Context.—Appendiceal mucinous neoplasms are considered enigmatic tumors of unpredictable biologic potential. Their importance lies in their potential to spread to the peritoneum and viscera in the form of gelatinous mucin deposits. Extra-appendiceal spread of these tumors is the most common etiology of pseudomyxoma peritonei, which is a descriptive term encompassing a number of neoplastic and nonneoplastic peritoneal disorders. Many studies aimed at evaluating the biologic importance of appendiceal mucinous neoplasms and pseudomyxoma peritonei have employed inconsistent histologic criteria for their diagnosis and descriptive terminology for their classification. As a result, appendiceal mucinous neoplasms and associated peritoneal disease represents one of the most confusing and controversial areas in gastrointestinal pathology.

Primary appendiceal tumors are found in less than 2% of surgically removed appendices, but still pose a variety of diagnostic and therapeutic challenges. In particular, the classification and management of appendiceal mucinous neoplasms has proven problematic for both clinicians and pathologists. These tumors characteristically cause cystic dilatation of the appendix owing to accumulation of copious gelatinous material in the lumen (Figure 1, A and B). They may disseminate throughout the peritoneal cavity in the form of gelatinous deposits, termed pseudomyxoma peritonei (Figure 1, C and D). Many controversies surrounding appendiceal neoplasms and pseudomyxoma peritonei stem from the use of inconsistent histologic criteria for their diagnosis and philosophic differences of opinion regarding their pathogenesis. Several investigators have proposed classification schemes that employ similar terminology to describe lesions of variable biologic potential or that use dissimilar terms to describe the same entity. Moreover, an origin in the appendix is not suspected before surgery in many cases because patients present with ovarian or peritoneal tumors that are managed by gynecologists, rather than general or colorectal surgeons. These different clinical groups are usually familiar with some, but not all, of the terminology used to describe mucinous tumors of the appendix and peritoneum. As a result, management strategies across different institutions, or even among clinicians at the same institution, are not standardized. The purpose of this review is to provide a comprehensive discussion of the biologic potential of, and proposed classification schemes for, appendiceal mucinous neoplasms and pseudomyxoma peritonei.

WHAT IS PSEUDOMYXOMA PERITONEI?

Pseudomyxoma peritonei is a term used to describe mucinous ascites or mucin deposits within the peritoneal cavity. Pseudomyxoma peritonei consists of organizing pools of mucin within peritoneal fat or on the serosal surfaces of the viscera, which contain variable numbers of neoplastic epithelial cells. Most cases reflect dissemination of an appendiceal mucinous neoplasm, in which case, mucin pools that contain scant strips and clusters of low-grade neoplastic epithelial cells are typical (Figure 2, D), similar to those present in the appendiceal mucosa (Figure 2, A and B). However, pseudomyxoma peritonei is not synonymous with a neoplasm nor are all neoplastic cases derived from the appendix. Ruptured diverticula of the appendix and colon may spill mucin into the peritoneal cavity, and mucin-producing carcinomas of the colon, pancreas, and other organs may disseminate throughout the peritoneum in the form of gelatinous ascites. Unfortunately, much of the earlier literature is of limited value in assessing the biologic potential of appendiceal mucinous neoplasms and pseudomyxoma peritonei. Most reports before 2000 did not distinguish between neoplastic and nonneoplastic etiologies for pseudomyxoma peritonei, appendiceal and nonappendiceal neoplasms, or...
cytologically low- and high-grade tumors in the peritoneal cavity. In our practice, we generally avoid using *pseudomyxoma peritonei* as a diagnostic term and limit its inclusion in pathology reports to a comment aimed at facilitating communication with clinicians.

**ORIGIN OF PSEUDOMYXOMA PERITONEI**

The combined results of several studies published in the early 1990s implicated the appendix as a likely site of origin in most of nearly 100 patients with pseudomyxoma peritonei but also suggested that some cases may be derived from either the ovary or peritoneum. Prayson et al. evaluated a series of 10 men and 9 women with pseudomyxoma peritonei and found that 94% of patients had appendiceal mucinous neoplasms, including all of the women with ovarian tumors. Seidman et al. found a high frequency of bilateral ovarian mucinous tumors, or right-sided ovarian mucinous tumors in unilateral cases, among women with concomitant mucinous tumors of the appendix, leading them to conclude that pseudomyxoma peritonei may be derived from either site or represent a primary peritoneal neoplasm. Young et al. studied 22 appendiceal mucinous neoplasms associated with mucinous ovarian tumors and noted that tumors in both sites were histologically similar. They also found ovarian disease to be bilateral in most cases, whereas unilateral ovarian tumors showed a right-sided predominance. Unlike Seidman et al., however, they concluded that these features suggested a primary appendiceal origin with secondary ovarian involvement.

Molecular data further support the notion that pseudomyxoma peritonei is usually derived from the appendix, rather than the ovary or peritoneum. Cautrecasas et al. analyzed *KRAS* mutational status in 6 synchronous mucinous tumors of the appendix and ovary, 5 (83%) of which showed identical *KRAS* mutations in codon 12 in tumors from both sites. Chuaqui et al. analyzed loss of heterozygosity on chromosomes 5 and 17 in synchronous appendiceal and ovarian mucinous neoplasms obtained from 12 patients. They found either loss of heterozygosity at the same locus or no loss of heterozygosity in paired tumors in 75% of cases. Subsequent studies have shown progressive loss of heterozygosity in ovarian mucinous tumors, when compared with synchronous appendiceal neoplasms, leading most investigators to conclude that most pseudomyxoma peritonei cases are derived from appendiceal mucinous neoplasms, whereas an ovarian origin is considered a rare occurrence.

Figure 1. Mucinous neoplasms often cause appendiceal distention (A) because of massive accumulation of extracellular mucin within the lumen (B). The neoplasms may spread to the serosal surfaces of the viscera (C) or form gelatinous tumor deposits in the omentum (D).
PERIAPPENDICULAR MUCIN DEPOSITS (LOCALIZED PSEUDOMYXOMA PERITONEI)

Not uncommonly, surgical pathologists encounter appendiceal resection specimens with mucin deposits on the appendiceal serosa, within the mesoappendix, or limited to the right lower quadrant (Figure 3, A and B). Extra-appendiceal mucin deposits limited to the periappendiceal area are usually devoid of neoplastic epithelial cells (acellular), although one may infrequently observe strips or clusters of neoplastic mucinous epithelial cells in periappendiceal mucin, similar to cases with widespread peritoneal disease (Figure 3, C and D). Yantiss et al. evaluated the prognostic implications of peritoneal mucin localized to the right lower quadrant in 65 patients with appendiceal mucinous neoplasms. Fifty patients (77%) had acellular extra-appendiceal mucin, and 15 (23%) had periappendiceal mucin deposits that contained scant mucinous epithelium with low-grade cytologic features. At follow-up, 48 (96%) patients without extra-appendiceal epithelium were disease free (mean, 52 months), whereas 33% of patients with any neoplastic epithelium outside the appendix developed widespread peritoneal tumor deposits, including one patient who died of disease (mean, 38 months). Notably, 2 patients with acellular periappendiceal mucin developed disseminated peritoneal disease, but neither of those appendices was submitted entirely for histologic examination. These results emphasize the importance of adequate sampling in determining the prognosis of patients with appendiceal mucinous neoplasms and indicate that tumors without extra-appendiceal neoplastic epithelium are associated with an excellent prognosis.

CLASSIFICATION OF APPENDICEAL MUCINOUS NEOPLASMS AND PSEUDOMYXOMA PERITONEI

The proposed classification schemes for appendiceal mucinous neoplasms and pseudomyxoma peritonei reflect differences of opinion regarding the fundamental nature of mucin deposits in the peritoneum and comparisons between them are summarized in the Table. Some investigators think that peritoneal mucin deposits are the consequence of appendiceal rupture and spillage of mucin and “adenomatous” epithelium into the peritoneal cavity, rather than carcinoma. They argue that appendiceal mucinous tumors frequently lack infiltrating, malignant glands and desmoplastic stroma and note that
extra-appendiceal epithelium usually shows bland cytologic features insufficient for a diagnosis of malignancy. On the other hand, there are compelling reasons why the American Joint Committee on Cancer, World Health Organization, and most other investigators consider pseudomyxoma peritonei to be carcinoma. First, some carcinomas are extremely well differentiated with minimal atypical cytologic features, so low-grade cytology does not exclude a diagnosis of malignancy. Second, parenchymal invasion of solid organs is common in patients with pseudomyxoma peritonei and is generally considered a feature of malignancy. Third, some cancers, particularly mucinous or colloidal carcinomas may invade tissues with a broad, pushing growth pattern, so one need not see infiltrating glands or desmoplasia to make a diagnosis of malignancy. Finally and most important, mucinous neoplasms that spread beyond the appendix are associated with progressive mucinous ascites, disease recurrence, and death in at least half of patients.

In a study of 184 epithelial noncarcinoïd appendiceal tumors, Carr et al13 found that mucinous neoplasms limited to the appendix pursued an indolent course, whereas those with extra-appendiceal spread were associated with decreased survival. These authors proposed that appendiceal mucinous neoplasms be classified as adenomas (or cystadenomas), tumors of uncertain malignant potential, and carcinoma. Adenomas were defined by the presence of mucinous neoplasia confined to the mucosa with intact muscularis mucosae, whereas tumors that showed mural invasion or proliferation of neoplastic epithelium outside the appendix were considered carcinomas. Neoplasms with pushing, but not infiltrative, mural invasion or acellular mucin pools on the serosa were considered to be of uncertain malignant potential.

Misdraji et al15 later analyzed the histologic features of 107 appendiceal mucinous tumors, which they classified as either low- or high-grade based on cytoarchitectural features. Tumors with low-grade cytology were termed noninvasive mucinous cystadenocarcinomas, whereas peritoneal deposits containing overtly malignant cells were labeled as invasive mucinous adenocarcinomas. All patients with low-grade neoplasms confined to the appendiceal mucosa were free of disease at last follow-up (median, 6 years), whereas 67% of patients with peritoneal involvement experienced disease recurrence or death from disease. Patients with overtly malignant
peritoneal disease had 3- and 5-year survival rates of 90% and 44%, respectively, compared with 100% and 86%, respectively, among patients with low-grade peritoneal disease. The authors failed to identify any pathologic features in the appendiceal component that reliably predicted the presence or absence of pseudomyxoma peritonei and suggested that all low-grade tumors be labeled low-grade appendiceal mucinous neoplasm, regardless of the extent of disease, which would be documented in the pathology report.

Two years later, Pai and Longacre\(^6\) proposed an alternative classification scheme that built on that suggested by Carr et al.\(^13\) They recognized lesions confined to the appendiceal mucosa as adenomas but expanded the definition of mucinous tumors of uncertain malignant potential to include those tumors with mucosal disease at the proximal margin, those with mucin and epithelium in the appendiceal wall without obvious destructive invasion, and those in which the diagnosis of extra-appendiceal epithelium was in doubt. Mucin pools containing scant, low-grade epithelium outside the appendix were classified as mucinous neoplasms of low malignant potential, whereas those with destructive invasion were considered to represent adenocarcinomas.

This same group later analyzed 116 mucinous appendiceal neoplasms and modified their original classification scheme to a 4-tiered system.\(^7\) Low-grade tumors confined to the appendiceal mucosa were classified as adenomas, whereas similarly low-grade tumors with acellular extra-appendiceal mucin were considered to be of low risk for recurrence. High-grade tumors in the peritoneal cavity were classified as adenocarcinomas, similar to their prior proposal. Cytologically low-grade tumors with extra-appendiceal epithelium (previously termed mucinous neoplasms of low malignant potential) recurred in 21 of 27 cases (78%) and, thus, were reclassified as low-grade mucinous neoplasms with high-risk of recurrence. All patients with invasive carcinoma and who had available follow-up data died of disease with significantly decreased overall survival rates compared with patients with low-grade extra-appendiceal disease.

Other authors have devised classification schemes for pseudomyxoma peritonei based on the cytologic appearance of peritoneal epithelium. Ronnett et al\(^1\) considered pseudomyxoma peritonei with low-grade cytologic features to represent passive spread of adenomatous epithelium into the peritoneum, secondary to appendiceal rupture, and, thus, termed such cases disseminated peritoneal adenomucinosis (Figure 4, A and B). They consider mucinous tumors of the peritoneum with more-abundant, cytologically malignant epithelium to represent peritoneal mucinous carcinomatosis (Figure 4, E and F), and cases with both low- and high-grade features were designated peritoneal mucinous carcinomatosis, intermediate grade (Figure 4, C and D). The authors applied this classification scheme to 109 multifocal peritoneal mucinous tumors derived from the appendix, colon, or small intestine and compared survival rates among the 3 groups. All 65 cases of disseminated peritoneal adenomucinosis were derived from the appendix and were associated with 5- and 10-year survival rates of 75% and 68%, respectively. Both intermediate and high-grade mucinous carcinomas were more frequently derived from nonappendiceal primary tumors and pursued an aggressive clinical course with 5- and

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**Comparisons Among Classification Schemes for Appendiceal Mucinous Neoplasms and Pseudomyxoma Peritonei**

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Carr and Sobin,(^{11}) 2010</th>
<th>Misraji et al,(^{14}) 2003</th>
<th>Pai and Longacre,(^{17}) 2009</th>
<th>Ronnett et al,(^{1}) 1995</th>
<th>Bradley et al,(^{15}) 2006</th>
<th>AJCC and WHO(^{16,11}) 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor confined to appendix</td>
<td>Adenoma</td>
<td>Low-grade appendiceal mucinous neoplasm</td>
<td>Adenoma</td>
<td>NA</td>
<td>NA</td>
<td>Adenoma</td>
</tr>
<tr>
<td>Limited to mucosa</td>
<td>Adenoma</td>
<td>Low-grade appendiceal mucinous neoplasm</td>
<td>Adenoma</td>
<td>NA</td>
<td>NA</td>
<td>Adenoma</td>
</tr>
<tr>
<td>Low-grade cytology</td>
<td>Adenoma</td>
<td>Noninvasive mucinous cystadenocarcinoma</td>
<td>Adenoma</td>
<td>NA</td>
<td>NA</td>
<td>Adenoma</td>
</tr>
<tr>
<td>High-grade cytology</td>
<td>Adenoma</td>
<td>Low-grade appendiceal mucinous neoplasm</td>
<td>Uncertain malignant potential</td>
<td>NA</td>
<td>NA</td>
<td>Adenoma</td>
</tr>
<tr>
<td>Positive surgical margin</td>
<td>Uncertain malignant potential</td>
<td>Low-grade appendiceal mucinous neoplasm</td>
<td>Uncertain malignant potential</td>
<td>NA</td>
<td>NA</td>
<td>Invasive Mucinous Adenocarcinoma</td>
</tr>
<tr>
<td>Neoplastic epithelium in appendix wall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor beyond appendix</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Low-grade epithelium in peritoneal mucin</td>
<td>Invasive mucinous adenocarcinoma</td>
<td>Invasive mucinous adenocarcinoma</td>
<td>High-risk for recurrence</td>
<td>Disseminated peritoneal adenomucinosis</td>
<td>Low-grade mucinous carcinoma peritonei</td>
<td>Low-grade mucinous adenocarcinoma</td>
</tr>
<tr>
<td>High-grade epithelium in peritoneal mucin</td>
<td>Invasive mucinous adenocarcinoma</td>
<td>Invasive mucinous adenocarcinoma</td>
<td>Invasive mucinous adenocarcinoma</td>
<td>Peritoneal mucinous carcinomatosis</td>
<td>High-grade mucinous carcinoma peritonei</td>
<td>High-grade mucinous adenocarcinoma</td>
</tr>
</tbody>
</table>

Abbreviations: AJCC, American Joint Committee on Cancer; NA, not applicable; WHO, World Health Organization.
10-year survival rates of 50% and 21% for intermediate-grade peritoneal mucinous carcinomatosis and 14% and 3% for high-grade peritoneal mucinous carcinomatosis, respectively. Although these results suggest histologic grade is important in predicting behavior among peritoneal mucinous tumors, inclusion of intestinal carcinomas in the analysis of high-grade tumors makes it difficult to interpret the data.
Bradley et al.\(^5\) better demonstrated the importance of cytologic grade in predicting behavior of pseudomyxoma peritonei in a later study. These authors evaluated the natural history of 101 patients with appendiceal mucinous tumors and peritoneal disease, all of whom were treated in a similar fashion at a single institution. These authors used a 2-tiered system to classify pseudomyxoma peritonei. Low- and intermediate-grade tumors were considered to be low-grade mucinous carcinoma peritonei, whereas cases with severe cytologic atypia were classified as high-grade mucinous carcinoma peritonei. The authors found that low-grade mucinous carcinoma peritonei was associated with a significantly better 5-year survival rate (63%) than was high-grade mucinous carcinoma peritonei (38%).

The combined results of all of these studies can be summarized into several major points. First, tumors limited to the appendiceal mucosa have no potential for aggressive disease when completely resected, regardless of the degree of dysplasia, and, therefore, it is appropriate to classify them as adenomas or cystadenomas. Appendiceal mucinous neoplasms associated with acellular mucin limited to the appendiceal wall and/or mesoappendix are also cured by excision, in most cases and, thus, we consider these tumors to be adenomas as well. However, all neoplasms that are classified as adenomas should be completely submitted for histologic evaluation to exclude the possibility of extra-appendiceal epithelium. Clinicians should also be informed of the remote possibility that a small amount of extra-appendiceal epithelium may not be detected by sampling of tumors with acellular periappendiceal mucin and thus, clinical follow-up should probably be considered. Any proliferation of neoplastic epithelium beyond the muscularis mucosae is at risk for peritoneal dissemination and should be graded and staged as a carcinoma, as described in the World Health Organization classification and staging guidelines put forth by the American Joint Committee on Cancer.\(^6\)

The World Health Organization regards any neoplastic epithelial proliferation confined to the appendiceal mucosa as an adenoma. Appendiceal mucinous tumors with extra-appendiceal neoplastic epithelium are classified as mucinous adenocarcinomas and subcategorized as low- or high-grade because increasingly severe cytoarchitectural atypia is associated with poorer outcome.\(^11\) The American Joint Committee on Cancer staging guidelines assign tumor (T) stage for appendiceal mucinous neoplasms similar to those used for colonic adenocarcinoma, with the exception that T4a denotes both serosal involvement and extra-appendiceal disease limited to the right lower quadrant. Mucinous deposits beyond the right lower quadrant (pseudomyxoma peritonei) are also cured by excision, in most cases and, thus, we consider these tumors to be adenomas as well. However, all neoplasms that are classified as adenomas should be completely submitted for histologic evaluation to exclude the possibility of extra-appendiceal epithelium. Clinicians should also be informed of the remote possibility that a small amount of extra-appendiceal epithelium may not be detected by sampling of tumors with acellular periappendiceal mucin and thus, clinical follow-up should probably be considered. Any proliferation of neoplastic epithelium beyond the muscularis mucosae is at risk for peritoneal dissemination and should be graded and staged as a carcinoma, as described in the World Health Organization classification and staging guidelines put forth by the American Joint Committee on Cancer.\(^11\)

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**TREATMENT OF PSEUDOMYXOMA PERITONEI**

Treatment of pseudomyxoma peritonei has historically consisted of surgical debulking of gross disease, with or without various forms of chemotherapy. Recent years have seen a trend toward more aggressive management strategies that include multiple surgeries, complete peritonectomy, intraoperative intraperitoneal chemotherapy, and additional cycles of postoperative chemotherapy. Miner et al.\(^8\) retrospectively analyzed the relative contribution of histologic features of peritoneal disease, patient characteristics, and extent of treatment in 97 patients who underwent extensive debulking surgery, which achieved complete cytoreduction in 55% of cases. They found that low-grade cytology was independently associated with disease-free survival and that 90% of patients who achieved 10-year survival had tumors of low-histologic grade. Outcome data from other studies using these aggressive treatment strategies have also shown improved survival among patients with low-grade peritoneal disease compared with survival rates of those with high-grade tumors, which are probably not amenable to surgical management.\(^19\) Thus, therapeutic decisions largely rest on the distinction between low- and high-grade peritoneal disease.

**SUMMARY AND CONCLUSIONS**

Appendiceal mucinous neoplasms represent a relatively homogeneous group of neoplasms that pursue a predictable clinical course based on tumor stage and grade. Those confined to the appendiceal mucosa are cured by excision, whereas any proliferation of neoplastic epithelium beyond the mucosa places the patient at risk for peritoneal dissemination. The histologic grade of peritoneal disease is extremely important. Patients with low-grade tumors may benefit from aggressive management, consisting of a combination of chemotherapy and cytoreductive surgery, whereas those with high-grade tumors probably do not benefit from aggressive debulking but may be better served by systemic chemotherapy. Decisions regarding clinical management require clear communication among treating physicians, so adoption of a uniform reporting system for appendiceal mucinous neoplasms with peritoneal metastases by the World Health Organization and American Joint Committee on Cancer represents a major advancement in the field.

**References**


