

The preliminary experience in simultaneous treatment of rectal cancer and synchronous liver metastases with laparoscopy

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Background/aims: There is no consensus for laparoscopy first in patients with rectal cancer and synchronous liver metastases, whose metastases are confined to the liver. This study aimed to evaluate its indications for one-stage surgery in laparoscopy. **Materials and Methods:** Eighteen patients with rectal cancer and synchronous liver metastases, who had undergone laparoscopic colorectal resection and simultaneous treatment for liver metastases, were retrospectively reviewed. **Results:** Concomitant with laparoscopic colorectal resection, eight patients received liver resection simultaneously; 10 patients underwent a variety of down-staging management including local ablation, right hepatic portal vein ligation, and implantation of chemotherapy pumps into the hepatic artery. The colo-anal/rectal anastomoses were performed with a stapler or “pull-through” mode though the anus. Three patients underwent two-stage liver resection following tumor down-staging. Median survival time was 22.3 months. **Conclusions:** Laparoscopy approach for rectal cancer and synchronous liver metastases is feasible in selected patients. Colon pull-through anastomosis was a potential method to avoid abdominal incision and decrease the risk of anastomotic leakage. It is worth further investigation regarding its advantages over traditional modalities with a prospective randomized controlled study.

Key words: Laparoscopy, rectal cancer, liver metastases, synchronous, liver resection

Laparoskopik olarak rektal kanser ve eşlik eden karaciğer metastazlarının eş zamanlı tedavisiyle ilgili başlangıç tecrübeleri

Amaç: Laparoskopik tedavi rektal kanser ve senkron karaciğer metastazları için yeni bir alternatif olmuştur. Ancak, sadece karaciğer metastazı olan rektal kanser ve senkron karaciğer metastazları olan hastalar için ilk olarak laparoskopi yapılmasıyla ilgili bir konsensüs yoktur. Bu çalışmanın amacı, laparoskopik olarak tek basamaklı cerrahinin endikasyonlarını değerlendirmektir. **Gereç ve Yöntem:** Rektal kanser ve senkron karaciğer metastazlı laparoskopik kolorektal rezeksiyonla eş zamanlı karaciğer metastaz tedavisi gören 18 hasta retrospektif olarak değerlendirildi. **Bulgular:** Laparoskopik kolorektal rezeksiyonla birlikte, 8 hastaya eş zamanlı karaciğer rezeksiyonu, 10 hastaya lokal ablasyon, sağ hepatik portal ven rezeksiyonu ve hepatik arter içerisine metastaza yönelik kemoterapi pompası implante edilmesi gibi her türlü “down-staging” yöntemi uygulandı. Kolo-anal/rektal anastomoz stapler veya “pull through” yöntemiyle anüsten yapıldı. Üç hastaya “down staging” sonrası 2 aşamalı karaciğer rezeksiyonu yapıldı. Ortanca sağkalım süresi 22.3 aydı. **Sonuç:** Seçilmiş hastalarda rektal kanser ve senkron karaciğer metastazına yönelik laparoskopik yöntem uygulanabilir. Kolon “pull through” yöntemi abdominal insizyon ve anastomoz kaçığının önlenmesi açısından potansiyel bir yöntemdir. Prospektif randomize bir çalışmayla geleneksel yöntemlere üstünlüğü araştırılmaya değerdir.

Anahtar kelimeler: Laparoskopi, rektal kanser, karaciğer metastazları, senkron, karaciğer rezeksiyonu

INTRODUCTION

Synchronous liver metastases can be found in 15-25% of patients with colorectal cancer (1,2). In rectal cancer and synchronous liver metastases (RCLM), neoadjuvant chemotherapy was usually considered first before removing the primary tumor, even complicating with bleeding and intestinal obstruction (1). However, only a few patients can benefit from this strategy, mostly because either the metastases are considered unresectable from the beginning, or because they progress during treatment of the primary tumor. In the present series, patients were treated with laparoscopic approach first. This is theoretically appealing, as it provides for resection of the primary tumor and simultaneous resection of the liver metastasis, or for the more effective treatment of the liver metastasis with minimal invasiveness, thus avoiding the risk of complications due to either the primary tumor or liver metastasis progression, and with the opportunity for one-stage resection or “down-staging” treatment. In the present study, 18 patients with rectal cancer and synchronous liver metastases (RCLM) who underwent laparoscopic rectal cancer resection and simultaneous surgery for liver metastasis, which included surgical resection, liver arterial infusion chemotherapy or local ablation therapy from April 2005 to December 2010 were reviewed. The safety and feasibility of laparoscopy in simultaneous invasive treatment for RCLM were evaluated.

MATERIALS AND METHODS

Patients

From April 2005 to December 2010, 18 patients underwent laparoscopic simultaneous treatment for RCLM, who were identified as having no extra-hepatic metastasis with positron electron tomography (PET). There were 12 males and 6 females, aged 23-77 years, with a median age of 49 years. All of the studies were performed retrospectively by collecting and analyzing data from the patient records. This study was approved by the Institutional Review Board of our hospital. Two patients suffered blood loss, and two patients were complicated by incomplete intestinal obstruction. All patients were stage D according to Dukes classification, and the masses were no more than 5 cm in diameter and 4-10 cm from the anus. All liver metastases were less than 6 cm in diameter. Three cases had solitary metastatic lesions on the left lobe (2 cases in segment VI and 1 case in segment IV); 6 cases had less than 10 multiple lesions (4 cases located in the right-tri-segment and 2 cases located dominantly in the left-tri-segment, with 1-2 small tumors (<2 cm in diameter) in the right posterior lobe); and 4 cases had more than 10 diffuse lesions (Table 1). All liver functions were in Child's Grade A, and no other distal metastases were present. The pathologic findings included: a tumor-free surgical margin of more than 1 cm in all resected specimens, 9 well-differentiated adenocarcinomas, 5 poorly differentiated adenocarcinomas, and 4 mucinous adenocarcinomas.

Table 1. Patient characteristics, surgical background and surgical outcomes

Liver lesions	N	Location AV (cm)	Op (rectum) procedure (n)	Op (liver) procedure (n)	Prognosis
Unilateral	8	4-9	AR+CRA (3)	Seg VI (3)	Sur (50 m, 20 m, 9 m)
				Seg II-III (3)	D (26 m, 22 m, 14 m)
			LAR+PTA (2)	Seg IV (1)	Sur (38 m)
			SLAR+PTA (1)	Seg II-III-IV (1)	Sur (20 m)
R-tri-lobe	4	7-9	AR+CRA (2)	PVL+AL (4)	2-S-R, Sur (18 m)
			SLAR+PTA (1)		2-S-R, Sur (16 m)
			LAR+PTA (1)		D (18m), Sur (16 m)
L-tri-lobe (d)	2	5-6	SLAR+PTA (1)	AL (2)	2-S-R, D (29 m)
			LAR+PTA (1)		Sur (19 m)
Diffuse	4	6-10	AR, CRA (2)	CPI+AL (4)	D (21 m, 13 m, 9 m)
			AR, PTA (2)		Sur (15 m)

AL: Ablation. AR: Anterior resection. AV: Anal verge. CPI: Chemotherapy pump implantation. CRA: Colorectal anastomosis. D: Death. EBL: Estimated blood loss. L: Left. LAR: Low anterior resection. L-tri-lobe (d): Lesions located dominantly in left tri-lobe and 1-2 small lesions in right posterior lobe. OP: Operation. PTA: Pull-through anastomosis. PVL: Portal vein ligation. R: Right. Re: Resection. R-tri-lobe: Right tri-lobe. Seg: Segmentectomy. SLAR: Super low anterior resection. Sur: Survival. 2-S-R: 2-stage resection.

Surgical Treatment

Patients were placed in the supine position with the four limbs fixed to allow for steep changes in the table position; the trocar placement is shown in Figure 1. The surgical procedures included three stages: (i) laparoscopic exploration to exclude peritoneal carcinomatosis, metastatic status of regional lymph nodes or undetected liver deposits, (ii) laparoscopic rectal resection with mesorectal excision, and (iii) treatment of liver metastasis. The treatment modalities included liver resection for 8 patients and intratumor ethanol injection for the remaining 10 patients (including 4 patients with combined portal vein ligation (PVL) and 4 patients with combined hepatic arterial chemotherapy pump implantation) (Table 1). The anastomosis was divided into two types: 8 patients underwent colorectal anastomosis following tumor removal from the anus, and 8 cases underwent surgery similar to Bacon surgery - coloanal "pull-through" anastomosis. FOLFOX formula was administered to the patients after surgery.

Treatment for Liver Metastasis

Liver metastasis resection/ablation

All liver resections were performed using the same procedure with hemihepatic vascular occlusion in-

troduced by Tanaka (3). The limits of the resection were marked on the liver surface with diathermy approximately 2 cm from the lesion margin. Liver transection was performed by an endoscopic ultrasonic or electric dissector. Biliary and vascular radicles were clipped with laparoscopic clips and divided. In the left lateral segmentectomy, the lateral segment was mobilized by dividing the left triangular and falciform ligaments. Liver transection was performed using an electric dissector or harmonic scalpel (Ethicon Endo-surgery, USA). Small vascular or biliary pedicles were divided after electric coagulation or between clips. Portal and major hepatic veins were divided using a Hem-o-lock clip.

Intratumor ethanol therapy is one of the local methods widely used for hepatocellular carcinoma (HCC) ablation (4). The needle penetrated to the center of the tumor is guided by direct laparoscopic vision or B-mode ultrasound. According to the tumor size and therapeutic purposes, different quantities of alcohol were given. For extensive metastasis, the purpose was to shrink the tumor size. According to the diameter of tumor lesions, the estimated volume of alcohol injected was equal to the diameter plus 2 ml, with a total volume less than 30 ml. For small lesions (<3 cm in diameter) with future residual liver, sufficient quantities of alcohol should be injected to achieve complete tumor necrosis.

Chemotherapy pump implantation

Referring to the previous introduction by Feliciotti et al. (5), first, the gastroduodenal artery and hepatic artery were isolated and identified, and the junction with the loop of the hepatic artery from which it arises at a right angle was exposed. The right gastric artery and any accessory arteries branching off from the hepatic artery were then exposed and ligated. The dissection of the gastroduodenal artery at its origin from the hepatic artery was necessary for subsequent examination so that the tip of the intra-arterial catheter could proceed correctly inside the artery until it reached the junction with the hepatic artery, but did not enter it. The gastroduodenal artery was then isolated distally to where it disappeared behind the duodenum and was raised by passing a loop suture beneath the vessel. Once the gastroduodenal artery was prepared for approximately 3 cm, the silicone-beaded catheter of the perfusion system (Davol Hickman Subcutaneous Port-Titanium, C.R. Bard, Inc., Cranston, RI, USA), which had al-

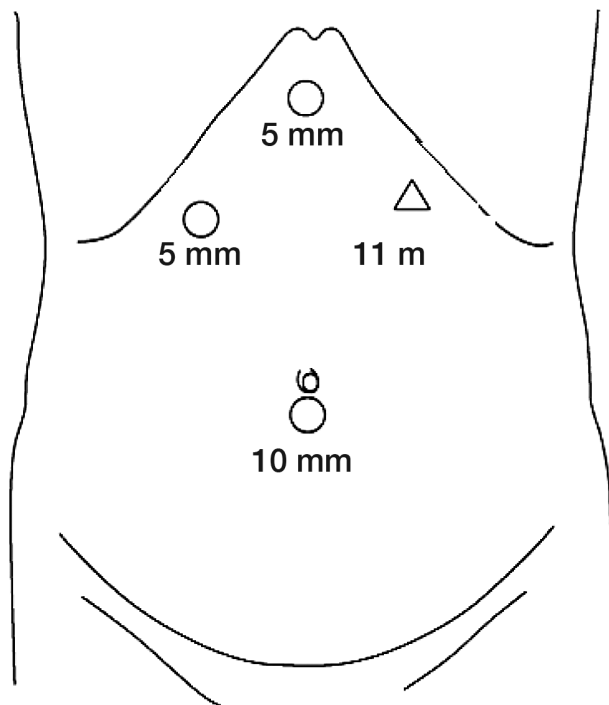


Figure 1. Trocar disposition for rectectomy and operative trocars for liver surgery are arranged along the drawn in the upper abdominal quadrants in relation to tumor location.

ready been flushed with heparinized saline, was completely introduced inside the peritoneal cavity. The extremity of the catheter that was going to be located intra-arterially was previously trimmed to the necessary length so that the first suture bead was at a distance of 5 mm from the tip of the catheter. The intra-arterial catheter was secured with two ligatures tied. The clip placed at the origin of the gastroduodenal artery from the hepatic artery was then gently removed with a grasper.

Right portal vein ligation

Referring to the previous introduction by Are's group (6), the portal triad was dissected from the right side using the harmonic scalpel. The bile duct was dissected and elevated to expose the main portal vein. Further dissection was performed in the cranial direction to identify the portal bifurcation. The right portal vein was then dissected and encircled with a vessel loop or clipped with titanium clips.

Rectal cancer treatment

In accordance with the laparoscopic total mesorectal excision (TME) principle (7), after exploration of the tumor location, the colon was ligatured approximately 10 cm adjacent to the tumor. Ligation of the inferior mesenteric vessels, complete mobilization of the splenic flexure, and partial or TME were conducted according to the location of the rectal cancer. Rectal dissection was performed 3 cm below the lower edge of the tumor and to the pelvic floor for mid and low rectal tumors with TME, expanding the anus and attempting to contain five fingers. Then, the colorectal specimen was extracted from the anus, and the colon specimen was resected; the tips of the residual colon were degermed with iodophor.

Colo-rectal/anal anastomosis

Reconstruction was performed by either a conventional stapled colorectal anastomosis for rectal tumors or colon pull-through anastomosis for patients with low rectal tumors or poor general condition. In general, the anastomosis pattern depended on the patient's general condition, tumor location and blood supply in the distal colon. For the patients in good general condition, the conventional stapled coloanal anastomosis was performed. If the patients were in poor general condition or had a low rectal tumor, the colon pull-through anastomosis was performed. The procedure highlights included: the colon was extracted from the anus, while assuring there was no extension of re-

sidual colon. In the expected "anastomosis" location, the seromuscular layer was sutured and ligated to the broken ends of the rectum. Below the location of the "anastomosis," the surplus colon was ligated for 30 minutes for delayed narcosis and shedding. The ischemic broken ends of the colon were sutured and ligated to the anal verge, and anal tube was implanted as a stent.

RESULTS

Fourteen patients (9 males, 5 females), 23–77 years old (median, 53 years), underwent a laparoscopic TME. Synchronous liver metastases were respectively resected (8 cases), or underwent ablation (2 cases), right PVL + ablation (4 cases), or CPI + ablation (4 cases) (Table 1). The mean in-hospital time was 11 days, with a range of 5–22 days. The patients' demographics, location of the primary rectal cancer, and distribution of liver metastases are shown in Table 1. The diameter of all primary tumors was less than 5 cm. The median operating time was 232 minutes (range, 190–310). The distance of the coloanal anastomosis from the anal verge was 3.5 cm (3.5 ± 2.6 , 2.5–4.0); a coloanal pull-through anastomosis was required in 6 patients with low rectal cancer and poor general condition. There were some complications, including 7 cases of fever, 3 cases of mild liver function abnormality, and 1 case of pulmonary infection. The anal function in all patients undergoing this procedure was evaluated within the 6th – 12th month postoperatively. In early stages, all of the patients' stool frequency increased, and the stool control was poor, but this lasted for only 3–6 months; the anal function was nearly normal. The median follow-up time was 27 months (range, 9–50). The average survival time was 22.3 months; none of the patients who had undergone curative resection had local recurrence. Most patients had an increase in stool frequency in the early stage. The median stool frequency was 3 (1–10) bowel movements per day; 3–6 months later, it had gradually returned to a normal level. Only 1 case had anal stenosis 5 months' postoperatively, which was relieved after anal expansion. All patients were administered chemotherapy with FOLFOX formula from 4–14 days (average, 8 days).

DISCUSSION

The routine treatment of RCLM is removal of the primary tumor followed by 3–6 courses of chemotherapy, and then, if the metastases are resectable,

by liver resection should be applied. However, only a few patients can benefit from this strategy, mostly because either the metastases are considered unresectable from the beginning, or because they progress during treatment of the primary tumor (1). However, some authors (9,10,12) consider resection of synchronous liver metastases along with the primary lesion warranted simply because this is the sole strategy with curative potential – a five-year survival of 25-38%. Recent studies reported that simultaneous resection of RCLM can be performed safely with similar short-term outcomes compared to staged procedures (10,13,14). A technical aspect that may relate to adverse outcomes for combined resections is safe for intestinal anastomosis when a Pringle maneuver is needed. Liver pedicle clamping can lead to an increased risk of anastomotic leakage because of the onset of intestinal edema (15,16). By laparoscopy, simultaneous resection for RCLM does not require occlusion of the whole hepatic inflow using hemihepatic vascular occlusion (17). Furthermore, the present series provided delayed coloanal anastomosis for patients with middle and low rectal tumor or poor general condition, who have a high prevalence of anastomotic leakage, while avoiding a prophylactic ileostomy.

Preparing for simultaneous resection for RCLM, the colorectal cancer and liver metastases must comply with the indications of laparoscopic liver resection and laparoscopic TME, including liver tumor location limited to segment II to segment VI and tumor size less than 5-6 cm (4). Otherwise, left or right hemi-hepatectomy is another option. Recently, many studies (13,14,17) demonstrated that laparoscopic resection for rectal cancer, combined with synchronous resection of liver metastases, is a safe and feasible procedure in selected patients. With regard to liver metastases that are very difficult to resect with laparoscopy, the simultaneous open operation for liver metastasis is also a good option (16,18).

However, only 20% of these patients with synchronous colorectal liver metastases can receive curative hepatic resection (19). Most patients underwent a down-staging treatment, and were expected to achieve a future two-staged operation. Down-staging of a tumor is an acceptable modality of treatment for patients with multiple or very large metastases when resection is initially not feasible. This modality can be used in an attempt to convert unresectable tumors into potentially re-

sectable ones. The down-staging treatment for unresectable tumors includes portal vein embolization (PVE) or PVL (inducing residual liver hypertrophy), local ablation of the tumor, and simultaneous neoadjuvant chemotherapy (20-22). These surgical procedures can be performed easily by laparoscopy.

The patients with downstaging treatments can be divided into two conditions. One condition may be considered ineligible for liver resection because the future liver remnant (FLR) is apparently too small to provide sufficient liver function. Selective PVE is an effective means of inducing ipsilateral atrophy and contralateral hypertrophy of the liver remnant, thus allowing safe resection. Following embolization, curative liver resection would be expected to be feasible in 50% of patients who were initially considered inoperable. Morbidity and mortality for resections with PVE are almost comparable to those for resections without PVE, and five-year survivals approach 37% (4). Two patients in this group had multiple right hepatic metastases, and the left lateral lobe accounted approximately for 20% of the liver volume. For safety, TME was conducted, and right liver portal vein branch ligation was performed. One week postoperatively, the patients underwent systemic chemotherapy. After two to three therapy courses, the feasibility of resection was re-evaluated. One case received two-stage radical resection of liver metastases. However, another patient had to abandon due to the occurrence of distant metastases. Laparoscopic right PVL was applied when right hepatic trisectionectomy was required in the presence of a small FLR and as part of a staged liver resection in patients with bilobar liver disease that spares segments I to IV.

In another condition of patients with down-staging treatments, though tumor metastases were found in the liver lobe bilaterally, most of the lesions were on one side; the lesions on the contralateral lobe were small single nodules. For this phenomenon, Adam et al. (22) suggested using two-stage hepatectomy to convert the above-mentioned non-resectable liver metastases into potentially curable cases. The first-stage resection is intended to remove the tumor in FLR and perform PVL for the lobe with multiple lesions, and this is followed by chemotherapy. The second-stage resection is only performed if it is potentially curative and only if enough parenchymal hypertrophy has occurred (18). Local ablation for the tumor

may be applied (22) in place of resection of the highest possible tumor lesions in the first stage. Intratumor ethanol injection has gained wide acceptance as a safe and effective treatment for tumors 3 cm or smaller, and the small tumor in FLR can be completely ablated with ethanol (4). In this series, two patients had tumors mainly in the left tri-lobe and 1-2 lesions 2-3 cm in diameter in the right posterior lobe. After two to three courses of chemotherapy following local ablation, one case was indicated for "two-stage" resection.

For those patients with the RCLM, the liver is usually the only organ of tumor metastasis. Therefore, the liver lesions resulted in fatality after the primary tumor was resected. For these patients, hepatic artery infusion (HAI) was often suggested to provide for the lesions in the liver (25). HAI of chemotherapy has been used in patients with unresectable metastases confined to the liver. Kemeny *et al.* (25) found that the combination of regional HAI floxuridine/dexamethasone and systemic oxaliplatin and irinotecan is an effective regimen for the treatment of patients with unresectable liver metastases from colorectal cancer, demonstrating a 47% conversion to resection. With laparoscopy, we successfully implanted a chemotherapy pump into the hepatic artery; meanwhile, the main lesions of the liver were administrated ethanol to induce tumor necrosis and reduce tumor burden. Postoperatively, HAI was provided for three patients. HAI is vital to prolong the survival of patients due to less chemotherapy systemic effects and higher local drug concentration (4). Massive tumor reduction may guarantee a better response to adjuvant chemotherapy, and the absence of repeated postoperative immunodeficiency improves patient immunological defense against tumor cells (4,25,26) and the quality of life, prolonging the survival time.

Total mesorectal excision (TME) is prone to anastomosis leakage, in particular, low colorectal anastomoses have an increased leakage risk compared

to other intestinal anastomoses. Scheele *et al.* (21) reported a high mortality rate from anastomotic leakage after low anterior resection associated with hepatectomy; moreover, the patients with RCLM were prone to anemia, incomplete obstruction, and malnutrition, which facilitates anastomosis leakage with conventional procedures (26). Once leakage occurs, it will delay the timing of chemotherapy and is usually fatal. Some surgeons perform ileostomy or colostomy to prevent the occurrence of anastomosis leakage, but this procedure requires a second operation and aggravates the disease. Referring to transanal colonic pull-through with delayed colo-anal/rectal anastomosis introduced by Facy's group (12) after low anterior rectal resection, the procedure was applied to patients with high-risk of anastomosis leakage in their series. When the surplus colon below the anastomosis decayed and shed, the pull-through colon and anal canal had already started to adhere circumferentially. Its advantage in avoiding a diverting ileostomy was validated by another recent study (27). This procedure was much more acceptable because it was safe and facilitated timely receipt of chemotherapy. The disadvantages were that stool frequency was higher in the early stages postoperatively and patients were prone to anastomosis stenosis. Therefore, expansion of the anastomosis would be necessary postoperatively.

In summary, laparoscopy approach "first" for RCLM is feasible in selected patients, when the primary rectal tumor appears suitable for resection, the liver metastasis appears suitable for resection, or potential indication of "two-stage" resection in laparoscopy. Colon pull-through anastomosis most likely becomes a potential anastomosis pattern for patients with poor general condition or low rectal carcinoma.

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