Borderline Ovarian Mucinous Tumors: Consensus Points and Persistent Controversies Regarding Nomenclature, Diagnostic Criteria, and Behavior

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This report focuses on the borderline category of ovarian mucinous tumors and summarizes the consensus points and persistent problems identified by experts in the field who participated in a consensus workshop on borderline ovarian tumors (see the article by Silverberg et al for details of this process). The consensus points and problems within the mucinous tumor category are addressed by considering the three interrelated issues of nomenclature, diagnostic criteria, and behavior using the following resources:

1. historical concepts
2. data from review of the literature, including new concepts from recent studies
3. opinions and experience of experts in the field

Specific issues to be addressed include:

1. recommended nomenclature for tumors conforming to the borderline morphologic category (see also the articles by Silverberg et al and Seidman et al)
2. diagnostic criteria for defining the various morphologic groups within the mucinous borderline tumor category, with special attention to:
    a. the lower limit of the borderline category for distinction from cystadenoma
    b. the upper limit of the borderline category, including the following two categories
        i. borderline tumor with intraepithelial (noninvasive) carcinoma
        ii. borderline tumor with microinvasion
    c. distinction of borderline tumor from the confluent glandular/expansile type of invasive mucinous carcinoma
3. clarification of the behavior of true primary ovarian borderline mucinous tumors by rigorously excluding the non-ovarian mucinous tumors that simulate primary ovarian mucinous borderline tumors when involving the ovaries
    a. ovarian mucinous tumors associated with pseudomyxoma peritonei (PMP)
    b. metastatic mucinous carcinomas with a deceptive pattern of invasion

Nomenclature for tumors conforming to the "borderline" morphologic category

The International Federation of Gynecology and Obstetrics (FIGO) Classification of 1971 designated an intermediate group of epithelial ovarian tumors as "cystadenomas with proliferating activity of the epithelial cells and nuclear abnormalities but with no infiltrative destructive growth (low potential malignancy)."[1] The World Health Organization (WHO) Classification of 1973 designated these tumors as "tumors of borderline malignancy (carcinomas of low malignant potential)."[2] Since then, three terms derived from these classification systems have been used to refer to these tumors: "borderline tumor", "tumor of low malignant potential", and "atypical proliferative tumor". To address the ideal nomenclature for these tumors it is useful to consider both their morphologic features and behavior, as the preferred term should be one that is both morphologically and clinically meaningful. Briefly, there are two types of borderline mucinous tumors recognized in the literature: gastrointestinal type and endocervical mucinous/Müllerian/seromucinous type. The gastrointestinal type of mucinous borderline tumor is

usually a unilateral, large, multicystic tumor with a smooth capsule in which the glands and cysts are lined by stratified, proliferative gastrointestinal type mucinous epithelium exhibiting tufted and villoglandular or papillary intraglandular growth and displaying variable (usually mild to moderate) nuclear atypia and lacking stromal invasion (Figures 1 and 2; see also the article by Seidman et al). Review of the literature on tumors meeting the diagnostic criteria for borderline mucinous tumor, gastrointestinal type, reveals that these tumors have demonstrated an overwhelmingly benign behavior.[3-33] Based on studies published from 1973 to 2002, specific aspects of the behavior of these tumors can be summarized as follows: 1. The vast majority of borderline mucinous tumors of gastrointestinal type are stage I; 2. Of over 500 stage I tumors reported, only ~1% of these patients have been reported to have died of disease (most of these fatal tumors had inadequate or an unknown degree of sampling; 3. A smaller number (~100) of so called advanced stage borderline mucinous tumors have been reported, with nearly 50% mortality. More than 85% of these tumors have been associated with the clinical syndrome of pseudomyxoma peritonei (PMP). However, recent studies have established that virtually all cases of PMP are of gastrointestinal (usually appendiceal), not ovarian, origin (see below).[34-42] Therefore, the existence of true primary ovarian borderline mucinous tumors of advanced stage is questionable. When these questionable advanced stage tumors are removed from the primary ovarian borderline mucinous tumor category, the remainder consists overwhelmingly of stage I tumors with benign behavior.

Based on the above observations and discussions at the workshop, the members of the panel addressing the mucinous borderline tumors agree that the three existing terms, 'borderline", "low malignant potential", "atypical proliferative", are synonymous and describe the same group of tumors. We agreed that the behavior of tumors conforming to this morphology (when well sampled, with careful exclusion of tumors associated with pseudomyxoma peritonei and metastases—see below) is overwhelmingly benign. The group currently is not able to recommend any single term as the preferred term. The group is willing to consider a more benign term than "borderline" or "low malignant potential" if additional data confirms the benign behavior. Possible terms that could be considered include but are not limited to "atypical proliferative mucinous tumor or cystadenoma" and "mucinous cystadenoma with atypia". The number of additional cases needed to confirm the behavior of these tumors was not determined. Based on the large number of cases already reported in the literature, some members of the group advocate the use of more benign terminology now but this was not the consensus opinion. Several consensus points emerged from the group discussion regarding the reporting of borderline tumors in future publications aimed at establishing the behavior of these tumors (see also the article by Silverberg et al). Briefly, it was agreed that because the length of follow-up reported in many studies of borderline tumors, including those cited above, is quite variable, future studies should focus on reporting cases with sufficiently long follow-up to establish meaningful data on behavior. In addition, reported cases should be rigorously evaluated to assure that they are properly classified and well sampled. Diagnostic criteria elaborated in recent studies and as described herein should be applied to properly classify tumors, with special attention to exclusion of metastases and cases of PMP of non-ovarian origin.[11,17,25,26,34] Tumors should be well sampled (the recommended sampling is 1 section per centimeter of greatest tumor diameter for tumors smaller than 10 cm and 2 sections per centimeter of greatest tumor diameter for larger tumors), with additional sections taken if review of the initial sections discloses any findings warranting further evaluation such as intraepithelial carcinoma, invasion, or features suggesting metastatic mucinous carcinoma.

In contrast to the gastrointestinal type of mucinous borderline tumor, the endocervical mucinous/Müllerian/seromucinous type is much less common, more frequently bilateral, can be intracystic or exophytic, architecturally resembles serous borderline tumors, and displays a combination of endocervical type mucinous and serous (ciliated cell) type epithelium, often admixed with other cell types (endometrioid, squamous). Based on a small number of studies, these tumors, including those with implants (> stage I) and intraepithelial and microinvasive carcinomas,

have demonstrated a benign behavior.[43-45] Only a small number of seromucinous carcinomas with a few disease related deaths or recurrences have been reported.[45,46] The consensus opinion regarding these tumors is that the term "seromucinous" is synonymous with the terms "endocervical-type mucinous" and "Müllerian" and can be used to designate this subtype. These tumors are distinctive and differ from the gastrointestinal type. Similarities to serous tumors are acknowledged (the occurrence of implants). Despite the overwhelmingly benign behavior reported to date, due to limited data there was a decision to offer no further comments regarding this group of tumors and a possible change in nomenclature to a more benign term. Therefore, the remainder of this discussion pertains only to the gastrointestinal subtype of mucinous borderline tumors.

Diagnostic criteria for defining the lower limit of borderline for distinction from cystadenoma

Specific criteria for determining the lower limit of the borderline mucinous tumor diagnostic category have not been established or evaluated in the literature. The members of the panel have agreed that a tumor composed predominantly of cystadenoma with a minor component of borderline tumor should be primarily diagnosed as a mucinous cystadenoma. The presence of focal borderline tumor can be commented on and quantified in the pathology report. A specific quantitative definition for what constitutes a minor component was not agreed upon other than to state that this minor component should certainly be much less than 50% of an adequately sampled tumor and less than 10% is a reasonable arbitrary figure to use to define a minor quantity. Most pathologists preferred the approach of requiring a comment on the presence of a minor borderline component so that these tumors can be identified for further study of tumor progression but not all agreed that this was necessary. Some raised concern that mentioning the minor borderline component might lead to overly aggressive treatment. However, this concern seems unwarranted given the established experience in the literature indicating that *bona fide* mucinous borderline tumors are virtually always stage I, have an overwhelmingly benign behavior, and can be managed conservatively.

Intraepithelial (noninvasive) carcinoma

Based on the FIGO and WHO classification schemes of the early 1970's, the sole criterion for distinguishing a mucinous borderline tumor from mucinous carcinoma was the absence of stromal invasion in the former. In 1973 and 1977, additional criteria were proposed for distinguishing mucinous carcinomas lacking obvious stromal invasion from mucinous borderline tumors. The criteria for mucinous carcinoma were expanded to include tumors displaying marked overgrowth of atypical epithelial cells manifested as epithelial cell stratification in excess of three layers, cribriform intraglandular proliferations, or finger-like projections of solid cellular masses without connective tissue support; these patterns were often accompanied by marked nuclear atypia. In addition, the presence of marked nuclear atypia alone was added as a diagnostic feature of mucinous carcinoma.[10,47] Since then, mucinous tumors lacking stromal invasion but displaying epithelial overgrowth and atypia have been referred to as "non-invasive", "intraglandular", or "intraepithelial" carcinomas. Proposed diagnostic criteria for intraepithelial carcinoma vary slightly among different studies.[11,17,25,26,48] All studies consider tumors with marked nuclear atypia as intraepithelial carcinomas. Some investigators also consider tumors displaying any of the following features alone or in combination as intraepithelial carcinomas: moderate nuclear atypia, epithelial stratification of four or more layers, or intraglandular cribriform or stroma-free papillary growth.[11,17,26,48] Based on review of the literature, 290 cases of stage I intraepithelial carcinomas have been reported, with 18 deaths due to disease (6.2%).[4,6,8-11,14,17,25,26,29,32,44,48] In these studies, very few advanced stage "intraepithelial mucinous carcinomas" have been reported, with a higher proportion of deaths due to disease (9 of 13 cases). In light of the ability of metastatic mucinous carcinomas to simulate borderline mucinous tumors with intraepithelial carcinoma (see below), the

possibility that some or all of these so called "advanced stage intraepithelial carcinomas" represent occult metastases is high.

Based on consideration of the above morphologic and behavioral aspects, the sole diagnostic criterion agreed to for the diagnosis of intraepithelial carcinoma is the presence of severe (grade 3) cytologic atypia (Figures 3 and 4). A minority of pathologists also consider complex intraglandular growth patterns (such as cribriform areas or stroma-free papillae), even in the absence of severe atypia, diagnostic of intraepithelial carcinoma. However, the consensus opinion is that excessive epithelial stratification and other complex intraglandular growth patterns, in the absence of severe atypia, can be seen in typical borderline mucinous tumors and should not be used to diagnose intraepithelial carcinoma (Figure 5). Additional studies should specifically address the significance of these intraglandular growth patterns in borderline tumors.

Borderline mucinous tumor with microinvasion

Microinvasion in borderline mucinous tumors has been defined as either small foci of stromal invasion characterized by single cells, glands, or small clusters/nests of mucinous epithelial cells within the stroma or as small foci of confluent glandular or cribriform growth within the stroma. Some investigators have used 3 mm in greatest linear extent or 10 square mm as the size limit for each individual focus but others have used 1, 2, and 5 mm as the upper limit for each focus, with no requirement regarding the number of such foci allowed.[9,11,17,25,26,48-50] Most reports do not provide great detail regarding the cytologic features of the invasive foci. Some tumors with microinvasion also have intraepithelial carcinoma (17 of 48 cases reported in the cited studies). Based on review of these studies, 37 microinvasive tumors with follow-up have been reported and no recurrences or deaths due to disease have been observed.[9,11,17,25,26,48-50] One additional case with 4 mm of microinvasion was reported to have resulted in death due to disease but this tumor had been inadequately sampled.[48] Thus, the prognosis of tumors with microinvasion appears to be excellent.

In one report, the term "microinvasive carcinoma" is specifically used for those tumors having both intraepithelial carcinoma and microinvasion, whereas mucinous borderline tumors with microinvasion but lacking intraepithelial carcinoma are referred to as "microinvasive borderline tumors".[11] There was debate among participants in the consensus workshop regarding the pathologic meaning of the terms "borderline tumor with microinvasion" ("microinvasive borderline tumor") and "borderline tumor with microinvasive carcinoma" and the clinical management implications of these diagnoses. Based on the description of these terms in the previously cited report, the latter diagnosis indicates foci of intraepithelial carcinoma are present whereas the former diagnostic term indicates intraepithelial carcinoma is absent. The appearance of the invasive foci (low-grade or borderline in appearance versus high-grade) has not been specifically defined for these two diagnostic categories. However, it appears that the term "microinvasive borderline tumor" is interpreted by some pathologists and clinicians as indicating the presence of invasive foci that appear similar to the borderline tumor (that is, low-grade; Figures 6 and 7) whereas the term "microinvasive carcinoma" is interpreted as a bona fide invasive carcinoma with a higher-grade appearance (Figure 8). It appears that some clinicians might recommend a more aggressive treatment approach for the latter diagnosis but not the former, despite the fact that two discrete forms of microinvasive tumors have not been sufficiently defined and studied in the literature. Thus, there was no clear consensus about the existence of two different types of microinvasive tumor and how to label them but it appears that many pathologists regard the two terms as synonymous. It was agreed that the amount of microinvasion should be quantified but there was no consensus on a size criterion. Some pathologists accept up to 5 mm but others do not, partly due to limited experience in the literature with this group of tumors. A comment can be made in the report that based on the limited data in the literature, tumors with up to 5 mm of microinvasion have demonstrated an excellent prognosis.[25] Additional studies should address the size criterion for

microinvasion, the significance of the number of microinvasive foci, and describe in detail the cytologic features of the microinvasive foci. Microinvasion should be carefully distinguished from gland rupture with the formation of mucin granulomas containing fragmented epithelium.

Distinction of borderline mucinous tumor from the confluent glandular/expansile type of invasive mucinous carcinoma

Recent studies of ovarian mucinous tumors have expanded the definition of invasive mucinous carcinoma to include a second type of invasion, termed the "confluent glandular" or "expansile" pattern of invasion.[17,25] In this pattern of invasion, the glandular epithelium is markedly crowded, with little intervening stroma, and interconnected in a confluent or labyrinthine pattern (Figure 9). Primary ovarian mucinous carcinomas commonly exhibit this pattern of invasion and the presence of an infiltrative pattern of stromal invasion should raise concern for metastatic mucinous carcinoma (see below).[25,51] Based on recent studies recognizing this pattern of invasion, it appears that patients with stage I mucinous carcinomas of this type have ~90% survival rate, with adverse prognosis almost exclusively associated with the infiltrative rather than the confluent glandular/expansile pattern of invasion (deaths due to disease in 5 of 21 versus none of 25 cases, respectively).[17,25,26] Most pathologists agree that the confluent glandular/expansile pattern reflects a type of invasive well differentiated mucinous carcinoma which should be diagnosed as such, although it was acknowledged that some pathologists may classify tumors with this pattern as intraepithelial carcinoma rather than invasive due to the difficulty with determining how much glandular confluence constitutes carcinoma. For tumors comprised predominantly of borderline tumor the focus/foci of confluent growth should measure more than the upper size limit allowed for a diagnosis of microinvasion to qualify for the diagnosis of invasive carcinoma, that is, more than 5 mm in greatest dimension according to criteria proposed by some investigators[25] or more than 3 mm in greatest dimension or 10 square mm in area according to the criteria of others.[17,26] It was recommended that tumors with a minor component of carcinoma be diagnosed as borderline/atypical proliferative/low malignant potential tumor with focus/foci of mucinous carcinoma, with some quantification of the focus/foci. Additional studies of tumors displaying this pattern are warranted.

Ovarian mucinous tumors associated with pseudomyxoma peritonei (PMP)

The term PMP has historically been applied as a pathologic diagnostic term to both indolent and aggressive mucinous neoplasms in the abdominal and pelvic cavities that produce mucinous ascites and/or abundant extracellular mucin, resulting in diagnostic confusion and unreliable data on prognosis. Recent studies have redefined PMP as a specific clinicopathologic syndrome in which mucinous ascites is accompanied by low-grade adenomatous mucinous epithelium, intimately associated with pools of extracellular mucin and fibrosis, almost invariably derived from ruptured appendiceal low-grade mucinous tumors.[35,36,52] These studies recommend either the term "disseminated peritoneal adenomucinosis"[35,36] or "involvement by low-grade appendiceal mucinous neoplasm"[52] as specific pathologic diagnostic terms for these low-grade peritoneal mucinous tumors. The term PMP is restricted to use as a clinical descriptor for the syndrome of mucinous ascites accompanied by these low-grade mucinous tumors and is maintained for historical continuity. This recommendation is based on the observation that peritoneal mucinous tumors with the histologic features of mucinous carcinoma are pathologically and prognostically distinct from the low-grade tumors.[35,36]

The debate over the site of origin of PMP has focused on women and determining the primary site has been problematic for several reasons. First, primary ovarian mucinous tumors do occur and can rupture, leading to spillage of mucin within the pelvic and abdominal cavities. Second, synchronous appendiceal and ovarian mucinous tumors associated with PMP are common. Third, the appendiceal mucinous tumors in cases of PMP can be ruptured and obliterated by copious

mucinous material and the associated fibrosis, making detection of a primary appendiceal tumor difficult or even impossible. Fourth, the ovarian mucinous tumors associated with PMP can be large and clinically evident and can simulate primary ovarian mucinous tumors both grossly and microscopically (Figure 10). Most often, these tumors are interpreted as primary ovarian borderline mucinous tumors. Thus, the combination of these factors often leads to interpretation of the ovarian tumor as the primary site of origin. However, recent morphologic, immunohistochemical, and molecular genetic studies have provided compelling evidence that virtually all cases of PMP are derived from an appendiceal mucinous tumor and the ovarian involvement is secondary.[34-42] In particular, the mucinous tumors in the ovaries in cases of PMP are usually smaller, more frequently bilateral, more frequently involve the surface and superficial cortex, and more frequently display pseudomyxoma ovarii when compared to primary ovarian mucinous tumors unassociated with PMP.[34] In contrast, primary ovarian atypical proliferative mucinous tumors and well differentiated mucinous carcinomas are typically larger, unilateral, usually confined to the ovarian stroma without surface involvement, and contain more abundant proliferative mucinous epithelium without prominent pseudomyxoma ovarii.[25] The mucinous tumors in the ovaries in PMP have the same cytokeratin 7/20 immunohistochemical phenotype as the associated appendiceal tumors (~80% are cytokeratin 7-negative and all are diffusely cytokeratin 20-positive) and this phenotype is distinct from that of primary ovarian mucinous tumors unassociated with PMP which are invariably diffusely cytokeratin 7-positive and variably positive for cytokeratin 20.[39,41,53] In addition, molecular genetic studies have demonstrated identical *ras* mutations in the synchronous appendiceal and ovarian tumors in PMP.[40,42] In conjunction with the morphologic and immunohistochemical data, the *ras* mutation data support the concept that PMP is a clonal process of appendiceal origin. This concept is further supported by other studies showing that ruptured primary ovarian mucinous tumors have not been associated with the subsequent development of PMP.[9,10,12,15,17] The rare exception to this theory of the appendiceal origin of PMP is the occurrence of mucinous tumors arising in ovarian mature cystic teratomas associated with PMP.[54] The mucinous tumors in the ovaries in these cases are histologically and immunohistochemically similar to those in cases of PMP of appendiceal origin.

There was consensus among panel members that the ovarian mucinous tumors associated with PMP are almost invariably derived from the gastrointestinal tract, usually the appendix. In view of this, they should be reported as secondary involvement of the ovary or metastatic to the ovary. Ovarian mucinous tumors with features consistent with or suggestive of secondary involvement in the setting of PMP should not be labeled with the same diagnostic terms used for primary ovarian tumors (cystadenoma, "borderline", "low malignant potential", or "atypical proliferative") so that clinicians are not confused about the established or suspected primary site. When intraoperative consultation with frozen section leads to diagnosis of a mucinous ovarian tumor in the setting of PMP the need for appendectomy should be conveyed to the surgeon and the pathologist should examine the entire appendix microscopically. For cases in which the appendix was not initially removed but morphologic and immunohistochemical features of the ovarian tumor support an appendiceal origin, the need for subsequent appendectomy should be determined by clinical factors.

Metastatic mucinous carcinomas with a deceptive pattern of invasion

Metastatic mucinous carcinomas are far more common than primary ovarian mucinous carcinomas and many are easily recognized as such when the ovarian tumors exhibit any or all of the following features: bilaterality, smaller size (typically less than 10 cm), ovarian surface involvement, a nodular pattern of involvement, and an infiltrative pattern of stromal invasion.[25,51,55] It is important to recognize that some metastatic mucinous carcinomas derived from the colon, pancreaticobiliary tract, appendix, and endocervix can have a deceptive pattern of invasion simulating a primary ovarian mucinous "borderline" tumor with intraepithelial carcinoma and not

infrequently some of these metastases display highly differentiated areas adjacent to carcinoma, simulating benign and "borderline" precursor lesions and suggesting primary origin in the ovary (Figures 11 and 12).[56-60] Recognizing such tumors as metastatic is especially problematic when the ovarian tumor represents the presenting finding of disease, is unilateral and large, and a primary mucinous carcinoma of another organ (most often the gastrointestinal tract, including the pancreaticobiliary system) is not identified. Efforts should be made to rigorously exclude metastatic mucinous carcinomas of non-ovarian origin from the primary ovarian mucinous tumor category. The presence of any of the above mentioned features characteristic of metastatic mucinous carcinomas, or extraovarian disease, should lead the pathologist to suspect metastatic carcinoma and should prompt the surgeon to examine the gastrointestinal tract, including pancreaticobiliary system, for a primary tumor. Immunohistochemical analysis can be useful for identifying those metastatic mucinous carcinomas that lack characteristic features of metastases and simulate primary ovarian mucinous tumors.[53]

Conclusions

Recent studies have refined the diagnostic criteria for the various categories of ovarian mucinous tumors. This has allowed for more accurate diagnosis of true primary ovarian mucinous tumors, particularly the borderline type, and their distinction from metastatic mucinous tumors (including secondary involvement by low-grade mucinous tumors in cases of PMP). Improved classification of these mucinous tumors has clarified the behavior of these tumors by excluding simulators from the borderline mucinous tumor category. The consensus process summarized in this and the accompanying articles has identified those points on which we agree and those issues needing further investigation. We generally agree about the diagnostic criteria that define the mucinous tumor subcategories but additional studies, particularly focusing on the less common and more problematic types, such as intraepithelial and microinvasive carcinomas, are warranted to firmly establish their behavior.

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