Appendiceal mucinous neoplasms: Controversial issues
Joseph Misraji, MD
Massachusetts General Hospital, GI Pathology Unit
Boston, MA

Bullet Points

- The classification of appendiceal mucinous neoplasms is controversial, particularly when the tumor has spread to the peritoneum. The introduction of compromise terminology has done little to end the debate.
- The nature of pseudomyxoma peritonei is controversial. Some pathologists consider classic pseudomyxoma peritonei to be spread of “adenomatous” epithelium from a ruptured appendiceal adenoma, whereas others insist that it is by definition “carcinoma”. Virtually all studies support that low grade tumors have a better prognosis than high grade tumors.
- Appendiceal mucinous tumors share molecular features with colorectal adenomas, while appendiceal serrated epithelial proliferations have molecular features in common with colorectal serrated polyps.
- The treatment of patients with peritoneal spread of appendiceal mucinous tumors is not standardized. Generally, patients with low grade peritoneal tumors benefit from surgical approaches whereas patients with high grade peritoneal tumors do not.

Introduction

In 1940, Woodruff and McDonald classified cystic mucinous tumors of the appendix into benign “mucoceles” and, when they showed “papillary arrangement of the mucous membrane” with hyperchromatic, elongate nuclei, “cystadenocarcinoma, grade 1”.29 In the 1960s and 1970s, doubts began to surface about the malignant nature of these seemingly non-invasive tumors, and they were re-classified as “mucinous cystadenomas” or “villous adenomas” of the appendix in keeping with the nomenclature for colorectal adenomatous polyps.8,11,15 However, this engendered the on-going controversy regarding the appropriate classification of those same tumors when they have seeded the peritoneal cavity with neoplastic mucinous epithelium that eventuates in the death of over 50% of these patients due to bowel obstruction. The debate continues today, and pits those pathologists who accept the concept of a ruptured adenoma with seeding of “adenomatous” epithelium in the peritoneal cavity1,22 against those who insist that the presence of epithelium proliferating outside the appendix is unequivocally adenocarcinoma.3,4 In between are pathologists who have introduced intermediate terms such as “borderline tumor of the appendix”,31 “mucinous tumors of low malignant potential”,19 and “low grade appendiceal mucinous neoplasm”18 to reconcile the benign appearance of the appendiceal tumor and often the peritoneal mucinous epithelium with its relentless and often fatal biologic behavior.

Pathologists who object to classifying appendiceal tumors with peritoneal spread as adenocarcinoma emphasize several factors about many of these cases:
- The classic appendiceal tumor associated with PP lacks destructive invasion of the appendiceal wall. Instead, “rupture”, “herniation”, or “diverticula” may have provided the tumor access to the peritoneum;
The appendiceal tumor looks the same regardless of whether PP is present, and thus the designation of adenocarcinoma rests on sampling by the surgeon or pathologist;

- The mucinous epithelium in the peritoneum is bland sometimes to the point of appearing “benign”;
- Lymph node metastases and parenchymal organ invasion are rare (except for the ovary), unlike more usual examples of peritoneal carcinomatosis; and
- Patients with classic PP have a much better prognosis with a much slower tempo of disease progression than patients with peritoneal mucinous carcinoma.

There are also compelling reasons to classify all tumors with PP as adenocarcinoma, a practice advocated by the WHO.

- Anywhere else in the GI tract, epithelium proliferating outside the primary organ, without a basement membrane, would be classified as malignant.
- Mucinous tumors in other organs such as the pancreas can be deceptively bland.
- Although classic “destructive invasion” of the appendix is often lacking, these pathologists argue that “pushing invasion” is poorly defined and under-recognized.
- Organ invasion occurs in a substantial minority of these cases, particularly of course in the ovary, but also in the spleen.
- Most significantly, once these tumors have seeded the peritoneum, they pursue a relentless often fatal course unless they are aggressively treated.

Within that context, we will examine the more common classification systems for appendiceal mucinous tumors and for pseudomyxoma peritonei, and the molecular basis of PP. We will also review serrated lesions of the appendix in brief.

1. **The classification of appendiceal mucinous tumors.**

In 1995, Carr and co-authors at the AFIP published one of the seminal works in this field. In their series of 184 tumors, they defined three categories of mucinous neoplasms: adenoma; mucinous tumor of uncertain malignant potential (UMP); and adenocarcinoma.

- Adenoma. Dysplastic tumors that had intact muscularis mucosae.
- Mucinous tumors of UMP. Dysplastic tumors that are difficult to classify as clearly benign or malignant, reflecting the poorly defined criteria for invasion in mucinous neoplasms and the possibility that well differentiated carcinomas may be invading in a “pushing” manner.
- Adenocarcinoma. Tumors that demonstrate invasive neoplastic cells present beyond the muscularis mucosae. Also, “evidence of growth of viable cells outside the appendix was used as a firm criterion of malignancy.”

This report introduced the term mucinous tumor of uncertain malignant potential into the lexicon of appendiceal pathology. However, UMP was not universally accepted, and not all pathologists were comfortable classifying these tumors as adenocarcinoma based on finding epithelium outside the appendix in the absence of either destructive invasion or malignant cytology. Furthermore, as with any classification system, there were a few gray zones that were difficult to resolve. For instance, 5 UMPs were described as having epithelium outside the appendix, including 3 with epithelial cells outside the right lower quadrant and one with bilateral ovarian...
mucinous tumors. It is unclear why these cases would not be classified as adenocarcinoma based on their criteria of growth of viable cells outside the appendix.

Recently, Drs. Pai and Longacre\textsuperscript{19} proposed a classification of appendiceal mucinous tumors based on the AFIP classification of Carr and Sobin.

- **Adenoma.** Simple or focally stratified columnar epithelium with goblet cells; mild to moderate atypia; mitoses but no atypical mitoses; no stromal invasion; no extra-appendiceal epithelium. Strictly used to refer to a neoplastic process which “once completely excised, is benign and does not recur”. Perforation with acellular mucinous ascites is acceptable.
- **Mucinous tumor of UMP.** Same as adenoma but 1) The proximal margin is involved; 2) Mucin with epithelium is present within the wall but not clearly invasive; 3) Any uncertainty exists whether there is epithelium within extra-appendiceal mucin.
- **Mucinous tumor of LMP.** Same as adenoma but neoplastic cells are present in peritoneal implants.
- **Adenocarcinoma.** An invasive mucinous tumor.

This classification introduces the term M-LMP for mucinous tumors that have spread to the peritoneum but are not clearly “invasive” (M-LMP), a seemingly minor modification from the AFIP classification but one that carries major philosophical implications. Once again, stage is the basis for tumor classification, a practice some pathologists find objectionable. As with the AFIP classification, there are a few gray zones between categories. The term “adenoma”, according to their definition, is strictly used for tumors that do not recur, a difficult criterion to apply prospectively in practice. For instance, according to their article, 20% of “adenomas” rupture, yet rupture can rarely be followed by pseudomyxoma peritonei. Finally, classifying tumors as UMP based on a positive margin is contrary to the usual custom of tumor reporting.

In 2003, we reported our experience with 107 low grade appendiceal mucinous tumors ranging from tumors confined to the appendix to those with bulky peritoneal tumor.\textsuperscript{18} We felt that since appendiceal tumors that are confined to the appendix (ergo, “mucinous cystadenoma” or “villous adenoma”) are indistinguishable from those that have spread to the peritoneum, a single term should be used to encompass low grade appendiceal mucinous tumors, regardless of their stage. This approach conforms to the manner in which other tumors are classified and staged. Given the resistance to the terminology of “ruptured adenoma”, we proposed the term “low grade appendiceal mucinous neoplasm” for these tumors, fully recognizing that this terminology was a compromise but one that we hoped would simplify tumor classification. Some authors object to the use of the term LAMN for tumors that are confined to the appendix and therefore benign. In our practice, when confronted with this situation, we use LAMN along with a note that clarifies that the term is analogous to “mucinous cystadenoma”. Others have suggested that LAMN be used only for tumors that have spread to the peritoneum but are confined to the right lower quadrant. However, it is precisely this reliance on stage as the basis for tumor classification that we were attempting to eliminate. The main difficulty, I think, in our approach is classifying non-invasive appendiceal tumors with high grade cytology but that are confined to the appendix as mucinous cystadenocarcinoma when they are usually cured by appendectomy. Perhaps a better approach that conforms with GI pathology in other areas would be:
• Appendiceal mucinous neoplasm with low grade dysplasia
• Appendiceal mucinous neoplasm with high grade dysplasia
• Invasive mucinous adenocarcinoma

The controversy over whether peritoneal spread mandates a diagnosis of adenocarcinoma notwithstanding, this approach allows us to make a diagnosis for the primary appendiceal tumor regardless of stage. Furthermore, presently the literature is rife with studies in which the terms “mucinous adenocarcinoma” or “mucinous cystadenocarcinoma” are used to refer to tumors which invasiveness is not specified, and this approach would enable us to compare data from different studies by ensuring that “adenocarcinoma” refers only to tumors with conventional “invasion”, as recognized for myriad other adenocarcinomas in the GI tract.

Table I: Comparison of various classification systems for low grade appendiceal mucinous tumors

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<tr>
<th>Carr and Sobin</th>
<th>Pai and Longacre</th>
<th>Misdraji et al.</th>
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<td>Adenoma</td>
<td>Adenoma</td>
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<td>Uncertain malignant potential</td>
<td>Uncertain malignant potential</td>
<td>Low grade appendiceal mucinous neoplasm*</td>
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<tr>
<td>Adenocarcinoma</td>
<td>Low malignant potential</td>
<td>(LAMN with peritoneal spread)*</td>
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<td>Invasive Adenocarcinoma</td>
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*Used only for tumors with low grade cytology. Tumors with high grade cytology classified as mucinous adenocarcinoma.

Recently, Drs. Bradley and Geisinger published an interesting and provocative review of the controversy in this area. They are among the pathologists who take the firm stance that any appendiceal tumor that leads to pseudomyxoma peritonei is, by definition, malignant. They view the concept of a “ruptured adenoma” as one that is based on morphologic observations that are purely conjectural. They aver that the diagnosis of well-differentiated mucinous adenocarcinoma applies to appendices in which the muscularis mucosae is obliterated by fibrous or hyalinizing tissue, which they believe represents a broad front of invasion by the mucinous tumor. These authors apparently do not agree with many authors that mucinous “adenomas”, in the course of their evolution, accumulate mucin and the resulting increased intraluminal pressure within the appendix results in fibrosis of the wall. However, this phenomenon is not unique to the appendix. Porcelain gallbladder with dysplasia and pancreatic intraductal papillary mucinous neoplasm are two examples of sometimes cystically dilated organs in which the fibrotic wall of the lesion is not assumed to be “broad front invasion”. One has to wonder why the appendix would be unique in generating mucinous tumors that so frequently show this particularly subtle evidence of invasion. And by their own admission, this means that “many appendiceal tumours formerly labeled ‘adenoma’ are outright carcinoma.” Woodruff and McDonald may have been correct after all!
2. Classification of pseudomyxoma peritonei (PP)

Certainly, all pathologists agree that PP is a neoplastic process and one that is low grade but progressive. The controversy, then, centers on whether the epithelium is ‘adenomatous’ or ‘malignant.’ Some pathologists equate “adenomatous” with “benign”, and this has raised objections since the process of PP is not “benign” as we understand that word. But, is it possible that the epithelium in PP is “adenomatous” (ergo, derived from an “adenoma” rather than a “carcinoma”)? Clearly, adenomatous epithelium, itself being neoplastic, might be able to proliferate in the peritoneum once it has gained access to it, but perhaps still lack the ability to invade tissue or metastasize. In fact, two reported cases of PP developing after resection of colonic adenomas in which the authors theorize that adenomatous epithelium contaminated the peritoneum suggests that this may be possible.9

In 1995, Ronnett et al.22 classified 109 cases of PP into a low grade variety named by them “diffuse peritoneal adenomucinosis” (DPAM) and a high grade variety designated by them peritoneal mucinous carcinomatosis (PMCA). In their study, they defined adenomucinosis as peritoneal neoplasm composed largely of mucin associated with fibrosis and containing scant strips of simple to focally proliferative mucinous epithelium with minimal cytologic atypia and rare mitotic figures. The primary appendiceal tumor from which the peritoneal tumor derived was an “adenoma” in all cases. In contrast, peritoneal mucinous carcinoma was diagnosed by them when the primary tumor was an appendiceal or colonic mucinous adenocarcinoma and the peritoneal lesions were characterized by more abundant proliferative epithelium, glands, nests, or individual cells, including signet ring cells, and demonstrating marked cytologic atypia. Not surprisingly, they found a significant difference in survival between these groups with 5 year survival being 84% for DPAM and 6.7% for PMCA. In between these two extremes were several cases with features mostly reminiscent of DPAM but with focal “well-differentiated adenocarcinoma” (PMCA-intermediate) that had intermediate survival. In a follow up study, Ronnett et al.21 reported that the DPAM group had a 10 year survival of nearly 70% whereas patients with PMCA had 10 year survival of less than 5%. In this report, the authors clarified that PMCA-I behaved similar to PMCA and should be incorporated into PMCA. These studies illustrate that if one strictly defines classic PP as low grade peritoneal mucinous tumors derived from a ruptured appendiceal adenoma, a homogenous group of patients can be identified that has a similar prognosis and disease course.

In the large study of pseudomyxoma by Bradley and Geisinger,3 the authors classified peritoneal mucinous tumors as DPAM, PMCA-I, and PMCA based on Ronnett’s criteria. They confirmed that tumors at the low grade end of the spectrum had a better prognosis than tumors at the high grade end. They proposed that all peritoneal mucinous tumors be classified as mucinous carcinoma peritonei, low grade or high grade. However, the authors limited their study to patients with bulky peritoneal disease, and suggested that tumors limited to the right lower quadrant be classified using less than malignant terminology.

In our study,18 we focused on low grade mucinous tumors of the appendix and peritoneum. We found that peritoneal tumors with high grade cytology, even without complex architectural growth patterns, had a worse prognosis than tumors with low grade cytology. Therefore, we restrict the term “LAMN” to only those cases with very bland or low grade cytology and
diagnose mucinous adenocarcinoma for tumors with high grade cytology. The tumors we classified as mucinous adenocarcinoma in the peritoneum would be classified as mucinous carcinoma peritonei, low grade, using criteria proposed by Bradley et al. and as DPAM using criteria proposed by Ronnett et al. We found that tumors limited to the right lower quadrant were likely to recur as full-fledged pseudomyxoma peritonei; therefore, there is no inherent difference between “localized pseudomyxoma peritonei” and diffuse disease apart from tumor bulk and we do not advocate using different terminology for tumors confined to the RLQ and those with bulky peritoneal disease.

Table II: Comparison of classification systems for pseudomyxoma peritonei.

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<thead>
<tr>
<th>Ronnett et al.</th>
<th>Bradley and Geisinger</th>
<th>Misdraji et al.</th>
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<tr>
<td>Diffuse peritoneal adenomucinosis</td>
<td>Mucinous carcinoma peritonei low grade</td>
<td>Involvement by LAMN*</td>
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<tr>
<td>Peritoneal mucinous carcinomatosis</td>
<td>Mucinous carcinoma peritonei high grade</td>
<td>Mucinous adenocarcinoma</td>
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*Limited to tumors with low grade cytology

In summary, from a broad perspective, pseudomyxoma peritonei is a low-grade malignant process, regardless of the terminology one uses to describe it. Within the context of that, higher grade proliferations behave worse than low grade ones.

3. Molecular biology of appendiceal tumors: Are appendiceal epithelial proliferations the appendiceal counterparts of colonic polyps?

A. Mucinous adenomas

Since the observations made in the 1960s that mucinous adenomas are morphologically similar to colonic villous adenomas, there has existed the unchallenged assumption that these tumors are the appendiceal counterparts of colonic villous adenomas that assume a circumferential configuration due to the physical constraint of the small appendiceal lumen. However, the appearance of the neoplastic mucinous epithelium in the typical mucinous cystadenomas, with its tall mucin vacuole that compresses the nucleus, differs from the usual colonic type adenoma with elongate hyperchromatic nuclei (although the latter morphology can be seen in the appendix as a component of a mucinous cystadenoma). Furthermore, while polypoid tubular adenomas in the appendix are rare, they occur in familial adenomatous polyposis. In a review of 71,000 appendectomy specimens over 40 years, Collins reported 33 “benign mucosal polyps” and 6 “malignant mucosal polyps” associated with congenital familial polyposis but no cases of “mucocele” or pseudomyxoma peritonei. Invasive carcinoma of the appendix has also been reported in FAP. Mucosal polyps in FAP would be under the same physical constraints as
sporadic cases. Therefore, the association of FAP with polyps in the appendix but not
cystadenomas or pseudomyxoma is difficult to explain if mucinous cystadenomas are simply
appendiceal versions of colonic adenomas.

Molecular studies of appendiceal mucinous tumors are limited, but up to now have shown
similar molecular changes to colonic adenomas. K-ras mutations are frequent in appendiceal
adenomas. Interestingly, in one study, k-ras mutations were found in all 16 appendiceal
tumors associated with PP but in only 11 of 16 (69%) of tumors not associated with PP,
suggesting that k-ras mutation was necessary, but not sufficient for appendiceal mucinous tumors
to spread to the peritoneum. In the study by Yantiss et al., 17 mucinous adenomas were
studied, none of which was associated with PP, and only 41% had k-ras mutations. Loss of
heterozygosity (LOH) of chromosome 5q has been reported in a minority of mucinous adenomas
(22% in one study and 11% in another). As regards microsatellite instability, mucinous
adenomas have shown preserved expression of DNA mismatch repair genes and no BRAF
mutations even when they have serrated crypts. In summary, these limited data indicate that
mucinous adenomas and PP arise through the chromosomal instability pathway and share
molecular changes with colorectal tubular adenomas.

B. Serrated lesions

Serrated polyps in the colorectum (some hyperplastic polyps, sessile serrated adenomas,
traditional serrated adenomas, and mixed polyps) have gained notoriety as precursor lesions in a
newly described pathway for colorectal tumorigenesis. The serrated pathway of colorectal
tumorigenesis is characterized by microsatellite instability, frequent loss of expression of DNA
mismatch repair genes, and frequent BRAF mutations. Histologically, the full spectrum of
serrated lesions can be seen in the appendix, as in the colon. In fact, many authors have
commented that serrated lesions are particularly prevalent in the appendix. Also, Rubio recently reported 10 serrated adenomas of the appendix (defined by serrated fronds in more than
50% of the dysplastic structures but without molecular confirmation) of which 4 were associated
with an invasive carcinoma suggesting that these lesions might be more aggressive than serrated
adenomas in the colon. However, until recently, molecular studies have been lacking to confirm
that the ‘serrated pathway’ is significant in the appendix or that these serrated lesions are related
to serrated polyps in the colon.

In a large study of serrated polyps of the appendix, Yantiss et al. classified appendiceal serrated
polyps as either non-dysplastic (hyperplastic polyp, sessile serrated adenoma) or dysplastic
(serrated adenoma, mixed polyp). They found no evidence that these lesions were more
biologically aggressive than colonic serrated polyps. In their study, most serrated polyps in the
appendix had either BRAF (29%) or KRAS (34%) mutations. However, among nondysplastic
serrated polyps, the prevalence of BRAF mutation was less than the prevalence in colorectal
serrated lesions (reported to be > 70%). BRAF mutations were less common in “dysplastic”
serrated polyps and invasive carcinoma arising in serrated polyps than in non-dysplastic ones,
suggesting that the biologic significance of BRAF-mutated polyps in the appendix is limited.
Also of interest was the finding that many BRAF mutations were present in a minority of the
DNA (usually ≤ 25%). In contrast, most polyps with KRAS mutations showed alterations in
>25% of the extracted DNA, and most of these were dysplastic polyps, indicating that KRAS
mutations may be more biologically important in appendiceal serrated polyps. Finally, in 4 cancers arising in serrated polyps, they were unable to establish a clear relationship between the molecular changes in the serrated lesion and the carcinoma; none of the serrated polyps adjacent to carcinomas harbored \textit{BRAF} mutations; and most carcinomas also lacked \textit{BRAF} mutations except for one case in which a \textit{BRAF} mutation was identified in a minority of the DNA in the carcinoma but not in the associated serrated polyp. In summary, the data of this study indicate that serrated polyps in the appendix may be neoplastic, even when they lack overt dysplasia. Furthermore, they share some of the molecular changes of serrated polyps in the colorectum. However, they concluded that it is unclear that the serrated pathway is a major contributor to tumorigenesis in the appendix.

We examined 44 serrated lesions of the appendix,\textsuperscript{24} and found that most cases qualified as either "mucosal hyperplasia" or LAMN with serrated crypt architecture. Although distinguishing hyperplastic lesions from SSA can be difficult even in the colon, 9 of 10 cases of "mucosal hyperplasia" were MSS and one showed MSI-H. Three of seven (43\%) SSAs showed MSI-L. The only SA and both of the LAMNs tested were MSS. Interestingly, two SSAs with MSI-L and the "hyperplastic" lesion with MSI-H were associated with right sided colon cancer whereas none of the MSS lesions were. We concluded that serrated lesions of the appendix can be classified in a manner similar to colonic serrated polyps; that the serrated pathway is potentially a factor in the genesis of serrated lesions in the appendix; and that the association between MSI and right sided cancers may indicate a field defect.

One consistent finding of the available molecular studies is that mucinous adenomas in the appendix (despite their frequently having serrated gland architecture) do not show molecular changes of the serrated pathway. Therefore, a major point of distinction is mucinous cystadenoma with serrated crypt architecture or another type of serrated lesion. Although molecular data supports that many of the lesions in the latter group are neoplastic rather than hyperplastic, they are not associated with pseudomyxoma peritonei, even when the appendix has ruptured.

4. Treatment of appendiceal mucinous tumors with peritoneal spread

The treatment of patients with peritoneal spread from an appendiceal tumor is not standardized. Dr. Sugarbaker at the Washington Cancer Institute in Washington, D.C. has been a strong advocate of aggressive treatment of these patients. His method involves six peritoneal stripping procedures (called “peritonectomies”) including 1) greater omentectomy and splenectomy; 2) left upper quadrant peritonectomy; 3) right upper quadrant peritonectomy; 4) lesser omentectomy with cholecystectomy; 5) pelvic peritonectomy with rectosigmoid resection; and 6) antrectomy.\textsuperscript{25} Usually, patients do not require all 6 procedures (the reported mean being 3.4 procedures per patient).\textsuperscript{12} Peritonectomy is followed by intraoperative hyperthermic chemotherapy to expose the remaining tumor cells to the chemotherapeutic agent before adhesions develop that encase and protect tumor cells. This is often supplemented postoperatively by additional cycles of combined intraperitoneal and systemic chemotherapy. Using these aggressive techniques, Sugarbaker et al. reported 5 year survival of 86\% for patients with complete cytoreduction and adenomucinosis; 50\% for patients with hybrid or mucinous carcinoma and complete cytoreduction; and 20\% for patients with incomplete cytoreduction.\textsuperscript{26}
These protocols are associated with a 35% morbidity and 5% mortality rate. A favorable outcome is highly correlated with completeness of cytoreduction, yet complete cytoreduction is difficult to achieve, especially in patients with diffuse abdominal disease. Dr. Sugarbaker repeatedly emphasizes that patient selection affects the success of this procedure, creating a selection bias in his results. He notes that “noninvasive” histopathology is extremely important in selecting patients who are most likely to benefit from this treatment strategy and that patients with “hybrid” and mucinous adenocarcinoma do not receive as much benefit from these aggressive approaches. In the end, it is unclear whether Sugarbaker’s survival statistics are truly better than those reported by other centers.

The data in these various clinical studies are difficult to compare, given the variable way they are reported, the lack of consistent histopathologic classification, and the variable treatment strategies. However, the data suggest that there is a subset of patients with low grade disease that benefits from aggressive surgical resection of tumor, and that patients with high grade peritoneal malignancy are not surgical candidates. Beyond that, many of the details including what constitutes “peritonectomy” and the role of chemotherapy remain the subject of controversy. For instance, at MGH, patients with “pseudomyxoma peritonei” are offered “debulking” without intraoperative peritoneal chemotherapy, and patients with “peritoneal adenocarcinoma” are referred for systemic chemotherapy.

**Conclusion: The search for consensus**

In the end, much of the controversy surrounding appendiceal mucinous tumors is philosophical. In practice, we can all agree that there is a distinct subset of appendiceal mucinous tumors that lacks usual forms of destructive invasion but has a propensity to spread to the peritoneum and ovaries, frequently progresses to the clinical syndrome known as "pseudomyxoma peritonei", and often results in the demise of the patient despite the bland histology of the mucinous epithelium. The inconsistent classification of these tumors hampers our ability to understand these tumors and their biology. For instance, in a series of 37 appendiceal and ovarian “carcinomas” associated with PP, Gough et al. reported that all of the “cystadenocarcinomas” were diploid whereas only 48% of “adenocarcinomas” were diploid, a potentially intriguing statistic but one that is difficult to interpret. Therefore, the GI pathology community should strive to reach a consensus by agreeing on a classification that can be universally applied if not universally accepted. Finally, we must work with our clinical colleagues to define the histopathologic parameters that determine which patients will benefit from surgical therapies and which will not.

**References**


Appendiceal Mucinous Neoplasms
Controversial Issues

Joseph Misdraji, M.D.
GI pathology Unit
Massachusetts General Hospital
jmisdraji@partners.org
Controversies surrounding low grade appendiceal mucinous neoplasms and pseudomyxoma peritonei

1. The source of mucinous epithelium in pseudomyxoma peritonei (appendix, ovary, metaplasia of the peritoneal lining).
2. Whether concomitant ovarian mucinous tumors are independent primaries or metastatic from the appendix.
3. The significance of localized pseudomyxoma peritonei (right lower quadrant only).
4. The classification of appendiceal mucinous tumors.
5. The nature of the epithelium in pseudomyxoma peritonei.
6. Treatment of pseudomyxoma peritonei.
Historical Background

- 1842 Rokitansky recognizes the first mucocele of the appendix.
- 1884 Werth describes gelatinous material in the peritoneal cavity, and ascribed it to an ovarian cyst.
- 1901 Fraenkel reports finding pseudomyxoma peritonei (PP) in a male patient due to a ruptured cyst of the appendix.
- 1940 Woodruff and McDonald at Mayo Clinic classify 146 mucinous cystic tumors of the appendix.
  - “Benign mucocele”
  - Cystadenocarcinoma, grade 1 (malignant mucocele) – Papillary arrangement of the mucosa with hyperchromatic elongate nuclei. Only these can cause PP.
- In the 1950s, 60s, and 70s, doubts emerged about the malignant nature of these tumors when confined to the appendix. Since they resembled colonic adenomas, several authors used the term “mucinous cystadenomas” or “villous adenomas” to describe these tumors.
Ruptured adenoma
with seeding of the peritoneum
by “adenomatous” epithelium

Adenocarcinoma
with peritoneal carcinomatosis
Arguments for “Ruptured adenoma”

- “Destructive invasion” typical of adenocarcinoma is not seen in the appendix; rather, tumor accesses the peritoneum through “diverticula”, “herniations”, “ruptures”, “extravasations”.

- Classifying a tumor as “adenoma” or “carcinoma” based on finding epithelium outside the appendix is highly dependent on sampling by surgeon and pathologist to identify epithelium and contrary to the usual methods of classifying tumors.
Arguments for “adenocarcinoma”

- Broad front invasion is poorly defined and under recognized.
Pseudomyxoma peritonei: Review of the controversy

R.F. Bradley\textsuperscript{a,\*}, G. Cortina\textsuperscript{a}, K.R. Geisinger\textsuperscript{b}

\textsuperscript{a}Department of Pathology (GI/Liver), University of California at Los Angeles, Center for Health Sciences, 10833 LeConte Avenue, Los Angeles, CA 90095, USA

\textsuperscript{b}Department of Pathology, Wake Forest University Baptist Medical Center, Medical Center Boulevard, Winston Salem, NC 27157, USA
Adenoma – Dysplastic tumors that have intact muscularis mucosae.

Mucinous tumor of uncertain malignant potential (UMP)
- Dysplastic tumors that are difficult to classify as clearly benign or malignant, reflecting poorly defined criteria for invasion and the possibility of “pushing” invasion.
- Well differentiated mucinous epithelium pushing deeply into the underlying tissue without clear cut invasion, or mucin present in the wall or outside the appendix provided there was loss of m. mucosae.

Adenocarcinoma
- Tumors that demonstrate invasive neoplastic cells beyond the muscularis mucosae.
- “Evidence of growth of viable cells outside the appendix was used as a firm criterion of malignancy”.

AFIP Classification
Carr et al. Cancer 1995
• Low grade appendiceal mucinous neoplasm: All low grade appendiceal mucinous tumors, regardless of the presence or absence of pseudomyxoma peritonei.
• Mucinous cystadenocarcinoma, non-invasive
• Invasive mucinous adenocarcinoma
Pai and Longacre

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- Adenoma – Simple or focally stratified columnar epithelium without stromal invasion, mild to moderate atypia, no atypical mitoses. “Strictly used to refer to a neoplastic process which, once completely excised, does not recur.”
  - “…perforation is present in approximately 20% of cases”
- UMP – Same as adenoma but …
  - Proximal margin involved.
  - Mucin with epithelium in the wall, but not clearly invasive.
  - Any uncertainty exists whether there is epithelium within extra-appendiceal mucin.
- Low malignant potential – Same as adenoma but with epithelium in peritoneal implants.
- Adenocarcinoma – An invasive mucinous tumor.
Comparison of classifications of low grade appendiceal mucinous neoplasms

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<th>Misraji et al.</th>
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<td>Pseudomyxoma peritonei</td>
<td>Adenocarcinoma</td>
<td>Low malignant potential</td>
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Pseudomyxoma Peritonei

- Gross accumulation of mucin within the peritoneal cavity associated with mucinous epithelial implants.
- Although the controversy is sometimes framed as whether PP is “benign” or “malignant”, everyone agrees that PP is a progressive and frequently fatal disease; the controversy, then, is whether, in classical low grade PP, the epithelium originates from an appendiceal adenoma (and is therefore “adenomatous”) or a carcinoma.
Arguments that the epithelium in PP originates from an adenoma (and is therefore “adenomatous”)

- “Destructive invasion” typical of adenocarcinoma is not seen in the appendix; rather, tumor accesses the peritoneum through “diverticula”, “herniations”, “ruptures”, “extravasations”.
- Classifying a tumor as “adenoma” or “carcinoma” based on finding epithelium outside the appendix is highly dependent on sampling by surgeon and pathologist to identify epithelium and contrary to the usual methods of classifying tumors.
- The cytology of the peritoneal tumor is not “malignant”.
- Hematogenous spread to lymph nodes or outside the abdomen is rare.
- Parenchymal organ invasion is not typical.
- The tempo of disease progression is much slower, and the prognosis much better, than for usual peritoneal carcinomatosis.
- Adenomatous epithelium should be able to grow once outside the appendix.
Arguments refuting that the epithelium in PP is adenomatous

- Broad front invasion is poorly defined and under recognized.
- Epithelial cells outside the gut anywhere else would be considered cancer.
- Mucinous tumors elsewhere (e.g., pancreas) can be deceptively bland.
- Organ invasion occurs in a significant minority.
- Pseudomyxoma is frequently fatal if not treated aggressively and therefore “less than malignant” terminology is inappropriate and misleading.
Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis

*Ronnett et al. AJSP 1995*

- **Adenomucinosis:** Peritoneal neoplasm composed largely of mucin associated with fibrosis and containing scant strips of simple to focally proliferative mucinous epithelium with minimal cytologic atypia and rare mitotic figures. The primary appendiceal tumor in all cases was an “adenoma”.

- **Mucinous carcinomatosis:** Peritoneal lesions characterized by more abundant proliferative epithelium, glands, nests, or individual cells (including signet ring cells), and demonstrating marked cytologic atypia. The primary was an appendiceal or colonic mucinous adenocarcinoma.

- **Intermediate cases:** Mostly resembled DPAM but with focal “well differentiated adenocarcinoma”.

Ronnett et al. Cancer 2001
Pseudomyxoma Peritonei of Appendiceal Origin: A Clinicopathologic Analysis of 101 Patients Uniformly Treated at a Single Institution, With Literature Review

Robert F. Bradley, MD,* John H. Stewart, IV, MD,† Gregory B. Russell, MS,‡ Edward A. Levine, MD,† and Kim R. Gitsinger, MD*


**FIGURE 6.** Kaplan-Meier curves comparing survival between the low-grade (MCP-L) and high-grade (MCP-H) variants of MCP.
Cumulative Survival

Interval Following Initial Diagnosis (years)

- LAMN with peritoneal spread
- Noninvasive mucinous adenocarcinoma with peritoneal spread

p = 0.0085

## Comparison of classifications of pseudomyxoma peritonei

<table>
<thead>
<tr>
<th></th>
<th>Ronnett et al.</th>
<th>Bradley and Geisinger</th>
<th>Misraji et al.</th>
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<tr>
<td>“Classic pseudomyxoma peritonei”</td>
<td>Diffuse peritoneal adenomucinosis</td>
<td>Mucinous carcinoma peritonei, low grade</td>
<td>Involvement by LAMN</td>
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<td>High grade peritoneal carcinoma</td>
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<td>Mucinous carcinoma peritonei, high grade</td>
<td>Well differentiated mucinous adenocarcinoma</td>
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<td>Peritoneal mucinous carcinomatosis</td>
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</table>
Historically, “palliative” surgical debulking was the mainstay of treatment. Intravenous or intraperitoneal chemotherapy was inconsistently used as adjuvant therapy or after recurrence.

Aggressive management strategies aim for “cure”. Involve 6 peritoneal stripping procedures to achieve “complete cytoreduction” (CCR), intraoperative hyperthermic chemotherapy, additional cycles of intraperitoneal and systemic chemotherapy.
Interpreting Outcome Data: Is aggressive therapy better?

- Aggressive protocols associated with 35% morbidity and 5% mortality rate.
- Patient selection affects the success of these protocols, creating a selection bias.
  - “Noninvasive” histopathology.
  - Radiologic evidence of small bowel sparing.
  - Minimal residual peritoneal disease after cytoreduction.
- Complete cytoreduction is difficult to achieve (34% Gough; 55% Miner; 75% Sugarbaker), and recurrence is frequent (28% Sugarbaker; 90% Miner). Promising ‘cure’ is misleading to patients.
### Outcome Data

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<th>Low Grade</th>
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<th>High Grade</th>
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<td>5 yr</td>
<td>10 yr</td>
<td>5 yr</td>
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<tr>
<td>Sugarbaker 1999</td>
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<td>50%</td>
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<td>ICR</td>
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</table>

CCR = complete cytoreduction; ICR = incomplete cytoreduction
Long-term Survival Following Treatment of Pseudomyxoma Peritonei

An Analysis of Surgical Therapy

Thomas J. Miner, MD, Jinru Shia, MD, David P. Jaques, MD, David S. Klimstra, MD, Murray F. Brennan, MD, and Daniel G. Coit, MD

Treatment consensus

- Patients with low grade tumors in the peritoneum benefit from surgery, although “debulking” vs. “peritonectomies with chemotherapy” is debated.
- Patients with high grade tumors in the peritoneum do not benefit from surgery, and may even be harmed by it.
The search for consensus

- There exists a rather uniform subset of low grade appendiceal tumors that lack infiltrative invasion but spread to the peritoneum as classic pseudomyxoma peritonei.
- The histologic grade of the peritoneal tumor will impact prognosis and treatment.
- The challenge facing us as GI pathologists is to arrive at a consensus classification that incorporates morphology and biology, that is clinically relevant, and that has sufficient resolution to be applicable for research on these tumors.