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Accuracy of intra-operative frozen section and its role in the diagnostic evaluation of ovarian tumors

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Summary

Objective: This retrospective study was undertaken to evaluate the accuracy and role of intra-operative frozen section in the diagnosis of ovarian tumors. *Materials and Methods:* Retrospective study of 804 ovarian frozen section results between June 2010 and June 2014 was examined to determine the accuracy of frozen section diagnosis. The intra-operative frozen section diagnosis was compared with the permanent (paraffin) section and the overall accuracy, sensitivity, specificity, and positive and negative predictive values of the frozen section were studied. *Results:* The overall accuracy to determine the status of malignancy was 92.6%. There were 38 (7.4%) false negative and no false positive frozen section diagnoses.The sensitivity, specificity, and positive predictive and negative predictive values for benign ovarian tumors were 100.0%, 97.0%, 91.3%, and 100.0%, respectively; for borderline tumors they were 64.3%, 97.0%, 91.5%, and 94.0%, respectively, and for malignant tumors they were 90.0%, 100.0%, 100.0%, and 85.5%, respectively. *Conclusion:* This study concluded that frozen section appears to be an adequate technique for the histopathological diagnosis of ovarian tumors, with some limitations observed among borderline and mucinous tumors.

Key words: Intra-operative frozen section; Permanent (paraffin) section; Ovarian tumors.

Introduction

Ovarian malignancy is a leading cause of mortality among women with gynecological cancers. The accuracy of frozen section is vital to the outcome and life quality of the patient with ovarian tumour.

Pre-operative evaluations are generally done according to the results of imaging studies and determination of serum levels of tumor markers of patients with an ovarian tumour. Since these methods have limited value for the recognition of ovarian cancer, the diagnosis and the course of the surgery are usually determined by frozen section examination during the operation [1,2].

In cases of ovarian tumors, intra-operative frozen sections play an important role because definitive pre-operative histology is not possible. Frozen section has been a reliable diagnostic procedure that helps in the categorization of tumors as benign, borderline, and malignant and is widely used to decide the surgical management.

This retrospective study was attempted to evaluate the accuracy and role of frozen section in the diagnosis of ovarian tumors in the present setting.

Materials and Methods

Retrospective study of 804 ovarian frozen section results between June 2010 and June 2014 was examined to determine the accuracy of frozen section diagnosis in pathologic department of first affiliated hospital of Xinjiang Medical University, China.

After careful macroscopic evaluation of the specimen, the number of sections frozen in a cryostat ranged from 1 to 4. Six to eight μm sections were stained with hematoxylin and eosin and were carefully interpreted. For each biopsy, the frozen section diagnosis was compared with the definitive paraffin diagnosis. To facilitate comparison, both the frozen section diagnosis and permanent section diagnoses were grouped as neoplastic lesions (benign, borderline, and malignant ovarian tumors), non-neoplastic lesions (unclassified simple cyst, corpus luteum cyst, endometriosis, follicular cyst, calcified nodule, and torsion), non-ovarian cases (leiomyoma and tuberculosis,. and deferred cases.

Frozen section diagnosis and permanent (final) histopathological diagnoses were concordant when both the diagnoses were within the same subgroup of malignancy (that is, epithelial, germ cell, and sex cord-stromal tumor). The results of the permanent sections were considered as the gold standard.

The cases with discordant diagnosis between frozen section and permanent section were reviewed as well as those that were deferred to establish if the deferral was surely appropriate. The deferred cases were excluded from the statistical analysis data.

According to the status of malignancy, the overall accuracy and four conventional indices (sensitivity, specificity, positive predictive value, and negative predictive value) of frozen section diagnoses were determined.

Results

The current study included 804 patients who underwent frozen section diagnosis. The median age of the patient was 44.5 (± 22.5) years (range 12-79).

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Table 1. — *Distribution of histological types of all cases according to final paraffin diagnosis (n=790).*

Tumor type	Benign	Borderline	Malignant	Total	%
Epithelial tumors				220	27.8%
Serous	48	37	45	130	16.5%
Mucinous	33	46	5	84	10.6%
Clear cell	0	1	5	6	0.7%
Germ cell tumors				259	32.8%
Mature teratoma	246	0	1	247	31.2%
Immature teratoma	0	0	3	3	0.38%
Dysgerminoma	0	0	5	5	0.6%
Yolk sac	0	0	2	2	0.2%
Mixed	0	0	2	2	0.2%
Sex cord stromal tumors				33	4.1%
Granulosa cell	0	0	7	7	0.9%
Sertoli-Leydig	0	0	5	5	0.6%
Fibroma	11	0	0	11	1.4%
Fibrothecoma	10	0	0	10	1.2%
Non-neoplastic lesions				248	31.4%
Unclassified simple cyst				95	12.0%
Corpus luteum cyst				51	6.4%
Endometriosis				25	3.1%
Follicular cyst				60	7.6%
Calcified nodule				11	1.4%
Torsion				6	0.7%
Non-ovarian				30	3.8%
Leiomyoma				28	3.5%
Tuberculosis				2	0.2%

Table 2. — *Intra-operative frozen section diagnosis and subsequent histopathological diagnosis in various categories of neoplasms (n=512).*

Frozen section	Final diagnosis (paraffin)			
	Benign	Borderline	Malignant	Total
Benign	348	30	3	381
Borderline	0	54	5	59
Malignant	0	0	72	72
Total	348	84	80	512

Table 3. — *Results of the frozen section analysis in agreement with the permanent histological findings in subgroups of neoplasms.*

Epithelial tumors	82.7% (182/220)
Serous tumors	88.5% (115/130)
Mucinous tumors	72.6% (61/84)
Clear cell tumors	100.0% (6/6)
Germ cell tumors	100.0% (259/259)
Mature teratoma	100.0% (247/247)
Immature teratoma	100.0% (3/3)
Dysgerminoma	100.0% (5/5)
Yolk sac	100.0% (2/2)
Mixed	100.0% (2/2)
Sex cord-stromal tumors	100.0% (33/33)
Granulosa cell tumors	100.0% (7/7)
Sertoli-Leydig cell tumors	100.0% (5/5)
Fibroma	100.0% (11/11)
Fibrothecoma	100.0% (10/10)

Diagnosis by frozen section was deferred in 1.7% (14/804) patients as no definitive opinion was possible on frozen section. Out of the remaining 790 patients, there were 31.4% (248/790) non-neoplastic lesions and 3.8% (30/790) were non-ovarian cases [i.e, 3.5% (28/790) leiomyoma cases and 0.2% (2/790) tuberculosis cases].

The final histopathological diagnosis were benign in 44.1% (348/790) patients, borderline in 10.6% (84/790) patients, and malignant in 10.1% (80/790) patients. Distribution of the tumors according to histology is given in Table 1.

Malignant cases also included 1.1% (9/790) tumors, which were metastatic to the ovary i.e, from the uterus (*n*=2), gastrointestinal stromal tumor (*n*=1), and appendix (*n*=4)].

The statistical analysis included 512 patients after excluding 14 deferred cases, 248 non-neoplastic lesions, and 30 non-ovarian cases.

There were 7.4% (38/512) false negative results on frozen sections but, there was no false positive result on frozen sections. Hence, frozen section agreed with final paraffin section diagnosis in 92.6% (474/512) cases. Thus, the overall accuracy of frozen section in determining the status of malignancy was 92.6%.

Table 2 (3x3 table) shows the comparison between the frozen and permanent section diagnosis in benign, borderline, and malignant ovarian tumors (*n*=512). When a benign ovarian tumor was diagnosed by means of frozen section analysis, the histopathological findings corresponded in 91.3% (348/381) of cases while 8.7% (33/381) findings were false negative [90.9% (30/33) on account of borderline ovarian tumors, i.e, 37.0% (20/54) of mucinous tumors and 16.6% (10/60) of serous tumors], [9.1% (3/33) on account of malignant ovarian tumors, i.e, 3.3% (2/60) of serous tumors, and 1.9% (1/54) of mucinous tumors].

When a borderline ovarian tumor was diagnosed by means of frozen section analysis, the histological findings corresponded in 91.5% (54/59) of cases, while 8.5% (5/59) findings were false negative [100% (5/5) on account of malignant ovarian tumors, i.e, 10.0% (3/30) of serous tumors and 7.1% (2/28) of mucinous tumors].

In cases of malignant ovarian tumors, the findings at frozen section diagnosis in all cases in agreement to the findings at the permanent section diagnosis, as there was no false negative result on frozen section.

Table 3, shows the results of frozen section analysis in agreement with the permanent histological diagnosis in subgroups of malignancies. Table 4, shows the statistical values of frozen section in the 3 categories of ovarian tumors in the present patients.

With respect to the malignant potential, the sensitivity was highest for benign ovarian tumors that is, 100.0%, the specificity, positive and negative predictive values for be-

Table 4. — *Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for intra-operative frozen sections in benign, borderline, and malignant ovarian tumors (n=512).*

	Benign(%)	Borderline(%)	Malignant(%)
Sensitivity	100.0%	64.3%	90.0%
Specificity	97.0%	97.0%	100.0%
PPV	91.3%	91.5%	100.0%
NPV	100.0%	92.0%	85.5%

nign ovarian tumors were 97.0%, 91.3%, and 100.0%, respectively, whereas the sensitivity was lowest for the borderline ovarian tumors, that is, 64.3%, the specificity, positive and negative predictive values for borderline ovarian tumors were 97.0%, 91.5%, and 92.0%, respectively. The sensitivity, specificity, and positive and negative predictive values for malignant ovarian tumors were 90.0%, 100.0%, 100.0%, and 85.5%, respectively.

Discussion

Despite great progress with image analysis of ovarian and pelvic tumors, histological diagnosis in paraffin sections remains definitive [3, 4]. The aim of intra-operative frozen sections is to probe into the type and stage of the disease and guide the surgeon with respect to the extent of resection, with particular concern for preservation of fertility. Frozen section is an important and helpful adjunct in the intra-operative diagnosis of ovarian tumors.

The diagnosis of ovarian malignancy is problematic in the absence of tissue histology. The correct management approach depends on accurate diagnosis and staging. The diagnosis achieved intra-operatively can also inform the surgeon about the possibility that it may represent metastasis. Frozen section accuracy plays a vital role in the correct surgical approach.

Accuracy of frozen section has been quoted by several studies to be fairly high, and this ranges from 73.0% to 98.0% in determining the status of malignancy [5-7]. The accuracy rates have consistently improved over the past decades, thus mirroring improvements in this technique. In the present study, the overall accuracy was 92.6% (474/512), which was comparable to the accuracy rates of previously reported studies [5, 8-17] as shown in Table 5.

In the current study, there were 7.4% (38/512) discordant diagnoses. There was no false positive frozen section result which was better than the previously reported studies as false positive result is harmful, as it might seriously compromise the patient's fertility. In previous studies [13-15, 17] false positive rates ranged from 0.4% - 3.4%. As in the current study, there was no false positive frozen section results therefore, all the discordant diagnoses (7.4%) were false negative. False negative rates

Table 5. — *Accuracy rates of frozen section for ovarian tumors, as seen in present and previously reported studies.*

Authors	Benign (%)	Borderline (%)	Malignant (%)	Overall (%)
Cuello M. [5]				97.9%
Ghaemmaghami F. [8]		44.0%	92.0%	92.7%
Gol M. [9]	98.0%	61.0%	88.7%	92.0%
Gorisek B. [10]	100.0%	76.1%	89.0%	84.7%
Ilvan S. [11]	100.0%	87.0%	87.0%	97.0%
Maheshwari A. [12]	100.0%	45.5%	93.5%	91.2%
Pinto P.B. [13]	94.0%	61.0%	98.0%	94.0%
Rakhshan A. [14]	99.0%	60.0%	92.0%	95.7%
Subbian A. [15]	90.4%	31.1%	91.5%	84.2%
Suprasert P. [16]	100.0%	84.2%	92.0%	93.8%
Washington P. [17]	98.2%	61.8%	79.6%	87.8%
Current study	100.0%	64.3%	90.0%	92.6%

Table 6. — *Sensitivity rates for benign, borderline, and malignant ovarian tumors in the current and previous studies.*

Authors	Benign (%)	Borderline (%)	Malignant (%)
Gol M. [9]	98.0%	61.0%	88.7%
Gorisek B. [10]	100.0%	76.1%	89.0%
Ilvan S. [11]	100.0%	87.0%	87.0%
Maheshwari A. [12]	100.0%	45.4%	93.4%
Pinto P.B. [13]	94.0%	61.0%	98.0%
Rakhshan A. [14]	99.0%	60.0%	92.0%
Sabbian A. [15]	90.4%	31.2%	91.5%
Suprasert P. [16]	100.0%	84.0%	92.0%
Washington P. [17]	98.2%	61.8%	79.6%
Rose P.G. [19]		44.8%	92.5%
Current study	100.0%	64.3%	90.0%

in previously reported studies [10, 11, 14-16] ranged from 3.4% - 15.3%.

In 2005, a meta-analysis of 18 studies on the correlation of frozen sections with histopathological findings was published, in which a sensitivity of 65.0% - 97.0% was established for benign and 71.0% - 100.0% was established for malignant ovarian tumors. Specificity was 97.0%-100.0% for benign tumors and 98.3% - 100.0% for malignant tumors [18], which are comparable to the results of current study. In the current study the sensitivity and specificity rates for benign tumors were found to be 100.0% and 97.0%, respectively, and for malignant ovarian tumors the sensitivity and specificity rates were found to be 90.0% and 100.0%, respectively. Generally, in frozen sections there is a high degree of sensitivity in diagnosing benign and malignant tumors. However, in contrast to these two groups of tumors, the sensitivity of borderline tumors in most studies have been found to be low, although a considerable improvement in the sensitivity rates have been noted in recent years. The sensitivity rate for borderline tumors in the current study was 64.3%. Table 6, shows the sensitivity rates in current and previously reported studies [9-17, 19].

The positive predictive values for benign, borderline, and malignant ovarian tumors in the current study were 91.3%, 91.5%, and 100.0%, respectively. These findings are consistent with the other studies, making over treatment an unlikely event. In previously reported studies [10, 12, 14, 16, 17, 19, 20] the positive predictive values for benign, borderline, and malignant tumors were ranged from 20.0% - 97.0%, 62.5% - 88.9%, and 91.1% - 100.0%, respectively.

In the present study, diagnostic problems especially occurred in mucinous and borderline tumors, as seen in previously reported studies [9, 20, 21]. Some authors mentioned that the experience of the pathologist is of crucial importance for the success of frozen section diagnosis [9, 22]. The present authors found that the reason for more diagnostic problems in mucinous tumors was larger tumor size, making the sampling inadequate at the time of frozen section. Inaccurate diagnosis also arises since mucinous tumors frequently contain benign, borderline, and malignant components in different areas of the same tumor, in contrast to the more uniform serous tumors [23]. In the current study, the result of frozen section diagnosis agreed with the permanent histopathological findings in 72.6% (61/84) of mucinous tumors. Therefore, the greatest number of diagnostic errors were found in the diagnosis of mucinous tumors that is, 27.4% (23/84), whereas the lowest number of errors were found in serous tumors diagnosis that is, 11.5% (15/130).

It is reported in a study [24] that extensive sampling on paraffin sections may prove that benign tumor is actually borderline or that the borderline tumor actually has frankly malignant areas. More sections may be sampled to enhance sensitivity for local borderline changes.

The clinicians and pathologists must be aware of the pitfalls of this method; therefore, a good communication established between them is necessary to obtain more accurate results and to minimize the number of deferred cases. The present authors still believe that the deferred cases were eliminated by good communication with the surgical team. Full interaction of surgeons and pathologists is essential to make the best of the procedure and promote an increase in diagnostic accuracy.

Conclusion

Conclusively, intra-operative frozen section is a beneficial and a vital test for diagnosing benign and malignant ovarian tumors, with some limitations observed among the diagnosis of borderline ovarian and mucinous tumors. Frozen section service can be more effective when the pathologist and the surgeon are fully aware of the uses and limitations of the intra-operative consultation, especially in the cases of borderline and mucinous, tumors frozen section service should be judiciously utilized.

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