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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

Discordant Diagnostic Terminology and Pathologic Grading of Primary Appendiceal Mucinous Neoplasms Reviewed at a High-Volume Center

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ABSTRACT

Background. Diagnostic terminology and grading of primary appendiceal mucinous neoplasms lacks uniformity. We sought to identify discordance in pathologic reporting by reviewing pathology slides for cases referred to our institution.

Methods. Using guidelines from Peritoneal Surface Oncology Group International (PSOGI) and American Joint Committee on Cancer 8th edition (AJCC8), we compared diagnostic terminology/grading of primary appendiceal mucinous neoplasms ($n = 115$) between pathology reports from referring institutions and review of slides by pathologists at our high-volume institution.

Results. There was discordance in pathologic terminology and grading of primary appendiceal mucinous neoplasms between referring institutions and our institution in 28% and 50% of patients, respectively. In particular, 24% of patients referred with mucinous adenocarcinoma (MACA) had LAMN on our review, and a higher grade MACA was found in 48% of patients referred with low-grade (G1) MACA and 16% of patients referred with high-grade (G2) MACA following our review. Discordance in tumor grade between primary and metastatic disease was seen in 19% of cases based on referred primary tumor grading compared with only 4% following our review. Systemic chemotherapy was unnecessarily administered to four cases of LAMN (6%) and inappropriately not administered to four cases of MACA (6%) before referral due to inaccurate diagnosis/grading by referring institutions.

Conclusions. We found significant discordance in diagnostic terminology/grading of primary appendiceal mucinous neoplasms following review of referred cases. Inaccurate pathologic assessment was associated with overtreatment or undertreatment with chemotherapy. These data highlight the need for pathologic review of such rare cases at high-volume centers.

Appendiceal mucinous neoplasms (AMN) are rare epithelial malignancies, with approximately 1000–2000 cases diagnosed each year in the United States.[1–3] These tumors are characterized by neoplastic epithelial cells containing abundant cytoplasmic mucin that is secreted into the lumen of the appendix. They have a high tendency for peritoneal metastasis, which occurs following rupture of the mucin-filled appendix or transmural invasion of mucin-secreting neoplastic epithelial cells. Peritoneal metastasis from AMN, referred to as pseudomyxoma peritonei (PMP) or mucinous carcinoma peritonei (MCP), is characterized by peritoneal dissemination of mucinous ascites and mucinous tumor nodules containing neoplastic epithelial cells.[4–7]

Cytohistologic features of neoplastic cells within these mucinous tumors are major determinants of prognosis and have been used to stratify patients into various proposed clinically relevant classification schemes.[8–17] These differing classification systems have led to significant confusion and controversy. Recently in 2016, the peritoneal surface oncology group international (PSOGI) provided expert consensus regarding terminology and pathologic reporting of AMN.[18,19] Similarly, the eighth edition of the American Joint Committee on Cancer

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(AJCC8) staging manual adopted the PSOGI diagnostic terminology and provided updated guidelines on the grading and staging of AMN.

Given the rarity of these tumors, myriad classification schemes, and persistent controversial aspects ("grey-zones") of terminology, grading, and staging, we hypothesized that there would be significant discordance in pathologic reporting of these cases between less experienced referring institutions and more experienced high-volume institutions. The objectives of this study were to (a) identify discordance in pathologic terminology/grading of primary AMN between less experienced referring institutions and our high-volume center, (b) assess correlation between primary tumor terminology/grade assigned by referring institutions and our center with corresponding metastatic disease for these cases, and (c) assess the impact of primary tumor terminology/grade assigned by referring institutions on appropriateness of systemic chemotherapy utilization prior to referral.

METHODS

Patients were included in this study if they (a) underwent cytoreductive surgery-hyperthermic intraperitoneal chemoperfusion (CRS-HIPEC) between 2002 and 2017 for AMN with peritoneal metastasis, (b) previously underwent resection of the primary neoplasm at an outside institution, and c) the pathology reports and slides of the primary neoplasm were reviewed at our institution. Pathology reports from referring institutions (considered "less experienced") and our institutional pathology report (considered "more experienced") for each case were retrospectively reviewed to assign terminology and grade consistent with updated classification schemes proposed by PSOGI/AJCC8. For a few cases in which our institutional pathology reports were unclear, a single expert pathologist (R.K.P.) re-reviewed the pathology slides. This study was approved by the Institutional Review Board at the University of Pittsburgh. Discordance rates were calculated as the total number of discordant cases to the total number of cases assessed in each category.

Classification of Primary Appendiceal Mucinous Neoplasms

At our institution, we utilize the PSOGI/AJCC8 classification systems to categorize primary AMN. Low-grade appendiceal mucinous neoplasms (LAMN) are defined as having low-grade cytology and any of the following: loss of the lamina propria and muscularis mucosae; submucosal fibrosis; "pushing" (expansile or diverticulum)-like growth into the wall; mural dissection of acellular mucin; or mucin and/or neoplastic epithelium outside the appendix wall. This "pushing" pattern of growth does not represent true "infiltrative" invasion and is not considered as evidence of adenocarcinoma. Rare primary AMN harboring high-grade cytology, including cribriform growth, loss of polarity with full-thickness nuclear stratification, enlarged nuclei, prominent nucleoli, numerous or atypical mitotic figures, but lacking "infiltrative" invasion are classified as high-grade appendiceal mucinous neoplasms (HAMN). In such cases, comprehensive histological evaluation of the appendix is performed to assess for "invasive" adenocarcinoma. Mucinous adenocarcinomas (MACA) of the appendix are defined by high-grade cytologic features and the presence of "infiltrative" stromal invasion into the wall of the appendix. Using the AJCC8 criteria for grading, primary MACA are either moderately differentiated (high-grade, G2) or poorly differentiated (high-grade, G3); G2 cancers exhibit high-grade cytology and "infiltrative" invasion, whereas G3 cancers also demonstrate signet ring cell differentiation. Whereas AJCC8 utilizes the terms well-differentiated (low-grade, G1) MACA and LAMN interchangeably, we utilize the term LAMN (not MACA G1) for such cases when lacking high-grade cytologic features and "infiltrative" invasion, and we classify them as moderately differentiated (high-grade, G2) MACA (not MACA G1) when they demonstrate any high-grade cytologic features and "infiltrative" invasion. This is because primary well-differentiated (G1) MACA are actually very rare.

Classification of Peritoneal Disease Derived from Appendiceal Mucinous Neoplasms

At our institution, we utilize PSOGI/AJCC8 criteria that advocate for a three-tiered classification system for peritoneal disease, based on the presence or absence of specific cytohistologic features, similar to those described by Davison et al.[10] and Shetty et al.[17] These criteria include "infiltrative" invasion, cytologic grade, tumor cellularity, angiolymphatic invasion, perineural invasion, and signet ring cells. Peritoneal disease is classified into well-differentiated (low-grade, G1) mucinous neoplasms (defined by AJCC8) or low-grade MCP (defined by PSOGI) demonstrating low-grade cytology, absence of "infiltrative" invasion, low tumor cellularity, and no signet ring cells; moderately-differentiated (high-grade, G2) MACA (defined by AJCC8) or high-grade MCP (defined by PSOGI) demonstrating high cytologic grade in the absence of signet ring cells; and poorly-differentiated (high-grade, G3) MACA (defined by AJCC8) or high-grade MCP with signet ring cells (defined by PSOGI) most often characterized by the presence of signet ring cells.

RESULTS

Between 2002 and 2017, primary epithelial appendix cancer pathology slides for 115 patients undergoing CRS-HIPEC at our institution were reviewed and compared with pathology reports from referring institutions. Median age of patients at CRS-HIPEC was 54.5 years and majority were female (55.7%). At the time of CRS-HIPEC, 31 patients (27%) had recurrent disease, whereas 84 patients (73%) had residual disease. Median intraoperative peritoneal carcinomatosis index (PCI) was 15. Complete cytoreduction (CC-0/CC-1) was achieved in 111 patients (96.5%; Table 1).

According to pathology reports from referring institutions, all patients had appendiceal mucinous neoplasms. A variety of terminologies were used by referring institutions to classify and grade primary AMN, including mucinous adenoma, mucinous cystadenoma, villous adenoma, mucinous neoplasm (unspecified), LAMN, HAMN, and MACA (unspecified, well-differentiated, moderately differentiated, poorly differentiated, signet ring cell). We consolidated outside pathologic terminology into the following categories, including 7 adenomas, 32 LAMN, 1 HAMN, 72 MACA, and 3 unspecified mucinous neoplasms. Following review of pathology slides at our institution, patients were diagnosed with 59 LAMN, 50 MACA, 5 goblet cell carcinoid tumors, and 1 nonmucinous adenocarcinoma.

There was discordance in pathologic terminology of primary AMN in 32 patients (27.8%) and discordance in pathologic grading in 57 patients (49.6%) between referring institutions and our institution. All seven cases of adenoma, the single case of HAMN, and the three unspecified mucinous neoplasms from referring institutions were LAMN following our review. All but one case of LAMN diagnosed at referring institutions were confirmed by our pathologists, with one case reassigned as MACA G2. Among the 27 MACA G1 cases diagnosed at referring institutions, there were 14 cases of LAMN and 13 MACA G2 cases, following our review. Of the 19 MACA G2 cases from referring institutions, there were 14 MACA G2 cases, 3 MACA G3 cases, 1 goblet cell carcinoid tumor, and 1 nonmucinous adenocarcinoma. Among the 18 MACA G3 cases diagnosed at referring institutions, there was 1 case of MACA G2, 13 MACA G3 cases, and 4 goblet cell carcinoid tumors. Of the 8 unspecified MACA from the referring institutions, there were 3 LAMN, 3 MACA G2, and 2 MACA G3 cases. The major discrepancy between referring institutions' pathology reports and our review of pathology slides for primary AMN involved reassignment of MACA G1 cases into LAMN and MACA G2 (Table 2). Histology slides of a representative case of LAMN that was referred to as a well-differentiated (G1) MACA (Fig. 1) and a moderately differentiated (G2) MACA, which also was referred to as a well-differentiated (G1) MACA (Fig. 2), are included.

Following CRS-HIPEC at our institution, pathologic assessment of metastatic disease revealed 57 cases of low-grade (G1) MCP, 32 cases of high-grade (G2) MCP, 20 cases of high-grade (G3) MCP with signet ring cells, 5 cases of goblet cell carcinoid tumor, and 1 case of nonmucinous adenocarcinoma. Following review of all primary AMN pathology at our institution (n = 109), there was minimal discordance in grading between the primary and metastatic disease. There were only four discordant cases overall (3.7%), with two cases of primary LAMN having high-grade (G2) MCP, and two primary MACA G2 cases having high-grade (G3) MCP. Conversely, we found frequent discordance (at least 21 cases, 19.3%) when comparing the referring institutions' pathology reports for primary AMN and the final pathologic diagnosis of metastatic disease at our institution. Of the 32 cases found to have high-grade (G2) MCP following CRS-HIPEC, 3 cases were referred with LAMN, 13 with MACA G1, 1 with MACA G3, and 2 with unspecified MACA. Of the 20 cases found to have high-grade (G3) MCP following CRS-HIPEC, 4 cases were referred with MACA G2, and 3 with unspecified MACA (Table 3).

To assess the impact of pathologic terminology/grading assigned by referring institutions on their decision to use (or not use) perioperative systemic chemotherapy for peritoneal metastases from AMN, we evaluated a subset of patients that underwent CRS-HIPEC at our institution more than 3 months following the initial diagnosis of peritoneal metastases (n = 68). Systemic chemotherapy was administered to 41 out of 68 patients (60.3%) in this subset before referral to our institution. Chemotherapy was administered

TABLE 1 Clinicopathologic and perioperative characteristics (n = 115)

Variable	Frequency
Age (year); median (range)	55 (24–78)
Female; n (%)	64 (56)
Disease status; n (%)	
Recurrent	31 (27)
Residual	84 (73)
PCI; median (range)	15 (0–36)
CC-score; n (%)	
CC-0	93 (82)
CC-1	18 (16)
CC-2/3	2 (2)

PCI peritoneal carcinomatosis index, *CC-score* completion of cytoreduction score

TABLE 2 Comparison of tumor terminology and grading for referred cases of primary appendiceal mucinous neoplasms (n = 115)

	Our pathology review				
	LAMN (n = 59)	MACA G2 (n = 32)	MACA G3 (n = 18)	GCC (n = 5)	NMACA (n = 1)
Referring Institution Pathology Report					
Adenoma (n = 7)	7				
LAMN (n = 32)	31	1			
HAMN (n = 1)	1				
MACA G1 (n = 27)	14	13			
MACA G2 (n = 19)		14	3	1	1
MACA G3 (n = 18)		1	13	4	
MACA (n = 8)	3	3	2		
Mucinous neoplasm (n = 3)	3				

LAMN low-grade appendiceal mucinous neoplasm, *HAMN* high-grade appendiceal mucinous neoplasm, *MACA* mucinous adenocarcinoma

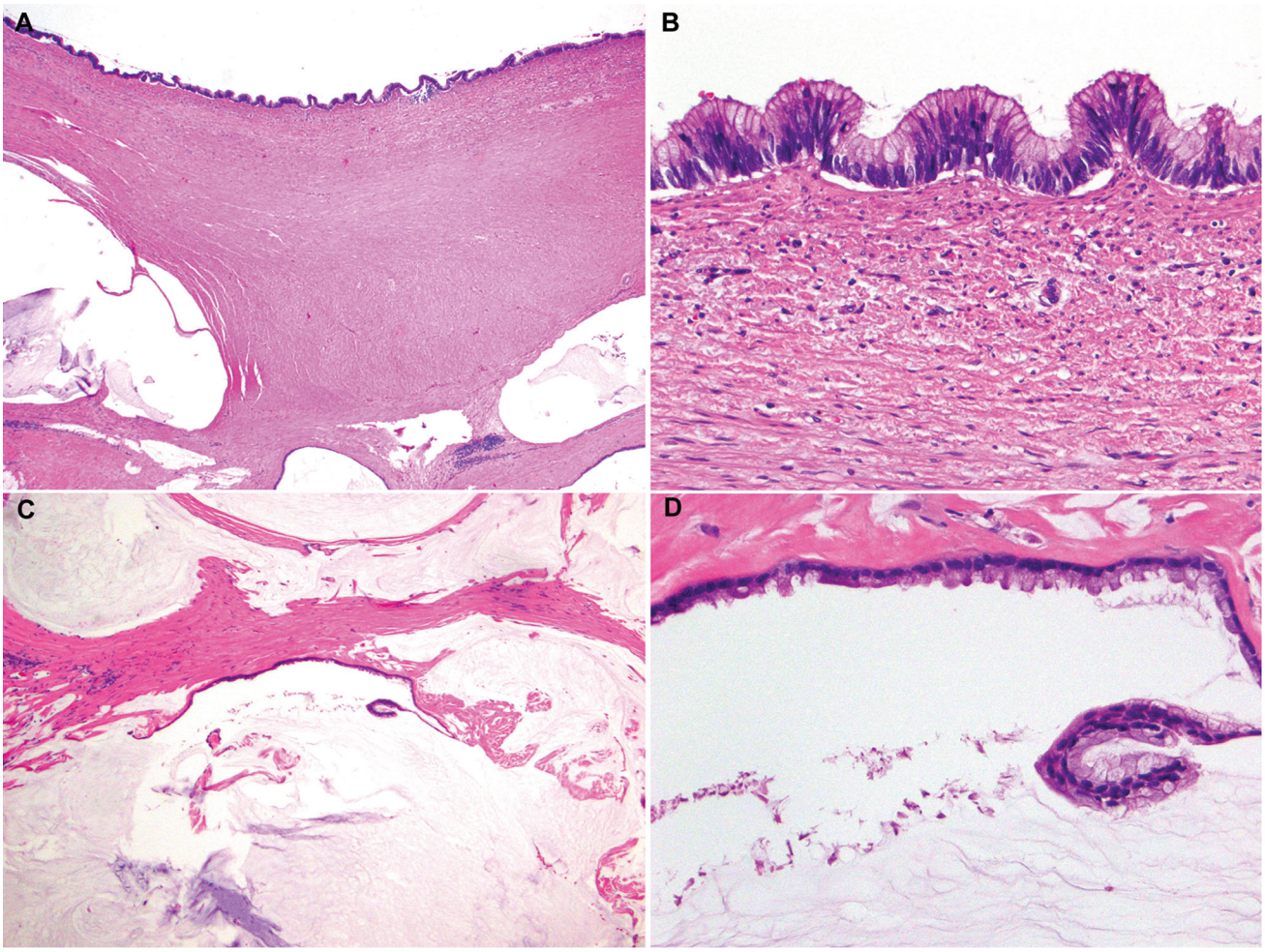

FIG. 1 **a** Primary appendiceal low-grade appendiceal mucinous neoplasm (LAMN) that was diagnosed as well-differentiated mucinous adenocarcinoma by the referring institution (2×). **b** The neoplasm demonstrates low-grade nuclear cytologic features and has no evidence of infiltrative invasion (20×). **c** The patient had peritoneal disease that also was diagnosed as well-differentiated mucinous adenocarcinoma by the referring institution (4×). The neoplasm in the peritoneum demonstrates low cellularity and no evidence of infiltrative invasion. **d** The neoplasm has low-grade nuclear cytologic features indicating a grade G1 neoplasm

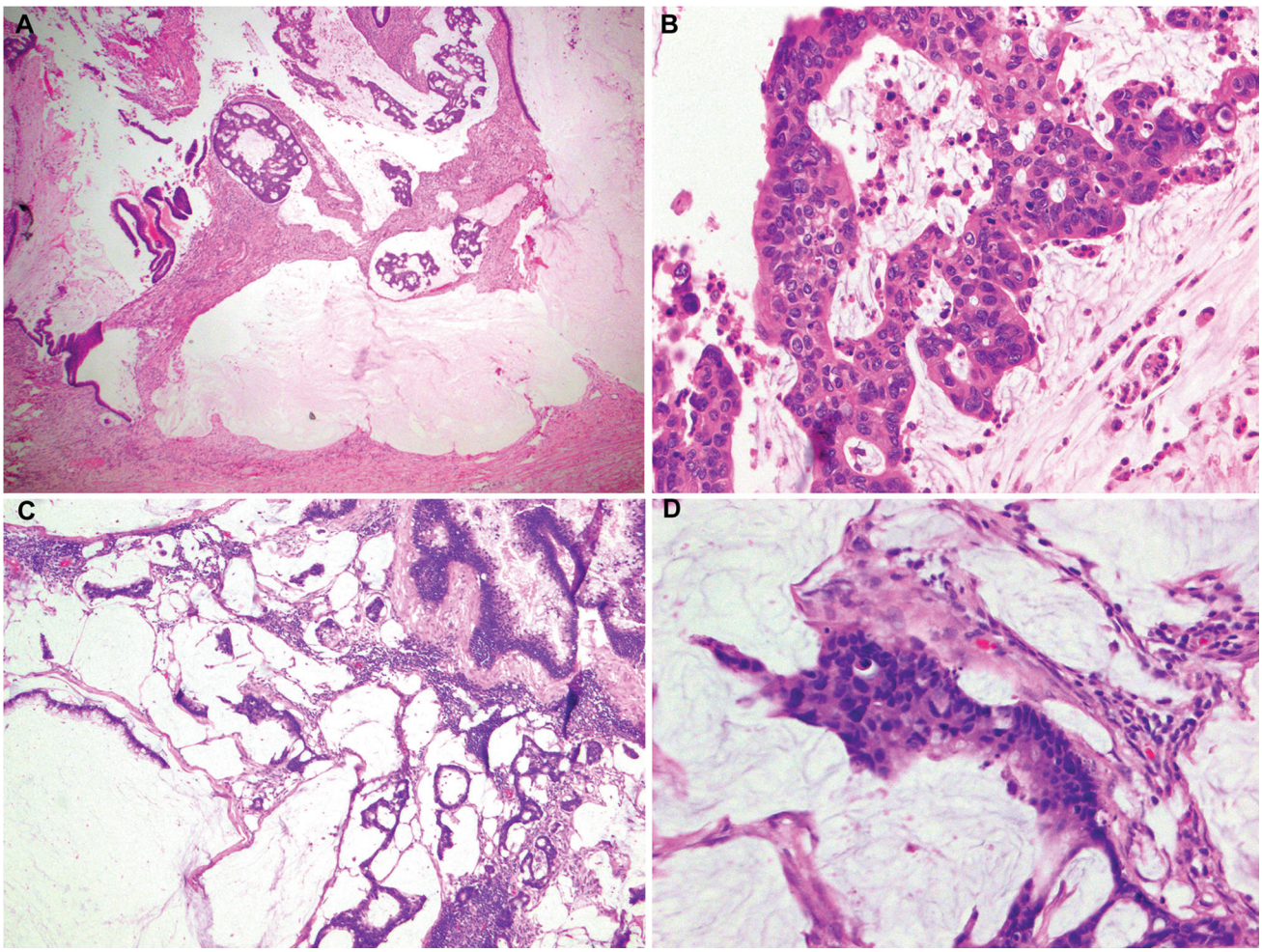

FIG. 2 **a** Primary appendiceal neoplasm diagnosed as well-differentiated mucinous adenocarcinoma by the referring institution (2×). The neoplasm demonstrates complex architecture and infiltrative invasion. **b** The neoplasm demonstrates high-grade nuclear cytologic features (20×) and is best classified as a moderately differentiated (G2) mucinous adenocarcinoma. **c** The patient has peritoneal disease, which also was diagnosed as well-differentiated mucinous adenocarcinoma by the referring institution (4×). The neoplasm in the peritoneum demonstrates high cellularity and evidence of infiltrative invasion. **d** The neoplasm has high-grade nuclear cytologic features indicating a grade G2 neoplasm

to three patients referred with primary LAMN (of which 2 cases were confirmed to be LAMN on our review) and six patients referred with MACA G1 (of which 2 cases were confirmed to be LAMN on our review). Therefore, we would consider unnecessary over-treatment with systemic chemotherapy in four patients diagnosed with LAMN following our review (5.9%). Chemotherapy was not administered to eight patients referred with primary MACA G1 (of which only 2 cases were MACA G2 on our review) and one patient each with MACA G2 and G3 (both of which had high-grade disease on our review as well). Therefore, we would consider undertreatment with systemic chemotherapy in four patients diagnosed with high-grade MACA following our review (5.9%; Table 4).

DISCUSSION

There is significant confusion in the pathologic reporting of AMN due to the rarity of the disease, numerous proposed classification schemes, lack of pathologists' expertise and persistent pathologic "grey-zones" of terminology and grading. Using newly proposed PSOGI and updated AJCC8 classification schemes for AMN, we identified discordance in pathologic terminology and grading of primary AMN between referring institutions (considered "less experienced') and our institution (considered "more experienced") in 27.8% and 49.6% of patients referred to our institution for CRS-HIPEC.

The major discordance between referring hospitals' pathology reports and our review of pathology slides for primary AMN involved reassignment of MACA G1 cases

TABLE 3 Comparison of primary and metastatic tumor terminology and grading for referred cases of primary appendiceal mucinous neoplasms (n = 109)

	Referring institution primary pathology	Our primary pathology
Low-grade (G1) mucinous carcinoma peritonei (n = 57)	Adenoma—7	LAMN—57
	LAMN—29	
	HAMN—1	
	MACA G1—14	
	MACA—3	
	Mucinous neoplasm—3	
High-grade mucinous carcinoma peritonei (G2) (n = 32)	LAMN—3	LAMN—2
	MACA G1—13	MACA G2—30
	MACA G2—13	
	MACA G3—1	
	MACA—2	
High-grade mucinous carcinoma peritonei (G3) (n = 20)	MACA G2—4	MACA G2—2
	MACA G3—13	MACA G3—18
	MACA—3	

Excluding 5 cases of goblet cell carcinoid tumors and 1 case of non-mucinous adenocarcinoma

LAMN low-grade appendiceal mucinous neoplasm, *HAMN* high-grade appendiceal mucinous neoplasm, *MACA* mucinous adenocarcinoma

TABLE 4 Impact of tumor terminology and grading on use of systemic chemotherapy before referral (n = 68)

Referring institution pathology report	Referring institution decision for systemic chemotherapy—NO (n = 27)	Our primary pathology	Referring institution decision for systemic chemotherapy—YES (n = 41)	Our primary pathology
Adenoma (n = 4)	4	LAMN	–	–
LAMN (n = 14)	11	LAMN	3	2 LAMN
				1 MACA G2
MACA G1 (n = 14)	8	6 LAMN	6	2 LAMN
		2 MACA G2		4 MACA G2
MACA G2 (n = 14)	1	MACA G2	13	8 MACA G2
				2 MACA G3
				1 GCC
				1 NMACA
MACA G3 (n = 17)	1	MACA G3	16	1 MACA G2
				11 MACA G3
				4 GCC
MACA (n = 4)	1	LAMN	3	1 MACA G2
				2 MACA G3
Mucinous neoplasm (n = 1)	1	LAMN	–	–

LAMN low-grade appendiceal mucinous neoplasm; *HAMN* high-grade appendiceal mucinous neoplasm; *MACA* mucinous adenocarcinoma

into LAMN (14 referred MACA G1 cases were reassigned as LAMN) or MACA G2 (13 referred MACA G1 cases were reassigned as MACA G2). Differentiation of LAMN from MACA often can be challenging, because cases of LAMN demonstrated tongues or a broad-expanding front of mucinous neoplastic epithelium pushing into the appendiceal wall that may be confused with "infiltrative" invasion, they may have neoplastic epithelium within mucin on the serosal surface of the appendix, and they may have focal areas of increased proliferation, or the occasional isolated glands in the stroma that may lead to an inaccurate diagnosis of MACA. The updated AJCC8

proposal utilizes the terms well-differentiated (low-grade, G1) MACA and LAMN interchangeably, whereas stating in the histologic grading section that "G1 tumors with peritoneal involvement may be categorized as LAMN with peritoneal involvement." This causes confusion since MACA by definition demonstrate "infiltrative" invasion, which is lacking in true low-grade (G1) tumors. In fact, cases of primary well-differentiated (G1) MACA are rare. We utilize the term LAMN (not MACA G1) for such cases when lacking high-grade cytologic features and "infiltrative" invasion, and we reclassify them as moderately differentiated (high-grade, G2) MACA (not MACA G1) when they demonstrate any high-grade cytologic features and "infiltrative" invasion. Moreover, the current proposed CAP (College of American Pathologists) proposal also states that histologic type of G1 tumors with peritoneal involvement are best recorded as LAMN. The interchangeable use of LAMN and MACA G1 by AJCC should be reevaluated to improve accuracy of pathologic reporting.

We found only four cases of discordant pathologic terminology/grading between primary neoplasms and metastatic disease following our review (overall discordance rate of 3.7%). Conversely, we found significant discordance between primary and metastatic disease grading when comparing primary tumor diagnosis assigned by referring institutions and post-CRS-HIPEC pathologic assessment of peritoneal disease at our institution (overall discordance rate of 19.3%).

Inaccuracies in diagnostic terminology/grading often adversely impacts subsequent clinical interpretation and management. While patients with low-grade (G1) MCP from LAMN do not benefit from systemic chemotherapy and generally demonstrate excellent long-term survival following optimal surgery, those with high-grade (G2/G3) MCP from high-grade (G2/G3) MACA likely benefit from combination of systemic chemotherapy and surgery. Based on our review of pathology for referred cases, four patients with LAMN/low-grade (G1) MCP were unnecessarily treated with systemic chemotherapy (chemotherapy overtreatment rate of 5.9%). Similarly, based on our review of pathology for referred cases, four patients with MACA/high-grade (G2/G3) MCP were inappropriately not treated with systemic chemotherapy before referral (chemotherapy undertreatment rate of 5.9%). Such cases do benefit from a combination of systemic chemotherapy and CRS-HIPEC for well-selected cases.

Despite recent updates and consensus guidelines for pathologic assessment, terminology, grading and reporting of AMN, there continue to be areas of controversy ("grey-zones") that require further clarification. The appropriate reporting of cytoarchitectural atypia spectrum into discrete grades remains challenging in cases with grade heterogeneity, for example in cases with questionable areas of increased cytologic atypia or proliferation in otherwise low-grade disease, focal areas of possible destructive invasion in otherwise predominantly low-grade disease, and questionable signet ring cells versus signet-ring cell-like morphology due to cellular degeneration.

This study has some important limitations, including its retrospective design, data collection from a single institution, and small sample size. This study required us to retrospectively review all pathology reports from referring institutions and some pathology reports from our institution and reassign tumor terminology and grading according to updated guidelines proposed by PSOGI and AJCC8. Because a variety of diagnostic/grading/classification schemes have been proposed over the extended time-period during which patients were included in this study, and the relatively recent guidelines from PSOGI/AJCC8 used to assess discordant reporting in this study, retrospective assignment of tumor terminology/grading may not accurately assess the primary objective. Data regarding preoperative chemotherapy administration before referral may not accurately represent clinical decision making for or against the use of systemic chemotherapy, because the therapeutic benefit for preoperative systemic chemotherapy is unclear and not considered the standard of care.

This study highlights significant discordance in pathologic terminology and grading of AMN between "less experienced" referring institutions and a single high-volume referral center where pathologists have significant experience assessing these rare tumors according to updated consensus guidelines proposed by PSOGI and AJCC8. These data suggest the need for pathologic review of all such cases by experienced pathologists at high-volume centers.

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DISCLOSURES None

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