Synchronous Metastatic Rectal Cancer Completely Resected After Multidisciplinary Planning and Treatment: A Case Report

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Abstract

Colorectal cancer is a common and significant public health concern. The liver is the most common site of metastasis, and colorectal cancer liver metastases (CRLM) may affect up to 60% of patients at some time during the course of their disease. Approximately 25% of patients are found to have synchronous CRLM at the time of diagnosis, and these patients have a worse prognosis than those who develop metastases later in their disease course. In the absence of extrahepatic disease, resection of CRLM with negative margins along with chemotherapy can lead to a 5-year overall survival rate of up to 60%. This report presents the case of a 48-year-old man diagnosed with rectal cancer and synchronous liver metastases that a multidisciplinary tumor board initially deemed to be unresectable because of large size and insufficient future liver remnant. The patient underwent FOLFOX chemotherapy with bevacizumab and experienced conversion to resectable hepatic disease. After neoadjuvant short-course radiation treatment to the rectum, the patient underwent combined low anterior resection of the rectum and a right hepatectomy and was rendered disease-free. The management of the patient's clinical course with correlation to the NCCN Clinical Practice Guidelines in Oncology for Rectal Cancer is presented in this report, including discussion of the role of chemotherapy in the conversion of CRLM to resectable status, the role of surgical metastasectomy, and postoperative surveillance of patients with colorectal cancer. (*JNCCN* 2013;11[Suppl 4]:S3–S8)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Discuss the NCCN Clinical Practice Guidelines in Oncology for Rectal Cancer recommendations for the management of potentially resectable synchronous metastatic disease
- Describe the role of chemotherapy with bevacizumab in the conversion of CRLM to resectable status

Case Presentation

A 48-year-old man presented to City of Hope Comprehensive Cancer Center (COHCC) with a diagnosis of rectal adenocarcinoma and synchronous liver metastases. For 1 year, the patient had been experiencing intermittent hematochezia, thinning stool, diarrhea, and a 50-pound weight loss. Colonoscopy was ultimately performed, revealing a friable mass in the proximal rectum, and biopsy revealed adenocarcinoma. The patient underwent staging with a contrast-enhanced abdominopelvic CT scan, demonstrating a 10- to 12-cm segment of thickened rectosigmoid colon extending to the proximal rectum, enlarged mesorectal lymph nodes (Figure 1A), and an 11-cm hypodense mass occupying most of the right lobe of the liver (Figure 1B). The patient presented to COHCC for treatment options.

The patient previously had undergone Mohs surgeries for removal of unknown-type skin neoplasms from his nose; however, he had no other medical problems or previous operations. The patient's father was treated for colon cancer in his 50s, diagnosed with prostate cancer in his 80s, and was currently alive. The patient had no family history of colorectal cancer, polyps, inflammatory bowel disease, or other malignancies, except lung cancer in a maternal grandmother.

Repeat CT scan of the chest/abdomen/pelvis at COHCC showed enlargement of the liver mass to 12 cm, with smaller satellite masses in the right lobe, and no pulmonary metastases. The patient's case was presented at a multidisciplinary tumor board conference attended by medical, surgical, and radiation oncologists; diagnostic and interventional radiologists; and pathologists. After presentation, the patient's liver disease was deemed to be initially unresectable because of insufficient future liver remnant. Mutational testing on the tumor biopsy specimen showed the tumor to be *KRAS* wild-type, and the mismatch repair proteins MLH1, MSH2, MSH6, and PMS2 were all intact via immunohistochemistry.

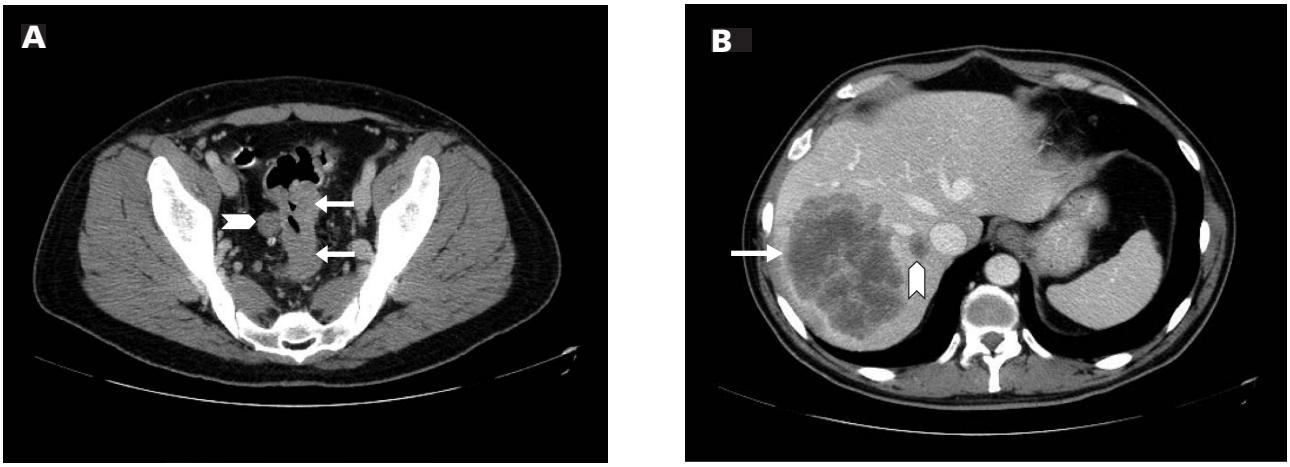

Figure 1 (A) Thickened segment of rectum with adenocarcinoma (arrows) and lymphadenopathy in the mesorectum (arrowhead). (B) Synchronous metastatic rectal cancer occupying most of the right lobe of the liver (arrow) and a satellite lesion adjacent to the inferior vena cava (arrowhead).

The patient underwent treatment with combination mFOLFOX6 chemotherapy with an infusion of yttrium-90 SIR-Spheres microspheres (Sirtex Medical Inc., Woburn, MA) during the first cycle. The patient's carcinoembryonic antigen (CEA) before treatment was 78.5 ng/mL. The patient continued treatment with mFOLFOX6/bevacizumab, and repeat imaging during treatment showed a decrease in the size of the liver lesion to 9 cm without new lesions. The patient underwent imaging every 2 months during chemotherapy with repeat tumor board presentations. Four months after beginning treatment, both the primary rectal cancer and the liver metastases were deemed to be resectable (Figure 2). The patient had undergone 8 cycles of therapy; however, bevacizumab was held and not given with the final round of chemotherapy. The CEA after treatment had decreased from 78.5 to 5.5 ng/mL.

Flexible sigmoidoscopy was performed as part of a preoperative evaluation, showing the tumor in the mid-rectum 12 cm from the anal verge. The patient was seen by the Radiation Oncology Department for possible short-course neoadjuvant pelvic radiation to improve local control, and was deemed to be a candidate. The patient received 5 Gy of external-beam radiation daily for 5 days, and was taken to the operating room for resection 1 week later, approximately 5 weeks after the last dose of chemotherapy, and 7 weeks after the last dose of bevacizumab.

At exploratory laparotomy, no other intraperitoneal disease was found. The patient underwent low anterior resection of the rectum with total mesorectal excision, colorectal anastomosis, and a diverting loop ileostomy; several bulky-appearing lymph nodes along branches of the inferior mesenteric artery were all resected. Intraoperative hepatic ultrasound showed the large right liver mass and no masses in the left lobe of the liver. Right hepatectomy and cholecystectomy were performed. During liver mobilization, dense edematous adhesions between the omentum, the hepatic flexure of the colon, and the liver were encountered, and edema in the ligaments of the liver, thought to be due to the yttrium-90 radioembolization. Postoperatively, the patient had a slow return of bowel function, and then subsequently excessive ileostomy output, which was ultimately normalized with dietary fiber and antimotility agents. Liver function tests normalized over the course of 1 week. The patient was discharged to home on postoperative day 14 in good condition.

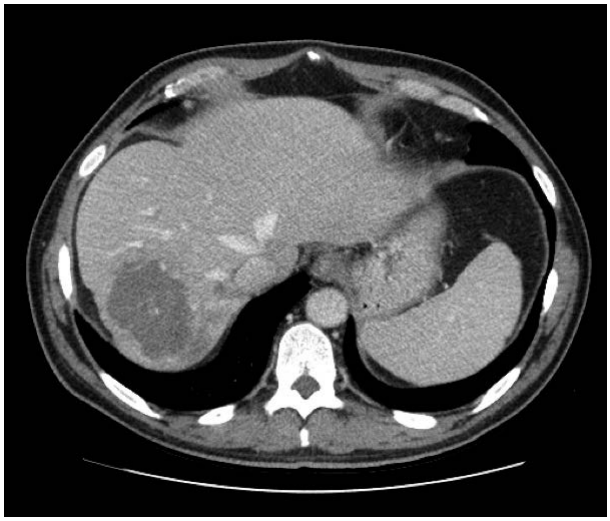

Figure 2 Metastatic rectal cancer after chemotherapy and selective internal radiation with yttrium-90 microspheres. The tumor in the right lobe is much smaller and is amenable to resection.

The final pathologic result from the low anterior resection showed a well-differentiated low-grade adenocarcinoma 8.5 cm in length, extending into the subserosa. Proximal, distal, and radial margins were all negative. Metastatic cancer was seen in 5 of 55 lymph nodes. Treatment effect was noted in the primary tumor, without lymphovascular or perineural invasion. An 8.5-cm metastasis with extensive necrosis was found in the liver, with negative resection margins. No tumor was seen in the resected gallbladder or periportal tissue. The final pathologic stage was ypT3,N2a,M1.

The patient is currently without evidence of disease 5 months postoperatively, and is awaiting ileostomy take-down in the future. The patient received an additional 4 cycles of postoperative mFOLFOX6/bevacizumab, completing a total of 6 months of perioperative chemotherapy. The CEA after resection has decreased to 0.5 ng/mL, and remains low. Postoperative CT shows enlargement of the left lobe of the liver, and no evidence of metachronous disease (Figure 3). Surveillance will consist of history and physical examination with CEA determination every 3 months for 2 years, then every 6 months for the next 3 years, with CT chest/abdomen/pelvis imaging every year, and colonoscopy in 1 year. If metachronous metastases are later detected that are isolated and resectable, the patient will be recommended to undergo metastasectomy.

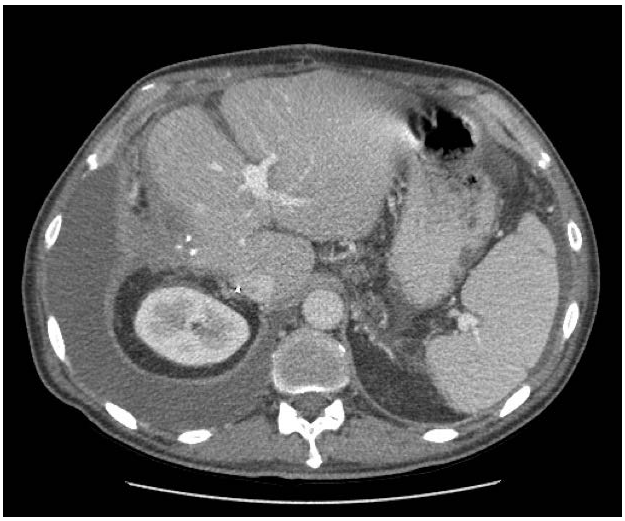

Figure 3 Postoperative surveillance CT shows enlargement of the left lobe of the liver, and no evidence of metachronous disease. Postoperative ascites is also seen adjacent to the liver.

Discussion

Colorectal cancer is a major public health concern, and the third most common malignancy and cause of cancer-related death in men and women, with approximately 143,000 new cases and 51,000 deaths estimated in the United States in 2013.[1] Metastatic disease is common, and the liver is the most common site of metastatic colorectal cancer. Approximately 25% of patients have colorectal liver metastases (CRLM) on presentation, and 60% of all patients will develop liver metastases at some time during the course of their disease.[2] Without treatment, patients with CRLM have a median overall survival (OS) of 6 to 12 months,[3] and with modern chemotherapy regimens, patients may have median OS of 20 to 24 months.[4] Surgical resection of CRLM affords patients the possibility of a cure, with 5-year OS ranging from 20% up to 60% in some series.[5,6] Unfortunately, only 15% to 25% of patients with CRLM are resectable at the time of presentation.[7] For those patients with resectable synchronous CRLM at presentation, the literature suggests that they have a worse prognosis and a shorter disease-free survival versus those with metachronous CRLM.[8]

For patients with initially unresectable hepatic disease without other sites of metastases, treatment options include palliative chemotherapy versus upfront neoadjuvant combination chemotherapy given in an attempt to convert the metastases to resectable. In one of the largest worldwide experiences with chemotherapy for conversion, Adam et al[9] reported their 11-year experience of 1439 patients with CRLM, of whom 1104 (77%) were initially unresectable. Patients underwent FOLFOX (70%), FOLFIRI (7%), or both regimens (4%), and ultimately 138 "good responder" patients (12.5%) were converted to resectability after a mean 10 cycles of chemotherapy. Rates of 5- and 10-year survival for the surgery group were 33% and 23%, respectively.

Multiple trials have shown that the addition of targeted antibody agents to chemotherapy, such as cetuximab (an anti–epidermal growth factor receptor [EGFR] antibody) or bevacizumab (a vascular endothelial growth factor [VEGF] antibody), leads to increased response and conversion rates in patients with unresectable CRLM. In the phase II multi-institution CELIM trial,[10] patients with unresectable CRLM were randomized to receive cetuximab with either FOLFOX6 or FOLFIRI chemotherapy. Response rates were 68% in the cetuximab/FOLFOX arm and 57% in the cetuximab/FOLFIRI arm. Ultimately, 20 of 53 FOLFOX patients (38%) and 16 of 53 FOLFIRI patients (30%) underwent an R0 liver resection.[10] Bevacizumab has also been shown to increase response rates with chemotherapy. In the First Bevacizumab Expanded Access Trial (First BEAT), bevacizumab was used in combination with the investigators' choice of fluoropyrimidine-based chemotherapy for patients with unresectable metastatic colorectal cancer. Of 1914 patients, 225 (11.8%) were able to undergo curative-intent surgery.[11]

Regarding the optimal management of potentially resectable synchronous metastatic disease, the NCCN Clinical Practice Guidelines in Oncology for Rectal Cancer recommend discussion of patient management in a multidisciplinary conference, attended in this patient's case, by surgical, medical, and radiation oncologists, and diagnostic and interventional radiologists and pathologists (to view the most recent version of these guidelines, visit NCCN.org). The synchronous metastatic disease was deemed to be unresectable, yet the patient was asymptomatic, thus the NCCN Guidelines for Rectal Cancer[12] recommend an attempt at conversion to resectability with a chemotherapy regimen known to have high response rates,[13] in this case FOLFOX/bevacizumab, followed by serial reassessments of resectability. NCCN believes that the best management of patients with cancer is in the context of clinical trials.

Participation in clinical trials is especially encouraged.[12]

As part of his care, the patient underwent liver-directed radioembolization therapy with yttrium-90 SIR-Spheres microspheres. Radioembolization was previously shown to provide survival benefit in the control of unresectable CRLM in small trials of highly selected patients. In a study reported by Mulcahy et al,[14] 72 patients with liver-dominant CRLM were treated with yttrium-90 microspheres at a median dose of 118 Gy. Tumor response was seen in 40.3% of patients; median OS from the date of diagnosis of metastases was 34.6 months and from the time of yttrium-90 treatment was 14.5 months. In a prospective multicenter phase III trial reported by Hendlisz et al,[15] 46 patients with chemotherapy-refractory CRLM were randomized to protracted infusional 5-FU or infusional 5-FU with yttrium-90 radioembolization given on the first day of each 3-week cycle, with the end point of time to metastatic progression in the liver. At median follow-up of 24.8 months, time to liver progression was significantly better in the radioembolization group (5.5 vs 2.1 months), as was median OS (10.0 vs 7.3 months). Radioembolization in combination with systemic chemotherapy for attempted conversion is still the subject of clinical trials.

Chemotherapy is associated with hepatotoxicity, including steatosis and steatohepatitis with irinotecan and sinusoidal congestion/dilation with oxaliplatin,[16,17] and close monitoring of patients for resectability every 2 months is warranted. During chemotherapy, this patient underwent imaging and tumor board presentation with the close involvement of the surgical team every 2 months.[18] When the disease was felt to be resectable, the patient was offered resection after waiting 1 month from the last dose of chemotherapy and, as recommended by the NCCN Guidelines for Colon Cancer, at least 6 weeks after the last dose of bevacizumab (to view the most recent version of these guidelines, visit NCCN.org).[19] Complete surgical resection of the CRLM based on anatomic grounds with negative margins was performed, leaving adequate hepatic function.

Short-course radiation therapy for rectal cancer with 25 Gy over 5 days, as opposed to traditional long-course chemoradiation of 45 to 50 Gy in 25 to 28 fractions with infusional or bolus 5-FU or oral capecitabine, is an option discussed in the NCCN Guidelines for Rectal Cancer.[12] In a Polish trial randomizing patients to preoperative short-course radiation or long-course chemoradiation, no differences in overall, disease-free survival, or local recurrence rates at a median 48-month follow-up were seen.[20] Although discussed in the NCCN Guidelines for Rectal Cancer,[12] short-course radiation is currently not part of the NCCN treatment algorithm for the primary treatment of rectal cancer (to view the most recent version of these guidelines, visit NCCN.org). Short-course radiation may be an appropriate choice in certain situations, especially in the case of this patient, in whom chemotherapy had been completed and the patient was to undergo resection 4 weeks later without time for long-course chemoradiation.

Conclusions

This report presents a complex case of synchronous metastatic rectal cancer successfully managed in a multidisciplinary fashion. Input and coordination from multiple specialties were essential in the care of this patient. Adherence to published national guidelines helps provide patients, such as this one, with the best chance of optimal outcomes.

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