

Borderline Ovarian Tumors: Diverse Contemporary Viewpoints on Terminology and Diagnostic Criteria With Illustrative Images

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The National Cancer Institute sponsored a Borderline Ovarian Tumor Workshop held in August 2003 in Bethesda, MD. This report was developed from discussions at the Workshop. The participants acknowledged several areas of disagreement on basic terminology issues and agreed that a glossary with example images would help clarify many commonly misunderstood issues. This report defines terminology used in the pathological description of borderline tumors and their variants, and illustrates examples of each of the most common entities. It also addresses controversial aspects of the definitions and issues involving specimen handling and reporting. For those issues where there is disagreement, the terminology and diagnostic approaches reflecting the differing views are presented.

Words have subtle power. Phrases that we intend as descriptions betray our notions of cause and ultimate meaning.

Stephen Jay Gould¹

The definitions and descriptions that constitute this report were developed in follow-up of the Borderline Ovarian Tumor (BOT) Workshop held on August

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This report contains statements that include a variety of suggestions and recommendations. In view of the wide range of opinions regarding the tumors under discussion, none of these statements is intended as, or should be interpreted as, representing the "standard of care."

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Key words: ovary, ovarian neoplasms, serous borderline tumor, atypical proliferative serous tumor, mucinous borderline tumor, atypical proliferative mucinous tumor, pseudomyxoma peritonei.

Abbreviations: APMT, atypical proliferative mucinous tumor; APST, atypical proliferative serous tumor; BOT, borderline ovarian tumor; E-BOT, endometrioid BOT; FIGO, International Federation of Gynecology and Obstetrics; M-BOT, mucinous borderline ovarian tumor; MPSC, micropapillary serous carcinoma; NMPSC, noninvasive micropapillary serous carcinoma; PMP, pseudomyxoma peritonei; S-BOT, serous borderline ovarian tumor; SM-BOT, seromucinous borderline ovarian tumor; WHO, World Health Organization.

27 and 28 in Bethesda, MD. Areas of controversy and disagreement described in this publication derive from discussions that took place at the conference, as well as from oral and electronic communications after the conference. All participants were given the opportunity to have their views included and to review the final manuscript. All participants have approved this report, indicating that they acknowledge that the report fairly characterizes the range of opinions on the subjects covered.

Two sets of illustrations accompany this report. Those printed in this issue show the most common appearances of the entities discussed. A more extensive set of web-based images can be found at the following URL:

<http://borderlineovariantumors.pathology.uic.edu>.

SEROUS TUMORS

Serous cystadenoma, serous cystadenofibroma

Definition:

A serous tumor lacking significant epithelial atypia or epithelial proliferation.² Foci resembling a serous BOT (S-BOT) may be present. Available data are insufficient to define a quantitative threshold for distinguishing a cystadenoma with insignificant focal proliferation from the earliest examples of an S-BOT, and there was no general agreement on the cutoff point. In practice, most participants consider that tumors in which foci of S-BOT compose <10% of the tumor should be classified as serous cystadenoma, and believe

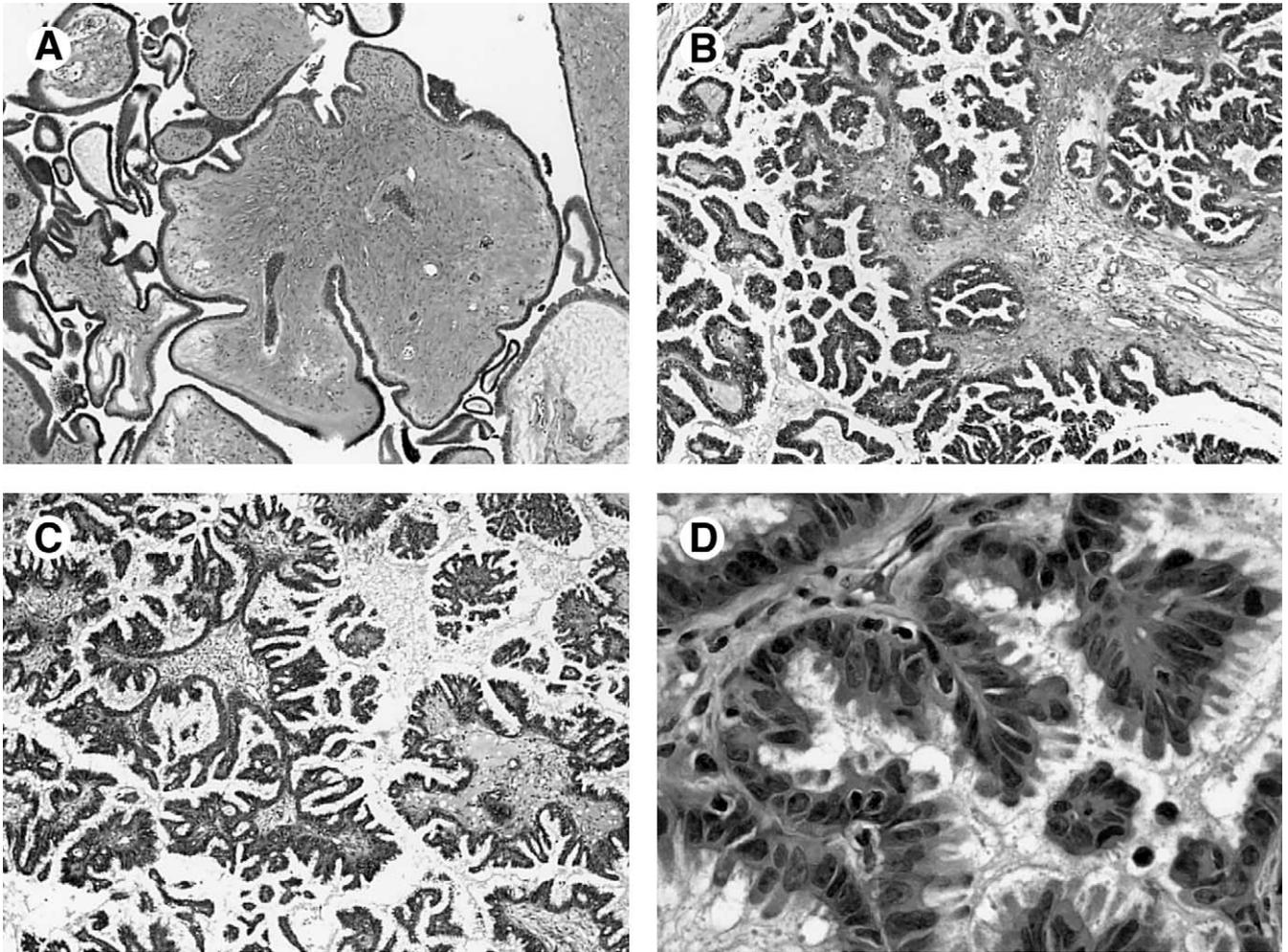


FIGURE 1. S-BOT/APST. This tumor is composed of large and small papillae with a range of epithelial stratification and tufting, from minimal (A) to more extensive (B and C). Hierarchical branching is best seen in (B). Glands containing papillae embedded in stroma and tangentially sectioned papillae in (B) are characteristic. (D) High magnification shows the low-grade cytological features.

that the term S-BOT, if used at all, should not appear in the diagnostic line, but rather should be confined to a comment with the size of the focus. Some participants prefer to append the phrase “with focal atypia” or “with focal proliferation” to “serous cystadenoma” in the diagnostic line in such cases. The 10% cutoff assumes careful gross examination and adequate directed sampling of the tumor.

S-BOT; atypical proliferative serous tumor (APST); serous tumor of low malignant potential

Note: The majority of Workshop participants preferred S-BOT over the other terms. There was no agreed-on preference for nonserous tumors. For consistency, in the remainder of this report the order of these terms is arbitrarily listed in the analogous order for the serous tumors.

Definition:

These tumors occupy a unique morphological zone between serous cystadenomas and serous carcinomas. They are distinguished from cystadenomas by obvious epithelial proliferation and tufting. As noted earlier, in practice most participants consider involvement of at least 10% of the tumor sufficient to warrant the designation S-BOT. S-BOTs are separated from carcinomas by the absence of ovarian stromal invasion that exceeds the amount designated as “microinvasion” (see below).

Description:

Low-power examination generally reveals an intracystic, complicated papillary proliferation with hierarchical branching (Fig 1A, B, and C), although in up to 30% of cases, the tumor may be exophytic or comprise

a mixture of intracystic and exophytic components. "Hierarchical" refers to the presence of large-caliber papillae that branch successively into smaller-sized papillae. Calcifications are often present. The cells lining the papillae are tufted and stratified, and frequently single cells or clusters of cells appear detached (Fig 1B, C, and D). The complex arrangements of papillae, especially when tangentially sectioned, may create the impression of glands containing papillae embedded in stroma (Fig 1B). These noninvasive elements maintain a characteristic distribution and are not surrounded by an edematous or desmoplastic stromal response (Fig 1B). Stromal invasion exceeding "microinvasion" (see below) is not permitted in S-BOTs.

The constituent cells are cuboidal and columnar, have eosinophilic cytoplasm, and may contain cilia (Fig 1D). A limited spectrum of cytological features is typical, with some cells resembling those of serous cystadenoma and others having features intermediate between those of cystadenoma and low-grade serous carcinoma. The nuclei are round to oval with smooth contours. Some tumors contain cells with grooved or creased nuclei. The chromatin may be dark-staining, but when more open, small nucleoli may be evident (Fig 1D). Macronucleoli are not seen. Mitotic figures are sparse. Morphologically noninvasive tumors with the typical architecture of S-BOT but with severe (grade 3) nuclear atypia are uncommon, and their classification is unclear² (see Appendix A).

Some participants³⁻⁶ object to the use of the term APST because they feel that this term (a) does not convey the potential for tumor recurrence; (b) may cause confusion in international communication which is essential for comparison of treatment results and performance of epidemiological and other research studies; (c) is not accepted by international organizations (ie, World Health Organization [WHO], International Federation of Gynecology and Obstetrics [FIGO]); (d) might disrupt FIGO staging; (e) would interfere with reporting to cancer registries; (f) may cause these patients to be lost to follow-up; and (g) would discourage complete surgical staging. In addition, these participants noted that the large number of nontumor deaths reported (see below) occurred in patients treated in the 1970s and 1980s with Alkeran (a highly toxic agent no longer used for ovarian cancer) for 24 or 36 months, and that the studies cited by proponents of the APST terminology did not have sufficiently long follow-up from which to draw conclusions about tumor behavior.

Some participants object to the use of the terms S-BOT and "serous tumor of low malignant potential"^{4,7-9} for the following reasons:

1. These terms imply a type of "cancer," leading many patients with these tumors (82% in one report¹⁰) to believe they have cancer.
2. Published data based on many retrospective studies and 6 prospective studies demonstrate a 99.5% survival rate for stage I tumors and a 98% to 100% survival rate for advanced-stage tumors

with noninvasive implants^{7,11}. Tumors with invasive implants are considered separately, because survival after a mean of 7.4 years is 66%, which suggests that they are low-grade carcinomas.¹¹

3. Studies that have reported recurrences usually have not provided pathologic documentation.
4. Deaths are more often due to a complication of therapy than due to tumor.¹²
5. The extent of histological sampling, and thus the likelihood that occult invasion was not sampled in cases that appear to have behaved aggressively, is often not described.¹¹

These participants maintain that the apparent "intermediate" behavior of these tumors is an artifact of combining a large group of benign tumors (ie, S-BOT lacking invasive implants or a micropapillary architecture) with a smaller group of malignant tumors (ie, those with invasive peritoneal implants or those with a micropapillary architecture).^{4,7,8}

Micropapillary S-BOT; serous borderline tumor with micropapillary features; noninvasive micropapillary serous carcinoma (NMPSC); micropapillary serous carcinoma (MPSC)^{2,11,13-21}

Note: The majority of Workshop participants preferred the term "micropapillary S-BOT."

Definition:

An S-BOT that contains at least one area of uninterrupted micropapillary growth measuring > 5 mm in maximum dimension and lacking stromal invasion.

Description:

A nonhierarchical papillary distribution distinguishes micropapillary S-BOT from typical S-BOT. Micropapillary S-BOT is marked by large-caliber fibrovascular cores entirely surrounded by long, slender, hairlike micropapillae creating a "Medusa's head" appearance (Fig 2A, B, and C). One group has suggested that the micropapillae are five times longer than they are wide.¹⁹ Micropapillary S-BOT may also feature fibrovascular cores surrounded by cribriform epithelium or a mixture of micropapillary and cribriform architectural patterns (Fig 2C).

The cytological features of micropapillary S-BOT are similar to those of typical S-BOT, but usually with slightly more atypical nuclear features and more nucleolar prominence (Fig 2D). Areas of grade 1 nuclear atypia with a monotonous appearance often coexist with areas exhibiting grade 2 nuclear features. If severe (grade 3) nuclear atypia is present, then the classification is unclear (see Appendix A).

Stromal invasion quantitatively beyond that permitted for microinvasion is not present. Carcinomas associated with micropapillary S-BOT are uncommon, but when they occur, they typically are cytologically low-grade and demonstrate an infiltrative micropapillary and/or cribriform architecture.^{2,13-15}

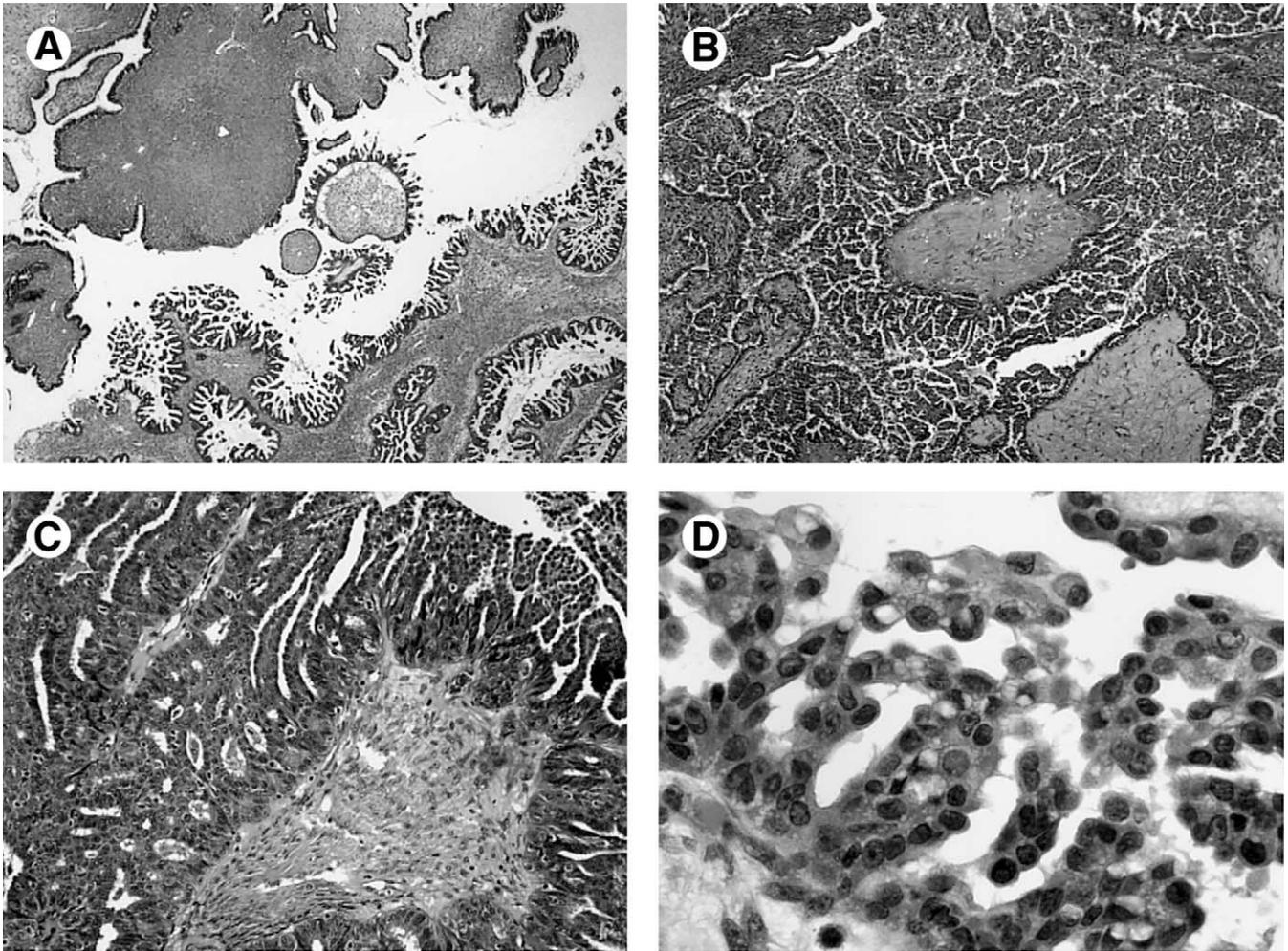


FIGURE 2. Micropapillary S-BOT. This tumor contains micropapillary growth in an area measuring greater than 5 mm in diameter and thus is classified as micropapillary S-BOT. In (A), note the contrast between an area of S-BOT at the top and micropapillary growth at the bottom. There is more extensive proliferation in (B), which shows long, slender micropapillae surrounding large fibrovascular cores without hierarchical branching. Both micropapillary and cribriform growth patterns are seen in (C). (D) High magnification illustrates a micropapillary S-BOT with cytological atypia close to the high end of the spectrum permitted for this diagnosis.

Some participants object to the terms MPSC and NMPSC, because they believe that the behavior of these tumors is more akin to that of typical S-BOTs.^{4,6,22} These participants point out that both micropapillary S-BOT (ie, MPSC/NMPSC) and typical S-BOT share the same risk factors for recurrence and that the prognosis for both lesions is equivalent when controlled for those risk factors (most notably, the presence or absence of invasive implants). These participants therefore object to the use of terms that imply malignancy, especially when invasive implants are not found.

Participants who prefer the terms MPSC and NMPSC^{4,7-9} point out that about 50% of all reported cases of advanced stage micropapillary S-BOT have been associated with invasive peritoneal implants.¹³⁻²¹ This observation suggests that the primary ovarian micropapillary tumor may be analogous to carcinoma in situ. Other participants note that these studies have been composed almost exclusively of consultation cases

and thus may reflect consultation bias and may not be representative of the general population.⁵

S-BOT with microinvasion; S-BOT with microinvasive carcinoma^{2,3,23-29}

Note: Some participants believe that the use of the term “microinvasive carcinoma” in the pathology report is not wise and can lead to possibly unnecessary staging procedures and overtreatment.

Definition:

Different size criteria have been used to define the upper limit for inclusion in this category. The most widely accepted criterion in the literature is that no single focus of invasion measures >3 mm in greatest linear dimension (many participants prefer 5 mm). A maximum area of 10 mm² for each focus has also been used.^{3,24,25,29} Multiple foci of invasion are permitted.

There are insufficient outcome data to support or refute any of these recommendations.

Description^{3,2,24,25,29}:

S-BOT with microinvasion and S-BOT with microinvasive carcinoma share the aforementioned size criteria. Some participants use the 2 terms interchangeably. Others use the terms for 2 different morphological patterns, as follows:

- S-BOT with microinvasion is believed by some participants to be characterized by single cells or small clusters of epithelial cells with eosinophilic cytoplasm budding off the base of the epithelium into the stromal cores of the papillae (Fig 3A). This is the most common appearance.
- S-BOT with microinvasive carcinoma is believed by some participants to be characterized by 1 or more foci architecturally resembling invasive low-

grade serous carcinoma appearing to arise within an S-BOT (Fig 3B). Typical patterns include nests and/or glands with a cribriform pattern and rounded aggregates of papillae. This type of invasion is relatively uncommon.

EXTRAOVARIAN LESIONS ASSOCIATED WITH SEROUS TUMORS

Peritoneal endosalpingiosis (benign müllerian inclusions)

Definition:

A common peritoneal lesion generally composed of a single gland or aggregates of glands lined by innocuous-appearing flattened, cuboidal, or columnar serous cells that are frequently ciliated.

Description:

Minor degrees of atypia, epithelial tufting, and blunt papillae may occur in endosalpingiosis. Greater degrees of proliferation are more characteristic of the noninvasive epithelial implants often associated with S-BOT.

Noninvasive peritoneal implant^{2,3,11,13-17,30-37}

Definition:

A serous-type epithelial proliferation that involves peritoneal surfaces and lacks invasion.

Description:

Two types of noninvasive peritoneal implants have been designated: “epithelial” and “desmoplastic.” The noninvasive epithelial implant is characterized by a papillary proliferation of serous epithelium that lines or appears “tacked on” to the peritoneal surface and does not demonstrate invasion of underlying tissue (Fig 4A). It is often found in smoothly contoured mesothelial-lined invaginations beneath the peritoneal surface. There is minimal to mild cytological atypia and no mitotic activity (Fig 4B). Psammomatous calcification is commonly present. The lesion often resembles the associated ovarian tumor.

The noninvasive desmoplastic implant is dominated by a granulation tissue-type fibroblastic proliferation that appears as a plaque on the peritoneal surface and contains small papillae, glands, or single cells (Fig 5A). Glands or gland-like structures are scattered, but are much less conspicuous than the fibroblastic component (Fig 5B, C, and D). Some investigators believe that the glandlike elements often resemble a reactive mesothelial proliferation. This type of implant often has a pseudoinvasive pattern that may lead pathologists unfamiliar with this entity to diagnose invasive carcinoma. When studying the lesion at low magnification, it is easy to draw a line between the implant and the adjacent tissue. Acute and/or chronic inflammation is common. Cytological atypia is usually mild (Fig 5D) but may be moderate and is very rarely marked. Mitotic

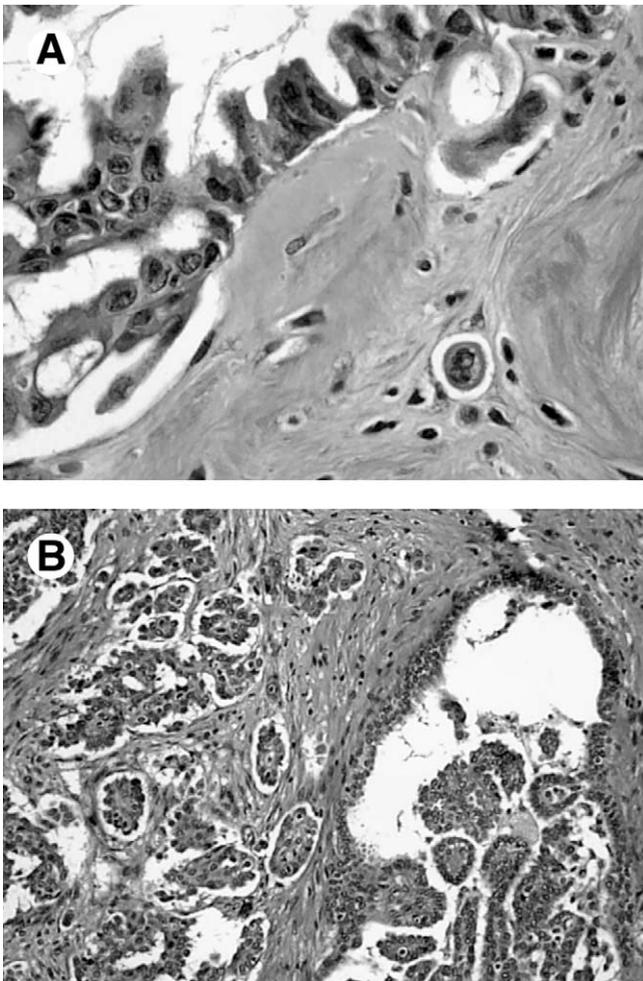


FIGURE 3. S-BOT with microinvasion/microinvasive carcinoma. (A) The most commonly encountered type is isolated cells or small groups of cells in stroma, with surrounding retraction spaces. This is referred to as S-BOT with microinvasion. (B) Some investigators also classify proliferations resembling low-grade serous carcinoma as S-BOT with microinvasion, but others use the term “S-BOT with microinvasive carcinoma.”

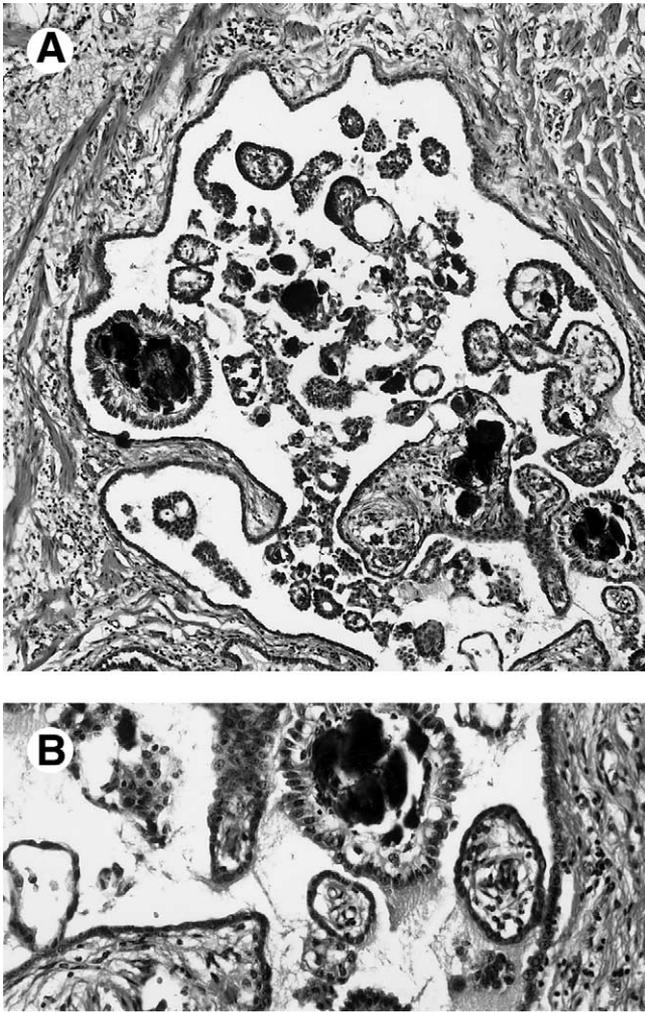


FIGURE 4. Noninvasive epithelial implant. (A) Low magnification shows papillary structures of differing caliber with prominent psammomatous calcification on the surface of an infolding of peritoneum. There is no invasion of underlying subperitoneal tissue. (B) Higher magnification shows relatively minimal cytological atypia.

activity is usually absent. The appearance of isolated single cells in the stroma, usually with abundant eosinophilic cytoplasm, has been interpreted as a form of invasion by a few investigators (even though it is not associated with a high recurrence rate), but most consider this a feature of the noninvasive desmoplastic implant. Of note, the term “desmoplastic” itself may be confusing, because in nearly all other settings it refers to a stromal response to invasive carcinoma. In addition, some of the stromal cells may be keratin-positive submesothelial cells (ie, multipotential subserosal cells) rather than myofibroblasts.³⁸ For these reasons, a few participants recommend avoiding the term “desmoplastic” and simply using “noninvasive implant.” However, some participants believe that the use of the term “implant” is misleading, because available data are insufficient to prove whether these peritoneal lesions actually originate from the ovarian tumor or arise in situ from the peritoneum.

Invasive peritoneal implant; invasive serous carcinoma^{2,3,11,13-17,30-37}

Definition:

A serous type of epithelial proliferation involving the peritoneum that displays invasion of adjacent or underlying tissue and usually closely resembles serous carcinoma, usually low-grade serous carcinoma.

Description:

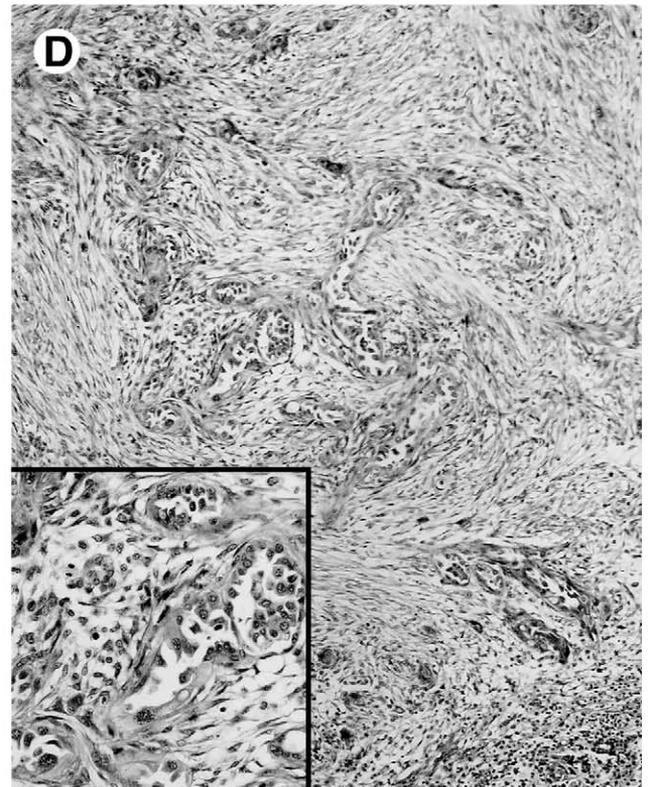
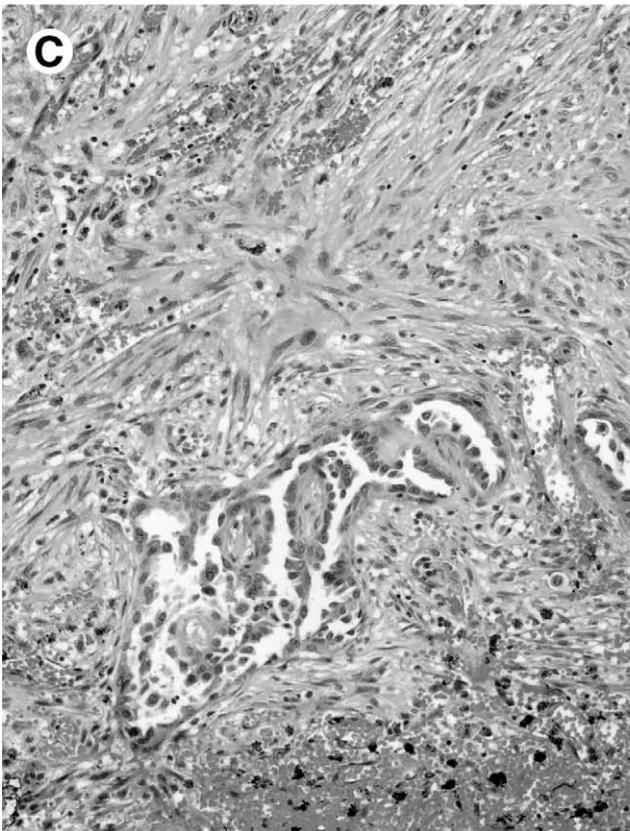
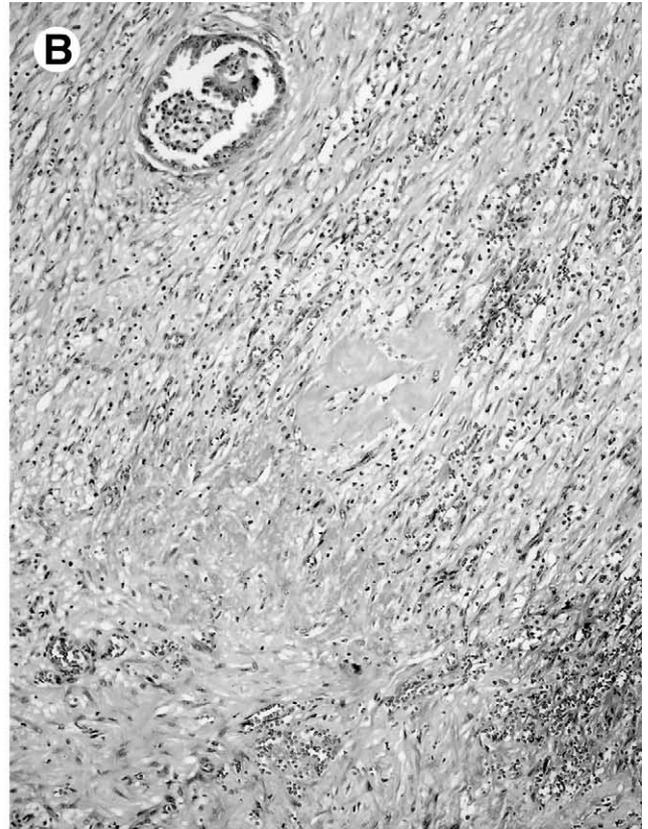
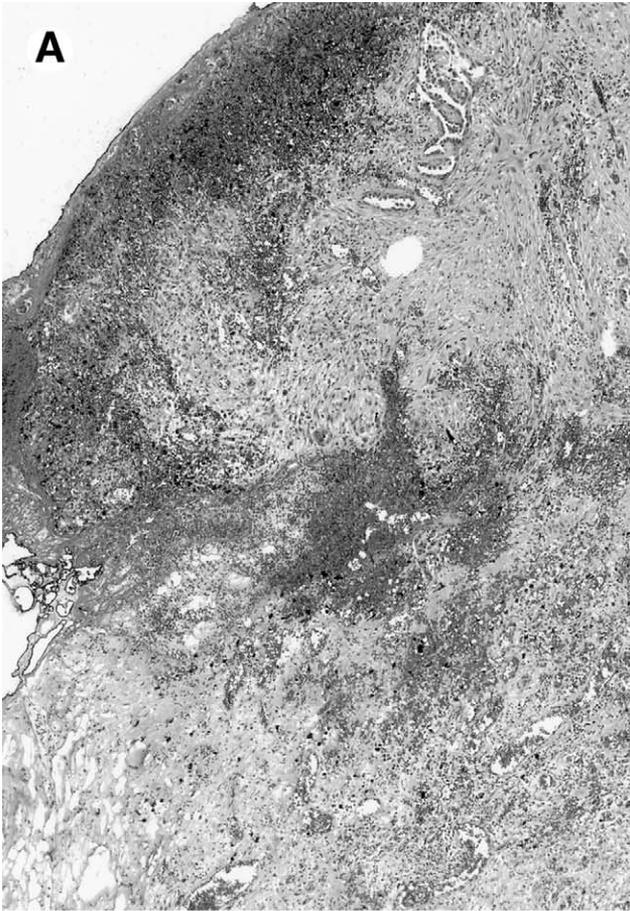
These lesions usually exhibit a haphazard infiltrative growth pattern characteristic of invasive carcinoma in virtually all other body sites (Fig 6). The invasion typically involves the peritoneum, subperitoneal tissue, and omentum and may also involve visceral structures, such as the bowel. Destruction of the normal architecture of the invaded tissue can usually be identified if the sample includes sufficient underlying tissue. Infiltrative glands, solid nests, and/or papillary structures are present (Fig 6A and B). Cytological atypia is usually mild or moderate; occasionally, severe cytological atypia resembling high-grade serous carcinoma is seen (Fig 6C). A few investigators also consider the presence of a micropapillary architecture and small solid nests of cells surrounded by a space or cleft evidence of invasion,³⁷ but most do not.

Distinguishing an invasive implant from a noninvasive implant is sometimes very difficult. The reproducibility of this distinction has not been formally tested. The most reliable feature that distinguishes the 2 entities is the presence or absence of invasion. Most investigators require invasion of underlying tissue to be present to diagnose an invasive implant, whereas others believe that underlying tissue invasion is not always needed to make the diagnosis of an implant associated with a poor outcome. These participants maintain that implants lacking unequivocal invasion but displaying a micropapillary architecture or small solid nests of cells surrounded by a space or cleft merit a diagnosis of invasive implant/invasive serous carcinoma, because they are associated with a poor outcome.³⁷ Accordingly, these investigators prefer designating these lesions, as well as those showing unequivocal invasion, as “low-grade serous carcinoma” rather than as “invasive implant,” acknowledging their morphology and their poor prognosis. This overcomes the oxymoron of classifying lesions that resemble carcinoma and are associated with a poor outcome as “S-BOT with invasive implants,” even if clear-cut invasion is not present.

S-BOT associated with serous epithelium in lymph nodes (lymph node involvement)^{2,11,26,28,39,40}

Definition:

Lymph node(s), usually from the pelvic or periaortic regions, containing a serous epithelial proliferation closely resembling the ovarian S-BOT. (Note: Because of these lesions’ uncertain origin, the use of the term “metastatic” is not recommended.)



Description:

These lesions often occupy subcapsular sinuses and have 2 patterns. One pattern is characterized by papillae that form rounded or nodular lesions and are frequently associated with endosalpingiosis (benign müllerian inclusion glands/cysts) (Fig 7A). Histological features of tissue invasion are not present. The other pattern is characterized by single cells and small clusters of rounded cells with eosinophilic cytoplasm in the nodal sinuses, similar to the cells seen with the more common type of microinvasion (see above). Some investigators believe that in some cases these are “deported” benign mesothelial cells and in other cases they may reflect “deported” epithelial cells from the surface of the ovarian neoplasm. Of note, mesothelial cells may occasionally be present in large amounts in lymph nodes of patients with S-BOT (Fig 7B).⁴¹

S-BOT involving lymph nodes must be distinguished from other lesions. Endosalpingiosis is by far the most common problem and is generally identical to its counterpart in the peritoneum (see above). These lesions can be found in the lymph node capsule, interfollicular zone, or perinodal soft tissue but are not present in the subcapsular sinuses (Fig 7A). A diagnosis of carcinoma should be considered when one encounters more than moderate cytological atypia, tumorous replacement of the nodal parenchyma, or an edematous or fibroblastic stromal response.

It is unknown whether these lesions are clonally related to the associated ovarian neoplasm (akin to a metastasis) or are independent. Some participants believe that because they do not adversely affect the prognosis (ie, the prognosis is excellent), and have not been proven to be clonally related to the ovarian tumor, they should not be considered “metastatic.”¹¹

Mucinous cystadenoma**Definition:**

A mucinous tumor composed of gastrointestinal-type epithelium lacking significant cytological atypia or epithelial proliferation.^{2,3} Foci resembling mucinous BOT (M-BOT) may be present. Although there was no agreement on the cutoff, in practice most participants allow this component to compose <10% of the tumor. In this latter situation, the diagnosis should be mucinous cystadenoma, and the M-BOT designation, if used at all, should be confined to a comment with the size of the focus and omitted from the diagnostic line. The phrase “with focal atypia” or “with focal proliferation” may also be appended to “mucinous cystadenoma” in such cases. Of note, as with the serous tumors, there are no published data on which to evaluate the 10% criterion.

M-BOT, gastrointestinal type; atypical proliferative mucinous tumor (APMT), gastrointestinal type; mucinous tumor of low malignant potential, gastrointestinal type^{2,3,42-46}

Definition:

These are mucinous tumors composed of gastrointestinal-type mucinous epithelium with atypical architectural and cytological features more marked than those seen in cystadenoma. In practice, most participants diagnose M-BOT when this component occupies at least 10% of the tumor. Stromal invasion is absent or, if present, does not exceed the amount that qualifies for microinvasion.

Description:

M-BOTs are characterized by glands and cysts of varying sizes and shapes separated by variable amounts of ovarian-type stroma in which the epithelial structures may be markedly crowded. The epithelium in some areas is single-layered, resembling mucinous cystadenoma. Areas of complex proliferation are marked by admixtures of bridging, stratification, and elongated simple or complex villous-like projections containing coarse or fine fibrovascular cores (Fig 8). The epithelium contains goblet cells, and the remaining epithelium resembles gastric foveolar epithelium. Cells with neuroendocrine granules may be present. There is a spectrum of nuclear atypia and mitotic activity that varies greatly among tumors and even in different areas of the same tumor (Fig 8). No well-documented cases with peritoneal implants have been reported. Localized collections of peritoneal mucin with or without rare epithelial cells may be seen when M-BOTs rupture. This condition should not be considered peritoneal implantation or pseudomyxoma peritonei (PMP) (see below).

Some participants object to the terms M-BOT and “mucinous tumor of low malignant potential,” because they imply a type of “cancer.”^{2,7,8} The vast majority (about 85%) of women with M-BOTs that appear to be in advanced stage have the syndrome of PMP, which is now known to be of gastrointestinal origin.^{2,45} Published data fail to corroborate malignant behavior in the remaining patients inasmuch as the survival rate is virtually 100% after excluding patients with PMP and with other metastatic carcinomas to the ovary, typically from the pancreas, biliary tract, or cervix, that can mimic an M-BOT.^{7,8}

Some participants object to the use of the term APMT, because it may create confusion in international communication, which is essential for comparison of treatment results and performance of epidemiologic and other research studies. The term APMT also does not communicate the potential for recurrence, might lead to patients being lost to follow-up, is not accepted by international organizations (WHO, FIGO), may interfere with

FIGURE 5. Noninvasive desmoplastic implant. (A) Low magnification shows an appearance dominated by a fibroblastic, granulation tissue-like proliferation forming a plaque-like lesion on the peritoneal surface, which is seen at the left and top. (A, B, C, and D) Scattered glands/gland-like structures are present and do not display an infiltrative pattern. The stroma is loose and has a sparse inflammatory infiltrate. (D, inset) Higher magnification shows mild to moderate cytological atypia and no mitotic activity. A hobnail appearance of the epithelium is apparent.

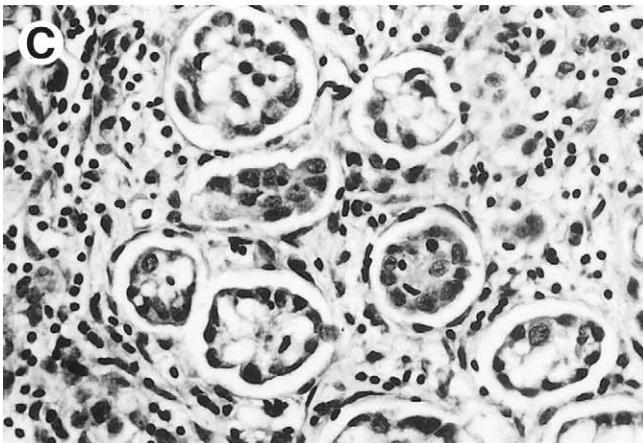
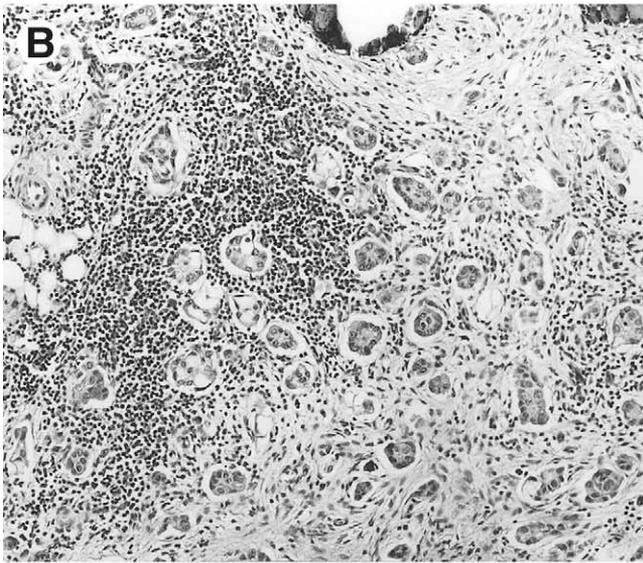
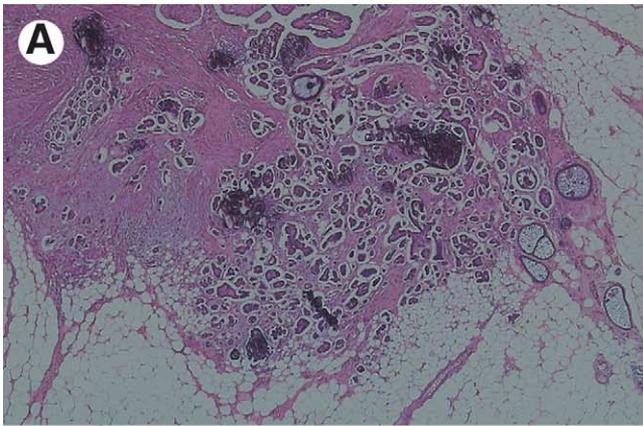


FIGURE 6. Invasive implant. (A) Low magnification and (B) intermediate magnification show a haphazard infiltrative pattern of small glands and solid nests. Many of the nests are surrounded by a space. (C) High magnification shows moderate cytological atypia. Both (B) and (C) show a prominent chronic inflammatory infiltrate. (Figure 6A courtesy of Dr. Jaime Prat.)

FIGO staging and with cancer registry reporting, and would discourage complete staging. In addition, some believe that the term M-BOT should be retained because of the heterogeneity of mucinous tumors and the difficulty of ruling out carcinoma, and that on rare occasions, some M-BOTs in cases with a negative appendix may be responsible for PMP (see below).

*Seromucinous BOT (SM-BOT); atypical proliferative seromucinous tumor; müllerian mucinous borderline tumor; atypical proliferative müllerian mucinous tumor; mucinous borderline tumor, endocervical-like type; atypical proliferative mucinous tumor, endocervical-like type; mixed epithelial borderline tumor; mixed epithelial type atypical proliferative tumor.*⁴⁶⁻⁴⁹

Definition:

A neoplasm characterized by complex epithelial proliferation without stromal invasion, architecturally

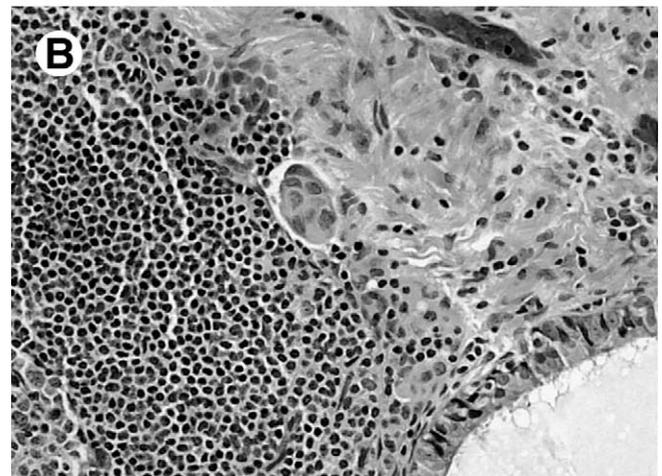


FIGURE 7. S-BOT with lymph node involvement. (A) S-BOT (upper right) is contrasted with endosalpingiosis (lower left). (B) Mesothelial cells in subcapsular sinuses can cause diagnostic confusion with S-BOT and metastatic carcinoma. Endosalpingiosis is also present.

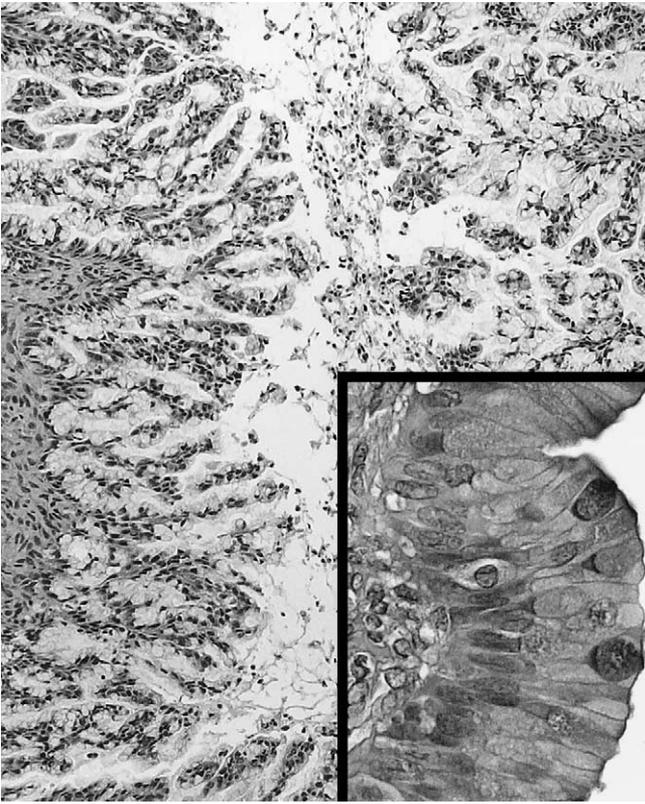


FIGURE 8. M-BOT, gastrointestinal type. Intermediate magnification shows a cystic tumor with stratified epithelium. (Inset) High magnification shows a cyst lined by columnar cells with mucinous cytoplasm and low nuclear-to-cytoplasmic ratio. The nuclei are round to oval, basally situated, and demonstrate only mild atypia. Goblet cells are also present.

resembling S-BOT, composed of endocervical-type mucin-containing cells. Many examples contain an admixture of cell types, including not only endocervical-type cells, but also serous, endometrioid, squamous, and indifferent (uncommitted) cells. It is unclear whether these are variants of the same tumor or represent related but different entities. Some participants prefer to classify these tumors as a variant of serous tumor, because the architecture, association with implants, and morphology of the implants more closely resemble those of S-BOT.

Description:

Low-power examination reveals an architecture similar to that of S-BOT with a complicated, hierarchical papillary growth with epithelial stratification and tufting (Fig 9A). The nuclear features are grade 1 or 2, and mitotic figures are sparse (Fig 9B). The cytoplasmic characteristics differ from those of S-BOT, however. Endocervical-type mucinous cells are columnar and contain apical cytoplasmic mucin that ranges from eosinophilic to amphophilic to lightly basophilic (Fig 9B). Serous or endometrioid differentiation, if present, re-

sembles that seen in their pure counterparts. Endometrioid cells may also have secretory features or squamous metaplasia. Indifferent or uncommitted cells are cuboidal, with eosinophilic cytoplasm (Fig 9B). Gastrointestinal differentiation (the presence of goblet cells, Paneth cells, or argyrophil cells) is not observed. Neutrophils tend to be numerous (Fig 9A).

Like S-BOTs, SM-BOTs may be associated with peritoneal endosalpingiosis. More specifically, and in contrast with S-BOTs, the incidence of associated endometriosis is quite high (approximately 40%^{48,49}). Also like S-BOTs, SM-BOTs can demonstrate micropapillary architecture, microinvasion, lymph node involvement, and destructive stromal invasion (in which case they are considered carcinomas or SM-BOTs with microinvasion).⁴⁷ The available data on SM-BOTs, especially those demonstrating microinvasion, are limited. Thus far, none have behaved in a malignant fashion.

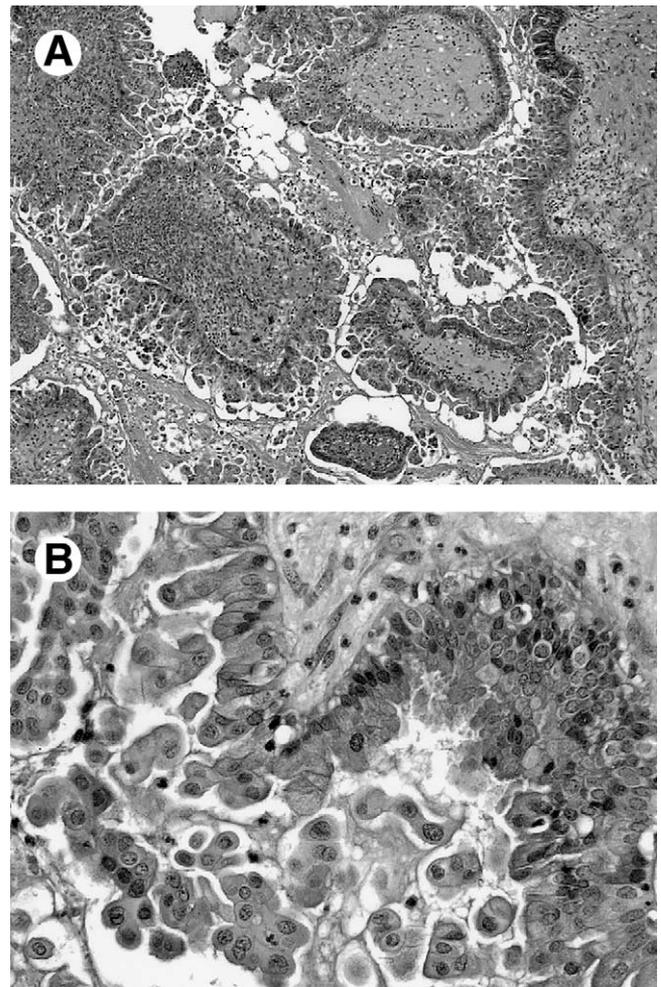


FIGURE 9. SM-BOT. (A) The low-power appearance resembles that of S-BOT. A few clusters of neutrophils are seen. (B) High-power examination reveals columnar cells with apical mucin, endocervical-type cells, and cuboidal cells with dense cytoplasm.

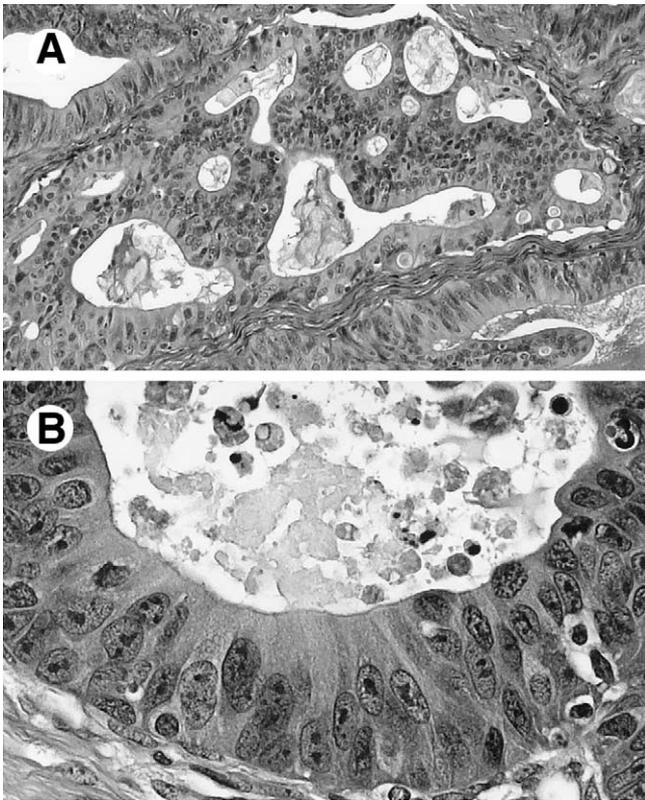


FIGURE 10. M-BOT with intraepithelial carcinoma. (A) This intraepithelial carcinoma at intermediate magnification is characterized by a cribriform architecture. (B) Intraepithelial carcinoma at high magnification shows columnar cells with cytologically malignant features. There is an increased nuclear-to-cytoplasmic ratio and the nuclei are enlarged, round to oval, show variation in size and shape, and contain prominent nucleoli and irregularly distributed chromatin.

M-BOT with intraepithelial carcinoma; M-BOT with carcinoma in-situ; M-BOT with noninvasive (intraglandular) mucinous carcinoma^{2,3,42-45,47}

Definition:

M-BOT with areas exhibiting the cytological features of carcinoma but not demonstrating stromal invasion (ie, carcinoma in situ). (A few participants object to the use of the term “carcinoma in situ” because the cells are not replacing preexisting normal ovarian surface epithelium.)

Description:

These tumors usually arise in a background of mucinous cystadenoma and M-BOT. The criteria for this diagnosis have varied. Common to nearly all of the proposed definitions is the presence of cytologically malignant features coupled with the absence of stromal invasion, and thus this is the recommended approach (Fig 10).

Some investigators have suggested an amount of complex proliferation as the upper limit allowable for intraepithelial carcinoma. Accordingly, labyrinthine architecture with cytologically malignant epithelium with

minimal or no intervening stroma that measures greater than the amount that qualifies for microinvasion (see below) qualifies as the confluent glandular or expansile pattern of invasive mucinous carcinoma.

M-BOT with microinvasion; microinvasive M-BOT; microinvasive mucinous carcinoma^{2,3,23,29,42-47}

Definition:

M-BOT with one or more foci of stromal invasion. Both 3 and 5 mm have been used as upper limits for each microinvasive focus; 10 mm² has also been used as a maximum area for each focus. Invasion beyond these limits warrants a diagnosis of invasive mucinous carcinoma. As with the corresponding serous tumors, some investigators separate microinvasive mucinous carcinoma from M-BOT with microinvasion, and others use the terms synonymously. In one report,⁴⁴ “mucinous borderline tumor with microinvasion” is used for those tumors lacking intraepithelial carcinoma, and “mucinous borderline tumor with microinvasive carcinoma” is used for those containing intraepithelial carcinoma. As noted earlier for the analogous serous tumors, some participants believe that the use of the term “microin-

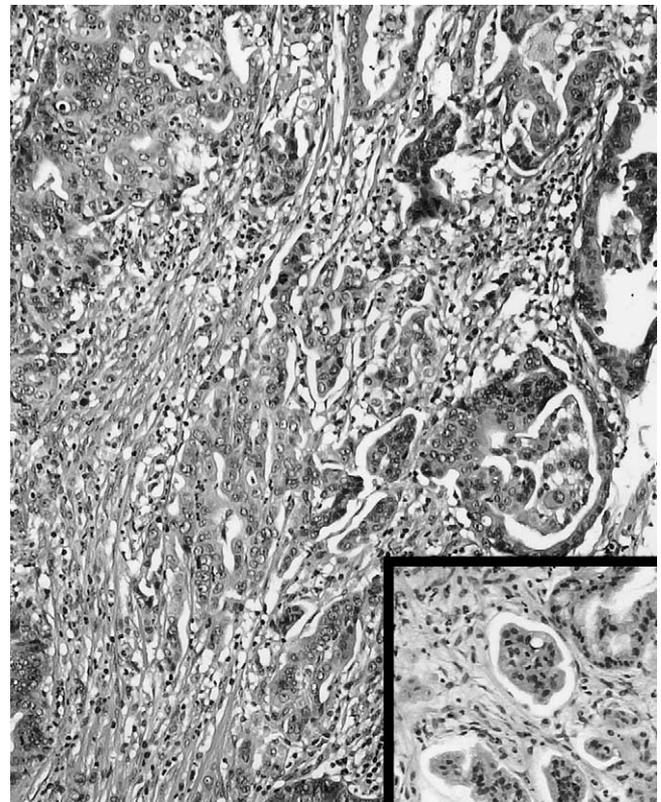


FIGURE 11. M-BOT, gastrointestinal type, with microinvasion. The microinvasive area illustrated here shows a focus of irregular nests that are haphazardly arranged within stroma and associated with a stromal reaction. This type of microinvasion is also referred to by some participants as “microinvasive carcinoma.” (Inset) Some of the nests are surrounded by a clear space. Other areas of the tumor exhibited classic features of M-BOT, gastrointestinal type (not shown).

vative carcinoma” in the pathology report is not wise and can lead to possibly unnecessary staging procedures and overtreatment.

Description:

One or more foci of invasion arise in a background of M-BOT and are either isolated in the stroma or bud off of the adjacent glands or cysts (Fig 11). The invasive foci have irregular glands, nests, or individual cells often surrounded by a clear space. They may show haphazardly infiltrative arrangements (Fig 11). Alternatively, they may appear as a confluent glandular pattern. The invasive cells may have abundant, dense eosinophilic cytoplasm, and their nuclei can have the same degree of atypia present in the background M-BOT or show more marked atypia. The stroma may show an altered response. Dissection of acellular mucin in the stroma (pseudomyxoma ovarii) does not constitute invasion, but if extensive should raise the possibility of an extraovarian primary tumor. (See the discussion of PMP below and the article by Ronnett et al elsewhere in this issue.) Some of those who separate microinvasive mucinous carcinoma from M-BOT with microinvasion consider the eosinophilic cells budding into the stroma as M-BOT with microinvasion and the other invasive patterns more characteristic of overt carcinomas as microinvasive mucinous carcinoma.

PMP and associated ovarian tumors; disseminated peritoneal adenomucinosis; peritoneal mucinous carcinomatosis; superficial organizing mucin; dissecting mucin with fibrosis; ovarian involvement by low-grade appendiceal mucinous neoplasm^{2,3,43,50-53}

Note: These are not synonymous terms; see the article by Ronnett et al elsewhere in this issue.

Definition:

PMP is a descriptive term that refers to the operative findings of mucinous ascites and/or mucoid nodules attached to peritoneal surfaces, usually associated with mucinous tumors in the ovary and appendix and occasionally other sites. Most participants believe that PMP should be used only as a clinical descriptor, not as a pathological diagnosis. These tumors are nearly always extraovarian in origin and should not be classified as primary ovarian tumors.

Description:

Superficial organizing mucin occurs on the surfaces of the peritoneum or ovaries and is composed of adherent mucin containing capillaries, fibroblasts, and mesothelial and inflammatory cells. Dissecting mucin with fibrosis (which in the ovary is designated “pseudomyxoma ovarii”) consists of pools of mucin surrounded by dense collagenous tissue. These 2 conditions typically display low cellularity in the mucin pools as strips of architecturally and cytologically low-grade mucinous epithelium, and can also be referred to

as “disseminated peritoneal adenomucinosis.” Most participants recommend reporting whether or not epithelium is present and, if so, whether it is benign or atypical. This condition is virtually always derived from a ruptured or dissecting low-grade mucinous neoplasm of the appendix, and thus the ovarian tumors can also be referred to descriptively as “ovarian involvement by low-grade appendiceal mucinous neoplasm.”

Metastatic mucinous carcinoma/peritoneal mucinous carcinomatosis is characterized by malignant mucinous epithelium, usually in the form of glands and/or signet ring cells and associated with pools of extracellular mucin. This is nearly always a metastatic neoplasm from a mucinous carcinoma of the appendix or intestines.

Endometrioid BOT (E-BOT), clear cell, and Brenner (transitional cell) tumors

Definition:

A tumor composed of endometrioid-type epithelium that displays a degree of proliferation, atypia, or both beyond that seen in an endometrioid adenofibroma.

Description:

The 2 histological patterns of this tumor are (1) an adenofibromatous architecture with markedly crowded glands, with architectural complexity resembling that seen in complex endometrial hyperplasia, and (2) a villoglandular-type papillary proliferation resembling well-differentiated endometrioid adenocarcinoma of the villoglandular type. An origin in endometriosis is commonly seen. Squamous (morular) metaplasia may be seen. The number of reported cases of these tumors associated with peritoneal implants is exceedingly small, and thus a reliable definition of this type of implant is not available.

Some participants object to the terms “borderline” and “low malignant potential” for the endometrioid, clear cell, and transitional (Brenner) cell variants because they imply a type of “cancer.” These tumors are very rare, and there are no well-documented tumor deaths.^{7,8} Hence, in the opinion of these participants, there are insufficient data to conclude that these tumors have any malignant potential. Some participants do not feel that it is appropriate to include these 3 uncommon types of borderline tumors in this report because these types were only briefly discussed at the meeting. Other participants feel that excluding these tumors from this report would introduce a bias because of their benign behavior.

E-BOT with microinvasion

Definition:

An E-BOT with 1 or more foci of invasion, each <5 mm. Alternatively, or in addition, an invasive area of up to 10 mm² for each focus has been suggested.

Description:

Invasion in an endometrioid tumor may have an irregular infiltrative pattern of endometrioid glands or a confluent proliferation of endometrioid glands and/or villoglandular papillae resembling well-differentiated endometrioid adenocarcinoma of the endometrium.

E-BOT with intraepithelial carcinoma**Definition:**

An E-BOT displaying glands and/or papillae lined by epithelium with cytologically malignant features but lacking stromal invasion.

Clear cell borderline tumor; atypical proliferative clear cell tumor; clear cell tumor of low malignant potential^{2,3}**Definition:**

A clear cell neoplasm resembling clear cell adenofibroma but displaying significant epithelial atypia and/or epithelial proliferation beyond that usually seen in an adenofibroma and lacking invasion. In situ and microinvasive forms have not been defined, nor have cases with peritoneal implants been reported.

Description:

These tumors are extremely rare and difficult to diagnose. Some clear cell carcinomas, usually those with a predominantly tubulocystic pattern, display very minimal atypia. In addition, the patterns of stromal invasion seen in clear cell carcinomas are often subtle, particularly in small or sparsely sampled tumors.

Brenner (transitional cell) tumor of borderline malignancy; atypical proliferative Brenner (transitional cell) tumor; Brenner (transitional cell) tumor of low malignant potential^{2,3}**Definition:**

A Brenner/transitional cell neoplasm that displays cytological atypia and/or epithelial proliferation beyond that seen in a benign Brenner tumor and lacks invasion. In situ and microinvasive forms have not been clearly defined, nor have cases with peritoneal implants been reported.

Description:

These tumors usually resemble papillary transitional cell neoplasms of the urinary tract. A benign transitional cell (Brenner) component may be present. The presence or absence of a benign Brenner component determines whether the tumor is a borderline/atypical proliferative Brenner tumor or a borderline/atypical proliferative transitional cell tumor, respectively.

APPENDIX A: GENERAL DEFINITIONS**Maximum size of an invasive focus.**

The maximum linear dimension of a focus of invasion in a single section. This measurement includes the stroma between the invading cells. Sizes of separate foci of invasion should not be added together for diagnostic purposes. Of note, the maximum dimension is a surrogate measure of invasive tumor volume, which is difficult to assess histologically.

Area of an invasive focus.

The area of a focus of invasion is measured in square millimeters and including the stroma between invading epithelial elements. Areas of separate foci of invasion should not be added together for diagnostic purposes.

Diameter-area relationships.

Area of a circle with diameter of 3 mm: 7.1 mm².

Area of a circle with diameter of 5 mm: 19.6 mm².

Diameter of circle with an area of 10 mm²: 3.56 mm.

Side of a square with an area of 10 mm²: 3.16 mm.

Proportion of a tumor involved by a histological pattern.

This is determined by estimating the combined area of the component (including the stroma) on all sections as a fraction of the total tumor area on all sections. This may be modified by taking into account gross features. For example, if a 15-cm cyst demonstrates a 1-cm papillary excrescence that microscopically demonstrates classic S-BOT, and the remainder of the cyst has a smooth attenuated lining both grossly and microscopically, then the borderline focus is considered to comprise <10% of the tumor. Because it would be appropriate to oversample the excrescence compared with the smooth lining of the cyst, it would be inappropriate to estimate the percentage of borderline tumor from the total area represented on the slides.

Invasion (stromal invasion; infiltrative destructive growth; destructive infiltrative growth; invasive carcinoma).

Invasion in the setting of ovarian epithelial tumors is equated with invasive carcinoma and with "infiltrative destructive growth," the phrase used in the 1971 FIGO definition.⁵⁴ There are several different patterns of invasion, none of which is unique to the ovaries. The most widely accepted patterns of invasion in primary ovarian epithelial tumors include (1) single cells infiltrating the stroma; (2) glands, papillae, and/or solid nests displaying a haphazard infiltrative pattern; and (3) solid sheets of epithelial cells. These patterns may also be seen in peritoneal implants, except that in noninvasive desmoplastic implants, single cells are often found dispersed in the stroma and are not considered invasive by most participants. In some settings, confluence is believed to reflect invasion (see below).

Confluence (confluent epithelial proliferation).

In the context of glands lined by neoplastic cells, confluence is characterized by a back-to-back glandular proliferation, often with a cribriform pattern lacking intervening stroma, resulting in a labyrinthine pattern. Papillary and solid patterns of epithelial proliferation may also display confluence. In some settings, confluence is considered evidence of invasion; however, this is a subjective assessment, and a specific size criterion at which confluence reflects invasion has not been validated. It is generally agreed that this is a difficult area and that there is no specific known size threshold at which a confluent proliferation is diagnostic of an invasive process.

Exophytic.

An exophytic ovarian tumor is characterized by papillae that project from the ovarian surface or tumor surface into the peritoneal cavity.

Ovarian surface involvement.

The intent of the assessment of “ovarian surface involvement” is to determine whether tumor cells are exposed to the peritoneal cavity by virtue of the gross architecture of the tumor. Thus, exophytic papillae lined by tumor cells that project from the surface of the ovary reflect ovarian surface involvement. Tumors that are entirely intracystic are not considered to demonstrate ovarian surface involvement. The presence or absence of tumor rupture or tumor cells in peritoneal washings or ascites does not influence this assessment.

Cytologically malignant, morphologically noninvasive serous tumors.

Although many experts classify such tumors as invasive serous carcinomas,² some participants prefer “serous carcinoma” (not otherwise specified) without appending “invasive,” to acknowledge that the invasive properties of these unusual neoplasms have not been defined. It is possible that these are in situ carcinomas. There are virtually no published data on the behavior of this type of tumor. More extensive sampling for histological examination is recommended, because areas of invasion are usually found in such tumors.

FIGO staging.

Patients with borderline tumors confined to the ovaries are FIGO stage I. Patients with pelvic peritoneal implants are FIGO stage II, and those with implants beyond the pelvis and/or with lymph node involvement are FIGO stage III. Stage IV borderline tumors (ie, those with parenchymal liver involvement or tumor beyond the peritoneal cavity) are exceedingly rare.³ If a borderline tumor appears to be stage IV, then further sampling of the primary tumor and implants to identify areas of obvious invasive carcinoma is recommended. Substages are defined as for ovarian cancer according to FIGO.⁵⁵ Some participants believe that the use of the

term “staging” is misleading because it implies “malignancy,” and, with the exception of tumors with invasive peritoneal implants, nearly all borderline tumors have a benign behavior.^{7,8}

APPENDIX B: SPECIMEN HANDLING AND REPORTING

Producing clear, detailed surgical pathology reports is critical for BOTs. Patients may present with suspected “recurrences” years after presentation, when the original blocks may no longer be available, the slides are faded or missing, and the patient’s physicians have retired. Generating a report that can withstand the test of time requires systematic attention to details related to (1) the gross pathology of the specimen, (2) the procedure for prosection and sampling for histology, and (3) particular diagnostic features and details.

It is recognized that the diagnosis of a BOT may first be considered only after the initial gross examination has been completed. In addition, ovarian tumors are often initially examined intraoperatively when time constraints exist. Therefore, the suggestions offered here may need to be applied retrospectively after slide review.

Specimens should be sent to pathology unopened and oriented. The unopened specimen should be weighed and measured. Involvement of the outer surface by adhesions, papillae, ruptured cysts, or rough areas should be recorded; if absent, this should be explicitly stated in the gross description. Examination of the specimen in consultation with the surgeon is encouraged, because the surgeon can often provide useful information related to sites of adhesion, density of adhesions, and time and location of rupture, if present. Inking of the surface in areas suspected of surface involvement can be of value in documenting surface involvement. Cystic locules should be opened, and the quantity, color, and consistency of cyst fluid described. The number and size range of cysts should be documented, and the distribution, size, nodularity and firmness of solid areas and papillae recorded. The presence of identifiable uninvolved ovarian tissue should be documented, especially in cystectomies. Photographing the specimen before and after sectioning, with attention to surface involvement and/or unusual features, can be of value.

Submission of appropriate sections and written documentation of the extent of sampling, especially with respect to reflecting grossly heterogeneous areas, are critical. It is important to sample and document adequate histological examination of solid or nodular areas, papillations, grossly distinctive foci, hemorrhagic areas, the ovarian surface, the tumor surface, and normal ovary, if possible. In general, tumors ≤ 10 cm should be sampled with a minimum of 1 section per centimeter of maximum tumor dimension. If the tumor is >10 cm, obtaining 2 sections per centimeter of maximum tumor dimension is recommended because of the exponential increase in tumor volume with lin-

ear increases in the diameter. Of note, these sampling recommendations have not been validated. These guidelines can be modified if there are large, smooth-walled cystic areas that are grossly benign and do not need to be extensively sampled. If unresolved questions remain after microscopic examination, then additional tissue should be embedded and documented in the gross pathology report.

All peritoneum submitted, including uterine serosa if present, should be meticulously examined. Peritoneal implants may appear as plaques, fine or coarse granules, firm fibrous areas, nondescript roughened areas, or a thin yellow or tan exudate. The fallopian tube serosa should be carefully examined and the tube serially sectioned at about 2-mm intervals. A grossly normal contralateral ovary and/or tube should be meticulously examined with particular attention to the peritoneal surfaces. Embedding an entire grossly normal ovary and/or tube can be of value. A grossly normal omentum should be meticulously examined and liberally sampled with at least 1 section per 2 cm of maximum dimension. (This recommendation has not been validated.) Of note, in one study of women with ovarian carcinoma, in cases with a grossly normal omentum, 22% contained metastatic carcinoma.⁵⁶ There are no analogous published data for BOTs.

The value of gross assessment in distinguishing carcinoma metastatic to the ovary from a primary ovarian tumor has received considerable attention, particularly with respect to mucinous tumors.^{2,3,45,57} Documentation of a single tumor mass (vs multiple masses or a multinodular mass) and unilateral disease support a diagnosis of an M-BOT. If an appendix is submitted, the organ should be embedded in its entirety.

The diagnostic section of the report should indicate the histological tumor type and whether surface involvement was present. For serous tumors, the presence of micropapillary foci (if >5 mm) should be noted, and, if present, the gross specimen should be reexamined and additional sections processed. If microinvasion and/or intraglandular/in situ carcinoma are present, then the size, multiplicity, and histological appearance of the focus or foci should be described in a comment with specific reference to slide numbers. Processing of additional sections can also be of value in such cases. Coexisting lesions, such as teratoma, endometriosis, endosalpingiosis, Brenner (transitional cell) tumor, and mural nodules, should be noted. Noting the absence of such lesions can be of value for mucinous tumors. In a comment, it can be of value to document information supplied by the operating surgeon that does not appear elsewhere in the pathology report, such as the time of rupture (ie, preoperative or intraoperative; if intraoperative, before or after peritoneal washings were obtained).

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