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CLINICOPATHOLOGICAL FEATURES AND PROGNOSTIC FACTORS FOR SURVIVAL IN PATIENTS WITH PRIMARY APPENDICEAL ADENOCARCINOMA

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Abstract – *Objective:* *Primary appendiceal adenocarcinoma accounts for 1% of colorectal tumors and is a rare malignancy. Peritoneal dissemination commonly occurs as part of the natural course of disease, following the sequence of luminal wall invasion, obstruction, and perforation.*

Patients and Methods: *Twenty patients with appendiceal adenocarcinoma were surgically treated in our hospital between 1990 and 2021. The clinicopathological features, preoperative diagnosis, intraoperative diagnosis, surgical techniques, postoperative adjuvant chemotherapy, chemotherapy, outcome, and prognostic factors for survival of patients with primary appendiceal adenocarcinoma were reviewed.*

Results: *Patients (8 males, 12 females), with an age from 35 to 94 years (mean: 72.8 years), were involved in the study. Before surgery, 7 (35%) patients were diagnosed with primary appendiceal adenocarcinoma and 13 were diagnosed with other conditions. 10 patients had stage I or II disease and 10 patients had stage III or IV disease. Sixteen patients received curative resection, while 4 received non-curative resection. The cumulative five-year survival rate was 62.1%. The preoperative and intraoperative diagnoses, pathological stage, and curative resection had a significant impact on survival.*

Conclusions: *The preoperative and intraoperative diagnoses, pathological stage, and curative resection had an important impact on survival of patients with primary appendiceal adenocarcinoma.*

KEYWORDS: *Primary appendiceal adenocarcinoma, Diagnosis, Stage, Curative resection, Prognostic factor, Survival.*

INTRODUCTION

Primary appendiceal adenocarcinoma accounts for 1% of colorectal tumors and is a rare malignancy (1). Peritoneal dissemination commonly occurs as part of the natural course of disease, following the sequence of luminal wall invasion, obstruction, and perforation (2). The early symptoms of primary appendiceal adenocarcinoma may be nonspecific, or they may mimic the clinical picture of appendicitis. Not surprisingly, most patients are diagnosed incidentally during exploration or at a late stage, when peritoneal or systemic dissemination has already occurred, as appendiceal adenocarcinoma is rarely diagnosed by colonoscopy (CS). Because of the low incidence, the outcomes associated with surgical therapy and chemotherapy are not well characterized. Few studies of primary appendiceal adenocarcinoma have been reported in the relevant literature, and the clinical characteristics and predictors of survival are not well elucidated or consistent (3-5). In this study, we reviewed the clinicopathological characteristics and outcomes of 20 cases of primary appendiceal adenocarcinoma that were managed in our hospital and analyzed the prognostic factors for survival.

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PATIENTS AND METHODS

Patients

Among 2,245 colorectal cancer surgery cases experienced at our hospital over a 32-year period from January 1990 to December 2021, there were 20 cases (0.9%) of primary appendiceal adenocarcinoma.

Methods

The clinicopathological features, preoperative diagnosis, intraoperative diagnosis, surgical treatment, postoperative adjuvant chemotherapy, recurrence, chemotherapy, outcome, and prognostic factors for survival of patients with primary appendiceal adenocarcinoma were reviewed. The parameters obtained from the medical records included the demographic data (patient age and sex), symptoms, preoperative diagnosis, intraoperative diagnosis, surgical treatment, histopathological findings, curative resection, postoperative adjuvant chemotherapy, postoperative chemotherapy, recurrence, and patient survival.

Evaluations

The clinical, surgical, and pathological findings were categorized according to the 9th edition of the Japanese Society of Cancer of the Colon and Rectum (2018). Malignant epithelial neoplasms of the appendix include adenocarcinoma, goblet cell carcinoid, and carcinoid tumor. The present study only included adenocarcinoma, as defined by 9th edition of the Japanese Society of Cancer of the Colon and Rectum (2018). All procedures were conducted in accordance with the ethical standards of the Responsible Committee on Human Experimentation (institutional and national) and with the 1964 Declaration of Helsinki and later versions. This study was approved by the Ethics Committee of Mitoyo General Hospital (approval number: 22-CR01-248; approval date, December 13, 2022). Patients signed the informed consent and gave their approval to participate in the study.

Statistical Analysis

Statistical analyses were performed using R version 4.2.2 with the survival package. The overall survival was calculated using the Kaplan-Meier method, and differences in survival were determined using the log-rank test. All tests were two-sided and p values of <0.05 were considered statistically significant.

RESULTS

Clinical characteristics

Between 1990 and 2021, 2,245 patients underwent resection of colorectal cancer in our hospital. Among these cases, the frequency of primary appendiceal adenocarcinoma was 0.9%. The patients were listed in chronological order. The patients (8 males, 12 females) were 35 to 94 years of age (mean: 72.8 years). The chief complaints were right lower abdominal pain in 9 cases, palpable abdominal mass in 3 cases, anemia in 3 cases, weight loss in 1 case, and no symptoms in 4 cases.

The preoperative and intraoperative diagnoses

The preoperative diagnoses included primary appendiceal adenocarcinoma, n=7 (35%); acute appendicitis, n=7; and carcinoma of the cecum n=5. A preoperative diagnosis of primary appendiceal adenocarcinoma was made by computed tomography (CT) in 7 cases and by CS in 2 cases. The intraoperative diagnoses included appendiceal adenocarcinoma, n=12; acute appendicitis, n=6; and carcinoma of cecum, n=2.

Surgical procedure

The surgical procedures included ileocecal resection, n=6; laparoscopic ileocecal resection, n=6; right hemicolectomy, n=5; ileocecal resection with total hysterectomy, n=1; partial resection of cecum, n=1; and appendectomy alone, n=1 (Table 1)

Histopathological findings and curability

Eight patients had elevated carcinoembryonic antigen (CEA) and three had elevated carbohydrate antigen 19-9 (CA19-9). The histopathological types included highly differentiated adenocarcinoma, n=12; moderately differentiated adenocarcinoma, n=5; and poorly differentiated adenocarcinoma (non-solid type), n=3. The depth of disease was as follows: T4b, n=2; T4a, n=8; T3, n=8; T2, n=2. The degree of lymph node metastasis was classified as follows: N3, n=1; N2, n=2; N1, n=7; and N0, n=10. The degree of lymphatic invasion was classified as follows: ly3, n=1; ly2, n=5; ly1, n=4; and ly0, n=9. The degree of venous invasion was classified as follows: v3, n=1; v2, n=3; v1, n=5; and v0, n=10.

TABLE 1. Clinical characteristics, diagnosis, and surgical treatment.

Case	*Age*	*Sex*	*Symptoms*	*Preoperative diagnosis*	*Diagnostic methods*	*Intraoperative diagnosis*	*Surgical treatment*
1	81	M	Rt. lower abdominal pain	Acute appendicitis	None	Acute appendicitis	Laparoscopic ileocecal resection
2	75	F	None	Appendiceal carcinoma	CT, CS	Appendiceal carcinoma	–
3	35	M	Rt. lower abdominal pain	Acute appendicitis	None	Acute appendicitis	–
4	76	F	None	Carcinoma of the cecum	–	Carcinoma of the cecum	–
5	79	F	Rt. lower abdominal pain	Appendiceal carcinoma	CT	Appendiceal carcinoma	Ileocecal resection
6	79	F	Anemia	Acute appendicitis	None	–	Ileocecal resection, hysterectomy
7	76	F	Weight loss	Carcinoma of the cecum	–	–	Rt. hemicolectomy
8	71	F	None	Appendiceal carcinoma	CT	–	Laparoscopic ileocecal resection
9	71	F	Rt. lower abdominal pain	–	CT	–	Rt. hemicolectomy
10	61	M	–	Acute appendicitis	None	Acute appendicitis	Ileocecal resection
11	56	M	Palpable abdominal mass	Appendiceal carcinoma	CT	Appendiceal carcinoma	–
12	58	F	–	Carcinoma of the cecum	None	Carcinoma of the cecum	Rt. hemicolectomy
13	81	F	Anemia	Appendiceal carcinoma	CT	Appendiceal carcinoma	Ileocecal resection
14	94	F	Rt. lower abdominal pain	Acute appendicitis	None	Acute appendicitis	Appendectomy
15	81	F	Anemia	Carcinoma of the cecum	–	Appendiceal carcinoma	Rt. hemicolectomy
16	71	M	Rt. lower abdominal pain	Appendiceal carcinoma	CT, CS	–	–
17	84	M	–	Acute appendicitis	None	Acute appendicitis	Ileocecal resection
18	66	M	–	–	–	–	Rt. hemicolectomy
19	82	M	None	None	–	Appendiceal carcinoma	Partial resection of the cecum
20	78	F	Palpable abdominal mass	Carcinoma of the cecum	–	–	Ileocecal resection

Abbreviations: CT: computed tomography; CS: colonoscopy.

TABLE 2. Histopathological type, TNM, stage, and curability.

Case	CEA (ng/mL)	CA19-9 (U/mL)	Histopathological type	TNM	ly	v	Stage	Curability
1	1.3	14.8	tub1	T3,N0,M0	ly0	v0	IIa	A
2	21.6	1079.5	por2	T3,N1a,M0	ly1	v1	IIIb	A
3	1.2	9	–	T2,N0,M0	ly0	v0	I	A
4	2.2	2.8	–	T4a,N1a,M1	ly1	v1	IV	C
5	3	15.7	tub1	T3,N0,M0	ly0	v0	IIa	A
6	53.1	<2.0	–	T4b,N0,M0	ly0	v1	IIb	A
7	26.1	<2.0	tub2	T4a,N3,M0	ly2	v2	IIIc	A
8	8.4	25.3	tub1	T3,N0,M0	ly0	v0	IIa	A
9	2.5	54.5	–	T4b,N2a,M0	ly2	v2	IIIc	A
10	2.8	11.7	–	T4a,N0,M0	ly1	v1	IIb	A
11	5.5	14.6	tub2	T3,N0,M0	ly0	v0	IIa	A
12	4.3	15.9	–	T4a,N1a,M1	ly2	v3	IV	C
13	5.7	None	tub1	T4a,N0,M0	ly0	v0	IIb	A
14	None	None	–	T3,N0,M0,RM1	ly0	v0	IIa	C
15	84.4	10000<	–	T4a,N2a,M1	ly3	v2	IV	C
16	0.3	None	tub2	T3,N1b,M0	ly2	v0	IIIb	A
17	None	None	tub1	T2,N1b,M0	lyx	vx	IIIa	A
18	None	None	–	T4a,N1b,M0	ly2	v1	IIIb	A
19	None	None	tub2	T3,N0,M0	ly0	v0	IIa	A
20	6	14	tub1	T4a,N1a,M0	ly1	v0	IIIb	A

Abbreviations: CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; tub1: Well differentiated adenocarcinoma; tub2: Moderately differentiated adenocarcinoma; por 2: Poorly differentiated adenocarcinoma (Non-solid type); ly: Lymphatic invasion; v: Venous invasion; A: Curative resection; C: Noncurative resection; RM1: Cancer invasion is seen on the surgical dissection surface.

The stage was classified as follows: stage I, n=1; stage IIa, n=6; stage IIb, n=3; stage IIIa, n=1; stage IIIb, n=4; stage IIIc, n=2; and stage IV, n=3. Curability resection was performed in 16 cases and non-curability resection was performed in 4 cases (Table 2).

Adjuvant chemotherapy, sites of recurrence, chemotherapy, and outcomes

Patients with stage III disease were treated with tegafur uracil (UFT) as postoperative adjuvant chemotherapy until 2007; stage IV or recurrent disease patients were treated with fluorouracil (5-FU) + levofolinate calcium (l-LV); stage III patients were treated with capecitabine (Cape) + oxaliplatin (OX) (CAPOX) or 5-FU + l-LV + OX (mFOLFOX) as postoperative adjuvant chemotherapy after 2014. Stage IV or relapsed patients were treated with mFOLFOX6 or 5-FU+l-LV+irinotecan hydrochloride hydrate (IRI) (FOLFILI) plus molecular-targeted agents.

As adjuvant chemotherapy, UFT was administered to three stage IIIb patients, CAPOX was administered to one stage IIIb patient, and mFOLFOX6 was administered to one stage IIIc patient. One patient with Stage IIIc received mFOLFOX6; and the other received oral UFT. The differences in postoperative adjuvant chemotherapy were due to differences in historical background.

Of the three stage IV cases, two had peritoneal metastasis and one had liver metastasis. One patient with histopathologically positive resection margins developed recurrence at the resection margin; one patient with stage IIIc disease and one patient with stage IIIb disease developed peritoneal and lung metastases, and one patient with stage IIIa disease developed peritoneal metastases.

One patient with stage IV disease received mFOLFOX6+cetuximab (CET), FOLFILI, UFT+calcium folinate (LV), FOLFILI+ bevacizumab (BEV), and FOLFILI+ ramucirumab (RAM), and one patient with stage IV disease received 5-FU+LV. The remaining stage IV patient could not receive chemotherapy because of multiple liver metastases. A patient who had received mFOLFOX6 as adjuvant chemotherapy developed lung and peritoneal metastases and received FOLFILI+BEV and FOLFILI+RAM. The remaining three patients with recurrent disease were treated with 5-FU+LV (Table 3).

TABLE 3. Adjuvant chemotherapy, recurrence, chemotherapy, and outcomes.

Case	*Adjuvant chemotherapy*	*Sites of recurrence*	*Chemotherapy*	*Outcome*
1	None	None	None	1Y6M alive
2	CAPOX	–	–	1Y7M alive
3	None	–	None	4Y4M alive
4	–	Peritoneum	mFOLFOX6+CET, FOLFILI, UFT+LV, FOLFILI+BEV, FOLFILI+RAM	4Y1M dead
5	–	None	None	4Y10M alive
6	–	–	–	5Y8M alive
7	mFOLFOX6	Peritoneum, lung	FOLFILI+BEV, FOLFILI+RAM	3Y10M dead
8	None	None	None	7Y6M alive
9	UFT	–	–	6Y4M alive
10	None	–	–	9Y6M alive
11	–	–	–	14Y alive
12	–	Peritoneum	5-FU+LV	8M dead
13	–	None	None	7Y3M alive
14	–	Stump of appendix	5-FU+LV	1Y6M dead
15	–	Liver	None	2M dead
16	UFT	None	–	14Y1M alive
17	None	Peritoneum	5-FU+LV	3Y7M dead
18	UFT	Peritoneum, lung	5-FU+LV	4Y3M dead
19	None	None	None	5M9Y alive
20	UFT	–	–	11Y6M alive

Abbreviations: CAPOX: capecitabine (Cape)+oxaliplatin (OX); mFOLFOX6: fluorouracil (5-FU)+levofolinate calcium (l-LV)+OX; CET: cetuximab; FOLFILI: 5-FU+l-LV+irinotecan hydrochloride hydrate (IRI); UFT: tegafur uracil; LV: calcium folinate; BEV: bevacizumab; RAM: ramucirumab.

Factors associated with survival and the prognosis

The median postoperative observation period was 52 months (2-169 months), and the outcomes were as follows: recurrence-free survival, n=13; primary death following peritoneal metastasis, n=3; primary death following peritoneal and lung metastases, n=2; primary death following liver metastasis, n=1; and primary death following resection margin recurrence, n=1 (Table 3). The cumulative five-year survival rate was 62.1% (Figure 1). The five-year survival rate of patients with a preoperative diagnosis of appendiceal adenocarcinoma was 100%, while the five-year survival rate of patients with other diagnoses was 42.3% (p=0.0245) (Figure 2). The intraoperative diagnosis of appendiceal adenocarcinoma, pathological stage, and curative resection had a significant impact on survival. The five-year survival rate of patients with an intraoperative diagnosis of appendiceal adenocarcinoma was 82.5%, whereas that of patients with other diagnoses was 29.2% (p=0.0327) (Figure 3). The five-year survival rate of patients with stage I or II disease was 89.9%, while that of patients with stage III or IV disease

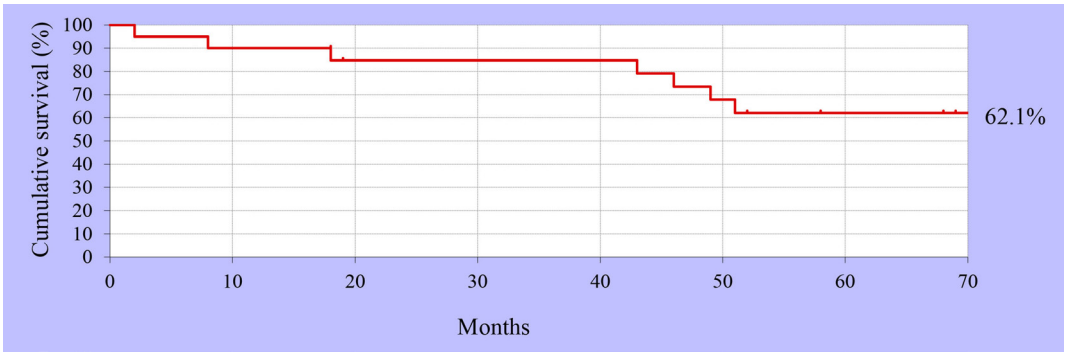

Fig. 1. Kaplan-Meier estimates of overall survival for patients who underwent surgical treatment (n = 20).

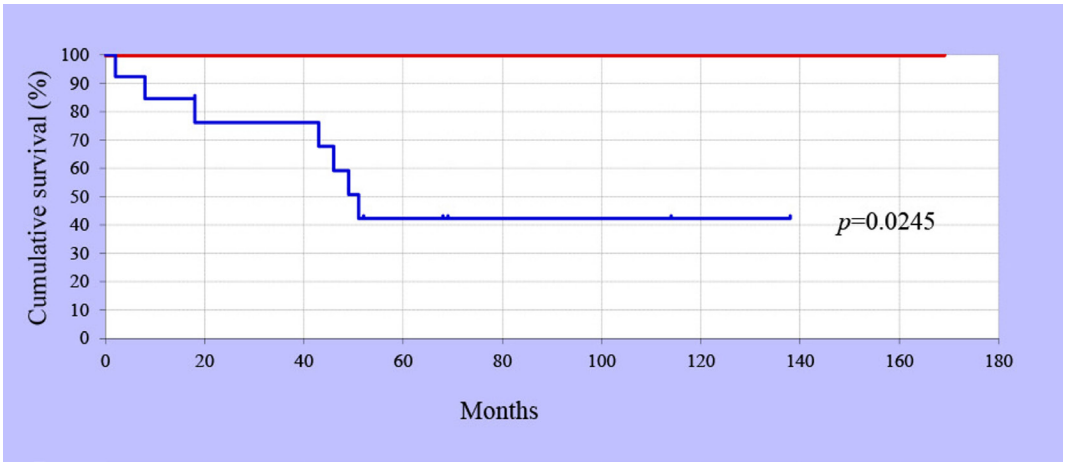

Fig. 2. Kaplan-Meier estimates of overall survival for patients with a preoperative diagnosis of appendiceal adenocarcinoma and other patients: the difference between the groups was statistically significant (p=0.0245, log-rank test). Red line = appendiceal adenocarcinoma (n=7); blue line = others (n=13).

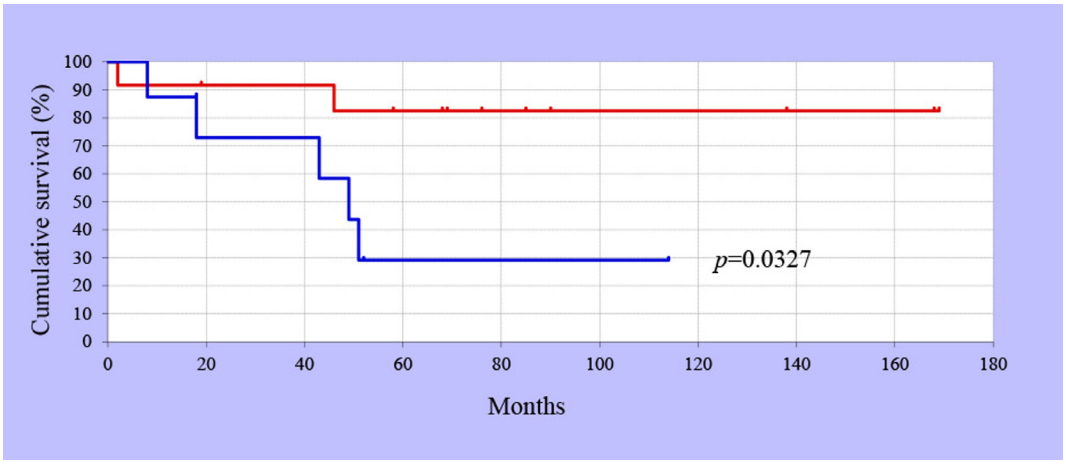

Fig. 3. Kaplan-Meier estimates of overall survival for patients with an intraoperative diagnosis of appendiceal adenocarcinoma and other patients: the difference between groups was statistically significant (p = 0.0327, log-rank test). Red line = appendiceal adenocarcinoma (n = 12); blue line = others (n = 8).

was 34.3% (p=0.0241) (Figure 4). The five-year survival rate of patients who received curative resection was 78.6%, while that of patients who received non-curative resection was 0 % (p<0.001) (Figure 5).

DICUSSION

Although the incidence of primary appendiceal adenocarcinoma has been increasing, it remains a relatively rare malignancy. Very little is known about the reason for its increase or prognostic factors for survival. In this study, 20 patients with primary appendiceal adenocarcinoma were identified from among 2,245 patients with colorectal cancer (incidence 0.9%). This rate is similar to that reported in another study (1). The age of predilection was 50-70 years, and the male-to-female ratio was 27:45, with a slight predominance among women (6,7). The mean age of the self-examined cases was slightly higher than that of the reported cases, and as in the reported cases, the self-examined cases included more women than men.

The preoperative definitive diagnosis of primary appendiceal adenocarcinoma is often difficult to make, and the correct diagnosis rate is reported to be 18-39% (6,7). In this study, the pre-diagnosis rate was 35%, which was in line with other reports. Seven patients with a preoperative diagnosis of primary appendiceal carcinoma were treated by ileocecal resection (n=5) and right hemicolectomy (n=2); all of these patients received curative resection.

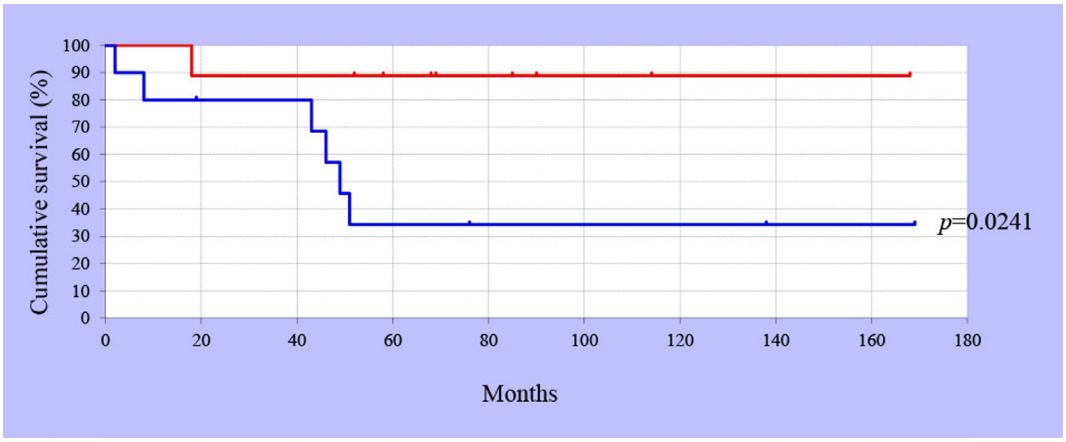

Fig. 4. Kaplan-Meier estimates of overall survival for patients with stage I or II disease and those with stage III or IV disease: the difference between groups was statistically significant (p = 0.0241, log-rank test). Red line = stage I or II (n=10); blue line = stage III or IV (n=10).

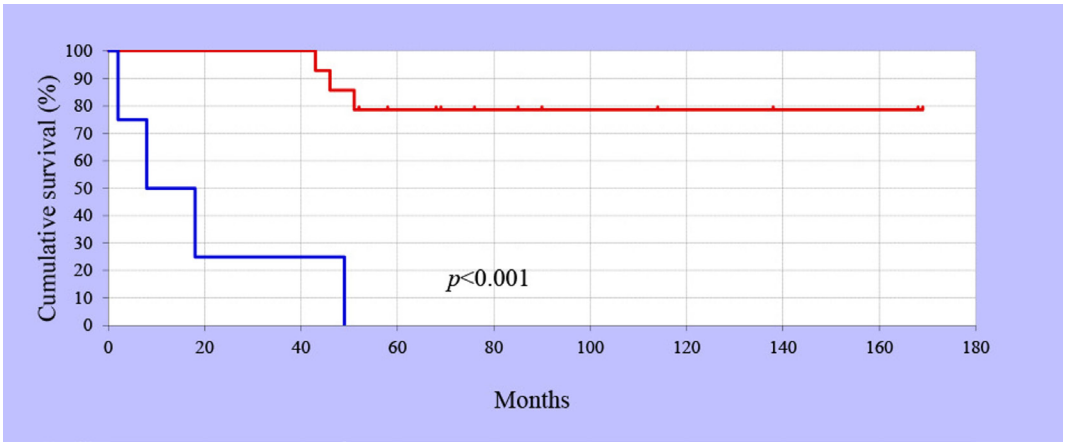

Fig. 5. Kaplan-Meier estimates of overall survival for patients who received curative treatment and those who received non-curative treatment: the difference between groups was statistically significant (p < 0.001, log-rank test). Red line = curability treatment (n = 16); blue line = non-curability treatment (n=4).

The intraoperative diagnosis of appendiceal adenocarcinoma is extremely important because the preoperative histopathological diagnosis and the diagnosis of the depth of carcinoma are rarely available. In this study, there were 5 cases in which a definitive diagnosis of appendiceal adenocarcinoma could not be made preoperatively, but in which the diagnosis was made intraoperatively based on gross findings or rapid pathology, and radical surgery was successfully performed in all patients.

Regarding the surgical procedure, the five-year survival rate of patients who receive appendicectomy alone is only about 20%, while that of patients who receive bowel resection with lymphatic dissection is reported to be 47-63% (8). Histologically, the intrinsic muscularis propria of the appendix is thin, making it easy for adenocarcinoma to reach the serosa, and its abundant lymphatic flow makes it prone to lymph node metastasis (8). Furthermore, the preoperative diagnosis is difficult, and many patients have advanced disease at the time of surgery; thus, ileocecal resection with lymph node dissection or right hemicolectomy is considered an appropriate surgical approach. In this study, 18 patients underwent colon resection with lymph node dissection, one patient underwent partial resection of the cecum, and the remaining patient underwent appendectomy alone.

Oikawa et al (9) reported 42 cases of appendiceal carcinoma, 36 (85.7%) had a depth of T3 or greater, 13 (31.0%) had positive lymph nodes, and 13 (31.0%) had concurrent peritoneal dissemination. In this study, 18 patients (90%) had a depth

of T3 or greater, 10 patients (50%) had lymph node metastasis, and 3 patients (15%) had concurrent peritoneal dissemination. Histopathological staging revealed stage III or IV disease in 10 patients (50%), and most patients had advanced disease. In this study, UFT was used for adjuvant chemotherapy until 2007, while CAPOX and mFOLFOX6 have been administered since 2014. The chemotherapy for non-curative or recurrent patients was 5-FU+LV until 2007, however, since 2014, it has been FOLFILI or mFOLFOX6 plus molecular-targeted agents. Patients who received 5-FU+LV had a survival time of 1 year or less, while FOLFILI or mFOLFOX6 plus molecular-targeted agents resulted in a survival time of 3 years or more.

Right-sided colon tumors are a worse prognosis than left-sided colorectal tumors. The presence of peritoneal metastases or pluri-organ metastatic involvement is predictive or poor prognosis and increased mortality in patients affected by metastatic colorectal cancer (mCRC). 5-FU-based chemotherapy is the traditional backbone of mCRC regimens, and it has been effectively improved with the addition of OX and IRI. Association of chemotherapy with drugs targeted against Vascular Endothelial Growth Factor (VEGF) and Epidermal Growth Factor Receptor (EGFR) pathways contributed to improve the overall survival up to 30 months after diagnosis (10).

The overall five-year survival rate of our entire patients cohort was 62.1%, and the overall five-year survival rate of patients who underwent curative resection was 78.6%. These outcomes are better in comparison to previous reports (6-7,10-13). In this study, we identified that the preoperative diagnosis, intraoperative diagnosis, pathological stage, and curative resection were prognostic factors with a significant impact on survival of patients with primary appendiceal adenocarcinoma. In this study, only primary appendiceal adenocarcinoma was included. Therefore, unlike previous reports (Table 4), the histopathologic type of the tumor was excluded as a prognostic factor. Although stage, tumor depth, and appendicectomy alone were previously reported to be the prognostic factors (6,7,11,13,14), in this study, stage and curative resection were identified as prognostic factors. What is completely different from previous reports is that the preoperative and intraoperative diagnoses were highly related to the prognosis, and to our knowledge, the present study is the first to report this result. As the accuracy of the preoperative and intraoperative diagnosis improved, incomplete surgical procedures such as appendectomy alone were eliminated, and ileocecal resection and right hemicolectomy with lymph node dissection were performed, and postoperative adjuvant chemotherapy was given to patients with lymph node involvement, which we believe contributed to improvement of the prognosis.

Advances in contrast-enhanced CT of the abdomen and CS are expected to further improve preoperative diagnostic capabilities in the future. The improvement of the intraoperative diagnosis is most important, and this should be improved by the introduction of an intraoperative rapid pathological diagnosis when appendiceal adenocarcinoma is suspected. In addition, advances in adjuvant chemotherapy for advanced appendiceal adenocarcinoma and in chemotherapy for stage IV and recurrent cases may contribute to the improvement of the prognosis.

TABLE 4. Recently reported appendiceal cancer series.

		Five-Year Survival		
Authors	*year*	*n*	*(%)*	*Prognostic Factors Identified*
Lenriot and Huguier[13]	1988	32	46	Dukes B2/C, treated with appendectomy alone
Nitecki et al[10]	1994	94	55	Grade, stage, treated with appendectomy alone, perforated appendix, colonic type
Cortina et al[12]	1995	13	43	Colonic type, presence of carcinomatosis
Connor et al[14]	1997	8	Not available	Not available
Proulx et al[15]	1997	23	32	Not available
McCusker et al[16]	2002	1,024	60-50	Not available
Kabbani et al[17]	2002	3	Not available	Nonmucinous type
Ito et al[6]	2004	36	46	Tumor depth, grade, Mucinous type
Hsu et al[7]	2008	34	46	Stage
This study		20	62	Preoperative diagnosis, intraoperative diagnosis, stage, curability

This study was associated with some limitations, including its single center, retrospective design. Thus, the findings may not be generalizable to a large population.

CONCLUSIONS

The preoperative diagnosis, intraoperative diagnosis, pathological stage, and curative resection were found to have a significant impact on survival in patients with primary appendiceal adenocarcinoma. A large multi-institutional study is necessary to further analyze the prognostic factors for primary appendiceal adenocarcinoma.

Conflict of interest:
The authors have no conflict of interest to declare.

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Ethics Committee:
Ethics Committee was granted by Mitoyo General Hospital (IRB Approval Code 22-CR01-248).

Informed Consent:
Patients signed the informed consent and gave their approval to participate in the study.

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