



CLINICAL STUDY OF SMALL BOWEL ADENOCARCINOMA WITH SURGICAL INTERVENTION

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Abstract – Objective: Small bowel adenocarcinoma (SBA) is a rare disease but its clinical features have been clearly elucidated. The present study clarified the clinicopathological characteristics, the effectiveness of the surgical procedure, neoadjuvant chemotherapy, and adjuvant chemotherapy of the patients with SBA.

Patients and Methods: The clinicopathological characteristics of 9 cases of SBA resected at our hospital were reviewed between 2004 and 2017.

Results: The mean age of the 9 patients (4 men, 5 women) was 69.6 (57-83) years. The sites included the duodenum (n=3), jejunum (n=3), and ileum (n=3). As neoadjuvant chemotherapy, S-1 was administered to a patient with a large duodenal adenocarcinoma invading the portal vein. The surgical procedures included partial resection of jejunum (n=3); partial resection of ileum (n=3); pylorus-preserved pancreatoduodenectomy (PD) (PPPD) with right hemicolectomy due to invasion of ascending colon (n=1); subtotal stomach-preserving PD (SSPPD) (n=1); and wedge resection of the duodenum (n=1). The stage was classified as follows: stage I (n=1), stage IIA (n=1), stage IIB (n=3), stage IIIA (n=1), stage IIIB (n=2), and unknown, (n=1). As adjuvant chemotherapy, S-1 was administered to three stage IIB patients, one IIIA patient, and one IIIB patient. Tegafur uracil (UFT) + calcium folinate (LV) was administered to one stage IIIB patient. The cumulative five-year survival rate was 77.8%.

Conclusions: Aggressive esophagogastroduodenoscopy, double-balloon endoscopy, and colonoscopy for symptoms such as anemia and abdominal pain, as well as intraoperative during abdominal surgery, would improve the prognosis of SBA.

KEYWORDS: Small bowel adenocarcinoma, Diagnosis, Surgical procedure, Neoadjuvant chemotherapy, Adjuvant chemotherapy,

INTRODUCTION

Small bowel adenocarcinoma (SBA) is a rare disease with few specific symptoms. There are no simple examinations to screen for the disease, so its early detection is difficult, and it is consequently detected at an advanced stage. Patients with metastatic disease have a poor prognosis, with reported median overall survival of <20 months among patients who receive chemotherapy^{1,2}. In most studies, surgical intervention provides curative resection in 40-65% of patients, with report-

ed 5-year survival rates of 40-60% for resected adenocarcinomas vs. 15-30% for non-resected adenocarcinomas³⁻⁶. Adenocarcinomas of the first and second portions of the duodenum require pancreatoduodenectomy (PD), whereas patients with a third and fourth portion can receive complete resection with segmental duodenectomy. For lesions of the jejunum and ileum, partial resection with the corresponding mesentery is required. Curative resection should generally include systemic regional lymphadenectomy, regardless of the primary tumor location.



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Recently, the National Comprehensive Cancer Network (NCCN) developed treatment algorithms for the management of SBA⁷.

We herein reviewed the clinical, pathological, and imaging characteristics of 9 cases of SBA following surgical resection.

PATIENTS AND METHODS

Patients

The clinicopathological characteristics of 9 cases of SBA resected at our hospital between 2004 and 2017 were reviewed.

Methods

The clinicopathological features, preoperative diagnosis, neoadjuvant chemotherapy (NAC), surgical treatment, postoperative adjuvant chemotherapy, recurrence, chemotherapy, and outcomes of patients with SBA were reviewed. The parameters obtained from the medical records included the demographic data.

Evaluations

The TNM classification and staging were described according to the TNM classification of malignant tumors, 8th edition (8). Patients who had tumors that involved the ampulla of Vater were excluded to avoid the inclusion of patients with primary ampullary tumors.

All procedures were 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 the Mitoyo General Hospital (approval number, 22-CR01-255; approval date, February 16, 2022).

Statistical analysis

Statistical analyses were performed using R version 4.2.2 with the survival package. Overall survival was calculated using the Kaplan-Meier method.

RESULTS

Clinical characteristics

The mean age of the 9 patients (male, n=4; female, n=5) was 69.6 (57-83) years.

The chief complaints were abdominal pain (n=2), anemia (n=2), vomiting (n=1), and palpable mass (n=1). The sites were the duodenum (n=3), the jejunum (n=3), and the ileum (n=3).

Preoperative examinations

Four patients had elevated carcinoembryonic antigen (CEA) levels and one had an elevated carbohydrate antigen 19-9 (CA19-9) level. Computed tomography (CT) revealed a tumor with contrasted margins and hypodense interior in the small intestine in 6 of 9 cases (66.7%). Three patients underwent esophagogastroduodenoscopy (EGD) for their duodenal lesions, and three patients were diagnosed with an adenocarcinoma by biopsy (Figure 1), while two patients with a jejunal lesion and an ileal lesion, respectively, were found to have a tumor by dou-

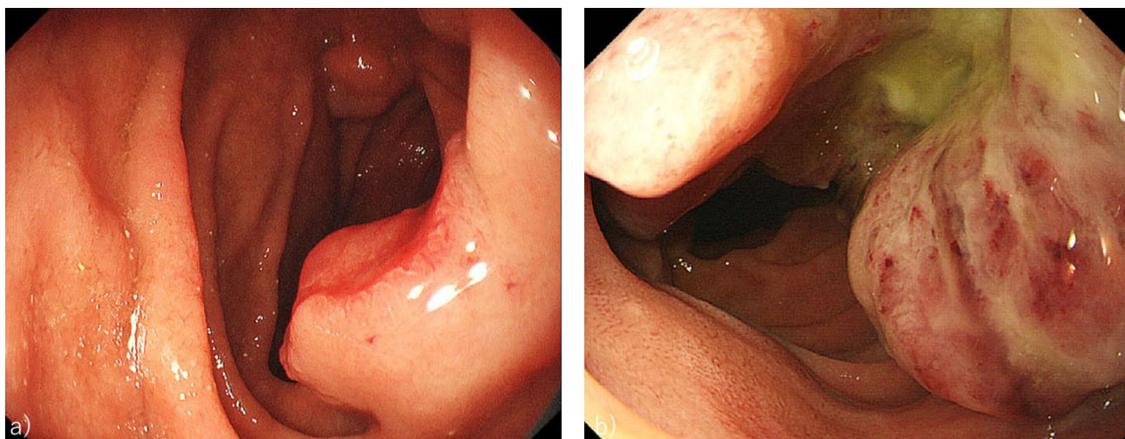


Fig. 1. Endoscopy findings. **a)** EGD showed a tumor with ulceration in the second portion of the duodenum, which was diagnosed by biopsy. **b)** EGD showed a large tumor in the second and third portion of the duodenum, which was diagnosed by biopsy.

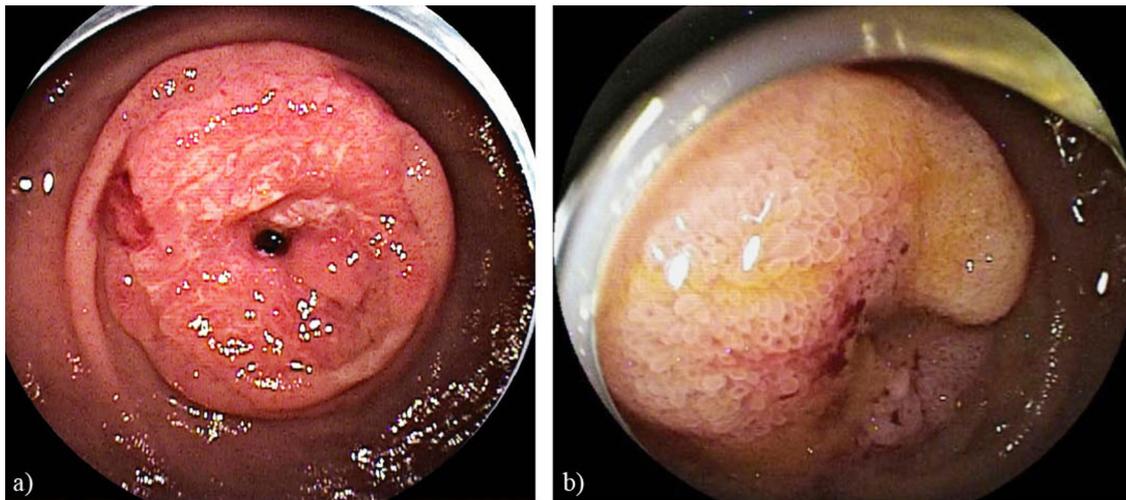


Fig. 2. Endoscopy findings. **a)** DBE showed a circumferential type 3 tumor in the upper jejunum, with pinhole-like stenosis, which was diagnosed by biopsy. **b)** DBE showed a circumscribed tumor with ulceration in the ileum 15 cm from the Bauhin valve, which was diagnosed by biopsy.

ble-balloon endoscopy (DBE) and were diagnosed with adenocarcinoma by biopsy (Figure 2). One patient with an ileal lesion was found to have a tumor by colonoscopy and was diagnosed with an adenocarcinoma by biopsy.

The preoperative diagnoses and metachronous or synchronous cancer

A preoperative diagnosis of duodenal adenocarcinoma was confirmed in 3 patients, both jejunal adenocarcinoma and ileal adenocarcinoma were diagnosed in 2 patients. Two patients were diagnosed with SBC during surgery for colorectal cancers.

Five (55.6%) of the nine patients had synchronous or metachronous cancer. One patient had four synchronous or metachronous tumors (Table 1).

Surgical procedure

The surgical procedures included partial resection of the jejunum (n=3), partial resection of the ileum (n=3), pylorus-preserved PD (PPPD) with right hemicolectomy due to invasion of ascending colon (n=1), subtotal stomach-preserving PD (SSPPD) (n=1) and wedge resection of duodenum (n=1) (Table 2).

Histopathological findings

The average tumor size was 47.4 (15-110) mm. The histopathological types included highly differentiated adenocarcinoma (n=3), moderately differenti-

ated adenocarcinoma (n=2), papillary adenocarcinoma (n=2), poorly differentiated adenocarcinoma (n=1), and mucinous adenocarcinoma (n=1). The depth of disease was as follows: T4 (n=5), T3 (n=1), T2 (n=1), and T1b (n=1). The degree of lymph node metastasis was classified as follows: N2 (n=2), N1 (n=1), N0 (n=5), and unknown (n=1). The degree of lymphatic invasion was classified as follows: ly3 (n=1), ly1 (n=2), and ly0 (n=6). The degree of venous invasion was classified as follows: v2 (n=3), v1 (n=2), and v0 (n=4). The stage was classified as follows: stage I (n=1), stage IIA (n=1), stage IIB (n=3), stage IIIA (n=1), stage IIIB (n=2), and unknown (n=1). The margin status was negative in all patients (Table 2).

NAC, adjuvant chemotherapy, sites of recurrence, chemotherapy after recurrence, the outcome, and survival

Patients with large tumors invading the portal vein, ascending colon, and pancreas were treated with S-1 (2 courses) as NAC. Contrast-enhanced CT after NAC revealed that the tumor was reduced in size and that portal vein invasion was no longer present (Figure 3). As adjuvant chemotherapy, S-1 was administered to three stage IIB patients, one IIIA patient, and one IIIB patient. Tegafur uracil (UFT) + calcium folinate (LV) was administered to one stage IIIB patient.

One patient who had received wedge resection of the duodenum developed local recurrence. The patient did not undergo additional surgery or chemotherapy because of his advanced age. A patient who had received partial resection of the jejunum and S-1 as adjuvant chemotherapy with stage IIB developed peritoneal metastasis. The patient had received paclitaxel (PTX); however, PTX was ineffective.

Table 1. Clinical characteristics, tumor location, diagnostic methods of, preoperative diagnosis, and synchronous or heterochronic cancer.

Case	Age	Sex	Symptoms	Site	CEA (ng/mL)	CA19-9 (U/mL)	Diagnostic methods	Preoperative diagnosis	Synchronous or metachronous cancer
1	83	M	None	Duodenum (second portion)	2.9	17.7	CT, EGD, Biopsy	Duodenal adenocarcinoma	Rectal cancer
2	65	M	None	Jejunum (20cm from the ligament of Treitz)	7.4	57.1	Intraoperative finding	None	Gastric cancer, Renal cell carcinoma, Transverse colon cancer, Esophageal Cancer
3	68	F	Abdominal pain, Vomiting	Jejunum (50cm from the ligament of Treitz)	14.6	7.2	CT, DBE, Biopsy	Jejunal adenocarcinoma	Renal cell carcinoma
4	64	F	Palpable mass	Duodenum (second and third portion)	1417.7	14.7	CT, EGD, Biopsy	Duodenal adenocarcinoma	None
5	57	F	Anemia	Duodenum (second portion)	1.5	22.0	" Intraoperative	"	Ascending colon cancer
6	73	M	None	Ileum (30cm from the ileocecal valve)	5.9	14.2	CT, DBE, finding	None	Rectal cancer
7	67	M	Abdominal pain, Vomiting	Ileum (15cm from the ileocecal valve)	1.5	3.9	Biopsy	Jejunal adenocarcinoma	None
8	72	F	Abdominal pain	Jejunum (10cm from the ligament of Treitz)	1.2	7.8	CT Colonoscopy,	Ileal adenocarcinoma	"
9	77	F	Anemia	Ileum (5cm from the ileocecal valve)	3.5	5.7	Biopsy	Ileal adenocarcinoma	"

CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9, CT: computed tomography, esophagogastroduodenoscopy, DBE: double-balloon endoscopy

EGD:

TABLE 2. Attitudes towards the COVID-19 vaccine (N=300).

Case	Surgical Procedure	Tumor size (mm)	Histopathological type	T	N	M	ly	v	Stage	Margin status
1	Wedge resection of duodenum	15	tub1	T1b	Nx	M0	ly0	v0	Unknown	R0
2	Partial resection of jejunum	42	por	T3	N0	M0	ly0	v1	IIA	''
3	''	30	tub2	T4	N0	M0	ly0	v2	IIB	''
4	PPPD, Right hemicolectomy	110	muc	T4	N1	M0	ly0	v0	IIIA	''
5	SSPPD	70	pap	T4	N0	M0	ly0	v0	IIB	''
6	Partial resection of ileum	20	''	T2	N0	M0	ly0	v0	I	''
7	''	20	tub1	T3	N2	M0	ly1	v2	IIIB	''
8	Partial resection of jejunum	50	''	T4	N0	M0	ly1	v1	IIB	''
9	Partial resection of ileum	70	tub2	T4	N2	M0	ly3	v2	IIIB	''

PPPD: pylorus-preserved pancreatoduodenectomy, SSPPD: subtotal stomach-preserving pancreatoduodenectomy, tub1: Well differentiated adenocarcinoma, tub2: Moderately differentiated adenocarcinoma, pap: Papillary adenocarcinoma, por: Poorly differentiated adenocarcinoma, muc, Mucinous adenocarcinoma, ly: Lymphatic invasion, v: Venous invasion

The median postoperative observation period was 118 (23-135) months. Two patients died of the primary disease and the remaining seven patients remain alive without recurrence (Table 3). The cumulative five-year survival rate was 77.8%.

DISCUSSION

The small intestine is the longest portion of the gastrointestinal tract and an organ that seldom receives attention, despite the functionally crucial role. SBA

can readily be overlooked by routine gastrointestinal examinations because of the anatomical features of the small intestine. The clinical characteristics, surgical procedure, chemotherapy, and prognosis of patients with SBA are not well known because of the rarity of this disease. Reports indicate that SBA accounts for about 0.1-3.0% of all carcinomas of the gastrointestinal tract (9-12).

Small bowel obstruction (SBO) represents a common emergency in elderly patients that accounts for ~15% of hospital admissions for acute abdominal pain in the USA and ~20% of cases needing

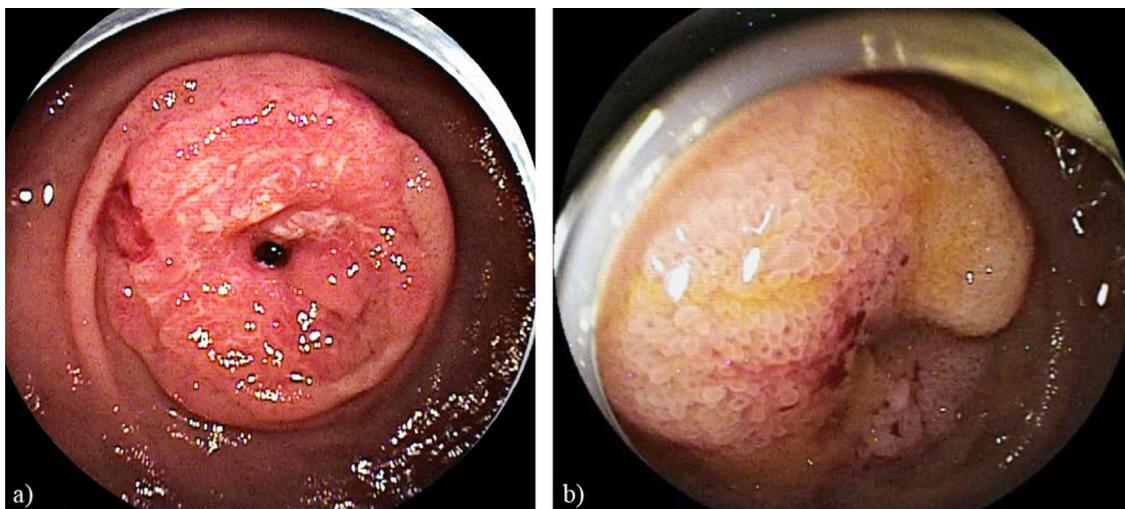


Fig. 3. Enhanced CT findings. **a)** CT showed a large duodenal tumor invading the portal vein (arrow). **b)** CT showed a duodenal tumor mildly reduced in size and without portal vein invasion after NAC (arrow).



TABLE 3. Neoadjuvant chemotherapy, adjuvant chemotherapy, recurrence, the outcome, and survival.

Case	Neoadjuvant chemotherapy	Adjuvant chemotherapy	Sites of recurrence	Chemotherapy after recurrence	Effect of chemotherapy after recurrence	Outcome
1		None	Local	None		1Y11M dead
2		”	None	”		5Y3M alive
3		S-1	”	”		9Y11M alive
4	S-1	”	”	”		9Y10M alive
5		”	”	”		10Y7M alive
6		None	”	”		8Y3M alive
7		UFT+LV	”	”		11Y3M alive
8		S-1	Peritoneum	PTX	No effect	3Y8M dead
9		”	None	None		10M7M alive

UFT: tegafur uracil, LV: calcium folinate, PTX: paclitaxel

acute surgical treatment (13). In 90% of cases, SBO is caused by adhesions, hernias, and neoplasms (14). SBO resulting from tumor occult blood in the stool and anemia are often noted as initial symptoms (15). Similarly, the current study found that the initial symptoms were primarily signs of bowel obstruction such as abdominal pain and nausea. In the present study, 3 had symptoms due to bowel obstruction and 2 had symptoms due to bleeding from the tumor.

EGD with endoscopic ultrasound is recommended during the initial workup and staging for detection and pathologic sampling when duodenal malignancy is suspected. In the present study, 3 patients were diagnosed with duodenal adenocarcinoma by EGD and biopsy. Several studies, both prospective and retrospective have reported on the effectiveness and safety of DBE for the workup of patients with SBA (16-18). In the present study, 2 patients were diagnosed with jejunal adenocarcinoma based on DBE and biopsy. We previously reported the effectiveness of DBE for SBA (19). A patient was diagnosed with ileal adenocarcinoma by colonoscopy and biopsy. Two patients underwent surgery for colorectal cancer when jejunal and ileal cancers were incidentally discovered during surgery. On contrast-enhanced CT SBA may appear as a solitary soft-tissue mass with annular or eccentric luminal narrowing. SBA can also appear as a discrete tumor mass or ulcerated lesion, usually involving a short segment and may cause partial or complete bowel obstruction. CT typically demonstrates heterogeneous attenuation and moderate enhancement (20). Contrast-enhanced CT seemed to be effective for diagnosing the presence of SBA to evaluate the extent of local tumor invasion and for the assessment of distant metastasis. In this study, five patients had SBA confirmed by contrast-enhanced CT.

Due to the relative rarity of SBA and association of the disease with several genetic syndromes, the NCCN panel recommends that all patients with a personal history of SBA should be counseled for familial malignancies and considered for risk assessment for various genetic syndromes, including Lynch syndrome, Peutz-Jeghers syndrome, familial adenomatous polyposis, and other polypoid mutations. In this study, five (55.6%) of the nine patients had synchronous or heterochronic cancer. A patient had four synchronous or heterochronic cancers.

For local (stage I-III) SBA, primary treatment consists of surgical resection with en bloc removal of the regional lymph nodes. The type of resection used to treat localized SBA depends on the location of the primary tumor. Segmental resection of the small bowel is often the mainstay or treatment, although duodenal tumors may require either PD or segmental duodenal resection. For tumors of the jejunum or ileum, segmentectomy is the preferred methods of resection. In this study, a patient with T1b depth underwent wedge resection for duodenal adenocarcinoma in the second portion, which resulted in local recurrence. We consider that the patient should have undergone PPPD or SSPPD.

Localized SBAs are treated with surgical resection, but local and distant recurrence are common, and the optimal perioperative therapy is unknown (21). In Case 4, the large duodenal adenocarcinoma in the second and third portion invaded the portal vein on preoperative enhanced CT. We determined that complete resection would be difficult and administered NAC with S-1. The tumor was reduced in size, the portal vein invasion was eliminated, and complete resection was achieved by PPPD with right hemicolectomy, without resection of the portal vein.

The NCCN recommends that six months of adjuvant treatment with fluorouracil (5-FU) plus levofo-

linat calcium (I-LV) plus oxaliplatin (OX) (FOLF-OX), capecitabine plus OX (CAPEOX), 5-FU/LV, or capecitabine for any locally advanced SBA with positive lymph nodes (stage III) (7). In this study, as adjuvant chemotherapy, S-1 was administered to three stage IIB patients, one IIIA patient, and one IIIB patient. UFT + LV was administered to one stage IIIB patient. One patient with stage IIB disease developed peritoneal recurrence.

As the initial intensive therapy for metastatic disease in SBA patients without prior platinum resistance, a panel recommended the choice of 3 chemotherapy regimens: FOLFOX, CAPEOX, or infusional 5-FU, LV, OX, irinotecan (FOLFOXILI); any of which may be combined with bevacizumab. For patients for whom intensive therapy is not appropriate, the treatment option would exclude the more toxic components of these regimens, with 5-FU/LV or capecitabine with or without bevacizumab recommended as the first-line therapy (7). In this study, the patient with peritoneal recurrence was managed in 2007, so there was no intensive treatment available, PTX was administered, and the effect was poor.

In most studies surgical intervention provides a curative resection in 40-65% of patients with SBA, with a reported 5-year survival rate of 40-60% for resected tumors vs. 15-30% for non-resected tumors (3-6). Curative resection is currently the only factor that can prolong patient survival. Consequently, an early and accurate diagnosis is crucial for improving patient outcomes. Recently, small bowel capsule endoscopy and flexible endoscopy have become available; these were initially used for suspected or known mid-gastrointestinal bleeding. Recent studies reported that 6-12% of patients with occult gastrointestinal bleeding were found to have small bowel tumors (22-24). In this study, the 5-year survival rate was 77.8%, which was relatively better in comparison to previous reports. The reasons for this are thought to be the use of DBE, EGD, and colonoscopy to aggressively diagnose anemia and other symptoms, and the intraoperative detection and curative resection of SBA during colorectal cancer surgery.

The present study is limited by its retrospective study design as well as the small study size (9 patients) and the fact that the study was performed at a single center, which may have introduced some bias.

CONCLUSIONS

We managed 9 patients who underwent surgical treatment for SBA. For local (stage I-III) SBA, the primary treatment consists of surgical resection with en bloc removal or the regional lymph nodes. Aggressive DBE, EGD, and colonoscopy for symptoms such as anemia and abdominal pain, as well

as intraoperative exploration during abdominal surgery, would improve the prognosis of SBA. NAC may be effective for severe locally invasive SBA without distant metastasis.

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AUTHORS' CONTRIBUTIONS:

Udaka T analyzed the data and wrote the manuscript. Udaka T, Endou I, Yoshida O, and Kubo M performed the surgery, and Asano H and Kubo M helped draft the manuscript. Nishiyama T, Watanabe N, Yoshida O, and Kubo M participated in revising the manuscript critically. All authors declare that they contributed to this article and that they read and approved the final version.

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CONFLICT OF INTEREST:

All authors declare that there are no conflicts of interest.

AVAILABILITY OF DATA AND MATERIALS:

All data generated or analyzed during this study are included in this published article.

CONSENT FOR PUBLICATION :

Consent to publish was obtained from the patient.

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