A case of successful cure of rectal adenocarcinoma and synchronous multiple hepatic metastases with massive biliary tumor thrombi by two-stage surgery and systemic therapy

Masanori Tsujie · Takao Tamura · Kotaro Kitani · Sayuri Isono · Katsuaki Sato · Koki Kimura · Mitsunori Ikeda · Mitsuru Iwama · Tsuyoshi Nakayama · Yoshinori Fujiwara · Masao Yukawa · Masahiro Watatani · Yoshio Ohta · Masatoshi Inoue

Received: 24 October 2012 / Accepted: 19 November 2012 / Published online: 20 December 2012
© The Japan Society of Clinical Oncology 2012

Abstract A 71-year-old female presented to our hospital with recent increase in diarrhea and body weight loss. Radiologic and endoscopic examinations revealed rectal adenocarcinoma with synchronous multiple liver metastases accompanied by widespread intrabiliary tumor thrombi. After primary tumor resection, systemic treatment using 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX), 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI), and panitumumab was given. The disease responded well to treatment and about two years after rectal surgery she underwent left hemihepatectomy with removal of tumor thrombi. Histological examination showed that intrahepatic bile ducts were filled with tumor thrombi indicative of a tubular adenocarcinoma resembling rectal adenocarcinoma. No tumor invasion was observed on the surgical margins. She received 5-fluorouracil and leucovorin as adjuvant treatment for six months, and she has not shown any evidence of recurrence for one year after hepatectomy.

Keywords Liver metastasis · Rectal cancer · Intrabiliary tumor thrombus

Introduction

Liver metastasis is the most common metastatic pattern in colorectal cancer (CRC). Approximately 10 % of all patients with CRC present with synchronous liver metastases in Japan [1]. The only therapeutic option for a possible cure against hepatic lesions is a surgical resection, which has been reported to be associated with a 27–40 % 5-year survival and give a survival advantage compared to patients not undergoing resection [2–5]. Moreover, with the development of more efficient cytotoxic and molecular targeted therapies, the opportunity of conversion of unresectable lesions into resectable ones by systemic treatment, so-called conversion therapy, has been increasing [6–12]. Here we report the case of rectal adenocarcinoma with synchronous multiple liver metastases accompanied by massive intrabiliary tumor growth successfully resected by two-stage surgery in combination with systemic therapies.

Case report

A 71-year-old female presented with recent increase in diarrhea, general fatigue, and body weight loss. Physical examination disclosed a palpable mass in epigastric region. Hematologic tests showed anemia [hemoglobin (Hb), 8.0 g/dL]. Biochemical tests showed high levels of tumor markers [carcinoembryonic antigen (CEA), 179.4 ng/mL; carbohydrate antigen (CA) 19-9, 216.6 U/mL], and biliary enzymes [alkaline phosphatase (ALP), 2178 U/L;

M. Tsujie (✉) · K. Kitani · S. Isono · K. Sato · K. Kimura · M. Ikeda · M. Iwama · T. Nakayama · Y. Fujiwara · M. Yukawa · M. Watatani · M. Inoue
Department of Surgery, Nara Hospital, Kinki University Faculty of Medicine, Otoda-chou 1248-1, Ikoma, Nara 630-0293, Japan
e-mail: tsujie@nara.med.kindai.ac.jp

T. Tamura
Department of Medical Oncology, Nara Hospital, Kinki University Faculty of Medicine, Otoda-chou 1248-1, Ikoma, Nara 630-0293, Japan

Y. Ohta
Department of Pathology, Nara Hospital, Kinki University Faculty of Medicine, Otoda-chou 1248-1, Ikoma, Nara 630-0293, Japan

gamma-glutamyl transpeptidase (γ -GTP), 727 U/L]. An inflammatory response was also higher than normal [WBC, 10400/ μ L; CRP, 1.19 mg/mL]. The colonoscopy showed an obstructive rectal tumor and a biopsy revealed a tubular adenocarcinoma. A computed tomography (CT) identified synchronous bilobar multiple liver metastases with widespread biliary tumor thrombi (Fig. 1). Magnetic resonance imaging (MRI) showed that tumor thrombi were extending into the right and left hepatic ducts causing cholangioec-tasis of peripheral biliary ducts (Fig. 2). Because there was no surgical indication for hepatic metastases, we planned to perform rectal cancer resection followed by systemic chemotherapy. She underwent Hartmann's operation in September 2009 (Fig. 3). Histological diagnosis of the

Fig. 1 An enhanced abdominal CT shows bilobar multiple low density area in the liver. The intrabiliary tumor thrombi are also observed (arrowheads)

Fig. 2 An abdominal MRI shows widespread biliary tumor thrombi extending into right and left hepatic ducts

Fig. 3 Macroscopic findings of the resected specimen of rectal adenocarcinoma

Fig. 4 Microscopic findings of the primary tumor indicate a well-differentiated adenocarcinoma

specimen was a well-differentiated adenocarcinoma (Fig. 4) invading into the uterine tube. There was no metastasis at the dissected lymph nodes.

After 30 days from surgery, 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) was initiated (Fig. 5). Between October 2009 and September 2010, a total of 23 courses of FOLFOX were given, and partial response (PR) with the marked decrease of CEA level was observed (Figs. 5, 6). In October 2010, an increase of CEA level was observed. Because the recovery from myelosuppression was delayed and the allergic reaction to FOLFOX occurred, we chose panitumumab alone instead of panitumumab with 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI). The disease showed PR again with CEA level dropping to normal (Figs. 5, 7), and 12 courses of panitumumab were given. Because of the augmentation of hepatic lesions and the occurrence of severe perionychia, FOLFIRI regimen was started in April 2011 (Fig. 5).

Fig. 5 Treatment schedule and the level of carcinoembryonic antigen (CEA). *Op* operation, *FOLFOX* 5-fluorouracil, leucovorin, and oxaliplatin, *FOLFIRI* 5-fluorouracil, leucovorin, and irinotecan, *Pani* panitumumab, *5-FU* 5-fluorouracil, *LV* leucovorin

Fig. 6 An abdominal CT after 20 courses of FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) shows partial response

After two courses of FOLFIRI, the CEA level increased again (Fig. 5). Therefore, panitumumab was added to FOLFIRI in July 2011 (Fig. 5). Until August 2011, seven courses of FOLFIRI and 16 courses of panitumumab were administered in total.

During about two years of systemic treatment, the macroscopic liver metastases and biliary tumor thrombi in the right lobe disappeared (Figs. 7, 8). Although the hepatic lesions in the left lobe also shrank, intrabiliary tumor thrombi deteriorated (Fig. 8). In order to investigate the range of extension of the tumor thrombi, endoscopic retrograde cholangiography (ERC) was performed (Fig. 9).

Although the thrombi extended into the left hepatic duct, the right hepatic duct and the common hepatic duct appeared intact. Therefore, we planned to perform resection of the whole hepatic lesions. In September 2011, she underwent left hemihepatectomy with the removal of intrabiliary tumor thrombi (Fig. 10).

Histological examination showed moderately differentiated tubular adenocarcinoma in the liver spreading into the biliary duct and causing cholangiectasis (Fig. 11). The metastases in the liver degenerated or underwent necrosis with calcification probably because of the effective systemic treatment. No tumor invasion was observed in the cut end of the left hepatic duct and the liver cut surface. Microscopic findings of the liver showed severe fibrosis, sinusoidal dilatation, and mild steatosis (Fig. 12).

Adjuvant chemotherapy using 5-fluorouracil and leucovorin was performed for six months, and she has not shown any evidence of recurrence for one year after hepatectomy.

Discussion

The incidence of colorectal liver metastases with macroscopic intrabiliary tumor growth has been reported to account for more than 10 % among surgically resected cases [13]. However, the rate of resectable synchronous liver metastases with macroscopic biliary tumor thrombi is very low. Okano et al. [13] reported that only one (6 %) out of 18 CRC patients with resectable macroscopic intrabiliary tumor growth had synchronous liver metastases.

Fig. 7 An abdominal CT after four courses of panitumumab shows partial response again and macroscopic liver metastases in the right lobe disappear

Fig. 8 An abdominal CT just before hepatectomy shows intrabiliary tumor growth in the left hepatic duct (arrowhead)

Sugiura et al. [14] reported that synchronous hepatic metastasis was observed in only one out of six CRC patients with resectable gross intrabiliary tumor thrombi. These results are compatible with the fact that the synchronous hepatic metastasis is an unfavorable factor for operability when compared with the metachronous type. In this case, however, the systemic treatment using FOLFOX, FOLFIRI, and panitumumab after primary tumor resection made it possible to perform successful resection of synchronous multiple liver metastases with widespread intrabiliary tumor growth. To the best of our knowledge, this is the first case report of liver metastasis with biliary tumor thrombi from CRC with successful downstaging from unresectable to resectable liver tumors after hepatectomy.

When FOLFOX treatment showed progressive disease (PD), the FOLFIRI regimen with or without cetuximab or

Fig. 9 An endoscopic retrograde cholangiography reveals that the right hepatic duct and common hepatic duct appear intact although the tumor thrombi extend into the left hepatic duct (arrowheads)

panitumumab is recommended for patients with wild-type KRAS tumors. In our case, FOLFOX showed good response and was well tolerated, and a total of 23 cycles of FOLFOX were administered until disease progression was observed. Because of the delayed myelosuppression and the occurrence of possible allergic reaction to 5-fluorouracil, we planned to choose panitumumab alone following FOLFOX instead of the combination treatment of FOLFIRI and panitumumab. The disease showed PR again, and we kept administering panitumumab alone without any cytotoxic drugs for about six months. These sequential good responses to different types of systemic treatments enabled the patient to undergo curative resection. Retrospective examination of the treatment course implies that the optimal timing of the conversion therapy could be earlier after panitumumab was given. However, at that time, we were able to still choose FOLFIRI, which is as promising as FOLFOX. Therefore, when panitumumab failed, FOLFIRI treatment was selected instead of liver resection.

In our case, massive intrabiliary tumor growth spread into the right and left hepatic ducts but did not cause obstructive jaundice. Sugiura et al. [14] also reported that only one out of six patients with intrabiliary tumor growth developed jaundice. This might be because of the expansive, noninvasive nature of the biliary tumor thrombi. In fact, the tumor thrombus of this case was very soft and neither invasive nor adhesive to the main bile duct wall.

In conclusion, recent advances in systemic treatment make it possible to have more opportunities to convert unresectable colorectal liver metastases into surgically resectable lesions, even when the tumor is accompanied by macroscopic biliary tumor thrombus. Therefore, surgeons and medical oncologists should cooperate closely to choose the best treatment including surgical resection.

Fig. 10 **a** Resected specimen of hepatic metastases. **b** Macroscopically, the tumor thrombi are located in the left hepatic duct (arrowheads). The thrombi are soft and are not invasive to the bile duct wall

Fig. 11 Histological findings of the intrabiliary tumor. The intrahepatic bile ducts are filled with tumor thrombi, which are indicative of a tubular adenocarcinoma and resemble the rectal adenocarcinoma

Fig. 12 Microscopic findings of the liver shows severe fibrosis, sinusoidal dilatation, and slight fatty degeneration

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Okuno K (2007) Surgical treatment for digestive cancer. Current issues—colon cancer. *Dig Surg* 24:108–114
2. Sasson AR, Sigurdson ER (2002) Surgical treatment of liver metastases. *Semin Oncol* 29:107–118
3. Martin LW, Warren RS (2000) Current management of colorectal liver metastases. *Surg Oncol Clin N Am* 9:853–876
4. Penna C, Nordlinger B (2003) Surgery and local treatments of liver metastases from colorectal cancer: how to improve results. *Scand J Surg* 92:90–96
5. Kato T, Yasui K, Hirai T et al (2003) Therapeutic results for hepatic metastasis of colorectal cancer with special reference to effectiveness of hepatectomy: analysis of prognostic factors for 763 cases recorded at 18 institutions. *Dis Colon Rectum* 46:S22–S31
6. Alberts SR, Horvath WL, Sternfeld WC et al (2005) Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a north central cancer treatment group phase II study. *J Clin Oncol* 23:9243–9249
7. Falcone A, Ricci S, Brunetti I et al (2007) Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 25:1670–1676
8. Coskun U, Buyukberber S, Yaman E et al (2008) Xelox (capecitabine plus oxaliplatin) as neoadjuvant chemotherapy of unresectable liver metastases in colorectal cancer patients. *Neoplasma* 55:65–70
9. Skof E, Rebersek M, Hlebanja Z et al (2009) Capecitabine plus irinotecan (XELIRI regimen) compared to 5-FU/LV plus irinotecan (FOLFIRI regimen) as neoadjuvant treatment for patients with unresectable liver-only metastases of metastatic colorectal cancer: a randomised prospective phase II trial. *BMC Cancer* 9:120–128
10. Min BS, Kim NK, Ahn JB et al (2007) Cetuximab in combination with 5-fluorouracil, leucovorin and irinotecan as a neoadjuvant chemotherapy in patients with initially unresectable colorectal liver metastases. *Onkologie* 30:637–643
11. Van Cutsem E, Rivera F, Berry S et al (2009) Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and

- fluoropyrimidines in metastatic colorectal cancer: the BEAT study. *Ann Oncol* 20:1842–1847
12. Folprecht G, Gruenberger T, Bechstein WO et al (2010) Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol* 11:38–47
 13. Okano K, Yamamoto J, Moriya Y et al (1999) Macroscopic intrabiliary growth of liver metastases from colorectal cancer. *Surgery* 126:829–834
 14. Sugiura T, Nagino M, Oda K et al (2006) Hepatectomy for colorectal liver metastases with macroscopic intrabiliary tumor growth. *World J Surg* 30:1902–1908