


Useful aspects of diagnosis of imprint cytology in intraoperative consultation of ovarian tumors: comparison between imprint cytology and frozen sections

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Background: In the intraoperative consultation of ovarian tumors, the histological diagnosis of frozen sections (FS) of large tumors is frequently difficult because of the limited number of tumor samples. The application of imprint cytology (IC), in which samples are obtained from wide areas of the tumors, is useful for intraoperative consultation. However, the useful aspects of IC have not been clearly defined. The present study is a detailed comparison of IC and FS that clearly defines the useful aspects of IC.

Methods: Fifty-five cases of ovarian tumors that were examined using both IC and FS were evaluated. The histological diagnoses consisted of benign (16), borderline (6), and malignancy (33). All of the malignant tumors consisted of various types of carcinoma.

Results: Benignity and malignancy were accurately diagnosed by both IC and FS. In the borderline group, the diagnostic accuracy of IC was very low (1/6: 16.6%) compared with FS (4/6: 66.6%). The diagnostic accuracy including benign, borderline, and malignant groups was 90.9% (50/55) for IC and 96.3% (53/55) for FS. Concerning the diagnosis of the types of carcinoma, the overall diagnostic accuracy of IC (25/31: 80.6%) was greater than that of FS (21/31: 67.7%), especially for the diagnosis of clear cell carcinoma (IC, 100%; FS, 80%) and mixed carcinoma (IC, 66.6%; FS, 16.6%).

Conclusion: The useful aspects of IC in the intraoperative consultation are the diagnosis of benignity or malignancy and the accuracy of diagnosing clear cell carcinoma and mixed carcinoma.

KEYWORDS

diagnosis using imprint cytology, histological diagnosis of frozen section, intraoperative consultation, ovarian tumors

1 | INTRODUCTION

For the intraoperative consultation of ovarian tumors, obtaining a precise evaluation of the gross morphology is important. Chen et al. described the relation between gross morphology and various ovarian diseases.¹

*These results were presented in part at the 32nd World Congress of the International Federation of Biomedical Laboratory Science, Kobe, 2016, and the study received the Good Poster Award.

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Even if the gross morphology is precisely evaluated in ovarian tumors, the intraoperative diagnosis depends on the histological evaluation of frozen sections.^{1,2} However, the histological diagnosis of frozen sections of large ovarian tumors is frequently difficult because of the limited number of tumor samples. In contrast, diagnosis using imprint cytology, in which samples are obtained from wide areas of tumors, is useful for the intraoperative consultation of ovarian tumors. Thus, in an intraoperative consultation, the application of both imprint cytology and histological diagnosis of frozen sections has been recommended for ovarian tumors.³⁻⁵

TABLE 1 Intraoperative accuracy of imprint cytology and frozen sections in 55 cases of benign, borderline and malignant tumors diagnosed by surgical resection tissues

Group (No. of cases)	Diagnosis of imprint cytology (No. of cases)	Histological diagnosis of frozen sections (No. of cases)
Benignity (16 cases)	Benignity (16 cases)	Benignity (16 cases)
Borderline (6 cases)	Benignity (3 cases)	Benignity (1 case)
	Borderline (1 case)	Borderline (4 cases)
	Malignancy (2 cases)	Malignancy (1 case)
Malignancy (33 cases)	Malignancy (33 cases)	Malignancy (33 cases)

Although the application of imprint or scrape cytology for the intraoperative consultation of ovarian tumors has been reported,^{3–11} only the study of Michael et al. compared the intraoperative consultation of cytology and frozen sections of ovarian tumors.⁶ In their study, the diagnostic accuracy of cytology was better than that of frozen sections, but a comparison of the cytology and frozen sections in each of the examined cases was not performed. Thus, in the present study, a detailed comparison of the cytology and frozen sections in the intraoperative consultation of ovarian tumors was performed, and the useful aspects of cytology in the intraoperative consultation of ovarian tumors were clearly defined.

2 | MATERIALS AND METHODS

Among the patients undergoing surgery for an ovarian tumor between June 1, 2013, and September 30, 2015, at Juntendo University Nerima Hospital, 55 patients who had both imprint cytology and histological diagnoses of frozen sections were selected. Samples for imprint cytology were obtained from several parts of the tumors presenting different gross morphology, and the samples underwent to Papanicolaou staining. Samples for frozen sections were obtained from a few areas of the tumors and processed in a conventional manner to produce frozen sections, and the tissue sections were stained with hematoxylin-eosin (H.E.).

Surgical resection tissues fixed in 10% formalin were routinely processed for light microscopy, and the histological diagnosis of the tissue sections was made by H.E. staining. When the histological diagnosis was difficult, immunostaining was also performed. The histological diagnosis of an ovarian tumor was established according to a newly published WHO classification.¹² The classification of mixed carcinoma in the ovary was not included in the WHO classification, but a previously published study of the imprint cytology of ovarian tumors described mixed carcinoma of the ovary; therefore, in the present study, the classification of mixed carcinoma was adopted.

The histological diagnoses of the surgical resections were divided into a benign group (16 cases), a borderline group (6 cases), and a malignant group (33 cases). The benign group consisted of fibrothecoma (5 cases), mucinous cystadenoma (4 cases), mature teratoma (2 cases), struma ovarii (2 cases), endometriotic cyst (1 case), serous cystadenofibroma (1 case), and fibrothecoma plus serous cystadenoma (1 case). The cases belonging to the malignant group were diagnosed as various types of carcinoma, including serous carcinoma (5 cases), mucinous carcinoma (3 cases), endometrioid carcinoma (7 cases), clear cell

carcinoma (10 cases), mixed carcinoma (6 cases), undifferentiated carcinoma (1 case), and metastatic adenocarcinoma (1 case). Based on the histological diagnosis of the surgical resections, the accuracy of intraoperative imprint cytology was evaluated, and the accuracy of imprint cytology and frozen sections was compared.

The present study is a retrospective study. The surgeons obtained written informed consent for performing the cytological and histological examinations from all patients when they underwent operation. The approval for assessing the patient demographic data was not obtained from the patients, therefore personal information from each of the patients was not included in the manuscript. The informed consent form and procedure were approved by the Research Ethics Committee of Juntendo University Nerima Hospital.

3 | RESULTS

The benignity and malignancy were diagnosed entirely by both imprint cytology and frozen tissue sections of the benign and malignant groups (Table 1). For the borderline group, the diagnostic accuracy of imprint cytology was very low (1/6: 16.6%) compared with that of frozen sections (4/6: 66.6%) (Table 1). In the 3 cases with seromucinous borderline tumors, an accurate diagnosis was not achieved by imprint cytology (Table 2), with under-diagnoses in 2 cases (Case Bord3 and Bord4) and an over-diagnosis in 1 case (Case Bord5). The diagnostic accuracy including benign, borderline, and malignant groups was 90.9% (50/55) for imprint cytology and 96.3% (53/55) for frozen sections.

Concerning the diagnosis of the different types of carcinoma, serous carcinoma (Table 2, Figure 1) and endometrioid carcinoma (Table 2, Figure 2) were diagnosed with the same accuracy using imprint cytology and frozen sections: serous carcinoma, imprint cytology (3/5, 60%) compared to frozen sections (3/5, 60%) and endometrioid carcinoma, imprint cytology (6/7, 86%) compared to frozen sections (6/7, 86%). In mucinous carcinoma, the diagnostic accuracy of frozen sections (3/3, 100%) was greater than that of imprint cytology (2/3, 66.6%) (Table 2, Figure 3). In contrast, the diagnostic accuracy of imprint cytology was greater than that of frozen sections for clear cell carcinoma (Table 2, Figure 4: imprint cytology, 10/10, 100%; frozen sections, 8/10, 80%) and mixed carcinoma (Table 2: imprint cytology, 4/6, 66.6%; frozen sections, 1/6, 16.6%). For the overall accuracy of the diagnoses of the abovementioned carcinomas, imprint cytology (25/31, 80.6%) was more accurate than frozen sections (21/31, 67.7%).

TABLE 2 Comparison among diagnosis of intraoperative imprint cytology, intraoperative frozen sections, and surgical resection tissues in 55 cases of ovarian tumors

Case No.	Diagnosis of imprint cytology	Histological diagnosis of frozen sections	Histological diagnosis of surgical resections
B1	Fibroma	Thecoma	Fibrothecoma
B2	Fibroma	Thecoma	Fibrothecoma
B3	Thecoma	Fibrothecoma	Fibrothecoma
B4	Fibroma	Fibroma	Fibrothecoma
B5	Thecoma	Fibrothecoma	Fibrothecoma
B6	Thecoma	Fibrothecoma + Serous cystadenoma	Fibrothecoma +serous cystadenoma
B7	Mucinous cystadenoma	Mucinous cystadenoma	Mucinous cystadenoma
B8	Mucinous cystadenoma	Mucinous cystadenoma	Mucinous cystadenoma
B9	Mucinous cystadenoma	Seromucinous cystadenoma	Mucinous cystadenoma
B10	Benign mucinous tumor	Mucinous cystadenoma	Mucinous cystadenoma
B11	Benign serous tumor	Serous cystadenofibroma	Serous cystadenofibroma
B12	Mature teratoma	Mature teratoma	Mature teratoma
B13	Mature teratoma	Mature teratoma	Mature teratoma
B14	Cystic lesion	Endometriotic cyst	Endometriotic cyst
B15	Struma ovarii	Struma ovarii	Struma ovarii
B16	Struma ovarii	Struma ovarii	Struma ovarii
Bord1	Serous borderline tumor	Serous borderline tumor	Serous borderline tumor
Bord2	Mucinous cystadenoma	Mucinous borderline tumor	Mucinous borderline tumor
Bord3	Adenofibroma	Mucinous cystadenoma	Seromucinous borderline Tumor
Bord4	Benign serous tumor	Seromucinous borderline tumor	Seromucinous borderline tumor
Bord5	Endometrioid carcinoma	Mucinous carcinoma	Seromucinous borderline tumor
Bord6	Clear cell carcinoma +mucinous carcinoma	Seromucinous borderline tumor	Endometrioid borderline tumor >> clear cell and seromucinous borderline tumors
SC1	Serous carcinoma	Serous carcinoma	Serous carcinoma
SC2	Serous carcinoma +mucinous carcinoma	Serous carcinoma	Serous carcinoma
SC3	Serous carcinoma	Endometrioid carcinoma	Serous carcinoma
SC4	Serous carcinoma +endometrioid carcinoma	Serous carcinoma +endometrioid carcinoma	Serous carcinoma
SC5	Serous carcinoma	Serous carcinoma	Serous carcinoma
EC1	Endometrioid carcinoma	Endometrioid carcinoma	Endometrioid carcinoma
EC2	Endometrioid carcinoma	Endometrioid carcinoma	Endometrioid carcinoma
EC3	Endometrioid carcinoma	Endometrioid carcinoma	Endometrioid carcinoma
EC4	Endometrioid carcinoma	Endometrioid carcinoma	Endometrioid carcinoma
EC5	Endometrioid carcinoma	Endometrioid carcinoma	Endometrioid carcinoma
EC6	Endometrioid carcinoma	Endometrioid carcinoma	Endometrioid carcinoma
EC7	Serous carcinoma	Poorly differentiated carcinoma	Endometrioid carcinoma

(Continues)

TABLE 2 (Continued)

Case No.	Diagnosis of imprint cytology	Histological diagnosis of frozen sections	Histological diagnosis of surgical resections
MC1	Endometrioid carcinoma	Mucinous carcinoma	Mucinous carcinoma
MC2	Mucinous carcinoma	Mucinous carcinoma	Mucinous carcinoma
MC3	Mucinous carcinoma	Mucinous carcinoma	Mucinous carcinoma
CCC1	Clear cell carcinoma	Clear cell carcinoma	Clear cell carcinoma
CCC2	Clear cell carcinoma	Clear cell carcinoma	Clear cell carcinoma
CCC3	Clear cell carcinoma	Clear cell carcinoma	Clear cell carcinoma
CCC4	Clear cell carcinoma	Clear cell carcinoma	Clear cell carcinoma
CCC5	Clear cell carcinoma	Clear cell carcinoma	Clear cell carcinoma
CCC6	Clear cell carcinoma	Clear cell carcinoma	Clear cell carcinoma
CCC7	Clear cell carcinoma	Clear cell carcinoma	Clear cell carcinoma
CCC8	Clear cell carcinoma	Clear cell carcinoma	Clear cell carcinoma
CCC9	Clear cell carcinoma	Serous carcinoma	Clear cell carcinoma
CCC10	Clear cell carcinoma	Metastatic adenocarcinoma	Clear cell carcinoma
Mix1	Mixed carcinoma: Endometrioid > Clear	Endometrioid carcinoma	Mixed carcinoma: Endometrioid > Clear
Mix2	Mixed carcinoma: Serous > Endometrioid	Endometrioid carcinoma	Mixed carcinoma Serous > Endometrioid
Mix3	Clear cell carcinoma	Endometrioid carcinoma	Mixed carcinoma: Clear > Serous > Endometrioid
Mix4	Mixed carcinoma: Endometrioid and Serous	Endometrioid carcinoma	Mixed carcinoma: Endometrioid and Clear
Mix5	Mixed carcinoma: Endometrioid and Serous	Endometrioid carcinoma	Mixed carcinoma: Serous > Endometrioid
Mix6	Mixed carcinoma: Endometrioid and Clear	Mixed carcinoma: Endometrioid and Clear	Mixed carcinoma: Endometrioid > Clear
Other1	Poorly diff. carcinoma	Serous carcinoma	Undiff. Carcinoma
Other2	Metastatic carcinoma	Metastatic carcinoma	Metastatic carcinoma

4 | DISCUSSION

Concerning the use of imprint cytology in intraoperative consultation of ovarian epithelial tumors, Nagai et al. examined the imprint cytology

of 354 consecutive surgical specimens, and reported that the accuracy of intraoperative imprint cytology was 87.1% for benign, 30% for borderline, and 83.6% for malignant tumors.⁹ They concluded that imprint cytology was significantly useful for the diagnosis of malignancy based

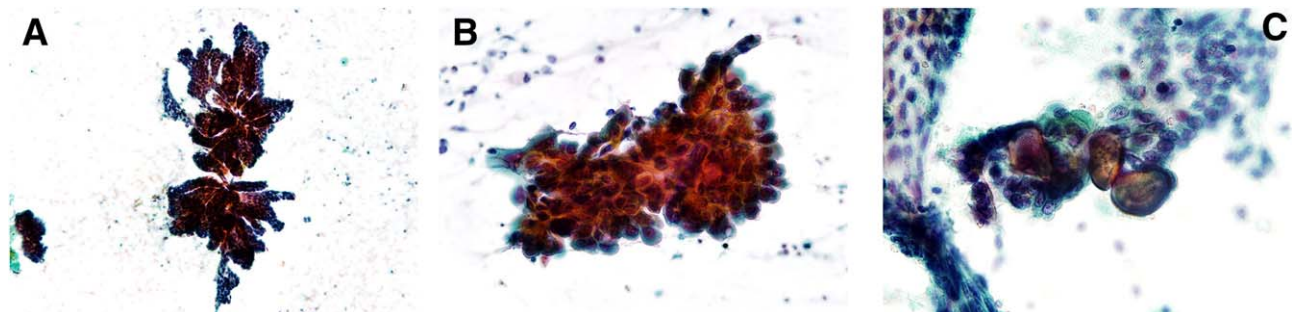


FIGURE 1 Imprint cytology of serous carcinoma (Case SC1). Note the papillary structure of high cellular epithelium (A), cuboidal epithelial cells with moderate to severe cellular atypia (B) and psammoma bodies (C). (Papanicolaou stain; A, $\times 100$, B, $\times 200$, C, $\times 400$) [Color figure can be viewed at wileyonlinelibrary.com]

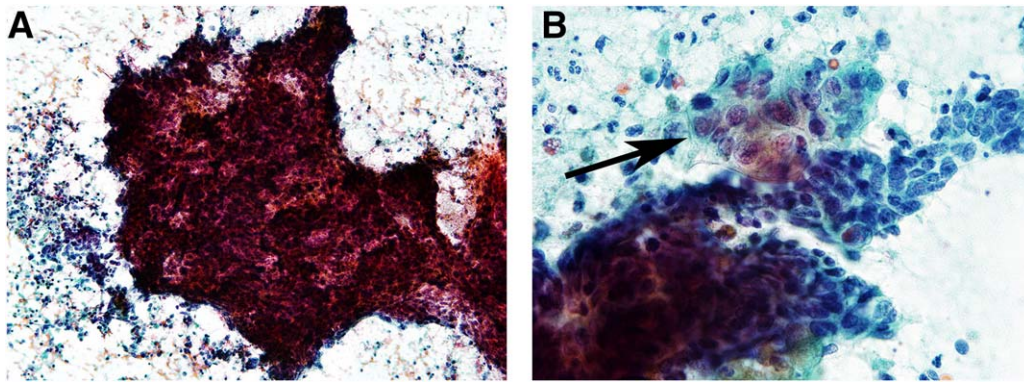


FIGURE 2 Imprint cytology of endometrioid carcinoma (Case EC1). Note the thick-layered cell clusters consisting of high cellular epithelial cells and a necrotic background (A), as well as squamous metaplasia (indicated by an arrow) and marked cellular atypia (B). (Papanicolaou stain; A, $\times 100$, B, $\times 400$) [Color figure can be viewed at wileyonlinelibrary.com]

on the operating characteristic curves.⁹ Thereafter, Khunamornpong and Siriaunkgul examined the scrape cytology of 131 cases of ovarian non-neoplastic lesions and tumors, and their accuracy was 95% for benign, 47% for borderline, and 98% for malignant tumors.¹⁰ No misdiagnosis was observed in the benign and malignant categories.¹⁰ The present study obtained results similar to those of the above-mentioned studies; both benign lesions and malignant tumors were accurately diagnosed by imprint cytology in intraoperative consultation. In addition, statistical analyses were not conducted in the present study due to our experiences in previously published studies that included statistical analyses,^{13–15} because all patients in both the benign and malignant groups were diagnosed by imprint cytology and frozen sections.

The intraoperative accuracy of imprint cytology in diagnosing borderline tumors was low in the present study. The intraoperative diagnosis of borderline tumors by cytology is difficult because of the admixture of benign and borderline areas in the same tumor, and the evaluation of stromal invasion was not possible by cytology.^{1,3,11} However, Kushima studied scrape or imprint cytology for intraoperative consultation in 6 cases that were under-diagnoses from the histological evaluation of frozen sections.¹¹ Among them, 3 cases (3/6, 50%) were

diagnosed as borderline tumors by cytology and 2 of the 3 cases had a borderline area $>30\%$.¹¹ His study suggested that borderline tumors could be more accurately diagnosed by intraoperative cytology when the borderline malignant areas are a main component of the tumor. In the recently published WHO report, the classification of ovarian tumors now includes a seromucinous borderline tumor.¹² The seromucinous borderline tumor can be subdivided into endocervical-type mucinous borderline tumor, and mixed-epithelial papillary cystadenomas of borderline malignancy of Mullerian type. The squamous dominance of mixed-epithelial papillary cystadenomas of borderline malignancy of Mullerian type was described by Nagai et al. and two of the authors of the present study (D.O. and T.M) were the co-authors of that article.¹⁶ According to our experience with mixed-epithelial papillary cystadenomas of borderline malignancy of Mullerian type, we performed the first trial of intraoperative cytology diagnosis of seromucinous borderline tumors in the present study. Subsequently, endocervical-type mucinous borderline tumors were under-diagnosed, and a mixed-epithelial papillary cystadenomas of borderline malignancy of Mullerian type was over-diagnosed. The present study involved a small number of cases of seromucinous borderline tumors. An intraoperative cytological study with a larger number of cases of

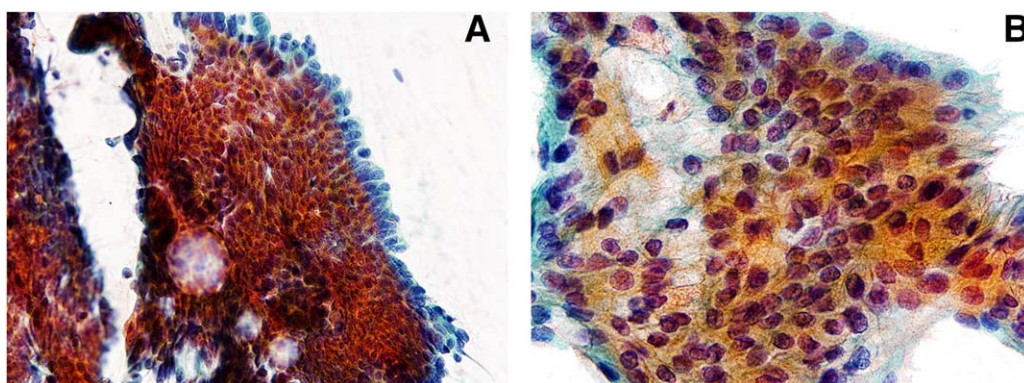


FIGURE 3 Imprint cytology of mucinous carcinoma (Case MC2). Note the thick-layered cell clusters consisting of columnar epithelial cells with moderate to severe cellular atypia (A) and mucinous pooling in the cytoplasm of atypical epithelial cells (B). (Papanicolaou stain; A, $\times 200$, B, $\times 400$) [Color figure can be viewed at wileyonlinelibrary.com]

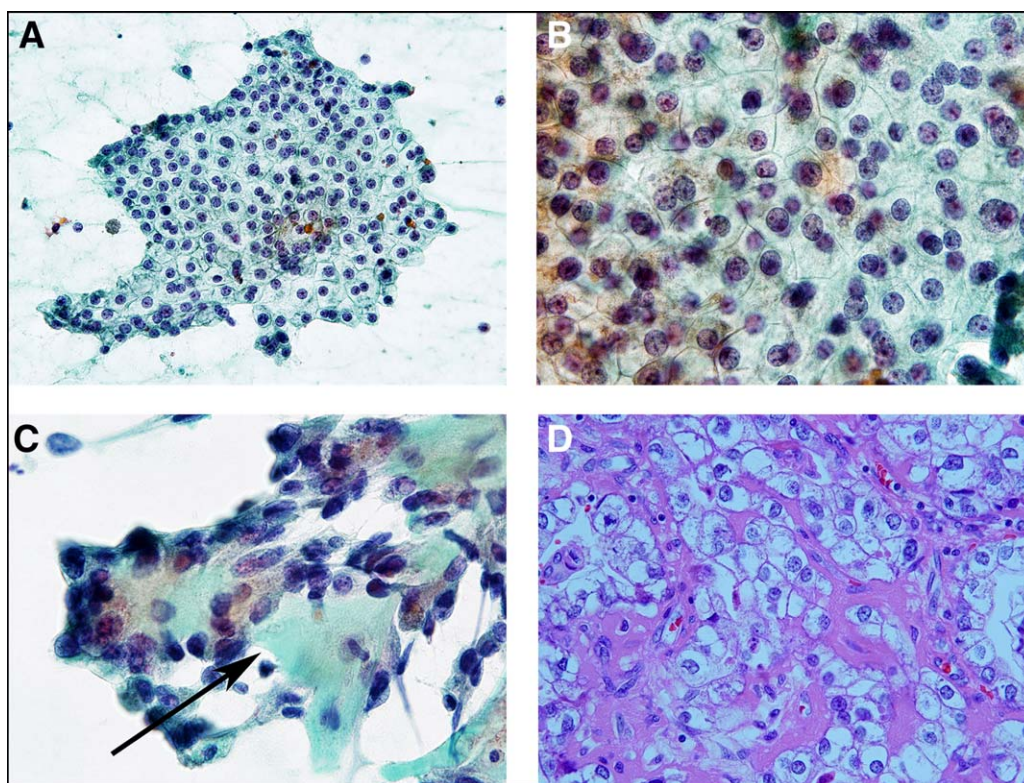


FIGURE 4 Imprint cytology and histology of clear cell carcinoma (Case CCC1). Note the sheet-like arrangement of epithelial cells with clear cytoplasm and moderate cellular atypia (**A and B**) and stromal hyalinization (**C**, indicated by an arrow) in imprint cytology. (Papanicolaou stain; **A**, $\times 200$, **B**, $\times 400$, **C**, $\times 400$). (**D**) Solid sheets composed of cells with clear cytoplasm surrounded by stromal hyalinization histologically. (HE stain, $\times 400$) [Color figure can be viewed at wileyonlinelibrary.com]

seromucinous borderline tumors is needed to examine the application of cytology to borderline tumor diagnosis.

Michael et al. performed a comparative study of intraoperative cytology and frozen sections in 63 cases and reported that cytology was slightly better than frozen sections.⁶ In contrast, in the present study, the histological diagnosis of frozen sections was slightly better than that of cytology. This difference may have been due to the different methods used to obtain cytological materials. Michael et al. used a combination of imprint cytology (40 cases), fine-needle aspiration cytology (38 cases), and scrapes (5 cases).⁶ FNAC and scrapes are superior to imprints,⁶ and this combination of methods may have led to their conclusion that cytology was better than frozen sections.

The comparison of intraoperative cytology and frozen sections in the present study indicates that imprint cytology is superior to frozen sections in diagnosing the histological types of carcinoma, such as clear cell carcinoma and mixed carcinoma. Overall, nearly 85% of malignant ovarian tumors are epithelial,¹ which contributes to the superiority of imprint cytology for the diagnosis of these tumors.

In conclusion, the useful aspects of imprint cytology in intraoperative consultation are the diagnosis of benignity or malignancy and the accuracy of diagnosing clear cell carcinoma and mixed carcinoma. In contrast, imprint cytology is difficult to use for the diagnosis of seromucinous borderline tumors.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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