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ORIGINAL ARTICLE

A 20-year single center experience in the surgical treatment of colorectal liver metastasis

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Summary

Purpose: *To present our experience in the treatment of patients with liver metastases from colorectal cancer.*

Methods: *The surgical and histopathological records of our department dating from 1st January 1997 to 31st December 2016 were examined, searching for patients who have undergone surgical treatment of colorectal liver metastasis.*

Results: *A total of 90 patients with colorectal liver metastases were treated in the last 20 years in our department. Their mean age was 65.28 years and 54 (60%) were male. The primary tumor was in the colon in 71 patients (78.9%) and in 19 (21.1%) patients in the rectum. Thirty-six (40%) patients presented with synchronous metastatic liver disease, from which 27 were subjected to simultaneous resection, 2 underwent a liver-first approach and 7 were subjected to resection of primary tumor first. Regarding the number of metastases 67 (74.4%) patients had single metastasis, 12 (13.3%) had 2 lesions, 4 (4.4%) had 3 lesions and 7 (7.8%) had 4-8 lesions. In-hospital and 30-day mortality was 3.85%. Median survival was 41 months.*

Conclusion: *Surgical resection is the treatment of choice for the management of liver metastasis from colorectal cancer and can be safely performed. Follow up of patients with colorectal cancer is imperative as metachronous metastasis presents in a significant percentage of patients with negative locoregional lymph nodes of the primary tumor. The order of resection doesn't seem to alter outcome in synchronous metastasis. Recurrence is common and re-resection if feasible is the only chance of cure.*

Key words: *colon, hepatectomy, intraoperative ultrasound, metachronous, synchronous, radiofrequency ablation*

Introduction

Colorectal cancer is one of the commonest primary malignant diseases both in males and females and actually it is the 3rd more common in incidence after the lung and the breast [1,2]. The most common site of colorectal cancer metastasis is the liver and hepatic metastases account for two thirds of the deaths of colorectal cancer patients [3,4]. Hematogenous dissemination through the portal vein is the more common route of metastasis [5]. More than half of the patients with colorectal cancer will develop metastatic disease to the liver, from which 15-25% are synchronous with the diagnosis of the primary tumor and about 15-57% develop metachronously [1,3,6].

From the patients with hepatic metastasis only 10-25% will have resectable hepatic metastatic disease at the time of diagnosis [2,3,6]. For patients with unresectable liver metastasis median surviv-

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al is 4.5-15 months and 5-year survival is limited [3,7]. Surgical resection may provide "cure" and is considered as the treatment of choice [1,4]. Following operative management of colorectal liver metastasis the 5-year survival rate is 20-59% [1,2,4,7] despite the fact that about 50-75% of patients will have a recurrence, more commonly presenting in the first 2 postoperative years [1,3,8]. Despite the development and advances of locoregional treatments including, radiofrequency ablation, microwave ablation, laser ablation, cryoablation, hepatic arterial infusion therapy, radioembolization, chemoembolization, external beam radiation therapy, percutaneous ethanol injection, surgical resection remains the treatment of choice [9-14].

The purpose of the present retrospective study was to report a single center's experience in the treatment of colorectal liver metastasis.

Methods

For the present retrospective study the hospitalization, surgical and histopathological records of our department were examined, searching for patients who had undergone surgical treatment of colorectal liver metastasis

The location of the primary tumor, either colon or rectum, and its staging according to Dukes classification were recorded.

The diagnostic modalities used to detect the metastasis and to perform preoperative staging was CT scan, MRI and PET-CT. Furthermore, the number of metastatic lesions in the liver were recorded, as well as whether the metastatic disease was synchronous or metachronous. In the patients with synchronous metastatic disease the surgical management that was employed was recorded as either simultaneous resection, resection of the primary tumor first followed by resection of the liver

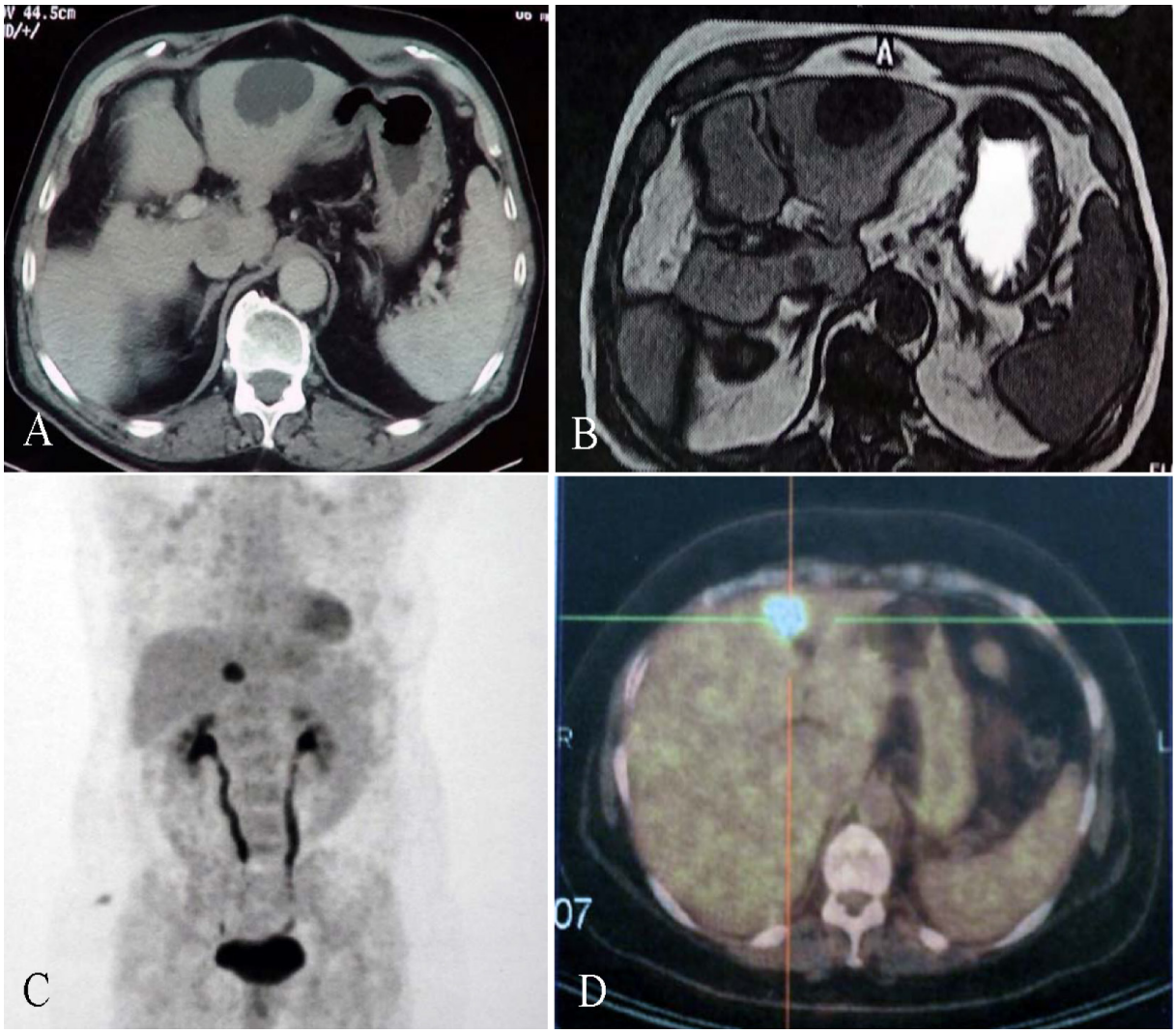

Figure 1. A: CT scan revealing a liver cyst at segment III and a recurrent liver metastasis at segment I. This patient underwent a simultaneous sigmoidectomy and segment V resection for a synchronous colon cancer liver metastasis 16 months ago. **B:** MRI scan of the patient in Figure 1A. **C:** PET scan demonstrating a single liver metastasis at segment IV. **D:** PET-CT demonstrating a single liver metastasis at segment IV.

disease at a later stage or resection of the hepatic metastasis first followed by resection of the primary tumor at a later stage. Also, the operative management used which included resection, radiofrequency ablation or a combination of both was studied. In patients who had undergone resection the type of hepatectomy was also recorded.

Complications and postoperative in-hospital mortality were registered and evaluated. Also, recurrences during the follow-up period and their treatment were also recorded. Finally, overall median survival was calculated.

Statistics

The data extracted from the study were summarized using statistical descriptive indices of central tendency and dispersion. Data appear as mean value±standard deviation or median and range, whenever more appropriate. The data were evaluated depending on presentation of normal distribution or not, using a normality test. All the statistical analyses were performed using the IBM SPSS Statistics (Version 22).

Results

During the last 20 years (1st January 1997 to 31st December 2016) a total of 90 patients with colorectal hepatic metastasis have been subjected to operative management in our department. Their mean age was 65.28 years (range 45-82), while 54 (60%) patients were male. Seventy one (78.9%) patients presented with a primary tumor in the colon while 19 (21.1%) had a primary rectal cancer. At the time of presentation, only 5 (5.6%) patients were in Dukes B1 stage, 20 (22.2%) were in stage B2,

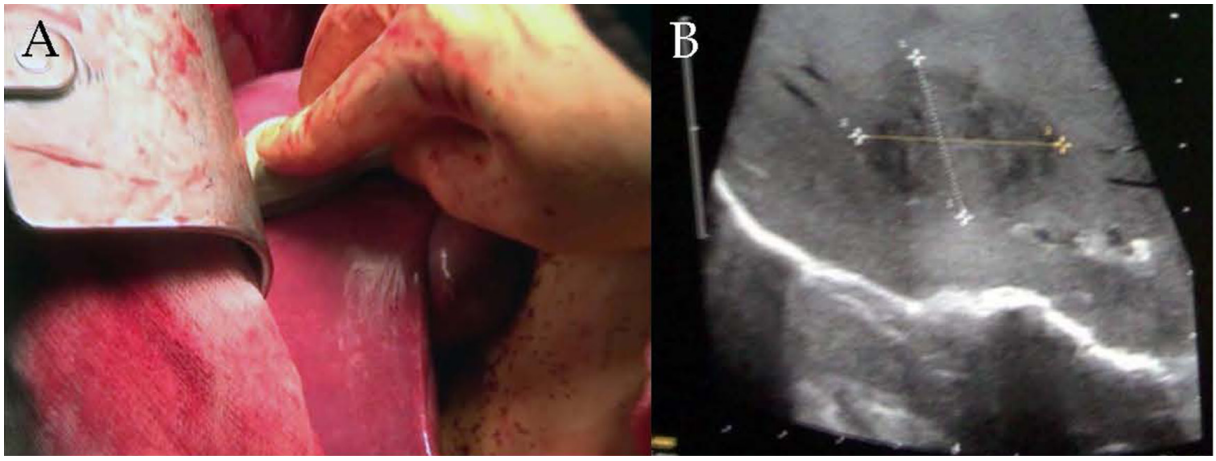

Figure 2. Intraoperative ultrasound. **A:** The ultrasound probe placed over the metastasis. **B:** Ultrasound image of the metastasis.

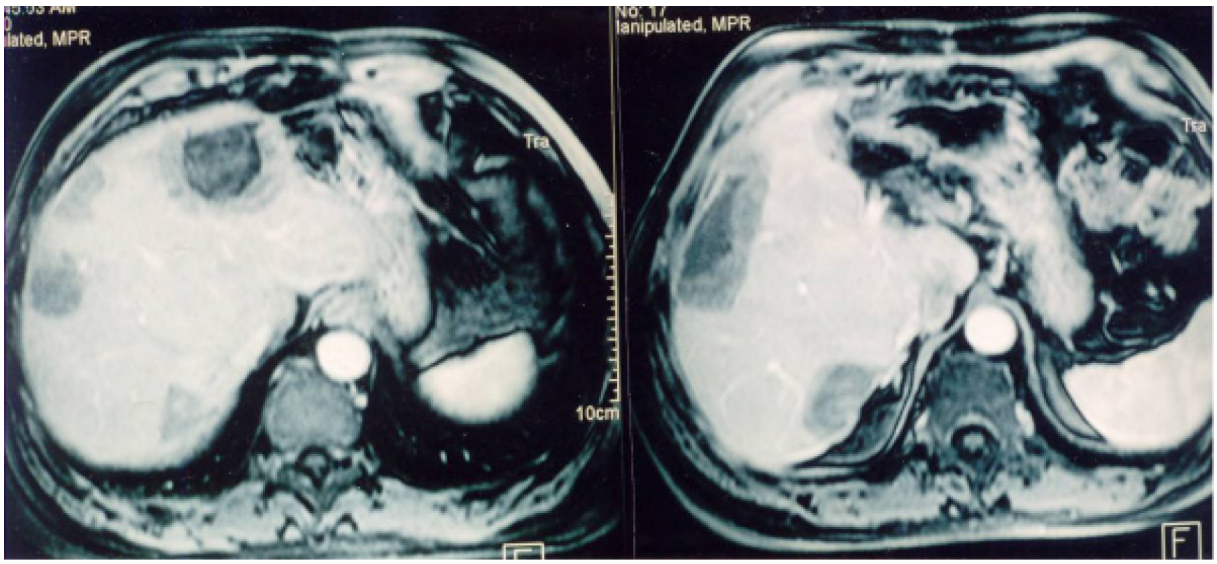

Figure 3. MRI scan in a patient 3 months after segmentectomies of lobes II and III, wedge resection of metastatic lesions located to segments IV and V and RFA of a lesion located to segment VII showing multiple new metastatic lesions in segments Iva, V, VI, VII, VIII.

29 (32.2%) were in stage C, and 36 (40%) were in stage D. The diagnostic modalities used to detect the metastasis were ultrasound (US), computed tomography (CT) (Figure 1A), magnetic resonance imaging (MRI) (Figure 1B) and positron emission tomography (PET) (Figure 1C) with or without CT (PET-CT) (Figure 1D).

From the 90 patients, 36 (60%) presented with synchronous metastasis while the remaining 54 (40%) developed metachronous metastasis and were diagnosed 3-47 months after the initial operation. Single metastasis was present in 67 (74.4%) patients, 2 metastases were present in 12 (13.3%), 3 metastases were present in 4 (4.4%) and 7 (7.8%) patients had 4-8 metastases.

A total number of 142 metastatic lesions were treated. Regarding the treatment of patients with synchronous metastasis, 27 (0.3%) patients underwent simultaneous resection, 7 (7.8%) underwent resection of the primary tumor first followed by resection of the liver lesions at a later stage and 2 (2.2%) patients were subjected to resection of the hepatic metastasis first followed by resection of the primary tumor at a later stage.

Intraoperative ultrasonography was performed in all cases (Figure 2). The management was surgical resection in 72 (0.8%) patients, radiofrequency ablation in 10 (11.1%) and a combination of these methods in 8 (8.9%) (Figure 3). From the patients that were subjected to hepatectomy, 10 (11.1%) underwent right hepatectomy, 5 (5.6%) left hepatectomy, 9 (10%) left lobectomy and 56 (62.2%) segmentectomies. The intended resection margin around the metastatic lesion was 1 cm or more, which has been achieved in 71 (78.9%) patients (Figure 4).

The mean period of hospitalization was 14.3 days and the mean intensive care unit (ICU) stay was 1.7 days. The recorded complications were bile leakage following liver resection reported in 4 patients from whom 3 were treated conservatively and one was managed with ERCP and stent

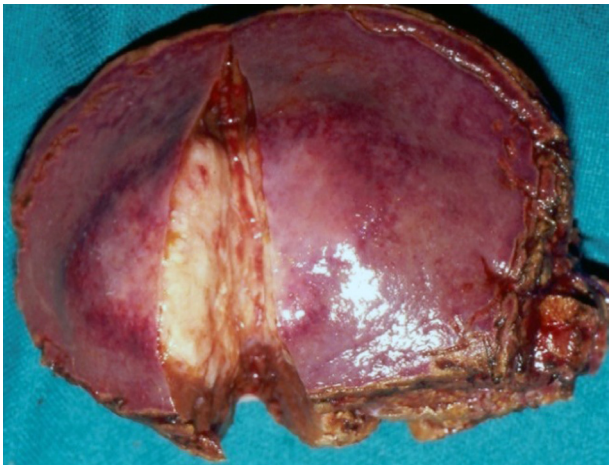

Figure 4. Wedge resection specimen with a single liver metastasis and a surgical margin of at least 1 cm.

Table 1. Patient characteristics, primary tumor characteristics, metastasis characteristics and treatment, complication, mortality and survival

Patient characteristics	*n (%)*
Age, years (mean)	65.28
Gender	
Male	54 (60)
Female	36 (40)
Primary tumor	
Colon	71 (78.9)
Rectum	19 (21.1)
Dukes stage	
B1	5 (5.6)
B2	20 (22.2)
C	29 (32.2)
D	36 (40)
Metastasis	
Metachronous	44 (48.9)
Synchronous	36 (40)
Simultaneous resection	27 (30)
Colorectal first	7 (7.8)
Liver first	2 (2.2)
Number of metastases	
1	67 (74.4)
2	12 (13.3)
3	4 (4.4)
4-8	7 (7.8)
Surgery	
Liver resection	72 (80)
Radiofrequency ablation	10 (11.1)
Both	8 (8.9)
Hepatectomy right	10 (11.1)
Hepatectomy left	5 (5,6)5
Lobectomy left	9 (10)
Segmentectomy	56 (62.2)
Complications	8 (8.9)
Bile leak	4 (4.4)
Fluid collection	2 (2.2)
Pulmonary embolism	1 (1.1)
Multiple organ dysfunction syndrome (MODS)	1 (1.1)
Death	3 (3.3)
Mortality (in-hospital – 30 days)(%)	3.85
Treatment of recurrence	
Re-resection	5 (5.6)
Radiofrequency ablation	1 (1.1)
Median survival (range)	41 (26-52)

placement. Abdominal postoperative fluid collections were noted in 2 patients who had undergone simultaneous resection and were treated by percutaneous drainage. Massive pulmonary embolism was noted in one patient who had been subjected to simultaneous resection which led to death on the 12th postoperative day. Multiple organ dysfunction syndrome was noted in one patient who died on the 6th postoperative day while still in ICU. In-hospital mortality and 30-day mortality were 3.85%.

Postoperative follow-up was carried out by chest and abdominal CT scan and evaluation of the tumor marker carcinoembryonic antigen (CEA) every 3 months for the first 2 years, then every 6 months for the following 3 years and then annually.

Recurrence developed in 6 (6.7%) patients in a period of 6-19 months following the primary surgical treatment of liver metastasis. Additional liver resection was performed in 5 of them while RF ablation was performed in one patient with a 2nd recurrence into the liver.

All patients received postoperative chemotherapy. Median survival was 41 months (range 26-52) (Table 1).

Discussion

The history of hepatic resection for the management of colorectal cancer liver metastasis begins in 1940 when Cattell described the first successful removal of liver metastasis [15]. However, only few attempts have been made afterwards to remove metastatic colonic carcinoma from the liver as in 1948 by Raven who performed a left lateral segmentectomy [15]. Forty years ago liver metastasis from colorectal cancer was considered a terminal and incurable disease and the 5-year survival was zero [16,17], until Wilson and Adson [17] in 1976 reported evidence of 5- and even 10-year survival in patients with solitary hepatic metastasis from colorectal cancer that were surgically resected and in 1978 a multicenter study in the USA revealed a 5-year survival rate of 20% in patients with colorectal cancer hepatic metastasis who were treated with hepatic resection [16]. Since then, a lot of studies from specialized hepatopancreatobiliary surgical centers or multicenter studies have shown that liver resection for the treatment of colorectal cancer metastasis can offer long term survival and even cure in some patients [3,18-20]. Median survival following liver surgery for colorectal metastasis resection ranges between 28 and 40 months [21].

Today resection of liver metastasis from colorectal cancer is considered the gold standard of care [11,22] and the only management with a potentially curative result. Liver surgery is considered safe as mortality below 5% and limited morbidity are constantly reported [5,11]. Classical contradictions for hepatic resection related to the location, size and number of lesions are no longer considered absolute [23] and surgical candidates are considered all the patients in whom a R0 resection with negative surgical margins of at least 1mm of all metastatic lesions can be performed and simultaneously there will be sufficient remaining liver parenchyma to maintain liver function [24]. By definition at least 2 continuous liver segments with intact blood supply and drainage and adequate biliary drainage must be preserved [24]. In the case of a normal functioning liver the future liver remnant should be at least 20-30% [23,24] while in cases of liver damage either due to chemotherapy or other reasons the remaining volume of the liver should be greater and at least 40% [24].

Meticulous follow-up of patients that have been surgically managed for colorectal cancer is necessary for the prompt diagnosis of metastatic liver disease and in order to offer a chance for cure and long term survival by the early identification of hepatic metastasis that increases resectability. It includes postoperative examination every 3 months for the first 2 years including tumor markers, chest x-ray and abdominal imaging, mainly ultrasound and CT scan and in selected cases MRI and PET-CT [25]. Follow-up is important in all patients as a high percentage of patients with Dukes B stage without lymph node involvement develop hepatic metastasis, as in our case series, which is in accordance to former studies where even stage A patients had liver metastasis [19]. Today while CT scan is still considered the first choice imaging modality, MRI has a better sensitivity and specificity but is more expensive and more time-consuming [26], a fact that limits its use. PET scan and its combination with CT (PET-CT) is very useful in detecting extra hepatic disease and can alter the patients' treatment in up to 25-31.6%, usually by upstaging the disease [27,28].

All patients with liver metastasis from colorectal cancer are staged as stage IV in the TNM classification. However, there are considerable differences in the prognosis and survival of these patients as it is a promiscuous group of patients. Prognostic factors that have been considered important in various studies include tumor differentiation, depth of wall invasion and lymph node status for the primary tumor, and age, large metastasis, multiple metastases, liver portal lymph node metastasis, extrahepatic disease, synchronous or metachronous disease, less than 12 months dis-

ease-free interval, preoperative CEA level, response to preoperative chemotherapy, resection at a high volume center, positive surgical margin, postoperative chemotherapy for the metastatic cases [3-5]. Clinical Risk Score (CRS) that has been proposed by Fong [29] includes a) preoperative CEA level greater than 200 ng/ml; b) number of hepatic metastasis greater than 1; c) size of the largest metastasis greater than 5 cm; d) disease-free interval less than 12 months from the diagnosis of the primary tumor to the discovery of the liver metastasis; and e) positive lymph node status of the primary colorectal cancer and is a valuable prognostic tool that has also been validated by others [29]. However, the most important prognostic factor of overall survival is the microscopic status of the resected margin and R1 resection compared to R0 is related to poorer outcome [5]. Moreover, the presence of extrahepatic disease is considered to be of great significance to prognosis [5].

The type of resection performed in order to remove the liver metastasis is not significant as long as negative microscopic margins have been achieved and there is no difference between non-anatomical and anatomical resections [5]. The main objectives of surgical therapy should be short liver ischemic time, low intraoperative blood loss, to preserve the liver as much as possible and minor postoperative morbidity and mortality [5,30]. Preoperative portal vein embolization of the segment that is going to be resected, should be used in cases that the future liver remnant is estimated to be inadequate in order to increase the residual liver volume [3,5]. Patients with bipolar metastases can be treated either by multiple simultaneous resections or by two-stage hepatectomy, firstly by resecting the metastasis of the future liver remnant and then after liver hypertrophy has developed (usually after portal vein ligation or embolization), a second major hepatectomy is performed [3,5,9]. While resection is the standard treatment for liver metastasis, ablation is useful for managing extensive metastatic disease that cannot be completely resected although it is accompanied by higher local recurrence rates [9].

The optimal treatment for patients with synchronous metastasis is still unclear [31,32]. There are three potential surgical strategies: a) simultaneous resection, b) resection of the primary tumor first followed later by liver resection, and c) "liver first approach" with resection of the metastasis after neoadjuvant chemotherapy first followed later by resection of the primary tumor [30,31]. In many patients with synchronous primary and metastatic disease, simultaneous resection is feasible, safe and effective and is justified [5,9,18,30]. However, in cases that the patient comorbidities or the severity of the surgery don't allow simultaneous resection, staged resection should be performed and the priority of the primary resection should be individualized to each patients based on the characteristics and complications of the colorectal tumor or the liver metastasis [5,9,18,30].

Most patients with colorectal liver metastases are not candidates for surgical resection and systemically administered chemotherapy is the only option [11]. Multidrug systemic chemotherapy has shown significant advances in the treatment of colorectal liver metastasis [3] and median survival has increased to 15-20 or even up to 30 months by the use of 5-fluorouracil, leucovorin and either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) [3,33]. Furthermore, the addition of biologic agents to systemic treatment such as cetuximab or bevacizumab has improved survival by 2-5 months [3, 5] but 5-year overall survival rate is less than 1% [3]. Perioperative chemotherapy, either adjuvant or neoadjuvant, results in longer overall and disease-free survival [22,28]. Adjuvant chemotherapy aims to prevent recurrence in the residual liver and to treat latent extrahepatic metastases [5]. Regarding postoperative chemotherapy patients are offered an oxaliplatin-based regimen, but definite data favouring adjuvant chemotherapy after R0 resection of colorectal liver metastasis are still missing [3,34]. Neoadjuvant chemotherapy aims to increase resectability, limit the extent of hepatectomy, treat micrometastases and determine the chemosensitivity of the disease [5]. Chemotherapy can downstage unresectable disease in about 33% of patients and allow the performance of hepatic resection [3,18]. Neoadjuvant chemotherapy can be given to high risk patients with initially resectable disease [22] and response to treatment is an important prognostic factor of improved survival [18].

Local, regional or distant recurrence is very common and about 60-80% of patients who underwent hepatic resection develop recurrence [23] and the majority of recurrences (85%) appear in the first 30 months following resection [23]. Increasing levels of tumor markers and/or surveillance imaging reveal the recurrent disease. In about 30% of patients with recurrent metastases the recurrence is confined in the liver and surgical resection or ablation offer the only possibility of cure despite the fact that surgical options are more limited due to prior surgery [3,23,28]. Morbidity and mortality of repeat liver resections are similar to those of primary hepatic resection [30].

Follow-up of patients subjected to hepatic resection for colorectal liver metastasis should be intense and includes clinical examination, chest,

abdominal and pelvic CT scan and CEA levels every 3 months for the first 2 years and then every 6 months for the next 5 years, as early recognition of a recurrence may allow repeat surgical effort that remains the only chance of cure [35].

In conclusion, surgical resection is the treatment of choice for the management of liver metastasis from colorectal cancer and can be safely performed even in the octogenarians, while morbidity and mortality have stabilized to low percentages. Follow-up of patients with colorectal cancer is imperative as metachronous metastases develop in a significant proportion of patients with negative locoregional lymph nodes of the primary tumor. Liver resection can be combined with ablation techniques in order to destroy all metastases and various methods can be used to increase resectability including portal vein embolization, two-stage hepatectomy and chemotherapy. The order of resection doesn't seem to alter the outcome in synchronous metastasis. Recurrence is common and re-resection, if feasible, is the only chance of cure.

Authors' contributions

Tsalis K and Ioannidis O contributed equally to this work. Ioannidis O, Cheva A, Parpoudi S, Kyziridis D, Antoniou N, Tatsis D, Konstantaras D, Savvala NA, Kitsikosta L collected the data. Ioannidis O, Kotidis E, Pramateftakis MG, Avgerinos A, Mantzoros I analyzed the data. Tsalis K and Ioannidis O designed and supervised the study. Ioannidis O, Cheva A, Parpoudi S, Kyziridis D, Antoniou N, Tatsis D, Konstantaras D, Savvala NA, Kitsikosta L significantly contributed to the literature review and linguistic formatting of the manuscript. Kotidis E, Pramateftakis MG, Avgerinos A, Mantzoros I revised it critically for important intellectual content. Tsalis K and Ioannidis O drafted the manuscript and were responsible for final proofreading. All authors have read and approved the final version to be published.

Conflict of interests

The authors declare no conflict of interests.

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