American Journal of Engineering Research (AJER)
e-ISSN: 2320-0847 p-ISSN: 2320-0936
Volume-14, Issue-9, pp-01-06
www.ajer.org
Research Paper Open Access

Clinicopathological Features and Treatments of Low-Grade Appendiceal Mucinous Neoplasm Confined to the Appendix

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Abstract
OBJECTIVE*: Low-grade appendiceal mucinous neoplasms (LAMNs) are a rare, and their clinical course varies from asymptomatic incidental findings to pseudomyxoma peritonei(PMP). Furthermore, only a few treatment guidelines have been established. The present study was designed to confirm the outcomes of patients diagnosed with LAMN confined to the appendix who underwent surgery.*
PATEINTS AND METHIODS*: This study included patients who underwent surgery at the Mitoyo General Hospital between January 2003 and December 2023. All patients were diagnosed with LAMN based onhistopathological findings of the resected specimen.Patients with other abdominal diseases, including PMP or malignant disease, were excluded from the study.*
RESULTS*: Nineteen patients were included in this study. The mean age was 60.0 years (range: 35-86). There were 7 (36.8%) male patients and 12 (63.2%) female patients. Preoperative computed tomography (CT)revealed a mucinous neoplasm in 19 patients (100%).The following procedures were performed: laparoscopic ileocecal resection (IC), n=8 (42.1%); laparoscopic appendectomy, n=7 (36.8%); laparoscopic right hemicolectomy, n=1 (5.3%); laparoscopic partial resection of the cecum, n=1 (5.3%);IC, n=1 (5.3%); and right hemicolectomy, n=1 (5.3%). Laparoscopic surgery was performed in 17 (89.5%) patients. The median follow-up period was 103 months (range: 3–240 months). There was no recurrence and the disease-free survival rate was 100%.*
CONCUSIONS: *Detailed multidirectional enhanced CT readings are important for preoperative diagnosis of LAMN. Laparoscopic IC was considered sufficient for LAMN confined to the appendix without PMP and with pathologically negative margins.*
Keywords: *Low-grade appendiceal mucinous neoplasm, Diagnosis, Treatment, Prognosis, Laparoscopy, Confined to the appendix, Ileocecal resection*

Date of Submission: 25-08-2025 Date of acceptance: 04-09-2025

I. INTRODUCTION

Mucinous neoplasia of the appendix is a rare condition that occurs in approximately 1% of the patients undergoing appendectomy[1].

The typical feature of low-grade appendiceal mucinous neoplasms (LAMNs) is the pattern of invasion of layers of the appendix known as “pushing invasion”. This can result in different patterns. They may be attenuated or absent in the muscularis propria.Frequently,they are fibrotic or hyalinized.Neoplastic epithelium growing over hyalinized or fibrotic stroma rather than the lamina propria or muscularis mucosae is a feature that promotes invasion[2]. The 4th edition of the World Health Organization (WHO) classification accepted LAMN as the official nomenclature[3].

The onset ofLAMN is insidious and lacks specific clinical features. Patients with LAMN often present appendicitis-like symptoms such as pain in the right iliac fossa, fever, nausea, and vomiting[4]. Although LAMNs confined to the appendiceal lumen do not show definitive malignant features, they can proliferate outside the appendix in a malignant fashion, resulting in the development of

pseudomyxoma peritonei (PMP), a life-threatening complication with a 10-year survival rate of 45%[5].Considering the uncertain potential for malignant progression, early and accurate preoperative identification of LAMNs confined to the appendix is crucial for decisions regarding prognosis and treatment strategy.Therefore, whenever suspected, as in the presence of a mucocele picture characterized by a distended mucus-filled appendix, either radiologically or intraoperatively, treatment should be surgical removal of the appendix with care to prevent the spillage of mucin, which can lead to PMP.

The present study was designed to confirm the outcomes of patients diagnosed with LAMN confined to the appendix who underwent surgery.

II. PATIENTS AND METHODS

Study Design and Participants

This retrospective study was approved by the Ethics Committee, Mitoyo General Hospital (23-CR01-289, dated March 1, 2024). A total of 19 patients who underwentsurgerybetweenJanuary 2003and December 2023at the Department of Mitoyo General Hospital, Kanonji, Japan. All patients were diagnosed with LAMN based on the histopathological findings of the resected specimen.
Patients with other abdominal diseases, including PMP or malignant disease, were excluded from the study.

Methods

Clinicopathological and surgicaloutcomes were collected from a prospectively maintained database, as well as from individual patient records when necessary.

Evaluations

The diagnosis of LAMN was based on the 2019 WHO pathological criteria (4). All patients underwent abdominal computed tomography (CT), tumor markers, such as carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9), in addition to the basic tests required for anesthesia before surgery.
This study was approved by the ethics committee of theMitoyo General Hospital (approval number: 23-CR01-289; approval date:February 1, 2024).

III. RESULTS

Demographics

Nineteen patients were included in this study. The mean age was 66.0 years (range: 35-86). There were 7 (36.8%) male patients and 12 (63.2%) female patients. The mean body mass index was 22.9 kg/m^2, and most cases were classified as American Society of Anesthesiologists class II (n=11, 57.8%). Seven patients (36.8%) complained of abdominal pain. Preoperatively, the mean WBC count was 6,057/μl, the mean, CEA was 4.6 ng/ml, and the mean CA 19-9 was 10.3 U/ml. Preoperative computed tomography (CT)revealed anappendiceal mucinous neoplasm in 19 patients (100%) (Figure 1).The average diameter on CT was 27.9 mm (15-60 mm). There were six cases (31.6%) with calcification on CT (Table 1).

Surgical outcomes

The surgical procedures included: laparoscopic ileocecal resection (IR),n=8 (42.1%);laparoscopic appendectomy,n=7(36.8%); laparoscopic right hemicolectomy,n=1 (5.3%); laparoscopic partial resection of the cecum,n=1 (5.3%);IR,n=1 (5.3%); and right hemicolectomy, n=1(5.3%). Laparoscopic surgery was performed in 17 (89.5%) patients. The average operation time was 110.3 minutes and the average blood loss was 48.4 ml. There was no perforation of the appendiceal mucinous neoplasm and there were no postoperative complications. The mean postoperative hospital stay was 9.9 days, and the mortality rate was 0%(Table 2).

Histopathological characteristics

All cases were diagnosed as LAMN based ona histopathological examination of the resected specimen. No pathologicalinvolvement of the margin was observed(Table 2).

Survival

The overall median follow-up period was 103 months (range: 3–240 months). There was no recurrence, and the disease-free survival (DFS) rate was 100% (Table 2).

IV. DISCUSSION

The Peritoneal Surface Oncology Group International (PSOGI) classified appendiceal neoplasms into four categories: LAMN, high-grade appendiceal mucinous neoplasm (HAMN), mucinous adenocarcinoma (MAC) and mucinous adenocarcinoma with signet ring cells (MAC-S)[6]. Their definition of appendiceal mucinous epithelia isregarded as a milestone[7]. In 2019, the WHO Health Organization classified most appendiceal noninvasive mucinous neoplastic lesions as LAMN[8]. All patients included in the present study were pathologically confirmed as LAMN. To avoid a possible outcome bias due to the pathological type, the present study only analyzed the characteristics of patients with LAMN confined to the appendix without PMP.

LAMN had been reported in the literature for a female-to-male ratio of 4:1 and tends to affect patients over 50 years of age[9]. However, the male-to-female ratio of this study was 1.7:1, and the average age was 66, which was inconsistent with literature reports. It is easily misdiagnosed as appendicitis and other diseases; patients are often diagnosed with the disease during intraoperative or postoperative pathology, resulting in iatrogenic destruction of the cyst wall and the spread of mucus into the abdominal cavity. Therefore, it is necessary to identify LAMN, and early surgical complete resection of the disease can improve the 5- or even 10-year survival rate of patients.

CT is important for the preoperative diagnosis of LAMN. CT has been demonstrated to be the fastest and most accurate method, with an accuracy rate of 89.7%[10]. The nomogram showed CT-specific signs of LAMN, including widening of the appendiceal lumen and a clear fat space around the appendix. LAMN is caused by the abnormal accumulation of mucinous tissue due to adenomatous hyperplasia of the appendiceal epithelium, which leads to an obvious expansion of the lumen. The diameter of the lumen ranged from 1.4 cm to 11cm, with an average diameter of approximately 3.2 cm. Calcification was observed in the cyst wall in 45% of the patients, with mild enhancement, a clear surrounding fat space, and no obvious lymph node enlargement[11]. On the enhanced CT, although no intralesional enhancement was noted in any cases, mild ring enhancement of the wall was observed in the arterial phase (Figure 2). LAMNs are hypovascularized tumors, and the enhanced rim represents the low vascularity of the tumor's blood supply in the wall. Moreover, progressive enhancement in the parenchymal phase reflected an internal fibrillar element and poor venous drainage, which was confirmed in the pathological images[12]. In the present study, we were able to diagnose appendiceal mucinous neoplasms on preoperative CT in all cases. Preoperative diagnosis of LAMN is very important for surgical methods and prognosis, so as to avoid the development of PMP. If CT shows low-density dilated appendix in the lower right abdomen, thin wall, clear surrounding fat space, calcification in the cyst wall, and progressive enhancement after enhancement, especially non-specific symptoms similar to appendicitis in middle-aged and elderly women, then the possibility of LAMN should be considered in time.

The previous consensus on the appropriate surgical extent was to select appendectomy or hemicolectomy based on a tumor diameter of 2 cm[13,14]. However, clinical practice recommends that appendectomy alone is safe for LAMN with negative margins and no evidence of perforation or peritoneal invasion irrespective of tumor size (grade of recommendation: strong recommendation based on moderate-quality evidence, 1B)[15]. This finding is supported by the results of several other studies. According to those studies, appendectomy with the entire mesoappendix for LAMN without perforation or perineal involvement is associated with very low recurrence rates[16-19].

Kwak et al[20]showed the results of the research plan,demonstrating that a favorable outcome can be obtained by securing a negative margin through single-incision laparoscopic cecal pole resection. In the present study, good outcomes were obtained when surgical procedures were performed to ensure margin negativity in patients diagnosed with LAMN. All patients had LAMN confined to the appendix without PMP. Our procedures included: laparoscopic IR, n=8 (42.1%); laparoscopic appendectomy, n=7 (36.8%); laparoscopic right hemicolectomy, n=1 (5.3%), laparoscopic partial resection of the cecum, n=1 (5.3%), IR, n=1 (5.3%), and right hemicolectomy, n=1 (5.3%). Laparoscopic surgery was performed on 17 (89.5%) patients. We believe that laparoscopic surgery is feasible in all cases. There was no recurrence and the DFS rate was 100%. Laparoscopic IRwas considered sufficient for LAMN confined to the appendix without PMP and with pathologically negative margins.

The present study was associated with several limitations. This study was conducted at a single center, and the study population was relatively small. Therefore, there may have been a selection bias.

V. CONCLUSIONS

LAMNs limited to the appendix lumen do not show definitive malignant features. Detailed multidirectional enhanced CT readings are important for the preoperative diagnosis of LAMN.Laparoscopic IR was considered sufficient for LAMN confined to the appendix without PMP and with pathologically negative margins.

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Figure Legends

Figure 1. Enhanced computed tomography (CT) shows a well-defined appendiceal lesion with curvilinear mural calcifications(arrow).
(a) Horizontal slice.
(b) Coronal slices.

Figure 2. The cystic wall was unevenly thickened with slight enhancement in the arterial phase(arrow).
(a) Horizontal slice.
(b) Coronal slices.

Table 1. Clinical characteristics

Table 2. Perioperative data

Figure 1

Figure 2

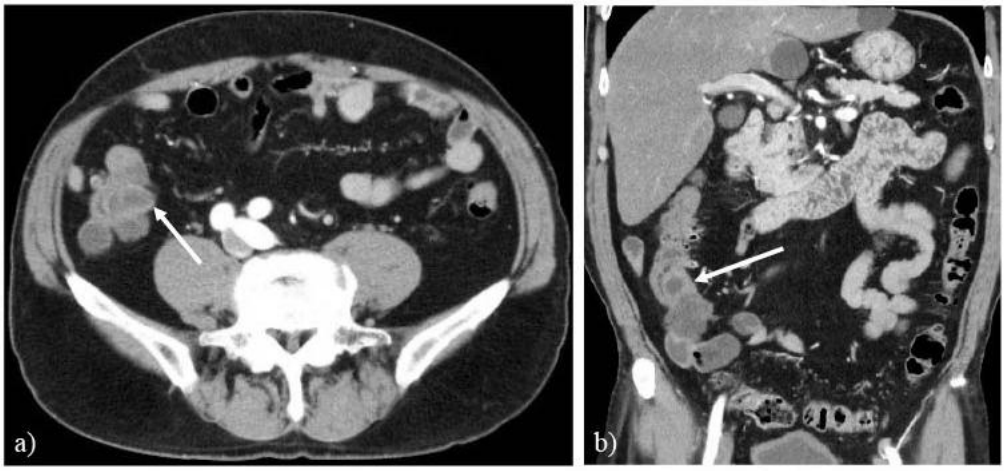

Table 1

Parameters	Results
Age (years), mean ± SD (range)	66.0 ± 12.6 (35-86)
Sex	
Male	7 (36.8%)
Female	12 (63.2%)
BMI (kg/m^2)	22.9 ± 4.0
ASA	
I	4 (21.1%)
II	11 (57.8%)
III	4 (21.1%)
Abdominal symptom	7 (36.8%)
WBC (/μl)	6057.4 ± 2204.2
CRP (mg/dl)	2.6 ± 10.9

CEA (ng/ml)	4.6 ± 2.8
CA19-9 (U/ml)	10.3 ± 8.1
Preoperative diagnosis	
Appendiceal mucinous neoplasm	19 (100%)
Maximal diameter on CT (mm)	27.9 ± 9.9
Calcification on CT	6 (31.6%)

Table 2

Parameters	Results
Surgery	
Laparoscopic ileocecal resection	8 (42.1%)
Ileocecal resection	1 (5.3%)
Laparoscopic appendectomy	7 (36.8%)
Laparoscopic right hemicolectomy	1 (5.3%)
Laparoscopic partial resection of caecum	1 (5.3%)
Right hemicolectomy	1 (5.3%)
Operation time (minutes)	110.3 ± 70.3
Blood loss (ml)	48.4 ± 123.3
Perforation during surgery	0 (0%)
Postoperative complications	0 (0%)
Pathological margin involvement	0 (0%)
Postoperative hospital stay (days)	9.9 ± 4.8
Mortality	0 (0%)
Recurrence	0 (0%)
Follow-up	
Death	0 (0%)
Disease-free survival	19 (100%)
Median of disease-free survival (months) (range)	103 (3-240)