Individualized Treatment Outcomes in Colorectal Cancer with Liver Metastasis

Karaciğer Metastazlı Kolorektal Kanserde Bireyselleştirilmiş Tedavi Sonuçları

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Abstract

Aim: Liver metastasis (LM) is the most common cause of death in colorectal cancer (CRC). In cases of recurrent LM, individualized aggressive local treatments are recommended for better survival outcomes. In this study, we aimed to present the health outcomes obtained in a group of highly selected patients with metastatic CRC.

Materials and Methods: We retrospectively reviewed the medical records of a total of 45 (28 males, 17 females) patients who were diagnosed with liver-metastatic CRC and underwent surgical treatment between March 2013 and November 2018.

Results: The median patient age was 61 years. Thirty-two patients were diagnosed with synchronous metastases, and 21 of these patients underwent synchronous surgery. The median time for metachronous metastases was 18 months. Twenty-three patients developed bilobar metastases, with a median number of 4 (1–18) metastases. Eleven (10 synchronous and 1 metachronous metastasis) patients underwent liver resection without perioperative chemotherapy while the other 34 received perioperative treatment. Parenchymal-sparing liver surgery (metastasectomy/segmentectomy) as performed in 34 patients was the most preferred surgical approach and, again in accordance with the oncological principles, surgery was combined with ablation procedures to treat 31 metastases in 10 patients. The median tumor size and surgical margin width were 35 mm and 3 mm, respectively. Surgical margin positivity was present in 4 patients, of whom only 1 developed local recurrence. In a median time of 12 months, a total of 20 patients developed recurrent LM, and 12 of them underwent secondary surgery. The median survival time was 32 months for all 45 patients and 36 months for the 12 patients who underwent secondary surgery due to recurrences.

Discussion and Conclusion: In CRC with LM, aggressive individualized multidisciplinary treatments can provide better survival outcomes in the long term. Synchronous or staged interventions are applicable with an acceptable morbidity and mortality. In patients with recurrent metastasis, parenchymal-sparing procedures should be preferred in order to increase the patient's chance of repeated surgical treatment.

Keywords: hepatectomy; liver resection; metastasectomy; microwave ablation

Öz

Amaç: Karaciğer metastazı (KM), kolorektal kanserde (KRK) en yaygın ölüm nedenidir. Daha iyi sağkalım sonuçları için reküren KM vakalarında bireyselleştirilmiş agresif lokal tedaviler önerilmektedir. Bu çalışmada iyi seçilmiş bir grup metastatik KRK hastasında kaydedilen sonuçları paylaşmak amaçlanmıştır.

Gereç ve Yöntemler: Mart 2013—Kasım 2018 döneminde karaciğer metastazlı KRK tanısı almış ve cerrahi tedavi görmüş olan toplam 45 (28 erkek, 17 kadın) hastanın tıbbi kayıtları retrospektif olarak incelenmiştir.

Bulgular: Medyan hasta yaşı 61 yıl idi. Otuz iki hastada senkron metastaz teşhis edilmiş olup bunların 21'i eş zamanlı ameliyat edilmişti. Metakron metastaz için medyan süre 18 aydı. Bilober metastaz gelişen 23 hastada medyan metastaz sayısı 4 (1–18) idi. On bir (10 senkron ve 1 metakron metastaz) hastada perioperatif kemoterapi uygulanmadan karaciğer rezeksiyonu yapılmışken diğer 34 hastada perioperatif tedavi uygulanmıştı. Parankima-koruyucu karaciğer cerrahisi (metastazektomi/segmentektomi) 34 hasta ile en çok tercih edilen cerrahi yaklaşım olurken yine onkolojik prensipler doğrultusunda 10 hastada 31 metastaz için cerrahi–ablasyon kombinasyonu uygulanmıştı. Medyan tümör boyutu 35 mm, medyan cerrahi marj genişliği 3 mm idi. Dört hastada cerrahi marj pozitif olup bunlardan sadece 1'inde lokal nüks gelişmişti. Toplam 20 hastada medyan 12 aylık dönemde reküren KM gelişmiş, bu hastalara tekrar cerrahi tedavi uygulanmıştı. Medyan sağkalım süresi 45 hastanın tümü için 32 ay, nüks nedeniyle sekonder cerrahi uygulanan 12 hasta içinse 36 ay idi.

Tartışma ve Sonuç: Karaciğer metastazlı KRK'de agresif bireyselleştirilmiş multidisipliner tedaviler uzun vadede daha iyi sağkalım sonuçları sağlayabilmektedir. Senkron veya aşamalı girişimler kabul edilebilir bir morbidite ve mortalite ile uygulanabilir. Reküren metastazlı hastalarda tekrar cerrahi tedavi görebilme şansını artırmak için parankima-koruyucu prosedürler tercih edilmelidir.

Anahtar Sözcükler: hepatektomi; karaciğer rezeksiyonu; metastazektomi; mikrodalga ablasyon

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer-related cause of death worldwide (1). Of all patients, 25% have liver metastasis (LM) at the time of diagnosis and almost 40% develop LM during the long-term follow-up (2). In CRC with LM, curative treatment and prolonged survival can be achieved only with surgical intervention (3,4). While the treatment of metastatic CRC was based on major hepatectomy in the past, today parenchymal-sparing liver surgery (PSLS) is a more popular option, providing comparable oncological outcomes with a lower morbidity and mortality. It also allows additional surgical interventions in patients with recurrent metastases (5–8). However, the timing of liver surgery has always been a controversial issue (9,10,11) with concurrent suggestions of more aggressive treatments (12).

While standardized treatment algorithms and guidelines provide various professional and procedural benefits, it is also known that comprehensive, interdisciplinary discussion of the treatment options in a particular case can be additionally beneficial to the patient in the long term (13,14). Although guidelines define the general boundaries of treatment, therapeutic decisions that also involve personal professional experience and consideration of case-specific clinical facts are common in diseases requiring surgical–oncological treatment, such as CRCs with LM.

Accordingly, in this study, we aimed to present the health outcomes obtained in a group of CRC patients who were consulted and treated curatively by a multidisciplinary medical team including two experienced oncological surgeons specializing in colorectal and liver surgery.

MATERIALS AND METHODS

We retrospectively reviewed and assessed the medical records (demographic data, surgery type, hospital stay, complications, secondary surgeries for recurrences, chemotherapy needs, and survival outcomes) of a total of 45 patients who were diagnosed with CRC-LM between March 2013 and November 2018. Each patient was discussed in a multidisciplinary meeting including a hepatobiliary surgeon, a colorectal surgeon, an interventional radiologist, a radiation oncologist, and a medical oncologist who specialized in gastrointestinal cancers. All operations were performed by the same hepatobiliary surgeon (KRS). Tumor classification and histopathological staging were performed according to the World Health Organization and American Joint Committee on Cancer (7th ed.) systems, respectively. Complications were graded according to the Clavien–Dindo (15) classification.

Sample selection

The study included patients who underwent curative local treatments (surgery, ablation, and radiotherapy). Patients who received palliative treatment, who had unresectable metastases in other organs or tissues, who showed progression during chemotherapy, who were noncompliant, and who could not tolerate the chemotherapy were excluded. Patients with resectable solitary metastases or oligometastases in other organs were included.

All patients underwent dynamic contrast-enhanced MRI during the preoperative liver examination and were evaluated with positron emission tomography–computed tomography (PET–CT) for systemic spread. The absence of recurrences and secondary colon tumors was confirmed by colonoscopy performed in the last 1 year. Abdominal CT with contrast was performed to evaluate the residual liver volume and vascular anatomy in patients scheduled for major liver resection. In all patients who underwent liver surgery, the operations were performed in accordance with the principles of surgical oncology including PSLS, so as to leave no macroscopic tumor tissue and preserve as much liver tissue as possible (with negative resection margins ≥10 mm when technically feasible and tumor-free margins when infeasible). Patients with actual lesions located deep inside the parenchyma and potential lesions in the residual liver tissue were treated with ultrasound-guided microwave ablation, performed intraoperatively by the same interventional radiologist, necrotizing the marginal tissues within at least 5 mm. For metastatic lesions located close to the major vascular structures or vi-

Table 1. Patient demographic and clinical data

		Total	Primary localization	
			Rectum (n=11)	Colon (n=34)
Age, yr, median (range)		61 (25–76)	59 (27–74)	62 (25–76)
Sex	Male	28	7	21
	Female	17	4	13
Number of metastases	1	12	4	8
	1–4	14	4	10
	>4	19	3	16
Metastasis localization	Right lobe	19	6	13
	Left lobe	3	—	3
	Bilobar	23	5	18
Metastasis interval	Synchronous	32	7	25
	Metachronous	13	4	9
Surgery for metastases	Metachronous	19	5	14
	Synchronous (liver-first)	26 (4)	6 (2)	20 (2)
Surgery type	Metastasectomy	21	7	14
	Segmentectomy (1–2 segments)	13	2	11
	Segmentectomy (>2 segments)	11	2	9
Concurrent ablation	Yes	10	3	7
	No	35	8	27

tal organs, subsidiary techniques (saline hydrodissection or clamping of the vascular structures) were used. All patients received adjuvant chemotherapy. The patients were followed up for a total of 5 years, with checkups involving biochemical screening and diffusion-weighted and dynamic contrast-enhanced MRI, given at four- and six-month intervals in the first two years and the following three years, respectively. Also, whole-body PET-CT screening was performed annually. Patients with disease recurrence were discussed by the multidisciplinary team for their chances of curative treatment, and in the cases where local control did not seem easily possible the second period of treatment was initiated with systemic chemotherapy.

Study ethics

Since this was a retrospective study based on the review of medical records, no official approval from an ethical review board was sought. However, during the study design a medical ethicist (MKT) was consulted for the ethical acquisition and use of the patient data. In accordance with this consultation and the principles of the Declaration of Helsinki, written informed consent was obtained from all subjects.

RESULTS

Data of an initial total of 98 patients were reviewed. The following patients were excluded: forty patients who were found not to be curatively treatable at the time of admission or after chemotherapy and who received palliative treatment, nine patients who showed progression during treatment, and four patients with unresectable metastases in the lungs (Figure 1). Thus, the remaining 45 patients (28 males, 17 females) with CRC-LM were included in the study.

The median patient age was 61 (range 25–76) years. The primary tumors were located in the rectum (n=12), sigmoid colon (n=17), right colon (n=11), and left colon (n=5). Patient demographic and clinical data (patient age and sex, time of the

Table 2. Data of the patients treated for recurrent liver metastases

Patient	Age/Sex	Primary	T&N stage	First side	1. recurrence side	Interval (mt)	2. Intervention	2. recurrence side	Follow-up	2. Interval (mt)	Status	Survival (mt)
1	64/M	Rectum	T3N1	Right	RL	24	Metastasectomy	—	—		DFS	56
2	49/M	Sigmoid	T4N2	Right	LL	15	Laparoscopic metastasectomy	Liver	Under CT	10	CT	56
3	25/F	Sigmoid	T4N2	Bilobar	LL	6	Left hepatectomy	Liver	Metastasectomy	6	DFS	72
4	66/M	Right	T3N1	Bilobar	RL+Lung	12	Segmentectomy and lung ablation	—	Ischemic heart disease	—	Exitus	42
5	52/M	Sigmoid	T4N2	Left	RL	3	Metastasectomy and ablation	Liver	Disseminated disease	6	Exitus	24
6	55/M	Sigmoid	T3N0	Right	LL	4	Metastasectomy and ablation	—	—	—	DFS	37
7	29/M	Rectum	T4N1	Right	Pelvic	12	Pelvic surgery	Pelvic	Ileus	10	Exitus	36
8	45/M	Rectum	T3N1	Right	RL	12	Metastasectomy	Liver	Under CT	12	CT	32
9	61/M	Left	T3N2	Bilobar	RL	6	Metastasectomy and ablation	—	—	—	DFS	16
10	65/M	Left	T4N1	Bilobar	Abdominal wall	12	Abdominal wall excision	—	—	—	DFS	22
11	65/M	Sigmoid	T3N1	Bilobar	RL	12	Ablation	—	Recurrent liver disease	9	Exitus	69
12	63/M	Sigmoid	T3N1	Left	RL	12	Ablation	—	—	—	DFS	16

CT: chemotherapy; DFS: disease-free survival; LL: left liver; RL: right liver

metastasis diagnosis, metastasis localization, and combination and type of medical and surgical treatment) are presented in Table 1.

The median time for metachronous metastases was 18 (4–30) months. The median number of metastases was 2 (1–18) for all 45 patients and 4 (2–18) for the 23 patients with bilobar metastases. Treatment was initiated with preoperative chemotherapy in 34 patients, including 3 patients with synchronous LM who underwent emergency colon surgery due to obstructive tumors. Liver resections were performed after a median of 4 (3–12) cycles of chemotherapy. In these 34 patients, a biological agent (bevacizumab or cetuximab) was added to the chemotherapy regimen, considering the pathological findings and primary tumor locations. In the other 11 patients (of whom 10 had synchronous and 1 had metachronous metastases), treatment was initiated with surgery, due to its technical feasibility, the small number of lesions (with a median of 4 [1–4] lesions), and the patients' eligibility for curative treatment. As long as possible, PSLS was the preferred method of treatment in accordance with the oncological principles.

In 10 patients with bilobar metastatic lesions that were located deep inside the parenchyma and thus did not allow limited resection (metastasectomy or segmentectomy), surgical treatment was combined with ablative treatment intraoperatively. A total of 31 metastases, with a median of 3 (1–8), were treated with radiofrequency or microwave ablation.

In 4 patients with synchronous LM, combined treatment with surgery and microwave ablation was performed with the "liver first" approach. For another patient, diagnosed with multiple bilobar metastases, the ALPPS (associated liver partition and portal vein ligation for staged hepatectomy) procedure was performed after 4 cycles of chemotherapy. Hyperthermic intraperitoneal chemotherapy (HIPEC) was added in the treatment of 3 patients scheduled for colon and liver surgery, due to colon tumor perforation in one of them and pelvic peritoneal and ovarian seeding metastases in the other two. In another patient, intraoperative radiotherapy

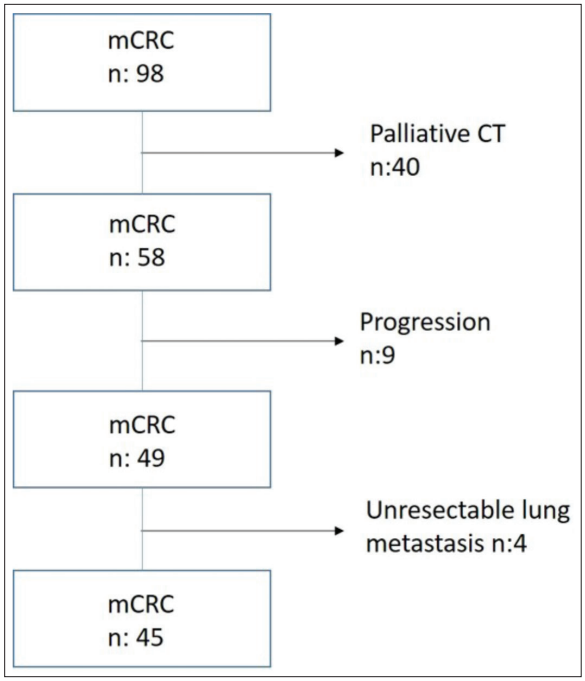

Figure 1. The exclusion flowchart

was added due to the invasion of the psoas muscle.

Forty-one patients underwent open surgery while 4 patients were treated with laparoscopic resection (2 segmentectomies, 2 multiple metastasectomies). The median hospital stay was 4 (2–12) days in liver resection alone while 6 (4–20) days in the case of synchronous resections. While no death occurred in the early postoperative period (within 30 days after surgery), 7 patients had Clavien–Dindo grade 1–2 complications and 2 developed intra-abdominal abscesses (Clavien–Dindo grade 3), both of which were treated with percutaneous drainage.

Pathological examination revealed well, moderately, and poorly differentiated tumors in 1, 39, and 5 patients, respectively. The median tumor size for all 45 patients was 35 (5–150) mm. For the 34 patients whose treatment was initiated with preoperative chemotherapy, the pre-treatment and post-treatment median tumor size was 35 (5–100) and 29 (4–90) mm, respectively (Image 1 and 2). The median surgical margin width was 3 (0–40) mm, and margin positivity was reported in 4 patients. In 8 of 18 patients for whom intraoperative frozen section examination was done, re-excision was performed due to tumors reported to be adjacent to the surgical margins. In four patients in whom it had been thought that no macroscopic tumor tissue was left unresected and that intraoperative frozen section examination was not necessary, it was reported that the tumors were adjacent to the surgical margins. These were patients who underwent combined treatment with surgery and microwave ablation due to multiple bilobar liver metastases.

Pathological examination of the primary colorectal cancers revealed T3N0 cancer in 2 patients, T3N1 in 19, T3N2 in 11, T4N0 in 3, T4N1 in 2, and T4N2 in 7. In one patient who received perioperative chemotherapy, the primary sigmoid colon tumor showed total response while the lymph node and liver metastases showed only mild regression (T0N1M1). Five (11%) patients had distant organ metastases with no lymph node metastasis.

Twenty patients showed recurrence in the liver, 3 in the lungs, 1 in the pelvis, and 1 in the abdominal wall. The median time for disease recurrence after the first surgery was 12 (4–24) months. Of the 20 patients with LM, 5 had solitary metastasis, 5 had 2–4 metastases, and 9 had multiple (>4) metastases. The recurrent lung and liver metastases of 12 patients were found suitable for local curative treatment (Image 3 and 4). Of these 12 patients, all survived the early postoperative period, 3 developed Clavien–Dindo grade 3 complications (2 abdominal abscesses and 1 empyema) and were treated with percutaneous drainage. The demographic, treatment and follow-up data of the patients are summarized in Table 2. The survival graphs are presented in Figure 2 and 3.

DISCUSSION AND CONCLUSION

The main goal in the treatment of metastatic CRC is to cure the disease, or otherwise prolong the survival time as much as possible. Although surgical resection is the most important treatment step for achieving this goal (3,4), significantly prolonged survival is often not possible without effective chemotherapy. Generally, the chance of curative treatment is less than 10% (16) and, even with the addition of radical surgery, the chance of cure is not greater than 20%, leading to a continuous search for better treatment options (17).

With satisfactory results reported in small, well-selected series of patients (18), liver resection has become a routine procedure to treat CRC-related LMs in eligible patients. Also, with the improvement in surgical technique and infrastructure, similarly promising outcomes have been reported in other patients in whom more aggressive treatments are used in combination with ablation procedures with curative intent. Thus, it has recently been agreed that the criteria of tumor number, tumor size, and tumor location might not be as important and determinative as they used to be (16–22).

In our series, 23 patients had multiple bilobar metastases. The median number of metastases was 4 (2–18). We preferred PSLS for the curative treatment of these patients, and a total of 31 metastases were treated with the combined use of microwave ablation in 10 of them.

Perioperative chemotherapy is used both to achieve curative treatment and prolonged survival and to expand the pool of candidates for surgical treatment. With chemotherapy, oncological outcomes similar to those in primary candidates for surgical treatment can become possible in patients initially ineligible for resections (12,23). In our series, we started with chemotherapy in 34 patients, 6 of whom were considered ineligible for surgical resection at the time of diagnosis. Liver resections were performed after a median number of 4 (3–12) cycles of chemotherapy.

The main principle in surgical oncology is to achieve negative surgical margins. The initial success criterion of negative margins ≥1 cm in CRC metastases subsequently changed with reports of comparable oncological outcomes achieved with narrower resection margins and more aggressive interventions successfully performed in combination with chemotherapy (18). Although margin negativity is still important, it is now known that microscopic positive margins (R1) that may increase the risk of recurrence may not be a contraindication to surgical treatment in the era of modern chemotherapy, given the local recurrence and long-term survival rates found similar to those reported in cases with negative surgical margins (24–28). That being the case, the definite contraindications to surgical treatment have been controversial; it has been recommended that patients who do not have disseminated liver metastases, uncontrollable primary tumors, and multivisceral metastases should be considered potential candidates for curative treatment (12,29).

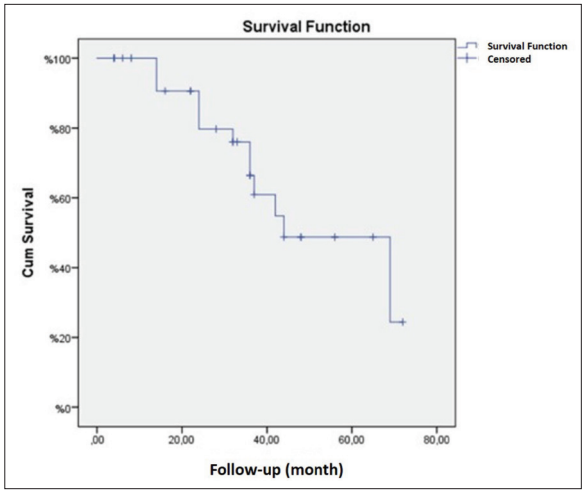

Figure 2. Survival graph for all 45 patients, with a median survival time of 32 (16–72) months.

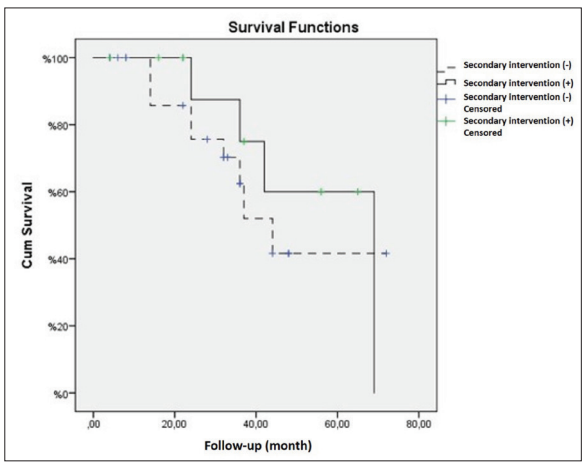

Figure 3. Survival graph for after the 1st and 2nd interventions (p=0.541). The median survival time was 36 (16–69) months after the 2nd intervention.

In our series, the median surgical margin width was 3 (0–40) mm. Surgical margin positivity was reported in four patients who underwent combined treatment with surgery and microwave ablation for multiple bilobar liver metastases. Of these 4 patients who received adjuvant chemotherapy with non-targeted agents, only one developed recurrence at the positive margin sides, which was treated with secondary resection and perioperative chemotherapy.

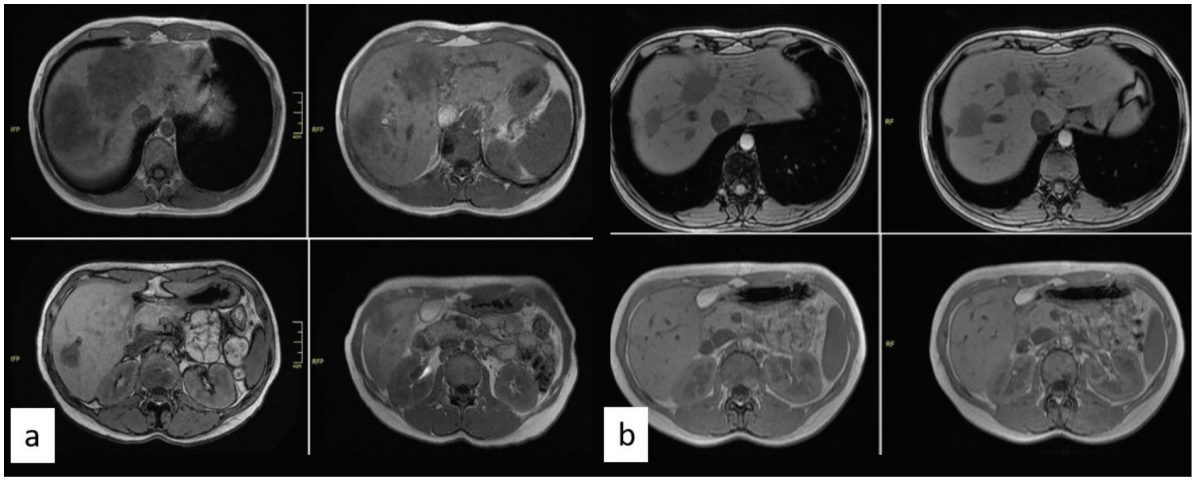

Image 1. a) Liver metastasis diagnosed synchronously in a 25-year-old woman; b) marked regression seen after six cycles of chemotherapy.

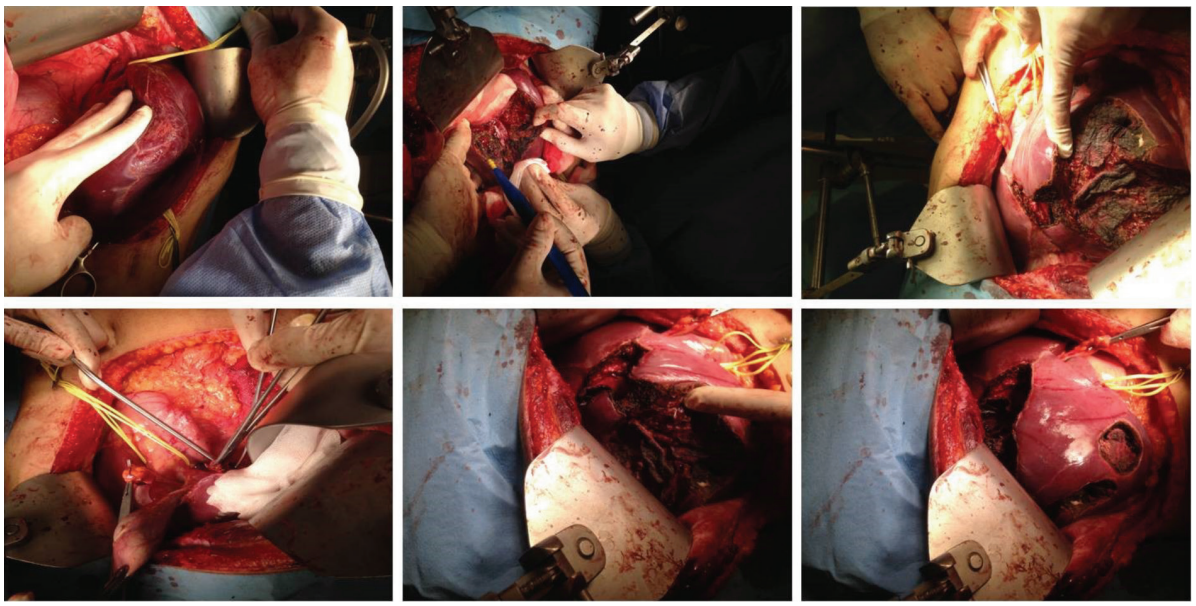

Image 2. Intraoperative view of the metastasectomy sides in the patient shown in Image 1.

The significant benefits achieved with effective chemotherapy have led to a change in strategies of surgical treatment. Replacing major hepatectomy, preserving as much parenchymal tissue as possible has become a common oncological principle (2,5,6). Similarly, in our series, most (34) patients were treated with minor liver resections, 11 underwent major anatomical liver resections, and 10 underwent combined treatment with surgery and ablation. No patient developed recurrence in the ablation area, except for two patients with multiple recurrent metastases.

The timing of surgical resection of synchronous CRC-LMs is still a controversial issue. While the preferred approach was staged (colon-first) resection in the past, an increasing number of recent studies have reported satisfactory perioperative outcomes with synchronous surgeries. Synchronous liver and colorectal resections are considered no more risky than liver surgery alone, and constitute an appropriate treatment option especially in cases of limited and easily accessible liver metastases, with no significant difference in oncological outcomes (9,10,30,31). However, there have also

been publications arguing that such comparisons would not be accurate due to the fact that patients undergoing synchronous surgeries are often highly selected (11,32–34). Perioperative outcomes are also controversial in patients needing synchronous major liver resection, given the cumulative risks of several surgical procedures performed on the same patient (9). Therefore, management and evaluation should be carefully conducted in such patients, considering all the complex treatment options including the liver-first approach, surgery in combination with ablation procedures, portal vein embolization for hypertrophy of the future liver remnant, and two-stage surgery (ALPPS), the feasibility and outcomes of which depend on the surgeon's experience and the surgical infrastructure (35–37). In our series, 21 of 32 patients with synchronous CRC metastases underwent synchronous operations. Of these 21 patients, 3 underwent major liver resection (>2 segments) and only 1 developed superficial wound infection. In four patients with bilobar metastases, surgery with the liver-first approach was combined with microwave ablation, and in one patient the ALPPS procedure was performed. While all patients survived the early postoperative period and the complication rates were similar, the median hospital stay was longer for the patients who underwent synchronous surgery (a median of 4 vs 6 days).

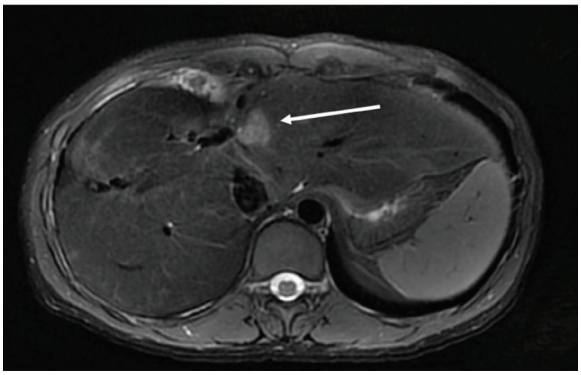

Image 3. Recurrent metastasis in the patient shown in Image 1 and 2, removed by left hepatectomy.

The main problem recorded in the long-term follow-up is recurrent LM (38,39). It has been shown that selected patients with recurrent LM have a chance of cure thanks to surgical procedures that can be repeated with morbidity and mortality rates comparable to those in primary resections (38). In our series, recurrences developed in a median time

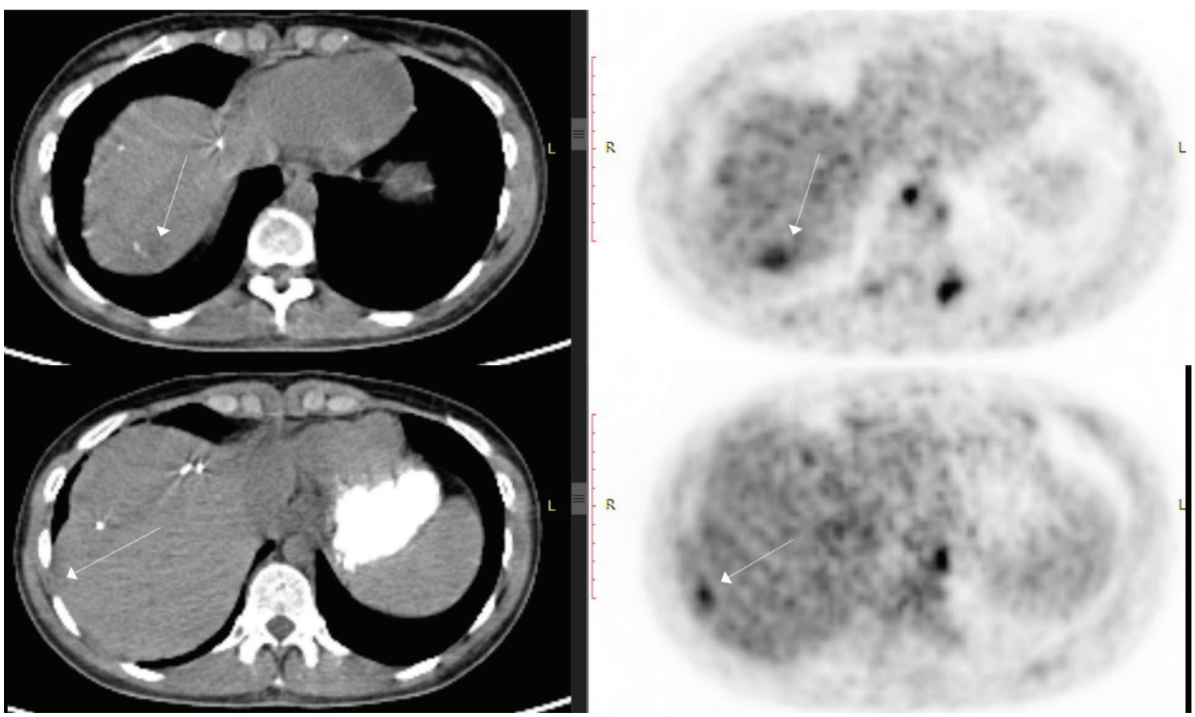

Image 4. Secondary recurrences in the patient shown in Image 1 to 3, treated with metastasectomy. She was alive in the 6th year after the diagnosis, and disease-free for the last 28 months.

of 12 (4–24) months in a total of 25 patients (of whom 20 had recurrence in the liver, 3 in the lungs, 1 in the pelvis, and 1 in the abdominal wall). Twelve patients were found eligible for secondary surgery; 6 underwent metastasectomy, 1 segmentectomy, 1 left lobectomy, and 2 percutaneous ablation. Tumor excision was also performed in 2 patients with recurrences in the abdominal wall and pelvis.

In conclusion, although tumor number, size and location are still important in the CRC metastasis and prognosis, these may not pose definite contraindications to surgical treatment with curative intent. More aggressive individualized multidisciplinary treatments can be performed for both local and systemic disease control. Considering the case-specific clinical facts, synchronous or staged interventions can be performed with an acceptable morbidity and mortality. The success rates for repeated interventions to treat recurrent metastases are almost equal to those for primary interventions. Preserving the liver parenchyma as much as possible is one of the most important factors that increase the patient's chance of repeated surgical treatment.

Conflict of Interest and Financial Disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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