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A 73-Year-Old Woman Treated for Rheumatoid Arthritis with Lower Rectal Carcinoma Who Underwent Abdominoperineal Resection, Lateral Regional Lymph Node Resection, and Partial Hepatectomy by Hand-Assisted Laparoscopic Surgery (HALS): A Case Report

Authors' Contribution:

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 73-year-old
Final Diagnosis: Lateral lymph node metastases • liver metastases • rectum carcinoma
Symptoms: Hematochezia
Medication: —
Clinical Procedure: Hand-assisted laparoscopic surgery
Specialty: Gastroenterology and Hepatology • Rheumatology • Surgery

Objective: Unusual clinical course
Background: This report describes the case of a 73-year-old woman treated for rheumatoid arthritis with lower rectal carcinoma who underwent abdominoperineal resection, lateral regional lymph node resection, and partial hepatectomy by hand-assisted laparoscopic surgery (HALS). More recently, HALS has proven to be useful in multiple organ resections.


Case Report: A 73-year-old woman who presented with hematochezia was diagnosed with lower rectal cancer and referred to our hospital. The patient had a history of rheumatoid arthritis and was taking oral nonsteroidal anti-inflammatory drugs. After further evaluation, the patient was diagnosed with stage IV rectal cancer with a metastatic liver lesion and a right lateral lymph node metastasis. All lesions were resected using HALS. A 50-mm longitudinal umbilical incision was created for use as a hand access site, and 3 ports with a diameter of 5 mm each were inserted into the lower abdomen to perform right lateral lymph node dissection and abdominoperineal resection. HALS was performed in the upper abdomen, where the liver was used to partially resect segment S6. The patient was discharged without complications 13 days after the operation.

Conclusions: In this complex case of advanced rectal carcinoma with liver metastases, use of the HALS surgical method was shown to be possible. Immunomodulatory treatment for rheumatoid arthritis may have influenced the outcome for this patient.

Keywords: Antirheumatic Agents • Arthritis, Rheumatoid • Hand-Assisted Laparoscopy • Hepatectomy • Lymph Node Excision • Rectal Neoplasms

Abbreviations: HALS – hand-assisted laparoscopic surgery; CL – conventional laparotomy; LAC – laparoscopic colorectal surgery; CT – computed tomography; TME – total mesorectal excision; XELOX – capecitabine plus oxaliplatin; LLND – lateral lymph node dissection; TMB – tumor mutational burden; MSI – microsatellite instability

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Background

During the past decade or longer, we have reported on more than 600 cases of hand-assisted laparoscopic surgery (HALS) for colorectal cancer with good survival outcomes [1-5]. HALS is used as an alternative to conventional open surgery or laparoscopic surgery; it requires insertion of the hand to maintain the pneumoperitoneum and, consequently, involves direct contact of the surgeon's arm with the abdominal wound [6]. For surgical treatment of rectal cancer in particular, HALS is now considered an excellent hybrid procedure between conventional laparotomy (CL) and laparoscopic colorectal surgery (LAC), with long-term results comparable to or better than CL in various aspects, including appearance [4,5]. More recently, HALS has also been shown to be useful for multiple organ resections, including those involving obstructive colorectal cancer, direct invasion to adjacent organs, and metastases [7-9]. Lastly, we comment on the possibility that immunomodulatory drugs used to treat rheumatoid arthritis may have affected the outcome for this patient [10,11]. This report describes a 73-year-old woman treated for rheumatoid arthritis with lower rectal carcinoma who underwent abdominoperineal resection, regional lymph node resection, and partial hepatectomy by hand-assisted laparoscopic surgery (HALS). More recently, HALS has proven to be useful in multiple organ resections.

Case Report

A 73-year-old woman presented to her physician with a chief concern of discomfort during defecation, beginning 2 to 3 months previously and accompanied by gradually worsening hematochezia. The patient had a medical history including rheumatoid arthritis and was taking oral nonsteroidal anti-inflammatory drug (NSAID) treatment (celecoxib). She was subsequently seen by a local physician, who performed lower gastrointestinal endoscopy and diagnosed advanced lower rectal cancer. Consequently, the patient was referred to our hospital in April 2018.

Laboratory testing showed anemia with a hemoglobin of 10.3 g/dL and a hematocrit of 33.6%. The tumor markers carcinoembryonic antigen (CEA) and CA 19-9 were increased to 17.6 (<5.0 ng/mL) and 58.1 (<37 U/mL), respectively. Barium enema examination revealed a 7-cm, circumscribed, elevated lesion extending from the lower rectum to the anal canal (Figure 1A). Lower gastrointestinal endoscopy showed a deep ulcer with white mass in the lower rectum. A type 3 bleeding tumor that partially reached the anal margin was diagnosed. Histopathological analysis of a biopsy indicated a moderately differentiated tubular adenocarcinoma (tub2). Contrast-enhanced computed tomography (CT) scans showed the rectal cancer was located mainly on the posterior wall and visualized

as a peripheral mass. A 30-mm metastatic mass was found in the lateral lymph nodes (Figure 1B), near the right closed hole lymph node (No. 283), and in the right lobe of the liver (Figure 2). Abdominal ultrasound confirmed the 30-mm metastatic lesion in the liver (section S6). Accordingly, the patient was diagnosed with stage IV advanced rectal cancer with a single metastasis of the liver (S6) and a metastasis of the closed foramen lymph node. Because progressive anemia due to hematochezia was affecting the patient's quality of life (QOL) and may have had an impact on immunity, we decided to perform HALS, which could achieve complete resection (R0) in a one-step procedure, rather than extensive laparotomy. HALS was performed by abdominoperineal resection, local lateral lymph node dissection, and partial hepatectomy (S6) through a 50-mm incision at the umbilicus for hand access.

We obtained written informed consent from the patient and her family to publish this case report and the accompanying images. We explained to the patient the fully voluntary nature of her selecting either conventional treatment or the treatment method using HALS, which is conducted as a standard procedure at our facility and is not a novel or experimental clinical practice.

Rectal-Anal Resection

For rectal-anal resection, monitors were placed on the left and right sides of the patient. The surgeon stood on the right side of the patient, and the camera was operated by an assistant on the left side. A 50-mm, longitudinal laparotomy incision was made at the umbilicus, and a visual inspection for intra-abdominal adhesions was performed. A wound retractor (Alexis Wound Protector-Retractor S; Applied Medical, Rancho Santa Margarita, CA) was placed into the incision created for use as a hand access site and insufflation was started; at the same time, three 5-mm ports were inserted from the middle of the left and right anterior superior iliac spines and 3 fingertips caudal to the upper pubis (Figure 3). HALS was started with the patient in the right lateral decubitus position with the head down [1-3]. The peritoneal maneuver was performed by the same procedure and technique as standard laparotomy. The fusion fascia of the sigmoid and descending colon were dissected until the layer for total mesorectal excision (TME) was reached (the left ureter and lower abdominal plexus were thereby identified and preserved). Next, the sigmoid mesocolon was incised. The left colonic artery bifurcation was confirmed, ligated, and dissected with a clip at the periphery of the bifurcation. The fascia was dissected at the front of the pouch of Douglas, from the right rectal wall to the caudal side. An incision was made to reach the deep portion of the pelvic floor, taking care not to damage the posterior vaginal wall. The pelvic floor muscles and the anococcygeal ligament were dissected by the HALS procedure. En bloc

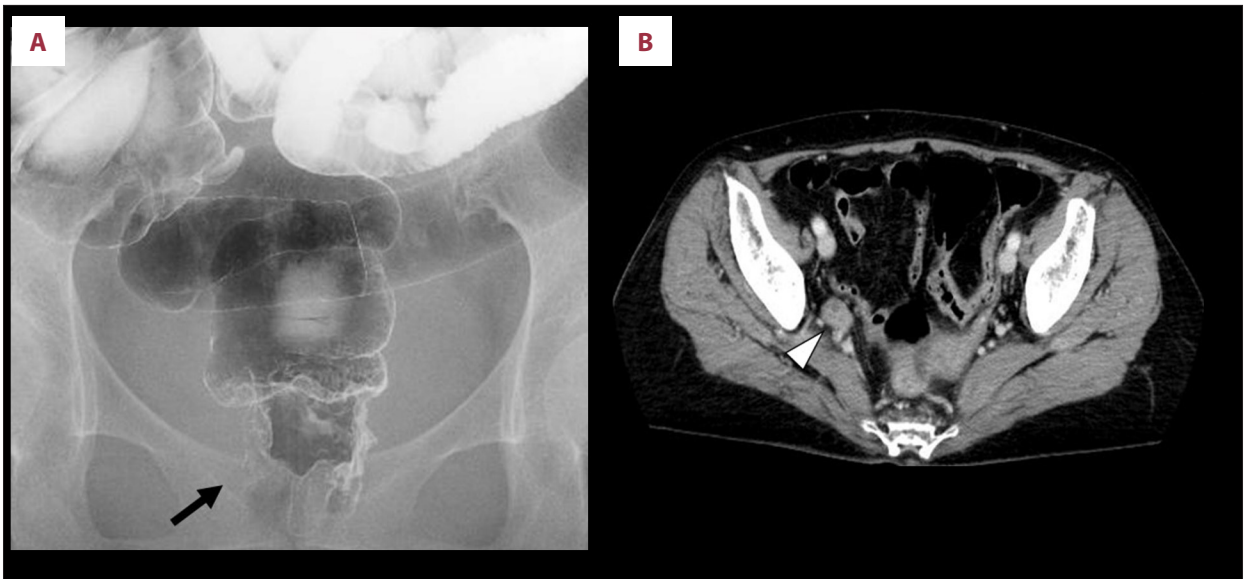


Figure 1. Preoperative imaging of rectal cancer and lymph node metastasis. (A) Barium enema imaging revealed a 7-cm, type 2, circumscribed lesion extending from the lower rectum through the anal canal (arrow). (B) A contrast-enhanced computed tomography scan of the pelvic area showed rectal cancer located mainly on the posterior wall, with metastasis present at the right lymph node (white arrowhead).

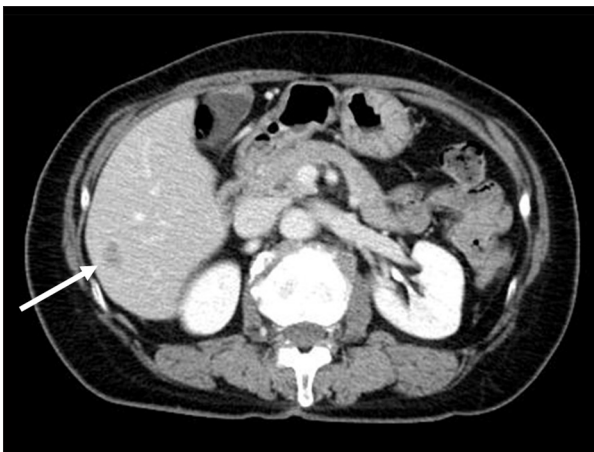


Figure 2. Preoperative imaging of metastatic liver lesion. Contrast-enhanced computed tomography scan of the upper abdomen showed a 3-cm metastatic tumor of the liver (segment 6 of the liver; arrow). (This finding was similar to the ultrasound and magnetic resonance imaging findings).

lymph node dissection was performed with an energy device centered on the right closed ureteral lymph node (no. 283), which appeared metastatic in preoperative imaging. Next, perineal fatty tissue was exposed from the laparotomy incision site, and extralevator abdominoperineal resection was performed. The colon and the sigmoid plexus were fully resected with complete removal of the external anal sphincter muscle group. Hemostasis was confirmed. The recto-anal resection site was packed and confirmed to be airtight.

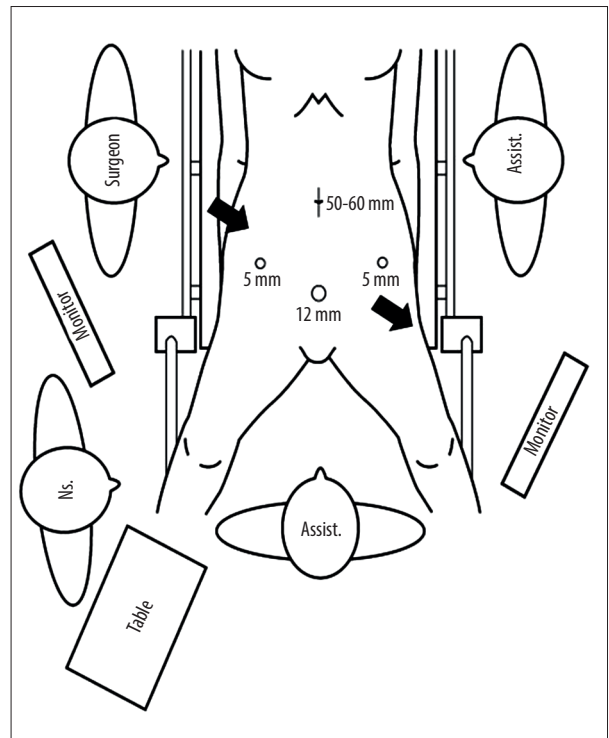


Figure 3. Diagram of location of ports and incision used in resecting the primary lesion. Arrows indicate the surgeon's line of sight for arranging ports from the lower abdomen to the pelvic floor for the hand-assisted laparoscopic surgery procedure.

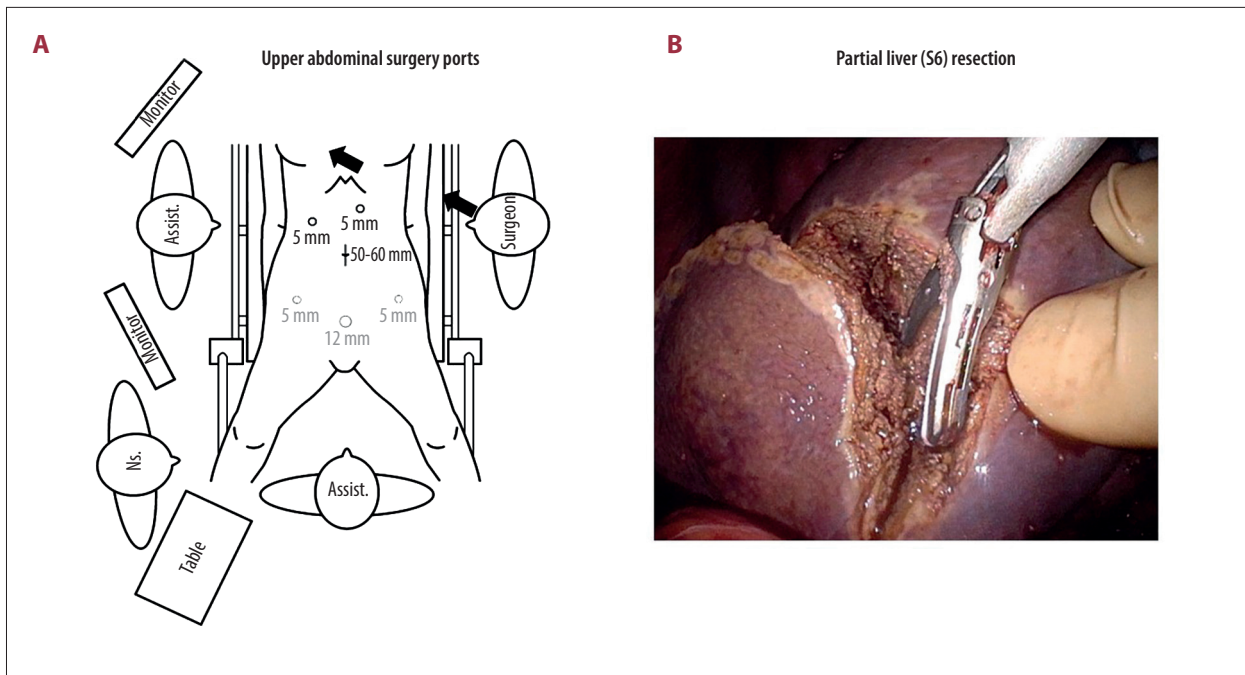


Figure 4. Upper abdominal surgery for partial resection of the liver (segment 6 of liver). (A) Diagram of port arrangement, with arrows indicating the surgeon's line of sight. (B) A 3-cm metastatic tumor in the liver (segment 6 of liver) was confirmed by intraoperative ultrasound and palpation. The intraoperative photograph shows partial hepatic resection performed with an ultrasonic coagulator.

Partial Hepatic Resection

Next, a liver specialist surgeon familiar with HALS joined the surgical team to perform the hepatic resection. The monitors were moved to the right side of the patient, with the surgeon standing at the left side. The camera port was inserted into the upper right abdomen at the location where a drain was likely to be placed external to the liver. At the left side of the epigastrium, two 5-mm ports were inserted to perform the Pringle maneuver at the hepatic hilar (Figure 4A). Preoperative diagnostic imaging and intraoperative ultrasound indicated that a metastatic liver tumor was present at S6 and its safe resection without damaging important vessels was deemed possible. Therefore, a partial hepatic resection was performed. A braid was passed through the foramen of Winslow, and blood circulation was interrupted by the Pringle maneuver by using a Nelaton catheter (No. 9). The bare area of the right lobe of the liver was incised and detached through the left edge of the inferior vena cava, and the liver was mobilized. The planned resection area was marked on the liver surface after palpation and intraoperative ultrasound examination with a probe previously inserted through the hand access site. Partial hepatectomy was performed with an ultrasonic coagulator (Figure 4B). The main Glisson group was dissected under the clip. After resection of the metastatic lesion, a drain was placed in an extrahepatic site.

Next, a drain was placed at the bottom of the pelvis using the port insertion site in the lower right abdomen, and the margin of the colon was secured using the HALS procedure to ensure an extra-abdominal route. A single-hole permanent artificial anus was placed in the lower left abdomen, and the operation was completed (Figure 5).

The total operation time was 7 hours 12 minutes, and the volume of blood lost was 701 ml. The duration of surgery was longer than expected because of insertion of a new port before liver resection, preparation for intraoperative ultrasound, and mobilization of the liver from the diaphragm. Exudates from areas of increased exfoliation and the resected rectum constituted 60% of the total volume of blood loss, which was verified by both intraoperative laparoscopic video and the surgical record.

Histopathology Specimens

Histopathology results for rectal resection specimens characterized an 80×70 mm, moderately differentiated, stage T3 mucinous adenocarcinoma (Table 1) (Figure 6A). Genetic testing indicated the patient was KRAS-positive, with mutation observed at KRAS codon12 [12]. Of 24 lymph nodes examined, 16 had positive results for metastasis, including the 28-mm right closed foramen lymph node (No. 283D). A 29-mm adenocarcinoma similar to the primary lesion was detected in the

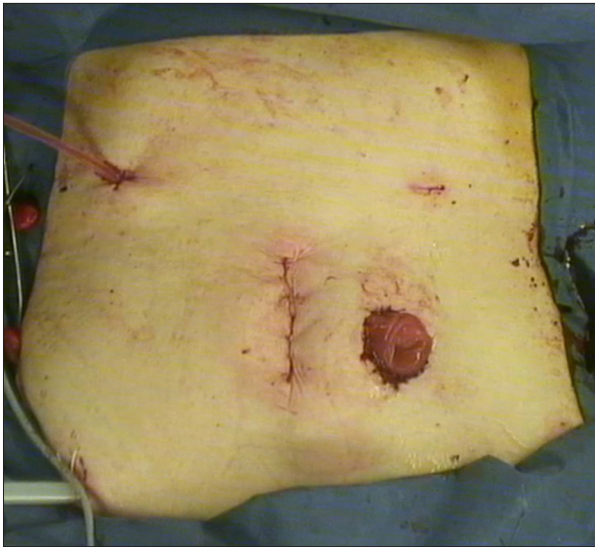


Figure 5. Photograph of the postoperative abdomen. A drain was placed by using the port insertion sites in the upper right (under the right diaphragm) and lower right (pouch of Douglas) abdominal areas. A permanent artificial anus was constructed in the lower left abdomen.

Table 1. Histopathology results of rectal carcinoma.

Histopathology characteristic	Result
Tumor site	Lower rectum
Tumor size	80×70 mm
Histological type	Moderately differentiated >Mucinous adenocarcinoma
Pathological stage/depth of invasion	pT3 (pA)
Pathological margins	
Proximal	190 mm
Distal	25 mm
Radial	1 mm
Lymphatic invasion	2
Venous invasion	1
Tumor deposits	Negative

p – pathological findings; T3 – tumor invades subserosa; A – adventitia; mm – millimeter.

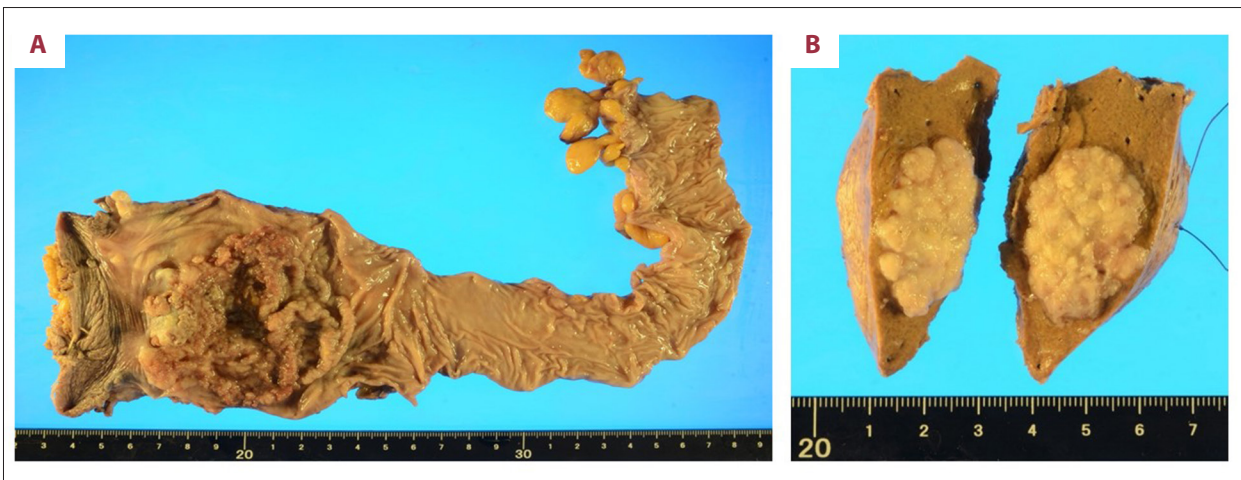


Figure 6. Resected specimens. (A) On rectal biopsy, a resected recto-anal specimen showed a type 2 lesion with a diameter of 80×70 mm; (B) A cut surface image of a specimen from the partially resected liver (segment 6 of the liver) showing an adenocarcinoma that was identical to the main lesion was detected and diagnosed as metastatic liver cancer

resected liver (S6) specimen and diagnosed as a metastatic tumor from the rectum (Figure 6B).

Postoperative Clinical Course

The patient had an uncomplicated recovery and was discharged from the hospital 13 days after surgery. Before starting adjuvant chemotherapy postoperatively, we performed a CT scan and abdominal ultrasound and confirmed the R0 status. The patient then started XELOX (capecitabine plus oxaliplatin)

therapy together with a molecular targeted drug (bevacizumab) at an outpatient clinic. Patients at our institution undergo CT scan and/or abdominal ultrasound every 2 to 3 months after surgery. This routine imaging detected the onset of multiple nodular metastatic foci (<5 mm) in the lungs and liver of this patient 5 months after surgery. During this period, the patient also experienced worsening rheumatoid arthritis, resulting in a change in her rheumatoid arthritis medications (water-soluble prednisolone and iguratimod, an immunomodulating disease-modifying antirheumatic drug). Chemotherapy

with tegafur, gimeracil, and oteracil potassium (S-1) plus irinotecan hydrochloride hydrate (IRI) for rectal cancer was initiated. However, the patient died approximately 11 months after the operation.

Discussion

In 2009, we first published a summary of our experiences with HALS in 10 patients with colorectal cancer. Since then, we have published several articles on various aspects of HALS minimally invasive surgery, including the lower costs and good safety and prognosis [5,13-15]. Even in this complex case of advanced rectal carcinoma with liver metastases, the use of the HALS surgical method was shown to be feasible [16].

The use of LAC has become widespread for radical surgery for colorectal cancer in Japan due to the advantages of LAC compared with the CL procedure, which is associated with difficulty visualizing the apex of the prostate and the deep pelvis. With a laparoscope, it is possible to magnify a lesion and share those images, thereby improving safety of the surgical procedure.

HALS initially was used for splenectomy. Because HALS allows the surgeon to use their left hand freely, hemostasis in sudden bleeding can be achieved with fingers, regardless of the size or weight of the tumor. Performing conventional upper abdominal surgery (eg, liver resection) and pelvic surgery (eg, abdominoperineal resection) simultaneously, as in the case described here, requires a large midline incision in the upper and lower abdomen. In contrast, using HALS enables a safe procedure conducted via a small umbilical incision of approximately 5 cm and 5 small port incisions. Moreover, HALS results in decreased wound pain, minimally invasive surgery, and improved ability to perform activities of daily living in the early postoperative period. Additionally, after the HALS operation, a single-hole artificial anus can be constructed safely and easily via retroperitoneal access to prevent parastomal hernia, prostatic prolapse, and internal hernia [17]. Presently, for approximately 7 types of surgical procedures for colorectal cancer, it is possible to perform a total colectomy via 2 to 3 ports [1-3].

When a LAC simulation was performed for this patient, it was judged that the lower abdominal operation could be performed using 5 ports and the upper abdominal operation achieved with 5 ports. Assuming 2 ports could be used for both procedures, a total of 8 or more ports would be required overall. Furthermore, a 50-mm laparotomy was estimated to be needed to obtain the specimen. In comparison, the HALS operation required a 50-mm hand access site at the umbilical site and only five 5-mm ports. The HALS access site also can be used for multiple lesions and other organ resections. Thus, HALS can be considered a safe, reliable procedure that is associated with

significantly reduced operative times when performed by experienced surgeons and relatively low-cost procedure for cases such as that reported here [16,18].

HALS is positioned between laparotomy and LACS. We previously reported that a surgeon certified as a specialist surgeon by the Japanese Society of Gastroenterological Surgery can perform the HALS procedure without difficulty [1,19]. A recent article reported that approximately 2% of surgeons who received training in laparoscopy had poor scores in a special perception test. However, because HALS can be performed under laparoscopy using the same procedure as that used for laparotomy, we consider HALS to be a viable procedural option [20].

Recently, final results of a large-scale randomized control trial (JCOG0212) of TME with or without lateral lymph node dissection (LLND) for stage II/III lower rectal cancer did not confirm the noninferiority of TME alone vs TME with LLND [21]. However, other reports have indicated that LLND was associated with significantly decreased local pelvic recurrence without significantly differing survival results, yet a retrospective analysis demonstrated no positive effect of LLND on patient outcome. These conflicting findings indicate that further investigation is warranted [22,23].

Hofheinz et al reported on neoadjuvant chemoradiotherapy (NACRT) for stage II/III lower rectal cancer. NACRT is used prior to resection when preoperative diagnostic imaging indicates nonresectable direct infiltration in the surrounding organs or when complete resection by a single surgery is deemed difficult due to multiple liver metastases in both lobes. However, a 6- to 8-week wait-and-see period often is required after radiotherapy [24]. The appearance or exacerbation of hepatoma and metastatic liver cancer can be assessed during chemotherapy, thereby increasing the likelihood of down-sizing or down-staging in cases of large stage T3/T4 tumors. Moreover, this approach reduces the technical difficulty of surgery and can result in the tumor ablation margin becoming negative (RM0).

In the case presented here, the patient had a hemorrhagic tumor and advanced anemia. Also, the patient had begun experiencing pain and emerging symptoms of stenosis. We presumed this patient had systemic disease with blood-borne metastatic resectable hepatic cancer (H1) [25-28]. Accordingly, we prioritized immediate resection followed by systemic chemotherapy (bevacizumab plus XELOX). In 2016, when we selected a molecularly targeted drug as part of this chemotherapy regimen, clinical guidelines did not indicate superiority of bevacizumab or anti-EGFR (epidermal growth factor receptor) monoclonal antibodies over other drugs. Therefore, we did not consider mutations in RAS and BRAF [27]. Our treatment strategy positioned radiation therapy as an optional treatment in case of postoperative local relapse [29]. However, a recently

published Japanese clinical guideline recommends deciding on the chemotherapy regimen after performing molecular testing and determining the tumor mutational burden (TMB) and microsatellite instability (MSI) status [28]. There are no reports of carcinogenicity associated with treatment using iguratimod, an immunomodulatory agent, for postoperative deterioration of rheumatoid arthritis or a comorbid medical disorder. However, some authors have expressed the opinion that long-term caution is indicated regarding the effects of such immunomodulatory therapies on tumor immunity [10,11].

Conclusions

In this complex case of advanced rectal carcinoma with liver metastases, the use of the HALS surgical method was shown to be feasible. Immunomodulatory treatment for rheumatoid

arthritis may have influenced the outcome of this patient. A new clinical guideline recommends deciding on the chemotherapy regimen after performing molecular testing and determining the TMB and MSI status.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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