Surgical treatment of colorectal liver metastases - a single center experience over 20 years

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ABSTRACT

Background: Increased frequency of hepatic resection and advances in oncological therapy dramatically improved the long-term outcome of the patients with colorectal liver metastases. The aim of the study is to present the short and long-term results after surgery in patients with colorectal liver metastases, in a single center, over the last two decades.

Method: Between 1995 and 2014, a curative-intent liver resection was performed in 526 patients with liver only metastases and 71 patients with both hepatic and extrahepatic metastases of colorectal origin.

Results: In patients with liver only metastases, the 1-, 3- and 5-years overall survival rates were 89%, 51.9% and 30%, respectively. The morbidity rates were higher in synchronous liver metastases undergoing simultaneous resection. The mortality and survival rates were similar for simultaneous and staged resections (p>0.05). The morbidity, mortality and survival rates for initially unresectable liver metastases rendered to resectability were similar to those of initially resectable metastases (p>0.05). In patients with hepatic and extrahepatic metastases, the survival rate was significantly lower than in patients presenting liver only metastases (p=0.001). Complete resection of the metastases was associated with significantly longer survivals, compared with a palliative hepatectomy (p=0.039).

Conclusion: Liver resection offers the chance of more than 5 years survival to 30% of patients with colorectal cancer liver metastases.

Key words: colorectal liver metastases, simultaneous resection, initially unresectable liver metastases.

INTRODUCTION

Colorectal cancer (CRC) ranks three among the cancers of adults and is the third leading cause of cancer death (1). In 2013 in Romania, colorectal cancer is ranked second as prevalence (after lung cancer) and ranks two as the number of cancer-related deaths (after lung cancer) (2).

The main cause of death in patients with colorectal cancer is metastatic...
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About 50-65% of patients with colorectal cancer will develop liver metastases (CRLM) (4) of which 16-25% are synchronous and 30-40% are metachronous (5-7). Other sites of CRC metastases involve peritoneum and ovary (15%), lung (10.2%), brain (1.7%) and bone (1.9%) (8).

The last 20 years experience has shown that for patients with CRLM, liver resection offers the highest survival rates, ranging between 25% and 50% at 5 years (9-12).

However, some issues related to the indication and the benefit of liver resection in peculiar situations, as well as the optimal timing of liver resection, is still a subject of debate. Simultaneous resection of the primary tumor with synchronous CRLM is still controversial. The benefit of recurrent metastases resection, although supported by several studies, is considered marginally effective by others.

In the last decade the possibility of conversion to resectability for some patients with initially unresectable CRLM became unquestionable, representing the main treatment choice for a prolonged survival in these patients. In addition, resection of the hepatic and extrahepatic metastases has become more widely used, with encouraging results.

In the present paper there are presented the results after liver resections for CRLM, in a large single center experience, over a period of 20 years.

**PATIENTS AND METHODS**

A retrospective study analyzed the prospectively introduced data of 597 patients (262 women and 335 men), aged between 24 and 84 years-old, diagnosed with CRLM, who underwent surgical treatment from January 1995 to December 2014 in the "Dan Setlacec" Center of General Surgery and Liver Transplantation from Fundeni Clinical Institute, Bucharest.

In the present cohort of patients, a total number of 670 liver resections were performed. Out of these, 73 were re-resections. The data were obtained both by studying medical records and surgical protocols from an electronic database recording patients who underwent hepatectomies for CRLM, established in our Department.

Morbidity, mortality and overall survival rates were calculated for the whole set and also for different subsets of patients (i.e., synchronous vs. metachronous CRLM, simultaneous resection vs. delayed resection, first liver resection vs. re-resection of recurrent CRLM, initially resectable CRLM vs. initially unresectable rendered to resectability, hepatic and extrahepatic metastases vs. liver only metastases).

The data are presented as number (percentage). The comparison between the groups was made using the Chi-square test. The survivals were assessed using the Kaplan-Meier curves; the log-rank test was used to compare the survivals between the groups. A p value less than 0.05 was considered statistically significant.

**RESULTS**

**LIVER ONLY COLORECTAL METASTASES**

In the 526 patients diagnosed with liver only colorectal metastases, 595 liver resections (69 iterative resections) were performed. Out of the 526 patients with liver only CRLM, 492 patients had initially resectable CRLM and 34 patients had initially unresectable CRLM rendered to resectability.

In patients with initially resectable CRLM, the morbidity rate was 32.72% (161/492) and the mortality rate was 2.84% (14/492). The 1-, 3- and 5-years survival rates were 89.1%, 54.7% and 31.2%, respectively. The median survival time was 38.7 months (figure 2).

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**Initially resectable CRLM**

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Out of the 492 patients with initially resectable CRLM, 272 had synchronous and 220 metachronous CRLM.

**Synchronous CRLM**

In patients with synchronous CRLM, the mortality rate was 4.04% (11/272). The overall morbidity rate was 39.33% (107/272) and the median survival time was 39.6 months.

The 1-, 3- and 5-years survival rates were: 88.6%,
50.6% and 30.8%, respectively (figure 3).

The 272 patients with "liver only" synchronous initially resectable CRLM underwent either simultaneous resections (214 patients) or staged resection (54 patients underwent initial resection of the primary tumor and then the metastasis resection – “delayed liver resection”, and in 4 patients was performed initial resection of the CRLM and subsequent resection of the primary tumor – „liver first approach”).

Simultaneous resection

The mortality rate was 4.2% (9/214), the morbidity rate was 42.9% (92/214) and the median survival time was 38.7 months. The 1-, 3- and 5-years survival rates were 88.7%, 52% and 31.1%, respectively (figure 4).

Out of the 214 patiens with simultaneous resection, 17 were treated by minimally invasive approach of the primary tumor (7 patients – robotic approach and 10 patients laparoscopic approach). In these 17 patients, liver resection was performed either through a right subcostal incision (13 patients), or by laparoscopic approach (4 patients).

Delayed liver resection

The mortality rate was 3.7% (2/54), the morbidity rate was 22.22% (12/54) and the median survival time was 37.8 months. The 1-, 3- and 5-years survival rates were 88.1%, 52.7% and 22.3%, respectively, similar to those achieved in patients with simultaneous resection (p=0.314) (figure 4).
The morbidity rate in patients with simultaneous resection was significantly higher compared with patients with delayed resection ($p=0.005$), but with no differences regarding the mortality rates ($p=1$).

Liver first approach

The liver first approach was applied to 4 patients (2 with tumor of the rectum and 2 with tumor of the colon, requiring difficult major hepatectomies). The overall morbidity rate was 75% with nil mortality.

Metachronous CRLM

In patients with initially resectable metachronous CRLM, who underwent liver resection (220/492), the mortality rate was 1.36% (3/220), the morbidity rate was 24.54% (54/220) and the median survival time was 37.8 months.

The 1-, 3- and 5-years overall survival rates were 89.8%, 51.8% and 31.7%, respectively (figure 3).

The survival rates after hepatectomy in patients with synchronous and metachronous CRLM were similar ($p=0.539$).

The morbidity rate was significantly lower in patients undergoing liver resection for metachronous metastases compared with patients with synchronous metastases ($p=0.001$). No differences of the mortality rates were observed between the groups ($p=0.084$).

The morbidity rate of patients with liver resection for metachronous metastases was similar to those recorded in patients with synchronous CRLM undergoing delayed liver resection ($p=0.255$). The mortality rates were also similar among these two groups ($p=0.859$).
Initially unresectable CRLM

In 34 patients with initially unresectable CRLM the conversion to resectability was achieved.

Portal vein ligation/embolisation (PVL/PVE) was performed in 18 patients in order to render to resectability initially unresectable liver metastases, but only 10 patients underwent further hepatectomy.

The morbidity and mortality rates after hepatectomy in this group of patients were 38.23% (13/34) and 2.94% (1/34), respectively. These results are not significantly different compared to those observed in patients with initially resectable CRLM ($p = 0.5724$ for the morbidity rates and $p = 1$ for the mortality rates).

The 1-, 3- and 5-years survival rates were 90.4%, 39.9% and 7.8%, respectively. The median survival time was 27.2 months (figure 2), similar to those achieved in patients with initially resectable metastases ($p=0.083$).

HEPATIC AND EXTRAHEPATIC CRLM

In 71 patients undergoing liver resection for CRLM there were present concomitant extrahepatic metastases. In these patients there were performed 75 liver resections (4 re-resections).

The morbidity rate was 35.2% (25/71) and the mortality rate was 5.63% (4/71).

Comparing the morbidity and mortality rates in patients with liver only metastases and hepatic and extrahepatic metastases, respectively, no differences were observed between the groups ($p=0.788$ and $p=0.266$, respectively).

In patients with hepatic and extrahepatic colorectal metastases, the median survival time was 18.2 months and the 1-, 3- and 5-years survival rates were 75.4%, 19.4% and 11.6%, respectively (figure 1), significantly lower compared with patients with liver only CRLM ($p=0.001$).

Out of these 71 patients with hepatic and extrahepatic metastases, 62 underwent complete resection of the metastatic burden, while 9 patients underwent macroscopic residual (i.e., R2) resections.

The 1-, 3- and 5-years survival rates in patients with hepatic and extrahepatic metastases with a complete resection were 76%, 23% and 14%, significantly higher compared with patients with an R2 resection: 50%, 13% and 0% ($p=0.039$) (figure 5).

LIVER RE-RESECTIONS FOR RECURRENT CRLM

Out of 597 patients with liver resections for CRLM, 64 patients underwent re-resections for recurrent CRLM.

In liver only CRLM group, 60 patients underwent 69 liver re-resections (52 patients had a single iterative resection, 7 patients had 2 iterative resections and 1 patient had three iterative resections).

In hepatic and extrahepatic metastases group, 4 patients underwent one liver re-resection, each.

Following the second hepatectomy, the morbidity
rate was 45.31% (29/64) and the mortality rate was 6.2% (4/64). Compared with the short-term results after the first liver resection, the morbidity rate after the second hepatectomy was significantly higher ($p=0.035$), with no differences of the mortality rates ($p=0.135$).

The 1-, 3-, and 5-years survival rates of the patients with liver re-resections for recurrent CRLM (calculated from the time of the first resection) were 98.3%, 67.7% and 27.6%, respectively. These survival rates appear to be higher compared with those achieved in patients with a single liver resection, albeit the statistical significance was not reached ($p=0.308$) (figure 6).

**DISCUSSIONS**

Liver metastases are the primary cause of death in patients with colorectal cancer. The management of these patients implies a multimodal treatment, which involves collaboration between surgeon, oncologist, chemotherapist, radiologist, pathologist, gastroenterologist and radiotherapist (13). Currently available therapeutic methods, in the treatment of these patients, are liver resection, ablative therapies, chemotherapeutic agents (5-FU, Oxaliplatin, Irinotecan), monoclonal antibodies (Bevacizumab, Cetuximab, Panitumumab), radioembolization (Yttrium microspheres) and chemobolization with microspheres loaded with Irinotecan (DEBIRI – drug eluting beads Irinotecan).

The data collected retrospectively in the last 2 decades have highlighted the fact that liver resection offers the highest rates of survival, and represents the only treatment that can offer the chance of curability for some of these patients (14). The data published in December 2014 in LiverMetSurvey (an international database that included patients with CRLM operated in 302 centers from 69 countries), based on the results reported for more than 23 400 patients operated for CRLM, showed that the survival rates achieved by hepatic resection is significantly higher ($p<0.01$) compared with any other therapy (12). It was also revealed that the association between hepatic resection and ablative therapy (for patients who could not benefit from an R0 resection) offered 1-, 3- and 5-years survival rates of 84%, 34% and 21%, respectively, significantly higher ($p<0.01$) compared with patients with only a palliative oncologic treatment. Moreover, a study evaluating the conditions associated with prolonged survival in patients with metastatic colorectal cancer showed that the only factors that were independently correlated with an increased survival were increasing frequency of liver resections and advances in chemotherapy (15).

The survival rates in the present cohort of patients were similar to those reported in other high-volume centers (16,17). For a growing number of patients with CRLM to benefit from the favorable results of liver resection, their indications were expanded in the past decade. Accordingly, the number and size of metastases,
their bilateral location and the age of the patient are no longer contraindications of liver resection (18, 19).

Currently, it is considered that CRLM are resectable (20) when a complete resection can be performed (R0) (21,22), at least two adjacent liver segments can be preserved with an adequate vascular inflow, outflow and bile drainage, and when the volume of the remnant liver exceeds 25-30% of the total liver volume (23-31).

Unfortunately, despite the extension of the frontiers of liver resection, the percentage of patients presenting with resectable CRLM at the moment of the diagnosis does not exceed 25% (32). To give the chance of a potentially curative resection to some patients with initially unresectable CRLM, in the last years few oncosurgical strategies have been introduced with the aim to allow conversion to resectability of these lesions (13,33-37).

In 2014 ESMO (European Society For Medical Oncology) classified unresectable CRLM into 3 groups: in the first two categories (groups 1 and 2) were included patients who potentially could be rendered to resectability, while the third group included patients with definitely unresectable metastases.

The onco-surgical strategies aiming conversion to resectability address to the groups 1 and 2 patients and include:

a) Hepatectomy after portal vein ligation/embolization (PVL/PVE) is a strategy recommended in patients without metastases in the residual liver, but whose future liver remnant (FLR) is below 30% of the total liver volume (TLV) (33). In our experience, by applying this technique, the resectability rate was 55.5% (10/18 patients), similar results being reported by other authors who employed this strategy (30,38,39).

To achieve a more important hypertrophy of the FLR in a shorter period of time, the ALPPS procedure (Associating portal vein ligation and liver partition for staged liver resection) was used in the last 5 years. It leads to higher rates of resectability than PVL/PVE (85-95%), but it is associated with increased rates of major morbidity (about 40%) and mortality (more than 10%) (40-43). Therefore, in present, it is considered that the indications of ALPPS are not fully established, yet, and the best way to perform this approach (up-front or after insufficient hypertrophy of the FLR following PVE, with or without transection of the right bile duct during the first procedure) has to be decided in the future.

b) "Two-stage" hepatectomy is indicated in patients with bilobar CRLM, presenting few metastases larger than 3 cm in the remnant liver, whose resection does not allow preservation of a sufficient FLR. Frequently, the first-stage liver resection is associated with right PVL in order to increase the volume of the FLR (44). By using this procedure, in our center, the rate of conversion to resectability was 45% (5/11 patients), lower than those reported by other authors (75-81%) (44,45). This lower rate of conversion could be explained by a more cautious attitude in performing the second resection in patients with marginally sufficient liver remnant (e.g. 20-25% of the TLV). That may explain the nil mortality rates in our experience; in contrast with up to 15% mortality rates reported by other authors (who achieved higher conversion rates) (45).

c) Hepatic resection associated with ablation of CRLM from FLR is mainly recommended for patients with bilobar metastases that cannot be completely removed due to the insufficient FLR. It consists in resection of the bulk metastatic burden and ablation of the metastases (lower than 3 cm in maximum diameter) located in the FLR (37,46,47). The survival of such patients was significantly higher than those reported for similar patients treated by palliative oncologic therapy.

d) Hepatectomy after shrinkage of liver metastases by chemotherapy is indicated in large liver metastases whose resection does not allow preservation of an adequate FLR, enough to avoid postoperative liver failure. Since 1996, the Paul Brousse group highlighted the possibility of practicing this onco-surgical approach, emphasizing that survival results are superior to those achieved by palliative chemotherapy (25,48,49). In addition, the use of monoclonal antibodies may lead to an increase rate of resectability in the initially unresectable CRLM (50,51).

In the present series, there were 34 patients with initially unresectable CRLM rendered to resectability. Morbidity and mortality rates, although higher in absolute value compared with patients with initially resectable liver metastases, were not statistically significant different. Other authors have shown higher rates of mortality in patients converted to resectability by "two-stage" liver resections, considering that this is determined by the more advanced state of the disease and the poorer biologic status of these patients, which could not allow them to overcome the consequences of postoperative complications (45). Similarly, in patients rendered to resectability after chemotherapy, many authors reported higher morbidity and mortality rates after hepatectomy, explaining this by the hepato-toxic potential of preoperative chemotherapy (52-55). For this reason it is recommended to perform the liver resection as soon as the metastases become resectable, as further prolongation of chemotherapy
may increase the risks of postoperative complications or missing metastases (56,57). Regarding the survival rates achieved in patients with initially unresectable CRLM rendered to resectability by different therapeutic methods, our results are similar to those reported in the other series (25,30,45,58-62).

Although it is widely accepted that the treatment of choice for initially resectable liver metastases is hepatic resection, the optimal timing of resection is still a topic of debate, especially in patients with synchronous liver metastases.

The results reported in this study (similar rates of mortality and survival achieved by simultaneous or staged resection) justify simultaneous resection of the primary tumor and liver metastases. Similar results were recently published by most authors dealing with this topic (63,64,66-66), recommending simultaneous resection of the primary tumor and synchronous CRLM in patients with colon cancer and requiring minor liver resection (64,67-69). Because of the higher morbidity and mortality rates reported by some authors (69,70) in patients undergoing simultaneous resection of the rectal tumor and/or major hepatectomies, few strategies were developed in the last years, aiming to reduce the rate of postoperative complications and deaths. Thus, minimally invasive approach of the primary tumor and replacement of major hepatectomies by ultrasound-guided limited liver resections of liver metastases could decrease the morbidity rates in patients undergoing simultaneous resection. In the present series there were 17 patients treated by minimally invasive approach of the primary tumor (7 patients – robotic approach of the rectal tumor and 10 patients laparoscopic approach). In these 17 patients, liver resection was performed either through a right subcostal incision (13 patients), or by laparoscopic approach (4 patients). The morbidity rate was 23.5% (4/17) and the mortality rate was nil. These lower morbidity rates (compared to those observed in patients undergoing simultaneous resection by open surgery), although not statistically significant (p = 0.297), seem to justify this approaches whenever possible. These results could be explained by the avoidance of delabrant incisions (which decreases the rate of abdominal wall postoperative complications) and the lower number of liver segments resected (which decreases the morbidity and mortality rates after liver resection) (71,72). Currently, we recommend robotic resection of rectal tumors and performing hepatectomy by right subcostal incision, using this incision also to remove the specimen of colorectal resection.

When major hepatectomies could not be replaced by minor liver resections, due to the higher rates of morbidity and mortality reported in patients undergoing simultaneous resection in such instances, a consensus conference held in 2012 recommended staged resections (67). Thus, in patients with borderline resectable synchronous CRLM should be take into account the initial removal of metastases (to avoid their progression to unresectability), postponing the resection of the primary tumor (for a later time). Similarly, in patients with tumors of the mid or low rectum requiring neoadjuvant radiotherapy it is recommended to perform initially the resection of liver metastases (especially when a major hepatectomy is needed), followed by radiotherapy and, subsequently, primary tumor resection (73,74). This approach was used in 4 patients from the present series, giving them the chance to undergo a complete resection of the primary tumor and liver metastases under safe conditions (mortality 0%). This strategy cannot be used in patients who have complications of primary tumor (obstruction /perforation), so that, in such situations it is recommended the initial resection of the primary tumor followed by subsequent hepatectomy.

The results achieved in our series are similar to those recorded in a multicenter study presented in 2013, which revealed that patients with synchronous colorectal liver metastases managed with either simultaneous or staged approach had similar perioperative and long-term outcomes (75).

Although synchronous liver metastases suggest a more aggressive disease, in our series the survival of these patients was not statistically significant lower than those achieved by liver resection in patients with metachronous liver metastases (p = 0.539). Similar observations were reported by other authors (76) who analyzed more than 1 000 patients. However, older studies suggest that the prognosis of patients with metachronous liver metastases is significantly better than those of patients presenting synchronous CRLM (11,46,77-79). The apparently better survival rates of patients undergoing hepatectomy for synchronous CRLM in the last years could be explained by the routine use of an efficient adjuvant chemotherapy, which can mitigate the potentially more aggressive behavior of synchronous metastases.

Nevertheless, it is known that more than 40% of patients who received potentially curative resection of CRLM will develop recurrent liver metastases during the first 2-3 years after surgery (80-82). Liver-only recurrence occurs in one third of these patients and liver re-resection was taking into account in order to
improve their survival (83). In the early 2000s several authors stated that liver re-resection brings a survival benefit similar to those of the initial liver resection (84-86). Thus, Weber et al considered that “liver re-resection resets the biological clock” (87). In our series, the survival (from the moment of the first resection) of the patients who received iterative hepatectomies was higher than those achieved in patients undergoing a single hepatic resection, but the difference was not statistically significant. The results achieved in the present series are similar with those reported, in the recent years, by other authors dealing with this subject, which consider that liver re-resection is safe, but is marginally effective (80,88,89).

The presence of concomitant hepatic and extrahepatic metastases represents a more advanced state of the metastatic disease (stage IVB in the 7th edition of the AJCC (American Joint Committee on Cancer) cancer staging manual). However, in the last decade, the presence of extrahepatic metastases is no longer considered an absolute contraindication to liver resection (90). Thus, in our series, the 5-years survival rate of 11.6% achieved after liver resection in such patients seems to be higher than the survival rates reported in similar patients receiving only palliative chemotherapy. Moreover, in patients with hepatic and extrahepatic metastases who underwent complete resection of the metastatic disease (R0), the survival rate at 5 years was 14%, significantly higher than the 5-years survival of 0% observed in patients who underwent only palliative liver resection (R2) \((p = 0.039)\). Similar survival rates were reported recently by other authors (91,92), which identified a few favorable prognostic factors in patients with hepatic and extrahepatic metastases: the presence of up to 5 liver metastases, extrahepatic disease located only in the lung, preoperative CEA < 10 ng/ml and location of the primary tumor in the left colon (93,94).

**CONCLUSION**

The progresses in liver resection increased dramatically the survival rates of patients with CRLM. Simultaneous resection provides similar mortality and survival rates as staged resections in most of the patients with synchronous CRLM. Whenever possible, major hepatectomies should be replaced by ultrasound-guided limited liver resections, and primary tumor should be approached minimally invasive. Even in patients with initially unresectable CRLM, the prognosis is improved by an aggressive multimodal treatment aiming their conversion to resectability. The presence of extrahepatic metastases is no longer a contraindication for hepatectomy, when complete resection (R0) of the metastatic disease could be achieved. Liver re-resection is a safe approach in patients with recurrent CRLM, improving their overall survival.

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