Preoperative Prediction of Malignancy and Surgical Treatment Strategy for Appendiceal Tumors: Multicenter Review of 51 Consecutive Cases

Koji Tamura (tamura.koji.589@m.kyushu-u.ac.jp)
Kyushu University
Takashi Ueki
Hamanomachi Hospital
Hiromichi Nakayama
Hamanomachi Hospital
Yusuke Watanabe
Hamanomachi Hospital
Masafumi Sada
Kyushu University
Kinuko Nagayoshi
Kyushu University
Yusuke Mizuuchi
Kyushu University
Kenoki Ohuchida
Kyushu University
Hitoshi Ichimiya
Hamanomachi Hospital
Masafumi Nakamura
Kyushu University

Research Article

Keywords: appendiceal tumor, appendiceal carcinoma, laparoscopic surgery, LAMN, mucinous neoplasm

Posted Date: September 23rd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2079504/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Langenbeck's Archives of Surgery on January 17th, 2023. See the published version at https://doi.org/10.1007/s00423-023-02807-6.

Abstract

Purpose: A diagnostic and treatment strategy for appendiceal tumors (ATs) has not been established. We aimed to evaluate our treatment strategy for ATs including laparoscopic surgery (LS) and to identify preoperative malignancy predictors.

Methods: A total of 51 patients were retrospectively reviewed. Data including tumor markers and imaging findings were compared between carcinoma and non-carcinoma patients. Validity of planned operation was evaluated based on pathological diagnosis.

Results: Twenty-five patients were diagnosed with carcinoma, 13 with low-grade mucinous neoplasm, and 13 with other diseases. Symptoms were more commonly present in carcinoma patients than in non-carcinoma patients (68.0% vs. 23.1%, p=0.001). Elevated CEA and CA19-9 were more frequently observed in carcinoma patients than in non-carcinoma patients (p<0.01 and p=0.04, respectively). Five carcinoma patients had malignancy on biopsy, compared with zero non-carcinoma patients. Significant differences were noted in the percentages of carcinoma and non-carcinoma patients with solid enhanced mass (41.7% vs. 0%, p<0.001) and tumor wall irregularity (16.7% vs. 0%, p=0.03) on imaging. Although the sensitivity was not high, the specificity and positive predictive value of these findings were 100%. Forty-two patients (82.4%) underwent LS as minimally invasive exploratory tool and/or radical operation, of whom 2 were converted to open surgery for invasion of adjacent organ. None of the patients had intraoperative complications or postoperative mortality.

Conclusion: Clinical symptoms, elevated tumor markers, and worrisome features of solid enhanced mass and tumor wall irregularity on imaging can be malignancy predictors. For management of AT patients, LS is feasible and useful for diagnosis and treatment.

Introduction

Appendiceal neoplasms are rare diseases, being identified in 0.9–2% of appendiceal specimens [1, 2]. Preoperative histological diagnosis of appendiceal tumors is difficult because of the anatomical characteristics, and appendiceal neoplasms are sometimes diagnosed unexpectedly after emergency surgery for acute appendicitis. Appendiceal tumors have a wide variety of types. In the 5th edition of the World Health Organization (WHO) classification, these tumors are classified into the following categories: adenocarcinoma, mucinous neoplasm, serrated lesion/polyp, and neuroendocrine neoplasm (NEN) [3].

The most common malignancies of the appendix are mucinous and non-mucinous adenocarcinomas. Furthermore, 15.8% of mucinous and 43.9% of non-mucinous adenocarcinoma patients have lymph node metastasis (LNM) [4], and LNM is an independent factor for recurrence-free survival and overall survival in appendiceal carcinoma patients [5]. Although the clinicopathological and molecular characteristics of appendiceal carcinoma differ from those of colorectal cancer (CRC), patients with appendiceal carcinoma who underwent right-side colectomy (RC) with lymph node dissection (LND) had a better prognosis than those who underwent appendectomy alone, and therefore RC with LND is usually recommended as a radical surgery [6–8].

Mucinous neoplasms include low-grade appendiceal mucinous neoplasm (LAMN), high-grade appendiceal mucinous neoplasm (HAMN), and mucinous adenocarcinoma. Regardless of the histological grade, mucinous neoplasms can lead to mucocele formation and pseudomyxoma peritonei (PMP) [9]. For LAMN or HAMN, appendectomy alone with negative resection margin is considered sufficient, while mucinous adenocarcinoma usually requires RC with LND [10]. However, reaching a differential diagnosis between LAMN/HAMN and carcinoma is often difficult preoperatively, and thus the surgical treatment strategy for mucinous neoplasms remains controversial. To reach a decision for the surgical approach, detection of these tumors on preoperative imaging is important. Computed tomography (CT) can help to confirm an appendiceal tumor and may suggest a specific diagnosis [11]. However, CT cannot provide a histological diagnosis, unlike colonoscopy for CRC, and thus a preoperative definite diagnosis is difficult unless the tumor invades the appendiceal orifice and/or cecum. It is also difficult to confirm the preoperative diagnosis of other rare tumors, including NEN, lymphoma, and benign disease, because these tumors have fewer specific image findings. Only a few studies have focused on the preoperative findings, diagnosis, and treatment strategy of appendiceal tumors to date [12].

Recently, the number of procedures involving laparoscopic surgery (LS) has been increasing in a variety of surgical fields [13]. Several studies reported that LS can be used for safe and radical resection of CRC and appendiceal tumors [14]. LS may have advantages of not only reduced invasiveness but also utility as an intraoperative diagnostic tool for cases without a definite preoperative diagnosis.

The aim of this study was to determine malignancy predictors using clinical data and preoperative imaging findings for patients with appendiceal tumors, and to evaluate the validity of performed operations based on the preoperative and postoperative diagnosis. We also discuss the usefulness of LS for appendiceal tumors and review our surgical treatment strategy for appendiceal tumors.

Methods

The present study was approved by the Ethics Committees of Hamanomachi Hospital and Kyushu University Hospital (approval numbers, 2020-48 and 2020 – 503, respectively), and was conducted according to the Ethical Guidelines of the Helsinki Declaration. The medical records of 51 consecutive patients who were preoperatively and/or histologically diagnosed with appendiceal tumors at the Department of Surgery, Hamanomachi Hospital, and the Department of Surgery and Oncology, Kyushu University Hospital, between 2011 and 2021 were retrospectively reviewed. Data including demographic characteristics, clinical symptoms, preoperative imaging findings, preoperative and postoperative diagnosis, operative findings and procedures, and postoperative outcomes were collected.

If available, serum levels of carcinoembryonic antigen (CEA) (normal limit, < 5.0 ng/mL at Hamanomachi Hospital; <3.2 ng/mL at Kyushu University Hospital) and carbohydrate antigen 19 – 9 (CA19-9) (normal limit, < 37 ng/mL) were reviewed. For preoperative assessment, enhanced CT and/or magnetic resonance imaging (MRI) findings were evaluated in all patients. In cystic tumor patients, the maximum tumor diameter was determined based on preoperative CT/MRI. Acute appendicitis patients who were postoperatively proven to have appendiceal carcinoma were included, while patients who underwent appendectomy for acute appendicitis without a neoplastic lesion were excluded.

Based on the preoperative imaging findings and/or the tumor biopsy findings during colonoscopy, an appropriate operative procedure was selected in each patient (Fig. 1). The first choice for the operative procedure was LS. If LS was not applicable, open surgery was performed. For a definite malignant tumor or possible malignant tumor, laparoscopic RC (including right-hemi-colectomy and ileocecal resection) (LS-RC) with LND was planned. For a possible nonmalignant tumor or apparent benign tumor, laparoscopic appendectomy or cecectomy (LS-A/C) without LND was performed. RC was also selected for nonmalignant cases to obtain the appropriate surgical margin during surgery. Intraoperative frozen pathology was evaluated during LS-A/C as needed, and if the pathological diagnosis was malignant tumor, LS-RC with LND was subsequently performed in the same operation. If the appendectomy specimen for appendicitis was found to contain advanced carcinoma, additional RC with LND was performed. For patients with suspicion of PMP, exploratory laparoscopy with or without appendectomy was planned first, and further treatment was considered.

Based on the 2019 WHO Classification, the postoperative diagnosis in each patient was categorized into the following cohorts. Carcinoma included appendiceal cancer (adenocarcinoma, mucinous adenocarcinoma, goblet cell carcinoma) and cecal cancer. Cecal cancer around the orifice of the appendix, which had been preoperatively diagnosed as appendiceal tumor, was also included because it obstructed the appendiceal lumen and made the appendix swollen. Other tumor lesions were LAMN and neuroendocrine tumor (NET), and the remaining rare conditions, such as malignant lymphoma (ML), adenoma, sessile serrated adenoma/polyp (SSA/P), hyperplastic polyp, chronic appendicitis, and diverticulitis were categorized as others. PMP patients originating from appendiceal tumor were included.

Comparisons between carcinoma and non-carcinoma patients were performed using the chi-square test or Mann–Whitney U-test as appropriate. A probability value of < 0.05 was considered statistically significant. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each preoperative finding for the diagnosis of malignancy were calculated. All statistical analyses were conducted using JMP Pro version 15.1.0 (SAS Institute Inc., Tokyo, Japan).

Results

Patient characteristics and surgical procedures

A total of 51 patients underwent surgery for appendiceal tumors (Table 1). According to the postoperative pathological diagnosis, 25 patients were diagnosed with carcinoma (14 adenocarcinoma including 1 cecal carcinoma, 10 mucinous adenocarcinoma, 1 goblet cell carcinoma), 13 with LAMN, 3 with NET, 9 with benign lesion, and 1 with ML. Benign lesions included chronic appendicitis, adenoma, SSA/P, hyperplastic polyp, diverticulitis, and appendiceal endometriosis (Supplemental Table 1–3). Of the total 51 patients, 23 were men and 28 were women. The mean ages of the carcinoma and non-carcinoma patients were 61.0 ± 16.4 years (range, 31–88 years) and 59.0 ± 13.2 years (range, 29–84 years), respectively ($p = 0.63$; Table 1).

Twenty-three patients had symptoms: 12 had abdominal pain, 2 had back pain, 2 had melena, 1 had fever, 2 had palpable abdominal mass, and 4 were diagnosed as acute appendicitis at the initial operation. Seventeen of the 25 carcinoma patients had at least one symptom, as did 2 of the 13 LAMN patients and 4 of the 10 patients with other diseases. None of the 3 NET patients had symptoms. When the numbers of patients with clinical symptoms were compared, symptoms were significantly more common in carcinoma patients than in non-carcinoma patients ($p = 0.001$; Table 1).

As shown in Fig. 1, the surgical procedure was selected based on the preoperative tumor markers and imaging findings or definite pathological diagnosis if obtained. Thirty-three patients who were preoperatively diagnosed with carcinoma or possible malignant tumor

underwent RC and one patient (case K51; Supplemental Table 1) who was preoperatively diagnosed with mucinous cystic tumor underwent LS-RC to obtain the surgical margin. Among these 34 patients, the pathological diagnosis was appendiceal carcinoma in 22, cecal carcinoma in 1, LAMN in 9, ML in 1, and diverticulitis in 1. In 3 patients who underwent appendectomy with a diagnosis of acute appendicitis and were proven to have advanced appendiceal carcinoma, RC with LND was subsequently performed as a curative operation (cases H12, H13, and K39; Supplemental Table 2).

LS-A/C was performed for possible non-carcinoma lesions in 12 patients, comprising 4 with LAMN, 3 with chronic appendicitis, 2 with adenoma, 1 with SSA/P, 1 with hyperplastic polyp, and 1 with appendiceal endometriosis. In 4 of these 12 patients, intraoperative frozen pathology was evaluated to determine whether the appendectomy specimens contained malignant tissue, and none of them required additional resection. In 3 patients who underwent LS/open-A with a diagnosis of chronic appendicitis, the pathological diagnosis was NET-G1, which did not require additional treatment. The patients with possible PMP underwent exploratory surgery for a definite diagnosis.

Among the patients with LAMN, no patients had LNM or distant metastasis. The median surveillance period was 26 months (range, 5–75 months). None of the patients had recurrence of mucinous neoplasms during the surveillance period.

Preoperative serum levels of tumor markers

Among the patients whose serum CEA levels were measured preoperatively, 13 of 21 carcinoma patients, 4 of 11 LAMN patients, and 1 chronic appendicitis patient with concomitant gastric cancer had elevated CEA. There was a significant difference between the numbers of carcinoma and non-carcinoma patients with elevated serum CEA ($p < 0.01$; Table 1). For elevated CEA as a malignancy predictor, the odds ratio was 5.55 (95% confidence interval, 1.50–20.28), the positive predictive value (PPV) was 0.72, and the negative predictive value (NPV) was 0.68.

Similarly, among the patients whose serum CA19-9 levels were measured preoperatively, 5 of 17 carcinoma patients showed elevated CA19-9, while only 1 LAMN patient among 21 non-carcinoma patients had elevated CA19-9. The number of carcinoma patients with elevated serum CA19-9 was significantly higher than that of non-carcinoma patients ($p = 0.04$; Table 1). For elevated CA19-9 as a malignancy predictor, the odds ratio was 8.33 (95% confidence interval, 1.10–59.02), the PPV was 0.83, and the NPV was 0.63

Preoperative imaging findings as malignancy predictors

Forty patients, including 18 carcinoma patients, underwent preoperative colonoscopy, and malignant tumor was suspected in 8 patients. The other patients showed normal findings or submucosal tumor-like elevation. Among the 8 patients, 5 were diagnosed with adenocarcinoma and 1 with ML by biopsy, consistent with the postoperative diagnosis. Among the patients who underwent colonoscopy, the sensitivity of positive biopsy was not high (27.8%), but the specificity and PPV were 100% (Table 2).

Table 1
Clinical characteristics of the study population

	Carcinoma	Non-Carcinoma (n = 26)			Total	*p* value
	(n = 25)	LAMN	NET	Others	(n = 51)	(Ca vs Non-Ca)
		(n = 13)	(n = 3)	(n = 10)		
Age, mean	61.0 ± 16.4	62.1 ± 15.3	56.3 ± 12.6	55.8 ± 10.4	59.5 ± 2.1	0.63
Gender						
Male	9	9	1	4	23	0.20
Female	16	4	2	6	28	
Symptoms						
Presence	17	2	0	4	23	0.001
Absence	8	11	3	6	28	
CEA (ng/ml)						
Normal	8	7	2	8	25	< 0.01
Elevated	13	4	0	1	18	
NA	4	2	1	1	8	
CA19-9 (ng/ml)						
Normal	12	9	2	9	32	0.04
Elevated	5	1	0	0	6	
NA	8	3	1	1	13	
Surgical procedure						< 0.001
Lap-RC	19	6	0	2	27	
Open-RC	4	3	0	0	7	
Lap-C/A	0	4	2	8	14	
Lap-Exp	1	0	0	0	1	
Others	1	0	1	0	2	

LAMN, low grade appendiceal neoplasm; NET, neuroendocrine neoplasm; Ca, carcinoma; *NA*, not available; Lap-/Open-RC, laparoscopic/open- right-side colectomy; Lap-C/A, laparoscopic cecectomy/appendectomy; Lap-Exp, exploratory laparoscopy

Table 2. Preoperative imaging findings

Preoperative findings		Carcinoma			Non-carcinoma			*p* value	Sensitivity	Specificity	PPV	NPV
		Non-MucCa (n = 15)	MucCa (n = 10)	Total (n = 25)	LAMN (n = 13)	Others (n = 13)	Total (n = 26)	(Ca vs Non-Ca)	(%)	(%)	(%)	(%)
TCS*	tumor biopsy: *carcinoma*	4	1	5	0	0	0	< 0.01	27.8	100	100	62.9
CT/MRI**	solid enhanced mass	7	3	10	0	0	0	< 0.001	41.7	100	100	65.0
	cyst with solid component	0	3	3	1	0	1	0.26	12.5	96.2	75.0	54.3
	tumor wall irregularity	3	1	4	0	0	0	0.03	16.7	100	100	56.5
	enhanced wall thickness	2	1	3	1	1†	2	0.57	12.5	92.3	60.0	53.3
	increasing tumor size	0	0	0	2	0	2	0.17	0	92.3	0	50.0
	calcification	0	2	2	1	0	1	0.5	8.3	96.2	66.7	53.2

*Analyzed only in patients who underwent TCS (n = 40); **Preoperative imaging was not available in in one adenocarcinoma patient (underwent appendectomy in other hospital); †malignant lymphoma

MucCa, mucinous adenocarcinoma; LAMN, low-grade appendiceal mucinous neoplasm; PPV, positive predictive value; NPV, negative predictive value; TCS, total colonoscopy; PMP, pseudomyxioma peritonei

The preoperative imaging findings for 24 carcinoma patients (imaging was unavailable in 1 patient) are shown in Table 2. Among these patients, 10 had solid enhanced lesion, 3 had cystic tumor with solid component, 4 had tumor wall irregularity, 3 had enhanced tumor wall thickness, 2 had calcification, and 3 had apparent PMP findings. There were significant differences between the numbers of carcinoma and non-carcinoma patients having solid enhanced mass ($p < 0.001$) and tumor wall irregularity ($p = 0.03$) (Fig. 2a–d). The feature with the highest sensitivity was solid enhanced mass (41.7%), while the sensitivity of the other features was not high. However, the specificity and PPV of solid enhanced mass and tumor wall irregularity were 100%, indicating that these findings are good malignancy predictors (Table 2). Meanwhile, the specificity and PPV of cyst with solid component were 96.2% and 75%, respectively.

Regarding the tumor size of mucinous neoplasms, the median mucocele size of LAMN was 50 mm (range, 20–120 mm) and the median size of mucinous adenocarcinoma was 55 mm (range, 21–100 mm). There were no significant differences in the tumor sizes between the numbers of carcinoma and non-carcinoma patients.

Laparoscopic surgery

LS was selected in 42 of the 51 patients (82.4%), of whom 1 ML patient and 1 carcinoma patient required conversion to open surgery for invasion of adjacent organ by the tumor (case K34 in Supplemental Table 3 and case K46 in Supplemental Table 2). Planned open surgery was performed in 9 patients for various reasons, including volume reduction/salvage surgery for PMP, postoperative state of open abdominal surgery, and abdominal wall invasion of the bulky carcinoma. The other operations were completed with the planned LS.

Three patients had Grade IIIa postoperative complications (Clavien–Dindo classification): minor anastomotic leakage, sepsis due to fungemia, and intraabdominal abscess. No patients had intraoperative complications or postoperative mortality.

Discussion

In this retrospective multicenter review, the authors identified worrisome features for malignancy of appendiceal tumors. These features included clinical symptoms and elevated serum CEA and/or CA19-9 as well as solid enhanced mass and/or tumor wall irregularity on CT or MRI. The majority (96%) of the patients in our carcinoma cohort had at least one of these findings. Thus, if colonoscopy is unavailable or

fails to reveal carcinoma, RC with LND is recommended as a curative operation for treatment of appendiceal tumor in patients with these findings. Although some researchers reported a retrospective case series of 13 appendiceal cancer patients in which carcinoma was not suspected preoperatively [7], and other researchers demonstrated that surrounding soft tissue thickening and tumor wall irregularity were non-specific findings because they could be caused by inflammation as well as malignancy [11, 12], we consider that the relatively high PPV of each feature may help us to select the proper treatment.

Among the 18 carcinoma patients who underwent colonoscopy followed by biopsy in our cohort, carcinoma was suspected in 7 (38.9%) and the biopsy was positive for carcinoma in 5 (27.8%). Trivedi *et al*. [15] reported that a malignant tumor diagnosis was made in only 2 of 64 (3.1%) appendiceal carcinoma patients showing PMP by biopsy during preoperative colonoscopy, and their positivity rate for cancer was lower than that in the present study. This discrepancy may be due to the biological differences between mucinous adenocarcinoma, in which the tumor cells tend to invade the appendiceal wall with abundant mucin, and tubular adenocarcinoma, in which the cells tend to form a solid mass and sometimes spread over the lumen into the cecum. Although its diagnostic sensitivity is not sufficiently high, colonoscopy may reveal indirect findings, such as cecal or ileal mucosal changes, and may indicate the extent of the disease. Thus, we recommend total colonoscopy for all patients with appendiceal tumors if applicable, especially for patients with the worrisome features of carcinoma.

When considering appendiceal cystic tumor cases only, it is important to distinguish mucinous adenocarcinoma from LAMN and other benign lesions, because LNM or distant metastasis are significantly less common in LAMN patients than in mucinous adenocarcinoma patients [4, 5, 16]. In our LAMN cohort containing 4 patients who underwent LS-A/C, no patients had LNM or developed postoperative recurrence during the surveillance period. Because patients with LAMN were shown to have a good prognosis and RC with LND did not contribute to increased disease-specific or overall survival, extended resection for LAMN may not be necessary [17, 18]. While all 9 mucinous adenocarcinoma patients in our cohort showed at least one of the worrisome features, there was no difference between mucinous carcinoma and LAMN in tumor size, with the mean diameter being as large as 5 cm. Therefore, these features can assist surgeons to choose appropriate operative procedures for patients with large cystic tumors.

The frequency of epithelial tumors has been increasing over the past few decades according to the Surveillance, Epidemiology, and End Results (SEER) database [1]. In our study, the most frequent neoplasm was appendiceal cancer, similar to the SEER database, and these neoplasms were often discovered unexpectedly in resected specimens. Actually, 3 patients were diagnosed with adenocarcinoma after undergoing appendectomy for acute appendicitis. Although it is usually difficult to identify a malignant tumor in acute appendicitis patients, malignant tumors in patients with appendicitis seem to be associated with increasing age [19]. The ages of our 3 patients were 46, 57, and 74 years, and were higher than the peak incidence age for typical acute appendicitis [20]. Furthermore, Sugimoto *et al*. [21] demonstrated that patients with complicated appendicitis had a higher incidence of appendiceal tumors than patients with uncomplicated appendicitis. In our cohort, 2 of the 3 patients had complicated appendicitis with abscess formation. For the management of acute appendicitis, especially in patients with older age or complicated appendicitis, surgeons should pay attention to the possible presence of malignancy and should confirm the levels of CEA and CA19-9 preoperatively. It is also important to avoid spilling the contents of the appendix during surgery, based on the possible existence of malignant cells [22].

Regarding other neoplasms, NEN was diagnosed in 0.1–0.3% of patients after appendectomy in a previous study [23]. In the present study, 3 patients with NET-G1 were incidentally diagnosed after resection, and none of these patients showed any abnormalities of the appendix on retrospective assessment of their preoperative imaging findings. The majority of appendiceal NEN cases are < 1 cm in size and confined to the distal appendix, which may render a preoperative diagnosis difficult [11, 23]. Regarding ML, these cases are also incidentally diagnosed as causes of acute appendicitis [24]. In the present study, there was only one ML patient, and the symptom in this case was acute appendicitis. The published articles on imaging features of appendiceal lymphoma are mainly limited to case reports, and thus the specific imaging features remain unknown [24]. Although we selected a treatment strategy for these neoplasms based on the corresponding guideline, preoperative histological diagnosis of such neoplasms is difficult unless the tumors have a relatively large size and invade into the cecum.

Recently, the number of cases treated by LS has been increasing, and decreased rates of intraoperative and postoperative complications have been reported [13]. In our study, 42 patients (82.4%) were planned to undergo LS, and only 2 of these patients (4.8%) were converted to open surgery for invasion of adjacent organ. Kim *et al*. [14] compared the perioperative short-term outcomes between LS and open surgery cases, and showed the safety and feasibility of LS for appendiceal mucocele. Inoue *et al*. [25] focused on the long-term outcomes of LS for appendiceal tumors, and showed that LS was comparable to open surgery. In addition to the superior short-term and long-term outcomes, another advantage of LS is the possibility for diagnostic exploration of the appendix itself and entire abdomen to investigate peritoneal dissemination under magnified vision. Moreover, LS-A/C is relatively easy to perform and allows acquisition of a specimen for

intraoperative pathological diagnosis. Diagnostic LS followed by A/C would be a better option, especially in older and/or vulnerable patients with appendiceal tumors for which cancer could not be ruled out.

The present study has some limitations. It was a retrospective study, and the total number of cases was relatively small. Consequently, the statistical power was weak, and it was relatively difficult to detect definite malignant features on preoperative findings. In addition, the median postoperative surveillance periods varied, and the long-term outcomes were unknown, especially for LAMN patients. Further investigations are necessary to establish a preoperative diagnosis and treatment strategy for appendiceal tumors.

In conclusion, although definite preoperative diagnosis of an appendiceal tumor is difficult, clinical symptoms, preoperative tumor markers, and some imaging findings can be worrisome features for malignancy. The possible presence of malignancy should be kept in mind in patient with older age or complicated acute appendicitis. For the clinical management of appendiceal tumor patients, LS is feasible and useful for intraoperative diagnosis and surgical treatment.

Declarations

Acknowledgments: The authors thank Dr. Reiko Yoneda in the Department of Pathology at Hamanomachi Hospital for special assistance in the pathological findings. The authors also thank Alison Sherwin, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

References

1. Hatch QM, Gilbert EW (2018) Appendiceal Neoplasms. Clin Colon Rectal Surg 31(5):278–287. https://doi.org/10.1055/s-0038-1642051
2. Connor SJ, Hanna GB, Frizelle FA (1998) Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. Dis Colon Rectum 41(1):75–80. https://doi.org/10.1007/BF02236899
3. Assarzadegan N, Montgomery E (2021) What is New in the 2019 World Health Organization (WHO) Classification of Tumors of the Digestive System: Review of Selected Updates on Neuroendocrine Neoplasms, Appendiceal Tumors, and Molecular Testing. Arch Pathol Lab Med 145(6):664–677. https://doi.org/10.5858/arpa.2019-0665-RA
4. Matsui S, Murata K, Fukunaga Y, Takeda T, Fujii M, Yamaguchi T, Kagawa Y, Mizushima T, Ohno Y, Yao T, Doki Y, Sugihara K (2020) Analysis of Clinicopathological Characteristics of Appendiceal Tumors in Japan: A Multicenter Collaborative Retrospective Clinical Study- A Japanese Nationwide Survey. Dis Colon Rectum 63(10):1403–1410. https://doi.org/10.1097/DCR.0000000000001676
5. Takeyama H, Murata K, Takeda T, Fujii M, Kagawa Y, Kawachi H, Yamaguchi T, Noura S, Masuishi T, Inoue A, Takii Y, Suto T, Sakamoto K, Tei M, Kishimoto M, Yao T, Sugihara K, study group of appendiceal neoplasms in Japan Society of Colorectal Cancer Research G (2022) Clinical Significance of Lymph Node Dissection and Lymph Node Metastasis in Primary Appendiceal Tumor Patients After Curative Resection: a Retrospective Multicenter Cohort Study. J Gastrointest Surg 26(1):128–140. https://doi.org/10.1007/s11605-021-05070-6
6. Gahagan JV, Whealon MD, Phelan MJ, Mills S, Pigazzi A, Stamos MJ, Nguyen NT, Carmichael JC (2017) Lymph Node Positivity in Appendiceal Adenocarcinoma: Should Size Matter? J Am Coll Surg 225(1):69–75. https://doi.org/10.1016/j.jamcollsurg.2017.01.056
7. Cortina R, McCormick J, Kolm P, Perry RR (1995) Management and prognosis of adenocarcinoma of the appendix. Dis Colon Rectum 38(8):848–852. https://doi.org/10.1007/BF02049842
8. Tokunaga R, Xiu J, Johnston C, Goldberg RM, Philip PA, Seeber A, Naseem M, Lo JH, Arai H, Battaglin F, Puccini A, Berger MD, Soni S, Zhang W, Hwang JJ, Shields AF, Marshall JL, Baba H, Korn WM, Lenz HJ (2019) Molecular Profiling of Appendiceal Adenocarcinoma and Comparison with Right-sided and Left-sided Colorectal Cancer. Clin Cancer Res 25(10):3096–3103. https://doi.org/10.1158/1078-0432.CCR-18-3388
9. Smeenk RM, van Velthuysen ML, Verwaal VJ, Zoetmulder FA (2008) Appendiceal neoplasms and pseudomyxoma peritonei: a population based study. Eur J Surg Oncol 34(2):196–201. https://doi.org/10.1016/j.ejso.2007.04.002
10. Misdraji J (2015) Mucinous epithelial neoplasms of the appendix and pseudomyxoma peritonei. Mod Pathol 28 Suppl 1:S67-79. https://doi.org/10.1038/modpathol.2014.129
11. Pickhardt PJ, Levy AD, Rohrmann CA, Jr., Kende AI (2003) Primary neoplasms of the appendix: radiologic spectrum of disease with pathologic correlation. Radiographics 23(3):645–662. https://doi.org/10.1148/rg.233025134

12. Lim HK, Lee WJ, Kim SH, Kim B, Cho JM, Byun JY (1999) Primary mucinous cystadenocarcinoma of the appendix: CT findings. AJR Am J Roentgenol 173(4):1071–1074. https://doi.org/10.2214/ajr.173.4.10511181
13. Shiroshita H, Inomata M, Akira S, Kanayama H, Yamaguchi S, Eguchi S, Wada N, Kurokawa Y, Uchida H, Seki Y, Ieiri S, Iwazaki M, Sato Y, Kitamura K, Tabata M, Mimata H, Takahashi H, Uemura T, Akagi T, Taniguchi F, Miyajima A, Hashizume M, Matsumoto S, Kitano S, Watanabe M, Sakai Y (2022) Current Status of Endoscopic Surgery in Japan: The 15th National Survey of Endoscopic Surgery by the Japan Society for Endoscopic Surgery. Asian J Endosc Surg 15(2):415–426. https://doi.org/10.1111/ases.13012
14. Kim TK, Park JH, Kim JY, Kim BC, Kang BM, Min SK, Kim JW (2018) Safety and feasibility of laparoscopic surgery for appendiceal mucocele: a multicenter study. Surg Endosc 32(11):4408–4414. https://doi.org/10.1007/s00464-018-6182-4
15. Trivedi AN, Levine EA, Mishra G (2009) Adenocarcinoma of the appendix is rarely detected by colonoscopy. J Gastrointest Surg 13(4):668–675. https://doi.org/10.1007/s11605-008-0774-6
16. Yamaguchi T, Murata K, Shiota T, Takeyama H, Noura S, Sakamoto K, Suto T, Takii Y, Nagasaki T, Takeda T, Fujii M, Kagawa Y, Mizushima T, Ohno Y, Yao T, Kishimoto M, Sugihara K, Study Group of Appendiceal Neoplasms in the J (2021) Clinicopathological Characteristics of Low-Grade Appendiceal Mucinous Neoplasm. Dig Surg 38(3):222–229. https://doi.org/10.1159/000513973
17. Young S, Sueda SK, Hotta M, Sung ML, O'Connor VV, Leung AM (2020) Surgical management of appendiceal mucinous neoplasm: Is appendectomy sufficient? J Surg Oncol 122(6):1173–1178. https://doi.org/10.1002/jso.26108
18. Nasseri YY, Zhu R, Sutanto C, Wai C, Cohen JS, Ellenhorn J, Artinyan A (2019) Role of right hemicolectomy in patients with low-grade appendiceal mucinous adenocarcinoma. Am J Surg 218(6):1239–1243. https://doi.org/10.1016/j.amjsurg.2019.07.035
19. Skendelas JP, Alemany VS, Au V, Rao D, McNelis J, Kim PK (2021) Appendiceal adenocarcinoma found by surgery for acute appendicitis is associated with older age. BMC Surg 21(1):228. https://doi.org/10.1186/s12893-021-01224-0
20. Bhangu A, Soreide K, Di Saverio S, Assarsson JH, Drake FT (2015) Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. Lancet 386(10000):1278–1287. https://doi.org/10.1016/S0140-6736(15)00275-5
21. Sugimoto T, Nagasue Y, Tanaka E, Yokomizo H (2022) Comparison of the risk of appendiceal tumors in uncomplicated and complicated appendicitis. Surg Endosc. https://doi.org/10.1007/s00464-022-09246-2
22. Jiang L, Liu Z, Tong X, Deng Y, Liu J, Yang X, Chan FSY, Fan JKM (2021) Does the time from symptom onset to surgery affect the outcomes of patients with acute appendicitis? A prospective cohort study of 255 patients. Asian J Endosc Surg 14(3):361–367. https://doi.org/10.1111/ases.12870
23. Holmager P, Willemoe GL, Nielsen K, Grondahl V, Klose M, Andreassen M, Langer SW, Hansen CP, Kjaer A, Federspiel BH, Knigge U (2021) Neuroendocrine neoplasms of the appendix: Characterization of 335 patients referred to the Copenhagen NET Center of Excellence. Eur J Surg Oncol 47(6):1357–1363. https://doi.org/10.1016/j.ejso.2021.02.005
24. Shahmanyan D, Saway B, Palmerton H, Rudderow JS, Reed CM, Wattsman TA, Faulks ER, Collier BR, Budin RE, Hamill ME (2021) Burkitt-type lymphoma incidentally found as the cause of acute appendicitis: a case report and review of literature. Surg Case Rep 7(1):215. https://doi.org/10.1186/s40792-021-01283-8
25. Inoue A, Murata K, Komori T, Takeda T, Fujii M, Yamaguchi T, Yamaguchi T, Masuishi T, Shiota T, Morita S, Suzuki Y, Ito M, Kanemitsu Y, Shiozawa M, Yasui M, Kagawa Y, Sugihara K, Study Group of Appendiceal Neoplasms from the Japan Society of Colorectal Cancer Research G (2021) Open versus laparoscopic surgery for primary appendiceal tumors: a large multicenter retrospective propensity score-matched cohort study in Japan. Surg Endosc 35(10):5515–5523. https://doi.org/10.1007/s00464-020-08046-w

Figures

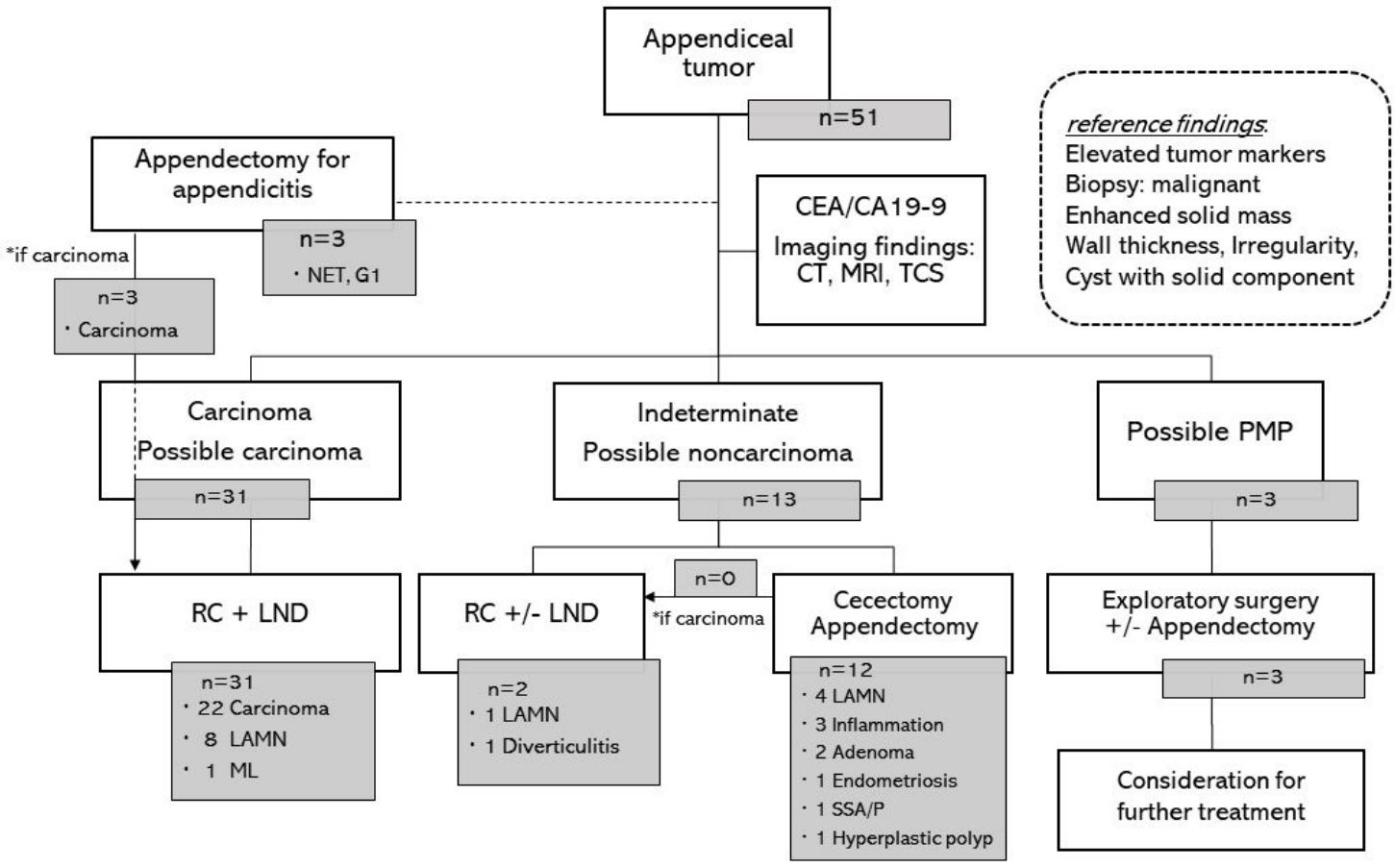

Figure 1

Surgical treatment strategy for appendiceal tumors and case numbers in the present study. According to the preoperative serum levels of tumor markers (CEA and/or CA19-9) and imaging findings with or without tumor biopsy findings during colonoscopy, an appropriate surgical procedure was selected in each patient. NET, neuroendocrine tumor; TCS, total colonoscopy; PMP, pseudomyxoma peritonei; RC, right-side colectomy; LND, lymph node dissection; LAMN, low-grade appendiceal mucinous neoplasm; ML, malignant lymphoma; SSA/P, sessile serrated adenoma/polyp.

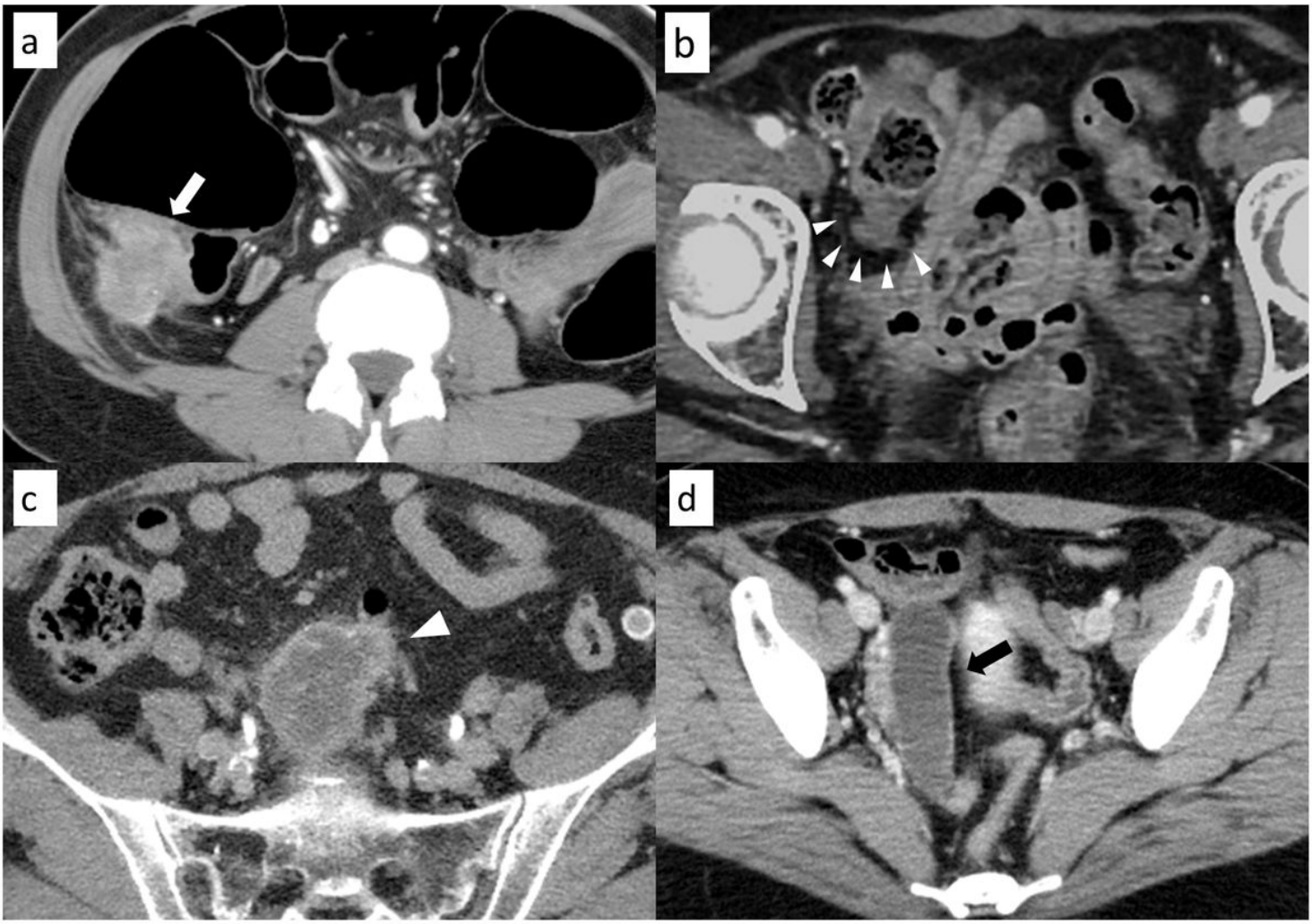

Figure 2

Representative imaging findings as worrisome features on abdominal contrast-enhanced computed tomography. (a) A typical solid enhanced mass (white arrow), which was diagnosed as non-mucinous adenocarcinoma. (b) A non-enhanced solid mass lesion at the peri-appendix (white arrowheads). The pathological diagnosis was appendiceal endometriosis. (c) A cystic mass with enhanced tumor wall irregularity (white arrowhead). The pathological diagnosis was mucinous adenocarcinoma. (d) A cystic and dilated appendix without tumor wall irregularity (black arrow). The pathological diagnosis was low-grade appendiceal mucinous neoplasm.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tablessupplementfinal.xlsx