



Conversion surgery by hand-assisted laparoscopic surgery following chemotherapy for rectal cancer with H3 liver metastases: a case report

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Background: Recent advancements in molecularly targeted chemotherapy for stage IV colorectal cancer have enabled the possibility of complete resection in primary colorectal cancer, which often involves distant liver or lung metastases, by aggressive surgical resection followed by multi-combination chemotherapy.

Case description: A 73-year-old man treated previously for hyperuricemia, hypertension, and a dissecting abdominal aortic aneurysm was referred to us after an incidental finding of multiple liver masses on abdominal ultrasound during follow-up for the aneurysm. A detailed examination by contrast-enhanced computed tomography revealed a ring-enhancing mass larger than 5 cm in diameter in segment 3 of the liver and more than 6 low-density areas with total diameter of 1 to 2 cm in both lobes. A barium enema examination revealed a Borrmann type 2 lesion covering two-thirds of the circumference of the colon, with a 5-cm major axis in the rectosigmoid colon. Biopsy revealed a well-differentiated adenocarcinoma. The patient was diagnosed with stage IV rectal cancer. Because there was no intestinal obstruction, we administered 9 cycles of bevacizumab with capecitabine and oxaliplatin as chemotherapy. Subsequent diagnostic imaging revealed the metastatic lesions in liver segment 3 had reduced to 2 low-density areas with a diameter of 8 mm, and the other hepatic metastases had disappeared; the main tumor had flattened and shrunk. Therefore, we used hand-assisted laparoscopic surgery (HALS) to perform anterior resection of the rectosigmoid colon and partial resection of liver segment 3 as conversion therapy. The patient was discharged 10 days after surgery. The rectal lesion was a well-differentiated adenocarcinoma with a depth of invasion of p-MP and a spread of L0, V0, and pN0. The partial hepatectomy did not indicate viable cancer cells; only necrotic, lysed tissue was observed. Postoperative chemotherapy involved 4 cycles of bevacizumab with capecitabine and oxaliplatin. At more than 42 months postoperatively, no metastasis or recurrence has been observed.

Conclusions: This rare case demonstrates that conversion surgery can be a viable option following systemic chemotherapy in patients with advanced colon cancer and H3 liver metastases.

Keywords: Hand-assisted laparoscopic surgery (HALS); rectal cancer; conversion therapy; partial hepatectomy; case report

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Introduction

Many molecularly targeted therapeutic agents recently have been developed for the treatment of tumors, enabling significant advancements in chemotherapy for stage IV colorectal cancer since introduction of 3-drug regimens including fluorouracil and leucovorin plus oxaliplatin (FOLFOX) or plus irinotecan (FOLFIRI). An anti-vascular endothelial growth factor antibody, bevacizumab (B-mab), and the anti-epidermal growth factor receptor (anti-EGFR) antibodies panitumumab and cetuximab are now available for treatment of wild-type RAS and BRAF tumors, including in colorectal cancer (1,2). Furthermore, the use of dose-selection methods for molecularly targeted drugs used for localized lesions has drastically improved clinical results (3). At our hospital, if complete resection (R0) is considered possible for primary colorectal cancer (in which distant metastasis to the liver and lungs often occurs), aggressive surgical resection is prioritized and multi-combination chemotherapy is given after surgery.

For cases in which resection is difficult or impossible, systemic chemotherapy is given while considering conversion surgery and evaluating response to chemotherapy via diagnostic imaging every 3 to 4 months (4). For patients with stage IV cancer with H3 liver metastasis and without abdominal symptoms (including ileus), 9 cycles of B-mab with capecitabine and oxaliplatin (B-mab + XELOX) are given as systemic chemotherapy; significant efficacy of this approach has been confirmed (1).

We present a case in which surgical treatment involved anterior resection and simultaneous partial hepatectomy performed using hand-assisted laparoscopic surgery (HALS). Postoperative histopathological examination revealed that liver metastases were necrotic and lysed, and no viable cancer cells were found. Accordingly, the treatment was considered to have achieved pathologic complete response (p-CR) or R0. Postoperative chemotherapy involved 4 cycles of B-mab + XELOX. Presently, more than 3 years after the surgery, no metastases have recurred. We present the case together with a literature review, in accordance with the CARE reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-245/rc>).

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the Helsinki Declaration (as revised in 2013). Written informed consent was obtained

from the patient and family for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal. We explained to the patient that the choice between conventional treatment vs the method described here was entirely voluntary. HALS is conducted as standard procedure and is not considered a novel or experimental clinical practice.

The patient was a 73-year-old man with a history of conservative medical treatment for a dissecting abdominal aortic aneurysm, hypertension, and hyperuricemia. He had been seen recently at a nearby clinic for treatment of existing diseases and a follow-up abdominal ultrasound, which revealed multiple liver masses. On the basis of these incidental findings, the patient was referred to our hospital for detailed examination and treatment; he had no presenting complaint. Physical examination was unremarkable, with no signs of anemia or jaundice and no noteworthy abdominal findings. Blood tests showed no anemia (hemoglobin, 14.4 g/dL; hematocrit, 44.0%), and the uric acid level (5.9 mg/dL) was within the normal range due to the effects of ongoing therapy. The tumor markers of carcinoembryonic antigen (4.9 ng/mL), carbohydrate antigen 19-9 (16.6 U/mL), protein induced by vitamin K absence or antagonist II (31 mAU/mL), and alpha-fetoprotein (3.1 ng/mL) were within normal ranges. Upper gastrointestinal endoscopy showed no abnormalities. A barium enema examination revealed a Borrmann type 2 tumor covering two-thirds of the circumference of the colon; the tumor had a 5-cm major axis in the rectosigmoid colon, 18 cm from the anal margin (*Figure 1A*). Lower gastrointestinal endoscopy revealed a hemorrhagic ulcerative lesion with a peripheral ridge covering two-thirds of the circumference of the colon, consistent with the results of the barium enema; biopsy of the lesion indicated a well-differentiated adenocarcinoma (*Figure 1B*). A computed tomography (CT) scan revealed thickening in the rectosigmoid colon, which was thought to be the main lesion. Metastatic lesions greater than 5 cm in diameter with ring enhancement were seen in both lobes of the liver, especially in segment 3, and other liver metastatic lesions of 1 to 2 cm in diameter were observed. In total, 5 or more lesions were identified, indicating H3 liver metastases (*Figure 1C,1D*).

The patient was diagnosed with metastatic liver cancer (H3) with advanced rectal cancer, and he was treated with 9 cycles of B-mab + XELOX chemotherapy. Chemotherapy just before surgery was performed without B-mab. After chemotherapy, the main rectal lesion had

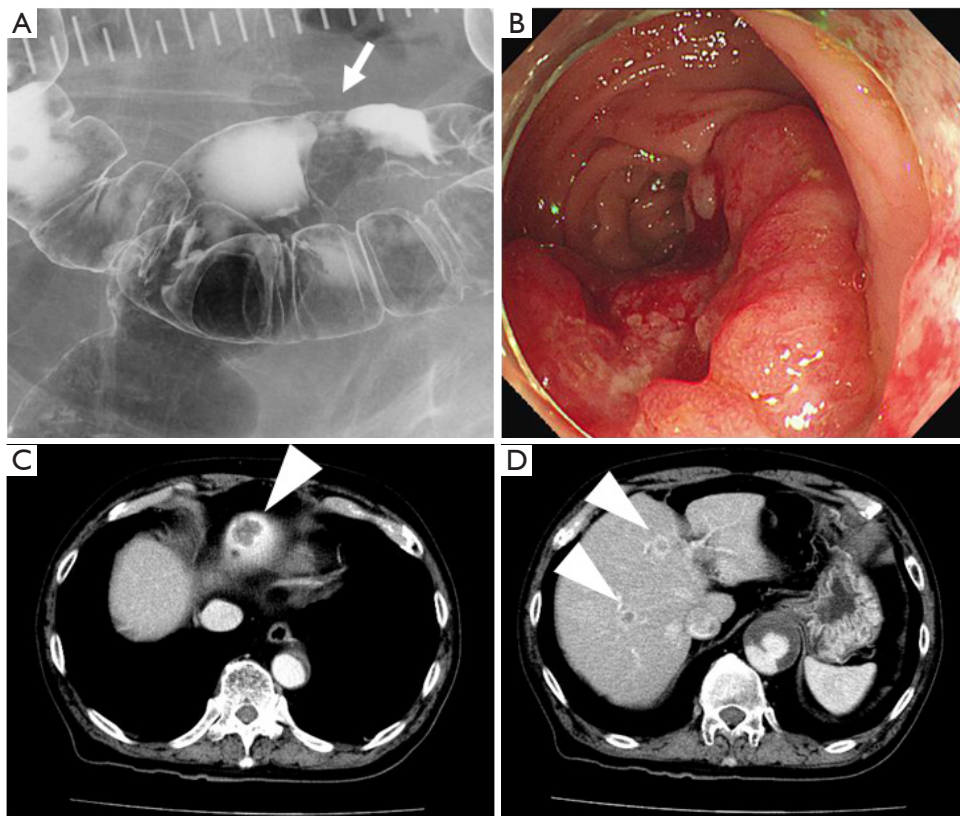


Figure 1 Pre-chemotherapy imaging. (A) Barium enema examination revealed a Borrmann type 2 tumor covering two-thirds of the circumference of the colon, with a 5-cm major axis in the rectosigmoid colon at 18 cm from the anal margin (white arrow). (B) Lower endoscopy revealed a hemorrhagic lesion with protrusion, ulceration, and a peripheral ridge covering two-thirds of the colon circumference. Biopsy showed a well-differentiated adenocarcinoma. (C,D) Contrast-enhanced computed tomography showed 5 or more ring-enhancing lesions in both lobes of the liver; the lesion in segment 3 was >5 cm in diameter. H3 metastasis was diagnosed (white arrowheads).

become a type IIa-like small ridge, which was shown by barium enema examination to have shrunk (*Figure 2A*). Lower gastrointestinal endoscopy also showed type IIa-like redness and an adenocarcinoma surrounded by white scars (*Figure 2B*). On CT, the main lesion had become unclear; the lesions in liver segment 3 had become 2 low-density areas of 8 mm in diameter, and the other liver metastases had disappeared (*Figure 2C*). Given these findings approximately 1 year after initiating chemotherapy, 1-stage conversion surgery was deemed possible by using HALS to perform anterior resection of the rectosigmoid colon and partial resection of liver segment 3.

Surgical technique

Partial resection of liver segment 3

The upper abdominal operation was started using 3 ports. A

50-mm vertical incision in the umbilical region was used as the access site for insertion of the surgeon's hand (*Figure 3*). The excision area was marked while identifying the metastatic lesion by using the intraoperative ultrasound probe inserted via the hand access site after carefully palpating the lesions (*Figure 4A,4B*). Sanada braid was inserted through a paramedian port and passed through the foramen of Winslow. Using a No. 9 Nelaton catheter, the Pringle maneuver was performed 3 times to accomplish partial liver resection (5). Hemostasis was achieved by manual compression with the left finger before completing liver resection.

Anterior resection of rectosigmoid colon

The lower abdominal surgery used the hand access site at the umbilical region and 5-mm ports placed at the midline and in the left lower abdomen (*Figure 5A,5B*). Total mesorectal

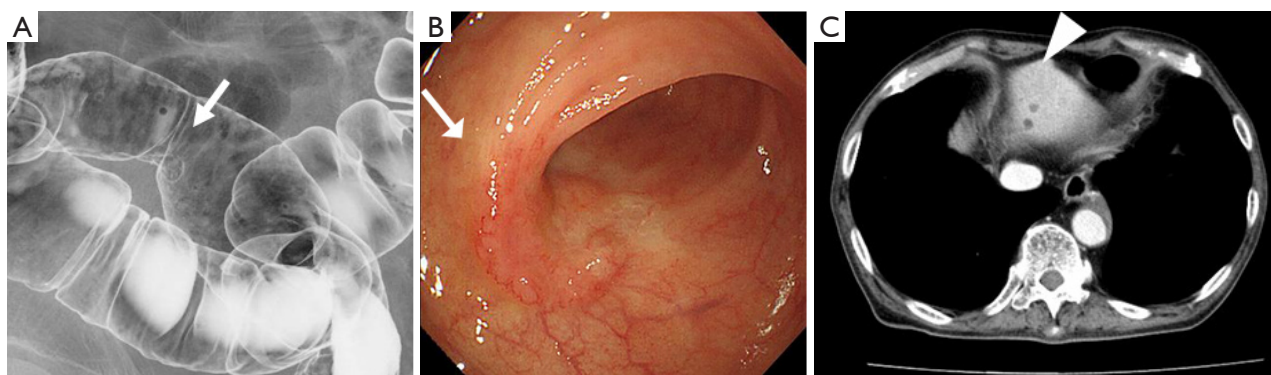


Figure 2 Post-chemotherapy imaging. (A) Barium enema examination revealed the main rectal lesion was significantly reduced, appearing as a small, type IIa-like elevation (white arrow). (B) Lower endoscopy showed the main rectal lesion was type IIa-like, with redness and small erosions; the surrounding area was markedly reduced and exhibited white scarring (white arrow). (C) Contrast-enhanced computed tomography indicated liver metastases showed shrinkage of metastases in liver segment 3 to low-density areas 8 mm in diameter. The other metastatic lesions had disappeared (white arrowhead).

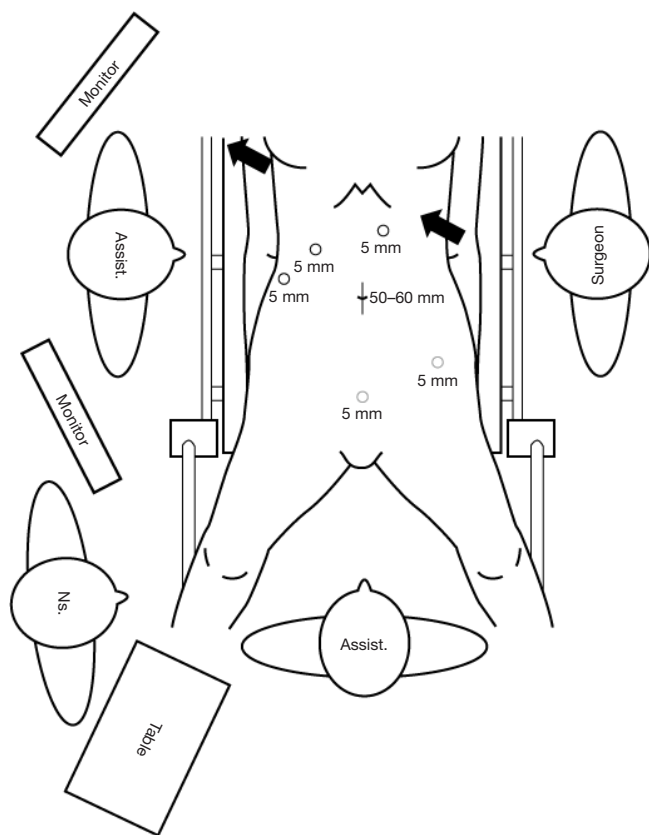


Figure 3 Schematic of port arrangement for partial resection of liver segment 3 using HALS. The upper abdomen operation by HALS used 3 ports and a 50-mm umbilical longitudinal incision for the hand access site (Arrows indicate surgeon's line of sight). HALS, hand-assisted laparoscopic surgery.

excision was performed on the sigmoid colon via the lateral approach. While maintaining the layer preserved with the lower abdominal plexus, an incision was made in the sigmoid mesocolon to ensure a safety margin of 30 mm on the anal side of the tumor; the rectum was dissected all around, taking care to avoid damaging the intestinal wall. The lesion was dissected with a double clip at the site where the left colic arteries and veins from the inferior mesenteric arteries and veins were preserved. The anvil head of a circular stapler was inserted through the anus and placed in the rectal stump, and the modified double-stapling technique with vertical division of the rectum was used (Figure 5C). The drain was placed, the wound was closed, and the operation was completed (6-9). Operation time was 4 hours and 47 minutes, and the amount of blood loss was 340 mL.

Histopathological findings

The tumor was a well-differentiated rectosigmoid adenocarcinoma; 25 mm × 20 mm in diameter; p-MP, p-RM0, L0, V0; and with no lymph node metastases (0/14) (Figure 6A,6B). A thorough histopathological examination of the partially resected area revealed no viable cancer cells, suggesting pathological R0 rectal cancer (Figure 6C,6D). The test for the RAS/BRAF mutation was negative.

Postoperative clinical course

The postoperative course was favorable, and the patient was discharged without complications at 10 days postoperatively.

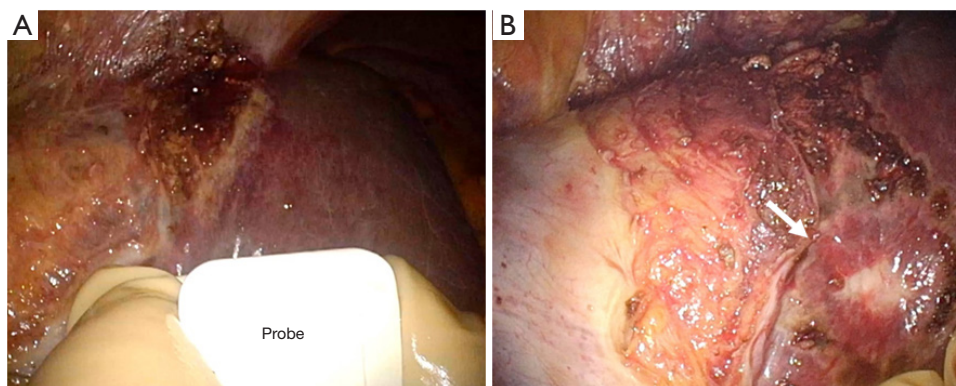


Figure 4 Photograph during operation. (A) Liver metastases were sought by palpation and use of an ultrasound probe inserted via the hand access site. (B) The excision area was marked with an electric knife (white arrow).

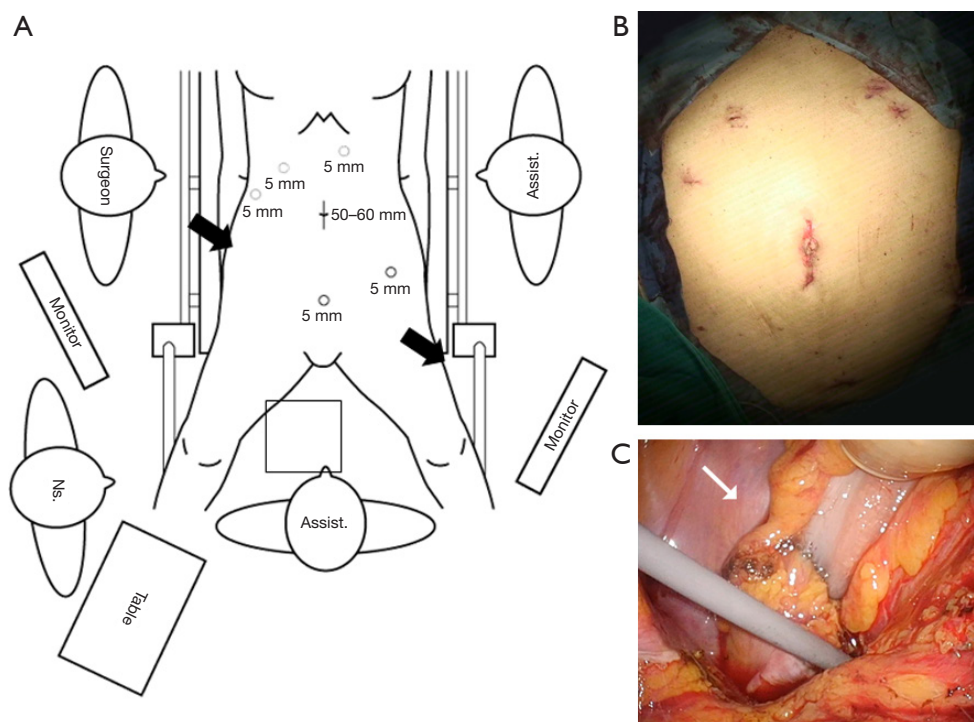


Figure 5 Anterior resection of the rectosigmoid colon using HALS. (A) Schematic of lower abdominal operation. Two ports were newly inserted in the left lower abdomen. The longitudinal umbilical incision was used as the hand access site. (Arrows indicate surgeon's line of sight). (B) Photograph of abdominal wound during surgery. (C) Modified double-stapling technique with vertical division of the rectum was performed via the anus (white arrow). HALS, hand-assisted laparoscopic surgery.

Following discharge, the patient received 4 cycles of B-mab + XELOX as an outpatient. Per the patient's request, the therapy regimen was changed to capecitabine only, which was continued for 1 year. At the time of this report, the patient has received more than 41 months of postsurgical

follow-up without metastasis or recurrence.

Discussion

When colorectal cancer with distant metastases is treated

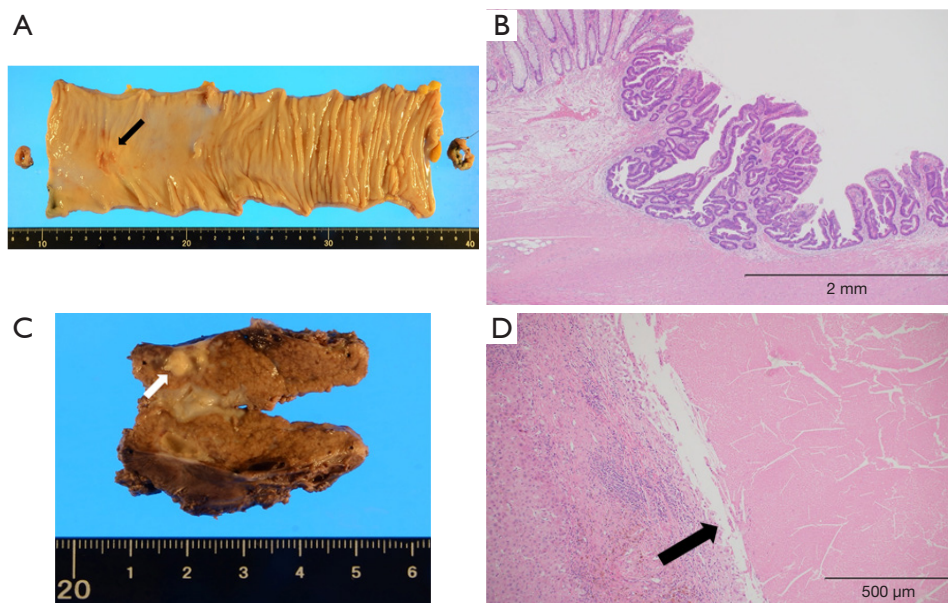


Figure 6 Excised specimens. (A) Rectosigmoid excision specimens show a well-differentiated rectosigmoid adenocarcinoma (25 mm × 20 mm in diameter; p-MP, p-RM0, L0, V0) (black arrow). (B) Histopathological findings. The primary colorectal cancer was a well-differentiated adenocarcinoma (H&E stain, ×12.5). (C) The partial resection of liver segment 3 was 10 mm in diameter, and the cut surface was white (white arrow). (D) A cut surface image of a partially resected liver segment 3 specimen revealed no viable cancer cells (black arrow) (H&E stain, ×40).

with systemic chemotherapy and subsequent diagnostic imaging indicates the therapeutic effect has made complete resection possible, conversion surgery often is performed if warranted by the patient's general condition (4). This approach differs from neoadjuvant chemoradiotherapy aimed at achieving local control (ie, preserving the anus when the anal margin is secured) and ensuring the circumferential resection margin on the posterior surface of the tumor, especially in advanced lower rectal cancer. Namely, systemic chemotherapy is appropriate for systemic disease with cancer cells spread throughout the body in distant metastases. For patients with breast cancer, the prognosis is good when p-CR is achieved through downstaging by neoadjuvant chemotherapy for chest wall invasion and distant lymph node metastasis, followed by excision (10). However, the effect of such treatment on overall survival remains unclear (11). In colorectal cancer with distant metastases, excising only the primary lesion results in rapid expansion of distant liver and lung metastases. Unless there is an oncological emergency (e.g., bleeding, perforation, or intestinal obstruction), chemotherapy should be initiated first; the optimal timing of surgery should be determined by monitoring the effect of

chemotherapy.

In the case presented, reduction of metastatic liver cancer was achieved by 4 cycles of chemotherapy delivered before surgery. An additional 5-cycle course was then administered while performing diagnostic imaging, which subsequently showed no metastatic lesions other than those in liver segment 3. Conversion therapy took approximately 1 year from diagnosis to surgical resection. Fortunately, in this case, resection was possible without any new metastatic lung or liver lesions.

At the time we were selecting a molecularly targeted drug for inclusion in the chemotherapy regimen in this case, current (2016) clinical guidelines did not indicate superiority of B-mab and anti-EGFR antibodies over other drugs. Because the patient strongly requested that treatment be initiated as soon as possible, irrespective of the RAS result, we selected B-mab as the first-line therapy (12). Although treatment guidelines provided no relevant supporting evidence, we used the same previously effective regimen for postoperative chemotherapy on the basis of its presumed effectiveness against potentially persisting circulating tumor cells (13,14). Revised clinical guidelines (2019) recommend B-mab for right colorectal cancer and

anti-EGFR antibodies for left colorectal cancer based on RAS and BRAF results. If this patient relapses in the future, we will include the tumor mutational burden (TMB) and microsatellite instability (MSI) status tests and will select molecular targeted therapy based on the results of RAS•BRAF tests (15). Evaluation of additional cases with distant metastases is needed to determine the optimal timing of surgery to achieve the best long-term prognosis.

We have treated 70 patients with B-mab + XELOX as first-line therapy for stage IV colorectal cancer, of whom 7 patients (10%) were able to receive conversion therapy. Of those 7 patients, 4 (57%) had no macroscopic tumor remnant. To date, 4 years is the longest follow-up period among the patients we have treated with this regimen. However, many patients experience relapse of residual liver cancer, and multidisciplinary treatment and long-term follow-up are necessary. Other considerations include dosing for various chemotherapy regimens (including oral anti-cancer drugs) and treatment duration.

Laparoscopic surgery has become widespread in Japan, and its application to the liver and pancreas has become popular (16). However, palpation is effective in searching for lesions that have shrunk due to chemotherapy (as in this case), and intraoperative ultrasound examination enables determination of the exact resection range. Furthermore, in the HALS procedure, the surgeon can use the incision made during open surgery. Because it is easier to operate on the surface of the liver and HALS facilitates tactile examination (unlike the ultrasonic probe used to examine the abdominal cavity), HALS makes it possible to simulate a 3-dimensional image in the horizontal, vertical, and deep planes. The liver is the largest organ in the abdominal cavity, and tactile sensation is important in detecting microscopic lesions to ensure safe removal of the affected region. The HALS procedure is considered safe and effective because hemostasis can be achieved during hepatectomy by applying appropriate pressure to stop bleeding, even with a large incision, and hemostats can be attached easily during the procedure.

In conclusion, this case report describes our experience with a patient with advanced (stage IV) rectosigmoid colon cancer with multiple H3 liver metastases who underwent conversion surgery after 9 cycles of systemic chemotherapy and achieved p-CR (R0). No metastasis or recurrence has been observed after 4 cycles of postsurgical chemotherapy and more than 41 months of follow-up. Based on the case and relevant literature presented, conversion surgery aimed at R0 is a viable option when the general condition of the

patient supports this goal.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-245/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-245/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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