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Enlighten – Research publications by members of the University of Glasgow <u>http://eprints.gla.ac.uk</u> Outcomes of Low-Grade Appendiceal Mucinous Neoplasms with Remote Acellular Mucinous Peritoneal Deposits

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Running head: LAMN with MPD

Conflicts of interest: none

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SYNOPSIS

Outcomes were analyzed for patients treated for low-grade appendiceal mucinous neoplasms (LAMN) with remote mucinous peritoneal deposits (MPD). Patients with acellular remote MPD had better outcomes on average than patients with cellular MPD. Approaches such as active surveillance may have a role in selected patients with LAMN and AMPD.

ABSTRACT

Background: Occasionally, low-grade appendiceal mucinous neoplasms (LAMN) present with mucinous peritoneal deposits (MPD) localized to periappendiceal tissue or diffused throughout the peritoneum. This study was aimed at evaluating the relevance of mucin cellularity for predicting outcomes of LAMN with remote MPD.

Methods: The records of patients with LAMN and remote MPD who underwent initial assessment at a comprehensive cancer center in 1990–2015 were reviewed, and diagnostic procedures, treatments, and outcomes were analyzed.

Results: Of 48 patients included in the analysis, 19 had cellular MPD (CMPD) and 29 had acellular MPD. Of 33 patients who underwent cytoreductive surgery, 30 had a complete cytoreduction. The three patients with an incomplete cytoreduction had CMPD. In follow-up (median, 4 years), six patients died of the disease. All six had CMPD. Of 11 patients who had progression of disease, 10 had CMPD.

Conclusion: Cellularity of remote MPD is an important determinant of disease outcome in LAMN. Approaches such as active surveillance may have a role in selected patients with LAMN and AMPD.

Mucinous appendiceal neoplasms represent one-third of epithelial appendiceal tumors, forming a heterogeneous group.^{1,2} Although low-grade appendiceal mucinous neoplasms (LAMN) are considered slow growing and indolent, a proportion of them present with mucinous peritoneal deposits. These deposits may be localized to periappendiceal tissue or diffusely spread throughout the peritoneal cavity (LAMN with remote mucinous peritoneal deposits [MPD]). LAMN with remote MPD follow an indolent but variable disease course with a poorly defined mortality; overall survival at 10 years ranges from 46 to 63%.^{1,3} Currently, cytoreductive surgery (CRS), or tumor debulking, with or without intraperitoneal chemotherapy is the most common treatment strategy for metastatic appendix tumors regardless of cellularity of mucin.^{4,5} Such an approach may reduce recurrence and progression to the clinical syndrome of pseudomyxoma peritonei, characterized by the massive accumulation of mucin within the peritoneal cavity.^{6,7} However, in view of biological heterogeneity and variable outcomes, such aggressive treatment may not be necessary in all patients.

Few studies to date have focused on reporting outcomes for LAMN with MPD in relation to cellularity of mucin. Cellularity of peritoneal mucin is one of the features thought to provide prognostic information. MPD can be cellular (containing epithelial components) or acellular (completely devoid of cells). Several studies have reported better outcomes in patients with acellular MPD (AMPD) than in patients with cellular MPD (CMPD).^{6,8-10} Yantiss et al. published the first study reporting on cellularity of mucin within the right lower quadrant. In their multi-center study, they examined the prognostic significance of LAMN with mucin localized to the periappendiceal tissue. Seven of 65 patients developed diffuse mucinous ascites following complete macroscopic resection: 5 (33%) of 15 patients with cellular mucin and 2 (4%) of 50 patients with acellular mucin.¹¹ There was one death from disease in the cellular-mucin group and no deaths in the acellular-mucin group.

It is unclear whether LAMN with MPD remote from the appendix or right lower quadrant behave similarly. Although previous studies have not specifically addressed the prognostic value of cellularity of MPD beyond the right lower quadrant, among three series of LAMN patients with remote MPD a single recurrence was reported among 15 patients with AMPD (see Supplementary Table 1).⁸⁻¹⁰

Recent AJCC classifications have sought to address the apparent prognostic difference between acellular and cellular MPD, with a new subclassification for disease outside the right lower quadrant. Based on results of previous studies^{8,9,10} demonstrating improved outcome in patients with AMPD in addition to the observation that disease recurs in a small subset of patients, LAMN with AMPD is now classified as M1a and LAMN with CMPD is classified as M1b in the 8th edition of the AJCC staging manual.¹² However, given the paucity of data in this area, further studies are necessary to support this new subclassification.

The aim of the present study was to compare the rates of peritoneal recurrence and progression to the syndrome of pseudomyxoma peritonei between patients with AMPD and patients with CMPD remote from the right lower quadrant. Our hypothesis, based on the above findings, was that the risk of disease progression is lower in patients with remote AMPD than in patients with CMPD. If this hypothesis is correct, it may be appropriate to consider less radical interventions for patients with remote AMPD, similar to patients with LAMN and localized periappendiceal mucin, who are typically observed in the absence of progression of disease.

METHODS

We included patients older than 18 years with a diagnosis of LAMN with MPD remote from the appendix who were assessed at Memorial Sloan Kettering Cancer Center (MSK) between 1990 and 2015. LAMN patients with localized periappendiceal mucin on presentation (mucin involving only the serosa of the right ovary, terminal ileum,

mesoappendix, or cecum) were excluded. The study was approved by MSK's Institutional Review Board.

We searched the MSK pathology database, Darwin, using the keywords mucin and pseudomyxoma peritonei. This initial search yielded >3000 potential cases, which were reviewed to determine suitability for inclusion. In cases deemed appropriate for inclusion, electronic medical records were reviewed, and data were collected on age at diagnosis, sex, and date of initial diagnosis. In addition, we collected data on the index diagnostic procedure and MPD sampling based on the magnitude of operation and volume of sampling: (i) biopsy alone, (ii) appendectomy with or without a salpingo-oophorectomy, and (iii) CRS, including segmental colectomy. In patients who underwent a biopsy or appendectomy/salpingo-oophorectomy, the sampling of mucin varied and, unlike in CRS patients, did not involve removal of all visible disease. Data on treatment and outcomes including disease recurrence and patient deaths were also collected.

There is no International Classification of Diseases code for LAMN that indicates degree of cellularity of peritoneal deposits. The determination of CMPD or AMPD was therefore based on review of pathology reports issued by specialized pathologists at the time of tissue acquisition. All patients were considered to have macroscopic remote MPD at the time of initial sampling. The index sampling method of the MPD was variable and ranged from potentially nonrepresentative diagnostic biopsies to localized resection or more extensive CRS. Where clarification on the pathology reporting or terminology used was required, a pathology review was performed by an expert pathologist (J.S.). Mucin-specific terms and phrases identified in the pathology reports that were deemed to indicate AMPD included "acellular," "devoid of cells," and "no epithelium seen." Mucin-specific terms and phrases that were deemed to indicate CMPD included "cellular," "containing epithelium," and "adenomucinosis." Histological examples of CMPD and AMPD are shown in Fig. 1. All tumors were classified as low grade, or well differentiated (G1) according to the

8th edition of the AJCC staging manual.¹² These tumors lack invasive features and contain tall columnar cells with low-grade cytologic atypia without signet ring cells. Signet ring features were not present in any of the cellular deposits.

At the index assessment at MSK, patients underwent a CT scan of the abdomen and pelvis, and data were collected on whether the patient had visible peritoneal disease at initial operative assessment. We then reviewed the initial recommendation made by the consulting MSK surgical or medical oncologist, which was typically confirmed at a multidisciplinary conference. These initial treatment recommendations were grouped into two categories: observe the patient or perform CRS within 6 months of initial diagnosis. Data on the completeness of cytoreduction for patients who underwent CRS were recorded as Sugarbaker cytoreduction completeness scores.¹³ Any subsequent surgical procedures were also recorded.

Patients were followed up with regular clinical examination in addition to at least annual CT scans. Survival and recurrence data were based on the information obtained during follow-up. The date of death or last known follow-up was used to estimate survival. The first date of progression or recurrence documented on a CT report or in clinical notes was recorded as the date of recurrence. Patients with inadequate follow-up (\leq 12 months) were excluded from the analysis. Statistical analysis of overall, progression-free, and recurrence-free survival was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL) and the Kaplan-Meier method for constructing survival curves. Subgroups were compared by the log-rank test, with statistical significance defined as P < 0.05.

RESULTS

Between 1990 and 2015, 71 patients with a diagnosis of LAMN with remote MPD were seen for an initial assessment at MSK. Twenty-three of those patients were excluded because

they were seen for a second opinion or a pathology review alone or they did not have more than 12 months of follow-up. The patients' baseline clinical and pathological characteristics and recommended treatments are listed in Table 1.

Four patients had undergone CRS without intraperitoneal chemotherapy prior to initial evaluation at MSK: two within 12 months of presentation at MSK and two >12 months earlier (range, 3–37 months). At initial assessment at MSK, a diagnosis of LAMN with either CMPD (19 patients, 40%) or AMPD (29 patients, 60%; Supplementary Fig. 1) was made based on pathology findings. CT identified visible disease in 33 patients (69%): 15/29 with AMPD and 18/19 with CMPD (Fig. 2).

The initial treatment recommendation at MSK was CRS within 6 months for 40 patients and observation for 8 patients. Of the 8 patients who were recommended initial observation at MSK, sampling of MPD was performed as part of a biopsy in 1 patient, appendectomy/salpingo-oophorectomy in 3 patients, and CRS at other institutions in 4 patients. None of the patients in the observation group had demonstrable abdominal disease on CT scan. Two of the 40 CRS patients pursued treatment at other institutions, and 38 underwent surgery at MSK with a plan for complete cytoreduction. At laparoscopy, 2 of the 38 patients had no visible or pathological (frozen section) evidence of disease, and therefore CRS was not performed. In three other patients, CRS was not attempted due to the presence of extensive disease. Complete CRS to no gross residual disease was achieved in 30 (91%) of the remaining 33 patients. The three patients in whom complete CRS was not achieved (cytoreduction completeness score 2 [moderate residual disease]) had CMPD on initial sampling. In 27 patients, intraperitoneal chemotherapy was used as an adjunct to CRS. Of the 29 patients with AMPD, 25 were recommended to undergo CRS. Five patients were upstaged from AMPD to CMPD after CRS. Two of the five patients had index sampling with biopsy alone; four of the five had visible disease on baseline CT.

As almost half of the patients were initially seen at MSK in 2010–2015, the median follow-up for the 40 survivors was 4 years (min-max, 1-17 years). Of the eight patients who died, six died of disease; all six had CMPD. Following initial management at MSK, 11 of the total 48 patients had progression of disease during the follow-up period: 10 of the 19 patients in the CMPD group and 1 of the 29 patients in the AMPD group (Table 2). Of the 38 patients who underwent CRS at MSK within 6 months after initial assessment, 9 had subsequent progression of disease. The Kaplan-Meier curves for disease-specific survival (P = 0.03) and progression-free survival (P < 0.001) were well stratified by cellularity of MPD (Fig. 3 and Supplementary Fig. 2). The single patient with remote AMPD who had progression 6 years after diagnosis was initially observed after appendectomy. CRS was recommended at the time of progression but was postponed due to medical comorbidities, and the patient ultimately pursued treatment elsewhere with no further follow-up available.

The actuarial progression-free survival rates at 1, 3, and 5 years were 77%, 64%, and 46% for patients with CMPD (including patients upstaged to CMPD after debulking; n = 24) in comparison to 100% at 5 years in the APMD group (n = 24). The actuarial overall survival rates at 1, 3, and 5 years were 100%, 88%, and 88% for the CMPD group in comparison to 100% at 3 years and 91% at 5 years in the AMPD group. Of note, within the small subset of 4 patients who did not undergo CRS (Supplementary Fig. 1), no disease progression was reported with median follow-up of 44 months (range 36-70 months).

Of the 19 patients with CMPD, 10 had a baseline peritoneal cancer index (PCI) score > 20. Five of those patients developed recurrent disease, and three died of disease. Of the 29 patients with AMPD, 2 had a baseline PCI score > 20. Neither of the two patients had a recurrence after cytoreduction.

Of the 38 CRS patients, 5 subsequently underwent additional abdominal surgery. One of the five patients underwent resection of a pulmonary recurrence. That patient had CMPD. The

remaining four patients had AMPD. One of the four patients underwent a right colectomy due to the presence of an incidental 2-cm carcinoid in the CRS appendix specimen, another patient underwent incisional hernia repair, and two others underwent procedures (right colectomy and resection of an adnexal lesion) for unrelated abdominal abnormalities detected incidentally on follow-up imaging.

DISCUSSION

This study differs from previously published studies in that it focused specifically on LAMN with AMPD remote from the right lower quadrant. Our findings indicate that LAMN patients with remote AMPD have longer progression-free survival and longer overall survival on average than LAMN patients with CMPD. In the 29 LAMN patients with remote AMPD in our study, the risk of disease recurrence or progression after initial diagnosis was 3.4%. The better outcomes in AMPD patients cannot be attributed to treatment alone and likely reflect an indolent biology.

Of the total 20 LAMN patients with remote AMPD in four previous studies,^{8-10,14} only 1 experienced disease progression.¹⁰ Thus, for the combined 49 patients (including 29 from our study), the rate of disease recurrence was 4%. It is not possible to determine whether initial management influenced outcomes, due to unmeasurable selection bias. However, the proportion of patients who were initially managed by observation in the four previous studies appears to range from 20 to 39%. The two patients with remote AMPD who experienced progression were initially managed by appendectomy and initial observation (rather than CRS). They experienced progression more than 5 years after initial diagnosis.

The results of these studies are similar to those reported by Yantiss et al., in which LAMN patients with pariappendiceal AMPD had a low rate of recurrence (2/50).¹¹ Similarly, Pai et al.⁸ reported outcomes for 116 patients with appendiceal mucinous neoplasms over a 30-year period, including 17 patients with LAMN and copious extra-appendiceal mucin, defined by the authors as mucin visualized on gross inspection. For this group, outcomes were reported for 14 patients with a mean follow-up of 84 months. One of the 14 patients had a recurrence. Of the patients with mucin outside the right lower quadrant, long-term outcome was available for two patients, neither of whom had a recurrence during 163 and 206 months of follow-up.

Additional reports with similar findings to those above include the series by Davison et al.,¹⁴ which reported outcomes for 65 patients with LAMN. Five of the 65 patients had AMPD. None of the five patients died or had a recurrence during a median 32 months of follow-up (1-44 months). As part of a wider series, Misdraji et al.¹⁵ reported outcomes for 10 patients with LAMN and AMPD associated with ovarian or fallopian tube involvement. Follow-up was available for 7 of the 10 patients; 2 of the 7 died of disease. It was not stated whether the ovarian or tubal involvement included cellular deposits or whether the deposits were remote from the right lower quadrant. In addition, Carr et al.⁶ described outcomes for 184 patients with appendiceal neoplasms. The outcomes for the 11 patients with AMPD were not detailed specifically, but extra-appendiceal epithelial deposits and extra-appendiceal mucin outside the right lower quadrant were associated with poorer survival, although it is not possible to determine cellularity of these remote MPD based on the description.

Of the 29 patients considered to have only remote AMPD on the basis of initial biopsy, 5 (17%) were found to have CMPD during definitive surgery. We attribute this finding to the fact that MPD can have a heterogeneous distribution, with AMPD at some sites and CMPD at other sites, resulting in sampling error on limited diagnostic biopsies. Occult cellularity may be present even when a diagnosis of AMPD is made on the basis of adequate

sampling. In cases where the representative sample is of low volume, the potential for sampling error should be considered and discussed with the patient when formulating a treatment plan. We now perform laparoscopic biopsies in four quadrants of the abdomen with the goal of obtaining more representative samples. If pathologic analyses return a report of AMPD, this information along with a consideration of the degree of sampling and the CT findings informs the discussion with the patient on the selection of an appropriate management plan.

In our study, the presence of visible disease on CT did not correlate with MPD cellularity, but the absence of visible disease did: patients who had no visible remote disease on CT were much more likely to have AMPD than CMPD. Of the five patients who were upgraded to CMPD after CRS, only one had no visible disease on CT. Absence of MPD on imaging provides reassurance on the adequacy of sampling, and in our study it was an important consideration for treatment recommendations. All of the patients who were observed in the current study had no evidence of MPD on initial CT.

The potential limitations of our study include the limited follow-up, the small sample size, selection bias, and referral bias. Due to the small number of patients, we chose not to stratify this heterogeneous population by disease burden on presentation, which may have confounded initial management choices and subsequent outcomes. We also could not stratify the patients who underwent CRS according to the level of completeness of cytoreduction. However, since patients with rare cancers are likely to seek expert care at a comprehensive cancer center, our relatively small sample may in fact be representative of the disease at large.

CONCLUSIONS

Our results support the recent change to the AJCC classification of MPD (M1a vs M1b) and suggest that observation is a viable option for selected patients with AMPD identified on initial diagnosis, particularly when the sampling or biopsy is deemed to be representative and there are normal findings on imaging. The risk of disease progression and mortality in LAMN patients with AMPD appears to be very low. In patients managed by close observation in our study, recurrence tended to be a late phenomenon, and based on previous reports, such recurrence appears to be salvageable. Imaging every 12 months is our preference, given the low rates of recurrence and progression.¹⁶

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FIGURE 1. Histological appearance of cellular (A) and acellular (B) MPD.

FIGURE 2. Initial treatment recommendations.

FIGURE 3. Progression of disease (POD) in relation to MPD cellularity. Log-rank *P* < 0.001.

Characteristic	No. of Patients (%)
Age (y)	
<55	29 (60)
55-75	18 (38)́
>75	1 (2)
Sex	
Female	31 (64)
Male	17 (36)
Male	17 (30)
Year of initial assessment	
1990–1999	9 (19)
2000–2009	17 (35)
2010–2015	22 (46)
Index diagnostic procedure	
Biopsy	6 (13)
Appendectomy \pm salpingo-oophorectomy	25 (52)
Segmental colectomy or CRS	17 (35)
Remote MPD on initial sampling	
CMPD	19 (40)
AMPD	29 (60)
	29 (00)
√isible disease on baseline CT	
No	15 (31)
Yes	33 (69)
CRS at any point	
No	4 (9)
Yes	44 (91)*
nitial recommendation at MSK	
Observe	0 (17)
	8 (17)
CRS within 6 months	40 (83)
Progression of disease after initial management plan	
No	37 (77)
Yes	11 (23)
Alive	40 (83) [†]
Thirty-eight of the 44 CRS patients underwent the surge	

TABLE 1. Patient and Treatment Characteristics (n = 48)

who underwent a CRS elsewhere either prior to or after the initial assessment had a repeat CRS at MSK.

[†]Median follow-up, 4 years. Of the eight deaths, six (13% of total patients) were from disease.

Characteristic	No. of Patients (%)		_
	CMPD (n = 19)	AMPD (n = 29)	P
Index diagnostic procedure			
Biopsy	3 (16)	3 (10)	
Appendectomy ± salpingo-oophorectomy	5 (26)	20 (69)	
Segmental colectomy or CRS	11 (58)	6 (21)	0.1
MPD on baseline CT	18 (94)	16 (55)	0.004
MSK recommendation for CRS within 6 mo.	15 (79)	25 (86)	0.5
CRS at any point	18 (94)	26 (90)	0.5
Remote CMPD on CRS*	17 (94)	5 (22)	<0.001
Complete CRS at MSK (n = 33) [†]	9 (75)	21 (100)	0.18
Progression of disease	10 (53)	1 (3)	<0.001
Alive	12 (63)	28 (97)	
Deaths	7 (37)	1 (3)	
From other causes	1 (5)	1 (3)	
From disease	6 (32)	0	0.018

TABLE 2. Disease and Treatment Characteristics in relation to Mucin Cellularity (n = 48)

*Data were available for 41 of 44 patients who underwent CRS.

[†]CRS was not performed for 5 of the 38 patients for whom it had been planned at MSK: 2 of the 5 had no residual disease at laparoscopy and 3 had extensive disease.