

Case Report

Two Cases of Long-Term Survival of Advanced Colorectal Cancer with Synchronous Lung Metastases Treated with mFOLFOX6/XELOX + Bevacizumab

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Keywords

Colorectal cancer · Complete response · Long-term survival · Bevacizumab · Lung metastasis

Abstract

Background: Colorectal cancer (CRC) with lung metastases has an unfavorable prognosis. However, nowadays, even advanced CRC can have a favorable outcome in certain cases. A complete response (CR) is a rare event in advanced CRC with lung metastases. Herein, we report 2 rare cases of advanced CRC attaining a CR. **Case Presentation:** Case 1 was a 58-year-old man who underwent laparoscopic ileocecal resection for cecum cancer with multiple metastases to the lungs in 2011. We performed treatment with mFOLFOX6 and bevacizumab chemotherapy in August 2011. After 11 courses, computed tomography (CT) revealed a CR to chemotherapy in February 2012. He has remained disease-free for 5 years and 3 months. Case 2 was a 70-year-old woman who underwent laparoscopic ileocecal resection for cecum cancer in August 2010. Recurrence of multiple metastases to both lungs was detected in November 2010. We started treatment with XELOX and bevacizumab chemotherapy in January 2011. In

January 2011, CT after 14 courses revealed disappearance of the lung lesions, thereby indicating a CR. She has remained disease-free for 5 years and 4 months. **Conclusion:** We encountered 2 patients with CRC with lung metastases who were treated with chemotherapy leading to a CR. Cases resulting in such a desirable outcome are extremely rare.

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Introduction

The prognosis of colorectal cancer (CRC) with lung metastases is extremely poor [1]. Formerly, pulmonary metastases indicated hematogenous dissemination and were indicative of incurable disease. Owing to advances in surgical treatment and drugs, CRC with pulmonary metastases is nowadays considered curable in select cases. The treatments for lung metastases in patients with CRC are slightly controversial, and there are no available evidence-based preoperative chemotherapy regimens. In addition, a long-term complete response (CR) is rare in advanced CRC with lung metastases. Here, we report the long-term survival of 2 patients with CRC with synchronous lung metastases who were treated with chemotherapy and achieved a CR.

Case Presentations

Case 1

A 58-year-old man visited his previous physicians with a complaint of right lower abdominal pain. He was referred to our hospital for a complete examination and treatment. His medical history revealed hypertension and hyperlipidemia. His carcinoembryonic antigen and carbohydrate antigen 19-9 (CA 19-9) levels were normal. Colonoscopy and enema examination revealed a type 2 tumor in the cecum with stenosis (Fig. 1a, b). Abdominal computed tomography (CT) demonstrated an enhanced and thickened cecum wall with multiple metastases to both lungs (Fig. 1c, 2a–d). His abdominal pain continued because of the subileus, and we considered surgery. A laparoscopic ileocecal resection with regional lymph node resection was performed in July 2011; the histological examination revealed poorly differentiated adenocarcinoma. The final diagnosis was T4a(SE)N0M1b stage IVB disease, according to the 7th Union for International Cancer Control guidelines. We administered mFOLFOX6 (tegafur, gimestat, and otastat potassium 5-fluorouracil [200 mg/m² i.v. bolus on day 1, followed by a 2,400 mg/m² i.v. continuous infusion over 46 h], levofolinate calcium [400 mg/m² i.v., on day 1], oxaliplatin [85 mg/m² i.v., on day 1]) and bevacizumab (5 mg/kg i.v., on day 1) chemotherapy in August 2011. The patient completed 12 courses of this regimen without severe adverse effects. He developed grade 1 nausea and grade 2 hypertension. CT after the 4th course demonstrated a reduction in the size of the lung lesions in October 2011 (Fig. 2e–h). After the 11th course in February 2012, the metastatic lung lesions showed a CR to chemotherapy on CT (Fig. 2i–l). He has remained disease-free for 5 years and 3 months since the last dose of chemotherapy.

Case 2

A 70-year-old woman with melena was referred to a previous hospital. She was diagnosed with rectal cancer and visited our hospital for treatment. Her medical history included hypertension, appendicitis, and bilateral breast cancer after mastectomy 4 years before. The

laboratory data, including serum levels of carcinoembryonic antigen and CA 19-9, showed no abnormalities. Colonoscopy and enema examination demonstrated a type 3 tumor in the rectosigmoid (Fig. 3a, b). CT revealed thickening of the left wall of the rectosigmoid with no apparent regional lymph nodes and distant metastasis (Fig. 3c). A laparoscopic low anterior resection with regional lymph node resection was performed in August 2010, and the histology revealed moderately differentiated adenocarcinoma. The final diagnosis was T3(SS)N0M0 stage II disease according to the 7th Union for International Cancer Control guidelines. Recurrences of multiple metastases to both lungs were detected in November 2010. Histological examination of biopsy specimens from the lung lesions suggested lung metastases from CRC (Fig. 4a–c). We started treatment with XELOX (capecitabine [orally twice daily 2,000 mg/m²/day, on days 1–15] and oxaliplatin [130 mg/m² i.v., on day 1]) and bevacizumab (5 mg/kg i.v., on day 1) chemotherapy in January 2011. After 2 courses, she developed grade 2 peripheral neuropathy according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0; therefore, we administered capecitabine monotherapy from the 3rd course onwards. Grade 3 hand-foot syndrome developed during the 6th course; therefore, the 7–9th courses were administered with a 20% dose reduction, and the 10–27th courses with a 40% dose reduction. CT after the 12th course demonstrated the disappearance of two-thirds of the lesions in October 2011 (Fig. 4g, h). In January 2012, CT after the 14th course revealed the disappearance of the last lung lesion (Fig. 4j), thereby indicating a CR. A total of 5 years and 4 months after attaining a CR, the patient is attending regular follow-ups and has not experienced recurrence or metastasis.

Discussion

CRC is the third most commonly diagnosed cancer in men and the second in women, causing about 61,000 deaths per year globally [2]. The Japanese Society for Cancer of the Colon and Rectum (JSCCR) reported the following 5-year survival rate in patients with metastatic CRC (mCRC): cecum, 12.5%; rectosigmoid, 19.8%; and all sites, 18.8% [1]. The incidence of synchronous lung metastasis is 2.4%; this is the third most common organ of metastasis after the liver in 10.9% and the peritoneum in 4.5% of cases [1]. Without treatment, patients with mCRC have an overall 5-year survival rate of less than 10% [3]. The approval of oxaliplatin, irinotecan, and monoclonal antibodies (MoAbs) has brought changes in chemotherapy for mCRC. Currently, first-line treatments for patients with mCRC comprise chemotherapy (FOLFOX, FOLFIRI, or XELOX) regimens combined with MoAbs (an epidermal growth factor receptor inhibitor or the vascular endothelial growth factor inhibitor bevacizumab) [4, 5].

A CR is a rare event in advanced CRC. A recent systematic review and meta-analysis indicated that the addition of MoAbs to first-line chemotherapy for advanced CRC showed a significantly higher CR rate of 2.4% (35/1,935 patients; 95% confidence interval [CI]: 1.7–3.3) than first-line chemotherapy only, which had a CR rate of 1.3% (15/1,700 patients; 95% CI: 0.8–2.2) [6]. When differences in the MoAb type were considered, a combination with bevacizumab had a much higher CR rate of 3.1% (29/1,058 patients) than all other MoAbs. Japanese cancer centers reported a phase I/II clinical study of XELOX plus bevacizumab as first-line therapy in mCRC [7]. The CR rate was 3.2% (2/63 patients), and all CR cases had the addition of bevacizumab. In our cases, bevacizumab might have contributed to the achievement of a CR and long-term survival.

The treatments for lung metastases in patients with CRC are surgery, chemotherapy, and radiotherapy. If the lung metastases are unresectable but the primary tumor is resectable,

primary tumor resection and systemic chemotherapy are recommended [1]. The resection of lung metastasis can be considered in cases in which chemotherapy has successfully made localized metastasis to the lungs operable; this depends on individual factors, such as clinical symptoms, the state of the metastasis, and the patient's general condition. However, there is no definitive consensus on the indication criteria for pneumonectomy or the continuation of valid chemotherapy, and there are no available evidence-based preoperative chemotherapy regimens. In our cases, there were multiple metastatic lesions in both lungs; thus, they were not considered an indication for surgery. We continued effective chemotherapy while taking indications for surgery into consideration, so that a CR was achieved in the metastatic lesions. Fortunately, the patients are well and have been without any signs of tumor recurrence after the discontinuation of chemotherapy for a long period.

Cases of a CR in CRC with lung metastasis are exceedingly rare, and to the best of our knowledge, there are no reports of similar patients. It is important to study more cases with similar outcomes and investigate their molecular background to establish the characteristics associated with such responses.

Statement of Ethics

We reported this case report in compliance with the Helsinki Declaration. Ethical approval was obtained from the ethics committee of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research. When obtaining informed consent for the chemotherapy, general consent for publication and presentation were also obtained from the patients.

Disclosure Statement

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Author Contributions

Y.U. drafted the manuscript. Y.U., E.S., and K.Y. conceived the idea for the paper and helped to draft the manuscript. K.Y. proofread the paper. Y.U., E.S., and K.Y. participated in the clinical treatment. All of the authors read and approved the final version of the manuscript.

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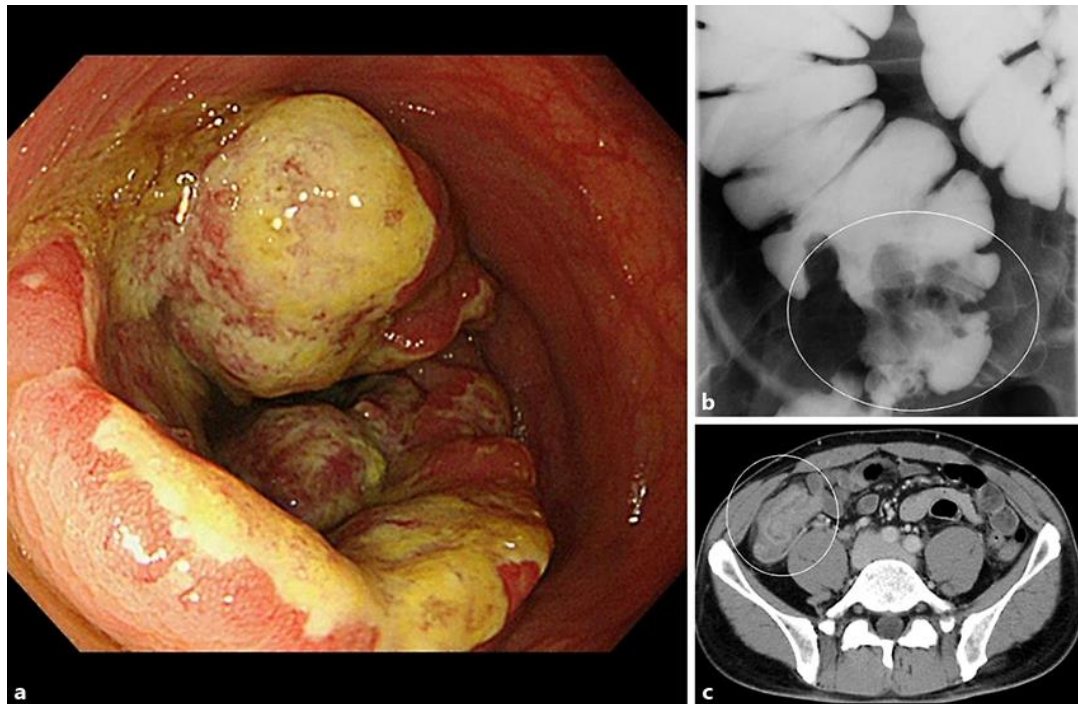


Fig. 1. **a** The endoscopic findings showed a type 3 tumor with stenosis in the cecum. **b** A barium enema revealed a defective area and an elevated lesion in the cecum. **c** Enhanced abdominal computed tomography showed an enhanced and thickened cecum wall with encasement.

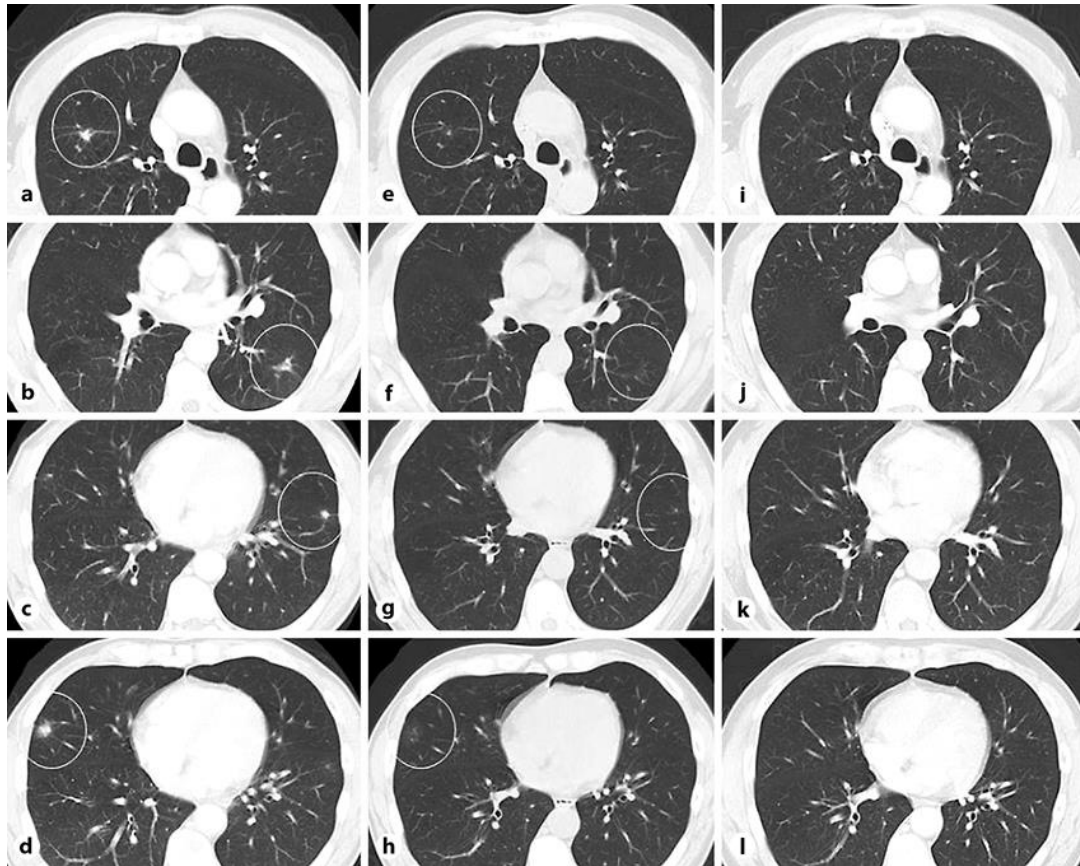


Fig. 2. Computed tomography (CT) at the first visit showed multiple lung metastases in June 2011 (a–d). After the 4th course of chemotherapy, CT demonstrated a reduction in the size of the lung lesions in October 2011 (e–h). After the 12th course of chemotherapy, all lung lesions had disappeared in February 2012 (i–l).

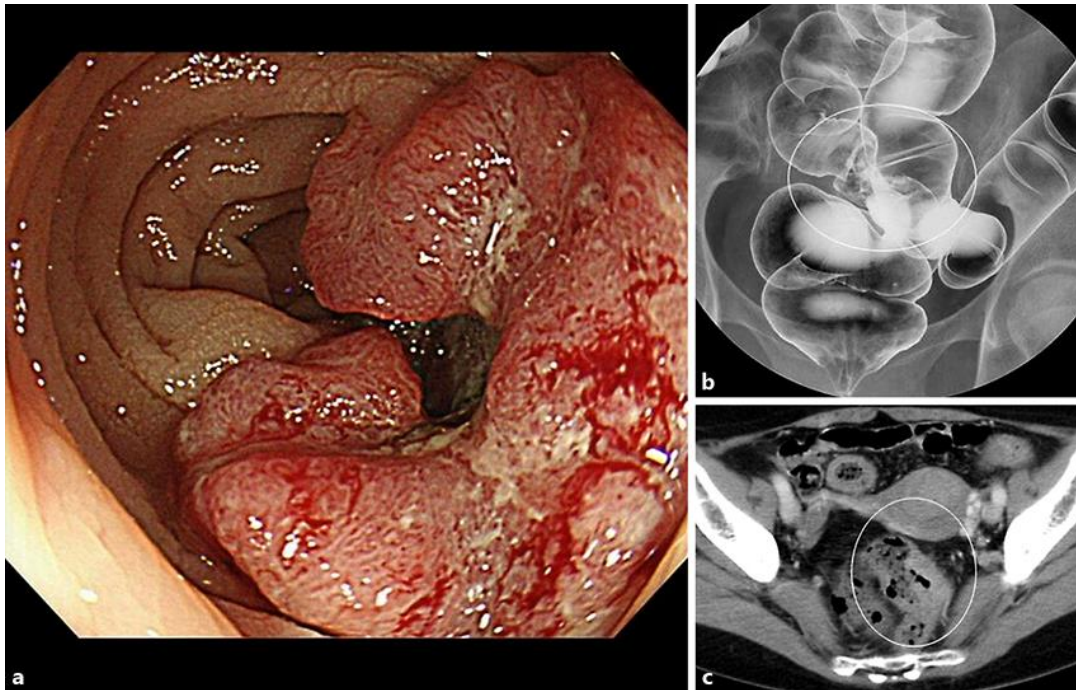


Fig. 3. **a** Endoscopic examination revealed a type 2 tumor on the left wall of the rectosigmoid. **b** Barium enema revealed mild stenosis and an ulcerative lesion in the rectosigmoid. **c** Enhanced abdominal computed tomography showed thickening of the left rectal wall.

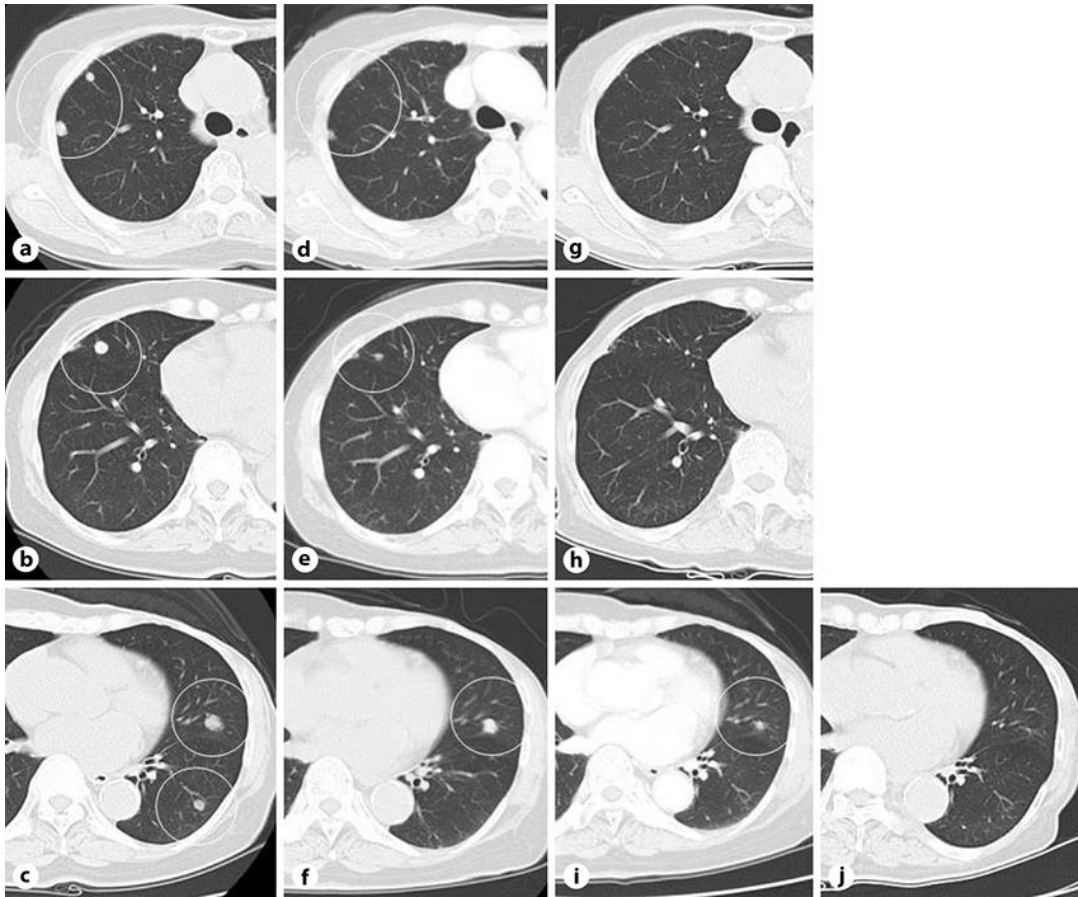


Fig. 4. In November 2011, computed tomography (CT) demonstrated recurrences of multiple metastases to both lungs (a–c). After the 4th course of chemotherapy, CT showed a reduction in the size of the lung metastases in April 2011 (d–f). After the 12th course, almost all lung lesions had disappeared; however, the left inferior lobe lesions remained in October 2011 (g–i). j In January 2012, all metastatic lung lesions showed a complete response to 14 courses of chemotherapy.