

**Review**

**Problems in the Pathological Diagnosis and Intraoperative Rapid  
Diagnosis of Mucinous Tumor of the Ovary**

Miki KUSHIMA

**Abstract:** The pathological (histological and cytological) diagnosis of mucinous ovarian tumors presents the following problems: 1) conflicting definitions of borderline tumors, intraepithelial carcinoma and microinvasive carcinoma, 2) mural nodules within mucinous cystic tumors, 3) differential diagnosis in primary vs. metastatic mucinous tumors, and 4) difficulties in the intraoperative rapid diagnosis of mucinous ovarian tumors. Mucinous adenocarcinomas may include benign and/or borderline tumor components in other areas of the tumor. Therefore for pathological diagnosis, the sampling of these tumors must include up to one histological section per 1 to 2 cm of tumor diameter as well as sampling of any suspicious lesions (multilocular and solid areas including mural nodules). The most important differential diagnosis for mucinous ovarian carcinoma is metastatic mucinous carcinoma. Histological findings from metastatic mucinous carcinoma from the appendix, large intestine, stomach, pancreas, and cervix are similar. In general, immunohistological staining, such as cytokeratin 7 (CK7) and CK20, is necessary to determine the origin of the cancer. False-negative diagnoses from frozen sections can occur due to limited sampling, as only a few frozen sections (1 or 2 in our hospital) can be taken from each tumor. Cytological specimens (scrape or imprint smears) which are sampled from any suspicious lesions or from almost all cut surfaces of the tumors can facilitate intraoperative rapid diagnosis of mucinous ovarian tumor.

**Key words:** pathology, ovarian tumor, mucinous tumor, adenocarcinoma, intraoperative rapid diagnosis

**Introduction**

The incidence of ovarian mucinous carcinoma is relatively high in Japan compared to Western countries. The incidence of mucinous carcinoma has been reported to be 8.5% of all malignant ovarian tumors in the USA<sup>1,2)</sup> compared with 16.3% in Japan<sup>3)</sup>.

Mucinous tumors are defined as surface epithelial-stromal tumors whose epithelial cells contain intracytoplasmic mucin, and are divided into benign, borderline and malignant types<sup>4)</sup>. As shown in Table 1, the incidence of mucinous ovarian tumors in Japan is higher than in Western countries. However, the diagnosis of mucinous tumors is difficult due to a variety of pathology problems (histological and cytological).

These general problems in the pathological diagnosis of the mucinous ovarian tumors are

Table 1. Incidence of cases of ovarian surface epithelial-stromal tumors

	Mucinous Tumors	Serous Tumors
Benign	90	46
Borderline	40	10
Malignant	21	28

Showa University Hospital 1997-2006

outlined below, and the practical value of scrape or imprint cytology in the intraoperative assessment of mucinous ovarian tumors at Showa University Hospital is discussed.

### *Problems in the pathological diagnosis of mucinous ovarian tumors*

The following problems impede the pathological (histological and cytological) diagnosis of the mucinous tumors: 1) conflicting definitions of borderline tumors, intraepithelial carcinoma and microinvasive carcinoma, 2) mural nodules within mucinous cystic tumors, 3) differential diagnosis in primary vs. metastatic mucinous tumors, and 4) difficulties in the intraoperative rapid diagnosis of mucinous ovarian tumors.

#### 1) Definitions of borderline tumors, intraepithelial carcinoma and microinvasive carcinoma

Benign mucinous tumors contain cysts lined by mucinous columnar epithelia with only minimal cellular stratification and slight nuclear atypia. The presence of minimal stratification and slight nuclear atypia does not define a borderline tumor (Fig. 1).

Borderline tumors have evident stratifications and enlarged atypical nuclei without obvious stromal invasion. Mucinous borderline tumors with marked cytological atypia and epithelial stratification with a papillary or cribriform pattern are classified as borderline tumors with intraepithelial carcinoma<sup>4)</sup>(Fig. 2). There are two types of mucinous borderline tumor: intestinal type (85~90%) and endocervical-like type (10~15%). In endocervical-like type tumors, the intracystic growth is composed of broad bulbous papillae similar to those in serous borderline tumors.

#### 2) Mural nodules within mucinous cystic tumors

Mural nodules in mucinous cystic tumors are malignant (anaplastic carcinoma, sarcoma and carcinosarcoma) or benign (sarcoma-like)<sup>1)</sup>. We reported "A case of mucinous cystic tumor with mural nodule" in the Slide Conference of the 8th Korea-Japan Joint Meeting for Gynecological Pathology in 2004 (Tokyo). Figure 3 shows an undifferentiated carcinoma in the mural nodule of a mucinous cystic tumor of the ovary.

#### 3) Differential diagnosis in primary vs. metastatic mucinous tumors

The most important differential diagnosis for mucinous ovarian carcinoma is metastatic mucinous carcinoma from other organs including appendix, large intestine, stomach, pancreas, or cervix. These tumors have histological findings similar to those of primary mucinous ovarian carcinoma.

In general, immunohistological staining, such as cytokeratin 7 (CK7) and CK20, is necessary

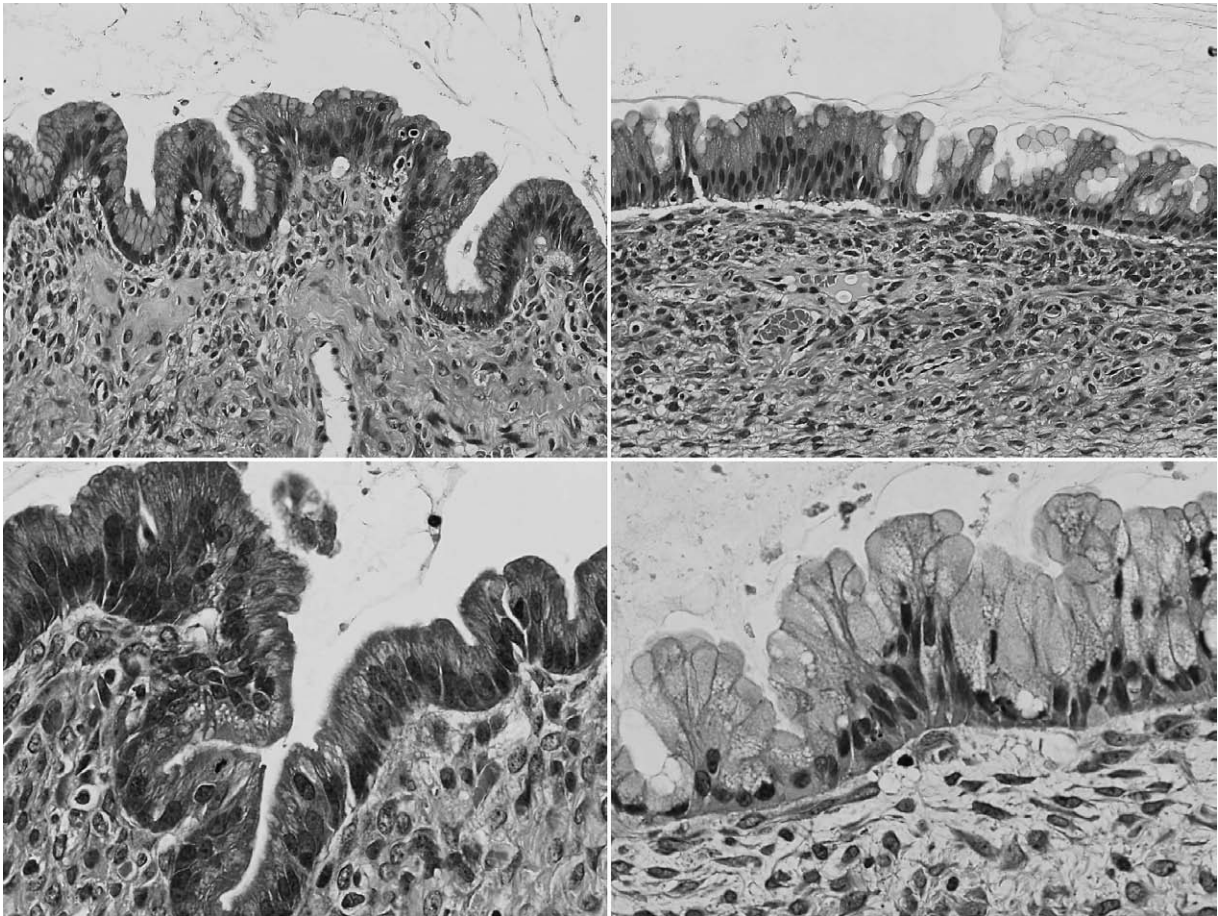


Fig. 1. Sections from a similar case indicate benign mucinous adenoma rather than mucinous borderline tumor

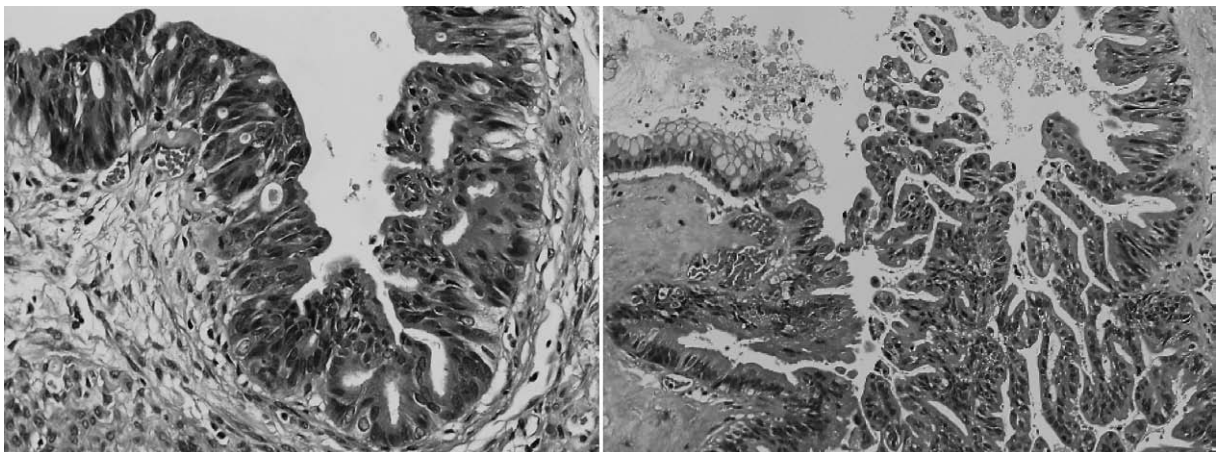


Fig. 2. Mucinous borderline tumor showing stratification and atypical nuclei without stromal invasion

to determine the origin of the cancer. However it is critical that all clinical information is evaluated together with these markers in considering a differential diagnosis<sup>1)</sup>.



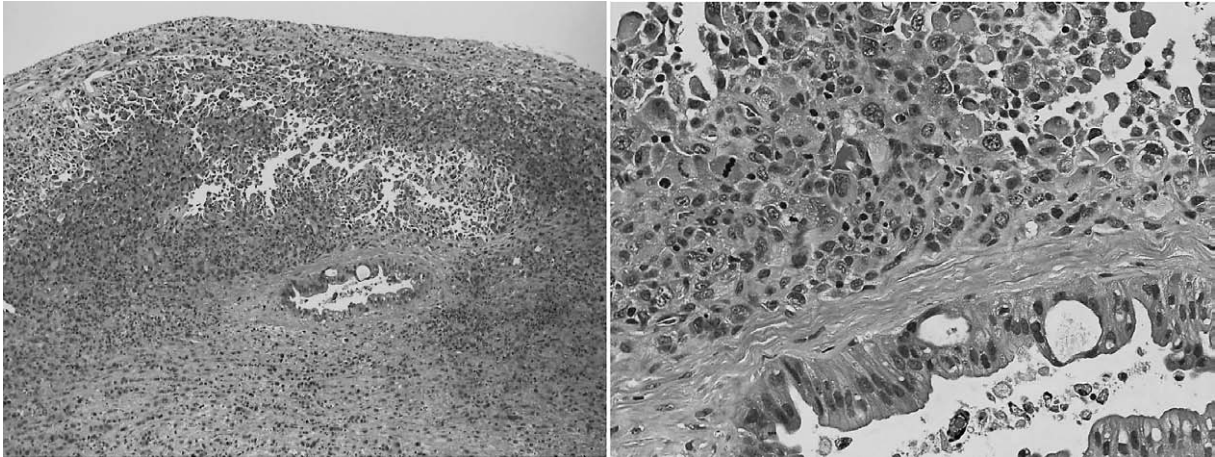


Fig. 3. Mural nodule in a mucinous cystic tumor. The solid tumor component is undifferentiated carcinoma

#### 4) Intraoperative rapid diagnosis of mucinous ovarian tumors

In the pathological diagnosis of mucinous ovarian tumors, mucinous adenocarcinoma may include benign and/or borderline components in other areas of the tumor, therefore, sampling must include up to one histological section per 1 to 2 cm of the tumor diameter as well as sampling of any suspicious lesions (multilocular and solid areas including mural nodules). When the tumor is confined to the ovaries, such as in borderline tumor, intraepithelial carcinoma and microinvasive carcinoma (with stromal invasive foci less than 10 mm<sup>2</sup>), the prognosis may be excellent. In peritoneal lesions including pseudomyxoma peritonei, a mucinous ovarian tumor with an infiltrative (invasive) implant is more aggressive than one with an expansile (non-invasive) implant.

#### *Intraoperative rapid diagnosis of mucinous ovarian tumors at Showa University Hospital*

The pathological diagnosis and clinicopathologic data from 151 cases of ovarian mucinous tumor from Showa University Hospital from 1997 to 2006 were reviewed. Specimens were taken from all mucinous cystic ovarian tumor samples (up to one histological section per 1 to 2 cm of the tumor diameter), including sampling of any suspicious lesions (multilocular and solid areas including mural nodules).

Table 2 shows a comparison of the results from frozen sections and cytological specimens (scrape or imprint smears) with those from permanent specimens. False-negative frozen section diagnoses occur due to limited sampling as only a few frozen sections (1 or 2 in our hospital) can be taken from each tumor<sup>5,6</sup>. Cytological specimens which are sampled from any suspicious lesions or from almost all cut surfaces of the tumor (Fig. 4) are useful in facilitating intraoperative rapid diagnosis of mucinous ovarian tumors. At Showa University Hospital, we have used scrape cytology with frozen sections for intraoperative rapid diagnosis as the diagnostic accuracy of the scrape cytology is superior to imprint cytology or frozen sections alone<sup>7</sup>. Laser Scanning Cytometry (LSC) is microscope-based cytofluorometry which is performed by scanning

Table 2. Comparison of rapid diagnosis and final diagnosis in 196 cases of surface epithelial-stromal tumor

Final diagnosis	Benign	borderline	malignant	sum
Rapid diagnosis				
Benign	71	11	1	83
Borderline	0	26	4	30
Malignant	0	3	80	83
sum	71	40	85	196

Number of the tumors



Fig. 4. Procedure to obtain specimens for cytology.

- 1) By using one glass slide, scrape the cells from the cut surface of the tumor, with as wide an area as possible.
- 2) Smear the cells another glass slide for cytological analysis.

alcohol-fixed propidium iodide-stained tumor cells from scrape or imprint smears for assessment of DNA ploidy (Table 3). An aneuploid DNA pattern by LSC in the atypical cells suggests that they may be derived from a borderline or malignant mucinous tumor.

Pathologists and surgeons must be aware of the limitations of frozen sections in the diagnosis of mucinous ovarian tumors to ensure that the appropriate surgical procedure is selected for each patient and to prevent under- and over-treatment<sup>8,9)</sup>. Surgeons should take whole resected ovarian tumors to the pathology laboratory with the clinical data from the patient. The assessment of mucinous borderline tumors is a particularly difficult problem. Scrape or imprint cytology is considered to be helpful in facilitating intraoperative rapid diagnosis. In addition, clinical information such as CT and MRI imaging, tumor markers, and macroscopic findings are helpful for intraoperative rapid diagnosis.

Table 3. Mucinous ovarian tumors. Under-diagnosis using frozen sections, benign ; permanent sections, borderline malignancy

Case#	Borderline % of the area of the HE specimens	Cytology	LSC	Ascites
1	30%	positive	aneuploidy	—
2	10%	positive	—	negative
3	5%	negative	diploidy	—
4	15%	negative	aneuploidy	—
5	40%	positive	—	—
6	5%	negative	diploidy	negative

LSC : Laser Scanning Cytometry

## Conclusions

Macroscopic findings and sampling are very important for intraoperative rapid diagnosis of ovarian tumors.

Scrape or imprint cytology is useful<sup>7-9)</sup> for confirming a frozen section diagnosis because of the wide area of tumor sampling. Ploidy pattern analysis by LSC may also be useful for a rapid diagnosis.

Pathologists and surgeons must be aware of the limitations of frozen section diagnosis of mucinous ovarian tumors to ensure appropriate surgical procedures are performed and to prevent under- and over-treatment.

## References

- 1) Lee KR, Tavassoli FA, Prat J, *et al.* Surface epithelial–stromal tumours. In *Tavassoli FA, Devilee P, eds. Pathology and genetics of tumours of the breast and female genital organs*. Lyon: IARC Press; 2003. pp117–145. (World health organization classification of tumours; 4)
- 2) Partridge EE, Phillips JL, Menck HR. The national cancer data base report on ovarian cancer treatment in United States hospitals. *Cancer*. 1996;**78**:2236–2246.
- 3) Nakajima H, Siota M, Nishida T. Benign ovarian tumor, Consideration in detail. In *Taketani Y, Aono T, Aso T, et al. eds. Sanfujinka no ryosei shuyo: shikyukinshu, ransonoshu, nyuboshuyo*. Tokyo: Nakayama Shoten; 1999. pp80–139. (Comprehensive handbook of women’s medicine; 39). (in Japanese).
- 4) Wootipoom V, Dechsukhum C, Hanprasertpong J, *et al.* Accuracy of intraoperative frozen section in diagnosis of ovarian tumors. *J Med Assoc Thai*. 2006;**89**:577–582.
- 5) Tempfer CB, Polterauer S, Bentz EK, *et al.* Accuracy of intraoperative frozen section analysis in borderline tumors of the ovary: a retrospective analysis of 96 cases and review of the literature. *Gynecol Oncol*. 2007;**107**:248–252.
- 6) Stewart CJ, Brennan BA, Hammond LG, *et al.* Intraoperative assessment of ovarian tumors: a 5-year review with assessment of discrepant diagnostic cases. *Int J Gynecol Pathol*. 2006;**25**:216–222.
- 7) Khunamompong S, Siriaunkgul S. Scrape cytology of the ovaries: potential role in intraoperative consultation of ovarian lesions. *Diagn Cytopathol*. 2003;**28**:250–257.
- 8) Shidham VB, Dravid NV, Grover S, *et al.* Role of scrape cytology in rapid intraoperative diagnosis. Value and

limitations. *Acta Cytol.* 1984;**28**:477-482.

- 9) Stewart CJ, Brennan BA, Koay E, *et al.* Value of cytology in the intraoperative assessment of ovarian tumors: a review of 402 cases and comparison with frozen section diagnosis. *Cancer Cytopathol.* 2010;**118**:127-136.

[Received December 11, 2012 : Accepted December 28, 2012]