Successful treatment of unresectable advanced rectal cancer with liver metastases by hemostasis re-irradiation of the rectal cancer and palliative low-dose whole-liver radiation therapy: a case report

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CASE REPORT

Successful treatment of unresectable advanced rectal cancer with liver metastases by hemostasis re-irradiation of the rectal cancer and palliative low-dose whole-liver radiation therapy: a case report

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Abstract
A 72-year-old man was admitted to the hospital with fatigue. Colonoscopy revealed a 50 × 50 mm rectal tumor with bleeding. Based on close inspection, he was diagnosed with unresectable advanced rectal cancer with multiple liver metastases. Chemotherapy was administered as 10 cycles of bevacizumab + mFOLFOX6 and 7 cycles of bevacizumab + FOLFIRI. Nine months later, he presented with hematochezia and progression of anemia. It was difficult to stop the bleeding via endoscopy. He underwent radiation therapy (39 Gy in 13 fractions), and hemostasis was confirmed. Then, further chemotherapy was performed with 3 cycles of bevacizumab + FOLFIRI and 2 cycles of TAS102. However 14 months after the initial visit, he presented with right hypochondralgia and abdominal fullness due to the progression of multiple liver metastases. Palliative low-dose whole-liver radiation therapy (WLRT) (30 Gy in 10 fractions) was performed. He developed Grade 2 nausea, but his right hypochondralgia reduced, liver dysfunction improved, and he successfully completed radiotherapy. At approximately the same time his anemia progressed, and colonoscopy revealed recurrent bleeding from the tumor. Re-irradiation (15 Gy in 5 fractions) of the rectal tumor was carried out and a blood transfusion was performed for the bleeding. He was discharged after confirmation the anemia had not progressed. Few reports have been published on the use of both palliative re-irradiation to stop bleeding from rectal cancer and palliative low-dose WLRT. Based on our experience with this case, we believe that palliative radiotherapy can be useful in treating patients with a poor prognosis.

Keywords Palliative radiotherapy · Low-dose whole-liver irradiation · Hemostasis re-irradiation

Introduction

Active bleeding sometimes occurs in unresectable rectal cancer, making it difficult to maintain hemostasis. Liver metastasis is one of the most common metastatic sites of unresectable rectal cancer [1]. Progression of liver metastasis causes complications such as pain, fatigue, and liver dysfunction. We herein report a case of unresectable advanced rectal cancer with multiple liver metastases that was successfully treated with palliative radiotherapy.

Case report

A 72-year-old man was admitted to the hospital with fatigue that had lasted for several months. His medical history was 15 years of diabetes mellitus and hypertension, both of which had been controlled with oral medications. He had no known allergic reactions to medications or foods. He did not smoke cigarettes, and he drank alcohol only occasionally.

Lower gastrointestinal endoscopy showed a 50 × 50 mm infiltrative ulcerative type rectal cancer located 15 cm from the pectinate line of the anal canal (Fig. 1a). Mild stenosis was found around the tumor, but a scope could pass through the stenosis. An abdominal contrast-enhanced computed tomography (CT) scan revealed numerous metastases in

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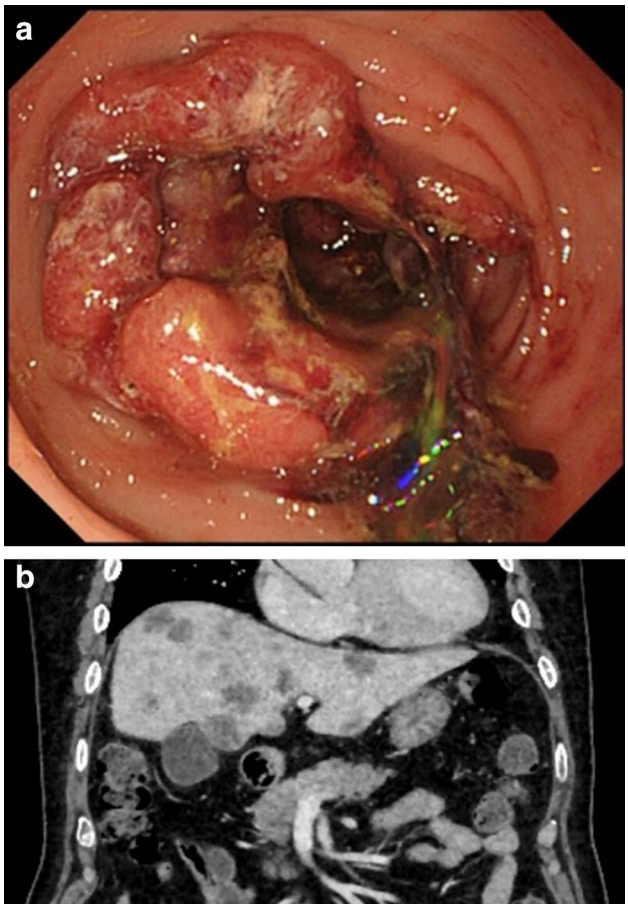

Fig. 1 **a** Lower colonal endoscopic examination revealed the infiltrative ulcerative-type rectal cancer located 15 cm distance from pectinate line of anal canal. **b** Abdominal contrast computed tomography (late phase) revealed numerous metastases in both lobes of the liver

both lobes of the liver (Fig. 1b). Parameters for the CT were as follows: 2 mm slice thickness, 50 × 50 cm field of view, and settings of 150 mA and 120 kV (16-row multidetector CT; Alexion, Toshiba Medical System; Otawara, Japan). He was diagnosed with unresectable advanced rectal cancer with multiple liver metastases. Chemotherapy was administered with 10 cycles of bevacizumab + mFOLFOX6 and 7 cycles of bevacizumab + FOLFIRI. Nine months after the initial admission, he presented with hematochezia and progression of anemia. It was difficult to stop the bleeding via endoscopy, so six units of blood transfusion were performed. He underwent radiation therapy (39 Gy in 13 fractions) (Elekta Synergy System, Elekta Ltd, Crawley, UK). Hemostasis was successfully confirmed (Fig. 2a–c). Then, further chemotherapy was performed with 3 cycles of bevacizumab + FOLFIRI and 2 cycles of TAS102.

However, 13 months after the initial visit, he presented with right hypochondrial pain and abdominal fullness. Abdominal diffusion-weighted magnetic resonance imaging (MRI) showed the progression of multiple liver metastases. Parameters for the MRI were as follows: gradient echo; TR/TE in ms: 1200/70; NSA: 5; matrix: 80 × 256; and *B* value: 1000 (MRI, Achieva; Philips Medical Systems, Best, the Netherlands). These metastatic lesions oppressed hepatic capsulitis (Fig. 3a). His prognosis was thought to be only a few months, and he wanted to remain at his home for the end of his life. Despite the use of an adequate dosage of opioid analgesics, his hypochondrial pain did not improve. This prevented him from being discharged from the hospital. At that time, his liver function was Child–Pugh Class B (no encephalopathy, no ascites, total bilirubin level: 2.7 mg/dL, albumin level: 2.3 g/dL, PT activity: 91.8%). After thorough discussion of treatment options with the patient, informed consent was given to perform palliative low-dose whole-liver radiation therapy (WLRT) (Fig. 3b). The dose of WLRT administered was 30 Gy in 10 fractions. The coverage of 95% of planned treatment volume was 30 Gy. He developed Grade 2 nausea, but his right hypochondrial pain reduced and the liver dysfunction was improved (total bilirubin: 2.7 → 1.2 mg/dL, aspartate aminotransferase: 53 → 35 IU/L, alanine aminotransferase: 10 → 13 IU/L, lactate dehydrogenase: 1813 → 863 IU/L). Thus, he successfully completed radiotherapy. Seven days after the palliative WLRT, his anemia progressed. Lower gastrointestinal endoscopy revealed recurrent bleeding from the tumor. It was difficult to completely stop the bleeding via endoscopy, so eight units of blood were transfused. Five months after the initial RT, the rectal cancer was re-irradiated. The prescribed dose was 15 Gy in 5 fractions (Fig. 4). He wished to return home as soon as possible, so we had to plan a short treatment course. On the 28th hospital day, he was discharged after confirmation that the anemia had not progressed. He succumbed to the disease after 7 weeks of re-irradiation (Fig. 5). During this period, he was free from right hypochondrial pain and abdominal fullness and there was no recurrence of bleeding from the tumor.

Discussion

Bleeding from unresectable digestive cancer sometimes reduces a patient's quality of life. There are many ways to stop bleeding from digestive cancer including endoscopic hemostasis, surgery, and vascular embolization. A number of reports have been published about palliative hemostatic irradiation for digestive cancer, but there have been no Phase III studies on this; the dose fractionation also remains controversial. Furthermore, only one case report could be found on the topic of palliative re-irradiation for gastric cancer with bleeding [2] and no mass study has been conducted about palliative re-irradiation for colon cancer.

Our first prescribed dose was relatively higher (39 Gy in 13 fractions) than that typically used for hemostasis

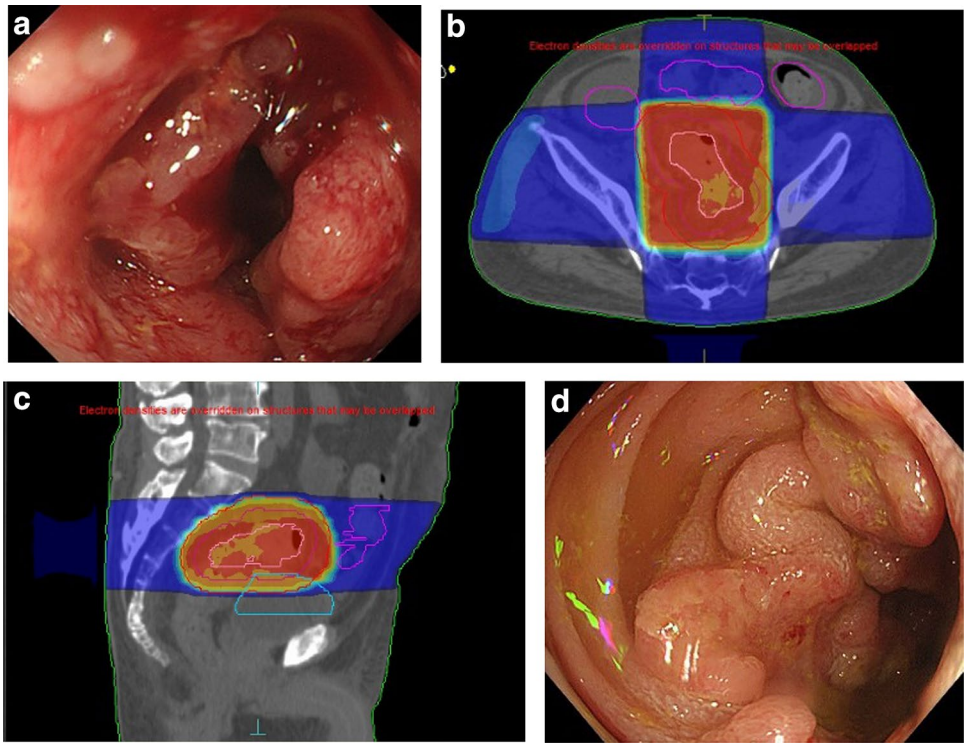

Fig. 2 **a** Lower colonal endoscopic examination when he presented with hematochezia (before hemostasis radiotherapy). **b** Abdominal computed tomography. Orange area is the target zone of hemostasis radiotherapy. Pink line shows outer wall of rectal cancer (Gross target volume). The red color zone indicates 100% of prescribed dose (39 Gy). The green color zone indicates 95% of prescribed dose. The blue color zone indicates 50% of prescribed dose. **c** Sagittal image of abdominal computed tomography before first irradiation to the rectal cancer. **d** Lower colonal endoscopic examination that was performed 1 month after hemostasis radiotherapy

radiotherapy for gastric cancer (20–30 Gy) [3–5]. The radiotherapy administered was based on the previous studies [6]. The radiation dose may be reduced when used for treatment of gastric cancer. However, in this case, frequent blood transfusions were needed before the first palliative irradiation, and it was difficult for the patient to return to our hospital frequently because he lived far away. Hence, our treatment plan was to increase the dosage as much as possible within safe limits.

On the other hand, there are not many studies about palliative WLRT for relief of right hypochondrial pain or sensations of fullness, and there is no consensus about safe dose fractionation or duration to prevent radiation induced hepatitis. To the best of our knowledge, there are 9 studies about low-dose palliative radiotherapy alone for liver metastases (Table 1: [7–15]) (searching on the PubMed, from 1954 to 2018). In these studies, patients received WLRT with 1.5–8 Gy fractions per day up to 8–37.5 Gy. Median survival was 10–20 weeks among the 5 traceable studies. The analysis of the primary site in the 9 previous studies revealed that most of the primary sites were the colon and rectum, followed by the stomach, lung, and pancreas (Fig. 6). Only one study of palliative WLRT compared its efficacy and complications in hepatocellular carcinoma (HCC) with liver metastases [14] and reported no significant differences between the two categories. Hoyer et al. recommended 2 Gy fractions of up to 30–35 Gy for palliative WLRT in a 2012 critical review [16]. To summarize the previous studies of WLRT, the appropriate population and advantage or disadvantage of palliative WLRT are as follows: the appropriate population are patients with symptoms (pain, abdominal discomfort, etc.) of liver metastasis or HCC. The advantage or main target of palliative WLRT is to improve the quality of life of patients by reducing the compression symptom and improving liver dysfunction caused by the occlusion of the intrahepatic bile duct. The disadvantage of this therapy is the same as the general complication of irradiation. In addition, an irradiation dose greater than the liver tolerance level confers a risk of acute hepatic insufficiency.

In this case, we chose 30 Gy in 10 fractions based on the literature to avoid radiation-induced hepatitis. The patient's right hypochondrial pain and sense of abdominal distension was improved. In the case of multiple metastases in the liver spreading to whole liver and causing liver dysfunction, we cannot expect a long-term prognosis. For this reason, we prioritized symptomatic improvement using short-term radiotherapy and gave less consideration to the delayed toxicity. This was the rationale for the 10-day radiation this time, so we administered 30 Gy in 10 fractions. The liver dysfunction improved and radiation-induced hepatitis did not develop. We did not measure the pain scale score this time, but the patient's complaints of abdominal pain disappeared. Re-irradiation to the rectal cancer was carried out with 15 Gy in 5 fractions. The rationale for this dose fraction was as follows: first of all, we had already reported successful salvage of hemostasis via twice radiotherapy for gastric cancer (the salvage dose was 15 Gy) [17–19]. The patients did

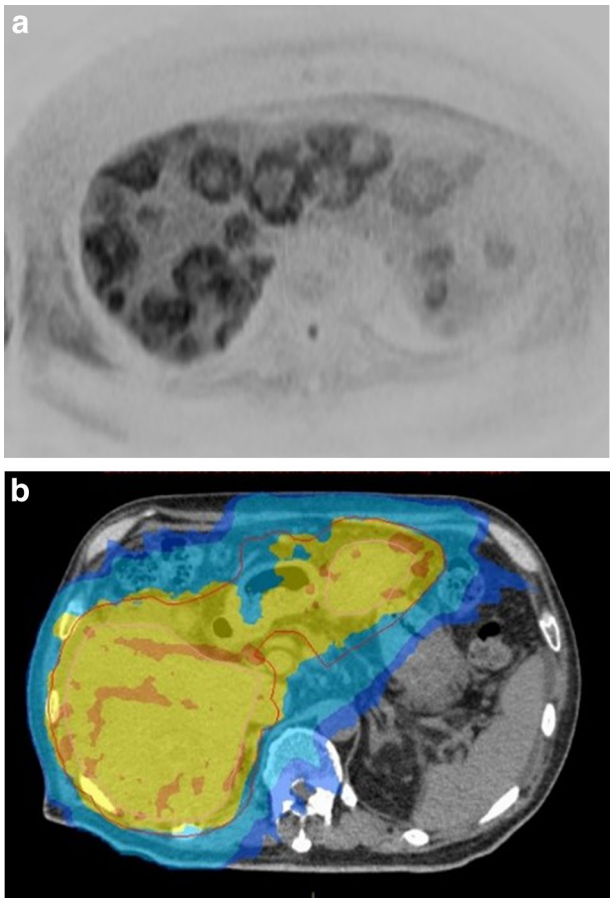

Fig. 3 **a** Abdominal diffusion-weighted magnetic resonance imaging showed the progression of multiple liver metastases. **b** Abdominal computed tomography of the target zone of palliative low-dose whole-liver radiation therapy. Gross target volume is the whole liver. The yellow color zone indicates 100% of prescribed dose (30 Gy). The light blue color zone indicates 95% of prescribed dose. The blue color zone indicates 50% of prescribed dose

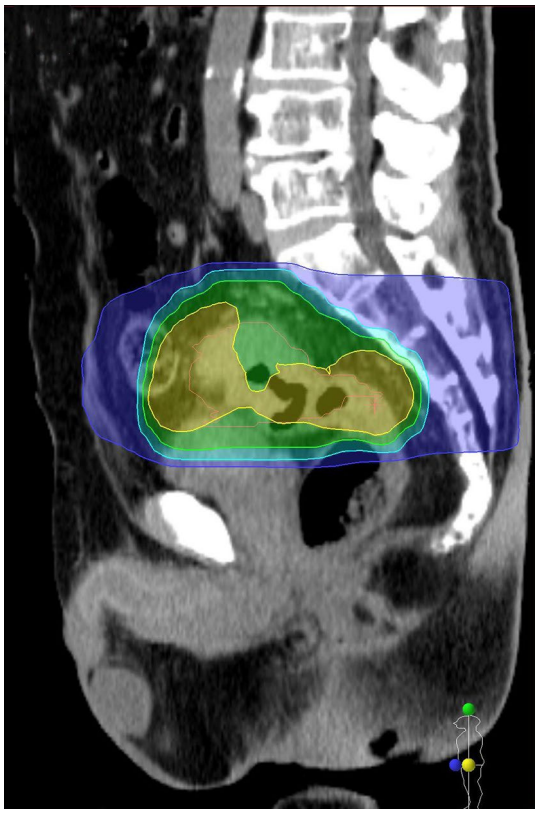

Fig. 4 Sagittal image of abdominal computed tomography before re-irradiation to the rectal cancer

not develop Grade 2 or worse adverse events. Hemostasis re-irradiation was carried out based on those reports. The tolerable doses of the rectum and colon are different. In general, the rectum and colon can tolerate up to 60 and 45 Gy, respectively [20]. In this case, the total dose was 54 Gy, so for the surrounding colon, the total dose seems high. However, the rectum is difficult to irradiate while partially avoiding the colon, because the rectal cancer is located in the pelvis.

Second of all, we had to plan a short treatment period because the prognosis was poor and he wished to return home as soon as possible. No complication developed and he was able to spend his remaining time at home without any episode of gastrointestinal bleeding. He passed away 7 weeks after discharge due to deterioration of his general condition.

Conclusion

This case of unresectable advanced rectal cancer with liver metastases was successfully treated with re-irradiation to the rectal cancer and palliative low-dose whole-liver radiation therapy. We believe that palliative radiotherapy can be useful for patients with a poor prognosis.

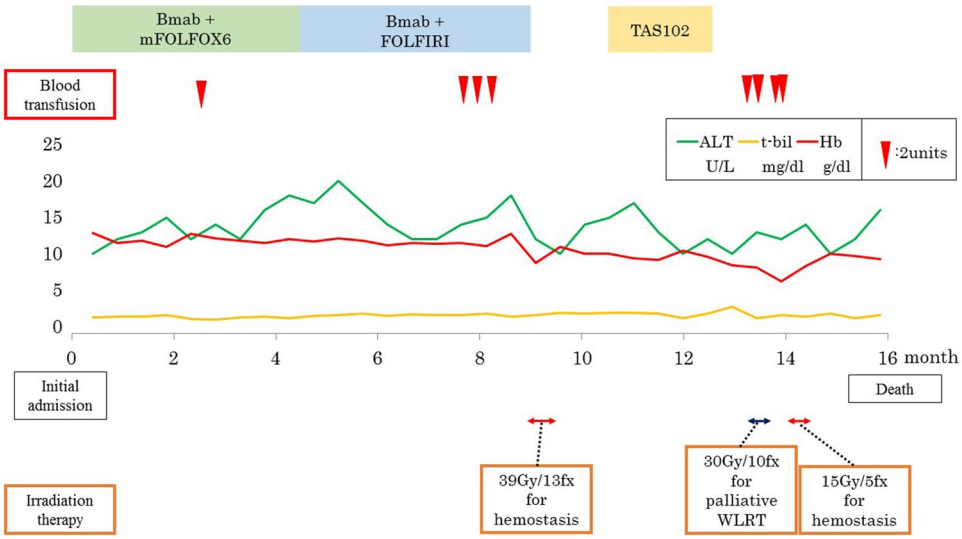

Fig. 5 His clinical course from initial admission to death with laboratory data

Table 1 Past studies about low-dose palliative radiotherapy alone for liver metastases

No.	Year	Number of patients	Dose fractionation (Gy)	Single dose (Gy)	Interval	Median survival	References
1	1954	36	20–37.5			–	[7]
2	1975	11	25	1.5	Everyday	–	[8]
3	1977	20	19–31			–	[9]
4	1978	55	24	3	Everyday	20 w	[10]
5	1981	109	21–30	1.6–3	Everyday	11 w	[11]
6	1993	173	27–33	1.6	Twice a day	17 w	[12]
7	2003	28	10	5	2 days	10 w	[13]
8	2013	41	8	7–8	1 day	–	[14]
9	2015	27	9–18	1.5–1.8	Everyday	19.6 w	[15]

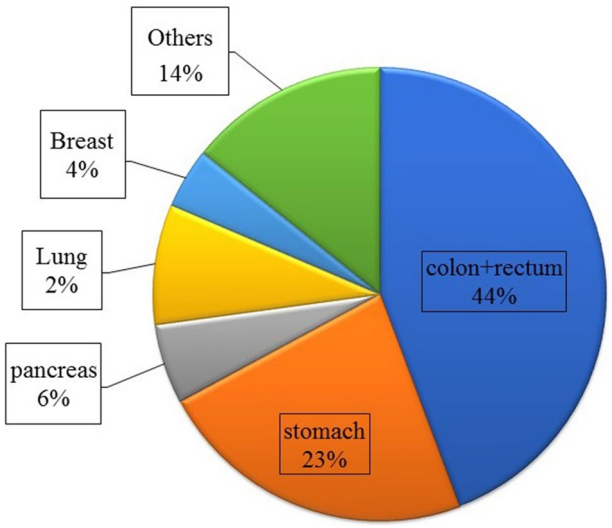

Fig. 6 Analysis of the primary site in past 9 studies revealed colon and rectum are most common and the second most common primary site was the stomach

Compliance with ethical standards

Conflict of interest Takeshi Yasuda, Osamu Tanaka, Sadanari Hayashi, Yuki Nakahata, Yuriko Yasuda, Tatsushi Omatsu, Akihiro Obora, Takao Kojima, Masayuki Matsuo and Nobuaki Yagi have no conflict of interest.

Informed consent Informed consent was obtained from the patient for being included in the study.

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