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SHORT COMMUNICATION

Pathologic complete response after palliative 3rd line chemotherapy with capecitabine alone in metastatic colorectal cancer

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Abstract We report the case of a 46-year-old female who showed excellent clinical outcomes after palliative 3rd line capecitabine monotherapy followed by 2nd liver metastasectomy. She had been diagnosed with colon cancer with liver metastasis and initially treated with synchronous colectomy and liver metastasectomy. But she experienced immediate relapse in liver and received palliative 1st line FOLFIRI and 2nd line FOLFOX, both of which failed to show responses. Capecitabine alone as palliative 3rd line treatment did show clinical response in this patient, indeed, and she received 2nd liver metastasectomy which revealed pathologic complete response. In this report, we intended to emphasize that response to chemotherapy could be an important factor in patients who are potential candidates for metastasectomy and that catching the very moment of repeated metastasectomy is in the state of the art.

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Introduction

Capecitabine monotherapy in metastatic colorectal cancer (mCRC) is known to show about 20% response rate in 1st line chemotherapy and rare objective response in patients previously treated with fluoropyrimidines. Here, we present the case of a patient who achieved pathologic complete response with 2nd liver resection after 3rd line palliative capecitabine monotherapy. This patient experienced immediate relapse after curative surgery in liver with multiple metastatic lesions unfortunately, and to make matters worse, she did not respond to either 1st line FOLFIRI or 2nd line FOLFOX6. She was compelled to be treated with capecitabine monotherapy as 3rd line treatment, which is not recommended in current guidelines. She did show clinical response to this unwilling 3rd line chemotherapy with capecitabine alone, did catch her second opportunity for curative surgery and then finally did achieve pathologic complete response. In this case, we intend to discuss and consider the role of preoperative chemotherapy in mCRC and the very moment of metastasectomy.

Case report

A 46-year-old female was diagnosed with ascending colon cancer with multiple liver metastases in her routine medical examination at September 2006. She had no relevant previous medical history. Colonoscopic finding revealed a fungating mass at ascending colon (Fig. 1a) and pathologic diagnosis was well-differentiated adenocarcinoma (Fig. 1b). Initial serum carcinoembryonic antigen (CEA) level was 55.0 ng/ml and an abdominal computed tomographic (CT) finding revealed multiple metastatic lesions mainly in right lobe of liver (Fig. 1c). She received right hemicolectomy

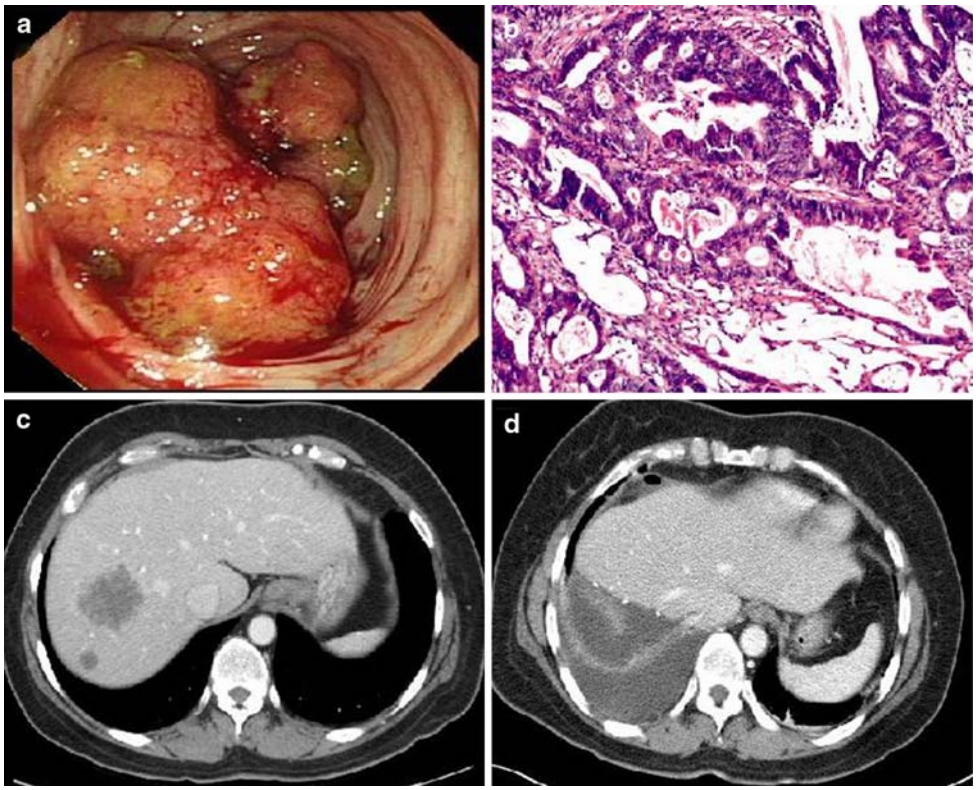

Fig. 1 **a** Initial colonocopic finding, **b** microscopic finding, **c** initial computed tomography of muliple liver metastases, **d** computed tomography after first metastasectomy

with right hemihepatectomy and segment IV tumorectomy of curative intent on 9 October 2006, and final pathologic diagnosis was T2N1M1; well-differentiated adenocarcinoma with mucinous component (40%), proper muscle invasion (T2), 2 out of 24 regional lymph nodes (N1) and 7 metastatic adenocarcinomas in liver (M1). Of 7 metastatic lesions in liver, 6 in right lobe and 1 in segment IV of liver, the largest tumor size was 5.7 cm in diameter and the very closest safety margin was measured to be 0.5 mm. Postoperative CEA level decreased to 0.7 ng/ml, and postoperative CT findings revealed no residual metastatic lesion was present (Fig. 1d).

Immediate postoperative chemotherapy was planned but delayed for about 1 month because of wound problems, and when she was admitted for chemotherapy after wound problems were resolved, two metastatic lesions were newly found in liver at CT taken on 1 December 2006 (Fig. 2a, b). Serum CEA level at that time was 2.6 ng/ml. She was initially treated with simplified FOLFIRI (irinotecan 180 mg/m^2, leucovorin (LV) 200 mg/m^2, 5-fluorouracil (5-FU) 400 mg/m^2 bolus on day 1 and 5-FU 2,400 mg/m^2 continuous infusion for 46 h) as 1st line palliative chemotherapy. Response after three cycles of FOLFIRI was progressive disease, and then she received three cycles of FOLFOX6 (oxaliplatin 85 mg/m^2, LV 200 mg/m^2, 5-FU 400 mg/m^2 bolus on day 1 and 5-FU 2,400 mg/m^2 continuous infusion for 46 h) as 2nd line palliative chemotherapy whose response was also progressive disease (Fig. 2c, d). Serum CEA level increased to 6.7 ng/ml after three cycles of FOLFIRI and 13.7 ng/ml after three cycles of FOLFOX6, respectively. She could not afford any targeted agent such as cetuximab because of her financial problems, thus capecitabine alone (2,500 mg/m^2/day on days 1–14 in a 3-week schedule) was administered as 3rd line palliative chemotherapy. Six cycles of capecitabine were performed between April 2007 and September 2007, and two dose reductions with two cycle delays were made due to repeated occurrences of grade 3 hand-foot syndrome. Serum CEA level decreased from 13.7 to 1.9 ng/ml after the third cycle and to 3.9 ng/ml after the 6th cycle of capecitabine monotherapy. The CT findings after the 6th cycle of capecitabine alone revealed disease stabilization (Fig. 2e, f), but we valued these results combined with CEA decrements as maximal response. So we planned second metastasectomy of liver for her treatment of curative intent.

She underwent second metastasectomy of liver as treatment of curative intent on 4 October 2007. This surgery was performed safely without any event or complication (Fig. 3a, b). Serum CEA level after this second surgery was 2.2 ng/ml. Pathologic examination of two metastatic lesions in liver revealed no viable tumor only with acellular mucin pools (Fig. 3c). These findings were compatible with pathologic complete response to capecitabine monotherapy.

She recovered without any event from her second surgery and continued to be treated with capecitabine alone from 1 November 2007. She will be treated with additional

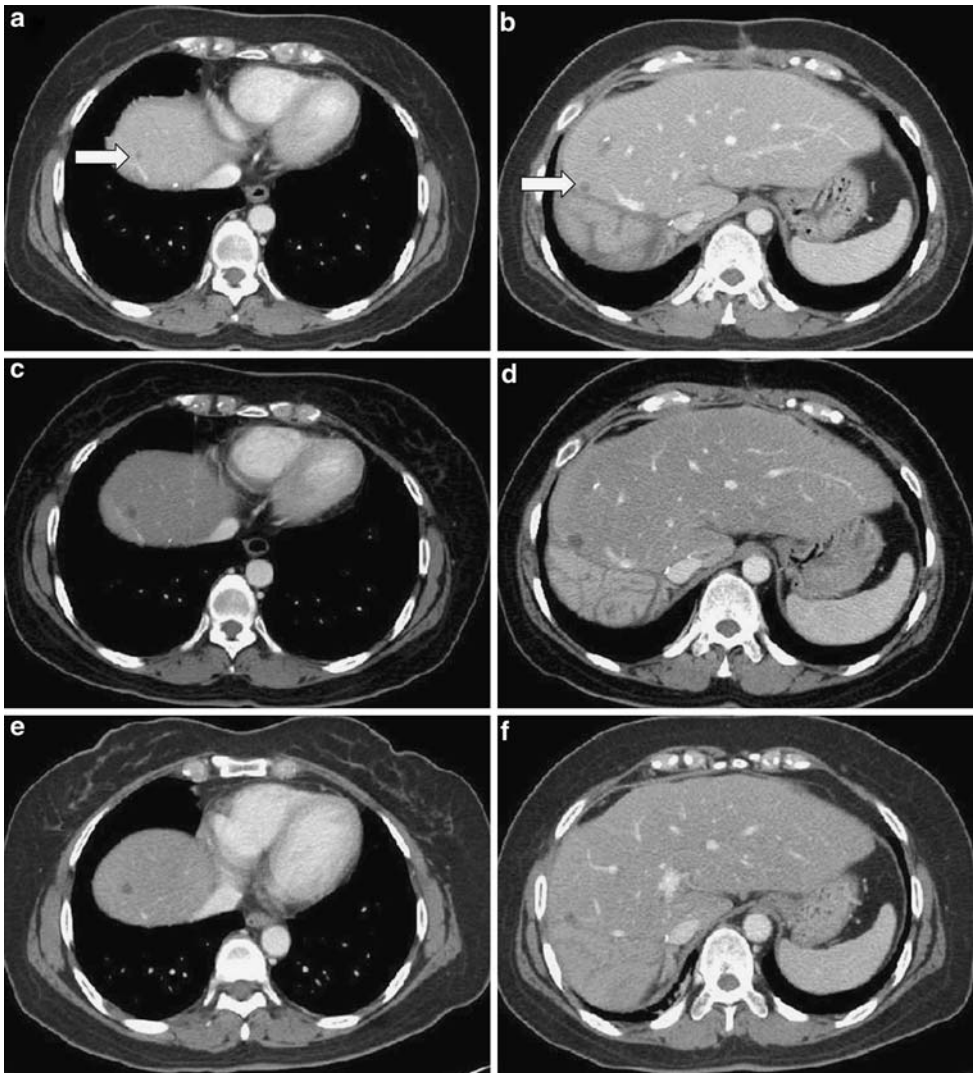

Fig. 2 **a**, **b** New liver metastases (*arrow*) detected at 7 weeks after first surgery. **c**, **d** Progressive disease after 2nd line chemotherapy. **e**, **f** Stable disease after 3rd line chemotherapy

6 cycles of capecitabine monotherapy and we expect that in spite of this she will maintain clinical and pathological complete response.

Discussion

Liver metastasectomy for patients with liver metastasis of colorectal cancer is still the only hope for cure despite the recent advances of 1st line palliative chemotherapy [6, 7, 15]. The 5-year survival rates in patients who underwent liver resection ranged from 30 to 40% compared to about 5% in patients who were not treated with surgical resection [10, 25]. However, most of these cases of liver metastasis were initially considered to be unresectable with current criteria for liver resection; only about 10 to 20% of patients can be treated with surgery of curative intent [11, 16, 24]. Factors associated with poor prognosis after liver metastasectomy include positive resection margin, presence of extrahepatic metastasis, prior lymph node positivity of primary tumor, shorter disease-free interval, multiple metastatic lesions, larger tumor size, high CEA level and high grade of histology [2, 11]. In our patient, several poor prognostic factors were present; multiple metastatic lesions, high serum CEA level, lymph node positivity of primary tumor and a 5.7-cm-sized largest metastatic tumor. Of course, someone would have a thought that initial surgery should not be performed in this patient. Initial surgery for colon cancer with synchronous multiple liver metastasis is still controversial, but among these poor prognostic factors, multiplicity and extrahepatic metastasis would not be a contraindication anymore if all of them could be resected and not a few number of long-term survivors were reported [8, 12, 16, 25].

Several efforts were made to improve resectability and survival in patients with metastatic colorectal cancer who could be potential candidates for metastasectomy; neoadjuvant chemotherapy, preoperative portal vein embolization,

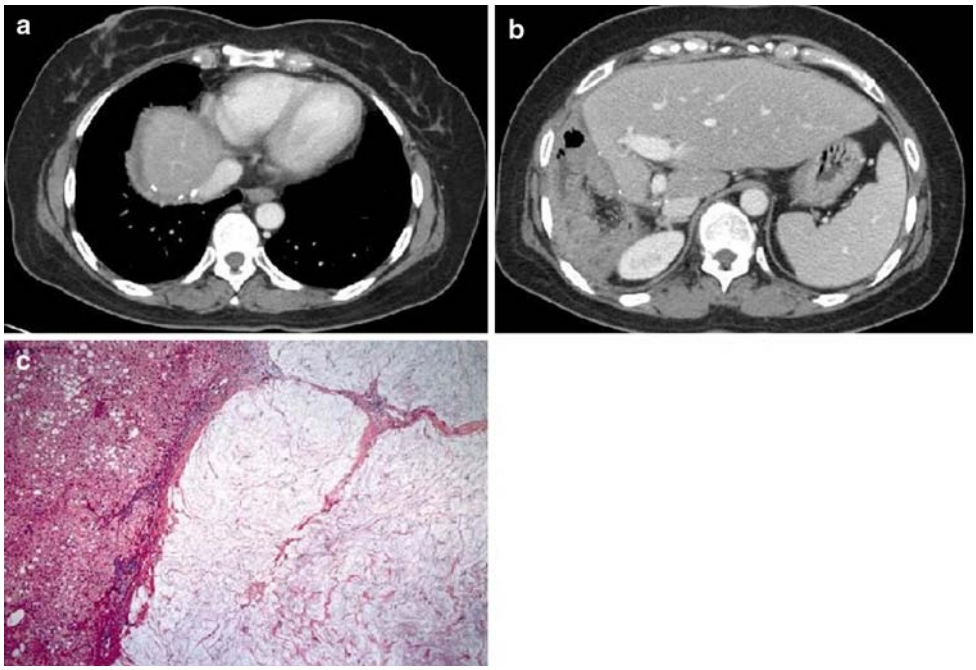

Fig. 3 **a**, **b** Computed tomography after second metastasectomy. **c** Microscopic finding of resected tumor

intraoperative local treatment modalities and repeated liver resections [4, 5, 9, 20–23]. In many of these trials, neoadjuvant chemotherapy for potentially resectable disease or initially unresectable disease is in the limelight of clinical practice recently. Chemotherapeutic agents for neoadjuvant settings are the same for those of metastatic settings; oxaliplatin or irinotecan plus fluoropyrimidines with or without targeted agents. Not only improved resectability but also improved overall survival was reported in several trials [20–22]; thus preoperative chemotherapy for metastatic colorectal cancer could be a reasonable option for patients considered to be treated with metastasectomy.

Neoadjuvant chemotherapy should be effective in terms of response rate to improve resectability and prevent disease progression before resection, thus trials mentioned earlier adopted most effective chemotherapeutic agents as 1st line settings. Response to chemotherapy is one of the many prognostic indicators for further liver resection [1]. Adam et al. reported 5-year overall survival rate was much lower for patients who progressed after preoperative chemotherapy (8%) than for those who showed partial response (37%) or stable disease (30%) ($P < 0.0001$). Five-year disease free survival rate was also lower for patients with disease progression (3%) than those with partial response (21%) or stable disease (20%) ($P = 0.02$). All patients in this study were previously untreated which means they were treated with 1st line chemotherapy before surgery. Then, could we consider surgical resection of metastasis whenever patients are responsive to chemotherapy, regardless of previous treatments: 2nd line or 3rd line chemotherapy?

Capecitabine alone showed about 20% of response rate as 1st line palliative chemotherapy [27], thus capecitabine monotherapy for 1st line neoadjuvant setting should not be recommended because of its lower response rate than other combination chemotherapy. Furthermore, capecitabine alone showed no or very few objective response in patients with fluorouracil-resistant disease in previous trials [13, 18], thus the current guideline of National Comprehensive Cancer Network (NCCN) does not recommend the use of single agent capecitabine as a salvage therapy after failure to a fluoropyrimidines-containing regimen. However, capecitabine as 3rd line treatment played a successful role of neoadjuvant chemotherapy in our patient and achieved pathologic complete response furthermore. Pathologic complete response rate of liver metastasis after 1st line FOLFOX4 was 24% (6/25) in a small study [3], but there was no report of pathologic CR after 3rd line chemotherapy.

It is uncertain why capecitabine alone achieved excellent response in our patient despite previous failure to FOLFIRI and FOLFOX. One possible explanation could be found in the individual variation of enzymatic activities, such as thymidine synthase (TS), thymidine phosphorylase (TP) and dihydropyrimidine dehydrogenase (DPD). Several trials on the correlations between these enzyme activities and clinical outcomes were reported, yet the controversy continues [14, 17, 26]. Another possible explanation is on the histologic subtype. A previous report is present on good response to capecitabine in patient with peritoneal carcinomatosis of mucinous histology [19]. Responses to chemotherapy could be different according to the histologic subtypes, but it still needs much more evidences.

In conclusion, we present an elated case of a patient who achieved pathologic complete response with 2nd liver

metastasectomy after 3rd line palliative capecitabine monotherapy which was always ignored, and this case could emphasize that response to chemotherapy at any time could be an important indicator for deciding a follow-up surgery of curative intent.

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