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Tumor Disappearance on Positron Emission Tomography Computed Tomography after mFOLFOX6 plus Bevacizumab Treatment for Postoperative Peritoneal Metastasis of Sigmoid Colon Cancer

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Abstract
Objective: *Peritoneal metastasis (PM) presents a common and unfavorable evolution of colorectal cancer (CRC), which is estimated to occur in up to 19% of patients after radical surgery and has been estimated to be the cause of death in more than half of CRC patients. We report a case in which PM disappearance on positron emission tomography computed tomography (PET-CT) was treated with mFOLFOX6 plus bevacizumab following 5-FU/l-LV plus bevacizumab as second-line treatment.*
Case presentation: *A 50-year-old man with anemia was referred to our hospital. Colonoscopy revealed a type 2 tumor in the sigmoid colon. Enhanced computed tomography (CT) showed wall thickening of the sigmoid colon, enlarged nearby lymph nodes, and amidotrizoic acid in the small intestine originating from the tumor. Laboratory investigations revealed decreased hemoglobin (5.5 g/dl), mildly elevated carcinoembryonic antigen (CEA; 6.6 ng/ml), and elevated carbohydrate antigen 19-9 (CA19-9; 60.8 U/ml). Therefore, we diagnosed the patient with clinical stage IIIC sigmoid cancer (cT4b [small intestine]), N1, M0).*
Results: *We performed sigmoidectomy with D3 lymphadenectomy and partial resection of the jejunum. At four months after surgery, enhanced CT showed PM. First-line chemotherapy with FOLFILI and panitumumab was initiated. After nine courses, enhanced CT in March 2019 showed an increase in PM. We concluded that the first-line chemotherapy was ineffective. Second-line chemotherapy with mFOLFOX6 plus bevacizumab was initiated every two weeks. After eight courses were administered, chemotherapy was switched to 5-FU/l-LV plus bevacizumab due to increased numbness in the hands and feet. In January 2021, the patient's CEA and CA19-9 levels decreased to within normal limits, and PM decreased. Fifty-one courses of 5-FU/l-LV plus bevacizumab were administered. PET-CT in February 2023 showed complete disappearance of PM. At seven months after the discontinuation of 5-FU/l-LV plus bevacizumab, PET-CT showed the complete disappearance of PM.*
Conclusions: *Chemotherapy with 5-FU/ l-LV plus bevacizumab after mFOLFOX6 plus bevacizumab can be managed safely and has been demonstrated to be effective in treating PM of sigmoid colon cancer.*
Keywords: *Sigmoid cancer, peritoneal metastasis, mFOLFOX6, complete response, PET-CT, bevacizumab, 5-FU/l-LV*

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I. INTRODUCTION

Colorectal cancer (CRC) is the third and second most common cancer in males and females, respectively (1). Peritoneal metastasis (PM) presents a common and unfavorable evolution of CRC that is estimated to occur in up to 19% of patients after radical surgery, and has been estimated to be the cause of death in more than half of patients with CRC (2). Systemic chemotherapy is considered the mainstay treatment for patients with PM (3), even though PM is associated with shorter median survival in comparison to other metastatic sites (16.3 months for isolated PM) (4).

5-fluorouracil (5-FU) became the only cytotoxic drug indicated for CRC in the 1990s (5), when the adaptation of continuous infusion of this agent was found to have improved the median overall survival from 12 to 15 months (6). Since then, FOLFILI (folinic acid, bolus/continuous fuorouracil, and irinotecan) regimens (7)) or 5-FU/l-LV + oxaliplatin (OX) (mFOLFOX6 regimen (8)) have been found to further improve overall survival (OS) and have become the main chemotherapeutic treatment options for CRC. A randomized crossover trial showed that the outcomes of patients treated with these combination regimens were not statistically different, with patients receiving these agents in any sequence surviving a median of 18-20 months (9, 10). The addition of panitumumab or bevacizumab to cytotoxic chemotherapeutic combinations proved feasible and appeared to be more effective than cytotoxic chemotherapy alone (11). These new options for metastatic CRC raised the question of which is the optimal biologic monoclonal antibody-chemotherapy combination.

We herein report the case of a patient with sigmoid cancer who developed postoperative PM. Positron emission tomography computed tomography (PET-CT) showed the disappearance of PM with mFOLFOX6 plus bevacizumab following 5-FU/l-LV plus bevacizumab as the second-line treatment after surgery.

II. CASE PRESENTATION

A 50-year-old man was referred to our hospital because of anemia. Laboratory investigations revealed a decreased hemoglobin (5.5 g/dl). An analysis of his tumor marker levels revealed a slightly elevated carcinoembryonic antigen (CEA) level (6.6 ng/ml), and an elevated carbohydrate antigen 19-9 (CA19-9) level (60.8 U/ml).

Colonoscopy revealed a type 2 tumor in the sigmoid colon (Fig. 1). A histopathological examination of the biopsy specimen of the sigmoid colon tumor revealed moderately differentiated adenocarcinoma. Enhanced computed tomography (CT) showed wall thickening and enlargement of the nearby lymph nodes (Fig. 2), and non-enhanced CT showed amidotrizoic acid in the small intestine originating from the tumor (Fig. 3). Based on these findings, the patient was diagnosed with sigmoid cancer. Surgery was performed. Intraoperatively, we observed sigmoid cancer invading the jejunum; therefore, sigmoidectomy with D3 lymphadenectomy and partial resection of the jejunum were performed in March 2018. The diagnosis was adenosquamous carcinoma 50 × 30 mm in size, pT4b (SI, jejunum), int, INFb, ly1, v2, pN1a, M0, Stage IIIC according to the Union for Internal Cancer Control TMN classification of malignant tumors (8^{th} edition) (12).

The patient was discharged on the 8th day after surgery with a good postoperative course. Because the patient had stage IIIC disease, postoperative adjuvant chemotherapy with capecitabine (Cape) + OX (CAPOX) was initiated. During adjuvant chemotherapy, PM was observed on abdominal contrast-enhanced CT in July 2018 (Fig. 4).

Molecular targeting tests showed RAS wild-type, BFAF wild-type, and microsatellite instability (MSI) high type. Therefore, first-line chemotherapy with FOLFILI plus panitumumab was initiated, and nine courses were administered. Non-enhanced CT of the abdomen in March 2019 showed increased PM (Fig. 5). The CEA (29.4 ng/ml) and CA 19-9 (210.1 U/ml) levels were elevated. Based on these findings, we concluded that FOLFILI plus panitumumab was ineffective.

We initiated second-line chemotherapy with mFOLFOX6 plus bevacizumab every two weeks. After eight courses, chemotherapy was switched to 5-FU/l-LV plus bevacizumab due to grade 3 peripheral sensory neuropathy in the hands and feet according to the Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 (13). In January 2021, the CEA and CA19-9 levels decreased to within the normal limits. After 51 courses of 5-FU/l-LV plus bevacizumab, non-enhanced CT revealed markedly reduced PM. In January 2023, non-enhanced CT showed no evidence of PM (Fig. 6). In February 2023, PET-CT revealed the complete disappearance of PM (Fig. 7). Seven months after the discontinuation of 5-FU/l-LV plus bevacizumab, PET-CT showed complete disappearance of PM. The patient's only adverse events with 5-FU/l-LV plus bevacizumab, according to CTCAE v 5.0, were grade 1 fatigue and a grade 2 creatinine increase.

III. DISCUSSION

CRC is the second leading cause of cancer-related death in Japan. PM occurs in 4.5% of Japanese patients with metastatic CRC, and this rate is second only to that of liver metastasis at 10.9% (14). The prognosis of CRC patients with PM was shown to be poor in comparison to those with other organ metastases (e.g., liver and lung metastasis), with a 1-year survival rate of 33%. Moreover, PM diminishes the quality of life due to ascites retention, malnutrition, and intestinal obstruction. Bevacizumab plus multiple cytotoxic agent therapy (CAT) was reported to be superior to cetuximab plus CAT for patients with PM, as measured by progression-free survival (PFS) and OS. For the subset of patients with PM, bevacizumab-based triplet chemotherapy was superior to cetuximab-based triplet chemotherapy, as measured by PFS (9.6 vs. 6.1 months, respectively) and OS (26.3 vs. 12.7 months), but not for patients without PM (PFS, 10.6 vs. 9.1 months; OS, 27.9 vs. 30.7 months; $p < 0.05$) (15).

Mayanagi et al (16) reported that younger age, pT4 level, lymph node involvement, and D2 lymphadenectomy were associated with recurrent PM in patients who underwent curative resection for colon cancer. In our case, younger age, pT4 level, and lymph node involvement were risk factors for recurrent PM after surgery. In particular, we believe that invasion of sigmoid colon cancer into the jejunum is a major cause of peritoneal recurrence.

The NCCN guidelines recommend anti-EGFR antibody treatment as first-line therapy for left-sided colon cancer, but not for metastatic right-sided colon cancer (17). In our case, molecular targeting tests showed RAS wild-type, BFAF wild-type, and MSI high-type. Therefore, we initiated the treatment with FOLFILI plus panitumumab. After nine courses, enhanced CT showed an enlarged peritoneal tumor; therefore, we considered that treatment with FOLFILI plus panitumumab was ineffective. Second-line chemotherapy with mFOLFOX6 plus bevacizumab was initiated every two weeks. After eight courses, enhanced CT showed a decreased peritoneal tumor, we concluded that treatment with mFOLFOX6 plus bevacizumab was effective; however, the patient developed grade 3 peripheral sensory neuropathy in his hands and feet (according to CTCAE v 5.0). We therefore initiated treatment with 5-FU/l-LV plus bevacizumab. After 51 courses, the peritoneal tumor completely disappeared on PET-CT. Seven months after the discontinuation of 5-FU/l-LV plus bevacizumab, PET-CT showed the complete disappearance of PM. First-line FOLFILI plus panitumumab was ineffective for PM after sigmoid colon cancer surgery; however, the second-line 5-FU/l-LV plus bevacizumab after mFOLFOX6 plus bevacizumab was effective. These results suggest that bevacizumab plays an important role as a molecular-targeted agent.

There are few reports of patients with PM of CRC who have been treated with chemotherapy with radiographic or histopathological disappearance. As far as we were able to find in the literature, there were 15 cases, including our own (Table 1). The median age of the 15 patients (male, n=10; female, n=4) was 62 years (range: 44-74 years), and most of the patients were relatively young. Four patients received chemotherapy before surgery because curative treatment was not possible. These regimens included CAPOX, panitumumab plus mFOLFOX6, FOLFOXILI, and pembrolizumab. The surgical treatments varied from in-office procedures such as colostomy to pancreaticoduodenectomy (PD) surgery with vascular reconstruction. Advances in chemotherapy may increase the chances of cure for patients with PM caused by CRC.

IV. CONCLUSIONS

We reported the case of a patient with sigmoid cancer and PM after surgery. The disappearance of PM on PET-CT was observed with 5-FU/l-LV plus bevacizumab after mFOLFOX6 plus bevacizumab. The present case demonstrates that chemotherapy with 5-FU/l-LV plus bevacizumab after mFOLFOX6 plus bevacizumab can be safely and its efficaciously applied in the treatment of PM in a patient with sigmoid cancer.

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Figure Legends

Fig. 1
Colonoscopy shows a type 2 circumscribed tumor in the sigmoid colon.

Fig. 2
Abdominal enhanced CT shows the enlargement of the tumor in the sigmoid colon (arrow).
(a) Horizontal slice.
(b) Coronal slices.

Fig. 3
Abdominal non-enhanced CT shows amidotrizoic acid in the small intestine originating from the tumor (arrow).
(a) Horizontal slice.
(b) Coronal slices.

Fig. 4
Abdominal enhanced CT shows peritoneal recurrence.
(a) Peritoneal tumor: horizontal slice (arrow).
(b) Perihepatic ascites: horizontal slice (arrow).

Fig. 5
Abdominal non-enhanced CT shows the markedly enlargement of the peritoneal tumor (arrow).

Fig. 6
No evidence of PM was observed on non-enhanced CT.
(a) Horizontal slice.
(b) Coronal slices.

Fig. 7
No evidence of PM was observed on PET-CT.
(a) Horizontal slice.
(b) Coronal slices.

Table 1
Patients with peritoneal metastasis of colorectal cancer who showed radiographic or histopathological disappearance after treatment with chemotherapy.

Fig. 1

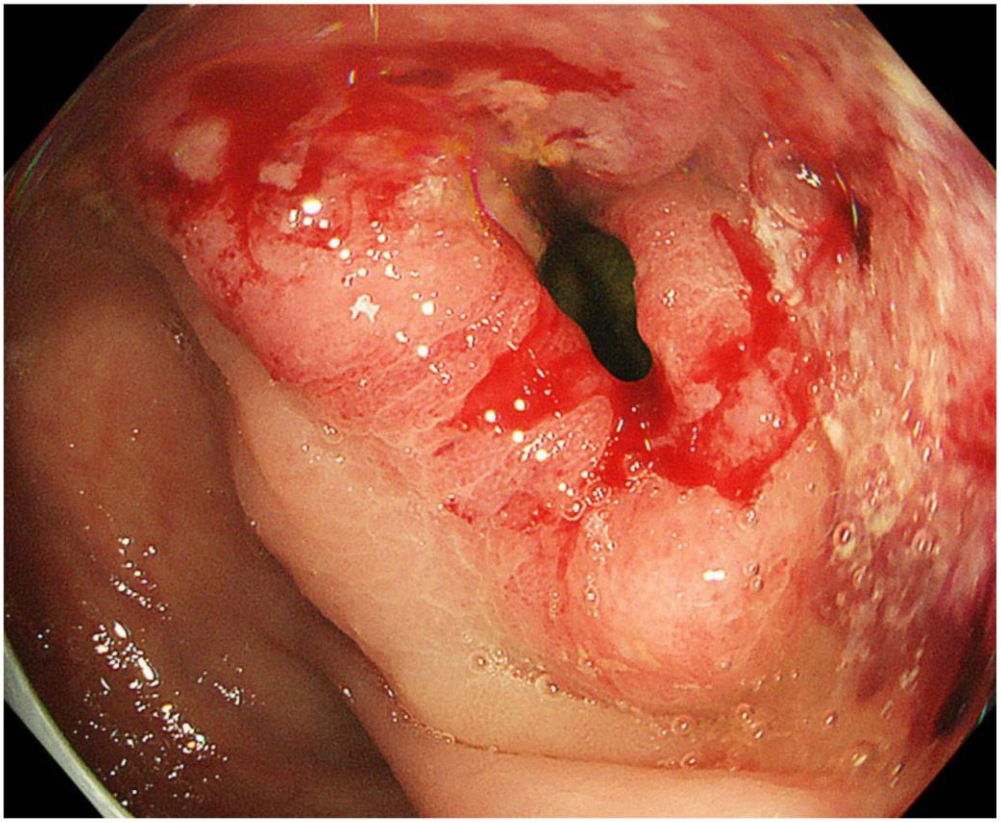

Fig. 2

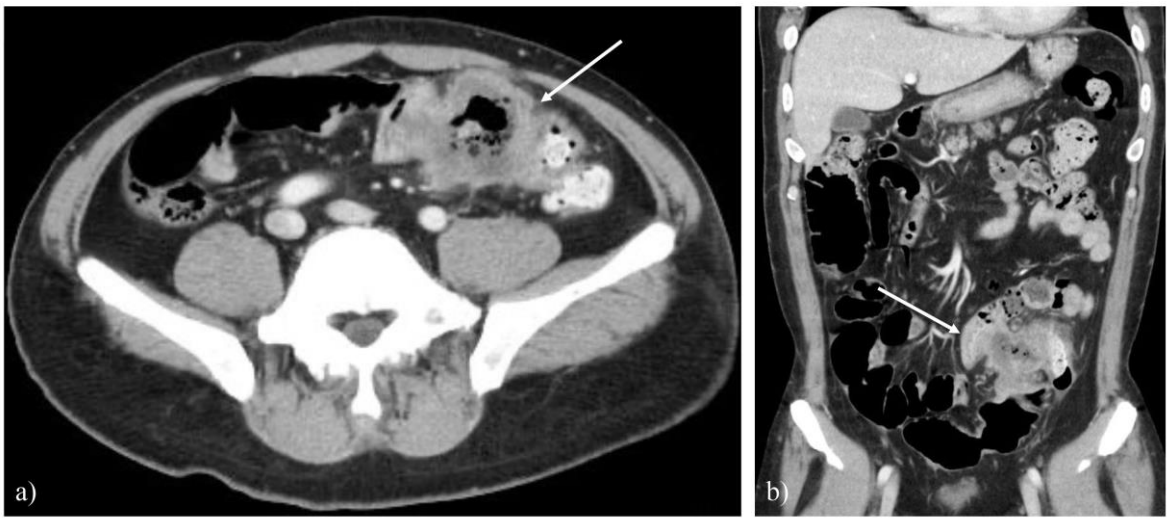

Fig. 3

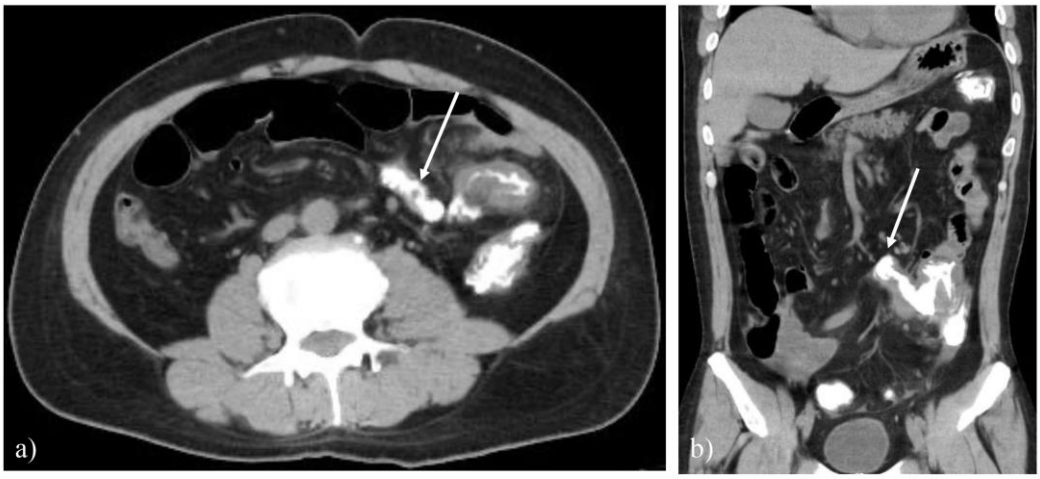

Fig. 4

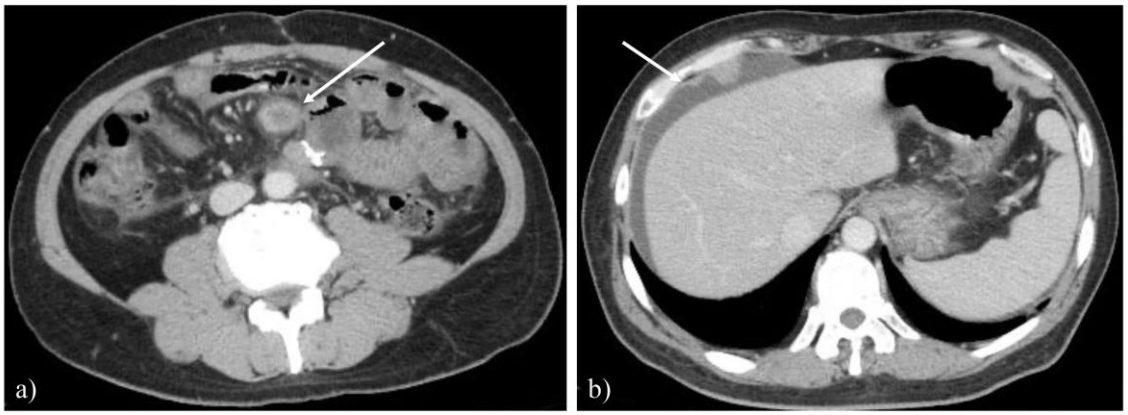

Fig. 5

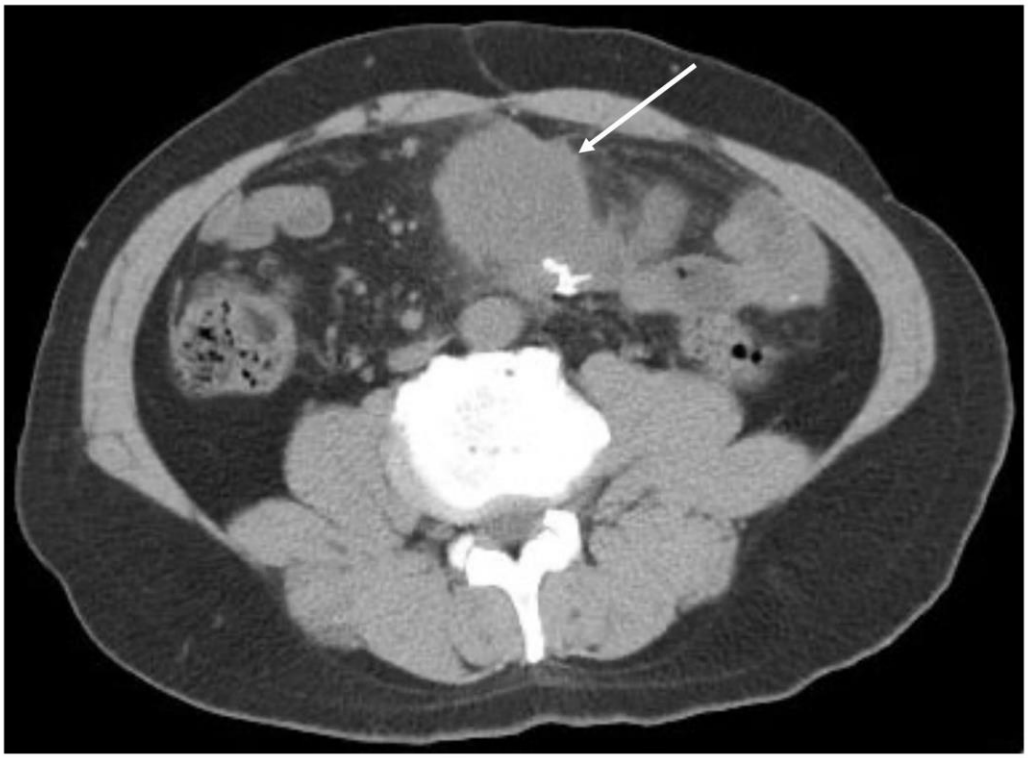

Fig. 6

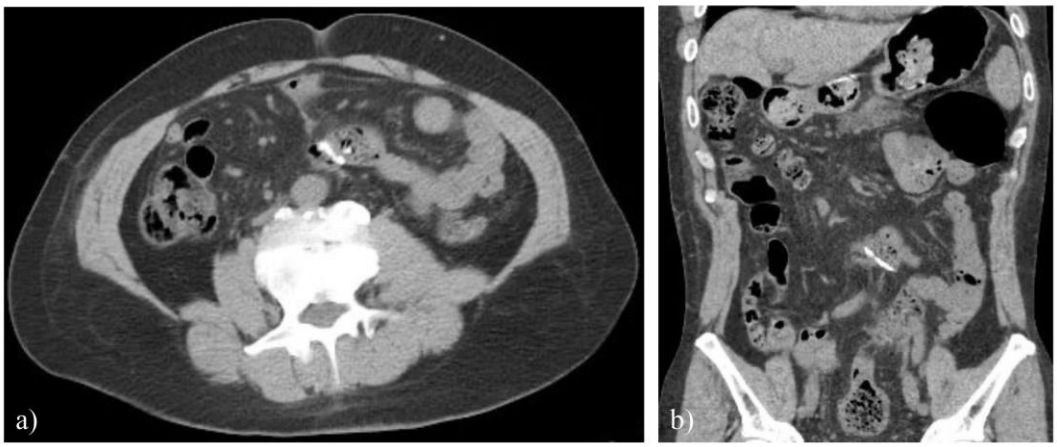

Fig. 7

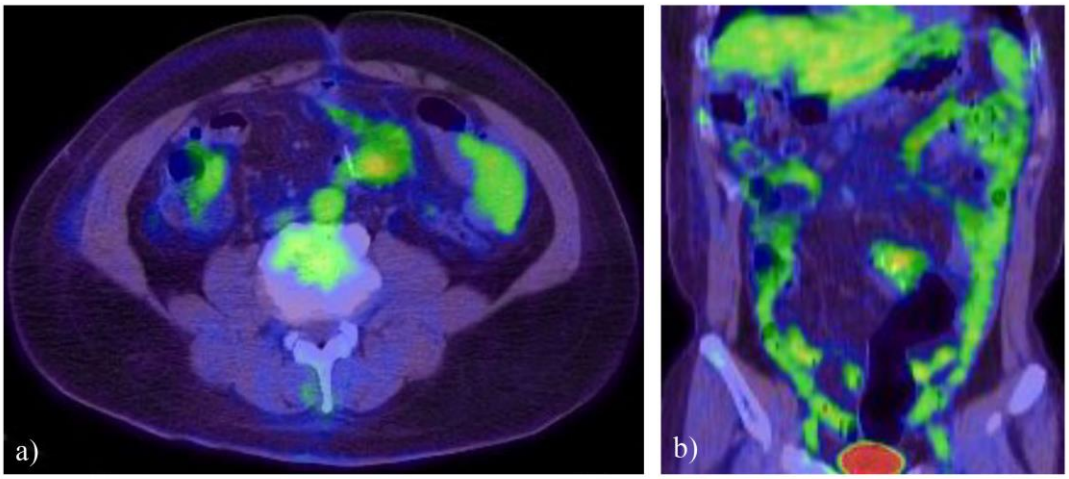

Table 1

No	Year	First Author	Age	Sex	Primary site	Preoperative chemotherapy	Surgical treatment	Sites of metastasis	Postoperative chemotherapy	Response
1	1993	Iida A (18)	60	F	Ascending colon	None	Rt. hemicolectomy	Peritoneum, liver, LN	Methotrexate plus 5-FU, Uracil /Tegafur	Complete response
2	2004	Mochizuki R (19)	67	F	Ascending colon	None	Rt. hemicolectomy	Peritoneum, liver, LN	5-FU plus hepatic arterial infusion (5-FU)	Complete response
3	2008	Huh JW (20)	47	M	Sigmoid colon	CAPOX	Anterior resection with radiofrequency ablation of hepatic metastases	Peritoneum, liver	None	Complete response
4	2012	Okamura S (21)	62	M	Ascending colon	None	Rt. hemicolectomy with transverse colostomy	Peritoneum, LN	SOX	Complete response
5	2012	Tajima Y (22)	69	M	Rectsigmoid	None	Hartmann's procedure, after chemotherapy left lateral segmentectomy of liver	Peritoneum, liver	mFOLFOX6	Complete response
6	2013	Iwata N (23)	62	M	Rectum	None	Low anterior resection	Peritoneum, LN	CAPOX plus BEV	Complete response
7	2016	Ibuki Y (24)	50's	M	Sigmoid colon	None	Transverse colostomy, after chemotherapy sigmoidectomy	Peritoneum	SOX plus BEV	Complete response
8	2019	Tokuhara K (25)	67	M	Ascending colon	PANI plus mFOLFOX6	Ileostomy, after chemotherapy rt. hemicolectomy and ileostomy closure	Peritoneum	PANI	Complete response
9	2019	Wang Z (26)	44	M	Rt. side colon	None	Open surgery	Peritoneum	5-FU plus BEV plus IRI plus CET	Complete response
10	2021	Zhang Y (27)	64	F	Rectum	None	Miles' resection	Peritoneum	Regorafenib plus Sintilimab	Complete response
11	2021	Baik H (28)	54	F	Hepatic flexure colon	None	Laparoscopic rt. hemicolectomy	Peritoneum, LN	FOLFOX plus BEV, Regorafenib	Complete response

12	2022	Tonello M (29)	50	M	Ascending colon	None	Rt. hemicolectomy, after chemotherapy resection of the previous ileocecal anastomosis and PD with vascular reconstruction	Peritoneum	CAPOX plus BEV, Nivolumab	Complete response
13	2022	Tominaga T (30)	45	M	Ascending colon	FOLFOXILI	Extended rt. hemicolectomy	Peritoneum	None	Complete response
14	2023	Smith HG (31)	74		Transverse colon	Pembrolizumab	Extended rt. hemicolectomy	Peritoneum, LN	None	Complete response
15	Our case	Udaka T	50	M	Sigmoid colon	None	Sigmoidectomy with partial resection of jejunum	Peritoneum	mFOLFOX6 plus BEV, 5-FU/l-LV plus BEV	Complete response

PD: pancreaticoduodenectomy, CAPOX: Capecitabine plus oxaliplatin, SOX: S-1 plus oxaliplatin, PANI: panitumumab, BEV: bevacizumab, LN: lymph node, M: male, F: female, CET: cetuximab, IRI: irinotecan hydrochloride hydrate

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