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Original Article

Diagnostic Accuracy of Frozen Section in Ovarian Tumors: A 12-Year Review

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ABSTRACT

Background and objective: To determine the diagnostic accuracy and pitfalls of frozen section in ovarian tumors in one of the largest university affiliated gynecologic oncology centers in Tehran, and determine the cause of discrepancies.

Materials and Methods: We retrospectively analyzed the results of frozen section and permanent diagnoses of ovarian masses by reviewing the reports in the department of Pathology of Imam Hussein Hospital from 1997 to 2009.

Results: Among 1498 cases of ovarian lesions, only 187 patients had both frozen and paraffin section diagnoses (age range 10-82 yr). 71.7% of these cases had complete concordance, 26.7% had partial and 1.6% had no concordance. The overall sensitivity and specificity of frozen section diagnosis were 100% and 99.3%, respectively. The sensitivity of frozen section diagnosis for benign, borderline, and malignant lesions was 99.3%, 100% and 94.9%; and the specificities were 100%, 98.9% and 99.3% respectively.

Conclusion: Our results show high sensitivity and specificity of frozen section diagnosis in ovarian masses. Pathologist's misinterpretation was the only cause of discrepancies.

Keywords: Ovary Neoplasms, Frozen section

Introduction

Frozen section (FS) diagnosis is proved to provide helpful information during surgery to guide the surgeon for appropriate therapeutic decision. Differentiation between malignant and benign pathology prior to and during surgery is of outmost importance in patients with adnexal mass. Over- and under-treatment as well as unnecessary two stage operations can prevented only when FS diagnostic accuracy reaches that of

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permanent sections.

Many studies have confirmed the accuracy of FS diagnosis for assessment of the ovarian masses, with acceptable sensitivity (71-97%) and specificity of more than 95% (1-8); however, it has limitations, mostly for borderline, mucinous and large tumors (1,4,5,7,9-14). Despite its restrictions, FS is an important and reliable diagnostic tool in the management of patients with ovarian tumors (1-8). No information is available in Iran concerning the diagnostic accuracy and pitfalls of FS in ovarian tumors.

We decided to study retrospectively the reliability of FS diagnosis of ovarian masses in one of the major referral centers for gynecologic oncology of Shaheed Beheshti University of Medical Sciences during a period of 12 years.

Materials and Methods

In this retrospective study, we reviewed the reports of all ovarian lesions between April 1997 and March 2009 in the Department of Pathology, Imam Hussein Hospital, one of the major gynecological referral centers in Tehran. There were a total of 1620 cases; 122 of which were normal and were excluded from the study. Totally, 187 cases had both frozen and permanent diagnosis and the remainder had either frozen or permanent diagnosis.

During intraoperative consultation, the fresh specimen was examined grossly for evidence of rupture, size, consistency, as well as external and internal vegetations. One to three sections were taken by attending pathologist from the representative portions of the lesion, including solid areas, vegetations and cyst walls. The tissue was frozen in a cryostat (-25°C) and 6-7μ sections were prepared and stained with Hematoxylin and Eosin (H&E). The slides were examined under the light microscope by one or more general pathologists. After formalin fixation, additional representative sections (at least 1 section per 1 cm of tumor) were taken for paraffin embedding and routine H&E staining. The definitive diagnosis was made after thorough microscopic examination of all the slides. In this institution, no gynecopathologist is practicing and the lesions were evaluated by four general pathologists with a 15 to 25 year experience in the field of general pathology. Histological diagnosis was made according to the criteria in pathology textbooks for diagnosis of ovarian lesions (15, 16). For histological typing of tumors, the International Federation of Gynecology and Obstetrics (FIGO) recommendations (17) were followed. No cytology specimen was available before the operation.

The reports of frozen and permanent sections were evaluated according to the status of benignancy and malignancy and the histological type of the lesions. The results of frozen and permanent sections were classified into three groups: benign, borderline and malignant. The result of the permanent section was used as a gold standard. The definitive diagnosis deferred to paraffin section analysis when the tumors were large, in borderline tumors (reported “at least borderline tumor” at FS examination) and when the nature of tumor was such that extensive sectioning was needed to rule out malignancy, such as solid teratomas.

The ovarian masses were classified as epithelial stormal tumors (serous, mucinous, endometrioid and Brenner tumor), germ cell tumors (teratoma, dysgerminoma, choriocarcinoma and yolk sac tumor), sex cord tumors (granulosa-theca cell tumor, fibroma, fibrothecoma and sertoli-leydig cell tumor). The term

simple cyst was used for all non-neoplastic cystic lesions such as cystic follicles, follicular cysts and corpus luteal cysts. Others in Table 1 include Burkitt's lymphoma [1], lipoma [1], scattered stromal hyperplasia [1], severe stromal proliferation [2], subcapsular hyalinization [1], cortical fibrosis [2], and infected hydatid cyst [1]. Others in Table 2 include Burkitt's lymphoma [1] and tuberculosis [1]. others in Tables 3 & 4 include all shows other cases including lesions other than epithelial, germ cell and sex cord tumors. The tumors with no specific diagnosis and diagnosed as "benign tumor" or "malignant tumor", not otherwise specified (18 cases), were not included in the statistical analysis in Table 4. Factors like tumor size and weight were not of our consideration in the study because of incomplete information.

The overall sensitivity, specificity, false positive (FP), false negative (FN), positive predictive value (PPV), negative predictive value (NPV) of FS were determined according to the type of the lesions, the accuracy of histological tumor types, as well as for benign border line and malignat tumors.

The cases were graded into three degrees of diagnosis concordance to clarify the accuracy of the intra operative diagnosis:

1- The FS diagnosis was exactly the same as the final diagnosis (complete concordance).

2- The FS diagnosis was not incorrect but was too broad to qualify as complete concordance (partial concordance).

3- The FS diagnosis was incorrect and different from the final diagnosis (no concordance).

All statistical analyses were performed using SPSS, version 17. To describe data we used mean, standard deviation, median and percent. To evaluate the agreement of the methods we utilized sensitivity, specificity, NPV, and PPV.

In this study, no ethical issues were involved; only the pathology reports were reviewed retrospectively, and the patients were anonymous. The articles used as references are valid and the information taken are reported unchanged.

Results

During the study period, a total of 1498 ovarian masses were assessed in Imam Hussein Pathology Department. Overall, 7.4% (103) of cases were malignant, 1.1% (16 cases) borderline and 91.5% (1273 cases) benign lesions in permanent diagnosis. In FS analysis, 18.6% (54 cases) were malignant, 5.2% (15 cases) borderline and 76.3% (224 cases) benign lesions. The number of cases which were diagnosed by FS examination was 106 (7.1%) and no more tissue was received subsequently; 1205 (80.4%) had permanent diagnoses with no intraoperative request for FS examination and 187 (12.5%) masses had both FS and permanent diagnoses.

The histological type of all specimens which had either permanent or frozen diagnosis is listed in Tables 1 and 2, respectively. The results of the categorization of the types of tumors are listed in Tables 3 and 4. The concordance between the FS diagnosis and the final histological diagnosis is summarized in Table 5. The sensitivity and specificity for the epithelial, germ cell, sex cord and other tumors in cases which had both FS and permanent diagnosis are listed in Table 6. Patient's age ranged between 10 and 82 years. The average age for each histological tumor type is listed in Table 7.

Table 1 - Histological types according to paraffin diagnosis

Type	Number	Percentage	
		In same histo. type	In all tumors
Cysts (benign)	851	61.1	
Serous tumors:	219	15.7	
Benign	163	74.4	11.7
Borderline	12	5.5	0.9
Malignant	44	20.1	3.2
Mucinous tumors:	81	5.8	
Benign	70	86.4	5.0
Borderline	3	3.7	0.2
Malignant	8	9.9	0.6
Endometrioid tumors:	60	4.3	
Benign	52	86.7	3.7
Malignant	8	13.3	0.6
Teratomas:	71	5.1	
Benign	71	100	5.1
malignant	0	0	0
Dysgerminoma	3	0.2	
Choriocarcinoma	1	0.1	
Fibroma	7	0.5	
Granulosa-theca cell T.	9	0.6	
Sertoli-Leydig tumors:	1	0.1	
Benign	1		
malignant	0	100	0.1
		0	0
Metastasis to ovary	23	1.6	
Leiomyoma	1	0.1	
Endometriosis	1	1.4	
PCO*	2	0.1	
Brenner tumors:	3	0.2	
Benign	1	33.3	0.1
Borderline	1	33.3	0.1
Malignant	1	33.3	0.1
Fibrothecoma	5	0.4	
Inflammation	9	0.6	
EP**	3	0.2	
Torsion (benign)	9	0.6	
Gynandroblastoma	1	0.1	
Yolk sac tumor	5	0.4	
Others*:**	9	0.6	
Benign	8	88.9	0.6
Malignant	1	11.1	0.1

* Polycystic ovary; ** Ectopic pregnancy.

*** See the text for details

Table 2- Histological types of ovarian tumors according to FS* diagnosis

Type	Number	Percentage	
		In same histo. type	In all tumors
No specific diagnosis:	18	6.1	
Benign, NOS**	9	50	3.1
Borderline, NOS	1	5.5	0.3
Malignant, NOS	8	44.4	2.7
Cysts (benign)	89	30.3	
Serous tumors:	48	16.4	
Benign	26	54.2	8.9
Borderline	6	12.5	2.0
Malignant	16	33.3	5.5
Mucinous tumors:	49	16.7	
Benign	38	77.5	13.0
Borderline	7	14.3	2.4
Malignant	4	8.2	1.4
Endometrioid tumors:	17	5.8	
Benign	13	76.5	4.4
Malignant	4	23.5	1.4
Teratomas:	33	11.3	
Benign	31	93.9	10.6
Malignant	2	6.1	0.7
Dysgerminoma	0	0.0	
Choriocarcinoma	0	0.0	
Fibroma	4	1.4	
Granulosa-theca cell tumor	9	3.1	
Sertoli-Leydig tumors:	1	0.3	
Malignant	1	100	0.3
Benign	0	0	0
Metastasis to ovary	6	2.0	
Leiomyosarcoma	1	0.3	
Leiomyoma	2	0.7	
Endometriosis	2	0.7	
Brenner tumors:	1	0.3	
Borderline	1	100	0.3
Benign	0	0	0
Malignant	0	0	0
Fibrothecoma	2	0.7	
Inflammation	3	1.0	
Torsion (benign)	4	1.4	
Germ cell tumor, NOS	2	0.7	
Others*:**	2	0.7	
Benign	1	50	0.3
Malignant	1	50	0.3

* Frozen section;** Not otherwise specified.

* See the text for details.

Table 3- Tumors with permanent diagnosis

Type	Number	Percentage
Epithelial	363	26.0
Germ cell	80	5.7
Sex cord	23	1.6
Others	926	66.5

Table 4- Tumors with FS* diagnosis

Type	Number	Percentage
Epithelial	115	41.8
Germ cell	35	12.7
Sex cord	16	5.8
Others	109	39.6
No specific diagnosis	18	-----

* Frozen section

Table 5- Concordance between the FS* and paraffin diagnosis

Concordance	Number	Valid percent	Cumulative percent
Complete concordance	134	71.7	71.7
Partial concordance	50	26.7	98.4
No concordance	3	1.6	100.0
Total	187	100.0	

* Frozen section

Table 6- Sensitivity, specificity, PPV*, NPV**, true negativity, false positivity, false negativity and true positivity of FS*** diagnosis

	TN	FP	FN	TP	Sensitivity	Specificity	PPV	NPV
Epithelial	65	1	0	20	100.0	98.5	95.2	100.0
Germ cell	18	0	0	3	100.0	100.0	100.0	100.0
Sex cord	3	0	0	7	100.0	100.0	100.0	100.0
Others	52	0	0	7	100.0	100.0	100.0	100.0
Total	138	1	0	37	100.0	99.3	97.4	100.0

*Positive predictive value **Negative predictive value

*** Frozen section

Table 7- Average age for each histological type

	Mean	Standard Deviation	Median	Minimum	Maximum
Cyst	41	12	45	10	82
Serous tumor	43	16	45	13	80
Mucinous tumor	42	16	40	17	82
Endometrioid tumor	32	10	28	18	55
Teratoma	34	17	30	10	78
Dysgerminoma	23	5	22	18	28
Choriocarcinoma	47	.	47	47	47
Fibroma	44	17	38	26	67
Granulosa-theca cell tumor	51	18	57	22	76
Sertoli-leydig tumor	29	.	29	29	29
Metastasis to ovary	50	14	50	26	82
Smooth muscle tumors	45	.	45	45	45
Endometriosis	38	14	42	16	61
PCO*	32	8	32	26	37
Brenner tumor	58	10	62	47	66
Fibrothecoma	37	18	48	16	52
Inflammation	50	16	48	27	72
EP**	30	6	28	26	37
Torsion	27	14	21	14	56
Gynandroblastoma	22	.	22	22	22
Yolk sac tumor	23	7	23	16	34
Others	40	14	45	18	60

* Polycystic ovary **Ectopic Pregnancy

Discussion

Intraoperative FS diagnosis is being used more frequently for management of many conditions due to its improved diagnostic accuracy. Imaging studies and serum level determination of tumor markers in patients with ovarian masses have limitations for the recognition of malignancy. Since most patients with ovarian tumor undergo surgery without a definite tissue diagnosis, the diagnosis and the course of the surgery are usually determined by employing intraoperative FS technique. Benign lesions are managed conservatively, malignant and borderline lesions undergo complete pelvic clearance, omental biopsy or omentectomy, and staging procedures (4, 6). In borderline tumors, however, conservative surgery could be performed to preserve fertility, with excellent long-term survival (18). Therefore, accurate intraoperative diagnosis is imperative.

Many studies have assessed the accuracy of FS analysis in ovarian tumors (1-14,19-23). Borderline ovarian epithelial tumors have always been a major cause of pitfall in FS diagnosis with less reliable results compared to benign and malignant tumors (1,2,4,5,8-10,13,14,20). Houck *et al.* (10) reviewed 140 borderline ovarian tumors including 80 serous, 47 mucinous, 11 mixed and 2 endometrioid types. The overall mean diameter was 13.7 cm (1-70 cm); 10.2 cm for serous and 20.1 cm for mucinous tumors. In 60% of cases, frozen section diagnoses agreed with permanent diagnoses. Over diagnosis was reported in 10.7% and 29.3% of cases were under diagnosed. Tumors types other than serous ($P < 0.001$), tumors larger than 20 cm ($P= 0.039$), and tumors confined to the ovaries ($P= 0.009$) were more likely to be under diagnosed in univariate analysis. When

all variables were included in a multiple regression model, only histology was a significant predictor of under diagnosis. The PPV for borderline tumors by FS was 89.3%. Tempfer *et al.* (23) reviewed 29 studies investigating the accuracy of frozen section analysis of borderline ovarian tumors. An overall sensitivity and PPV were 71.1% and 84.3%, respectively, with 6.6% over-diagnosis and 30.6% under-diagnosis. Tumor size >3 cm was the only independent factor related to under-diagnosis by FS in borderline tumors (14). Others studies also report a less than 90% overall sensitivity for borderline tumors (1,2,4-6,8,9,13,20).

Puls *et al.* (12) evaluated the effect of tumor weight on accuracy of frozen section in serous and mucinous ovarian tumors by reviewing 189 serous and 105 mucinous tumors. The mean weight of the tumors was 1042 g; they were divided into 3 weight groups: ≤ 450 g, 450-1360 g, and > 1360 g. By increasing the weight in serous tumors, the sensitivity fell from 96.2% to 93.8% to 75%, respectively, as did in mucinous tumors from 91.7%,87.5% to 66.7%, respectively, in each weight category. The greatest number of under diagnosis of malignant tumor as borderline tumors happened in mucinous tumors weighing > 1360 g (50%). In general, 23% of tumors were diagnosed as borderline which proved to be malignant by paraffin sections and with tumors > 1360 g, sensitivity was only 69%.

In our review of the English Medical literature, 55 to 71% of tumors were benign, 5.9-17% borderline and 19.4- 34.6% malignant (2,4,7,8,21). The reported overall accuracy of FS was between 91.2 to 97% (4-8), and diagnostic discrepancy of 9.7% (7). Overall sensitivities and specificities of 71.1-97% and 95-100% were reported (6,11,23). Sensitivity of FS for diagnosis of benign, borderline and malignant ovarian lesion was 98-100%, 44-87% and 83.5-94%, respectively (1, 4-6, 8-10, 13,21); and specificities were 43-97%, 98-99% and 98.3-100%, respectively (4-6). In this retrospective study, we found the overall sensitivity rate of 100% and specificity of 99.3%, which agrees with data from literature. The sensitivity of frozen section diagnosis for benign, borderline, and malignant lesions was 99.3%, 100% and 94.9%; and the specificities were 100%, 98.9% and 99.3%, respectively. We had no false negative result, and only one false positive result. The high sensitivity and specificity of borderline tumors in our study compared to the literature could be due to the small number of borderline tumors (9) in our cases.

The causes of diagnostic discrepancy in different studies included sampling error (1,7,8,11), pathologist misinterpretation (1,2, 7,8), and suboptimal slide preparation (7). With increase in the size of ovarian tumors, a decrease in the sensitivity of frozen section was observed (8,12,13,20); taking additional number of sections for a mass larger than 10 cm may reduce the error in large tumor, to some extent (13,14). However, in Brun's study (2) tumors smaller than 10 cm were associated with a risk of misdiagnosis in borderline tumor in addition to tumor histology.

Limited sampling, pathologist expertise, and lack of communication between pathologists and surgeons are also important for the accurate FS diagnosis (1,2). Sampling error and pathologist's misinterpretation were the most common causes of over-diagnosis and suboptimal slide preparation caused under-diagnosis in some studies (7,8). In Obiakor's study (11), 82% of discrepancies were due to limited sampling. FS was most reliable for small serous tumors and the majority of disagreements were in borderline (mostly misdiagnosed as benign) and mucinous tumors (1,2, 4, 5, 8-10, 13,14 ,20). Ovarian mucinous tumors may contain malignant, borderline and benign areas in the same tumor and extensive sampling is required for definitive diagnosis. Mucinous histology as well as large tumor size appear to be the most powerful predictors of misdiagnosis (16,24).

Differentiation of primary ovarian epithelial tumors from metastatic adenocarcinoma may be challenging, especially in tumors with

mucinous and/or endometrioid differentiation and bilateral involvement. Clinical data, surgeon's detailed examination of the abdomen and immunohistochemical studies may be required for correct diagnosis (1).

Overall PPV and NPV are reported to be 84.3-100% and 95.3-99%, respectively (11, 22, 23). PPV for benign, borderline and malignant lesions were 92%, 62% and 100%, respectively (8). PPV in our study was 97.4-100% and was less for epithelial tumors.

Our discrepant cases were as follows: 1- a malignant serous tumor was diagnosed as malignant granulosa-theca cell tumor by FS. 2- FS diagnosis of a yolk sac tumor was malignant mucinous tumor. 3- A malignant granulosa-theca cell tumor was proved to be metastatic tumor to ovary by paraffin sections. 4- A mucinous cystadenoma which was diagnosed as serous cystadenocarcinoma at FS examination (pathologist's inexperience).

In the misdiagnosed yolk sac tumor, the cut surface of the mass was very similar to a malignant mucinous tumor with abundant mucoid material and multicystic appearance. In addition, glandular structures were present in microscopic examination, rendering the misinterpretation. Poorly differentiated serous tumors, granulosa cell tumor and metastatic tumors to ovary, too, can be misinterpreted as other malignancies (24, 25). Out of nine borderline tumor which had both frozen and permanent diagnoses, one serous and one mucinous tumors were diagnosed as (at least) borderline tumor at intraoperative consultation, but confirmed to be malignant after taking more sections at permanent diagnosis.

It is advocated in some papers that intraoperative diagnosis of ovarian tumors should be made by experienced (sinior) pathologists or pathologists with expertise in gynecologic oncology (1,2,7,9). In our retrospective study, this factor could not be assessed due to absence of a gynecopathologist practicing in the center.

Conclusion

This study confirms the reliability and accuracy of frozen section in the intraoperative evaluation of ovarian masses in our center. However, the number of borderline tumors was low (total of 16, nine of which had both frozen and permanent), which definitely influences the accuracy of the method in our study. Although the pathologist's misinterpretation was the only cause of discrepancies in our study, experienced pathologist could still be relied on for intraoperative consultation of ovarian tumors.

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