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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

A Multi-institutional Study of Peritoneal Recurrence Following Resection of Low-grade Appendiceal Mucinous Neoplasms

Joel M. Baumgartner, MD, MAS[1], Amitabh Srivastava, MD[2], Nelya Melnitchouk, MD[3], Michael G. Drage, MD, PhD[4], Aaron R. Huber, DO[4], Raul S. Gonzalez, MD[5], Phoenix Bell, MD[2], Elizabeth Wu, MD[6], Murray Resnick, MD[6], Kiran Turaga, MD, MPH[7], Elizabeth Poli, MD[7], Jesus Esquivel, MD[8], Jeremiah Deneve, DO[9], Kaitlyn J. Kelly, MD[1], Jula Veerapong, MD[1], and Andrew M. Lowy, MD[1]

[1]Department of Surgery, University of California San Diego, La Jolla, CA; [2]Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [3]Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [4]Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY; [5]Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; [6]Department of Pathology and Laboratory Medicine, Warren Alpert School of Medicine, Brown University, Providence, RI; [7]Department of Surgery, University of Chicago, Chicago, IL; [8]Department of Surgery, Frederick Health Hospital, Frederick, MD; [9]Department of Surgery, University of Tennessee Health Science Center, Memphis, TN

ABSTRACT

Background. Peritoneal dissemination of low-grade appendiceal mucinous neoplasms (LAMNs), sometimes referred to as pseudomyxoma peritonei, can result in significant morbidity and mortality. Little is known about the natural history of localized (non-disseminated) LAMNs.

Objective. The goal of this study was to evaluate the risk of peritoneal recurrence in patients with localized LAMNs.

Methods. We performed a multi-institutional retrospective review of patients with pathologically confirmed localized LAMNs. Baseline characteristics, pathology, and follow-up data were collected. The primary endpoint was the rate of peritoneal recurrence.

Results. We identified 217 patients with localized LAMNs. Median age was 59 years (11–95) and 131 (60%) patients were female. Surgical management included appendectomy for 124 (57.1%) patients, appendectomy with partial cecectomy for 26 (12.0%) patients, and colectomy for 67 (30.9%) patients. Pathology revealed perforation in 46 patients (37.7% of 122 patients with perforation status mentioned in the report), extra-appendiceal acellular mucin (EAM) in 49 (22.6%) patients, and extra-appendiceal neoplastic cells (EAC) in 13 (6.0%) patients. Median follow-up was 51.1 months (0–271). Seven (3.2%) patients developed a peritoneal recurrence, with a median time to recurrence of 14.4 months (2.5–47.0). Seven (15.2%) patients with histologic evidence of perforation had recurrence, versus no patients (0%) without perforation ($p < 0.001$); five (10.2%) patients with EAM versus two (1.2%) patients without EAM ($p = 0.007$), and one (7.7%) patient with EAC versus six (2.9%) patients without EAC ($p = 0.355$) had recurrence.

Conclusions. This multi-institutional study represents the largest reported series of patients with localized LAMNs. In the absence of perforation or extra-appendiceal mucin or cells, recurrence was extremely rare; however, patients with any of these pathologic findings require careful follow-up.

Joel M. Baumgartner and Amitabh Srivastava have contributed equally to this manuscript.

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J. M. Baumgartner, MD, MAS
e-mail: j1baumgartner@ucsd.edu

Appendiceal neoplasms are discovered in approximately 1% of all appendectomies performed.[1] The most common appendiceal neoplasms include carcinoid tumors (aka neuroendocrine tumors), mucinous and non-mucinous invasive adenocarcinomas, and non-invasive mucinous neoplasms. The term low-grade appendiceal mucinous neoplasms (LAMNs) was first described by Misdraji et al.[2] and is defined as non-invasive mucinous appendiceal epithelial neoplasms with low-grade atypia.[3,4] LAMNs can be associated with appendiceal perforation, extra-appendiceal acellular mucin (EAM), and/or extra-appendiceal neoplastic cells (EAC).

LAMNs can disseminate throughout the peritoneal cavity, giving rise to diffuse mucinous peritoneal metastases, referred to as pseudomyxoma peritonei (PMP), disseminated peritoneal adenomucinosis (DPAM), or low-grade mucinous carcinomatosis peritonei (LGMCP).[4] The risk of peritoneal dissemination developing in patients presenting without initial evidence of visible peritoneal involvement is not well-defined. Small retrospective series have estimated the risk at 0–75%, depending on the presence of appendiceal perforation, EAM, or EAC.[5–11]

Using a large multi-institutional cohort, we sought to better define the risk of peritoneal recurrence in resected localized LAMNs.

METHODS

Study Design

This was a retrospective multi-institutional cohort study of patients who underwent resection for localized (non-disseminated) LAMNs with clinical follow-up. Data were collected from seven treatment teams at nine institutions with Institutional Review Board approval. Inclusion criteria included patients with pathologically confirmed LAMNs (by review of surgical specimen blocks and/or slides by index institutions) using 2019 World Health Organization (WHO) pathologic criteria,[3] without peritoneal dissemination/metastases (by review of available operative notes, pathology specimens and reports, and perioperative imaging reports; patients with contiguous mucin extending to the right lower quadrant or pelvis were included, while those with discontinuous peritoneal implants were excluded), who underwent surgical resection of the appendix (appendectomy, right hemicolectomy/cecectomy) and surveillance/follow-up at the index institution.

Data Collection

Data were collected from review of the medical records or from pre-existing research databases at each institution (from 1986 to 2018), and included demographic details, operative details, pathologic information, surveillance data, development and treatment of peritoneal recurrence, and date of last follow-up and vital status (alive with no evidence of disease, alive with evidence of disease, dead of other cause, dead of index cause). Since all included institutions were peritoneal surface malignancy referral centers, many of the cases were initially treated at other institutions. In these instances, pathologic specimens and the outside medical records were reviewed at the referral institution. In all cases included in this study, the pathologic specimens were reviewed to ensure they met the 2019 WHO criteria for LAMN.

For the literature review, English-language studies were identified from PubMed (2003–2020), which included patients with initially localized/non-disseminated LAMNs using the modern histologic LAMN definition, data on the presence of extra-appendiceal mucin and/or neoplastic cells, and had clinical follow-up of at least 2 years. Search terms were used and connected by the Boolean operators AND/OR, and included appendix, mucocele, and mucinous neoplasm. The median follow-up, presence of EAM or EAC, and the proportion of patients with peritoneal recurrence were collected.

Follow-Up

Surveillance was defined as any subsequent visit/test for the purpose of monitoring for the recurrence of LAMNs, and the following types of surveillance were measured: imaging follow-up for those with any surveillance imaging [ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), etc.] or clinical follow-up for those with any clinic visit and/or serologic tumor markers for surveillance. Patients with no surveillance had no evidence of imaging or clinical follow-up for the purpose of monitoring for LAMN recurrence. Patients with unknown surveillance had unclear evidence of subsequent imaging and clinical follow-up for LAMN monitoring (i.e. they had further visits or imaging for unknown reasons). Those not surveyed or with unknown surveillance status had their medical record reviewed for recurrence and survival details. Time from the date of initial operative treatment (i.e. the earlier date in patients who underwent initial appendectomy followed by colectomy) to last follow-up and/or recurrence were used for follow-up, surveillance, and time-to-recurrence and/or death endpoints.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 26.0 (IBM Corporation, Armonk, NY, USA), and dichotomous variables were compared using Chi square analyses or Fisher's exact test. *P*-values < 0.05 were considered statistically significant. Concordance was calculated by dividing the sum of true positives and true negatives by the sum of true positives, true negatives, false positives, and false negatives. The Kaplan–Meier technique was used to estimate follow-up and time to recurrence.

RESULTS

Baseline Characteristics and Surgical Treatment

Overall, 217 patients met the eligibility criteria and had adequate follow-up from the participating institutions. The majority of patients (69.1%) underwent appendectomy with or without partial cecectomy (not requiring an ileocolic anastomosis) (Table 1). Six patients (2.8%) underwent initial appendectomy followed by interval right hemicolectomy once a diagnosis of LAMN had been made. Seven patients (3.2%) underwent hyperthermic intraperitoneal chemotherapy (HIPEC) as part of definitive surgical therapy after an initial diagnosis of LAMN.

All patients had pathologic confirmation of localized LAMNs according to the 2019 WHO criteria.[3] Examples of the histologic spectrum of LAMNs are shown in Fig. 1. Histologic evidence of appendiceal perforation was identified in 46 (21.2%) cases, but was not reported or was unknown in the remainder of cases ($n = 171$, 78.8%) (Table 1). Gross description of perforation noted at the time of initial surgery was reported in 25 (11.5%) cases, and was reported to be absent in 87 (40.1%) cases and unknown in 105 (48.4%) cases. Concordance between gross and histologic perforation status was 84%. Forty-nine (22.6%) patients had EAM seen on the submitted specimen, whereas 13 (6.0%) patients had extra-appendiceal mucin with neoplastic cells, and 155 (71.4%) patients had neither. All 13 patients with EAC were also noted to have

TABLE 1 Baseline characteristics, surgical treatment, and pathologic details

Variable	*n* (%) or median (range)
Total	217 (100)
Sex	
Male	86 (39.6)
Female	131 (60.4)
Age, years	59 (11–95)
Surgical treatment[a]	
Appendectomy	124 (57.1)
Appendectomy/partial cecectomy	26 (12.0)
Colectomy[b]	67 (30.9)
HIPEC[c]	
No	210 (96.8)
Yes	7 (3.2)
Histologic perforation	46 (21.2)
No EAM[d] or EAC	155 (71.4)
EAM	49 (22.6)
EAC	13 (6.0)
Lymph node metastasis (if removed, $n = 76$)	0 (0)
Positive proximal margin	
Negative	191 (88.0)
Positive	8 (3.7)
Unknown	18 (8.3)

[a]For the LAMN (not including other previously scheduled procedures)

[b]Initially or after initial appendectomy, includes ileocecectomy, right hemicolectomy, total abdominal colectomy

[c]As initial definitive surgical treatment (i.e. not after recurrence)

[d]Acellular mucin only (without neoplastic cells)

HIPEC hyperthermic intraperitoneal chemotherapy, *EAM* extra-appendiceal (acellular) mucin, *EAC* extra-appendiceal neoplastic cells, *LAMN* low-grade appendiceal mucinous neoplasm

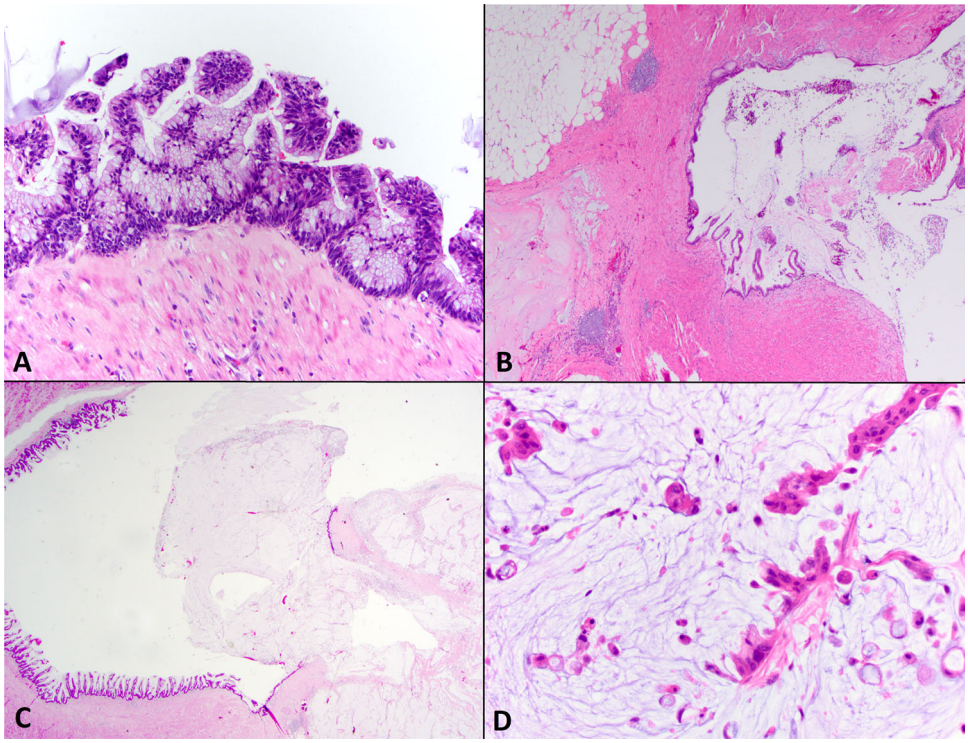

FIG. 1 The morphological spectrum of LAMN. **a** The neoplastic epithelium shows mucinous differentiation and neoplastic hyperchromatic nuclei with enlargement and stratification (40); **b** the neoplastic lesion can dissect into muscularis propria with acellular mucin pools in the appendiceal wall or the mesentery (4×); **c** perforated LAMN with acellular mucin pools (4×); and **d** serosal mucin deposits with neoplastic cells (40×). All photomicrographs were stained with hematoxylin and eosin. *LAMN* low-grade appendiceal mucinous neoplasm

(cellular) extra-appendiceal mucin. Eight patients with histologic perforation (17.4% of the 46 patients with perforation) had no evidence of EAM or EAC. Seven (3.2%) patients had a proximal appendectomy margin positive for neoplastic epithelial cells (acellular mucin at the margin was not recorded as a positive margin); all of these patients had undergone appendectomy and did not undergo subsequent resection.

Follow-Up and Recurrence

The median follow-up time was 51.1 months (range 0–270.6) (Table 2). Some patients were lost to follow-up after their perioperative visits for LAMN resection, including one patient who had no clinical follow-up after discharge from appendectomy. Nineteen patients (8.8%) were lost to follow-up after 6 months and 36 patients (16.5%) were lost to follow-up after 12 months. Seventy-four (34.1%) patients underwent surveillance by imaging (26.3%) or clinical visits without imaging (7.8%). Forty-five (61.6%) of those surveyed had EAM or EAC, and 32 (43.8%) had histologic perforation. Of the 57 patients who underwent surveillance imaging, 44 (77.2%) underwent CT and 12 (21.1%) underwent MRI (one with unknown imaging modality), at a median initial interval of 6 months (range 1–14). Forty-four (20.3%) patients had tumor markers [carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19–9, and/or CA 125] drawn after initial surgical management for surveillance. Of those surveyed by any modality, the median number of surveillance visits was two (range 1–17), and these patients were surveyed for a median of 22.2 months after surgery (range 0.49–194.3). Of those without surveillance data (n = 143), only 16 (23.5%) had EAM or EAC, and 10 (14.7%) had histologic perforation.

TABLE 2 Outcomes

Variable	n (%) or median (range)
Follow-up, months	51.1 (0–270.6)
Surveillance	
None	67 (30.9)
Clinical	17 (7.8)
Imaging	57 (26.3)
Unknown	76 (35.0)
Peritoneal recurrence	7 (3.2)
Time to recurrence, months	14.4 (2.5–47.0)

Seven (3.2%) patients had peritoneal recurrence. Of those who recurred, three (42.9%) had previously undergone appendectomy alone, two (28.9%) underwent appendectomy with partial cecectomy, one (14.3%) underwent right colectomy, and one (14.3%) underwent appendectomy followed by right colectomy (Fig. 2). All had a negative proximal margin and all had histologic evidence of appendiceal perforation. Five (71.5%) patients had acellular extra-appendiceal mucin, one (14.3%) patient

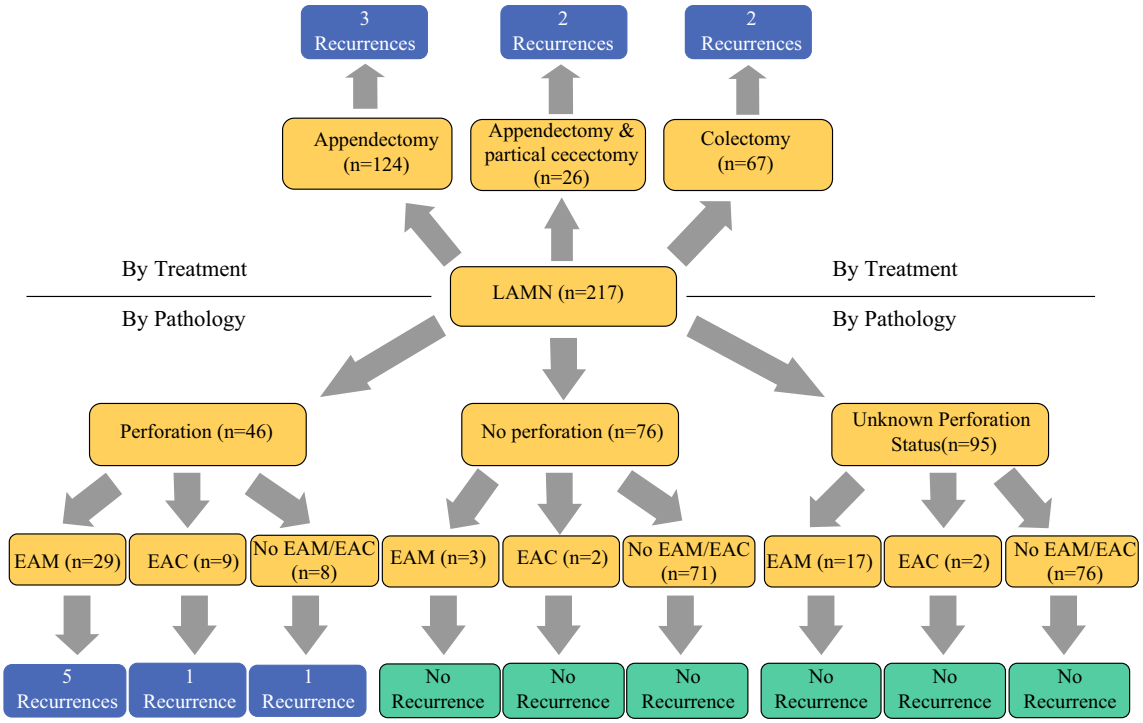

FIG. 2 Recurrences by treatment and pathology. *LAMN* low-grade appendiceal mucinous neoplasm, *EAM* extra-appendiceal mucin, *EAC* extra-appendiceal neoplastic cells

had extra-appendiceal mucin with neoplastic cells, and one (14.3%) patient had no extra-appendiceal mucin or neoplastic cells at the time of initial appendectomy. No patients underwent HIPEC at the time of initial definitive surgical management. All patients who recurred were being surveyed by imaging, and the median time to recurrence was 14.4 months (range 2.5–47.0). Six of the seven patients who recurred (85.7%) did so within 24 months of their initial LAMN resection, and five of the seven patients who recurred (71.5%) were subsequently treated with CRS/HIPEC, one (14.3%) by CRS alone, and the other (14.3%) by unknown treatment. One patient died in the postoperative period (on postoperative day 12) after CRS/HIPEC, one patient was lost to follow-up after diagnosis of peritoneal dissemination, and the remaining five patients had a median follow-up of 5.3 months (range 1.3–72.2) and remain alive at the time of last follow-up.

The presence of histologic perforation or EAM on initial pathology was associated with peritoneal recurrence (Table 3). Evidence of gross perforation was also correlated with a higher risk of peritoneal recurrence (12.0%) than those without evidence of gross perforation (3.4%, $p = 0.019$). Patients with either EAM or EAC had a higher risk of peritoneal recurrence than those without (9.7% vs. 0.6%, $p = 0.002$). In the absence of histologic perforation, EAM, or EAC ($n = 147$), no patients had a peritoneal recurrence after median follow-up of 52.5 months (range 0.2–270.6). The presence or absence of HIPEC, resection type (appendectomy vs. colectomy), or pathologic margin status were not associated with peritoneal recurrence.

Subgroup analysis was performed on 129 patients who had the entire appendix submitted for pathologic evaluation and > 12 months of follow-up. In this subgroup, there were five patients with peritoneal recurrence who recurred after a median of 15.3 months (range 12.9–47.0). Patients with histologic perforation and EAM had higher rates of peritoneal recurrence (20.0% and 12.5%, respectively) than those who did not (0% and 1.9%, $p < 0.001$ and $p = 0.015$, respectively).

Twenty-two (10.2%) patients died during the follow-up period. Due to the low number of deaths, the median overall survival was not reached. The 1-, 3-, and 5-year overall survival rates were 97.2%, 94.9%, and 93.5%, respectively.

The current cohort was included in a review of the literature, which encompassed published series of localized LAMNs without initial peritoneal dissemination, with pathologic data on the presence of extra-appendiceal mucin and cells, and with at least 2 years of follow-up (Table 4). Pooled analysis revealed the overall risk of peritoneal recurrence was 4.6–0.7% for those without EAM or EAC, 6.2% for those with EAM, and 23.8% for those with EAC.

TABLE 3 Factors associated with peritoneal dissemination

Variable	No peritoneal dissemination [*n* (%)]	Peritoneal dissemination [*n* (%)]	*p* value[a]
Total	210 (96.8)	7 (3.2)	
Histologic perforation			
None	76 (100)	0 (0)	< **0.001**
Perforation	39 (84.8)	7 (15.2)	
EAM			
None	166 (98.8)	2 (1.2)	**0.007**
EAM	44 (89.8)	5 (10.2)	
EAC			
None	198 (97.1)	6 (2.9)	0.355
EAC	12 (92.3)	1 (7.7)	
EAM or EAC			
None	154 (99.4)	1 (0.6)	**0.002**
Yes	56 (90.3)	6 (9.7)	

Significant *p* values are in bold

[a]Fisher's exact test

[b]At the time of initial diagnosis

EAM extra-appendiceal (acellular) mucin, *EAC* extra-appendiceal neoplastic cells, *HIPEC* hyperthermic intraperitoneal chemotherapy

DISCUSSION

The majority of patients diagnosed with LAMN present with synchronous peritoneal dissemination, although published series are likely susceptible to reporting bias.[7] Previously published reports of patients with LAMNs who presented without gross peritoneal dissemination included only small case series of typically < 75 patients.[5–11] We were able to accumulate the largest reported such series using data from multiple institutions. Determination of the risk of peritoneal recurrence in patients with resected LAMNs is critical for risk stratification and to guide surveillance recommendations as peritoneal dissemination is associated with significant morbidity and mortality.[12]

In most cases, appendectomy alone is curative for patients with localized LAMNs. We found that peritoneal recurrence is rare in patients with resected LAMNs without initial peritoneal dissemination, i.e. 3.2% after a median follow-up of 51 months. In our cohort, peritoneal recurrence was more likely with perforation of the appendix (15.2%) and if extra-appendiceal mucin (10.2%) was found on final pathology. As expected for a localized noninvasive neoplasm, we did not find a reduced rate of peritoneal recurrence with performance of colectomy or HIPEC at the time of initial surgical management. The risk of lymph node metastasis with LAMNs is low, as reported in the literature,[13] and, as expected, no patients in the current study had positive lymph nodes among those with lymph nodes removed ($n = 76$). Therefore, unless there is direct involvement of the cecum or ascending colon, or diagnostic uncertainty (i.e. unclear grade of tumor), formal ileocolectomy is not recommended.

When we added our data to previously reported series of LAMNs without initial peritoneal dissemination, we found that EAM and EAC on initial pathology are associated with a higher risk of future peritoneal recurrence, as noted in some of the included individual series.[5,6,8,11] The overall rate of peritoneal recurrence in our series was slightly lower than that seen in the included series (3.2% vs. 5.7%), which is likely due, in part, to the lower rate of EAM/EAC in our cohort than in the other series. We and others[6] have found the presence of EAM was associated with a higher risk of recurrence, but the association between EAC and recurrence did not reach statistical significance. Fournier et al. found extra-appendiceal mucin was not a risk factor for peritoneal recurrence or overall or disease-free survival, but that report did not distinguish EAM from neoplastic cells and most patients had peritoneal dissemination at the time of diagnosis.[14] Other series have concluded that the risk of peritoneal recurrence was higher in the presence of EAC than in the presence of EAM.[5,8,11] Among those with EAC, our series had a lower rate of peritoneal recurrence than the other included series (7.7% vs. 31.0%).[5,6,8,9,11] These differences may not be statistically significant due to sampling errors from small individual cohorts, namely from the lower number of EAC cases in our series versus the other included series (6.0% vs. 19%),[5,6,8,9,11] whereas the combined data suggest an increased risk of recurrence with either EAM or EAC. These differences may also be due to the lack of submission of the entire appendix for pathologic review in some cases in our series, leading to underreporting of EAC in our series.

TABLE 4 Summary with literature review

Pathologic status	Peritoneal recurrence (*n*)	Total (*n*)	Peritoneal recurrence (%)	Median follow-up (months)
All	21	461	4.6	
No EAM or EAC				
Pai et al.[8]	0	16	0	59
McDonald et al.[7]	0	16	0	40
Foster et al.[5]	0	2	0	50
Tiselius et al.[9]	0	30	0	61
Guaglio et al.[6]	1	14	7.1	58
Wong et al.[10]	0	40	0	32
Current	1	155	0.6	52
Total	2	273	0.7	
EAM				
Yantiss et al.[a]	1	44	2.3	36
Pai et al.[8b]	1	12	8.3	48
Foster et al.[5]	1	8	12.5	50
Tiselius et al.[9]	0	9	0	61
Guaglio et al.[6]	1	19	5.3	58
Wong et al.[10]	0	5	0	45
Current	5	49	10.2	44
Total	9	146	6.2	
EAC				
Yantiss et al.[a]	2	10	20	36
Pai et al.[8b]	3	4	75	53
Foster et al.[5]	4	10	40	50
Tiselius et al.[9]	0	2	0	61
Guaglio et al.[6]	0	3	0	58
Current	1	13	7.7	65
Total	10	42	23.8	

[a]May have included up to eight patients in the current cohort

[b]Including only those with disease in the right lower quadrant

EAM extra-appendiceal mucin, *EAC* extra-appendiceal neoplastic cells

Appendiceal perforation has been found to be a risk factor for peritoneal dissemination in other series.[5,15] All patients with peritoneal recurrence in our series had microscopic evidence of appendiceal perforation. Thirty-nine patients in our series (32.0% of those with histologic perforation reported) had evidence of appendiceal perforation but did not develop peritoneal dissemination. In our series, we elected to report histologic perforation as this was known in more cases than gross (intraoperative) perforation status. Perforation is not uniformly documented in surgical pathology or operative reports, nor was it reported in some published series of localized LAMNs.[8] There are also no uniform criteria for reporting histologic or gross perforation, therefore many cases of perforation are likely underreported. In the present series, there were five patients who had no evidence of histologic perforation but who had extra-appendiceal mucin or neoplastic cells. This may be due, in part, to incomplete submission of the entire appendix for review in some cases. Furthermore, we and others have documented several cases of patients with gross synchronous peritoneal dissemination with no obvious perforation at the site of the primary LAMN,[7,16] perhaps demonstrating the ability of sites of small appendiceal perforations to close. Although perforation may be a prerequisite for peritoneal dissemination (indeed no patients in our series had peritoneal recurrence without appendiceal perforation), transmural dissemination of neoplastic cells from the appendix without perforation may occur in some cases, which would also give rise to gross peritoneal dissemination. Given the uncertainty regarding perforation status, we feel it is best to weigh the presence or absence of EAM/EAC more highly than perforation

status when assessing the risk for peritoneal recurrence (particularly since EAM/EAC status is part of uniform staging for LAMN and is more widely reported).

Seven patients in our series had a positive proximal margin on the initial appendectomy specimen, but none of these patients had further resection and none recurred. This has also been observed in other series,[17] which questions the need for further resection for microscopically positive appendectomy margins unless further surgery (i.e. for exploration) is already indicated.

Surveillance of patients after resection of LAMNs without gross peritoneal dissemination is controversial. Our findings suggest the risk of peritoneal recurrence is lower than previously published reports, yet the morbidity and, potentially, the mortality of delayed diagnosis of peritoneal recurrence is high. For patients referred for LAMN surveillance after initial resection, we recommend the following work-up to identify synchronous peritoneal dissemination: complete review of the operative note and, ideally, discussion with the initial surgeon to ascertain the extent of peritoneal exploration (if any); submission of the entire appendix for histologic evaluation and review of the pathology by an expert pathologist; postoperative imaging 6–12 weeks after surgery to identify radiographic evidence of residual disease; and laparoscopy for work-up of any suspicious clinical or radiographic findings. Evaluating subsequent surveillance protocols for localized LAMNs was not the goal of the present study and is difficult to study in this rare disease with heterogeneous behavior; however, there are reports on the use of laparoscopy,[5] imaging,[9] and tumor markers[14] for surveillance in this disease. We found 0% recurrence in patients without perforation, EAM, or EAC after a median follow-up of 52 months, and, on literature review, we found 0.7% recurrence in patients without EAM or EAC after a median follow-up of 54 months. Given the negligible risk of recurrence in patients without perforation or extra-appendiceal mucin or neoplastic cells, we recommend no further surveillance in this group (after confirmation of lack of gross peritoneal dissemination). Given the lack of recurrence seen after 5 years, and the fact that 86% of recurrences occurred within 2 years, we recommend serial imaging in a patient with perforation, EAM, or EAC, per the schedule shown in Fig. 3. This strategy is similar to the surveillance described by Guaglio et al.[6]. Our suggested surveillance strategy would require prospective analysis with suitable follow-up for validation.

There are several limitations to our study. Despite a rigorous review, there were still missing data in our cohort due to data collection from multiple institutions, by surgeons or pathologists, and, in some cases, dating back over 20 years. Complete information regarding whether the initial resection was performed laparoscopically or minimally invasively, and regarding the extent of the peritoneum evaluated at that time, was not available. However, none of the cases with initial resection prior to the year 2000 (and were presumably open) recurred, suggesting there was not a higher rate of synchronous peritoneal dissemination in this subgroup. There were also cases were the entire appendix was not submitted for pathologic review by the referring institution, potentially leading to underreporting of histologic perforation, EAM, and EAC. While we were able to confirm the pathologic criteria for LAMNs were met in each case, and we made every attempt to exclude cases that had known synchronous peritoneal dissemination, the surgical management, surveillance strategies, and treatment of recurrence were variable by institution and provider. Some patients in our series had limited follow-up as patients are generally referred to the index tertiary/quaternary institution, typically after appendectomy, where surveillance is initiated, but some patients are lost to follow-up. Incomplete or uncertain surveillance information may have potentially led to underreporting of peritoneal recurrences.

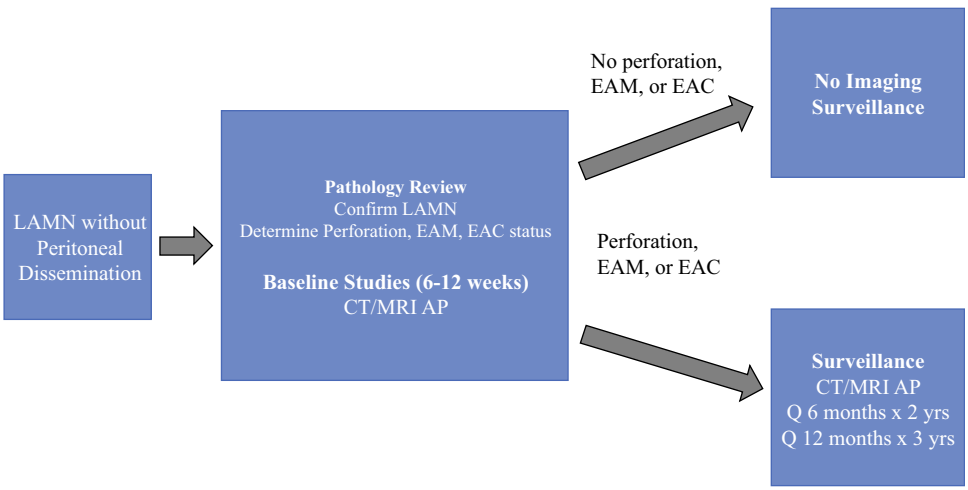

FIG. 3 LAMN management algorithm. *LAMN* low-grade appendiceal mucinous neoplasm, *EAM* extra-appendiceal mucin, *EAC* extra-appendiceal neoplastic cells, *CT* computed tomography, *MRI* magnetic resonance imaging, *AP* abdomen/pelvis

We did not include cases where the follow-up visit or imaging was for an unknown reason in the surveillance group. Therefore, our estimates of surveillance visits were likely undercounted. Nevertheless, we were able to obtain follow-up information from review of the medical records in the majority of patients not under surveillance, but this was not defined as surveillance data. Thus, patients not under surveillance (as we defined it) who developed symptomatic recurrence and were subsequently confirmed to have recurred or who died of recurrence, would potentially still have been captured by medical record review. It is possible that some recurrences were underreported, as they were either clinically insignificant or were merely not discovered on chart review.

There are no published longitudinal cohort studies of large numbers of patients with these rare tumors from single institutions, including from peritoneal surface malignancy referral centers. LAMNs are also not reported by the Surveillance, Epidemiology, and End Results (SEER) program or the National Cancer Database (NCDB). Thus, retrospective, multi-institutional cohort studies are the best way to analyze large numbers of these patients. The literature review was also limited by heterogeneity in surveillance and follow-up, unclear perforation status for many studies, as well as relative uncertainty regarding the presence of peritoneal dissemination at the time of initial surgery. Heterogeneity is perhaps an unavoidable consequence of this rare disease that is often diagnosed incidentally. Determination of peritoneal dissemination was made at the time of the original surgery, but this may not have been adequately assessed in all cases. This is highlighted in our series by two patients who developed peritoneal dissemination less than 12 months after the initial tumor resection, suggesting gross peritoneal dissemination was likely present at the time of initial appendectomy rather than true recurrent peritoneal metastases. Alternatively, early peritoneal recurrence is possible, as is occasionally seen after complete cytoreduction and HIPEC for LAMNs with peritoneal dissemination,[18] possibly due to genetic heterogeneity within this disease. Ideally, complete peritoneal assessment is made at the time of appendectomy; however, inadequate peritoneal assessment is a real-world problem as a neoplasm is often not suspected and the appendectomy is typically not performed by a surgeon with experience treating these tumors, in which case the operative note and/or discussion with the surgeon who performed the procedure is necessary. Our series appears to be the largest reported series of localized LAMNs, and we feel that our results are generalizable and are based on data that are available to the surgical oncologist being referred similar patients.

CONCLUSIONS

Peritoneal recurrence after resection of LAMNs without gross peritoneal dissemination is rare, particularly in patients without appendiceal perforation or extra-appendiceal mucin or cells. Surveillance of patients with localized LAMNs should be directed by these risk factors, as well as the morbidity associated with peritoneal recurrence.

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