Case Report

Aggressive Multimodality Treatment for Advanced Rectal Cancer

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A case of advanced rectal cancer treated by aggressive local and systemic treatment who has survived more than 7 years from initial recurrence is presented. A 55-year-old woman was diagnosed with advanced lower rectal cancer and underwent a low anterior resection with complete removal of all regional lymph nodes and total mesorectal excision. The tumor was diagnosed as a moderately differentiated adenocarcinoma, pStage IIIB (T3, N2a, M0). Twenty-six months after the initial surgery, local recurrence in the pelvis was detected by computed tomography, and total pelvic exenteration with distal sacrectomy (TPES) was performed after systemic chemotherapy with a molecular-targeted drug. Six months after the TPES, multiple lung metastases were detected. Consequently, the patient underwent radiofrequency ablation (RFA) and chemotherapy. The disease has since been controlled for 38 months. As volume control is essential for cancer treatment, it may be important to combine appropriate local therapy with systemic therapy to metastatic or recurrent sites in order to achieve much longer disease control.

Key words: colorectal cancer, recurrence, total pelvic exenteration, radiofrequency ablation, systemic chemotherapy

Colorectal cancer (CRC) is one of the leading causes of cancer-related death worldwide [1, 2]. Some CRCs develop recurrence after curative resection, but resection of recurrent sites sometimes contributes to longer survival [3-8]. On the other hand, many cases develop repeat recurrence after re-operation. In the past 10 years, molecular-targeted drugs and new anticancer regimens such as oxaliplatin/5FU/LV (FOLFOX) and irinotecan/5FU/LV (FOLFIRI) have enabled patients with metastatic or recurrent CRCs to have long survival periods, with median overall survival of more than 20 months [9-12], whereas systemic chemotherapy alone provides limited improvements in survival. It seems important to give appropriate local treatments, in addition to systemic therapy, to patients with metastatic or recurrent CRCs. This manuscript reports a patient with recurrent rectal cancer who underwent systemic chemotherapy and aggressive local treatment, including total pelvic exenteration with distal sacrectomy (TPES) to local recurrence in the pelvis and

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radiofrequency ablation (RFA) to lung recurrence, who has survived for 7 years after the first recurrence.

**Case Report**

A 55-year-old woman visited a previous hospital in 2004 with a complaint of bloody stool. The results of a subsequent colonoscopy and a barium enema study led to a diagnosis of lower rectal cancer. She was thus referred to Okayama University Hospital for the management of her rectal cancer. A computed tomography (CT) scan and the colonoscopy showed a tumor measuring 35 mm at the lower rectum, regional lymph node swelling, and no distant metastases. Based on a diagnosis of locoregionally advanced lower rectal cancer, a low anterior resection with complete removal of all regional lymph nodes and total mesorectal excision (TME) was performed. Histopathologically, the surgical margin was negative for cancer. Based on the classification of the seventh edition of the International Union against Cancer [13], the tumor was diagnosed as a moderately differentiated adenocarcinoma, pStage IIIb (T3, N2a, M0). Genetic analysis performed with a direct sequencing method showed wild-type **KRAS** and **BRAF** oncoproteins with stable microsatellite status. Postoperatively, the patient developed major leakage, which led to rectovesical and rectovaginal fistulas, and consequently a diverting ileostomy was created.

In 2007, 26 months after the initial surgery, a CT scan detected local recurrence in the pelvis. Magnetic resonance imaging showed a recurrent tumor at the pelvic surface of the sacrum (Fig. 1). She had undergone 11 courses of FOLFIRI (irinotecan 150 mg/m², l-leucovorin 200 mg/m², and 5-fluorouracil 400 mg/m² bolus plus infusion of 2,400 mg/m²/46 h of a 2-week cycle) for 6 months, and the tumor response at 3 months was stable disease (SD), but at 6 months it was progressive disease (PD), according to the RECIST guideline criteria [14]. Therefore, her chemotherapy regimen was changed to mFOLFOX6 with bevacizumab (oxaliplatin 80 mg/m², l-leucovorin 200 mg/m², 5-fluorouracil 400 mg/m² bolus plus infusion of 2,400 mg/m²/46 h and bevacizumab 5 mg/kg of a 2-week cycle), and the tumor response remained in SD status throughout 41 courses of the regimen. In 2010, while the patient was undergoing chemotherapy, TPES was performed for the local recurrence since new recurrent lesions had not appeared. Histopathologically, the tumor was diagnosed as a moderately differentiated adenocarcinoma, indicating metastasis from the rectal cancer, and the surgical margin was negative. After this very invasive surgery, she was discharged without serious postoperative complications and received a careful follow-up examination. Six months after the TPES, multiple lung metastases involving both lungs were detected by a thoracic CT scan. Among the metastatic lesions, there were 2 tumors, each measuring about 30 mm in diameter, at a right lower lobe of one of her lungs. The tumors were treated with 48 Gy of stereotactic radiation therapy (SRT), and shrank after that. At almost the same time as the SRT, XELOX (oxaliplatin 130 mg/m² and capecitabine 1,000 mg/m² twice daily on days 1 to 15 of a 3-week cycle) was started, but the regimen was changed to irinotecan with cetuximab (irinotecan 150 mg/m² and cetuximab 250 mg/m² on days 1 and 8 of a 2-week cycle) due to oxaliplatin allergy at the third course. After 10 courses of irinotecan with cetuximab, only one of the metastatic lesions had grown. CT-guided percutaneous RFA was performed for the tumor that had grown (Fig. 2). The regimen was restarted after the RFA, but the remaining lung

![Fig. 1](image-url)  
**Fig. 1** Magnetic resonance imaging shows a local recurrent tumor invading the surface of the sacrum (arrow).
metastatic tumors slowly grew during the following 8 courses of irinotecan with cetuximab, so her regimen was changed to XELIRI with bevacizumab (irinotecan 150 mg/m², capecitabine 1,000 mg/m² twice daily on days 1 to 8 and bevacizumab 10 mg/kg of a 2-week cycle). Immediately after XELIRI with bevacizumab was started, all remaining lung metastatic tumors showed cavitary change with size regression (Fig. 3). At the time of writing, 7 years after initial recurrence, the patient have undergone the regimen, and was doing well without new metastases. Her clinical course is shown as Fig. 4.

**Discussion**

Patients with CRC can expect a long survival period if they undergo curative resection, but those with regional lymph node metastases recur with a relatively high probability [2]. Local recurrence in the pelvis remains common after excision of rectal

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**Fig. 2** Chest computed tomography scan shows a lung recurrent tumor treated with radiofrequency ablation (RFA) (A, before RFA; B, during RFA; C, 1 month after RFA).

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**Fig. 3** Chest computed tomography scan shows a lung recurrent tumor treated with XELIRI (capecitabine and irinotecan) with bevacizumab (A, before treatment; B, after treatment).
cancers, although this is decreasing due to the use of TME [15]. Recurrent tumors in the pelvis often invade neighboring organs, including the bladder, prostate, uterus, vagina, pelvic wall, and sacrum, and excision of such neighboring organs to achieve satisfactory histologically negative surgical margins is complicated. TPES is a very invasive procedure and often causes complications such as urinary tract infection and pelvic sepsis [7, 8]. Quality of life in patients with TPES may decrease due to double ostomies (colostomy and urostomy); therefore, it is necessary to choose surgery carefully. However, there are no other therapies, including chemotherapy and radiotherapy, for locally recurrent CRCs that are equal in effectiveness to surgical excision [7, 8]. A previous study of 44 cases treated by TPE for local recurrent CRCs found that the 5-year overall survival rate was 34% and that independent factors for good prognoses were a negative resection margin, a long-term local disease-free interval (>12 months), and an absence of pain radiating to the buttock or further [16]. We should not hesitate to perform surgical excision for patients with local recurrence if there is a possibility of histologically negative surgical margins.

Lung recurrence is also a common recurrence pattern for rectal cancers, and surgical excision is now standard therapy for resectable lung recurrence sites, with 5-year overall survival of almost 30-45% [5, 6]. Since lung metastases often recur after surgical resection, and because thoracic surgery decreases a patient’s physical status, including respiratory function, there is a limit to curing by resection alone. Our institution has performed CT-guided percutaneous RFA for lung tumors, including early primary lung cancer and metastatic lung cancer, since 2001. The complications of RFA have mainly been pneumothorax and pleural effusion; most occurrences of these are mild and do not require a chest tube. Regarding mid-term outcomes, the 3-year overall survival rate is approximately 50% [17]. We are planning a prospective clinical trial for RFA toward metastatic lung tumors of CRCs. Considering repeatability, the preservation of respiratory function, and minimal invasiveness, RFA can be an effective treatment for lung recurrence of CRCs.

Since they appeared in the early 2000s, new anticancer regimens such as FOLFOX and FOLFIRI have prolonged the survival of patients with metastatic and recurrent CRC, and molecular-targeted drugs have led to long survival [9-12]. However, treatment by systemic chemotherapy alone has limited potential to prolong survival to, for example, more than 5 years. Although these new anticancer regimens are effective, cancer-free status as a result of surgical treatment seems to be elusive. Table 1 shows cases in our department with recurrent CRCs that were treated with curative local treatment at least twice in
addition to systemic chemotherapy between 2004 and 2011. In our department, 6 cases, including this case (case 6), underwent curative local treatment for recurrent sites of CRCs at least twice, and all 6 cases appeared to achieve relatively long disease control. It is important to conduct appropriate local treatments at appropriate timing, in addition to systemic therapy, as volume control is essential for cancer treatment.

In this case, mutations of KRAS and BRAF oncogenes and microsatellite status were analyzed, and no mutation was found in the primary tumor. KRAS mutation is widely known to be a negative predictive factor of anti-EGFR antibody [18]. It was recently reported that CRCs with nonmicrosatellite instability + BRAF mutation had a poor prognosis [19]. Such analyses of the mutation spectrum will be further used as prognostic and predictive factors for CRCs in the future.

In conclusion, aggressive multimodality therapy, including not only systemic but also appropriate local therapy, is important for patients with repeatedly recurrent CRCs to achieve long survival.

References

Table 1 Characteristics of cases with recurrent CRCs and undergoing curative local treatment twice or more

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Primary tumor</th>
<th>Location</th>
<th>Stage</th>
<th>Histology</th>
<th>MS status</th>
<th>KRAS/BRAF status</th>
<th>Age</th>
<th>Duration from initial surgery</th>
<th>Site treatment</th>
<th>Site treatment</th>
<th>Site treatment</th>
<th>Site treatment</th>
<th>Status</th>
<th>Duration from 1st recurrence</th>
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<tr>
<td>1</td>
<td>Female</td>
<td>Colon</td>
<td>IIIB</td>
<td>Mod.</td>
<td>non MSI</td>
<td>BRAF mutation</td>
<td>KRAS mutation</td>
<td>55</td>
<td>37 months</td>
<td>Ultrasound, LN Resection</td>
<td>Local non-ILT</td>
<td>Local non-ILT</td>
<td>Local non-ILT</td>
<td>dead</td>
<td>57 months</td>
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<td>2</td>
<td>Male</td>
<td>Rectum</td>
<td>IIIC</td>
<td>Muc.</td>
<td>non MSI</td>
<td>KRAS mutation</td>
<td>KRAS mutation</td>
<td>74</td>
<td>12 months</td>
<td>Local Resection</td>
<td>Lung Resection</td>
<td>Liver RFA</td>
<td>Lung RFA</td>
<td>alive</td>
<td>28 months</td>
</tr>
<tr>
<td>3</td>
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<td>Colon</td>
<td>IIIA</td>
<td>Mod.</td>
<td>non MSI</td>
<td>KRAS mutation</td>
<td>KRAS mutation</td>
<td>16</td>
<td>16 months</td>
<td>Lung Resection</td>
<td>Lung Resection</td>
<td>Lung Resection</td>
<td>Lung Resection</td>
<td>alive</td>
<td>27 months</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>Rectum</td>
<td>IIIB</td>
<td>Mod.</td>
<td>non MSI</td>
<td>KRAS mutation</td>
<td>Both Wild type</td>
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<td>5 months</td>
<td>Local Resection</td>
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<td>Lung Resection</td>
<td>Lung Resection</td>
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<tr>
<td>5</td>
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<td>Mod.</td>
<td>non MSI</td>
<td>KRAS mutation</td>
<td>Both Wild type</td>
<td>58</td>
<td>27 months</td>
<td>Both Wild type</td>
<td>Both Wild type</td>
<td>Both Wild type</td>
<td>Both Wild type</td>
<td>alive</td>
<td>80 months</td>
</tr>
</tbody>
</table>

Mod./Muc, moderately differentiated/mucinous adenocarcinoma; MS(I), microsatellite (instability); LN, lymph node; non-ILT, non-indication for local treatment.


