Original Article

Role of Frozen Section in Surgical Management of Ovarian Neoplasm

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Abstract

Objective: Cancers of the adnexae, including ovarian and fallopian tube, constitute the eighth most common cancers among women worldwide. Surgery remains the cornerstone in the management of ovarian cancer. Intraoperative frozen section diagnosis of ovarian tumors is widely used in making this distinction and to decide the course of surgery. Therefore, the accuracy of this technique is very important. The aim was to determine the overall accuracy, sensitivity, specificity, and predictive values of frozen section for ovarian tumors and to evaluate the role of frozen section in the surgical management of ovarian tumors.
Materials and Methods: This was a descriptive longitudinal study conducted in the gynecology department of a tertiary care hospital. During the 1 ½ year period of data collection, frozen section was performed among 60 cases of ovarian neoplasms. The overall accuracy, sensitivity, specificity and predictive values of frozen section for benign, borderline and malignant categories of ovarian tumors were studied.
Results: Out of the 60 patients of ovarian tumors, frozen section diagnosis showed that 43 (71.7%) tumors were benign, 11 (18.3%) were malignant and 6 (10%) were of borderline nature. Final histopathological diagnosis showed that 45 (75%) tumors were benign, 11 (18.3%) were malignant and 4 (6.7%) were borderline. Frozen section for benign tumors had 95% sensitivity, 100% specificity, 100% positive predictive value (PPV) and 88% negative predictive value (NPV). Malignant tumors had 90% sensitivity, 97% specificity, 90% PPV and 97% NPV with frozen section. However, frozen section had low sensitivity (75%) and PPV (50%) for borderline tumors. Specificity was 94% and NPV 98% in this group of tumors.
Conclusion: Frozen section was found to be an accurate and useful modality in the intraoperative evaluation of patients with ovarian neoplasm. The results can help to decide the type and extent of surgery.

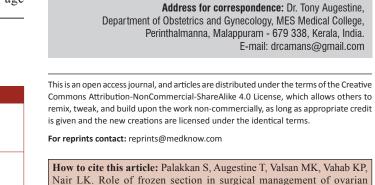**Keywords:** Frozen section, ovarian tumors, sensitivity, specificity

INTRODUCTION

Cancers of the adnexae, including ovarian and fallopian tube, constitute the eighth most common cancers among women worldwide.[1] Both, developed and the underdeveloped regions of the world are affected, although the incidence is double in the former when compared to the latter zones. Factors associated with an increase in ovarian cancer risk are advancing age, nulliparity, and family history of the disease. Ovarian cancer is relatively rare before the age of 40 and increases steadily thereafter and peaks at peri/postmenopausal age.

Two thirds of patients with ovarian tumors present in Stage III.[1] This is due to the asymptomatic nature of the disease and the lack of effective screening methods for ovarian cancers, unlike cervical cancers. Early diagnosis of ovarian cancer is generally incidental with more prevalent use of sonography. At present, the two most effective screening

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methods for ovarian cancer are transvaginal sonography and tumor marker estimation.

Preoperative imaging and tumor markers have only limited value in differentiating between benign, borderline and malignant categories. Intraoperative frozen section diagnosis of ovarian tumors is widely used in making this distinction and to decide the course of surgery. Therefore the accuracy of this technique is very important. The accuracy of frozen section diagnosis of benign and malignant ovarian tumors is generally quite good. Careful intraoperative assessment of tumor and the use of frozen section especially in those tumors with solid components will help achieve a high accuracy rate.[2]

MATERIALS AND METHODS

This was a descriptive longitudinal study conducted for a period of 18 months in the Obstetrics and Gynecology Department of a Tertiary Care Hospital (M. E. S Medical College, Perithalmanna) in South India after obtaining approval from the Institutional Ethical Committee (Approval No. IEC/MES/02/2012 obtained on Jan. 10th, 2012). An informed written consent was obtained from those enrolled for the study. Among the 60 cases of ovarian neoplasm who underwent frozen section 23 patients had laparotomy and 37 had laparoscopic surgery. Frozen section was done in patients with clinically benign looking tumors (on preoperative imaging or intraoperative inspection) with raised CA-125, adnexal mass in a patient with a past history of malignancy at another site and young patients with ovarian neoplasms desirous of fertility preservation.

A detailed history included; demographic data, symptoms, menstrual and marital history, history of exposure to any high risk factors, personal and family history. Ultrasonography was done by an experienced operator and when an ovarian tumor was detected, the tumor characteristics were documented. All patients with a complex ovarian mass with suspected extraovarian involvement/ureteric involvement/lymph nodal involvement and/or moderate to massive ascites were subjected to a computed tomography scan. Frozen section was done in all ovarian tumors of uncertain nature after inspection at staging laparotomy. Extent of surgery was guided by the results of frozen section.

A staging laparotomy was performed and the tumor was first removed. The unfixed tumor was immediately handed over to the frozen section laboratory, with all the clinical details of the patient. After gross examination of the tumor, sections were obtained from representative areas at the discretion of the pathologist. The number of sections frozen ranged from 1 to 4 and was decided based on the type and size of the tumor. In all tumors diagnosed as borderline, at least two sections were

frozen. This was done with a Cryostat. Seven to 8 μm sections were obtained and stained with h and e and toluidine blue. All the sections were studied microscopically under low and high power by two pathologists. The frozen section diagnosis was conveyed to the surgical team who proceeded with the appropriate surgery. The average time taken for the entire procedure (sending the sample to obtaining the result) was approximately 20 min. The frozen section diagnosis was categorized as one of the following: primary epithelial ovarian neoplasm – benign, borderline or malignant; primary ovarian germ cell tumor, metastatic carcinoma to ovary, benign nonneoplastic conditions and no definite opinion possible. Frozen section diagnosis was later compared to the final paraffin section diagnosis. For the statistical analysis, the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL, USA) was used.

RESULTS

Frozen section was performed among 60 cases of ovarian neoplasms during a period of 18 months.

Sociodemographic profile
The present study group constituted patients from second to seventh decade. Maximum number of patients belonged to the age group 21–40 years. The youngest patient in our study was 18 years old and the eldest was of 76 years.

Clinical features
Among the 60 patients studied, the most common presenting symptom was pain abdomen (76.6%). The other symptoms observed were dyspepsia, mass abdomen, menstrual irregularity, constipation and urinary symptoms in the descending order of frequency. Forty-seven (78.3%) patients in the present study were multiparous.

Sonological characteristics
Among the 60 cases, 33 (55%) were 10 cm or more in size. In 11 patients with ovarian malignancy, 10 had tumor size of 10 cm or more and one had tumor size of <10 cm. This ovarian malignancy with a smaller tumor size (<10 cm) was a papillary serous cystadenocarcinoma. Most of the ovarian tumors were unilateral. Of the 9 (15%) bilateral tumors four were found to be malignant. Two were mucinous cystadenocarcinoma and the other two were serous cystadenocarcinoma. We observed that the consistency of 30 (50%) tumors were purely cystic and 30 (50%) had evidence of solid components. Among malignant ovarian neoplasms, 2 (18%) were purely cystic and 9 (82%) had evidence of solid components.

Multiloculated tumors were 42 (70%) and the rest 18 tumors were uniloculated. Of the 11 cases of ovarian malignancies, 10 (91%) were multiloculated and only one was uniloculated.

Ascites was present in 12 (20%) of total patients. Nine (82%) of patients with ovarian malignancies had ascites.

Tumor marker-CA-125

In the present study, serum CA-125 levels more than 35 U/ml were found in 25 (42%) cases. Serum CA-125 levels more than 200 U/ml were found in 8% of cases. In 11 patients with histologically proven malignant tumors, 7 cases (64%) had elevated values of serum CA-125.

Accuracy of frozen section

Out of the sixty patients of ovarian tumors, frozen section diagnosis showed that 43 (71.7%) tumors were benign, 11 (18.3%) were malignant and 6 (10%) were of borderline nature. Final histopathological diagnosis showed that 45 (75%) tumors were benign, 11 (18.3%) were malignant and 4 (6.7%) were borderline. Among the 60 cases, according to final histopathological examination report to 49 (82%) were surface epithelial tumors, 6 (10%) were germ cell tumors, 2 (3.3%) were metastatic, 2 (3.3%) endometriotic cysts, and one was a sex cord stromal tumor.

Out of the 49 cases of surface epithelial tumors, 36 were benign (22 serous and 14 mucinous), 4 were borderline tumors (1 serous and 3 mucinous) and 9 were malignant (7 serous and 2 mucinous). There were 6 germ cell tumors which included 5 teratomas and a case of struma ovary. One of the metastatic tumor was a Krukenberg tumor with primary in the stomach. The other case of metastatic tumor was from a colonic malignancy. The only sex cord stromal tumor found in this study was fibrothecoma.

A total of 63 specimens underwent frozen section examination. Of these, 3 cases (4.48%) were deferred to permanent sections. Of the remaining 60 cases, the discordant diagnostic frequency was 6.6% while the concordant diagnostic frequency was 93.4%. Out of the 60 ovarian tumors, 4 (6.6%) frozen section reports were incompatible with the final histopathological examination reports [Table 1]. There was one frozen section report where frozen section showed borderline mucinous cystadenoma and the final histopathological examination report turned out to be mucinous cystadenocarcinoma. There were two benign tumors that were incorrectly diagnosed as borderline (one mucinous and one serous) by frozen section. There was one borderline mucinous cystadenoma that was misdiagnosed as malignant mucinous cystadenocarcinoma at frozen. It should be noted that the term "benign" included benign ovarian neoplasms and benign nonneoplastic conditions like endometriosis.

The overall accuracy of frozen section was 93%. In the present series, we found that frozen section had high sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for benign and malignant ovarian tumors. Frozen section for benign tumors had 95% sensitivity, 100% specificity, 100% PPV and 88% NPV. Malignant tumors had 90% sensitivity, 97% specificity, 90% PPV and 97% NPV with frozen section. However, frozen section had low sensitivity (75%) and PPV (50%) for borderline tumors. Specificity was 94% and NPV 98% in this group of tumors [Table 2]. Two metastatic tumors were accurately diagnosed to be metastatic intraoperatively by frozen section.

DISCUSSION

Intraoperative histological assessment of ovarian tumors help clinicians to select an appropriate surgical procedure for patients, avoiding both under and over-treatment. Benign lesions are usually managed conservatively and a similar approach may be taken in some patients with borderline tumors or even for a selected few with malignant tumors, who wish to preserve their fertility. However, most patients with borderline or malignant tumors undergo complete pelvic clearance, omentectomy, and appropriate staging procedure. Therefore, intraoperative frozen section should ideally be used to accurately discriminate between benign, borderline and malignant ovarian tumors and also identify those malignancies of extraovarian origin.[3] The present study was conducted to examine the role of frozen section in managing ovarian tumors.

The present study group constituted patients from second to seventh decade. Maximum number of patients were in the age group of 21–40 years. The proportion of patients of various age groups in the present series were comparable to the previous studies. The youngest patient in our study was 18 years old and the eldest was of 76 years. The mean age for malignant tumors was 52 years and that for borderline tumors was 40 years.

Table 1: Comparison between frozen section diagnosis and final histolopathologic diagnosis of ovarian tumors (*n*=60)

Frozen section diagnosis	Final histopathologic diagnosis		
	Benign	Borderline	Malignant
Benign (*n*=43)	43	0	0
Borderline (*n*=6)	2	3	1
Malignant (*n*=11)	0	1	10
Total (*n*=60)	45	4	11

Table 2: Sensitivity, specificity, and positive and negative predictive values of frozen section

	Benign (%)	Borderline (%)	Malignant (%)
Sensitivity	95.56	75	90.91
Specificity	100	94.64	97.96
PPV	100	50	90.91
NPV	88.24	98.15	97.96

PPV: Positive predictive value, NPV: Negative predictive value

Sonological characteristics

In our study most of the patients with malignant ovarian tumors had tumor size more than 10 cm, presence of solid components, multilocular nature and presence of ascites on imaging. The parameters which were found to be statistically significant ($P < 0.05$) in predicting ovarian malignancy in our study were tumor size more than 10 cm, presence of solid components and presence of ascites. Even though most of the patients with malignant ovarian tumors had multilocular nature, this parameter was found to be statistically insignificant ($P > 0.05$). This could be probably due to the lesser number of malignant cases in this study. In a study by Timmerman *et al*., several parameters were used to predict malignancy by conventional ultrasonography which included (1) irregular contour (2) ascites (3) at least four papillary structures (4) multilocularity, with a largest diameter of at least 100 mm and (5) high color content on color Doppler examination.[4] In another study by Minaretzis D *et al*., tumors which were more than 9 cm in size, bilateral, multilocular and solid in consistency were found to have increased risk of malignancy.[5]

Tumor marker-CA-125

In the present study, CA 125 levels were raised above 35 U/ml in 64% of women with malignant tumors. However, the association between raised CA 125 level and ovarian malignancy was found to be statistically insignificant ($P = 0.194$). In our study we observed 37% of benign masses having raised CA 125 level affirming that CA 125 cannot reliably distinguish between a malignant and a benign ovarian tumor. Jacobs and Bast found that about 50% of patients with Stage I disease had elevated levels of CA 125.[6] Vasilev *et al*. found that CA 125 levels were raised above 35 U/ml in 78% of women with malignant masses but also in 22% of those with benign masses.[7]

Accuracy of frozen section

Out of the 60 ovarian tumors, 4 (6.6%) frozen section reports were incompatible with the final histopathological examination reports. There was one false negative report where frozen section could not identify a mucinous malignant tumor. There were two benign tumors that were diagnosed as borderline (one mucinous and one serous) by frozen section (false positives). There was also a case of a mucinous borderline tumor that was diagnosed as a malignant tumor (overestimation). It should be noted that the diagnosis "benign" included benign ovarian neoplasms and benign nonneoplastic conditions like endometriosis.

The overall accuracy of frozen section diagnosis of ovarian masses was 93.3% in the present study. The overall accuracy was found to be within the range of 90%–97% from the previous available series.[8-14]

In the present series we found that in case of benign tumors frozen section had 95.5% sensitivity, 100% specificity, 100% PPV and 88.24% NPV. Frozen section had 90.91% sensitivity, 97.96% specificity, 90.91% PPV and 97.96% NPV for malignant tumors. However, frozen section had low sensitivity (75%) and PPV (50%) for borderline tumors.

In accordance with the previous published studies, it was observed that frozen section had high sensitivity, specificity and predictive values in the prediction of benign and malignant neoplasms of the ovary, but had low sensitivity and PPV for borderline tumors.[3,15-17] It was also noted that inaccurate diagnosis occurred more commonly with mucinous tumors than other histological types.[3,15-17]

The accuracy of frozen section diagnosis can be affected by various factors including sampling error, quality of frozen section and experience of pathologists.[18] Sampling error was considered to be the major reason for the diagnostic discrepancy in most studies.[12] This is particularly true in some groups of tumors, in which there was remarkable heterogeneity of tumors from areas to areas within the same ovarian mass, such as mucinous tumors and teratomas. A single mucinous ovarian tumor may sometimes contain benign, borderline and malignant components, in contrast with serous tumors.[19-21] Frozen section may fail to sample the most severe lesion or frankly malignant area in a limited number of sections intraoperatively.[12] Morphological complexity of borderline tumors was found to be the cause for inaccurate diagnosis of borderline tumors during frozen section.[3]

Another probable reason for low PPV for borderline tumors in the present study may be the lesser number of borderline tumors. PPV and NPV are directly related to prevalence of the disease. Number of frozen sections sampled also correlate with the accuracy of the test. In our study one to four frozen section samples were taken based on size and type of tumor. In case of borderline tumors at least two sections were sampled. Wang *et al*. recommended that multiple frozen section samples may help increase the accuracy in the diagnosis and taking one frozen section per each 10 cm diameter of the mass was suggested.[9] Other factors that can influence frozen section diagnosis are the quality of sections prepared by this technique that limits the evaluation of cellular detail and the experience of pathologists which were not of major concern in our case. The two benign cases inaccurately over diagnosed by frozen section as borderline did not have critical therapeutic implications in our study since both patients were young and underwent conservative management. One borderline case in this study, which was over diagnosed as malignant was of a 60 years old who underwent a completion surgery. This kind of over diagnosis may have had serious

therapeutic implications for a younger patient because an extensive cytoreductive surgery would have been unnecessary for her. One malignant tumor which was underdiagnosed as borderline was a 54 years old who underwent a completion surgery considering the age and parity status.

Conclusion

The overall accuracy of frozen section diagnosis in ovarian tumors was found to be 93.3% in comparison with final histopathologic diagnosis. Frozen section diagnosis had high sensitivity, specificity and positive and NPV s for benign and malignant neoplasms of the ovary. Frozen section was found to be an accurate and useful modality in the intraoperative evaluation of patients with ovarian neoplasm. The results can help to decide the type and extent of surgery.

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Conflicts of interest
There are no conflicts of interest.

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