

Seven-year survival with no recurrence after conversion surgery for pancreatic ductal adenocarcinoma with peritoneal metastasis treated with intraperitoneal and intravenous chemotherapy: A case report

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Received June 20, 2025; Accepted September 8, 2025

DOI: 10.3892/mco.2025.2908

Abstract. Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis, particularly PDAC with peritoneal metastases. The present report describes a case of distal pancreatectomy (DP) following ip and iv chemotherapy for PDAC with peritoneal metastases, with long-term survival after CS. A 62-year-old man was referred to Tonan Hospital (Sapporo, Japan) for ip and iv chemotherapy after being diagnosed with unresectable pancreatic body adenocarcinoma with peritoneal dissemination at another hospital. The patient was administered four cycles of ip paclitaxel (ipPTX) plus ivPTX plus S-1, followed by four cycles of ipPTX plus fluorouracil plus leucovorin, irinotecan and oxaliplatin. After 9 months of preoperative treatment, the disappearance of peritoneal dissemination was confirmed; thus, the patient underwent DP. The histopathological diagnosis was ypT2, ypN0, ypM0 and ypStage IB, and the histologic response to chemotherapy was grade IIb, according to the Evans classification. Postoperative adjuvant chemotherapy including ipPTX was administered for 12 months. The patient survived without recurrence for 7 years after the CS.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis, particularly PDAC with peritoneal metastases (1-4). PDAC with peritoneal metastases makes it difficult to maintain chemotherapy because of cancerous ascites, bowel obstruction, nutritional status deterioration, and poor performance status (5). Recently, multidisciplinary treatments combining chemotherapy and surgery have been introduced for PDAC with peritoneal metastases. Additionally, long-term survival is achieved by conversion surgery (CS) after intraperitoneal (ip) and intravenous (iv) chemotherapy (1,3,6). Yamamoto *et al* (1) reported that implementation of chemotherapy including ip chemotherapy may improve survival in patients with PDAC with peritoneal dissemination because of the high proportion of patients in which conversion surgery is performed. For example, the authors reported a conversion rate of 23% in the ip paclitaxel (ipPTX) group compared with a conversion rate of 4% in the control group (P=0.005). Herein, we report a case of distal pancreatectomy following ip and iv chemotherapy for PDAC with peritoneal metastases that achieved long-term survival after CS, indicating the efficacy of ip and iv chemotherapy combined with CS for PDAC with peritoneal metastases.

Case report

A 62-year-old man was referred to our hospital for ip and iv chemotherapy after being diagnosed with unresectable pancreatic body adenocarcinoma with peritoneal dissemination via laparotomy at another hospital. His cancer antigen 19-9 (CA19-9) level increased to 4,678 U/ml. The tumor mass was obscure on plain computed tomography (CT) (Fig. 1A) because the patient could only undergo plain CT due to contrast media allergy. The tumor could not be identified on positron emission tomography-CT, or magnetic resonance imaging; however, a 16.3 mm hypoechoic mass was identified in the pancreatic body

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Abbreviations: PDAC, pancreatic ductal adenocarcinoma; PCI, peritoneal cancer index; CS, conversion surgery; ip, intraperitoneal; iv, intravenous; CT, computed tomography; DP, distal pancreatectomy; ipPTX, intraperitoneal paclitaxel; MST, median survival time; FOLFIRINOX, fluorouracil plus leucovorin, irinotecan, oxaliplatin; GnP, gemcitabine plus nab-paclitaxel

Key words: PDAC, peritoneal dissemination, CS, intraperitoneal and intravenous chemotherapy, DP

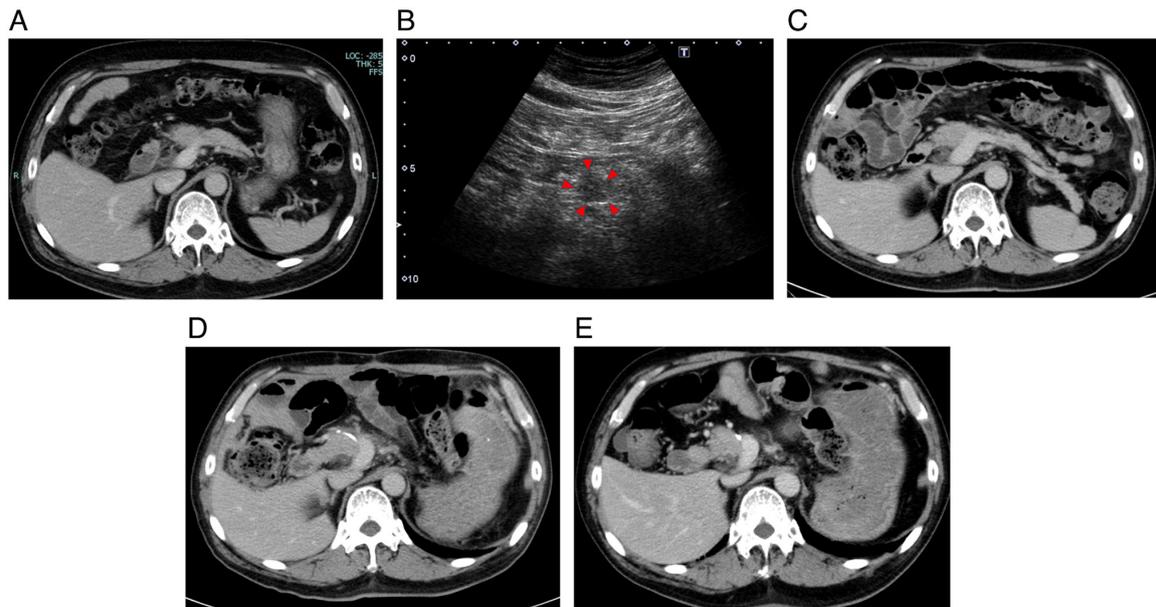


Figure 1. Imaging findings. (A) Abdominal CT before preoperative chemotherapy. The mass was obscure. (B) Abdominal ultrasound before preoperative chemotherapy: A 16.3-mm hypoechoic mass was identified in the pancreatic body (surrounded by red arrowheads). (C) Abdominal CT before CS: No new lesions were observed. (D) Abdominal CT after CS: No abnormal findings. (E) Abdominal CT 7 years after CS. No new lesions were observed. CS, conversion surgery; CT, computed tomography.

on abdominal ultrasonography (Fig. 1B). There was an ambiguous hypoechoic lesion on the pancreatic body on endoscopic ultrasonography, and the biopsy of the lesion showed features of adenocarcinoma. The pathological findings of the peritoneal nodules sampled during laparotomy was also adenocarcinoma (Fig. 2A). In this case, based on histological features and comparison with previously confirmed pancreatic cancer, and the absence of any other findings of cancer causing peritoneal dissemination on positron emission tomography-CT, a diagnosis of metastatic pancreatic cancer was established. An abdominal access device was laparoscopically implanted, which revealed many white peritoneal nodules in the greater omentum and lower abdomen (Fig. 3A). The peritoneal cancer index (PCI) of the patient was 16. The patient was treated with 4 cycles of ipPTX (20 mg/m²) and S-1 (80 mg/m²/day) plus ivPTX (50 mg/m²) for 3 months in a single-center clinical trial. After confirming negative peritoneal washing cytology via the abdominal access device, a histology of the second laparoscopy-obtained sample showed peritoneal dissemination. At that time, the PCI was as low as 1. Given the fact that residual dissemination was still present, and the patient's general condition was tolerable, we considered an outcome of CS to have become clearer and decided to intensify the therapy to 4 cycles of ipPTX (20 mg/m²) and FOLFIRINOX (5-fluorouracil, 400 mg/m²; leucovorin, 200 mg/m²; irinotecan, 180 mg/m²; and oxaliplatin, 85 mg/m²) for 5 months for greater and improved efficacy. During the ipPTX plus FOLFIRINOX treatment, the patient experienced grade 3 device-related infection, grade 3 catheter-related infection, but no hematologic toxicities or abdominal infections were observed. A third laparoscopy and histological examination showed no peritoneal dissemination, and peritoneal lavage cytology was negative

(Fig. 3B). The PCI values were as low as 0. Preoperative CT revealed no new lesions (Fig. 1C), and the CA19-9 level decreased to 63 U/ml. Distal pancreatectomy revealed no liver metastases or peritoneal dissemination (Fig. 2B). The range of resection was determined by preoperative imaging diagnosis on CT scan, indicating no obvious vascular invasions, infiltrations or distant metastasis, and intraoperative negative lavage cytology and no signs of vascular invasions or metastasis including peritoneal metastasis. The tumor mass detected on preoperative abdominal ultrasonography was located at the left side of the portal vein of the pancreatic body. Given the above findings, a standard distal pancreatectomy was performed. Operation time was 316 min, and blood loss was 325 ml. The patient was uneventfully discharged on postoperative day 13, and postoperative CT showed no abnormalities (Fig. 1D). Histological diagnosis was ypT2, ypN0, ypM0, R0, and yp Stage IB (according to the eighth edition of the Union for International Cancer Control TNM classification). The effect of preoperative chemotherapy was grade IIb according to the Evan's classification (7) (Fig. 2C and D). IpPTX and S-1 were administered for 6 months as postoperative adjuvant chemotherapy for six months, followed by ipPTX alone for six months. During postoperative chemotherapy, he experienced grade 2 enterocolitis, and grade 2 laryngitis, but no other specific adverse events. For the specific follow-up measures after the surgery, we performed physical exams, contrast-enhanced CT, and monitored CA19-9 using blood tests. Initially, the patient underwent non-contrast CT due to an allergy to contrast media, but following premedication with 300 mg hydrocortisone, contrast-enhanced CT could be safely performed. The last follow-up at 84 months after CS confirmed no evidence of recurrence, including CT showing no new lesions (Fig. 1E) and no increase in

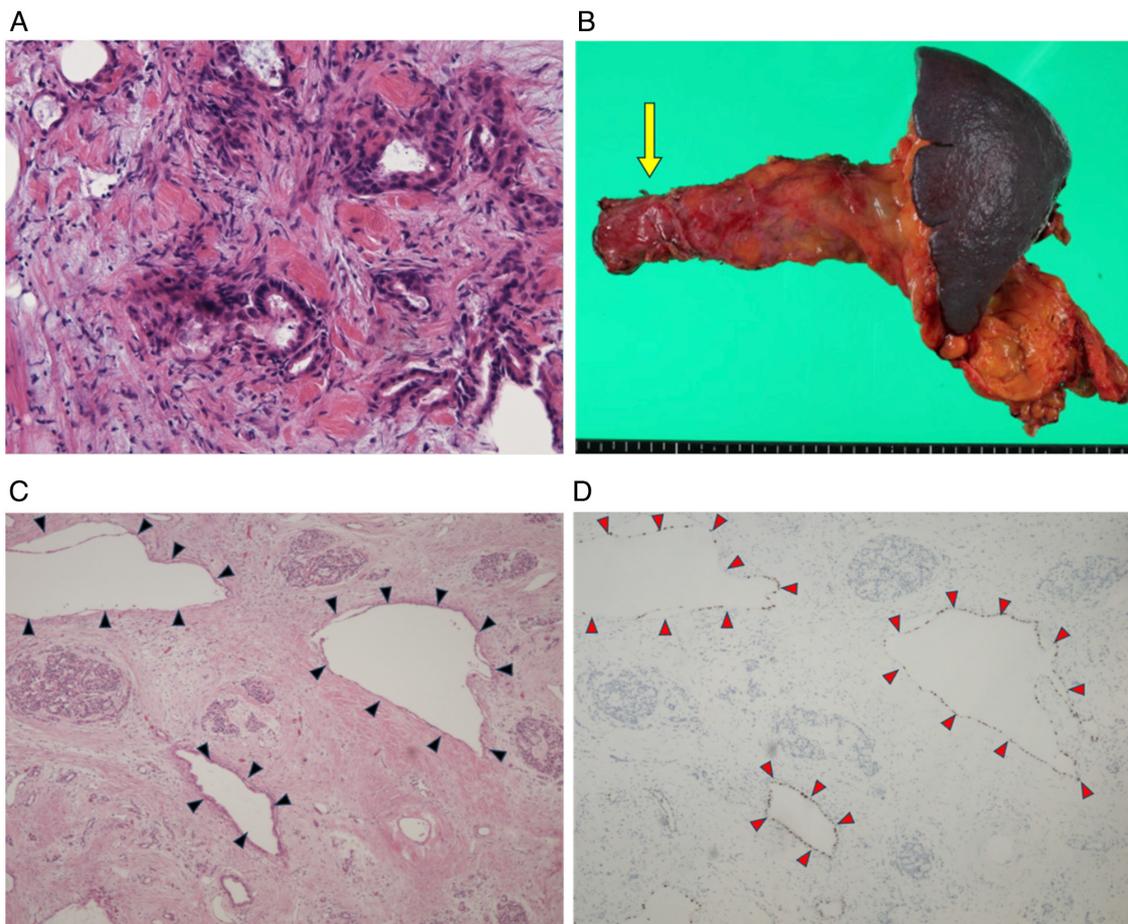


Figure 2. Pathological findings. (A) Pathological findings for hematoxylin and eosin staining of the peritoneal sample before preoperative chemotherapy: Adenocarcinoma. Magnification, x100. (B) Surgical specimen of distal pancreatectomy: Lesion of tumor (indicated by a yellow arrow). (C) Pathological findings for hematoxylin and eosin staining of the pancreas resected by distal pancreatectomy. Glandular structures with irregular margins were observed (surrounded by black arrowheads). Macrophages and granulation were observed in these glandular structures, indicating the effect of preoperative chemotherapy. Magnification, x40. (D) p53 immunostaining findings: p53 expression was increased in the cells of the glandular structures (surrounded by red arrowheads). Magnification, x40.

CA19-9 levels. The patient survived without recurrence for 7 years after CS.

Discussion

The prognosis of patients with PDAC with peritoneal metastases is extremely poor. A population-based analysis conducted between 2005 and 2015 reported that peritoneal metastases was observed in 7.7% of patients with PDAC, and median survival time (MST) of these cases was 3.4 months for the pancreatic head, 2.3 months for the body, and 2.2 months for the tail (8). Peritoneal metastases are associated with the development of intestinal obstruction, massive ascites, and malnutrition, leading to poor performance status, which may in turn partially or completely prevent the patient from undergoing chemotherapy (3,8,9).

Patients with PDAC with peritoneal metastases are generally treated with the same systemic chemotherapeutic regimens as those with other distant metastases (5). The standard regimens for unresectable PDAC are fluorouracil plus leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) (10) or gemcitabine plus nab-paclitaxel (GnP) (11). The MST was 11 months for FOLFIRINOX and 8.5 months for GnP.

However, the prognosis of PDAC with peritoneal metastases remains poor (MST=6 weeks) (4). One of the reported reasons for poor prognosis is that systemically administered anticancer drugs do not necessarily reach optimal concentrations in the peritoneal cavity (3,12-14).

Recently, chemotherapy combined with ip chemotherapy has been introduced in patients with PDAC and peritoneal metastases (1,3,14,15). The efficacy of ip chemotherapy for other cancers, particularly gastric and ovarian cancers, has been reported in phase II trials. A single-center phase II study by Ishigami *et al* (12) on ipPTX and S-1 plus PTX for gastric cancer with peritoneal metastases reported an MST of 22.5 months and a 1-year survival rate of 78%. In a phase II study of ipPTX for ovarian cancer with peritoneal metastases by Markman *et al* (13), 61% of the patients achieved complete response. A combination of chemotherapy with ipPTX is considered more effective than systemic chemotherapy alone because it exposes peritoneal lesions to high concentrations of anticancer drugs without increasing their blood concentration (1,14,16). Ishigami *et al* (16) reported that ip and serum PTX concentrations remained effective for over 72 and 48 h, respectively, indicating that the ipPTX concentration remained extremely high for a long

Table I. Adverse events and outcomes during chemotherapy.

Adverse event	Grade	Timing	Management	Outcome
Device-related infection	3	During cycle 3 of ipPTX + FOLFIRINOX	Antibiotics, surgical removal	Resolved
Catheter-related infection	3	During cycle 3 of ipPTX + FOLFIRINOX	Antibiotics, catheter removal	Resolved
Enterocolitis	2	During post-operative ipPTX + S-1	Hydration	Improved
Laryngitis	2	During post-operative ipPTX + S-1	Anti-inflammatory treatment	Resolved

Hematologic toxicity and abdominal infection were not observed in this case. FOLFIRINOX, fluorouracil plus leucovorin, irinotecan, oxaliplatin; ipPTX, intraperitoneal paclitaxel.

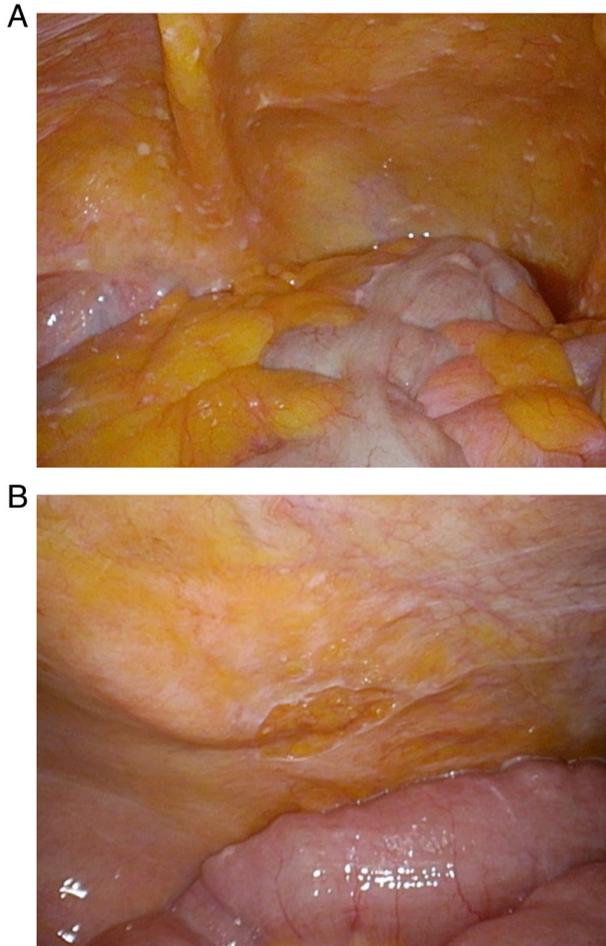


Figure 3. Diagnostic laparoscopy findings. (A) Before preoperative chemotherapy: Several peritoneal white nodules were observed. (B) After preoperative chemotherapy, two portions of white peritoneal nodules were sampled and no peritoneal dissemination was observed. Negative peritoneal lavage cytology was observed.

period, and area under the blood concentration-time curve was much higher than that obtained by ivPTX. However, comprehensive pharmacokinetic studies specific to ipPTX in PDAC are limited, so it is considered that further studies are needed to confirm the above findings in a larger cohort. Additionally, it is reported that ipPTX is relatively safe with less adverse events when compared with systemic chemotherapy, even for patients with massive amounts of ascites with poor performance status (17).

Furthermore, the efficacy of ip and iv chemotherapy and subsequent CS has been reported in PDAC with peritoneal metastases (1,3,6). A multicenter phase II trial of ipPTX and S-1 plus PTX for PDAC with peritoneal metastases reported (3) an MST of 16.3 months, 1 year survival rate of 62%, and conversion rate of 24%. A group that underwent CS also had a significantly higher overall survival than a group that did not (27.8 vs. 14.2 months, $P=0.038$). A multi-center phase II study of ipPTX and systemic GnP therapy for PDAC with peritoneal metastases by Yamada *et al* (6) reported an MST of 14.5 months, 1 year survival rate of 61%, and conversion rate of 17%. Overall survival was significantly longer in a group that received CS than in a group that did not (MST: not reached vs. 12.4 m, $P=0.004$). In a similar retrospective study, Yamamoto *et al* (1) reported an MST of 27.4 months in patients who underwent CS, and 11.3 months in those who did not ($P<0.001$). Considering the fact that the conversion rate for patients with unresectable locally advanced PDAC was reported to be 29% and MST for patients who underwent CS was 31 months (18), ip and iv chemotherapy promises to be an effective therapy in terms of conversion rate and prognosis of patients who achieve CS. The criteria for CS in these trials were as follows: no decline in performance status, size reduction of the primary tumor, decline in tumor markers, negative cytology, disappearance of peritoneal metastases, and a treatment duration of at least 8 months. A treatment approach based on all the above criteria seems to lead to a better prognosis for patients who achieved CS.

However, at present, the number of reports on the efficacy of CS after ip and iv chemotherapy for PDAC with peritoneal metastases is limited. There have been failed attempts at ipPTX therapy; for example, a study by Ishigami *et al* (16) failed to show the statistical superiority of ipPTX plus systemic chemotherapy, owing to a crucial imbalance in the high amount of ascites in an experimental group and a crossover use of ip therapy in a control group (19). The 2024 National Comprehensive Cancer Network guidelines do not recommend ip and iv chemotherapy for the treatment of PDAC with peritoneal metastases due to limited evidence, whereas our case offers rare insight into a successful outcome. In our case, although the therapy was not recommended, the decision of performing the therapy was made based on multidisciplinary discussion and patient-specific factors, including isolated peritoneal metastasis and observing good response to initial therapy. A phase III trial of ip and iv chemotherapy for PDAC with peritoneal metastases is currently in progress (14).

In our case, the patient completed a preoperative treatment with ip and iv chemotherapy for >8 months (1,20), which is one of the criteria for CS. Additionally, imaging studies did not show other distant metastases, and the CA19-9 level decreased to <100 U/MI (1,21), Peritoneal washing cytology via the abdominal access device was negative, and the disappearance of peritoneal dissemination was confirmed by staging laparoscopy. The criteria for CS were also met. Successful CS was the main contributing factor to the 7-year survival without recurrence. The second reason is the favorable effect of CT with ipPTX. The peritoneal dissemination virtually disappeared, there were no lymph node metastases, and negative surgical margins were achieved. The effect of preoperative chemotherapy was grade IIB, according to the Evans classification. Third, the patient received long-term postoperative adjuvant chemotherapy with ip PTX plus S-1 for 6 months, followed by ipPTX for 6 months. The 7-year recurrence-free survival with CS after ip and iv chemotherapy in this case may be extraordinary; however, ip and iv chemotherapy is a promising treatment for PDAC with peritoneal metastases, and if followed by CS, long-term survival may be expected. In contrast, although ip and iv chemotherapy is generally well tolerated, Satoi *et al* (3) reported grade 3/4 hematologic toxicity, adverse events other than hematologic toxicity, superior mesenteric artery thrombosis, anaphylactic reactions and abdominal access device related infections. In this case, the patient experienced grade 3 device-related infection and grade 3 catheter-related infection during preoperative ipPTX+FOLFIRINOX, and grade 2 enterocolitis and grade 2 laryngitis during postoperative ipPTX+S-1; however, there were no hematologic toxicities, thrombosis, or anaphylactic reactions (Table I). Given the above findings, although adverse events were rather limited and the therapy was generally well tolerated for this case, they could not be entirely avoided. Patients undergoing this therapy should be closely monitored for adverse events that may, at times, become severe or life-threatening. Another limitation of this case was that the diagnosis of adenocarcinoma of the peritoneal dissemination originating from pancreatic body adenocarcinoma was not immunohistologically confirmed before preoperative chemotherapy. Based on histological features and comparison with previously confirmed pancreatic cancer, and the absence of any other findings of cancer causing peritoneal dissemination, a clinical diagnosis of peritoneal metastasis of pancreatic cancer was established, but immunohistochemistry was not performed for the peritoneal nodules after the primary laparotomy, and it should have been conducted to achieve a more precise diagnosis by adding immunohistological analysis.

In conclusion, combination therapy with intraperitoneal PTX plus chemotherapy is a promising treatment for PDAC with peritoneal metastases. If followed by CS, long-term survival may be expected. Because our findings represent a single case, further clinical trials are required to validate the efficacy of this approach.

Acknowledgements

The authors would like to thank Mr. David Hochman for reviewing the language of this article.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MT is the main author of this paper. JM, YT and SH proofread the manuscript. MT, JM and YT confirm the authenticity of all the raw data. MT, JM, YT and SH made substantial contributions to conception and design, and acquisition of data, and analysis and interpretation of data, and were involved in drafting the manuscript and revising it critically for important intellectual content. MT, JM, YT and SH participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved. YO contributed by providing pathological images, offering pathological diagnoses, and giving expert pathological advice. YS served as the attending physician and operating surgeon and provided comprehensive details of the clinical course and made critical revisions to the manuscript draft. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent for publication was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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