



## Mucinous Tumors of The Ovary: Current Diagnosis in Histopathological Perspective

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### ABSTRACT

Epithelial malignant tumors account for around 90% of all ovarian malignancies and are the deadliest gynecological malignancies and mucinous borderline ovarian tumors are the most common cases in Asia. According to World Health Organization (WHO) 2020, mucinous ovarian tumors are divided into mucinous cystadenoma, borderline mucinous tumor and mucinous carcinoma. Histopathological features of benign, borderline and invasive mucinous carcinoma can be found together in one tumor. The coexistence of these varied morphological features makes it difficult to establish a diagnosis due to the limited section evaluated and the large size of tumor. It can contribute to inaccurate diagnosis due to heterogeneity of the morphological features. Metastatic mucinous tumors which often resemble primary mucinous tumors in the ovaries.

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### 1. Introduction

Epithelial malignant tumors account for around 90% of all ovarian malignancies and are the most deadly gynecological malignancies.<sup>1,2</sup> According to statistical data from WHO (World Health Organization), there were 14.1 million cases of malignancy throughout the world in 2012 and ovarian malignancies ranked 18th of all malignancies most common by organ and the 7th most common malignancy in women worldwide.<sup>3</sup> Ovarian epithelial malignancies contribute to 150,000 deaths each year worldwide.<sup>4</sup>

Based on data from the Indonesian Cancer Registry in 2011, malignant ovarian tumors rank 5th among all the most common malignancies by organ and 3rd most common malignancies in women in Jakarta.<sup>5</sup> Archive data from the Department of Anatomic Pathology, Faculty of Medicine, University of Indonesia/Cipto Mangunkusumo Hospital (2004 - 2013), mucinous epithelial tumors were the most common type (719 people) followed by serous ovarian epithelial tumors (457 people) and endometrioid types.<sup>5</sup>

According to the World Health Organization (WHO) 2020, mucinous ovarian tumors are divided into benign, borderline and malignant mucinous

tumors. This classification is carried out based on growth patterns, nuclear atypia and the presence or absence of invasion of the stroma and confluent growth. Borderline mucinous ovarian tumors are the most common cases in Asia (70% of borderline/atypical proliferative tumors) and the second most common in North America and Europe (30-50% of borderline/atypical proliferative tumors).<sup>6</sup>

The histopathological features of benign tumors, borderline tumors and invasive mucinous carcinoma can be found together in one tumor.<sup>6,7</sup> The coexistence of these varied morphological features makes it challenging to establish a diagnosis due to the limited sections evaluated and the large size of the tumor. This can contribute to inaccurate diagnosis due to the possibility of missed foci of microinvasion carcinoma.<sup>8</sup> The difficulty of making a diagnosis, especially borderline mucinous ovarian tumors, is due to the heterogeneity of the morphological features such as microinvasion, intra-epithelial carcinoma, and mural nodules. For this reason, selection and sampling play an essential role in the accuracy of the diagnosis made.

This literature review aims to provide information and study histopathological aspects

regarding the latest classification of mucinous ovarian tumors based on WHO 2020 and is expected to increase accuracy in diagnosis which influences the prognosis and patient management.

## 2. Discussion

### Comparison of the classification of ovarian mucinous tumors based on WHO 2003 and 2020

There are differences in the classification of mucinous ovarian tumors based on WHO 2003 and WHO 2020. In WHO 2020 there are simplifications so that the classification of mucinous ovarian tumors becomes fewer. This classification can be simplified in the comparative table for the classification of ovarian mucinous tumors below.<sup>7-9</sup> (Table 1).

### Classification of mucinous ovarian tumors based on WHO 2020.<sup>6,10</sup>

According to WHO 2020, mucinous ovarian tumors are divided into mucinous cystadenomas and adenofibromas, borderline mucinous tumors and mucinous carcinomas.

#### Benign mucinous tumor

##### Mucinous cystadenoma

Definition of a benign mucinous ovarian tumor is a cystic tumor lined with gastrointestinal mucinous epithelium. Mucinous cystadenoma accounts for around 80% of all primary mucinous ovarian tumors with a wide age range of sufferers, an average of 50 years. The most common symptoms are pain and an abdominal or pelvic mass.<sup>11</sup>

Macroscopically, it is cystic, unilateral (95%) with a smooth outer surface, unilocular to multilocular, measuring up to/more than 30 cm (average 10 cm). Microscopically, it consists of multiple cysts and glands lined by single columnar epithelium with intracellular mucin.<sup>11</sup> Focal papillary growth can be found. The ovarian stroma may border the epithelium which may be cellular with areas of luteinized stroma. Areas of mucin pooling in the stroma can also be found.

##### Mucinous adenofibroma

Mucinous adenofibroma is a benign ovarian tumor with epithelial cells containing intracytoplasmic mucin and a fibrotic stroma. This is a type that is rarely found. The age of the sufferers ranges from 15 to 65 years. Macroscopically, it is a mass that is usually smaller than a mucinous cystadenoma, multicystic with a solid component. The macroscopic appearance resembles that of a malignant tumor so that intraoperative frozen section diagnosis is very helpful to avoid unnecessary extensive surgery for patients.<sup>11</sup>

Microscopically, it consists of a prominent and solid fibrous stroma lined by high columnar epithelium<sup>7,12</sup> (Figure 1).

### Mucinous borderline/atypical proliferative mucinous tumor.

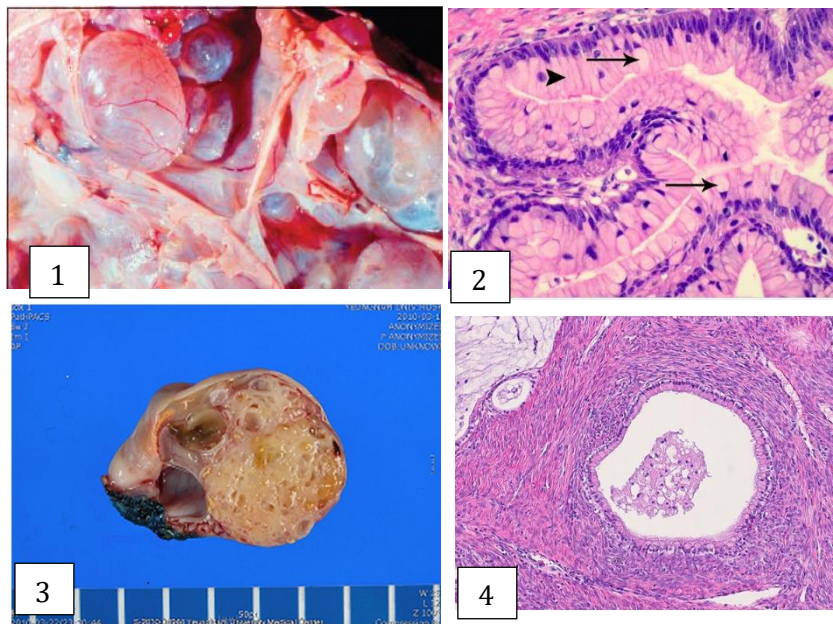
Definition of borderline mucinous tumor is a tumor consisting of gastrointestinal-type cells containing mucin with mild to moderate atypical with greater proliferation than benign mucinous tumors but without stromal invasion.

Borderline mucinous tumors account for 10% of mucinous ovarian tumors and 30-50% of all borderline epithelial ovarian tumors.<sup>13</sup> It is the second most common borderline/atypical proliferative tumor type in North America and Europe (30-50%) and is the most common type in Asia (70%). The age of patients ranges from 13-88 years with an average age of 40-49 years accompanied by abdominal mass, usually unilateral. Bilaterality needs to be considered as metastatic carcinoma. Macroscopic, tumors measuring up to 50 cm (average 21.5 cm), generally unilateral, slippery outer surface. Consisting of small to large cysts filled with mucin, solid parts can also be found. Cysts are usually slippery-walled but can also be ulcerative or with solid parts. Mucinous tumors are known for their heterogeneity of morphological features. In a tumor mass can be found benign, borderline and malignant parts at once, therefore adequate sampling is necessary. This is because the focus of carcinoma can be hidden. Sampling should consist of 1 piece per cm of the largest tumor dimensions in tumors measuring less than 10 cm, mainly focusing on solid parts or that look different from the surrounding area. If the tumor reaches a size of 10 cm or more, sampling should be taken 2 pieces per cm of the largest tumor dimensions.<sup>9</sup>

Microscopic, cysts are lined with gastrointestinal epithelium in the form of pyloric gastric type epithelium, goblet cells, neuroendocrine cells, and sometimes paneth cells. Epithelium can be stacked, villous or filiform papillae with mild to moderate enlargement of cell nuclei, hyperchromatic and sometimes pseudo stratification but high-grade nuclear features are not found. Areas of proliferation of more than 10% of the total tumor volume can be categorized as borderline mucinous tumors. Pseudomyxoma ovarii can be found in 20% of cases. The rupture of glands containing mucin can cause an inflammatory reaction of granulomatous in the stroma, known as granuloma mucin. Mucinous borderline tumors with intraepithelial carcinoma show proliferation cell of 4 layers or more, focus with cribriform pattern or stroma-free papillary architecture, or show epithelial layer with medium to severe atypical nuclei or a combination of these features. Components of intraepithelial carcinoma can range from less than 5% to more than 90% (Figure 2).<sup>7</sup>

**Table 1. Comparison of the classification of ovarian mucinous tumors based on WHO 2003 and 2020.<sup>6,9</sup>**

WHO Classification 2003		WHO Classification 2020	
<b>Benign tumor</b>			
Cystadenoma	8470/0	Cystadenoma	8470/0
Cystadenofibroma			
Adenofibroma	9015/0	Adenofibroma	9015/0
Mucinous cystic tumours with mural nodule			
Mucinous cystic tumours associated with pseudomyxoma peritonei			
Borderline tumor	8472/1		
Mucinous borderline tumor, intestinal type		Mucinous borderline tumor	8472/1
Mucinous borderline tumor, endocervical-like.			
<b>Malignant tumor</b>			
Mucinous adenocarcinoma	8480/3	Mucinous carcinoma	8480/3
Mucinous cystadenocarcinofibroma	9015/3		

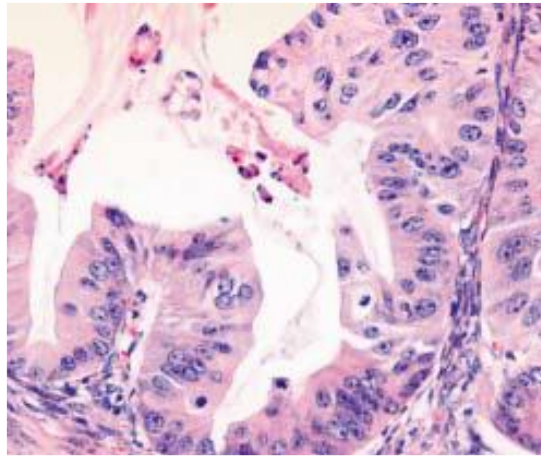


**Figure 1 . Benign mucinous tumor. Mucinous cystadenoma (1 and 2)<sup>11</sup>. Mucinous adenofibroma (3 and 4)<sup>11,12</sup>**

When the diagnosis of borderline mucinous tumors with intraepithelial carcinoma is established, more pieces of tissue are needed to remove them from invasive carcinoma.<sup>3,14</sup> If a large enough area of proliferation with a cribriform pattern or stacked epithelium of more than 3 layers is found without the discovery of core atypia, it is not included in the category of intraepithelial carcinoma.<sup>11,15,16</sup>

Classification of mucinous borderline ovarian tumors by micro invasion refers to the discovery of small foci of stromal invasion less than 5 mm or 10 mm<sup>2</sup> wide at the largest linear without limitation on the number of focuses. Micro invasion characteristics include single cell images, glands, clusters / nests, confluent small foci of glands or cribriform patterns with mild to moderate atypia.<sup>8,15,17</sup>

Only 5% of mucinous borderline tumors occur bilaterally. The presence of bilateral tumor in both ovaries can be thought of as metastatic lesions from elsewhere. Usually in patients with old age with a tumor size of less than 10 cm. Common metastatic mucinous tumors include adenocarcinoma of the pancreas and colon which often resemble primary mucinous tumors in the ovaries.<sup>2,11</sup> Microscopically these metastatic tumors can show benign, borderline or malignant images. Often mucinous ovarian tumors with pseudomyxoma peritonei are metastatic tumors that mostly originate from low-grade appendix mucinous tumors. Primary borderline mucinous tumor reactive to cytokeratin (CK).<sup>8</sup> Inhibin can also be used as a tumor marker for mucinous borderline tumors and mucinous



**Figure 2. Borderline mucinous tumor with intraepithelial carcinoma. (H&E, ×200)**<sup>7</sup>

carcinoma.<sup>11</sup> Metastatic mucinous tumors provide high expression of cytokeratin (CK) 20, CDX2, CA19.9, and MUC 2 and low expression of cytokeratin (CK) 7, CA125, and MUC5AC.<sup>2</sup>

The mucinous glands can rupture with extravasation of mucin to the stroma and can cause datia cell reactions and chronic inflammation. When the focus expands with or without epithelial cells and in the absence of histiocytes or other inflammatory cell reactions, the diagnosis of pseudomyxoma ovarii can be established.

In mucinous ovarian tumors, mural nodules can be found, although rare. The incidence is between 2-5 per million cases and can be found in borderline mucinous ovarian tumors or mucinous ovarian carcinoma.<sup>6,7</sup> Mural nodules are histologically divided into benign and malignant lesions. Types of mural nodules include reactive sarcoma-like mural nodules that are often found in mucinous borderline ovarian tumors and foci of anaplastic carcinoma and sarcomatous nodules found in mucinous carcinoma. Reactive nodules are usually characterized by hemorrhagic, while neoplastic nodules give an idea of solid consistency and are white in color but the two often overlap.<sup>13,15,16</sup>

Sarcoma-like mural nodules are clinically benign, often found in middle-aged women, average 39 years, measuring 0.6-6 cm, in the form of brownish-red nodules and firmly bordered. Nodules are almost always multiple. Histologically, heterogeneous cells with atypical spindle cells and inflammatory cells, can also be found mononuclear or binuclear giant cells that are pleomorphic. Mitosis is usually relatively numerous (less than 10/10LPB) without vascular invasion.<sup>18</sup> Immunohistochemical staining usually show reactive with vimentin and weak positive cytokeratin reviews (focal). Sarcoma-like mural nodules are thought to originate from sub mesothelial mesenchymal cells that may undergo stimulation and proliferation.<sup>7,18,19</sup>

#### **Mucinous carcinoma**

Mucinous ovarian carcinoma is a malignant epithelial tumor consisting of gastrointestinal-type cells containing intracytoplasmic mucin. It occupies

3-4% of all primary ovarian carcinomas and should be excluded from carcinomas that metastasize to the ovaries.<sup>20</sup> The average age of patients is 45 years. Sufferers usually present with an enlarged and painful stomach. Most tumors are confined to the ovaries. Early-stage mucinous carcinoma provides a good prognosis. Surgery play an important role in the management of early-stage and metastatic mucinous carcinoma. Chemotherapy is usually given to patients with stage II and above.<sup>21</sup>

Macroscopically mucinous malignant tumors of ovarian have a large size, ranging from 8–40 cm, an average of 16–19 cm. Generally unilateral, solid, and cystic containing mucin. Microscopically, more than 80% of mucinous ovarian carcinomas have components of intestinal type, mucinous borderline ovarian tumors or mucinous cystadenomas or both, are thought to be a progression from benign to malignant neoplasia The remaining 20% showed a malignant picture. The diagnosis of invasive mucinous ovarian carcinoma must meet the criteria for stromal invasion, greater than 5 mm or more than 10 mm<sup>2</sup>.<sup>2</sup> Characterized by 2 different invasion patterns that can be encountered simultaneously in one tumor, namely confluent / expansile pattern and infiltrative pattern.

Confluent/expansile patterns, also called noninvasive patterns in some studies. Intraglandular are characterized by irregular, back-to-back glands or images of malignant glands with no or minimal stromal involvement with an area exceeding 10 mm<sup>2</sup> or more than 3mm in any two linear dimensions (figure 3).

Infiltrative pattern indicates a clear stromal invasion can be in the form of glands, clusters of cells or individual cells. Stromal infiltration is often accompanied by desmoplastic stromal reactions or the presence of extracellular mucin. Mitosis is numerous and abnormal mitosis is often found. Bilateral mucinous ovarian carcinoma is only reported in about 5% of cases. Bilateral tumors with a tumor diameter of less than 10 cm can be considered and thought of as metastatic and likely to originate outside the ovary.<sup>6,7,11</sup> (Figure 4).

Mural nodules such as mucinous borderline ovarian tumors can also be found with focal anaplastic carcinoma, 0.5-12 cm in size, single or multiple, sometimes consisting of necrotic and bleeding areas.<sup>18</sup> Microscopic images can provide an overview of:

1. Large rhabdoid cells with a large eosinophilic cytoplasm, eccentric nuclei and one or more prominent nucleoli.
2. Sarcomatoid spindle cell with atypical and vesicular nuclei with herringbone pattern.
3. Pleomorphic cell

Mural nodules can invade surrounding tissues to blood vessels, reacting strongly with cytokeratin. However, if the result is negative with cytokeratin, it does not rule out anaplastic carcinoma because anaplastic cells may not express cytokeratin. These lesions are almost always found in mucinous borderline tumors or mucinous carcinoma, rarely in cystadenomas. Although initially thought to have a poor prognosis, recent data indicate that these nodules when found in stage I mucinous cystic tumors without rupture may provide a favorable prognosis.<sup>11</sup>

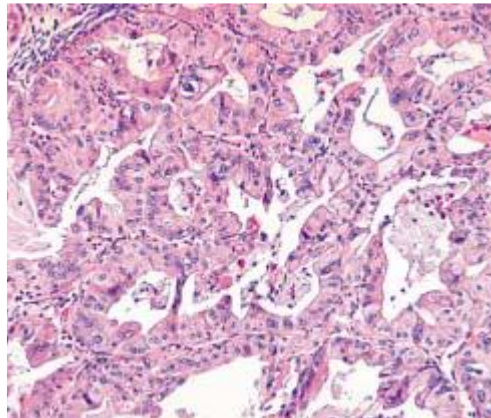
Mural nodules with malignant images are found in women of old age, indecisively bordered, larger than mural nodules with benign images or commonly called sarcoma-like mural nodules, yellow, pink or red with areas of necrosis.

Microscopic, these lesions show uniform sarcomatous cells, may consist of fibrosarcoma or rhabdomyosarcoma or undifferentiated sarcoma. Vascular invasion can be found and has a poor prognosis. In one tumor, mural nodules can be found in various types with mixed morphological features.<sup>11,15,18</sup>

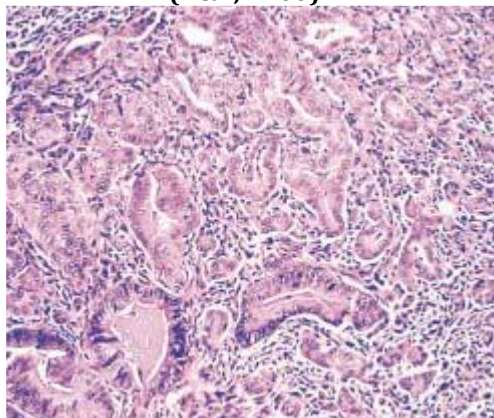
Invasive mucinous carcinoma with a confluent/expansile pattern has a better prognosis than the infiltrative pattern, with a survival rate of 90% in the confluent pattern and less than 50% in the infiltrative pattern.<sup>6,15,22</sup> Most mucinous carcinomas are limited to one ovary (stage 1) and have a good prognosis with 5-year survival of 98% and 35% in stages II-IV.<sup>14</sup>

### 3. Conclusion

The classification of mucinous ovarian tumors includes benign mucinous tumors divided into mucinous cystadenomas and mucinous adenofibromas, mucinous borderline tumors and mucinous carcinomas. In mucinous borderline tumors there is a heterogeneity of histological features that can make it difficult to establish a diagnosis such as intraepithelial carcinoma, microinvasions and mural nodules. Mural nodules, although rare to be found in benign tumors of mucinous to mucinous carcinoma, are histologically divided into benign and malignant lesions.



**Figure 3. Expansile/confluent type invasion. (H&E, ×100).<sup>15</sup>**



**Figure 4. Mucinous carcinoma with invasion of infiltrative type (H&E, ×100).<sup>7</sup>**

Types of mural nodules include reactive sarcoma-like mural nodules that are often found in mucinous borderline ovarian tumors and foci of anaplastic carcinoma and sarcomatous nodules found in mucinous ovary carcinoma. The presence bilateral tumor in both ovaries can be thought of as metastatic lesions from elsewhere. Mucinous carcinoma is characterized by 2 different invasion patterns that can be found together in one tumor, namely confluent / expansive patterns and infiltrative patterns. Invasive mucinous carcinoma with a confluent/expansive pattern has a better prognosis than with an infiltrative pattern. Most mucinous carcinomas are limited to one ovary (stage 1) and have a good prognosis with 5-year survival of 98% and 35% in stages II-IV.

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