Impact of Referral Center Pathology Review on Diagnosis and Management of Patients With Appendiceal Neoplasms

Jolanta Jedrzkiewicz, MD; Yoko Tateishi, MD, PhD; Richard Kirsch, MD, PhD; James Conner, MD, PhD; Danielle Bischof, MD, MS; Andrea McCart, MD; Robert Riddell, MD; Aaron Pollett, MD, MS; Emily L. Taylor, MS; Anand Govindarajan, MD, MS

• Context.—Data regarding the clinical impact of subspecialist pathology review of appendiceal neoplasms are limited.

Objective.—To determine whether pathology review by gastrointestinal pathologists at a tertiary-care referral center resulted in significant changes in the diagnosis and clinical management of appendiceal neoplastic lesions.

Design.—We conducted a retrospective review of all patients with an initial diagnosis of appendiceal neoplasm referred to a tertiary-care referral center in Ontario, Canada, from 2010–2016. The discordance rate between original and review pathology reports, the nature of discordances, and the impact of any discordance on patient management were recorded.

Results.—A total of 145 patients with appendiceal lesions were identified (low-grade mucinous appendiceal neoplasm [n = 79], invasive mucinous adenocarcinoma [n = 12], “colorectal type” adenocarcinoma [n = 12], goblet cell carcinoma and adenocarcinomas ex goblet cell carcinoma [n = 24], and other lesions/neoplasms [n = 20]). One or more changes in diagnoses were found in 36 of 145 cases (24.8%), with changes within the same category of interpretation (n = 10), stage (n = 7), grade (n = 6), and categoric interpretation (n = 5) being the most common. In 10 of 36 patients (28%), the diagnostic change led to a significant change in management, including recommendation for additional surveillance, systemic chemotherapy, additional surgery, or discontinuation of surveillance.

Conclusions.—Subspecialist pathology review of appendiceal neoplastic lesions led to a change in diagnosis in 36 of 145 cases (24.8%), of which nearly 30% (10 of 36 cases) led to a change in clinical management. The overall rate of clinically significant discordances was 7% (10 of 145). Our findings suggest that subspecialist pathology review of appendiceal neoplasms referred to specialized centers is justified.

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A large proportion of appendiceal neoplasms are first identified during pathologic review of appendectomies performed for presumed benign causes. The most common include well-differentiated neuroendocrine tumors (“carcinoids”), mucinous tumors, goblet cell carcinoids, and invasive adenocarcinomas. Clinical management is highly dependent on tumor type, histologic grade, pathologic stage, and resection margin status, and can vary from radical surgery to systemic chemotherapy or surveillance. Therefore, accurate pathologic assessment plays a critical role in patient management.

Challenges exist in the evaluation and reporting of appendiceal mucinous neoplasia, and can be related to both varied terminology and inherent difficulties in assessing certain histologic features. For example, low-grade mucinous neoplasms (LAMN) may be confused with potential mimics (eg, epithelial hyperplasia/regeneration in the setting of appendicitis or diverticular disease), extra-appendiceal mucin or neoplastic epithelium may be difficult to distinguish from artefactual contamination (“carry-over”) during grossing, degenerating mucinous epithelial cells may be mistaken for a signet ring cells, and the line between low-grade and high-grade (overtly infiltrative) mucinous tumor can be blurred.

In localized low-grade mucinous appendiceal neoplasms, the presence or absence of epithelial cells in extra-appendiceal mucin is one of the most critical prognostic factors. The limited literature suggests that the risk of recurrence as pseudomyxoma peritonei is in the region of 4% when acellular mucin is limited to the right lower quadrant, but it increases to around 36% if neoplastic epithelium is present in the mucin. In disseminated (stage...
IV) mucinous appendiceal neoplasia, tumor grade is the most important histologic determinant of prognosis and treatment. Two retrospective studies have shown that tumor grade using a 3-tiered system is the most important predictor of survival in stage IV appendiceal mucinous neoplasia; the prognostic importance of tumor grade is further supported by 2 large retrospective studies analyzing data from the Surveillance, Epidemiology, and End Results (SEER) and National Cancer Database.12–14 Patients with pseudomyxoma peritonei secondary to low-grade (G1) appendiceal mucinous neoplasms are generally treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, whereas those with high-grade (G2 and G3) mucinous adenocarcinoma will likely require systemic chemotherapy. Such differences in therapy underscore the importance of accurate tumor grading.

General surgeons may not be accustomed to treating these rare appendiceal tumors and therefore often refer patients to subspecialized centers for care. Mount Sinai Hospital in Toronto is a referral center for patients with appendiceal neoplasia diagnosed in the province of Ontario who might require additional treatment or surveillance. As part of quality assurance, surgical resections are reviewed by the gastrointestinal pathologists at Mount Sinai Hospital to confirm the original diagnosis and evaluate additional histologic features that may influence clinical management decisions.

The objectives of this study were to determine how often a second pathology review resulted in a change in the pathology report and how often this impacted patient care.

**Materials and Methods**

This retrospective study included all patients receiving a diagnosis of an appendiceal neoplasm at an outside institution whose pathology was reviewed between January 1, 2010, and November 16, 2016 at Mount Sinai Hospital. The anatomic pathology laboratory information system was searched to identify tumors originating from the appendix using the key words “appendix” and “appendicet.” Procedure types included appendectomies, appendectomies with cecal cuffs, piecemeal resections of appendix, and colectomies. Cases were excluded if the pathology review was requested by the original pathologist at an outside center for the purposes of initial diagnosis. Original pathology reports from the referring hospital were available in all cases and were compared with reports from the second review, to identify any diagnostic discordances.

The types of discordance were categorized as “change in categorical interpretation,” “change within the same category,” “change in threshold,” “change in grade,” “change in margin status,” “change in stage,” “change in lymph node status,” “minor,” or “other.” A “change in categorical interpretation” was assigned to cases showing a discordance in a diagnostic category (eg, neoplastic to nonneoplastic or benign to malignant). A “change within the same category” was assigned to cases in which the diagnoses, although different, fell into the same broad category (eg, goblet cell carcinoid versus adenocarcinoma ex goblet cell carcinoid). A “change in threshold” was assigned to diagnoses with a different level of interpretative confidence and would typically be associated with words like “atypical,” “suspicious,” or “favor.” Of note, differences in terminology (eg, mucinous tumor of uncertain malignant potential versus LAMN), identified in 37 reports, were not considered to represent a discordance. Reports from all cases of identified potential discordances were reviewed by 4 participating gastrointestinal pathologists to confirm or exclude the discordance and to reach consensus on the category of the discordance. The proportion of patients with discordances between original and review diagnostic reports was recorded.

A clinical chart review was performed for all patients with discordant pathology. The patients’ age, sex, and date of diagnosis were recorded, as were any changes in clinical management arising from the change in pathologic diagnosis. All patients were assessed by gastrointestinal surgical oncologists specializing in appendiceal- and peritoneal-based malignancies. Both original and review pathology reports were evaluated prior to any treatment decisions. All patients were reviewed at multidisciplinary tumor boards, and management was based on consensus recommendations. Changes in management included changes in surgical intervention, chemotherapy, surveillance/follow-up, and future treatment recommendations. Additionally, the patients’ status was assessed during their last documented follow-up. All data were tabulated and assessed in Excel spreadsheet, Microsoft Office Professional Plus 2016. This study was approved by the Mount Sinai Hospital Research Ethics Board.

**Results**

A total of 145 patients were included in the study, of whom 97 were men and 48 were women (male to female ratio: 2.02), with a median age of 56 years and mean age of 55 years. Specimens included 25 right hemicolectomies and 120 appendectomies (9 with subsequent right hemicolectomy). A total of 136 cases showed 1 appendiceal tumor, 2 cases had 2 tumors, and 7 cases showed nonneoplastic process/benign lesions according to the final diagnosis rendered at Mount Sinai Hospital (Figure 1). Although reporting terminology varied during the study period, the cases would now best correspond to the following current (American Joint Committee on Cancer [AJCC] 8th edition) categories: low-grade mucinous appendiceal neoplasm (LAMN; n = 79), invasive mucinous adenocarcinoma (n = 12), “colorectal type” (nonmucinous) adenocarcinoma (n = 12), goblet cell carcinoid and adenocarcinomas ex goblet cell carcinoid (n = 24), and other lesions/neoplasms (n = 20). Of the 79 LAMNs, no extra-appendiceal neoplastic epithelium was identified in 37, extra-appendiceal neoplastic epithelium was identified in 9, and pseudomyxoma and/or ovarian metastases were present in 33.

Overall, 36 of 145 cases had 1 or more changes in diagnostic interpretation, resulting in an overall discordance rate of 24.8%. A total of 41 diagnostic discordances were identified in 36 cases (32 cases had a single discordance, 3 cases had 2 discordances, and 1 had 3 discordances). The types of discordances are summarized in Figure 2. In 10 of 36 patients with a diagnostic discordance (27.7%) or in 10 of 145 overall cases (7%), the diagnostic change led to a significant change in management, including a recommendation for further surveillance (n = 2), chemotherapy (n = 5), additional surgery (n = 2), or discontinuation of further surveillance (n = 3; Table). Four patients had a change of diagnosis from LAMN to reactive epithelial changes (n = 3) or sessile serrated adenoma (n = 1), which led to discontinued surveillance (n = 3) or a change in plans for margin revision surgeries (n = 2). Additionally, 5 patients had a change in tumor grading, from low grade (ie, LAMN by AJCC 8th edition) to high grade (ie, mucinous adenocarcinoma by AJCC 8th edition) with or without a signet ring cell component, leading to completion helicobacter chemoba...
disease, 1 patient died of an unknown cause, and 1 patient was lost to follow-up.

**DISCUSSION**

This study found a discordance rate of around 25%, or in 36 of 145 cases, between original pathology reports and second review performed by experienced gastrointestinal pathologists at our institution. In 10 of 36 discordant cases (28%) or 10 of 145 overall cases (7%), the second review resulted in a material change in clinical management. The most common changes affecting clinical management included a change from LAMN to reactive atypia, and changes in tumor grade (Table). Alterations in management included changes in the surveillance plan, administration of systemic chemotherapy, or completion hemicolectomy. These findings suggest that routine pathology review of appendiceal neoplasms may be justified at specialized centers, both for patient management and quality improvement purposes. Rates of diagnostic discordance have been studied in many organ systems; however, data regarding diagnostic discordance in appendiceal neoplasia remain limited.\(^\text{15-17}\) In addition, to our knowledge there have been no prior studies evaluating the clinical impact of second pathology review in patients with appendiceal neoplasia.

With respect to diagnostic discordance, our findings are comparable with those of previously published studies.\(^\text{16,17}\) For example, Valasek et al\(^\text{16}\) reported a diagnostic discordance rate of 28.3%, which is similar to the rate of 24.8% (36 of 145 cases) in our study. Overinterpretation of reactive (often hyperplastic) epithelial changes as LAMN has previously been identified as a potential diagnostic pitfall.\(^\text{16}\) Complicated diverticular disease involving the appendix can induce epithelial changes that may mimic neoplasia, including hypermucinous epithelium with nuclear enlargement, hyperchromasia, and pseudostratification, which can be further complicated by the presence of perforation with extra-appendiceal mucin. These changes can result in misdiagnosis as LAMN, as has been previously reported, and our study further highlights this important diagnostic pitfall and its clinical implications.\(^\text{18}\)

Grading of mucinous tumors is another cause of diagnostic discordance with potential clinical implications, observed in several cases in our cohort. High-grade tumors have an increased risk of nodal and distant metastasis; therefore, completion hemicolectomy with nodal dissection...
and systemic chemotherapy may be indicated in these cases as part of the treatment.\textsuperscript{14,19,20} Davison and colleagues reported a high concordance rate for the grading of appendiceal mucinous tumors (94\% agreement; $\kappa = 0.91$); however, this study included subspecialist pathologists and cannot necessarily be extrapolated more broadly.\textsuperscript{14} Indeed, in our study, 15\% of discordances (or 6 of 41 discordances) were related to grade, suggesting that interobserver variation in the grading of appendiceal mucinous tumors may be more marked between nonsubspecialist and subspecialist GI pathologists.

Our study has several strengths as well as limitations. The main strengths include the large cohort size of an uncommon group of tumors and the demonstration of an impact of a second review on patient management decisions. An additional strength of the study is that our center is the only referral center dealing with peritoneal malignancies in the province and are thus more representative of the broader population. We cannot, however, exclude the potential for referral bias. To mitigate the risk of falsely inflating the discordance rate, we specifically excluded cases where the review at our center was performed at the request of a referring center because of diagnostic uncertainty. Thus, all patients included in our study had a final diagnosis rendered by an outside pathologist, and the referral was made by the patient’s local surgeon or medical oncologist for further management based on the final diagnosis. Compared with appendiceal mucinous lesions, appendiceal neuroendocrine tumors were underrepresented in our cohort, likely reflecting both the scope of practice at our peritoneal malignancy clinic and a perhaps a greater comfort that surgeons may have in managing these patients without pathology review or clinical consultation. As such, the agreement rate of pathology review of appendiceal neuroendocrine tumors cannot be well evaluated in our study.

It should be noted that the data presented here were obtained from comparing consultation reports generated during the study period to the original reports. No additional slide review was performed to adjudicate differences in opinion specifically for this study, and long-term outcome data have not yet accrued. Thus, while the findings demonstrate the real-world impact of expert slide review on clinical management decisions in a tertiary care center, the purpose of this study was not to directly compare diagnostic accuracy between specialized gastrointestinal pathologists and general surgical pathologists. Finally, assessing diagnostic discordance in appendiceal neoplasia is especially challenging because of evolving nomenclature schemes, especially for mucinous tumors, which adds to the complexity of pathologic interpretation and can be a source of confusion for the clinical team.\textsuperscript{21} However, we did not consider nomenclature-only differences to represent discordances.

In conclusion, our data indicate that routine pathology review of appendiceal mucinous lesions by gastrointestinal pathologists at referral centers is justified, because almost
one-quarter of reviewed cases resulted in a change in diagnosis, with nearly 30% (36 of 145 cases) of those subsequently leading to a significant change in patient management.

References
1. Connor SJ, Hanna GB, Frizelle FA. Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. Dis Colon Rectum. 1998;41(1):75–80.
2. Marudanayagam R, Williams GT, Rees BI. Review of the pathological results of 2660 appendicectomy specimens. J Gastroenterol. 2006;41(8):745–749.
3. Smeenk RM, van Velthuysen ML, Verwaal VJ, Zoetmulder FA. Appendiceal neoplasms and pseudomyxoma peritonei: a population based study. Eur J Surg Oncol. 2008;34(2):196–201.
4. McCusker ME, Coté TR, Clegg LX, Sobin LH. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. Cancer. 2002;94(12):3307–3312.
5. Shenoy S. Goblet cell carcinoids of the appendix: tumor biology, mutations and management strategies. World J Gastrointest Surg. 2016;8(10):660–669.
6. Blackham AU, Swett K, Eng C, et al. Perioperative systemic chemotherapy for appendiceal mucinous carcinoma peritonei treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Surg Oncol. 2013;109(7):740–745.
7. Mohamed F, Cecil T, Moran B, Sugarbaker P. A new standard of care for the management of peritoneal surface malignancy. Curr Oncol. 2011;18(2):e84–96.
8. Overman MJ, Fournier K, Hu CY, et al. Improving the AJCC/TNM staging for adenocarcinomas of the appendix: the prognostic impact of histological grade. Ann Surg. 2013;257(6):1072–1078.
9. Arnason T, Kamionek M, Yang M, Yantiss RK, Misraji J. Significance of proximal margin involvement in low-grade appendiceal mucinous neoplasms. Arch Pathol Lab Med. 2015;139(4):518–521.
10. Pai RK, Beck AH, Norton JA, Longacre TA. Appendiceal mucinous neoplasms: clinicopathologic study of 116 cases with analysis of factors predicting recurrence. Am J Surg Pathol. 2009;33(10):1425–1439.
11. Yantiss RK, Shia J, Klimstra DS, Hahn HP, Odze RD, Misraji J. Prognostic significance of localized extra-appendiceal mucin deposition in appendiceal mucinous neoplasms. Ann J Surg Pathol. 2009;33(2):248–253.
12. Asare EA, Compton CC, Hanna NN, et al. The impact of stage, grade, and mucinous histology on the efficacy of systemic chemotherapy in adenocarcinomas of the appendix: analysis of the National Cancer Data Base. Cancer. 2016;122(2):213–221.
13. Shetty S, Natarajan B, Thomas P, Govindarajan V, Sharma P, Loggie B. Proposed classification of pseudomyxoma peritonei: influence of signet ring cell on survival. Am Surg. 2013;79(11):1171–1176.
14. Davison JM, Choudry HA, Pingpang JF, et al. Clinicopathologic and molecular analysis of disseminated appendiceal mucinous neoplasms: identification of factors predicting survival and proposed criteria for a three-tiered assessment of tumor grade. Mod Pathol. 2014;27(11):1521–1539.
15. Middleton LP, Feeley TW, Albright HW, Walters R, Hamilton SH. Second opinion pathologic review is a patient safety mechanism that helps reduce error and decrease waste. J Oncol Pract. 2014;10(4):275–280.
16. Valasek MA, Thung J, Collarpalle E, et al. Overinterpretation is common in pathological diagnosis of appendix cancer during patient referral for oncologic care. PLoS One. 2017;12(6):e0179216.
17. Arnold CA, Graham RP, Jain D, et al. Knowledge gaps in the appendix: a multi-institutional study from seven academic centers. Mod Pathol. 2019;32(7):988–996.
18. Hsu M, Young RH, Misraji J. Ruptured appendiceal diverticula mimicking low-grade appendiceal mucinous neoplasms. Am J Surg Pathol. 2009;33(10):1515–1521.
19. Carr NJ, Finch J, Ilesley IC, et al. Pathology and prognosis in pseudomyxoma peritonei: a review of 274 cases. J Clin Pathol. 2012;65(10):919–923.
20. Srintrapun SJ, Blackham AU, Russell G, et al. Significance of signet ring cells in high-grade mucinous adenocarcinoma of the peritoneum from appendiceal origin. Hum Pathol. 2014;45(8):1597–1604.
21. Carr NJ, Cecil TD, Mohamed F, et al; Peritoneal Surface Oncology Group International. 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. Am J Surg Pathol. 2016;40(1):14–26.