

Stage IV and recurrent colorectal cancer cured following multimodal therapy: A case series

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Received August 2, 2023; Accepted December 14, 2023

DOI: 10.3892/ol.2024.14250

Abstract. The treatment strategies for colorectal cancer (CRC) with distant metastasis or metastatic recurrence after resection of the primary tumor are controversial. In the present study, four cases of patients with advanced CRC with distant metastasis who achieved disease-free survival (DFS) for >5 years and were deemed potentially cured were reported. Case 1 was that of a 53-year-old male patient with rectal cancer and liver metastases (pT3N2bM1, pStage IV), and case 2 was that of a 58-year-old female patient with descending colon cancer (pT3N1M1, pStage IV) who had lung metastases at surgery and postoperatively. Both patients achieved DFS for >5 years after simultaneous or staged partial hepatectomy or pneumonectomy followed by chemotherapy. Case 3 was that of a 75-year-old male patient with transverse colon cancer (pT3N1M0, pStage IIIB) and case 4 was that of a 73-year-old male patient with sigmoid colon cancer (pT3N0M0, pStage IIA). These cases developed liver metastases after resection of the primary tumour and were subsequently treated with chemotherapy before or after partial hepatectomy. DFS for >5 years was achieved. All four patients were considered cured. The data revealed that even patients with CRC and distant metastases can potentially be cured following multidisciplinary treatment. In the present case report, the factors that enabled these patients to be considered cured were discussed and the aim was to improve the treatment strategy to cure CRC with distant metastasis or recurrence.

Introduction

Colorectal cancer (CRC) is one of the most common cancer types in Japan. The Japanese national database reports 150,000 new cases and 50,000 deaths annually. The overall 5-year survival rate of the disease is 71.4%, but the survival rate of patients with distant metastases (stage IV) is 16.8% (1,2). Worldwide, CRC is the third most common cancer and the second leading cause of cancer-related deaths, with 1.8 million new cases and 800,000 associated deaths annually. The overall 5-year survival rate is 64%, but the survival rate is 17% for patients with distant metastases (3,4). The treatment strategies for distant metastases or postoperative recurrence after resection of primary CRC are controversial.

At the International University of Health and Welfare (IUHW), Shioya Hospital (Yaita, Japan), a total of 172 patients underwent resection of CRC between January 2012 and December 2017. Among them, 10 patients had double primary CRCs and one patient had triple primary CRCs resulting in a total of 184 CRCs consisting of 11, 34, 58, 58, 22 and 1 CRC at stages 0, I, II, III, IV and unknown, respectively. A total of 22/172 patients were at clinical or pathological stage IV at the time of surgery and 38/150 patients with maximal stages I-III (25.3%; 1, 10 and 27 patients at stages I, II and III, respectively) at the time of surgery experienced postoperative recurrence. In the present study, two cases of patients with stage IV CRC at the time of resection of the primary tumor, and two cases of patients with stage II/III colon cancer and liver metastasis after resection of the primary tumors were reported. These four patients underwent resection of the primary tumor followed by multimodal therapies, and achieved disease-free survival (DFS) for >5 years, indicating that patients were considered cured. Until now, there have been no case series of potentially cured patients with CRC and distant metastasis from a single institution. Single center study has a merit of less variations in treatment strategies, surgical quality and pathological diagnosis and can be a pilot study for future multicenter studies to establish therapeutic strategies for curing patients with recurrent CRC and distant metastasis. The current study was approved by the Ethics Committee of the IUHW (Nasushiobara, Japan; approval no. 22-B-43), and written informed consent was obtained from the patients who could fully understand the content of the present study.

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Key words: colorectal cancer, metastasis, postoperative recurrence, disease-free survival, cure

Case report

Case 1. A 53-year-old male patient presented to IUHW, Shioya Hospital (Yaita, Japan) with a diagnosis of rectal cancer in November 2017. Contrast-enhanced computed tomography (CECT) revealed two liver metastases [10 mm in size in segment (S)3 and 7 mm in size in S4], and the patient was diagnosed with stage IV rectal cancer (Fig. 1A and B). Preoperative examination revealed a mild decline in respiratory function (Table I) (5-7). A low anterior resection was performed initially due to bleeding from the main tumor. Pathological examination revealed a moderately differentiated adenocarcinoma of stage pT3N2bM1, pStage IV, according to the American Joint Committee on Cancer TNM staging system (8). After 2 months of observation, imaging showed no increase in the number of liver metastases (Fig. 1C), and a partial hepatectomy was performed. Postoperatively, the patient was scheduled for 6 months (10-12 courses) of treatment with folinic acid (200 mg/m²), fluorouracil [400 mg/m² (bolus)], fluorouracil [2,400 mg/m² (46-h continuous intravenous infusion)] and oxaliplatin [85 mg/m²; (FOLFOX)], but the treatment was discontinued due to myelosuppression after the completion of three courses of treatment. The treatment plan was altered to capecitabine monotherapy (3,600 mg/day) for four courses, and chemotherapy was administered for 6 months after hepatectomy. The patient has been alive for 1,826 days since hepatectomy without recurrence. Patient follow-up was performed every 1-2 months at the outpatient clinic.

Case 2. A 58-year-old female patient was referred to IUHW, Shioya Hospital (Yaita, Japan) with a diagnosis of descending colon cancer (Fig. 2A and B) in January 2016. CECT showed four metastases measuring 8x6, 9x9, 2x2 and 1x1 mm in the right lung (Fig. 2C and D). The patient was diagnosed with stage IV colon cancer. First, a partial descending colon resection was performed. Pathological examination revealed that the tumor was a pT3N1M1, pStage IV mucinous adenocarcinoma. Since CECT showed no new metastatic lesions after a 5-month surveillance following initial surgery, partial right upper and lower lobectomies were performed. However, a new metastatic lesion, 8x6 mm in size, appeared in the left lung 2 months later (Fig. 2E). After a 6-month observation period, a partial left lower lobectomy was performed. After surgery, the patient received chemotherapy with 130 mg/m² oxaliplatin on day 1 and 1,000 mg/m² capecitabine, twice daily, for 2 weeks (CapeOX) for 4 months (7 courses), but further treatment was discontinued owing to neuralgia. The patient has been disease-free for 2,212 days since the last surgery. Patient follow-up was performed every 1-2 months at the outpatient clinic.

Case 3. A 75-year-old male patient was referred to IUHW, Shioya Hospital (Yaita, Japan) with a diagnosis of transverse colon cancer (Fig. 3A). The patient also had diabetes mellitus with 6.8% haemoglobin A1c (HbA1c; Table I). CECT showed no obvious distant metastasis, and a transverse colon resection was performed. Pathological examination revealed that the tumor was a pT3N1M0, pStage IIIB, moderately differentiated adenocarcinoma. After surgery, the patient underwent chemotherapy with capecitabine (3,600 mg/day) for 6 months

(8 courses). At 1 year and 8 months after surgery, three liver metastases measuring 27x21 and 10x6 mm in the right lobe and 17x11 mm in S4 (Fig. 3B and C) were found. Laboratory testing revealed that indocyanine green retention rate (ICG-R15) at 15 min was 14% (Table I), and the patient underwent a partial right-posterior segmentectomy and S4 local resection after two courses (1 month) of FOLFOX plus bevacizumab [folinic acid, 200 mg/m²; fluorouracil, 400 mg/m² (bolus), fluorouracil, 2,400 mg/m² (46-h continuous intravenous infusion), oxaliplatin, 85 mg/m² and bevacizumab, 5 mg/kg]. The patient has been disease-free for 2,035 days since the hepatectomy. Patient follow-up was performed every 1-2 months at the outpatient clinic.

Case 4. A 73-year-old male patient was referred to IUHW, Shioya Hospital (Yaita, Japan) with a diagnosis of sigmoid colon cancer without distant metastasis. The patient also had diabetes mellitus with 6.4% HbA1c (Table I). A laparoscopic sigmoidectomy was performed. Pathological examination revealed a pT3N0M0, pStage IIA, moderately differentiated adenocarcinoma (Fig. 4A). At 8 months postoperatively, imaging revealed two liver metastases measuring 17x14 and 2x1 mm in S3 and S5, respectively (Fig. 4B). The two lesions were identified by intraoperative ultrasonography and a local resection was performed to remove them. After surgery, the patient was treated with FOLFOX [folinic acid 200 mg/m², fluorouracil 400 mg/m² (bolus), fluorouracil 2,400 mg/m² (46-h continuous intravenous infusion) and oxaliplatin 85 mg/m²] for 6 months (10 courses). The patient has been disease-free for 2,402 days since hepatic resection. Patient follow-up was performed every 1-2 months at the outpatient clinic.

All cases. The clinicopathological characteristics of the patients at the time of surgery of the primary lesions and the information on the metastatic lesions are summarized in Tables I and II, respectively, and their clinical courses are shown in Fig. 5.

Discussion

Resection of distant metastases is as important as resection of the primary tumor to improve the prognosis of CRC (1,9,10). The 2019 Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines for the treatment of CRC recommend resection of the metastases if both primary and metastatic lesions are considered resectable (1). It is also recommended that surgical excision be considered for recurrence if lesions are resectable (1). However, no specific criteria have been defined for lesion resectability thus far.

Treatment strategies for hepatectomy vary among experienced surgeons (11). At IUHW, Shioya Hospital, hepatectomy for metastatic lesions is performed when cure or at least extension of prognosis is expected upon combination with chemotherapy. As a premise, patients should understand the significance of treatment and be willing to undergo this treatment. In addition, the following standards of general condition are to be met: i) Evaluation of condition by cardiologists using electrocardiogram and echocardiography as operable; ii) no requirement for daily oxygen inhalation; iii) no ascites and total bilirubin <2 mg/dl; and iv) creatinine <2.0 mg/dl,

Table I. Patient characteristics at the time of resection of the primary tumor.

Patient characteristics	Case 1	Case 2	Case 3	Case 4	Reference range
Age, years	53	58	75	73	NA
Sex	M	F	M	M	NA
ASA physical status classification system	1	2	2	2	NA
Charlson-Deyo comorbidity index (6)	2	2	3	3	NA
BMI, kg/m ²	21.9	22.2	23.5	24.2	18.5≤; <25
EF, %	NA	NA	81.9	NA	≥55
FEV1, liters	2.71	2.29	1.99	3.07	NA
FEV1, %	66.7	87.1	79.3	80	≥70
T. Bil, mg/dl	0.7	0.4	1.2	0.7	0.4-1.5
Alb, g/dl	4.0	3.8	4.5	3.7	4.1-5.1
ICGR15, %	NA	NA	14	NA	≤10
Cr, mg/dl	0.84	0.48	0.94	0.71	0.65-1.07
eGFR, ml/min/1.73 m ²	75.1	99.8	60.1	82.4	≥60
HbA1c, %	5.5	5.9	6.8	6.4	4.9-6.0
Onodera's prognostic nutrition index (7)	NA	39.5	46.2	38.1	NA
Tumor location	Rectum	Transverse colon	Descending colon	Sigmoid colon	NA
Surgery	Laparotomy	Laparotomy	Laparotomy	Laparotomy	NA
pT	3	3	3	3	NA
pN	2b	1	1	0	NA
cM	1	1	0	0	NA
pStage	IV	IV	IIIB	IIA	NA
Histology	Moderate	Mucinous	Moderate	Moderate	NA
Clavien-Dindo classification of surgical complications (8)	Surgical site infection (Grade I)	None	None	None	NA

ASA, American Society of Anaesthesiologists; BMI, body mass index; EF, ejection fraction; FEV1, forced expiratory volume in 1 sec; T. Bil, total bilirubin; Alb, albumin; ICGR15, indocyanine green retention rate at 15 min; Cr, creatinine; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; NA, not available/not applicable; M, male; F, female.

preferably <1.5 mg/dl. Resection area is determined according to ICG-R15. Poor Onodera's prognostic nutrition index (OPNI) (6) or low albumin does not preclude lower gastrointestinal surgery. Previous studies showed that cardiovascular evaluation and respiratory function, such as spirometry to measure forced expiratory volume 1 and the diffusing capacity of carbon monoxide, are deemed to be important for pneumonectomy, but these tests do not define the limitations of resection (12). For the cure of liver metastases, it was decided that resectability would primarily be based on the involvement of the portal vein and the muscular arteries (11). It is noteworthy that the intuition of experienced surgeons that a patient can tolerate treatment is important; however, it is not quantitative. In the present case report, all patients demonstrated normal cardiovascular, respiratory and liver function (Table I). Cases 2 and 4 demonstrated mildly low albumin levels and OPNI.

In cases 1 and 2, liver and lung metastases were detected by CECT before surgery. There are various studies on the possibility of performing liver resection simultaneously or in stages, but no conclusion was reached (13-15). Since it has been

reported that 60% of liver metastases recur within 2 years of metastasectomy (16), in the treatment strategy of the present study, two-stage surgery was carried out with a follow-up period of 1-3 months in between. By contrast, there is no standard for the surgical management of pulmonary metastasis in patients with CRC (17). There is also no consensus on chemotherapy and length of surveillance before pneumonectomy. Furthermore, the effect of lung metastasectomy on outcomes is controversial in metastatic CRC (18). Given that there are cases of cured patients such as case 2 in the present report, pneumonectomy should be considered if technically and physically feasible. If lung metastases reappear after pneumonectomy, an additional pneumonectomy may also lead to a favourable prognosis (19).

Regarding treatment first of either primary or metastatic cancer, the primary lesion was either treated alone or simultaneously with the metastatic lesion (20). On the other hand, a study reported that treating liver metastasis first leads to a good prognosis (20). In any case, repeated resection of metastases is considered to result in a good prognosis (21,22).

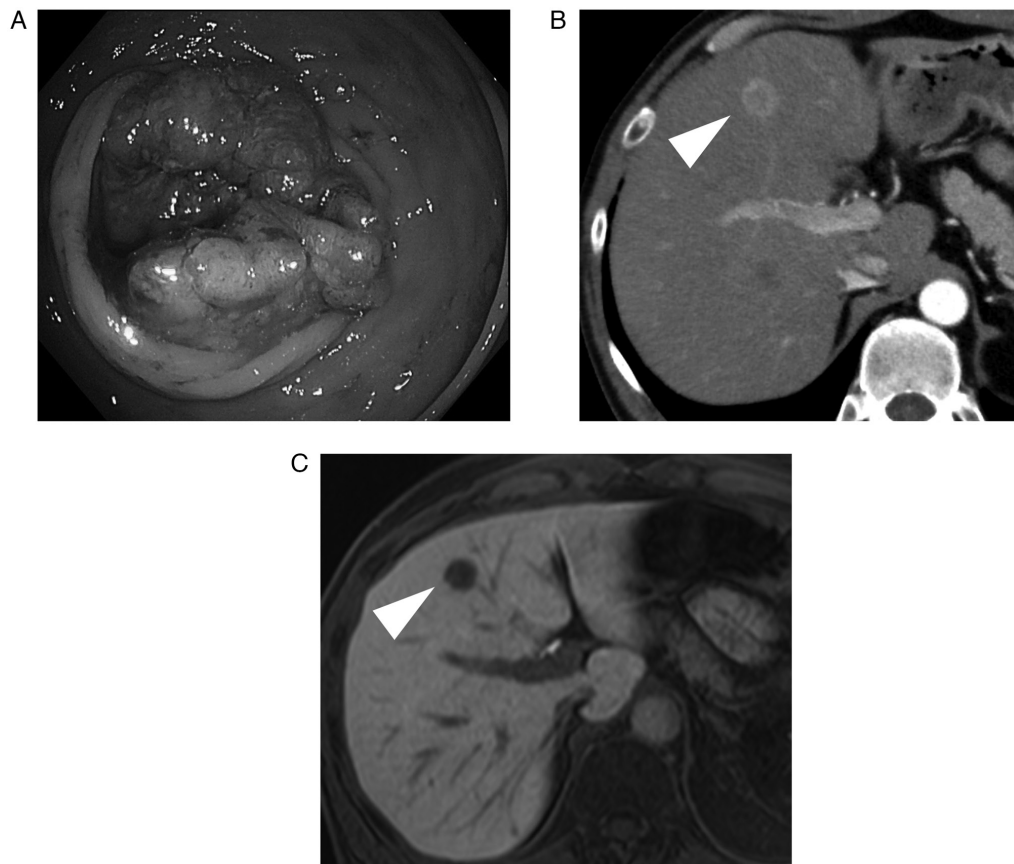


Figure 1. Clinical images of case 1. (A) Preoperative colonoscopy revealed a fungating rectal mass. (B) Computed tomography demonstrated a contrast-enhanced liver mass (10 mm in long diameter in S3), suggesting a metastasis of rectal cancer (white arrowhead). (C) Ethoxybenzyl-magnetic resonance imaging (T1-weighted image) showed that new liver metastases did not appear after 2 months of surveillance.

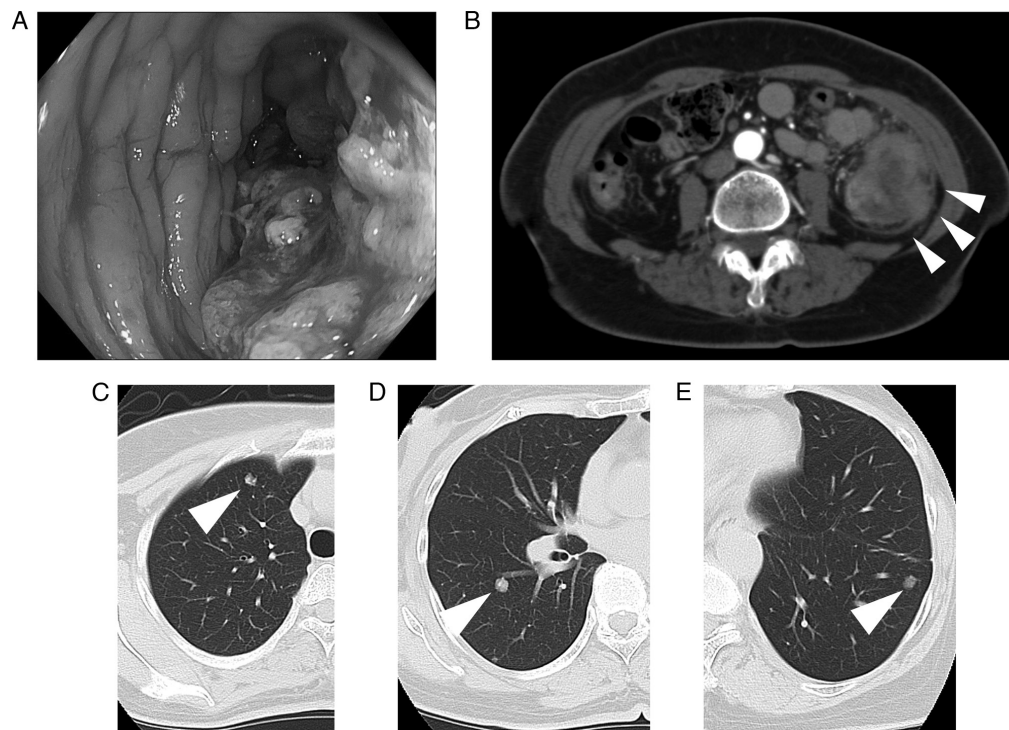


Figure 2. Clinical images of case 2. (A) Preoperative colonoscopy revealed an ulcerated tumor in the descending colon of case 2. (B) Computed tomography demonstrated the contrast-enhanced wall thickening of the descending colon (white arrowheads). Computed tomography revealed two metastases, (C) 8 and (D) 9 mm in diameter, in the right lung (white arrowheads). Partial right upper and lower lobectomies were performed after the resection of the primary lesion. (E) At 2 months after the right pneumonectomy, a new metastatic lesion appeared in the left lung (8 mm in long diameter; white arrowhead). A partial left lung resection was then performed.

Table II. Metastasis of colorectal cancer.

A, At resection of primary tumor				
Parameter	Case 1	Case 2	Case 3	Case 4
Organ of metastasis	Liver	Right lung	None	None
Number of metastasis	2	4	None	None
Site of metastasis, mm (site)	10x7 (S3), 7x5 (S4)	8x6 (Upper lobe), 9x9 (Lower lobe), 2x2 (Lower lobe), 1x1 (Lower lobe)	NA	NA
Metastasectomy	S3 and S4 local resection	Partial right upper lobectomy, right lower lobectomy	NA	NA
Clavien-Dindo classification of surgical complications	None	None	None	None
B, After resection of primary tumor				
Parameter	Case 1	Case 2	Case 3	Case 4
Organ of metastasis	None	Left lung	Liver	Liver
Number of metastasis	None	1	3	2
Site of metastasis, mm (site)	NA	8x6 (Lower lobe)	27x21 (Right lobe), 10x6 (Right lobe), 17x11 (S4)	17x14 (S3) 2x1 (S5)
Metastasectomy	NA	Partial left lower lobectomy	Right-posterior segmentectomy, S4 local resection	S3 local resection, right-anterior local resection
Clavien-Dindo classification of surgical complications	None	None	None	None
S, segment; NA, not applicable.				



Figure 3. Clinical images of case 3. (A) Preoperative colonoscopy revealed an ulcerated tumor in the transverse colon in case 3. At 20 months after resection of the primary tumor, three liver metastases were identified, with (B) two in the right lobe (27 and 10 mm in long diameter, respectively; white arrowheads) and (C) one in S4 (17 mm in long diameter; white arrowhead). None of the tumors involved the portal vein or muscular arteries, and they were considered resectable.

Chemotherapy after resection of the liver metastases has been reported to improve progression-free survival or DFS but has limited effects on overall survival times (23-25). However, a potential cure was achieved by doublet backbone

chemotherapy (FOLFOX) combined with a hepatic resection in cases 3 and 4. Further evidence is required for perioperative chemotherapy of a hepatic resection. Recently, chemotherapeutic regimen for metastatic CRC has been selected based

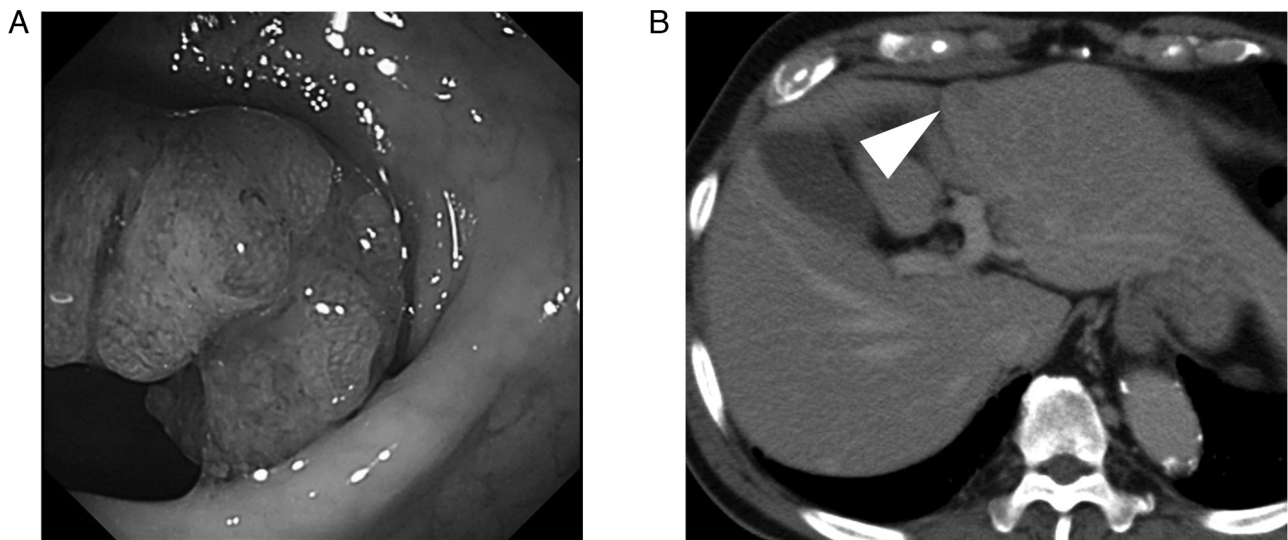


Figure 4. Clinical images of case 4. (A) Preoperative colonoscopy revealed a polypoid mass in the sigmoid colon in case 4. (B) Computed tomography revealed liver metastases 8 months after surgery (17 mm in long diameter in S3; white arrowhead).

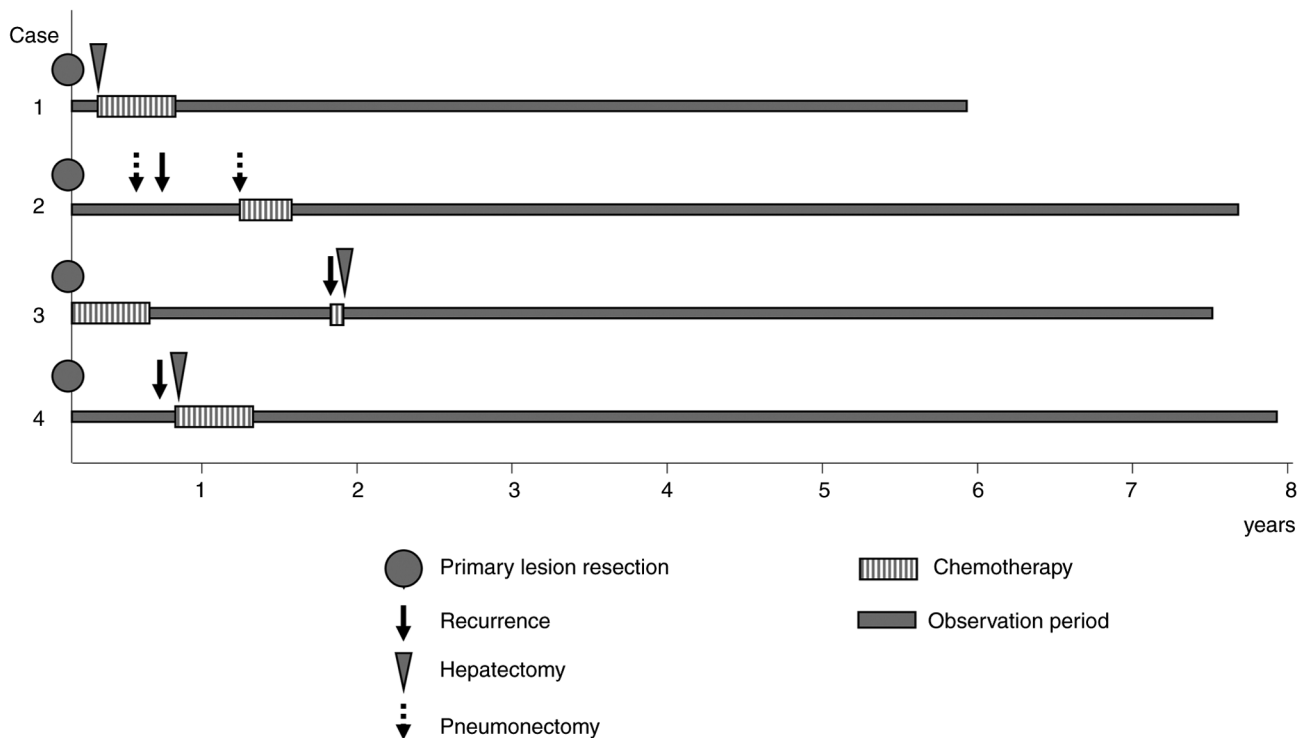


Figure 5. Clinical courses of the four patients. Closed circles indicate surgery, arrows indicate recurrence, arrow heads indicate hepatectomy, dashed arrows indicate pneumonectomy, hatched boxes indicate chemotherapy, and gray lines indicate observation period.

on specific molecular subtypes. Doublet (FOLFOX, CapeOX, S-1/oxaliplatin, 5-FU/leucovorin/irinotecan, S-1/irinotecan) and triplet (5-fluorouracil, oxaliplatin, irinotecan) backbone chemotherapy, immune therapy (pembrolizumab), anti-epidermal growth factor receptor antibodies (cetuximab and panitumumab) and anti-vascular endothelial growth factor antibodies (bevacizumab) were offered based on the presence of KRAS and BRAF gene mutations and microsatellite instability (26). These tailored therapies are expected to improve the cure rate of CRC in the near future.

Finally, according to the 2019 JSCCR guidelines for the treatment of CRC, radiation therapy is considered to have a limited therapeutic effect on colon cancer, excluding rectal cancer, and its main purpose is for palliative care and symptom relief (1). Treatment of lung metastases involves pneumonectomy and systemic chemotherapy but not radiotherapy; pneumonectomy is considered first if the metastatic lung tumor is resectable (1). None of the cured patients with advanced CRC at IUHW, Shioya Hospital had undergone radiation therapy. At present, pneumonectomy is recommended for patients aiming

for a complete cure. A case report on the therapeutic effect of radiation therapy for CRC was previously published (27). Radiotherapy, particularly stereotactic body radiation therapy (SBRT), is rapidly progressing as a non-invasive treatment modality. SBRT actually has the potential to be equally effective with less toxicity compared with surgery, particularly in elderly patients and those patients with comorbidities such as respiratory or heart failure. However, the recurrence rate may be higher in the SBRT cohort than in the surgery cohort, although a death rate may be similar in the two cohorts (28). The efficacy of radiation therapy may be demonstrated in future studies with larger sample sizes.

The present study has a limitation. In Japan, investigations of KRAS and BRAF gene mutations, and microsatellite instability have been available since April 2010, August 2018 and December 2020, respectively, using public insurance. Therefore, the patients of the present report could not undergo genetic testing. More cases might have been cured if the optimal therapy had been selected based on the genotype.

In summary, in the present report, the cases of four patients with CRC and distant metastasis who underwent multimodal treatment and were potentially cured were reported. Further case reports could improve the treatment strategies aimed at curing CRC with metastasis or recurrence.

Acknowledgements

The authors would like to thank Mr. Mitsuhiro Ono, Ms. Setsuko Hiraide and Ms. Rei Kotaki at the Department of Pathology, Shioya Hospital, International University of Health and Welfare (Yaita, Japan), for clerical assistance.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

YK and YI conceptualized the study and wrote the manuscript. MI designed the treatment strategy. YK, AH and MI treated the patients and collected the clinical data. YI performed the pathological diagnosis. YK and YI confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the International University of Health and Welfare (Nasushiobara, Japan; approval no. 22-B-43).

Patient consent for publication

Written informed consent was obtained from the patients for their information to be published in this study.

Competing interests

The authors declare that they have no competing interests.

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