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Case Report

A Long-Term Survival Case of Rectal Cancer With Multiple Pulmonary Metastases Treated With Multidisciplinary Chemotherapy

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Colorectal cancer (CRC) is a major cause of cancer morbidity and mortality worldwide, accounting for 8% of all malignant tumors in adults.[1] Although CRC survival rates are continually improving, many patients still die as a result of distant metastases.

Surgical resection has become the standard therapy for various metastatic malignancies to the lungs and liver.[2,3] Resection of pulmonary colorectal metastases may increase survival; however, the combination of liver and lung metastasectomies had a worse prognosis than pulmonary metastasectomy alone. The higher tumor recurrence after resection of both liver and lung metastases may account for the difference in prognosis.[4]

Historically, chemotherapy was used for the palliation of symptoms; however, in the last few years, the median overall survival of patients with advanced CRC has substantially increased from 12 months to approximately 21 to 22 months with the use of the full chemotherapeutic arsenal.[5] Recently, more effective chemotherapies, which include oxaliplatin or irinotecan (*e.g.*, FOLFOX, XELOX, or FOLFIRI), have resulted in superior survival benefits to those obtained with 5-fluorouracil (5-FU) in combination with leucovorin (LV) (5-FU/LV). In addition, many randomized clinical trials have demonstrated the advantages of combining bevacizumab with 5-FU/LV[6]; irinotecan, bolus-5-fluorouracil, and leucovorin (IFL)[7]; or FOLFOX4/XELOX[8]; while combinations of chemotherapeutic agents and monoclonal antibodies (*e.g.*, panitumumab) are used as a standard first-line treatment.

We report a case of locally advanced rectal cancer with multiple pulmonary metastases in which the primary tumor was locally resected and then all systemic chemotherapy agents were administered.

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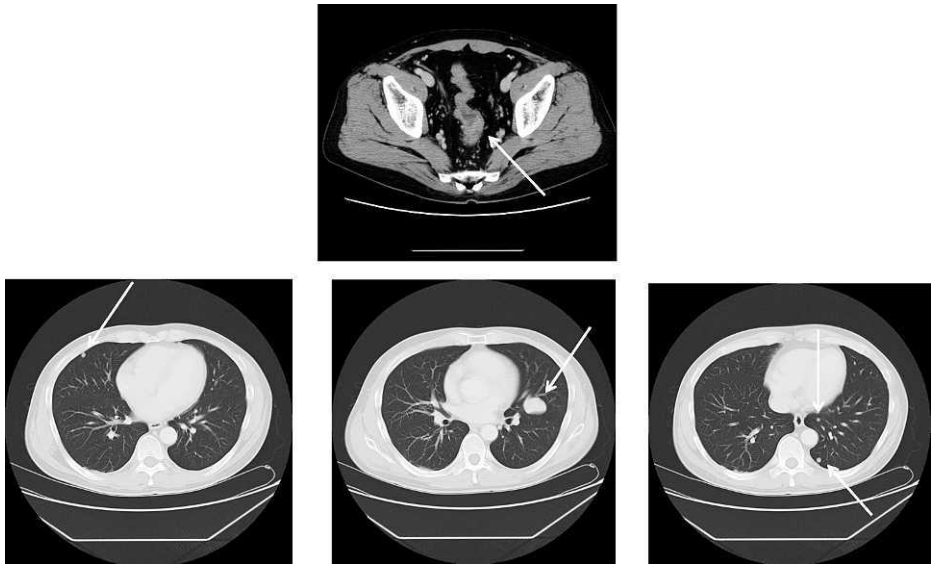

Fig. 1 The CT image shows a thickening of the rectal wall (Rs), a 33-mm pulmonary nodular lesion in the left lung field (S4), and multiple pulmonary nodular lesions of 1 cm or less in the left and right lung fields **(**arrow**)**.

The patient has survived for 66 months without negative effects on his quality of life (QOL).

Case Report

After admittance to the Fujioka General Hospital, a 43-year-old male patient underwent a computed tomography (CT) examination for follow-up of what appeared in an X-ray to be a lung tumor; the CT revealed a thickening rectal wall (Rs), a 33-mm pulmonary nodular lesion in the left lung field (S4), and multiple pulmonary nodular lesions of 1 cm or less in the left and right lung fields (Fig. 1). A colonoscopy revealed rectal cancer with a 5-cm semicircular, ulcerated mass. Microscopic examination of tumor biopsy specimens revealed moderately differentiated tubular adenocarcinoma. A medical team assessed the patient and recommended resection of the primary tumor followed by systemic chemotherapy because of a bleeding episode. A low anterior resection and D3 lymphadenectomy were performed. The value of preoperative serum carcinoembryonic (CEA) antigen level was 29.5 (ng/mL).

Fig. 2 Resected rectal colon. Histopathologically, moderately differentiated tubular adenocarcinoma, with subserosal, lymphovascular, and venous invasion, and lymph node metastasis.

The histopathologic diagnosis indicated moderately differentiated tubular adenocarcinoma with subserosal, lymphovascular, venous invasion and lymph node metastasis (Fig. 2). The patient underwent 14 courses of the FOLFOX6 [oxaliplatin (85 mg/m^2 on day 1), leucovorin (200 mg/m^2 on day 1), 5-FU (400 mg/m^2 as a bolus and 2400 mg/m^2 as a 46-hour continuous infusion)], and bevacizumab (5 mg/kg on day 1) regimen every 2 weeks. The second-line chemotherapy with the FOLFIRI [irinotecan (150 mg/m^2 on day 1), leucovorin (200 mg/m^2 on day 1), 5-FU (400 mg/m^2 as a bolus and 2400 mg/m^2 as a 46-hour continuous infusion)], and bevacizumab (5 mg/kg on day 1) regimen was started every 2 weeks. The value of serum CEA antigen level at that time was 6.2 (ng/mL). However, the patient experienced severe diarrhea [Common Terminology Criteria for Adverse Events (CTCAE) grade 3] during the fourth course; thus, irinotecan was omitted from the fifth course, and the

sLV5FU2 [simplified leucovorin (200 mg/m^2 on day 1), 5-FU (400 mg/m^2 as a bolus and 2400 mg/m^2 as a 46-hour continuous infusion)], and bevacizumab regimen was administered thereafter for the ninth course until the multiple pulmonary metastases became larger. Once again, the mFOLFOX6 and bevacizumab regimen was administered thereafter for 41 courses until the multiple pulmonary metastases became larger. The value of serum CEA antigen level at that time was 691 (ng/mL). For the third-line chemotherapy, the panitumumab (6 mg/kg on day 1) and mFOLFOX6 regimen was administered every 2 weeks, and the multiple pulmonary metastases shrank after 5 courses. The value of serum CEA antigen level at that time was 16.6 (ng/mL). The panitumumab and mFOLFOX6 regimen was administered thereafter for 8 courses until the multiple pulmonary metastases became larger and new liver metastases in S5 appeared. The value of serum CEA antigen level at that time was 150 (ng/mL). For fourth-line chemotherapy, the combination of a XELOX [capecitabine (2000 mg/m^2/d on day 1–14, orally), oxaliplatin (130 mg/m^2 on day 1)], and bevacizumab regimen was administered thereafter for 15 courses every 3 weeks. At that point, the patient only experienced numbness in his extremities (CTCAE grade 1). He remains well 66 months after the operation and has had no negative consequences affecting his QOL.

Discussion

At present, lung resection is the only treatment that offers a chance of long-term survival for patients with metastases of colorectal cancer. However, the rate of resectability for metastases present at the time of diagnosis is low. According to the colorectal cancer treatment guidelines of 2010, lung metastases are to be excised whenever possible. Saito *et al* reported that the 5-year survival rate after metastasectomy is 53.6% higher when mediastinal spaces and pulmonary hilum lymph node metastases are not present.[9] Yano *et al* reported that patients with either 1 or 2 lung metastases had a significantly better survival, with a 5-year survival of 54.3%, than did those with a greater degree of metastases ($P < 0.01$).[10] Moreover, the results of this study indicate that the patients without metastasectomy had a significantly worse survival, with a 5-year survival of 2.4%.[11]

Treatment of inoperable rectal cancer and colorectal metastases has changed dramatically over the past decade because of improvements in chemotherapy. Recently, novel agents have led to improvements in the prognosis of patients with metastatic colorectal cancer, and combination chemotherapy with oxaliplatin, 5-FU, and leucovorin is now routine in the treatment of metastatic colorectal cancer.[12] Moreover, the addition of bevacizumab, a monoclonal antibody against vascular endothelial growth factor, to 5-FU-based combination chemotherapy has resulted in significant and clinically meaningful improvement in survival among patients with metastatic colorectal cancer.[13] However, there are few studies in cases of colon cancer with long-term survival treated by chemotherapy for lung metastasis.

Grothey *et al* reported that it is important for prolonged survival to use 3 key drugs: 5-FU, irinotecan, and oxaliplatin, as cytotoxic agents.[14]

In the current case, it appears that the increased survival time depends on the use of the 3 key drugs. In addition, it appears that the increased survival time depends on the long-term use of the 2 drugs, oxaliplatin and bevacizumab. Maintenance of bevacizumab with a standard second-line chemotherapy has clinical benefits in patients with metastatic colorectal cancer.[15]

Oxaliplatin therapy increases the risk of vascular lesions and sinusoidal obstruction syndrome.[16] Bevacizumab is associated with hypertension and relatively low rates of certain potentially serious events, such as bleeding, gastrointestinal perforation, and arterial thromboembolism.[17] There was no significant side effect in our case, except for diarrhea as a result of using irinotecan. Other reports have described how bevacizumab improves the pathologic response with oxaliplatin-based chemotherapy and, more recently, how bevacizumab reduces the incidence of oxaliplatin-related sinusoidal injury.[18] Therefore, these results provide a rationale for the continued use of oxaliplatin and bevacizumab.

This case clearly demonstrates the survival potential of using systemic chemotherapy for the treatment of metastatic colorectal cancer as long as patients have no severe side effects. In cases in which lung metastases are inoperable, the aggressive chemotherapies have the potential to prolong the survival of colorectal cancer patients with lung metastases.

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