Original Article

The Accuracy of Intraoperative Frozen Sections in Epithelial Ovarian Tumor

Korrakot Soitong MD[1], Tharintorn Chansoon MD[1], Chompunoot Kongsawatvorakul MD[2]

[1] Department of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[2] Department of Obstetrics and Gynecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Objective: To evaluate the accuracy of the intraoperative frozen section in the diagnosis of epithelial ovarian tumor.

Materials and Methods: An observational study of epithelial ovarian tumor reports from patients that underwent surgery with intraoperative consultation at Ramathibodi Hospital, Thailand between 2013 and 2017 was done. The frozen section diagnoses were compared with the final surgical diagnoses and the overall accuracy, sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) were studied.

Results: One hundred sixteen ovarian specimen reports were reviewed, comprised of 74 (63.8%) benign, 21 (18.1%) borderline, and 21 (18.1%) malignant neoplasms. Nine cases (7.7%) were discordant diagnoses. The overall accuracy was 92.2%. The sensitivity and specificity for benign, borderline, and malignant neoplasms were 100%, 80.9%, and 76.2%, and 88.1%, 95.8%, and 100%, respectively. The PPV and NPV for benign, borderline, and malignant neoplasms were 93.7%, 80.9%, and 100%, and 100%, 95.8%, and 95.0%, respectively.

Conclusion: The intraoperative frozen section has high accuracy in the diagnosis of ovarian epithelial neoplasm. The results can be used in guidance on the extent and type of surgical management.

Keywords: Frozen section, Accuracy, Epithelial ovarian tumor

Received 15 May 2020 | Revised 25 September 2020 | Accepted 29 September 2020

J Med Assoc Thai 2021;104(2):214-8

Website: http://www.jmatonline.com

Ovarian cancer is the seventh most common cancer in women globally[1], and the sixth most common cancer in Thai women[2]. The epithelial ovarian tumor is classified into three categories, that are benign, borderline, and malignant. The surgical management for each category is different with cystectomy for benign tumors, oophorectomy or limited surgical staging for borderline tumors in younger patients who desire to preserve fertility, whereas extensive staging procedure is required for malignant tumor[3]. Despite the improvement in imaging technique and serum tumor marker, the preoperative diagnosis of ovarian tumor remains difficult[4]. The intraoperative frozen sections are a diagnostic tool to guide the decision of surgical type and extent for the surgeons[3]. Therefore, the accuracy of intraoperative frozen sections is crucial. The objective of the present study was to evaluate the accuracy of the frozen section compared with the final surgical diagnosis including determining the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Correspondence to:

Chansoon T.

Department of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 207 Rama VI Road, Thung Phaya Thai, Ratchathewi, Bangkok 10400, Thailand.

Phone: +66-2-2011667

Email: tharintorn.cha@mahidol.ac.th

How to cite this article:

Soitong K, Chansoon T, Kongsawatvorakul C. The Accuracy of Intraoperative Frozen Sections in Epithelial Ovarian Tumor. J Med Assoc Thai 2021;104:214-8.

doi.org/10.35755/jmedassocthai.2021.02.11473

Materials and Methods

The present study was an observational study approved by the Committee on Human Rights Related to Research Involving Human Subjects based (COA MURA2020/1016) on the Declaration of Helsinki, involving the ovarian specimens of patients who underwent surgery with intraoperative consultation for ovarian tumor at Ramathibodi Hospital, Thailand between January 1, 2013 and December 31, 2017. The final surgical diagnoses, which were diagnosed with epithelial ovarian tumor, were enrolled from the electronic database and then selected from the cases that have frozen section diagnoses. The keywords search included benign, borderline, malignant, and tumor subtype. The reports that had both frozen section diagnoses and final surgical diagnoses were reviewed to collect the data including age, tumor

subtype, specimen integrity, laterality, tumor size, number of frozen slides, and number of permanent slides.

The intraoperative consultations were performed within standard protocols. After registering into the system, the specimens were macroscopically examined by the pathologists in charge. The areas and number of slides of the ovarian specimen were carefully selected for frozen histological examination depending on the solidity, wall thickness, and suspicious features of malignancy. The specimens were frozen in cryostat and 5 microns of tissue sections were stained with hematoxylin and eosin. The frozen tissue and the remaining specimens were further adequately fixed in 10% buffered formalin and submitted for permanent processing per standard protocols. In general, the numbers of slides were at least 1 slide per 1 cm of maximal diameter in any tumor subtype and 1 to 2 slides per 1 cm in the mucinous subtype. The final surgical diagnosis was made by the same pathologists who done the frozen section diagnosis. The special studies were considered when appropriated.

The diagnoses were classified into three categories, which were benign, borderline, or malignant. According to the 2014 World Health Organization (WHO) classification, the diagnoses with focal epithelial proliferation were classified into the benign category. The diagnoses of the borderline tumor with microinvasion or intraepithelial carcinoma were classified into the borderline category[5]. The diagnoses with "at least" were classified accordingly to the main diagnosis. The frozen section diagnoses were compared with final surgical diagnoses. The discordant cases were defined as the final surgical diagnosis falling into different categories from the frozen section diagnosis. Then the discordant cases were classified into underdiagnosis or overdiagnosis. The accuracy, sensitivity, specificity, PPV, and NPV were calculated by 2×2 tables considering final surgical diagnosis as a gold standard. Statistical analysis was done using Stata Statistical Software, version 16 (StataCorp LLC, College Station, TX, USA).

Results

One hundred sixteen ovarian specimens were enrolled in the present study with a mean age of 52 years (15 to 87 years). They comprised of 54 (46.6%) right ovaries, 36 (31.0%) left ovaries, 24 (20.7%) bilateral ovaries, and two (1.7%) undefined side. Seventy-four (63.8%) specimens revealed previously opened surfaces, while 13 (11.2%) specimens were intact. The average tumor size was 10.7 cm, ranging from 1.8 to 30 cm. The mucinous neoplasms were the most frequent histologic subtype and had the largest size. The average sizes of mucinous, serous, clear cell, endometrioid, seromucinous, Brenner, and mixed subtypes were 14.0, 9.1, 12.4, 5, 15, 13.4, and 10.6 cm, respectively.

Table 1. Correlation of frozen section diagnosis and final surgical diagnosis

Frozen section diagnosis	Final surgical diagnosis			
	Benign	Borderline	Malignant	Total
Benign	74	4	1	79
Borderline	0	17	4	21
Malignant	0	0	16	16
Total	74	21	21	116

Frozen section diagnoses showed 79 (68.1%) benign neoplasms, 21 (18.1%) borderline neoplasms, and 16 (13.8%) malignant neoplasms. The final surgical diagnoses revealed 74 (63.8%) benign neoplasms, 21 (18.1%) borderline neoplasms, and 21 (18.1%) malignant neoplasms. The correlation between the frozen section and final surgical diagnoses is listed in Table 1. Overall, the cases with concordant diagnoses comprised 92.4% (107 cases), whereas cases with discordant diagnoses were 7.7% (nine cases). Additionally, four of 21 (19%) and one of 21 (4.7%) cases of the malignant tumors were diagnosed as borderline and benign tumors in the frozen section, respectively. In addition, four of 21 (19%) of the borderline tumors were diagnosed as the benign tumors in the frozen section.

All nine cases of discordant diagnosis (false-negative cases) were under-diagnoses. Four of nine discordant cases (44.4%) were mucinous subtype, followed by three (33.3%) serous, one (11.1%) endometrioid, and one (11.1%) mixed subtype. The details of discordant cases are shown in Table 2. Three cases were diagnosed with "focal epithelial proliferation" in frozen section diagnoses. Two cases (66.7%) were found to be borderline tumors in final surgical diagnosis. The term "borderline tumor at least" was diagnosed in 13 cases (11.2%) in frozen sections. Three cases (23.1%) and five cases (38.4%) were found invasive carcinoma and microinvasion in final surgical diagnosis, respectively.

The overall accuracy of frozen section diagnosis was 92.2%. The sensitivity and specificity for benign, borderline, and malignant neoplasms were

Table 2. Cases with discordant diagnosis between frozen sections diagnosis and final surgical diagnosis (n=9)

Frozen diagnosis	Final Surgical diagnosis	Under-/over-diagnosis	Age (year)	Size (cm)
Mucinous cystadenoma	Mucinous borderline tumor	Under-diagnosis	38	25
Mucinous epithelial tumor with focal epithelial proliferation	Mucinous borderline tumor	Under-diagnosis	41	6.5
Serous cystadenoma with focal epithelial proliferation	Serous borderline tumor	Under-diagnosis	55	25
Suggestive of Brenner tumor	Mixed borderline tumor (clear cell and endometrioid)	Under-diagnosis	47	5
Mucinous cystadenoma	Mucinous carcinoma	Under-diagnosis	41	18.5
Borderline mucinous tumor	Mucinous carcinoma	Under-diagnosis	52	15
Borderline mucinous tumor	Mucinous carcinoma	Under-diagnosis	77	13.5
Borderline serous tumor with microinvasion at least	Serous carcinoma	Under-diagnosis	56	1
Borderline epithelial tumor, at least	Endometrioid carcinoma	Under-diagnosis	47	7

Table 3. Results of the study in terms of sensitivity, specificity, positive predictive value, and negative predictive value (n=116)

	Benign (95% CI)	Borderline (95% CI)	Malignant (95% CI)
Sensitivity (%)	100 (95.14 to 100)	80.9 (58.09 to 94.55)	76.2 (52.83 to 91.78)
Specificity (%)	88.1 (74.37 to 96.02)	95.8 (89.57 to 98.84)	100 (96.19 to 100)
Positive predictive value (%)	93.7 (86.67 to 97.12)	80.9 (61.43 to 91.90)	100
Negative predictive value (%)	100	95.8 (90.39 to 98.21)	95.0 (89.84 to 97.61)

CI=confidence interval

100%, 80.9%, and 76.2%, and 88.1%, 95.8%, and 100%, respectively. The PPV and NPV for benign, borderline, and malignant neoplasms were 93.7%, 80.9%, and 100%, and 100%, 95.8%, and 95.0%, respectively. The accuracy of the present study is shown in Table 3.

Discussion

Intraoperative consultation is an important tool in guiding the type and extent of surgical management in ovarian epithelial neoplasm[3]. Therefore, intraoperative consultation should be reliable enough in using discrimination between benign, borderline, and malignant behavior of ovarian masses. The accuracy of the intraoperative frozen section in most of the literatures was fairly high. The present study showed an overall accuracy of 92.2%. The systematic review from the Cochrane database in 2016 that enrolled 11,181 women from 38 studies, reported that when defining the invasive carcinoma as a positive test, benign and borderline as a negative test, the average sensitivity and specificity were 90% and 99.5%, respectively. But when defining both borderline and invasive carcinoma as a positive test, and benign as a negative test, the average sensitivity increased to 96.5%, but the average specificity decreased to 89.5%[6].

In the present study, the sensitivity for malignant neoplasms was relatively low, when compared with benign and borderline categories. This may be due to higher rate of underdiagnosis in malignant cases, including one (4.8%) and four cases (19%) that were diagnosed as benign and borderline in the frozen section, respectively. The result was similar to other studies (69.2% to 90%), whereas the specificity for the malignant category was very high (99% to 100%). The results that were also observed in many studies were the high sensitivity for the benign category (95.6% to 100%)[4,7-10]. The accuracy of the present study and previous studies are compared in Table 4.

Among the three categories, the borderline tumor appears to be the most confusing category, carrying low sensitivity and specificity, stated by several studies[3,7,11,12]. A quantitative systematic review from Mediros et al including 3,659 women from 14 primary studies concluded that the accuracy rate for the malignant and benign ovarian tumor are high, but relatively low in borderline tumor[12]. Ratnavelu et al found that when the frozen section diagnosis was a borderline tumor, on average 21% would turn out to be malignancy in the final diagnoses[6]. In the present study, 19% of malignant tumors were underdiagnosed as borderline tumor in the frozen section.

The factor that widely describes affecting the accuracy of frozen section diagnosis is tumor subtype, especially mucinous subtype. Mucinous ovarian

Table 4. Accuracy of intraoperative consultation of the current study and the previous studies

Authors	Year	No. of cases	Benign		Borderline		Malignant	
			Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Current study	2020	116	100	88.1	80.9	95.8	76.2	100
Kung, et al.[7]	2019	1143	100	92.51	87.22	96.24	81.29	99.76
Muruthapongsatorn, et al.[8]	2019	150	100	94.3	88.9	95	79.6	100
Arshad, et al.[9]	2018	92	95.6	85.1	76.2	88.7	69.2	100
Abudukadeer, et al.[10]	2016	804	100	97	64.3	97	90	100
Brun, et al.[4]	2008	274	97	81	62	96	88	99

tumors have high false-negative frozen section diagnosis rate[3]. The meta-analysis from Huang et al verified that mucinous histology was associated with misdiagnosis of frozen section in borderline tumor. This could be explained by the mucinous tumor that commonly have larger size than others subtype and have tumor heterogeneity containing mixed area of benign, borderline, and malignant components[13]. The frozen section tissue usually submitted only one to three slides, which may not represent the whole part of the tumor, especially in the large tumor. Thus, the possible areas of borderline and malignant components might overlook[12].

The study from Muruthapongsatorn et al investigated the factor that led to misdiagnosis in ovarian tumor and found that the large tumor size, mucinous type, and borderline tumor were associate with false-negative reports in frozen section diagnoses[8]. Tranoulis et al demonstrated that the tumor diameter greater than 13 centimeters was associated with discordant diagnosis and the ratio of tumor size per number of frozen sections less than 8 was an independent predictor of the inaccuracy[14]. However, studies of Pongsuvareeyakul et al and Ayhan et al concluded that increasing the number of frozen section slides was not significantly increased the accuracy of the frozen section diagnosis[15,16].

In the present study, two out of three cases (66.7%) diagnosed as benign tumors with focal epithelial proliferation found to be borderline tumors in the final surgical diagnosis. The "focal epithelial proliferation", defined by a tumor that contains borderline foci less than 10% of the epithelial volume, was considered and managed as a benign tumor[5]. The diagnosis required adequate sampling of the specimen to be confident that the borderline area is actually not more than 10%. The diagnosis in frozen section should be well communicated with the surgeon regarding the possibility to be borderline tumor in final diagnosis.

The term "at least" was not uncommon in use to define the tumor when the pathologists suspected the malignancy but did not have sufficient evidence on the frozen section to definitive diagnosis. The study of Huang et al found that when "at least borderline tumor" was diagnosed in the frozen section, 45% of which had invasive carcinoma on the final diagnosis, whereas only 1.7% of which were invasive carcinoma when the frozen section diagnosis was "borderline tumor only"[17]. However, the decision to use this term may differ in individual person based on the pathologist experiences. In the present study, "at least borderline tumor" was used in 13 cases (11.2%), three cases (23%) had been changed to invasive carcinoma and five cases (38.4%) found the microinvasion in the final surgical diagnosis.

To avoid the misinterpretation of frozen section diagnosis, direct communication between pathologists and surgeons at the period of frozen section is essential for obtaining the important information, diagnostic uncertainty, and limitations of interpretation to minimize the intraoperative errors[3]. Furthermore, Kim recommended that the pathologists should review the patient's clinical history or ideally discuss with the surgeon before the operation to maximize the effective results[18].

The present study is limited by an observational study, which may have potential bias. The absence of an established protocol for frozen section requests may lead to some selection bias. Additionally, there was lack of blinding in the assessment of the final diagnosis and the frozen section diagnosis. Further blinded prospective studies are needed to investigate the diagnostic accuracy and factors affected the frozen section diagnosis.

Conclusion

Intraoperative frozen section is a valuable tool to detect the malignant potential of the epithelial ovarian tumor with high accuracy. The results can be

used in guidance on the extent and type of surgical management. The sensitivity and specificity are relatively low in borderline tumors. Limitations in the use of frozen section must be recognized, especially large tumor size, and mucinous subtype. The direct communication between pathologists and surgeons is essential to minimize the intraoperative errors.

What is already known on this topic?

The accuracy of intraoperative consultation in the diagnosis of ovarian neoplasm was fairly high but has many limitations and pitfalls that led to over- or under-treatment, especially in large tumor size, borderline tumor, mucinous subtype, pathologists experience, and technical errors.

What this study adds?

The results of the present study were concordance with the previous studies and confirmed that although it has many limitations, the intraoperative consultation still had high accuracy and was a reliable tool in the diagnosis of epithelial ovarian tumor. The present study also discussed about the factors affecting the accuracy, the details about definition of the tumors and uncertain term that could make the diagnostic pitfalls. Furthermore, this study emphasized that the communication between surgeons and pathologists was the utmost essential.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Webb PM, Jordan SJ. Epidemiology of epithelial ovarian cancer. Best Pract Res Clin Obstet Gynaecol 2017;41:3-14.
2. Imsamran W, Pattatang A, Supaattagorn P, Chiawiriyabunya I, Namthaisong K, Wongsena M, et al. Cancer in Thailand Vol. IX, 2013-2015. Bangkok: New Thammada Press; 2018.
3. Buza N. Frozen section diagnosis of ovarian epithelial tumors: Diagnostic pearls and pitfalls. Arch Pathol Lab Med 2019;143:47-64.
4. Brun JL, Cortez A, Rouzier R, Callard P, Bazot M, Uzan S, et al. Factors influencing the use and accuracy of frozen section diagnosis of epithelial ovarian tumors. Am J Obstet Gynecol 2008;199:244.e1-7.
5. Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO classification of tumours of female reproductive organs. France: Lyon:IARC; 2014.
6. Ratnavelu ND, Brown AP, Mallett S, Scholten RJ, Patel A, Founta C, et al. Intraoperative frozen section analysis for the diagnosis of early stage ovarian cancer in suspicious pelvic masses. Cochrane Database Syst Rev 2016;3:CD010360.
7. Kung FY, Tsang AK, Yu EL. Intraoperative frozen section analysis of ovarian tumors: a 11-year review of accuracy with clinicopathological correlation in a Hong Kong Regional hospital. Int J Gynecol Cancer 2019;29:772-8.
8. Muruthapongsatorn P, Inploy N, Prommas S, Smanchat B, Bhamarapravatana K, Suwannarurk K. The evaluation of intra-operative frozen section diagnosis accuracy of ovarian tumors; old fashioned not out of fashion. Asian Pac J Cancer Prev 2019;20:3697-701.
9. Md Arshad NZ, Ng BK, Md Paiman NA, Abdullah Mahdy Z, Mohd Noor R. Intra-operative frozen sections for ovarian tumors – a tertiary center experience. Asian Pac J Cancer Prev 2018;19:213-8.
10. Abudukadeer A, Azam S, Zunong B, Mutailipu AZ, Huijun B, Qun L. Accuracy of intra-operative frozen section and its role in the diagnostic evaluation of ovarian tumors. Eur J Gynaecol Oncol 2016;37:216-20.
11. Khan AH, Mamoon N, Usman M, Laleka US, Malik B. Accuracy of intra-operative frozen section in the diagnosis of female genital tract neoplasms. J Pak Med Assoc 2016;66:143-6.
12. Medeiros LR, Rosa DD, Edelweiss MI, Stein AT, Bozzetti MC, Zelmanowicz A, et al. Accuracy of frozen-section analysis in the diagnosis of ovarian tumors: a systematic quantitative review. Int J Gynecol Cancer 2005;15:192-202.
13. Huang Z, Li L, Li C, Ngaujah S, Yao S, Chu R, et al. Diagnostic accuracy of frozen section analysis of borderline ovarian tumors: a meta-analysis with emphasis on misdiagnosis factors. J Cancer 2018;9:2817-24.
14. Tranoulis A, Thomakos N, Sotiropoulou M, Rodolakis A. What is the accuracy of frozen section in the diagnosis of mucinous ovarian tumours? A 9-year review of performance in a Greek tertiary referral centre. Arch Gynecol Obstet 2018;297:185-91.
15. Pongsuvareeyakul T, Khunamornpong S, Settakorn J, Sukpan K, Suprasert P, Siriaunkgul S. Accuracy of frozen-section diagnosis of ovarian mucinous tumors. Int J Gynecol Cancer 2012;22:400-6.
16. Ayhan A, Ozler A, Dursun P, Haberal AN. Potential role of increasing number of sections in frozen section diagnosis of ovarian tumors. J Exp Ther Oncol 2016;11:245-50.
17. Huang M, Schlumbrecht M, Hunter T, Nadji M, Pinto A. Utility of frozen section in the evaluation of borderline ovarian tumors: a single institution experience. J Gynecol Obstet 2019;7:41-5.
18. Kim I. Intraoperative consultation for ovarian tumors. Yeungnam Univ J Med 2019;36:163-82.