A Consensus for Classification and Pathologic Reporting of Pseudomyxoma Peritonei and Associated Appendiceal Neoplasia

The Results of the Peritoneal Surface Oncology Group International (PSOGI) Modified Delphi Process

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Abstract: Pseudomyxoma peritonei (PMP) is a complex disease with unique biological behavior that usually arises from appendiceal mucinous neoplasia. The classification of PMP and its primary appendiceal neoplasia is contentious, and an international modified Delphi consensus process was instigated to address terminology and definitions. A classification of mucinous appendiceal neoplasia was developed, and it was agreed that "mucinous adenocarcinoma" should be reserved for lesions with infiltrative invasion. The term "low-grade appendiceal mucinous neoplasm" was supported and it was agreed that "cystadenoma" should no longer be recommended. A new term of "high-grade appendiceal mucinous neoplasm" was proposed for lesions without infiltrative invasion but with high-grade cytologic atypia. Serrated polyp with or without dysplasia was preferred for tumors with serrated features confined to the mucosa with an intact muscularis mucosae. Consensus was achieved on the pathologic classification of PMP, defined as the intraperitoneal accumulation of mucus due to mucinous neoplasia characterized by the redistribution phenomenon. Three categories of PMP were agreed—low grade, high grade, and high grade with signet ring cells. Acellular mucin should be classified separately. It was agreed that low-grade and high-grade mucinous carcinoma peritonei should be considered synonymous with disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis, respectively. A checklist for the pathologic reporting of PMP and appendiceal mucinous neoplasms was also developed. By adopting the classifications and definitions that were agreed, different centers will be able to use uniform terminology that will allow meaningful comparison of their results.

Key Words: appendiceal neoplasms, pseudomyxoma peritonei, appendix, peritoneum, Delphi technique

Pseudomyxoma peritonei (PMP) is a rare condition characterized by mucinous ascites and peritoneal implants, generally originating from a perforated mucinous tumor of the appendix.[1–6] Slow but relentless intraperitoneal growth without distant metastasis is typical. Occasionally, mucinous neoplasms from other organs, including ovary, colon, urachus, and pancreas, may present with the clinical appearances of classical PMP.[5–9] PMP rarely develops from primary ovarian neoplasia, and when it does so the lesion is typically a mature teratoma within which a mucinous neoplasm has developed.[10,11] Primary ovarian mucinous tumors can closely mimic appendiceal metastases histologically, although there are some morphologic features in the ovary that may point to the appendix as the source.[12]

The unique biological behavior of PMP makes classification of both the primary tumor and secondary peritoneal disease difficult and there has been considerable debate in the literature about the terminology of PMP and the mucinous appendiceal neoplasms that are its most common source. Unfortunately, the end result has been a variety of different proposed classi- fications[1–6,13] that can lead to confusion among treating clinicians.[14,15] Some of the terms used are contentious. For example, "adenomucinosis" for low-grade lesions is favored by some, but others believe it is unsuitable terminology.[13,15–17] It has also been recommended that the term "pseudomyxoma peritonei" should be used simply

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for the macroscopic appearance of mucinous ascites and not as a histologic diagnosis, or even abandoned completely,[1,6,15,17] but in the absence of an alternative terminology that is widely accepted PMP still appears as a histologic diagnosis in the 2010 World Health Organization (WHO) classification of tumors of the digestive system.[17]

A distinctive feature of PMP is the redistribution phenomenon. The mucus and the cells it contains follow the normal flow of peritoneal fluid and are "redistributed" within the peritoneal cavity to sites of fluid absorption through lymphatic lacunae and lymphoid aggregates.[18] Consequently, the tumor tends to spare mobile loops of small intestine but accumulates in other sites such as the pelvis, paracolic gutters, omentum, and liver capsule (Fig. 1). Bulky accumulations can form as the mucus is absorbed and epithelial cells "filtered out" and concentrated.

PMP has generally been classified according to the histology of the peritoneal disease rather than the primary tumor, and in this respect is unusual in oncology. Ronnett et al,[16] in a retrospective review, suggested that PMP could be classified into 3 prognostic groups: disseminated peritoneal adenomucinosis (low-grade group), peritoneal mucinous carcinomatosis (PMCA; high-grade group), and an intermediate group called PMCA-I; this classification was supported by others.[19] Conversely, other work suggested that a 2-tier system is preferable because the intermediate cases do not have a survival rate that is significantly different from other groups, although these intermediate cases were classified with the high-grade lesions by some (including the Ronnett group, who combined PMCA-I with PMCA based on their prognostic similarity)[20,21] and with the low-grade lesions by others.[13,22] In a consensus statement published in 2008, 44% of the participants used the Ronnett 3-tier classification, whereas 56% used a 2-tier classification.[23] Other authors have published evidence that PMP with signet ring cells has a significantly worse prognosis compared with other lesions classified as high grade and that signet ring cell involvement should be classified separately.[1,22,24]

These problems were discussed at the 2012 World Congress of the Peritoneal Surface Oncology Group International (PSOGI) in Berlin,[25] and it was proposed that a consensus method could lead to uniform terminology with an agreed set of definitions. The Delphi process is a consensus method that is applicable when there is lack of concordance of opinion because scientific evidence is lacking or contradictory.[26–28] It uses structured questionnaires that are sent to a panel of experts to assess the level of agreement. There are rounds of questioning in which the results of previous rounds are circulated to the participants, who have the opportunity to change their opinions in subsequent rounds in the light of the overall group response. Many individuals in diverse locations can participate on equal terms. The process is anonymous, which avoids dominance by influential individuals or special interest groups. As originally described, the Delphi process simply measures the degree of consensus among participants, but it can be modified to promote the development of consensus by allowing disagreements to be discussed and resolved.[28] We chose to use a modified Delphi process.

MATERIALS AND METHODS

Members of the panel of experts were identified by sending invitations to delegates who attended the 2012 PSOGI Congress in Berlin, and also to individuals who had published relevant and significant papers over the past 2 decades. Those who accepted the invitation were asked whether they knew of anyone else who should be asked to join the panel, and several other participants were identified in this way. There were 71 participants from 13 different countries. These individuals are listed in the Acknowledgements and reflect a broad representation of opinion by many leaders in the field. Thirty-four were

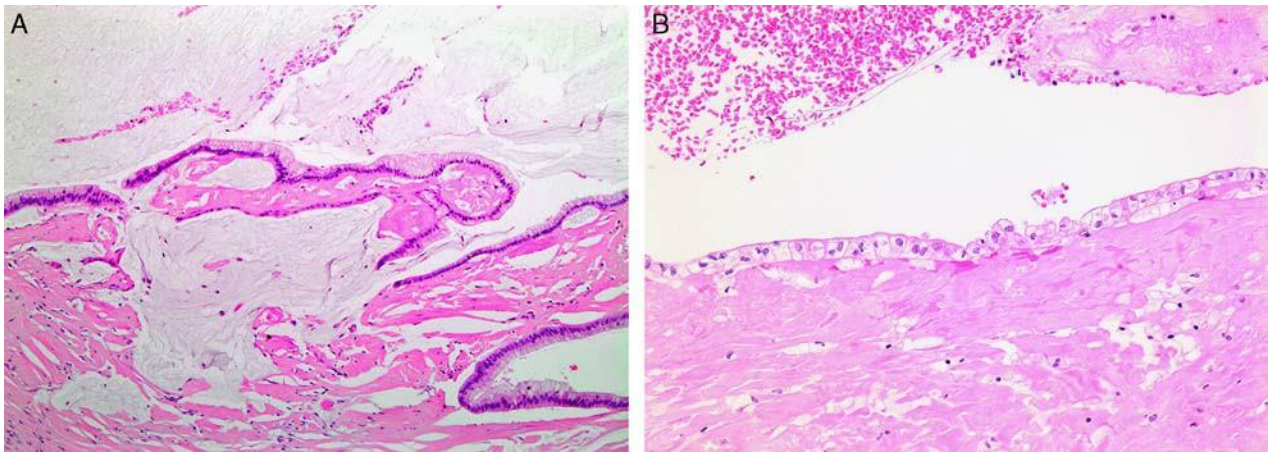

FIGURE 1. PMP derived from an LAMN. The specimen in (A) is from the right subphrenic space. The specimen in (B) is from the omentum and shows the hyaline fibrosis that is a common feature. Both specimens are classified as low-grade mucinous carcinoma peritonei/disseminated peritoneal adenomucinosis.

pathologists; the others were surgeons and medical oncologists.

The aim of the process was to reach a consensus on the terminology of PMP and appendiceal neoplasia, including goblet cell carcinoid but excluding other tumors with neuroendocrine differentiation. The 4 rounds of questions were all circulated by email along with the results of the previous round including the anonymized free-text responses from all the participants and comments from the lead coordinator (N.J.C.).

In round 1, the questions were designed to determine the range of opinions in the main areas of controversy and the free-text responses were analyzed thematically. This was followed by a 2-day conference held in May 2013 in Basingstoke, UK, to which all members of the expert panel were invited. The outcomes of round 1 were presented and discussed at this conference. The results of round 1 and the Basingstoke conference led to round 2, which, like round 1, encouraged discursive answers. For rounds 3 and 4, an attempt was made to distil the different opinions into choices between options so that the questions were based on simple voting as far as possible; there was still the opportunity for comments, but the voting allowed points of consensus to be identified clearly.

The result of voting is presented as a fraction in which the total number expressing an opinion is the denominator and the number of votes in favor is the numerator. For contentious questions, a consensus was defined as a two-thirds majority of voting participants excluding abstentions AND an absolute majority of all participants in that round. In the absence of a two-thirds majority, a simple majority was accepted for non-contentious issues.

RESULTS

The responses to round 1 demonstrated the extent of the problem. For peritoneal disease (ie, PMP), there were 6 different classifications used by panel members. Appendiceal lesions had an even wider range of terminology with 12 distinct classifications in use. It was particularly noteworthy that some of these classifications would use the term "adenocarcinoma" for lesions that others would call "low-grade appendiceal mucinous neoplasm," "mucinous tumor of uncertain malignant potential" or even "cystadenoma" (Fig. 2). Thus, a particular lesion could have a name implying malignant, uncertain, or benign behavior, depending simply on the terminology chosen by the reporting pathologist.

Nomenclature of Appendiceal Mucinous Neoplasms

The results are summarized in Table 1. This definition of appendiceal mucinous adenocarcinoma was agreed by 52/62 (84%):

- The term mucinous adenocarcinoma should be reserved for mucinous tumors with infiltrative invasion. They can be classified as well, moderately, or poorly differentiated.

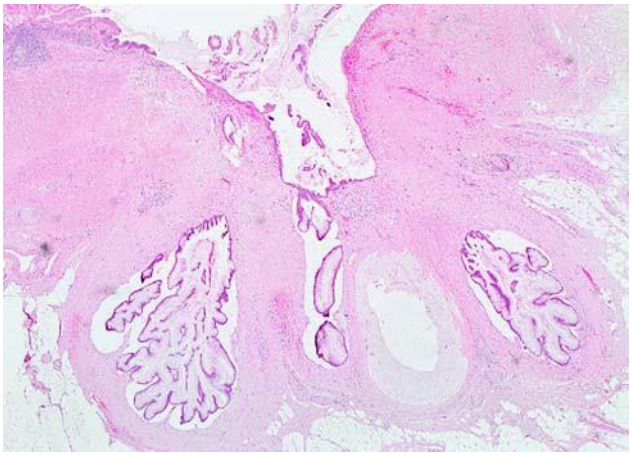

FIGURE 2. This appendiceal mucinous lesion consists of epithelium showing minimal cytologic atypia that is pushing into the underling appendiceal wall but without an infiltrative invasive pattern. In the consensus classification, the lesion is an LAMN.

In this context, infiltrative invasion is defined as in the footnote of Table 1 and illustrated in Figure 3. It can be distinguished from "pushing" invasion in which a broad front of cells expands into surrounding tissue without destructive features (Fig. 2). This pushing invasion is a common feature of low-grade appendiceal mucinous neoplasm (LAMN) and is often associated with fibrosis (Fig. 4), but not a desmoplastic response as defined above. The alternative classification of "adenocarcinoma" for tumors with any sort of invasive features and "adenoma" for any lesion without invasion, possibly with "mucinous tumor of uncertain malignant potential" for borderline cases, was discussed but was not supported by the majority of the panel.

There was discussion about the best name for lesions with the low-grade architectural features of LAMN but with high-grade cytologic features. The term high-grade appendiceal mucinous neoplasm (HAMN) was proposed and was supported by 30/44 (68%). This new term appears in Table 1 and is illustrated in Figure 5. We propose that HAMN should include lesions with high-grade dysplasia that is seen only focally, provided it is unequivocal.

The term signet ring cell carcinoma was supported for tumors in which >50% of cells show signet ring morphology (40/48, 83%), and the usual criterion that >50% extracellular mucin defines a lesion as mucinous applies. This appears in Table 1 and is consistent with the WHO classification of colorectal carcinomas and the reporting protocol of the College of American Pathologists.[29,30]

There was consensus that "cystadenoma" should no longer be recommended as a diagnostic term in the appendix (44/49, 90%). The term serrated polyp was supported for lesions that have serrated features resembling those of sessile serrated adenoma in the colon (Fig. 6).

TABLE 1. Classification of Noncarcinoid Epithelial Neoplasia of the Appendix

Lesion	Terminology
Adenoma resembling traditional colorectal type, confined to mucosa, muscularis mucosae intact	Tubular, tubulovillous or villous adenoma, low-grade or high-grade dysplasia
Tumor with serrated features, confined to mucosa, muscularis mucosae intact	Serrated polyp with or without dysplasia (low grade or high grade)
Mucinous neoplasm with low-grade cytologic atypia and any of: Loss of muscularis mucosae Fibrosis of submucosa "Pushing invasion" (expansile or diverticulum-like growth) Dissection of acellular mucin in wall Undulating or flattened epithelial growth Rupture of appendix Mucin and/or cells outside appendix	Low grade appendiceal mucinous neoplasm
Mucinous neoplasm with the architectural features of LAMN and no infiltrative invasion, but with high-grade cytologic atypia	High grade appendiceal mucinous neoplasm
Mucinous neoplasm with infiltrative invasion*	Mucinous adenocarcinoma—well, moderately, or poorly differentiated
Neoplasm with signet ring cells (≤ 50% of cells)	Poorly differentiated (mucinous) adenocarcinoma with signet ring cells
Neoplasm with signet ring cells (> 50% of cells)	(Mucinous) signet ring cell carcinoma
Nonmucinous adenocarcinoma resembling traditional colorectal type	Adenocarcinoma—well, moderately, or poorly differentiated

*Features of infiltrative invasion include tumor budding (discohesive single cells or clusters of up to 5 cells) and/or small, irregular glands, typically within a desmoplastic stroma characterized by a proteoglycan-rich extracellular matrix with activated fibroblasts/myofibroblasts with vesicular nuclei.

Definition of PMP

Although a few participants would prefer that "PMP" was abandoned altogether, the following definition of PMP was agreed (47/49, 96%):

- PMP is the intraperitoneal accumulation of mucus due to mucinous neoplasia characterized by the redistribution phenomenon. It can include mucinous ascites, peritoneal implants, omental cake, and ovarian involvement. It most commonly arises from appendiceal neoplasia.

Implicit in this definition is that PMP is a clinical syndrome, and that lesions with low-grade or high-grade histologic features can present clinically as PMP. The concept of redistribution, as discussed previously,[18] does seem to provide a way of distinguishing a lesion which most commonly arises in the appendix and is characterized by indolent growth generally confined to the peritoneal cavity, hence its inclusion in the definition.

It was agreed by 47/48 (98%) that PMP should be considered a malignant condition.

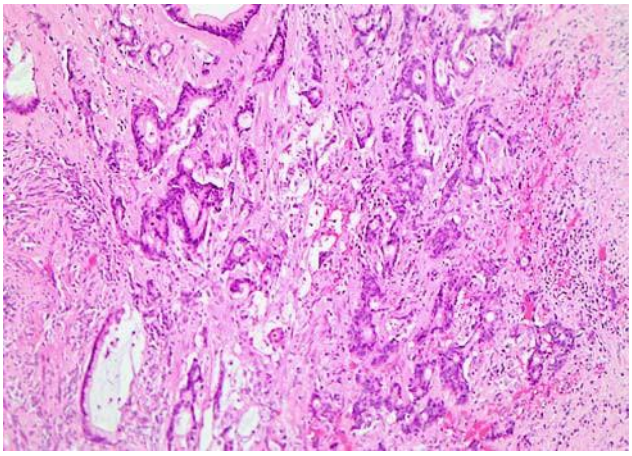

FIGURE 3. Infiltrative invasion in an appendiceal adenocarcinoma. Small, angulated glands are surrounded by desmoplasia.

Classification of PMP

Table 2 shows the consensus (57/62, 92%). Several participants stated they were unhappy with the term DPAM and felt it should be dropped, consistent with the controversy this term has caused in the literature.[13–15,17] However, it is widely used and the majority preferred to retain it as a synonym.

TNM Classification of PMP

Three options were offered for voting:

1. Staging should be based on whichever component (cells or mucin) has spread furthest.
2. Staging should be based on cells only; mucin should be disregarded.
3. The spread of cells and mucin should be assessed and recorded separately.

Of 62 participants, 22 (36%) voted for option 1, 15 (25%) for option 2, and 24 (39%) for option 3. Consequently, option 3 is used in the reporting checklist. Only

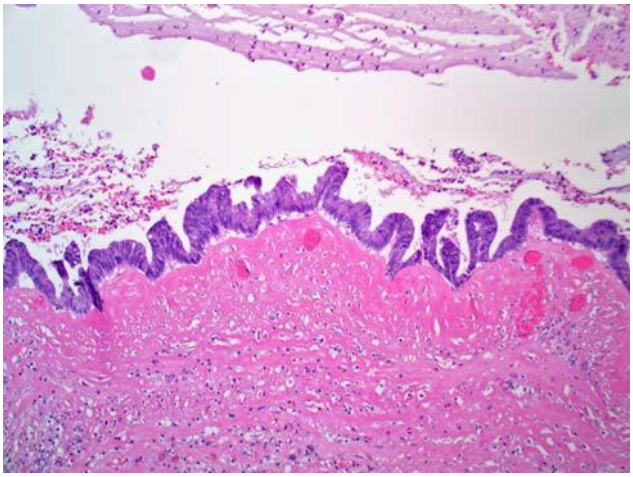

FIGURE 4. LAMN with hyaline fibrosis of the underlying tissue.

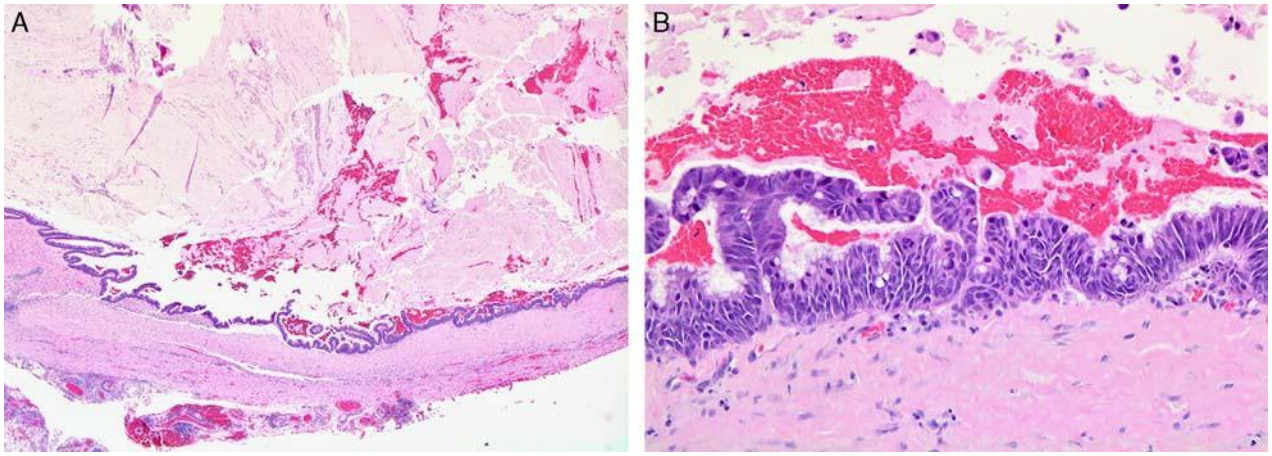

FIGURE 5. HAMN resembles an LAMN at low power (A) but the cytologic atypia is marked (B).

25% voted for option 2, so the overall consensus is that mucin should at least be considered in the staging process.

There was also discussion about the use of TNM to stage LAMN. In a vote, 39/60 (65%) were in favor of doing so. This is not quite a two-thirds majority, but it indicates considerable support for classifying LAMN using TNM criteria.

Grade in TNM Classification of PMP

The 7th edition of the TNM classification incorporates histologic grading for the staging of mucinous appendiceal tumors: stage IV disease without nodal metastasis is classified as IVA if well differentiated but IVB otherwise.[31] It was agreed by 47/48 (98%) that the grading should be of the peritoneal disease (ie, the PMP) rather than of the primary tumor. This is consistent with the fact that the grades appear only for stage IV.

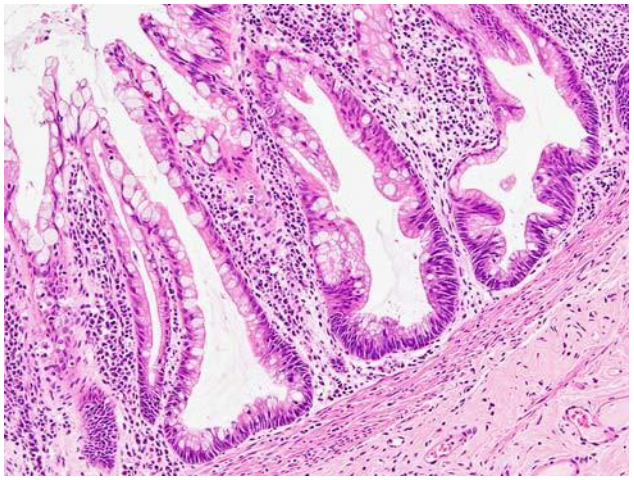

FIGURE 6. Serrated polyp of appendix without dysplasia. It closely resembles a sessile serrated adenoma of the colon. Note that the muscularis mucosae is intact.

Lymph Node Involvement and Grading

Some panellists suggested that tumors with nodal metastasis should automatically be classified as high grade. This was not supported by the majority, and the consensus was that lesions with low-grade morphology should be classified as such, even if nodal metastasis has occurred (32/48, 67%). Although rare, lesions with lymph node involvement and low-grade histology have been reported in the literature.[5,16,32]

Nomenclature of Goblet Cell Lesions

Many participants felt the name "goblet cell carcinoid" is misleading and inappropriate. However,

TABLE 2. Classification of PMP (Peritoneal Disease Component)

Lesion	Terminology
1. Mucin without epithelial cells	Acellular mucin (A descriptive diagnosis followed by a comment is likely to be appropriate, depending on the overall clinical picture. It should be stated whether the mucin is confined to the vicinity of the organ of origin or distant from it, ie, beyond the right lower quadrant in the case of the appendix. The term PMP should normally be avoided unless the clinical picture is characteristic.)
2. PMP with low-grade histologic features*	Low-grade mucinous carcinoma peritonei OR Disseminated peritoneal adenomucinosis (DPAM)
3. PMP with high-grade histologic features*	High-grade mucinous carcinoma peritonei OR Peritoneal mucinous carcinomatosis (PMCA)
4. PMP with signet ring cells	High-grade mucinous carcinoma peritonei with signet ring cells OR Peritoneal mucinous carcinomatosis with signet ring cells (PMCA-S)

*Omental cake and ovarian involvement can be consistent with a diagnosis of either low-grade or high-grade disease.

others pointed out that it is an established term recognized by tumor registries. Overall, there was overwhelming support for the principle of a new name with 55/61 (90%) agreeing that "goblet cell tumor" should be introduced as a synonym for "goblet cell carcinoid." There was support for classifying goblet cell lesions as mucinous or nonmucinous (33/42, 79%), the former having >50% extracellular mucin.

The concept of "adenocarcinoma ex goblet cell carcinoid" as defined by Tang et al[33] was preferred to the WHO term "mixed adenoneuroendocrine carcinoma" (MANEC).[17] Although MANEC could be used as a synonym, one reason for preferring the Tang terminology is that MANEC is arbitrarily defined as having gland-forming and neuroendocrine components comprising at least 30% of the tumor, which is not often the case in goblet cell lesions. However, 23/40 (58%) preferred not to include the subcategories of the Tang classification on the reporting checklist.

Reporting Checklist

Draft versions of a reporting checklist were circulated in rounds 2, 3 and 4. The final version (Fig. 7) is the result of numerous comments and suggestions, and reflects the consensus decisions of the panel.

DISCUSSION

The classification of PMP and mucinous appendiceal neoplasia has been controversial for many years.[1–8,13–17,22,34] With the development of curative treatment for PMP based on cytoreductive surgery and perioperative intraperitoneal chemotherapy, it is essential to harmonize terminology and diagnostic criteria, not only for the management of individual patients but also to allow comparison between institutions and different surgical techniques which can profoundly affect out- comes.[16,22,35] Cytoreductive surgery and perioperative intraperitoneal chemotherapy are now considered a standard of care for PMP,[36] and prognostic assessments from histopathology performed at institutions not using this technique must be approached with caution. Never- theless, pathologic appearances have been consistently demonstrated to be a key independent prognostic factor in PMP[5,13,16,20,35,37] and a uniform classification with prognostic significance is a crucial tool in clinical evalu- ation and therapeutic decision-making. The collective experience of the panel is that the clinical features of PMP can be produced by a range of histopathologic entities and we believe consistent reporting practices will facilitate the gathering of good data to help determine which le- sions are amenable to cytoreductive surgery.

Our aim was to develop a consensus by engaging leaders in the field in a modified Delphi process. A potential pitfall in the Delphi technique is bias in selection of the expert panel which can affect the final result.[27] We aimed to prevent this by inviting a wide range of individuals, including representatives from many different centers that treat large numbers of PMP patients, and then asking them to recommend anyone else who they felt should also be included.

Our method differs from a "classical" Delphi process in that questions were not simply statements to which the participants indicated a level of agreement, but instead encouraged discursive free-text responses that allowed analysis of complex themes and the introduction of new issues for discussion. Also, we invited the panel to a conference designed to facilitate interactive discussion and sharing of ideas in a way that would not be possible through on-line communication alone. It is notable that key authors of papers with different classifications attended the conference and participated in open discussion with experts with alternative viewpoints.[1,6,13,18,32,34]

Consensus was achieved on a range of issues. An important principle underlying the process was that identification of synonyms can facilitate consensus. If 2 different terms can be defined so they are equivalent, they can be used interchangeably and the diagnosis is clear irrespective of which system is most familiar to the user. An example is the interchangeable use of the terms intraepithelial neoplasia and dysplasia. Furthermore, since cancer registries recognize PMP as a classification and it appears in ICD-O, if alternative terminologies are proposed the way in which "PMP" is equivalent can be made explicit as in Table 2.

The consensus of the panel was that when "adenocarcinoma" is used for an appendiceal lesion it should imply infiltrative invasion characterized histologically by tumor budding, discohesive cells, angulated small glandular structures, and/or a desmoplastic response characterized by a proteoglycan-rich extracellular matrix and activated fibroblasts/myofibroblasts with vesicular nuclei.[38,39] Desmoplasia should be distinguished from bland fibrosis characterized by small, scattered fibroblasts within a dense, often hyaline, collagenous matrix, exemplified by the fibrous reaction to LAMN (Fig. 4). Some adenocarcinomas can have broad, expansile invasive fronts, but the presence of desmoplasia can be used a diagnostic criterion in this event.

A consequence of the consensus is that lesions beyond the mucosa without infiltrative invasion would be classified as LAMN or HAMN. The latter resemble LAMN in all essential respects except that high-grade cytologic atypia is present. "Noninvasive mucinous adenocarcinoma" has been used previously for such tumors,[1] but "HAMN" was preferred by the majority of the panel, who felt that linking "noninvasive" and "adenocarcinoma" is potentially inconsistent with the rest of the terminology, particularly because "pushing invasion" can be a feature of such lesions, while adenocarcinoma is defined by "infiltrative invasion." Polypoid adenocarcinomas which project entirely into the lumen are extremely rare in the appendix. They would be defined by the presence of an infiltrative pattern of invasion and/or desmoplasia, consistent with the definition.

In the classification of Pai et al,[34] "adenoma" was used for cytologically bland mucinous neoplasms clearly confined to the appendix without extra-appendiceal

Reporting Checklist for Appendiceal Mucinous Neoplasia and/or Pseudomyxoma Peritonei

Material in *italics* is optional and may be more relevant to research rather than routine reporting.
Note that the primary neoplasm and the peritoneal metastases are assessed separately.

Patient Details

Hospital Number	Name	DoB	Sex
Clinician	Sample Date	Consent form	

Clinical Details

Primary site	◯ Appendix ◯ Other (state) _____ ◯ Unknown
Previous appendicectomy?	◯ Yes: Date: _____ Diagnosis _____ Appendix entirely sampled? ◯ Yes ◯ No ◯ Not known ◯ No ◯ Not known
Previous mucinous tumor (other than in appendix)?	◯ Yes: Site: _____ Date: _____ Diagnosis _____ ◯ No ◯ Not known
Previous cytoreductions?	◯ Yes: Number of operations: _____ ◯ No ◯ Not known
Neoadjuvant therapy?	◯ Yes: Type _____ ◯ No
Clinical history and operative findings:	_____ _____
Cytoreduction:	◯ CC-0 (no visible disease) ◯ CC-1 (nodules <2.5 mm) ◯ CC-2 (nodules 2.5 mm - 25 mm) ◯ CC-3 (nodules >25 mm) *Peritoneal cancer index (PCI)* _____ *Confined to one quadrant?* ◯ *Yes (state which _____)* ◯ *No* ◯ *Not known / Not applicable*
Organs submitted:	◯ Appendix ◯ Greater Omentum ◯ Lesser Omentum ◯ Right Colon ◯ Transverse colon ◯ Left Colon ◯ Sigmoid ◯ Rectum ◯ Anus ◯ Subtotal colon ◯ Small bowel ◯ Gallbladder ◯ Liver segment ◯ Stomach (partial) ◯ Stomach (total) ◯ Spleen ◯ Right Ovary ◯ Left Ovary ◯ Uterus ◯ Umbilicus Peritonectomies: ◯ Right Parietal ◯ Left Parietal ◯ Pelvic ◯ Right Diaphragmatic ◯ Left Diaphragmatic ◯ Liver Capsule ◯ Falciform ligament ◯ Omental bursa ◯ Other: _____
Tumor bank:	◯ Yes: ◯ No ◯ Not known

FIGURE 7. (*continued*)

mucin or neoplastic epithelium. Such lesions should have essentially no risk of recurrence following complete resection. In the classification in Table 1, adenoma and serrated polyp would both be included in this category, although lesions with loss of muscularis mucosae would be called LAMN.

Davison et al[14] found that any of the following confer a worse prognosis in PMP of appendiceal origin: destructive invasion, high cytologic grade, high tumor cellularity, angiolymphatic invasion, perineural invasion, and signet ring cells. These features were used to classify lesions into 3 grades: G1 lacks all of these features; G2

Macroscopic

Description of specimen:

Block key:

Microscopic

PRIMARY SITE

◯ Appendix

◯ Other (give details in comments section): _____

◯ Primary site not included in specimen

APPENDIX (if present)

Type of appendiceal tumor, if present (indicate all that apply):

◯ Adenoma (State type: _____)

◯ Low grade appendiceal mucinous neoplasm (LAMN)
◯ High grade appendiceal mucinous neoplasm (HAMN)
◯ Mucinous adenocarcinoma*
◯ Non-mucinous adenocarcinoma (colorectal type)

◯ Goblet cell carcinoid (GCC)
◯ Mucinous goblet cell carcinoid*
◯ Adenocarcinoma ex GCC, mucinous*
◯ Adenocarcinoma ex GCC,non-mucinous

◯ Neuroendocrine tumor (other than GCC)**

◯ Other: _____

For carcinomas:

◯ Well differentiated (G1)
◯ Moderately differentiated (G2)
◯ Poorly differentiated (G3)
◯ Undifferentiated (G4)

For neuroendocrine tumors:

◯ Neuroendocrine tumor Grade 1
◯ Neuroendocrine tumor Grade2
◯ Neuroendocrine carcinoma

ki67 cell proliferation index: __%

Mitoses/10hpf: _____

Signet ring cells present?

◯ Yes – in mucin pools only
◯ Yes – within stroma
◯ No

If signet ring cells present:

◯ <10%
◯ 10% to 50%
◯ >50% (signet ring cell carcinoma)

Indicate furthest local extent of spread of mucin and c:ells

	MUCIN	CELLS
Confined to mucosa	◯	◯
Submucosa	◯	◯
Muscularis propria	◯	◯
Subserosal fat/mesoappendix	◯	◯
Beyond serosa (visceral peritoneum)	◯	◯
Directly invades adjacent structures	◯	◯ (specify: _____)

For appendicectomies:

◯ Margin clear (distance: _____mm)
◯ Margin not assessable
◯ Mucosal neoplasm present at margin
◯ Mural/extra-appendiceal epithelium or mucin present at margin

* Defined by >50% extracellular mucus.
** Using a reporting checklist specifically for neuroendocrine neoplasms is recommended.

FIGURE 7. (*continued*)

has 1 or more (except signet ring cells); and G3 has signet ring cells. Of note, "destructive invasion" in this study included not only infiltrative invasion as defined in Table 1, but also confluent cribriform growth, and small nests, glands, or single cells floating in small pools of mucin. The consensus classification in Table 2 divides PMP in which epithelial cells are found into 3 groups: low grade, high grade, and signet ring, which correspond to G1, G2, and G3 as described by Davison et al[14] and to PMP1, PMP2, and PMP3 as described by Shetty et al.[22] If

Other findings:

◯ Diverticulum (Site: tip / body / base)
◯ Extensive epithelial denudation
◯ Suppurative appendicitis
◯ Mural fibrosis
◯ Perforation through tumor (Site: tip / body / base)
◯ Perforation away from tumor (Site: tip / body / base)
◯ Other lesion: _____

Other features of tumor (optional):

Architectural pattern(s):

◯ *Flat strips of epithelium*
◯ *Villiform/papillary with fibrovascular cores*
◯ *Serrated*
◯ *Cribriform*
◯ *Single cells or small clusters in mucin pools*
◯ *Pushing, broad-front, expansile invasion*
◯ *Infiltrative, desmoplastic (classic) invasion*
◯ *Tumor budding/discohesive cells at invasion front*
◯ *Other:* _____

Cytologic atypia:

◯ *None*
◯ *Minimal*
◯ *Moderate*
◯ *Marked (high grade)*
◯ *Not assessable*

Mitotic activity:

◯ *Rare (0-2/10hpf)*
◯ *Occasional (3-5/10hpf)*
◯ *Abundant (>5/10hpf)*
◯ *Not assessable*

NODES

Site	Number examined	Number involved	Site	Number examined	Number involved
Mesoappendix			Omentum (gastro-epiploic)		
Right mesocolon			Stomach		
Left mesocolon			Spleen		
Other nodal basins (specify) _____					

Summary: Regional nodes: ◯ Positive ◯ Negative ◯ Not assessed
Non-regional nodes: ◯ Positive ◯ Negative ◯ Not assessed

VASCULAR AND PERINEURAL INVASION

Lymphovascular:	Perineural:
◯ Yes ◯ No	◯ Yes ◯ No

PERITONEAL DISEASE (includes omentum)

Mucinous disease involving peritoneum?
◯ Yes ◯ No

If yes, overall classification:
◯ Low grade mucinous carcinoma peritonei / DPAM (disseminated peritoneal adenomucinosis)
◯ High grade mucinous carcinoma peritonei / PMCA (peritoneal mucinous carcinomatosis)
◯ High grade mucinous carcinoma peritonei with signet ring cells / PMCA-S

Percentage of signet ring cells, if present: ◯ <10% ◯ 10-50% ◯ >50%

For appendiceal primaries:

Spread of acellular mucin:
◯ Acellular mucin confined to vicinity of appendix
◯ Acellular mucin beyond the right lower quadrant

Spread of epithelial cells:
◯ Epithelial cells confined to vicinity of appendix
◯ Epithelial cells beyond the right lower quadrant

FIGURE 7. (*continued*)

high-grade features are found, even focally, the lesion should be classified as high grade.[5,20,22]

In principle, any number of signet ring cells should classify a lesion as such, that is PMP3 in the Shetty system[22] and G3 in the Davison system.[14] However, Davison and colleagues required signet ring cells to be infiltrative and did not include cells floating in mucin pools that appeared degenerative. In another study, Sirintrapun et al[24] found that only signet ring cells invading tissue were of prognostic significance in 44 patients with

Other neoplasm involving peritoneum? ◯ Yes ◯ No	if yes, type: ◯ Goblet cell carcinoid ◯ Adenocarcinoma ex-goblet cell carcinoid ◯ Neuroendocrine tumor grade 1 ◯ Neuroendocrine tumor grade 2 ◯ Non-mucinous adenocarcinoma ◯ Other _____

Additional cellular features, if cells are present (optional):

Cytologic atypia:

◯ *None*
◯ *Minimal*
◯ *Moderate*
◯ *Marked (high grade)*

Mitotic activity:

◯ *Rare (0-2/10hpf)*
◯ *Occasional (3-5/10hpf)*
◯ *Abundant (>5/10hpf)*
◯ *Not assessable*

Architectural pattern:

◯ *Flat strip*
◯ *Villiform/papillary*
◯ *Serrated*
◯ *Cribriform*
◯ *Single cells or small clusters of cells floating in mucus*
◯ *Signet ring cells – discohesive*
◯ *Signet ring cells in confluent sheets*
◯ *Signet ring cells infiltrating stroma*
◯ *Infiltrative glands with irregular profiles*
◯ *Other* _____

Cellularity:

◯ *Acellular (no epithelial cells)*
◯ *Scant (<2% of mucinous component consists of cells)*
◯ *Moderate (2-19% of mucinous component consists of cells)*
◯ *High (≥20% of mucinous component consists of cells)*
◯ *Not assessable*

INVASION OF OTHER ORGANS

Organ invasion? (This includes any spread into the wall/parenchyma of the organ, whether infiltrative or not.) ◯ Yes ◯ No ◯ Not assessable	If yes, indicate organs involved: ◯ Ovary ◯ Spleen ◯ Large intestinal wall ◯ Small intestinal wall ◯ Stomach wall ◯ Myometrium ◯ Other: _____	Invasion pattern (indicate most aggressive pattern): ◯ Acellular mucin only ◯ Pushing, broad-front invasion by epithelium ◯ Infiltrative invasion by irregular glands or single cells with desmoplasia; includes tumor budding and discohesive cells at invasion front

NEOADJUVANT THERAPY

Neoadjuvant therapy given? ◯ Yes ◯ No ◯ Not known	Results of neoadjuvant therapy, if applicable: ◯ No significant histologic response ◯ Response: _____

TNM code:

COMMENTS:

_____

_____

PATHOLOGIST: **DATE:**

FIGURE 7. Reporting checklist.

high-grade disease. Furthermore, there may be significant interobserver variability when the number of cells with signet ring morphology is low.[14] This is an area in which diagnostic criteria remain to be defined consistently.

For cases in which epithelial cells are not found, "acellular mucin" was considered the best term (Table 2). Although other names have been suggested, for example "disseminated peritoneal mucinosis (DPM),"[40] they were

not supported by the panel. The term acellular mucin includes the picture seen when mucin simply extravasates from a mucinous tumor of the ovary (so-called organizing mucin). The presence or absence of cells in the peritoneal mucin is an important prognostic factor in PMP.[1,14,37,41,42]

An essential principle that was endorsed by the panel is that the histologic grade of the mucinous appendiceal primary and the peritoneal metastases may differ. Therefore, the classification of a lesion in Table 1 does not lead automatically to a corresponding classification in Table 2. For this reason, the panel felt, on balance, that using the same name for the appendiceal primary and the metastatic peritoneal disease was potentially confusing, and would not take into account those occasional cases in which there is discordance between the grade of the appendiceal and peritoneal lesions.

Some patients have LAMN with deposits in the ovary but only acellular mucin elsewhere in the abdomen or even an absence of peritoneal disease. The recognition that ovarian involvement can be part of the syndrome of PMP is helpful, since it allows a diagnosis of PMP even though cells are only found in the primary appendiceal lesion and the ovary.

Some participants pointed out that a lesion classified as high-grade mucinous carcinoma peritonei could have cytologic features that would be called low grade in a colorectal neoplasm. This is unavoidable unless a whole new nomenclature is proposed. The principle that names of appendiceal mucinous neoplasms do not correspond exactly with equivalent lesions in the colorectum is important.[14]

For lesions like those illustrated in Figure 6, the panel preferred "serrated polyp" to alternatives such as "sessile serrated adenoma." There were 2 main reasons: serrated lesions in the appendix have different mutations to their colonic counterparts, suggesting they are different types of neoplastic proliferation,[43] and some authors recommend "sessile serrated lesion" over "sessile serrated adenoma" in any case.[44] The panel supported the descriptive nomenclature of serrated polyp with or without dysplasia.

Although checklists for reporting appendiceal neoplasia exist, for example, the protocol published by the College of American Pathologists,[30] the panel identified a need for a checklist that specifically addresses the important features of PMP and its primary lesions. The result is shown in Figure 7. Although many participants commented on its length, all items were deemed important by at least some of the participants and the final version derives from multiple iterations. Histologic features used to classify lesions can be recorded as optional items; the criteria for cellularity of the peritoneal disease are based on those of Davison et al[14] with the addition of a "scant" group. The checklist could be modified for local use, but consistent recording of features on the checklist should promote meaningful comparison of findings between different centers. The optional information would not be required for routine reporting, but analysis of this sort of data could further our understanding of the correlation between histologic features and clinical outcome. For example, in some patients lesions classified as low grade on morphologic grounds behave aggressively.[45]

In patients with LAMNs confined to the appendix treated by appendicectomy, Arnason et al[46] found that the presence of neoplastic epithelium or acellular mucin at the proximal appendiceal margin was not associated with residual or recurrent disease. However, this series described only 16 patients, 6 of whom had a further surgical procedure, and on balance the panel preferred to include this information on the checklist.

Incidental neuroendocrine neoplasms are not uncommon in appendicectomy specimens, and the checklist conveniently includes the ability to record their presence. However, the checklist is designed specifically for patients with PMP and/or mucinous appendiceal neoplasms; for neuroendocrine tumors alternative reporting protocols may be more appropriate.

The modified Delphi process we describe was successful and productive, bringing together pathologists and clinicians from around the globe for open discussion to reach consensus on a controversial topic and ending long-standing confusion in terminology. The process may be applied to other disease entities and debateable terminology, and the panel members could be asked to contribute to future discussions, such as refining histologic criteria so that diagnostic groups are more uniform and reproducible.

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