specificity of the present study for benign, borderline and malignant tumours were 91.4%, 91.8%, 96.8%, respectively, with in the range of various other studies [5,8-11,13-15].

Limitation(s)

Limitations of the current study are relatively small sample size, and limited tissue sampling which is an inherent limitation of frozen section. Limited sampling especially in large ovarian tumours might be the reason for low sensitivity in borderline tumours and in mucinous tumours.

CONCLUSION(S)

Meticulous gross examination of the tumour tissue selection is important for accurate intraoperative diagnosis. The purpose of the rapid diagnostic procedure is of no useful, if the frozen diagnosis is not reported within minutes. Multiple tissue bits sampling can be done in histopathological diagnosis which helps in identifying the small microscopic foci of epithelial malignant change in a predominantly benign mass. The clinicians and pathologists must be aware of the pitfalls of this method; therefore, a good communication should be established between them to obtain more accurate results so as to minimise the number of deferred cases.

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