Accuracy of Intraoperative Frozen Section in Diagnosis of Ovarian Tumors

Virach Wootipoom MD*, Chawaboon Dechsukhum MD**,
Jitti Hanprasertpong MD*, Apiradee Lim***

** Department of Obstetrics and Gynecology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla*
*** Department of Pathology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla*
**** Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla*

Objective: *To determine the accuracy of intraoperative frozen section diagnosis of ovarian tumors according to malignancy status.*
Material and Method: *From May, 1999 to October, 2004 at Songklanagarind Hospital, a total of 229 ovarian specimens were transferred from the operating room to the Department of Pathology for intraoperative frozen section. All cases of deferred diagnosis and disagreement between frozen and permanent paraffin section were reviewed.*
Results: *Intraoperative frozen section diagnosis of all 229 ovarian specimens revealed 54.1% benign tumors, 8.3% borderline tumors, 30.6% malignant tumors, and 7% deferred diagnoses. The final paraffin section diagnoses revealed 52.4% benign tumors, 9.2% borderline tumors, and 38.4% malignant tumors. Mean tumor diameter of the agreement cases were 12.58 5.39 cm, disagreement cases were 17.64 6.83 cm, and deferred cases were 19.33 6.50 cm. The mean diameter of mucinous tumors was significantly different comparing between disagreement cases to agreement cases and deferred cases to agreement cases. The overall accuracy was 89.7%. Sensitivity was highest in the benign group at 98.2% and lowest in the borderline group at 57.1%. The sensitivity and specificity for benign, borderline, and malignant tumors were 98.2%, 57.1%, 86.1%, and 87.0%, 96.4%, 98.5%, respectively. The Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for benign, borderline, malignant tumors were 89.5%, 63.2%, 97.1% and 97.8%, 95.4%, 92.3%, respectively.*
Conclusion: *Intraoperative frozen section diagnosis appears to be an accurate technique for the histopathologic diagnosis of ovarian tumors. However, limitations in use of frozen section must be recognized such as large specimens, especially mucinous subtype. Regular re-evaluation or consultation concerning disagreements between frozen section diagnosis and final permanent paraffin diagnosis should be conducted by both surgeons and pathologists as part of quality assurance to determine the most appropriate intraoperative management for patients with ovarian tumors.*

Keywords: *Frozen section, Ovarian tumor, Accuracy*

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In the treatment of women with ovarian tumors, one factor used to determine the extent of surgical treatment required is the tumor's malignant potential. As ovarian tumors can be benign, borderline or malignant subtypes, the most accurate investigation for definite diagnosis of malignancy is needed both preoperatively and intraoperatively[1]. Preoperative evaluation with history taking, physical examination, various imaging studies or intraoperative gross examination of the tumor are unable to provide the most accurate diagnosis of the tumor's malignancy. This makes surgeons reluctant to complete the surgical staging procedure, not only because of increasing surgical morbidity from radical surgery, but also due to theissue of fertility, especially in young women of reproductive age for whom fertility is an important

Correspondence to : Wootipoom V, Department of Obstetrics and Gynecology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand. Phone: 0-7442-9617, Fax: 0-7442-9617, E-mail: Wvirach@ medicine.psu.ac.th

concern. The objective of intraoperative frozen section diagnosis is to guide the surgeon in determining the appropriate extent of the surgical field.

Overall accuracy of intraoperative frozen section diagnosis for ovarian tumors ranges between 89.8% and 97%[2-8]. Using final paraffin permanent pathologic section as a gold standard, the possible factors contributing to misdiagnosis in use of frozen section may include sampling error of a huge ovarian mass such as mucinous tumor, poor specimen quality, limited time available for the processing of frozen sections, and pathologist error in interpretation[9-11].

At Songklanagarind Hospital, the authors evaluated the frozen section accuracy as part of quality assurance. The authors compared the agreement of intraoperative frozen section with the final paraffin permanent diagnosis of ovarian tumors, especially in terms of malignancy. The results are used as a guide to improve the services to patients suffering from ovarian tumors.

Material and Method

From May 24, 1999 to October 28, 2004 a total of 229 ovarian specimens were submitted for intraoperative frozen section diagnosis at Songklanagarind Hospital. All specimens were processed, diagnosed and results reported back to the surgeons, usually within 30 minutes.

Of all ovarian specimens submitted for frozen section, the authors had not only cases of disagreement between frozen sections and final paraffin section reports, but also deferred cases, signifying inconclusive diagnosis from intraoperative frozen section. All cases of disagreement and deferred diagnosis were reviewed by our pathologists, comparing frozen and paraffin slides, with emphasis on malignancy. Finally, each frozen section diagnosis was compared to the definitive paraffin diagnosis and grouped as benign, borderline, malignant, or a deferred case.

The authors calculated the accuracy, sensitivity, specificity, positive predictive value and negative predictive value according to status of malignancy.

Results

The results from frozen section diagnosis revealed 54.1% benign tumors, 8.3% borderline tumors, 30.6% malignant tumors, and 7% deferred cases. The results of permanent section revealed 52.4% benign tumors, 9.2% borderline tumors, and 38.4% malignant tumors.

Out of 229 ovarian specimens submitted for frozen section, there were 22 cases (10%) of disagreement between frozen and final paraffin diagnosis and another 16 cases (7%) of deferred diagnosis. Table 1 and Table 2 show the numbers and mean diameters of the disagreement cases and deferred cases compared to agreement cases in the same subgroup.

All 22 cases of disagreement and 16 cases of deferred diagnosis were reviewed by our pathologists, comparing frozen and paraffin slides, with emphasis on malignancy.

After excluding cases of deferred diagnosis,

Table 1. Number and mean diameter of disagreement cases compared to agreement cases in the same subgroup of ovarian tumor

Type of tumor	Disagreement cases cm (± SD)		Agreement cases cm (± SD)		p value
	Number	Mean diameter	Number	Mean diameter	
Mucinous tumor	15	19.45 ± 6.51	60	13.00 ± 6.32	<0.001
Benign	1	32*	34	11.97 ± 4.92	-
Borderline	8	18.38 ± 6.07	7	15.86 ± 3.02	0.3394
Malignant	6	18.78 ± 5.75	19	13.79 ± 7.10	0.1230
Serous tumor	5	12.20 ± 4.92	23	11.48 ± 4.68	0.7590
Benign	-	-	10	12.70 ± 5.95	-
Borderline	1	8*	6	11.17 ± 4.17	-
Malignant	4	13.25 ± 5.0	7	10.00 ± 2.77	0.1906
Clear cell carcinoma	1	12*	-	-	-
Germ cell tumor (struma ovarii)	1	7*	-	-	-
Total	22		83		

* individual value

Table 2. Number and mean diameter of deferred cases comparing to agreement cases in the same subgroup of ovarian tumor

Type of tumor	Deferred cases cm (± SD)		Agreement cases cm (± SD)		p value
	Number	Mean diameter	Number	Mean diameter	
Mucinous tumor	9	19.33 ± 6.50	53	13.00 ± 5.62	0.0029
Benign	7	18.57 ± 5.65	34	11.97 ± 4.95	0.0031
Malignant	2	22.00 ± 11.31	19	13.79 ± 7.10	0.1510
Sex-cord stromal tumor	3	10.00 ± 3.61	18	11.28 ± 4.98	0.6671
Fibroma	1	13*	12	10.25 ± 3.70	-
Granulosa cell tumor	2	8.50 ± 3.53	6	13.33 ± 6.83	-
Germ cell tumor	2	16.00 ± 1.41	3	15.67 ± 3.10	-
Immature teratoma	1	15*	1	22*	-
Dysgerminoma	1	17*	2	12.50 ± 3.54	-
Necrotic tumor	1	5.4*	1	7.0*	-
Brenner tumor	1	7.0*	-	-	-
Total	16		75		

Table 3. Comparison of frozen section and permanent paraffin diagnosis according to malignant status

Frozen section	Permanent paraffin section			Total
	Benign	Borderline	Malignant	
Benign	111	8	5	124
Borderline	1	12	6	19
Malignant	1	1	68	70
Total	113	21	79	213

Table 4. Results of the study in terms of Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV)

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Benign tumor	98.2	87.0	89.5	97.8
Borderline tumor	57.1	96.4	63.2	95.4
Malignant tumor	86.1	98.5	97.1	92.3

213 cases that had both frozen and permanent paraffin diagnoses were compared and each diagnosis was grouped as benign, borderline, or malignant (Table 3).

Mean tumor diameter of the agreement cases were 12.58 ± 5.39 cm, disagreement cases were 17.64 ± 6.83 cm, and deferred cases were 19.33 ± 6.50 cm. The mean diameter of mucinous tumors was significantly different compared between disagreement cases to agreement cases and deferred cases to agreement cases. The overall accuracy of intraoperative frozen section diagnosis in the present study was 89.7%. The sensitivity and specificity for diagnosing benign, borderline, and malignant tumors were 98.2%, 57.1%, 86.1%, and 87.0%, 96.4%, 98.5%, respectively. The positive predictive value (PPV) and negative predictive value (NPV) for benign, borderline, and malignant tumors were 89.5%, 63.2%, 97.1% and 97.8%, 95.4%, 92.3%, respectively (Table 4).

Discussion

Intraoperative frozen section for use in diagnosis of ovarian tumors is of great value. In some cases

it can help surgeons avoid under-treatment or over-treatment of patients. At our institution, the authors make an effort to improve the frozen section accuracy. A review of the literature reveals overall accuracy of intraoperative frozen section diagnosis for ovarian tumor ranges between 89.8% and 97%[2-8]. The present study revealed an overall accuracy of 89.7%, which was near the lower limit of the accuracy range from the literature. After evaluation, the authors found some limitations of the frozen section diagnosis which needed to be improved such as sampling error, deferred cases, and interpretation error.

Sampling error has often been mentioned as one of the limitations of frozen section diagnosis. After pathologic slide revision, all disagreement cases in the present study were judged to be due to sampling errors. In the present study, the mean diameter of mucinous tumors in the disagreement group was significantly larger than the mean diameter of the mucinous tumor in the agreement group. As in two studies[3,12], the present results confirmed that most disagreement between frozen section diagnosis and final paraffin diagnosis were in large specimens, especially mucinous tumors. To minimize the chance of sampling error, performing multiple sections of at least one section for every 8-10 cm size of the mass is recommended in the frozen section diagnosis of mucinous ovarian tumors[6,12].

Deferred diagnosis is also one of the limitations of intraoperative frozen section consultation. From large meta-analysis, if borderline disease is classified as malignant, the likelihood of a deferred diagnosis in case of malignancy is 7%[13]. From the presented data, the authors had 16 deferred cases (7%), consisting primarily of mucinous and stromal tumors. One study also agreed with the present study that mucinous tumors, tumors resembling fibrothecomas, and extensive hemorrhage or necrosis always obscured the frozen section diagnosis[14]. The present study also found out that the mean diameter of the mucinous tumors in the deferred group was significantly larger than the mean diameter of the mucinous tumors in the agreement group.

Meta-analysis considered deferred results of frozen section as benign tumor because radical surgery should not be performed if malignant diagnosis is not confirmed[13]. This meta-analysis analyzed all the data and concluded that the likelihood ratio for malignancy in cases of deferred diagnosis is too small to justify radical surgery. In the present study, final paraffin diagnosis of the 16 deferred cases revealed only six malignant cases. This leads the authors to agree with the meta-analysis findings that indicate it is best to wait for final paraffin section results before deciding to perform radical surgery in a case of deferred diagnosis.

Interpretation error can occur in the process of frozen section diagnosis[9-11]. False positive results from misinterpretation, especially in young women of reproductive age, lead to over-treatment because radical surgery may be performed on the ovarian tumor patient instead of fertility-preserving surgery. The present study had one case of misinterpretation. The frozen section diagnosis was metastatic adenocarcinoma, while the final paraffin section diagnosis was struma ovarii. This patient presented with massive ascites and pelvic mass. The final diagnosis was pseudo-Meigs'syndrome. Struma ovarii can mimic ovarian carcinoma clinically, particularly if cystic and associated with ascites and elevated CA-125 level[15,16]. Preoperative and intraoperative diagnosis of malignant struma ovarii proved to be difficult, and some patients were subjected to radical surgery based on suspicious frozen section reports later proven to be benign struma ovarii[17].

In conclusion, intraoperative frozen section diagnosis is generally accurate and can be used as one piece of evidence for the surgeon to use in determining the type and extent of initial surgery to be performed. However, frozen section has limitations such as sampling error, deferred diagnosis and interpretation error. Good intraoperative communication between surgeons and pathologists and regular clinico-pathologic conferences, especially in cases with discordant diagnosis, can maximize accuracy and minimize limitations such as interpretation error and deferred diagnosis.

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การตรวจวินิจฉัยเนื้องอกรังไข่โดยใช้ชิ้นเนื้อแช่แข็งอย่างรวดเร็วในระหว่างการผ่าตัด

วิรัช วุฒิภูมิ, ชวบูลย์ เดชสุขุม, จิตติ หาญประเสริฐพงษ์, อภิรดี แซ่ลิ่ม

วัตถุประสงค์: *เพื่อหาความแม่นยำในการตรวจวินิจฉัยเนื้องอกรังไข่ โดยใช้ชิ้นเนื้อแช่แข็งอย่างรวดเร็วในระหว่างการผ่าตัด*

วัสดุและวิธีการ: *การทบทวนผลการวินิจฉัยเนื้องอกรังไข่โดยใช้ชิ้นเนื้อแช่แข็งอย่างรวดเร็วในระหว่างการผ่าตัดที่ถูกส่งตรวจ ณ ภาควิชาพยาธิวิทยา คณะแพทยศาสตร์ ม.สงขลานครินทร์ระหว่างเดือนพฤษภาคม พ.ศ. 2542 ถึง ตุลาคม พ.ศ. 2547 จำนวนทั้งสิ้น 229 ราย โดยได้มีการนำสไลด์มาตรวจทบทวนในรายที่ผลการวินิจฉัยมีความขัดแย้งกันหรือในกรณีไม่สามารถบอกผลการวินิจฉัยได้*

ผลการศึกษา: *ผลการวินิจฉัยเนื้องอกรังไข่โดยใช้ชิ้นเนื้อแช่แข็งอย่างรวดเร็วในระหว่างการผ่าตัด มีจำนวนทั้งสิ้น 229 ราย โดยผลการวินิจฉัยสามารถแยกเป็น เนื้องอกชนิดไม่ร้ายแรง 51.4% เนื้องอกชนิด borderline 8.3% เนื้องอกชนิดร้ายแรง 30.6% และไม่สามารถให้การวินิจฉัยได้ 7% โดยหลังจากนำชิ้นเนื้อดังกล่าวไปตรวจโดยใช้ paraffin-embedded tissue พบว่าให้ผลการวินิจฉัยเป็น เนื้องอกชนิดไม่ร้ายแรง 52.4% เนื้องอกชนิด borderline 9.2% และเนื้องอกชนิดร้ายแรง 38.4% ขนาดเฉลี่ยของก้อนเนื้องอกรังไข่ในกลุ่มที่การวินิจฉัยด้วยวิธีทั้งสองได้ผล ตรงกัน ขัดแย้งกัน และไม่สามารถวินิจฉัยได้คือ 12.58 $\pm$ 5.39 ซม, 17.64 $\pm$ 6.83 ซม, และ 19.33 $\pm$ 6.50 ซม ตามลำดับ ขนาดเฉลี่ยของเนื้องอกรังไข่ชนิด mucinous ในกลุ่มที่ผลมีความขัดแย้งกันและไม่สามารถบอกผลการวินิจฉัยได้มีขนาดใหญ่กว่าเนื้องอกชนิดเดียวกันในกลุ่มที่การรายงานให้ผลตรงกันอย่างมีนัยสำคัญ การวินิจฉัยโดยใช้ชิ้นเนื้อแช่แข็งอย่างรวดเร็วในระหว่างการผ่าตัด มีความแม่นยำ 89.7% ความไวของการตรวจ พบสูงสุดในกลุ่มเนื้องอกชนิดไม่ร้ายแรง คือ 98.2% และต่ำสุดในกลุ่มเนื้องอกชนิด borderline คือ 57.1% ความไวและความจำเพาะของการตรวจในกลุ่มเนื้องอกชนิดไม่ร้ายแรง เนื้องอกชนิด borderline และเนื้องอกร้ายแรง คือ 98.2%, 57.1%, 86.1% และ 87.0%, 96.4%, 98.5% ตามลำดับ โดยมี positive predictive value และ negative predictive value สำหรับการตรวจวินิจฉัยในกลุ่มเนื้องอกชนิดไม่ร้ายแรง ชนิด borderline และชนิดร้ายแรง เป็น 89.5%, 63.2%, 97.1% และ 97.8%, 95.4%, และ 93.2% ตามลำดับ*

สรุป: *การวินิจฉัยเนื้องอกรังไข่โดยใช้ชิ้นเนื้อที่ถูกแช่แข็งอย่างรวดเร็วในระหว่างการผ่าตัด นับว่าเป็นวิธีที่มีความแม่นยำสูงและมีประโยชน์เพื่อบอกแนวทางการรักษาในระหว่างการผ่าตัด อย่างไรก็ตามควรคำนึงถึงข้อจำกัดบางอย่างในการตรวจเช่น ก้อนเนื้องอกขนาดใหญ่ โดยเฉพาะเนื้องอกรังไข่ชนิด mucinous ดังนั้นในการดูแลรักษาผู้ป่วยเนื้องอกรังไข่ ควรมีการประเมินผลหรือการปรึกษาร่วมกันอย่างสม่ำเสมอระหว่างพยาธิแพทย์และสูตินรีแพทย์ในกรณี ที่ผลการวินิจฉัยโดยใช้ชิ้นเนื้อแช่แข็งอย่างรวดเร็ว และการวินิจฉัยโดยใช้ paraffin-embedded tissue ให้ผลขัดแย้งกัน เพื่อเป็นการควบคุมคุณภาพและให้การรักษาที่เหมาะสมในระหว่างการผ่าตัดแก่ผู้ป่วย*