

Short-term and Long-term Outcomes of 13 Cases of Low-grade Appendiceal Mucinous Neoplasm (LAMN)

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Aim: We evaluated the outcomes and treatment strategy for low-grade appendiceal mucinous neoplasm (LAMN) cases at our institution. **Methods:** We conducted a clinicopathological assessment of LAMN resection cases performed within the Department of Gastroenterology and General Surgery at Shimane University Hospital from July 2013 to December 2022. This retrospective study utilized medical information from medical records, including age, gender, surgical procedures, pathology results, and postoperative courses. **Results:** There were 8 males and 5 females, and the mean age was 67.4 years. Two cases were preoperatively diagnosed as appendicitis, and 11 cases were preoperatively diagnosed as appendiceal tumor. Laparoscopic appendectomy was performed in 5 cases, laparoscopic partial cecal resection in 4 cases, and laparoscopic ileocecal resection with lymph node dissection was performed in 4 cases. All resection margins were negative and there were no lymph node metastases. No additional treatment was given for appendectomy cases, and all cases were recurrence-free (median follow-up: 27 months [4–75 months]). **Conclusion:** If the distance between the resection margins is sufficient, the

postoperative follow-up period may be extended.

Keywords: low-grade appendiceal mucinous tumor, LAMN, primary mucinous tumor of the appendix, surgery, treatment outcome

INTRODUCTION

Low-grade appendiceal mucinous neoplasm (LAMN) is classified as one of the primary mucus-producing tumors of the appendix in the 3rd edition of the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma (2019) [1]. Appendiceal mucinous neoplasms are rare, with an estimated 3500 cases diagnosed annually in the United States [2]. If tumor rupture occurs, mucus leakage risks leading to pseudomyxoma peritonei (PMP), requiring immediate intervention if LAMN is suspected. LAMN is considered a borderline malignant tumor because of the potential for intraperitoneal leakage or splashing of contents after tumor rupture, which can cause PMP. Nonetheless, there were no adequate consensus for the optimal surgical approach and follow-up procedures for LAMN. This study aimed to evaluate the outcomes and treatment strategy for LAMN cases at our institution.

PATIENTS AND METHODS

We conducted a clinicopathological assessment of LAMN resection cases performed within the Department of Gastroenterology and General Surgery

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at Shimane University Hospital from July 2013 to December 2022.

This retrospective study utilized medical information from medical records, including age, gender, surgical procedures, pathology results, and postoperative courses. Surgical decisions were at the discretion of the attending physician based on preoperative evaluations and intraoperative findings. Postoperative follow-up followed the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines for colorectal cancer surveillance.

RESULTS

A total of 100 cases of appendiceal diseases were managed at our institution during the study period, among which 13 cases were diagnosed as LAMN. Table 1 shows clinical characteristics. The average age was 67.4 years old, with a male-to-female ratio of 8:5. The chief complaint was lower abdominal pain in four cases, while one patient was identified through fecal occult blood testing. Eight cases were asymptomatic at diagnosis. Tumor markers revealed slightly elevated CEA (>5.0 ng/ml) in 2 patients (5.1 and 5.3 ng/ml) and elevated CA19-9 (>37 U/mL) in 2 patients (66.6 and 71.9 U/mL). Appendectomy was performed on 5 cases with a preopera-

tive diagnosis of appendicitis and cases with a small tumor at the distal end of the appendix. Partial cecal resection (4 cases) was chosen for large tumors with perforated appendices and mucus adhesions, while ileocecal resection with lymph node dissection (4 cases) was opted for larger tumors with perforation and mucus adhesions around the appendix. All surgical margins were negative, and cases with lymph node dissection had no metastasis in the lymph node. Median postoperative follow-up was 27 months [4–75 months], with 12 patients alive and one death due to traffic trauma without recurrence. PMP did not develop during the observation period (Table 2).

DISCUSSIONS

There have been reports of complications with malignant tumors, with tumors exceeding 5 cm in size [3] and the presence of papillary prominence or mural nodules within the cyst suggesting cystadenocarcinoma, but the accuracy rate of preoperative diagnosis is low; around 50% [4], and malignant findings may be diagnosed on postoperative pathology, making the preoperative diagnosis of benign or malignant very difficult.

Considering these considerations, some experts

Table 1. Patient Background

No.	Age	Sex	Chief complaint	Appendicitis	Appendiceal cyst diameter (mm)	Preoperative lymph node swelling	Preoperative diagnosis	CEA (ng/ml)	CA19-9 (U/ml)
1	72	M	none	-	30	+	appendiceal tumor	5.1	23.1
2	56	M	none	-	32	-	appendiceal tumor	-	-
3	75	M	none	-	13	-	appendiceal tumor	5.3	71.9
4	71	F	right lower abdominal pain	+	12	+	acute appendicitis	-	-
5	84	M	none	-	22	-	appendiceal tumor	3	35.4
6	83	M	none	-	20	+	appendiceal tumor	3.2	15.7
7	80	M	none	-	50	-	appendiceal tumor	3.6	11.6
8	44	F	none	-	15	-	appendiceal tumor	2.4	15.6
9	46	F	abdominal pain	-	15	-	appendiceal tumor	-	-
10	79	F	none	-	11	+	appendiceal tumor	4.2	32.4
11	32	M	right lower abdominal pain	+	15	-	chronic appendicitis	3.5	15.4
12	83	M	abdominal pain	-	17	-	appendiceal tumor	4.6	66.6
13	71	F	fecal occult blood	-	25	+	appendiceal tumor	2.7	17

M: male, F: female

Table 2. Operative Technique, Pathological Diagnosis, and Postoperative Outcome

No.	Surgical procedures	Lymph node dissection	Tumor size (mm)	Tumor location	Surgical margin	Presence of perforation/rupture	Lymph node metastasis	Pathological classification†	Recurrence	PMP	Prognosis	RFS (months)
1	Lap. ileocaecal resection	D3	48	proximal	negative	-	none	Type II	none	none	death‡	4
2	Lap. ileocaecal resection	D3	60	total	negative	-	none	Type II	none	none	alive	6.3
3	Lap. partial cecal resection	-	20	proximal	negative	+	unknown	Type II	none	none	alive	15
4	Lap. appendectomy	-	35	distal	negative	-	unknown	Type II	none	none	alive	16.2
5	Lap. appendectomy	-	30	distal	negative	-	unknown	Type I	none	none	alive	20.1
6	Lap. partial cecal resection	-	40	distal	negative	-	unknown	Type I	none	none	alive	25.9
7	Lap. ileocaecal resection	D3	100	total	negative	-	none	Type I	none	none	alive	27
8	Lap. partial cecal resection	-	50	proximal	negative	-	unknown	Type I	none	none	alive	33.5
9	Lap. appendectomy	-	43	distal	negative	-	unknown	Type II	none	none	alive	39.3
10	Lap. appendectomy	-	35	distal	negative	-	unknown	Type I	none	none	alive	40
11	Lap. appendectomy	-	25	distal	negative	+	unknown	Type II	none	none	alive	64.6
12	Lap. appendectomy	-	45	distal	negative	-	unknown	Type II	none	none	alive	67.3
13	Lap. ileocaecal resection	D3	60	proximal	negative	+	none	Type II	none	none	alive	75

Lap: Laparoscopic, PMP: pseudomyxoma peritonei, RFS: Recurrence-free survival

†: Pathological classification by McDonald [11], ‡: Death due to traffic accident

suggested that, in cases where malignancy cannot be definitively ruled out, a desirable approach involves ileal resection or right semicolon resection with lymph node dissection of D2 or higher, aligning with the principles of colorectal cancer management [5]. Figure 1 shows surgical algorithm of appendiceal tumor at our institution.

Conversely, there is a viewpoint advocating that due to the infrequent occurrence of lymph node metastasis in LAMN, interventions such as ileal resection or right semicolon resection may prove excessively invasive, while surgical resection with clear margins could suffice [5]. Nonetheless, instances have been reported where mucinous cystadenomas developed from resection margins [7], underscoring the importance of performing resections at a considerable distance from the tumor to ensure sufficient clearance.

Moreover, considering that numerous cases where LAMN was resected without rupture did not progress to PMP [4] [5] [8-10], the development of PMP should primarily concern intraoperative ruptures. As such, it is crucial to prioritize a minimally invasive approach to prevent tumor rupture or destruction. Additionally, patients exhibiting high preoperative CEA levels, a tumor diameter of 5 cm or more, or localized nodules within the myxoma lumen face a heightened risk of cystadenocarcinoma [3]. Consequently, our approach entails ileal resection coupled with lymph node dissection.

Following the clinicopathologic classification suggested by McDonald *et al.* [11], our study encompassed 5 cases classified as Type I, characterized by the presence of mucus or endothelial cells within the appendiceal lumen, and 8 cases classified as Type II, involving deeper invasions beyond the sub-mucosal layer. Notably, Type II cases entail a substantial risk of evolving into PMP, warranting cytoreductive surgery. This extensive approach, which might involve hysterectomy, bilateral ovarian resection, mesh application, retinectomy, cholecystectomy, and peritoneal resection, should be tailored based on disease extent, age, and performance status. However, the high invasiveness of these treatments limits their widespread implementation, given the scarcity of capable facilities. Within our study cohort, over half the patients exhibited Type II disease, yet none

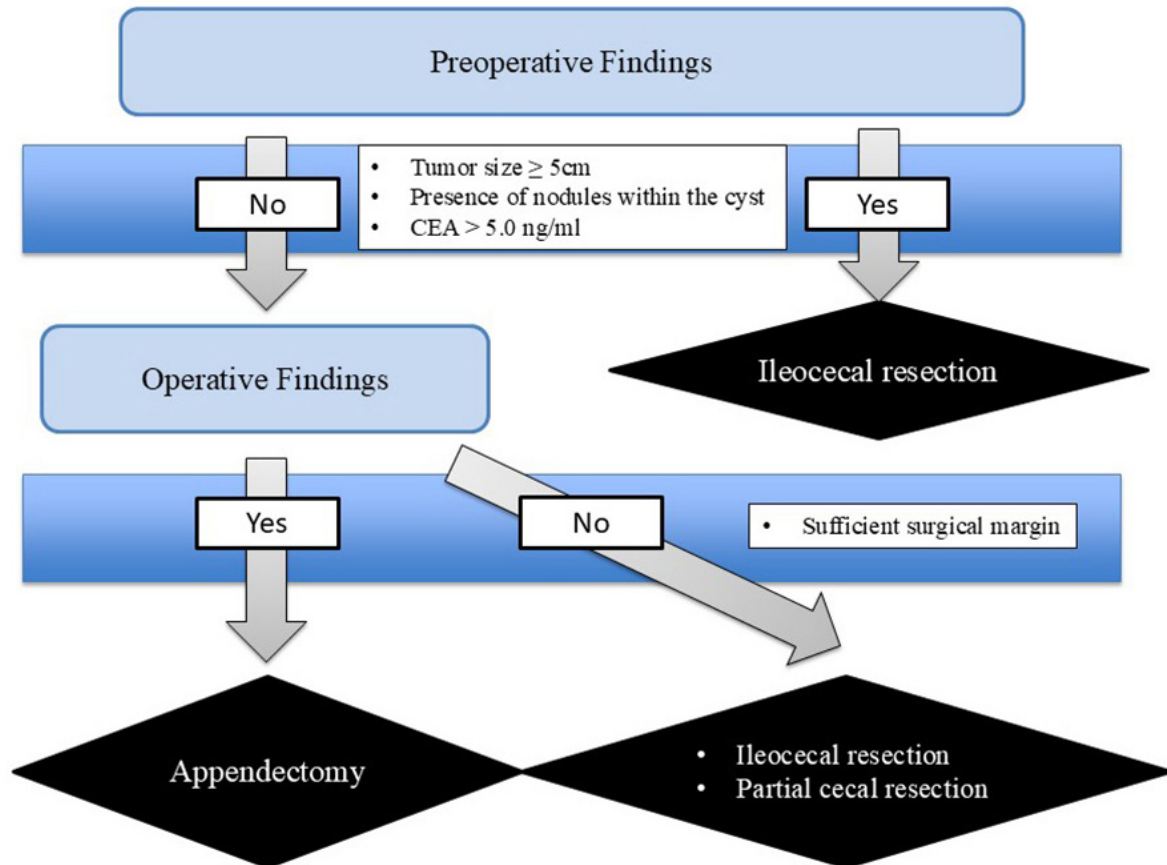


Figure 1. Surgical algorithm for appendiceal tumors of our institution

received supplementary treatment, nor did they encounter PMP development or relapse. Patients undergoing appendectomy alone received neither additional resection nor postoperative adjuvant chemotherapy. Consequently, further investigations, including in vivo analyses of recurrence mechanisms, remain imperative.

Once LAMN progresses to PMP, prognosis will be poor, with a five-year survival rate of 25% [12]. Therefore, routine monitoring and timely management of LAMN are critical to reduce likelihood of LAMN recurrence and progression to PMP and metastasis.

While LAMN harbors the potential to progress into PMP, a standardized postoperative follow-up approach is yet to be established. PMP is characterized by intraperitoneal expansion, direct organ involvement, and a paucity of symptoms. As a result, periodic imaging examinations employing techniques such as CT are deemed essential. However, given that the disease often attains an advanced stage by

the time symptoms manifest, current postoperative surveillance practices resemble those utilized for colorectal cancer. Moreover, delivering comprehensive information about rigorous follow-up, encompassing imaging evaluations, proves pivotal, especially for patients preferring to pursue follow-up care at alternative medical institutions.

CONCLUSION

Our evaluation of 13 surgically resected LAMN cases highlights the need for preoperative evaluation and treatment strategy development that considers the risk of LAMN recurrence despite its low-grade nature. As stated in previous literature, preoperative tumor markers and nodules within the cyst are high-risk factors for cystadenocarcinoma, so an ileocecal resection like that used for colorectal cancer should be selected. Because the size and location of the tumor are difficult to determine based on preoperative imaging tests, the possibility of avoiding PMP

recurrence can be increased by selecting a surgical technique that ensures reliable resection margins during surgery.

Ethical approval

This study was a single-center, retrospective, observational study, and was approved by the Medical Research Ethics Committee, Shimane University Faculty of Medicine (IRB number: 20230216-2). All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. Informed consent was obtained in the opt-out format on the website. Those who declined consent were excluded.

Additionally, the study was registered and published on UMIN-CTR (UMIN study ID: UMIN000050565).

Authorship

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Takahito TANIURA, Keisuke INOUE, Kazunari ISHITOBI, Kiyoe TAKAI, and Tetsu YAMAMOTO. Writing - review & editing, visualization, supervision, and project administration was performed by Masaaki HIDA-KA. The first draft of the manuscript was written by Takahito TANIURA, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

All authors have no conflicts of interest to disclose in connection with this paper.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, Takahito Taniura used ChatGPT 3.5 in order to English proof-reading. After using this tool/service, the author reviewed and edited the content as need and takes

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