Advances in the surgical treatment of colorectal liver metastases

Felipe José Fernández Coimbra[1], Thiago Costa Pires[2], Wilson Luiz da Costa Junior[3], Alessandro Landskron Diniz[4], Héber Salvador de Castro Ribeiro[3]

[1] Surgical Oncology; M.Sc. in Oncology, IHPBA, AHPBA, CBC, TECA; Director of the Department of Abdominal Surgery of Hospital AC Camargo, São Paulo, SP
[2] Surgical Oncology; Department of Abdominal Surgery of Hospital AC Camargo, São Paulo, SP
[3] Surgical Oncology; TCBC, TECA; Department of Abdominal Surgery of Hospital AC Camargo, São Paulo, SP
[4] Surgical Oncology; TCBC, IHPBA, TECA; Department of Abdominal Surgery of Hospital AC Camargo, São Paulo, SP

Summary

Colorectal cancer is the 3rd most common malignant neoplasm in the West. About 50% of patients develop liver metastases throughout the course of the disease. Those are responsible for at least two-thirds of deaths. Advances in surgical techniques and improvement in chemotherapy regimens have allowed offering treatment with curative intent to an increasing number of patients. This article reviews recent advances in the treatment of liver metastases, including strategies to increase resection (e.g., portal vein embolization, radiofrequency ablation, two-stage hepatectomy, conversion therapy and reverse treatment strategy) and hepatectomy in the presence of extrahepatic disease. Finally, the results of surgical treatment of liver metastases at the Hospital A.C. Camargo are briefly shown.

Keywords: Abdominal neoplasms; colorectal neoplasms; digestive system neoplasms; liver neoplasms; hepatectomy; colorectal surgery.

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Correspondence to:
Felipe José Fernández Coimbra
Rua José Getúlio, 579, conj 42 – Aclimação
São Paulo – SP
CEP: 01509-001
coimbra.felipe@uol.com.br

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Introduction

Colorectal cancer is the 3rd most common malignant neoplasm in the West. Approximately 50% of the patients develop liver metastasis during the disease evolution, which are responsible for at least two-thirds of the deaths[1-6]. To date, the only potentially curative therapy for these patients is the surgical treatment. However, only 10% to 20% are candidates to resection. When patients are submitted to complete resection, the five-year survival can range from 37% to 58% in the most recent series[6-8].

Although only some of these patients are candidates to surgical treatment, the absolute number of resectable individuals is significant. If a free estimate is made for the Brazilian population, based on the incidence rates supplied by the National Cancer Institute (*Instituto Nacional do Cancer* – INCA) for colorectal cancer in 2009/2010, which is 27,000 new cases/year, one can suppose that around 13,500 (50%) patients have or will have colorectal liver metastases (CRLM), of which 2,700 to 4,050 patients/year (20% to 30%) will be potential candidates for liver resections.

The increase in the number of surgical indications, with the inclusion of bilateral metastases, with no limit for the number and size of nodules, associated with the improvement in systemic treatment outcomes with the use of new regimens with high response rates (going from less than 20% to approximately 50%), can change patients that were initially unresectable into resectable ones and treatments that were initially palliative into curative ones[9-11].

The present article reviews the recent advances in the treatment of liver metastases, including strategies to increase resection and hepatectomies in the presence of extrahepatic disease. Finally, we briefly show the results of the surgical treatment of liver metastases in *Hospital A.C. Camargo.*

Resectability criteria

The capacity to remove all liver metastases with free margins and preserve a future remnant liver (FRL) of at least 20% of the total liver volume (TLV) in patients with a healthy liver, in the absence of unresectable extrahepatic disease, defines most cases regarding liver resectability. Moreover, it is necessary to guarantee adequate arterial and portal inflow, as well as biliary drainage and venous return (outflow). Some patients might need a FRL volume > 20%.

Patients that have been submitted to many chemotherapy cycles (intensive chemotherapy) need FRL of at least 30%, whereas for patients with chronic hepatopathy one can estimate 40%. There is still a great deal of controversy regarding what is considered intensive chemotherapy. In *Hospital A. C. Camargo*, that is considered as more than six cycles of the usual regimen carried out currently, such as FOLFOX (5-Fluorouracil and oxaliplatin), FOLFIRI (5-Fluorouracil and irinotecan) or FOLFOXIRI (5-Fluorouracil, oxaliplatin and irinotecan).

In patients candidate to extensive resections, it is necessary to calculate with higher accuracy the FRL volume. For that purpose, it is necessary to perform liver volumetry. The direct measurement of the FRL is performed by computed tomography (CT). Among the existing formulas, we used the one described by Vauthey *et al.* to calculate the standardized total liver volume[12-13] (Figure 1).

As for the margin, differently from what was believed in the past, a margin of at least 1 cm is not mandatory. Busquets *et al.*[14] in a multicentric study with 557 patients, compared the resection margins from 1 mm to 1 cm and observed that there was no significant difference in global and free-of-disease survival. Therefore, the main objective is to achieve free margins, even though the goal is a 1-cm margin[14].

Preoperative evaluation and staging examination

Initially, the sequelae of previous treatments (for instance, previous hepatectomy and chemotherapy) must be considered as well as patients' comorbidities (obesity, *diabetes mellitus*, alcohol consumption, liver cirrhosis). The morbidity associated with liver steatosis, very often a consequence of the systemic treatment, is a controversial issue, as although there is a histological liver lesion, its influence on mortality remains controversial[15].

The main examination to be carried out for the staging is the CT with a protocol for liver, where thin-section CT images are acquired (preferably in equipment with multidetectors) in four phases: pre-contrast, arterial, portal and equilibrium or late phase. It is considered the gold-standard by most specialized centers, as it allows the accurate assessment of resectability, the number of nodules and their association with liver structures and adjacent organs, in addition to performing the liver volumetry.

Other examinations can also be effectively performed, especially the magnetic resonance (MR), which allows the acquisition of images that are equivalent to the tomography in terms of quality. Some believe that at this time of preoperative chemotherapy and obesity, the MR can be very important, due to the higher capacity of differentiating areas of steatosis from secondary nodules, which has yet to be definitively demonstrated.

The colonoscopy must be always used to rule out the possibility of primary tumor recidivism. Chest images by x-rays or CT are also mandatory to assess the presence of lung metastases.

The positron emission tomography (PET)-CT is the new tool for the staging of these patients, but there is no consensus on its use to date. Fernandez *et al.* [16] evaluated 100 patients with liver metastases of colorectal origin that were submitted to PET-CT in the preoperative period and concluded that there are survival advantages when the 18F-Fluorodeoxyglucose (FDG) PET/CT is used, due to

better patient selection for surgery, with a 5-year survival of 58% being observed in this group of patients; however, the great criticism faced by this study is not comparing PET-CT with the currently available high-definition tomographic images. One must be aware of false-negative results after the chemotherapy. Thus, even when there is no uptake of a nodule visualized before the chemotherapy, the indication for resection is maintained, as the decreased sensitivity of PET-CT in detecting metastases post-chemotherapy is well-known[17], mainly before two weeks after its completion.

The PET-CT can also predict the response to chemotherapy when 18F-FU is used instead of 18F-FDG[18].

One of the most important questions regarding the re-staging post-chemotherapy is the discrepancy between imaging study results and surgical findings[19,20]. Angliviel *et al.*[20] showed that there is more than 50% of result discrepancy in CT findings post-chemotherapy at the re-staging when compared with the surgical findings. Carnaghi *et al.*[19] pointed out that both PET-CT and CT have limited sensitivity (60%) for re-staging of CRLM post-chemotherapy, especially for lesions < 1 cm.

Benoist *et al.*[21] evaluated 66 patients that had complete response at the imaging examinations after "neo-adjuvant" chemotherapy and were submitted to surgical exploration and systematic clinical follow-up. Of these, 32 had lesions identified at the surgery and 23 were identified at the clinical follow-up in the same sites of the previous lesion. The conclusion is that 83% of the patients that had a complete response at the imaging examinations have macro or microscopic residual disease or early recidivism. From our point of view, this information is of utmost importance for the indication of surgical exploration and resection of previously compromised areas, even in patients in whom complete radiological response was observed and for whom a curative treatment is intended.

Surgical treatment

The surgical procedure must be initiated with the systematic exploration of the abdominal cavity, with special attention when assessing the presence of extrahepatic disease. Colon, peritoneum, retroperitoneal lymph nodes, celiac trunk and hepatic hilum are evaluated and biopsies and microscopic examination of frozen samples are carried out in all suspected sites.

All assessment modalities are important during liver evaluation. The presence of nodules, post-chemotherapy scars, retractions or areas suggestive of fibrosis must be observed. At palpation, the presence of hardened, round, firm, or fibroelastic areas that can be superficial, easily palpable or deep can be noticed. These must be assessed carefully, as the presence of the liver parenchyma between the tumor and the examiner's hand can make the evaluation difficult. The examination must be carried out by surgeon by sliding the hands over the entire liver surface and it must always be bimanual, increasing the sensitivity to identify deep lesions, especially in the left lobe.

The intraoperative ultrasonography is currently an essential tool for staging and surgical planning and therefore, a mandatory examination in any liver surgery. It can identify 20% to 30% of the nodules that were not detected at the conventional examinations. In our country, Cohen MP *et al.*[22] demonstrated that the intraoperative ultrasonography in surgeries performed to resect liver metastases changes the surgical strategy in 25.7% of the cases and is extremely useful in identifying lesions < 1 cm.

The type of resection must guided by the number and location of lesions and by the need to attain tumor-free margins. The anatomic resections, that is, exeresis of liver segments or lobes, respecting the regions delimited by venous and arterial vascularization, in addition to the biliary drainage, are preferable, as they allow lower blood loss and carry a lower risk of compromised margins. However, there is no difference in survival regarding the non-anatomical resections, as long as the margins are free[23,24]. The types of resection are: segmentectomies, bi-segmentectomies, central hepatectomies, lobectomies, tri-segmentectomies, enucleations and combinations of these forms. Resections that are concomitant to the primary tumor are safe and feasible, as long as they are carried out by an experienced tem and follow the oncologic principles.

Strategies to increase resectability

As previously described, resectability is currently defined by a new paradigm, where the possibility of resection of liver lesions must be considered, as well as the complete resection of extrahepatic lesions and the quality (inflow-outflow) and quantity of remnant liver after the surgery and not exclusively by the tumor clinicopathological factors. Therefore, previously used criteria, such as number of nodules, size of lesions, bilateralism and presence of extrahepatic disease (as long as resectable) must be considered prognostic factors and not a contraindication for resection.

BEFORE: based on what was resected.
CURRENTLY: based on what will remain after resection.

Based on these principles, strategies are defined, which will allow the resection of extensive disease in several circumstances where they would previously be considered unresectable. Still, there are cases in which complete resection with FRL volume cannot be attained with the usual techniques. In this situation, other techniques are employed to increase resectability.

Portal vein embolization

In general, 20% of the normal FRL is considered safe after an extensive resection. However, the sectioning volume for FRL in patients with livers presenting steatosis, steatohepatitis (30% RLV) or cirrhosis (> 40%) must be higher. In general, the right lobe represents two-thirds of the liver volume and the left only one-third. Frequently, patients with multiple liver lesions are submitted to right hepatectomy extended to segment IV (or right tri-segmentectomy).

On average, these surgeries remove around 84% of the liver volume in the absence of compensatory hypertrophy of the remnant liver[25]. However, a high degree of individual variation can be observed in the volumes of liver segments and lobes. To prevent surgeries in patients with FRL lower than the desired volume, the portal vein embolization must be carried out to induce contralateral lobe hypertrophy[25].

The idea came from the observation that when there is invasion of a portal vein branch by the tumor, there is hypertrophy of the contralateral lobe. Technically it is performed through catheterization by radioscopy of the lobe or segmental vein, followed by vessel embolization by embolic material (coils, thrombin, cyanoacrylate, microspheres, etc). It is a relatively safe procedure; its rate of complications varies from 5% to 8%. Then expected volume growth of the FRL is of 8% to 16%[26-28].

The portal vein embolization is more frequently used as part of the multimodal treatment regimens, which include preoperative chemotherapy and hepatectomy, as most part of these patients already presents with more than one factor of poor prognosis, such as multiple lesions, bilobar lesions, compromised lymph nodes at the primary and extrahepatic metastases.

Some authors evaluated whether the use of CT before or after the portal embolization could impair liver hypertrophy; however, the results showed no impairment in liver hypertrophy when volume increase is desired[29,30].

Two-stage hepatectomy

In extreme situations, in which there are multiple metastases in both hepatic lobes, two-stage resections can be the best therapeutic option and the only chance of cure, preserving an adequate volume of FRL.

The initial results had a high rate of liver failure and postoperative mortality > 10%[31], very different from what is currently observed with the routine use portal vein embolization in specialized centers.

The recommendation is that at the first intervention, the removal of the liver metastasis be carried out in the liver parenchyma that one wishes to preserve (FRL), to prevent the excessive growth of metastases after the portal flow deviation by embolization. It is usually a parenchyma-sparing resection carried out in the lobe or segments that exhibit less disease damage (usually the left lobe) attaining tumor-free margins, and allowing the preservation of most of the lobe or segments in question. There is a 4-to-6 week interval to surgery and volumetry control is always performed before and after this period, to ensure that there is FRL with an adequate volume.

At the second stage of the procedure, a more extensive resection is performed, most often from the right lobe, which extends to the IV segment. It is seldom necessary to perform left portal vein embolization for right lobe hypertrophy, as the volume of the latter is hardly ever lower than the desired volume. As it is a complex procedure, it must be performed only in curative situations.

In several situations, CT is indicated during the time between the embolization and surgery, without the use of monoclonal antibody (Bevacizumab), when it is being used in the CT regimen. The objective is to prevent tumor growth during the period when waiting for the second phase of the surgery.

Radiofrequency

Another alternative to the two-stage surgery is the association of radiofrequency (RF) ablation with liver resection, which in some situations can expand the number of patients eligible for surgery. However, the RF has a higher risk of recidivism in comparison with the resection, mainly in lesions > 3 cm. It use must be restricted to cases in which the resection is not possible due to lack of adequate FRL volume[7].

Conversion therapy

Many patients have such extensive liver disease at diagnosis that they cannot be candidates to liver resection through any of the strategies mentioned before. However, there are cases in which the reduction of hepatic lesions through CT can enable the surgical treatment, transforming an initially unresectable disease into a resectable one. When the CT is used for that purpose, it is called conversion chemotherapy.

The conversion CT consists of administration of therapeutic regimens with a high rate of response, aiming at the decrease in tumor volume to allow the resection of metastases, while obtaining an adequate liver volume.

The main therapeutic options are FOLFOX or FOLFIRI, or a combination of both (FOLFOXIRI), with response rates of 48-66%[32-35], 39-62%[36-38] and 56-71,4%[39,40], respectively. According to some authors, there is a "conversion" in around 10% to 20% of individuals initially considered to unresectable[9], with survival rates similar to that observed in patients that are initially resectable[41]. Higher response rates can be obtained by adding target-therapy with cetuximab or bevacizumab.

CT duration must be only the necessary time for conversion to occur, with no predetermined number of cycles. The intention is to submit the patient to surgery as soon

as the lesions are resectable, preventing unnecessary liver toxicity that result from CT excess and also an eventual progression of the disease after a long period of treatment.

Thus, the patients must be followed together with the surgeon, through control image assessment every two months, aiming at detecting lesion response and identifying, as soon as possible, the moment when the metastases become resectable. If there is no adequate radiological response, a new CT scheme can be attempted, always aiming at conversion.

Extrahepatic disease

Traditionally, the presence of extrahepatic metastases of colorectal origin was considered an absolute contraindication for hepatectomy[42]. As a consequence of safer surgical procedures and the evolution of the effectiveness of CT schemes, hepatic resections started to be performed in association with extrahepatic metastasis resection, for selected groups of patients. The main sites of extrahepatic disease to be considered are: portal lymph nodes, peritoneum and lungs.

The metastases for portal lymph nodes in the context of CRLM result from the lymphatic drainage of the liver and thus, represent the local-regional dissemination of liver metastases[43]. Patients with macroscopic metastases for portal lymph nodes have an unfavorable evolution, with little chance of five-year survival[44,45]. However, it is possible to select patients with a better prognosis based on the location of the affected lymph nodes. Jaeck *et al.*[46] demonstrated that whereas patients with lymph node metastases along the common hepatic artery and celiac trunk have 0% 1-year survival, those with lymph node metastases located in the hepatoduodenal ligament had a 38% 3-year survival. These findings were confirmed by Adam *et al.*[47], who showed a 5-year survival of 25% in the analysis of 47 patients with peri-hepatic lymph node metastases in the hepatoduodenal ligament, whereas there were no survivors among those with metastases in the celiac or para-aortic trunk.

Therefore, only patients with hepatoduodenal ligament lymph node metastasis must be considered for liver resection. Those with retroperitoneal lymph node disease must receive palliative treatment.

The lungs, together with the liver, are the most common sites of metastases in colorectal tumors. Several studies have demonstrated that the resection of the lung disease can lead to long-term survival[48]. However, little has been studied on the presence of synchronic lung and liver metastases. Six studies addressed this question, showing that although it is often necessary to perform new resections per early recidivism, the global 5-year survival varies from 27-74%[49]. The main factors that seem to influence prognosis are: number of pulmonary lesions, number of hepatic lesions and the synchronic *versus* metachronic presentation.

Peritoneal carcinomatosis occurs in 13-25% of patients with colorectal tumors. If treated only with systemic CT, this condition leads to death in less than one year, with a median survival ranging from 5.2 to 6.9 months[50]. However, similarly to hepatic metastases, it is believed that it does not always represent disseminated systemic disease, but a local-regional form of dissemination (transmural deposit of tumor cells), which can be treated by peritonectomy and hyperthermic intraperitoneal chemotherapy (HIPEC)[51]. Thus, patients with restricted peritoneal disease can benefit from this treatment[52]. Two studies specifically addressed the association between peritoneal carcinomatosis and liver metastases. Carmignani *et al.*[53] evaluated 27 patients with peritoneal carcinomatosis, of which 16 had liver metastases as the only additional site of the disease and 4 other had liver and lung metastases. The procedures aiming at complete cytoreduction had a morbidity of 14.8%, with no deaths and a median survival of 15.2%. Elias *et al.* reported on the treatment of 27 patients with CRLM and synchronic peritoneal carcinomatosis, of which 14 patients had carcinomatosis detected preoperatively and 13, intraoperatively[54]. There was a postoperative death (4%) on 14th day due to undiagnosed peritonitis and the morbidity was 58%. With a median follow-up of 6.1 years, the global 5-year survival was 26.5%, with seven patients being disease-free; as for the cases of recidivism, only three had been located in the peritoneum. The only prognostic factor with statistical significance was the number of liver nodules > 2. However, these findings still need to be corroborated by other randomized studies with larger samples. Thus, well-selected patients, as long as they are submitted to treatment in specialized centers, can undergo the simultaneous treatment of liver metastases and peritoneal carcinomatosis.

Reverse treatment strategy

Patients with synchronic liver metastases are classically submitted to primary tumor resection, followed by long CT periods and subsequently, if there is no disease progression during this period, they are referred to liver resection[55,56]. However, patients with advanced liver disease can have metastasis progression during the primary tumor treatment, making the lesions unresectable. This problem becomes especially important in patients with rectal tumors (who often necessary need to undergo neoadjuvant RT, in which the concomitant CT has only a radiosensitizing function) and in those with surgical complications caused by the primary tumor treatment.

One strategy to attenuate this problem is to perform the liver resection together with the colorectal tumor resection. However, few patients are eligible for this procedure and there are considerable limitations for extensive hepatectomies[57,58].

An attempt to overcome the problem has been the use of a new treatment strategy, called the reverse treatment strategy, where there is an inversion of the classic treatment sequence[59,60].

Hence, liver metastases – the main determinants for the definition of the treatment curative characteristic – are treated before the primary tumor. Patients with asymptomatic colorectal tumor with large, but resectable liver metastases or patients with initially unresectable metastases that achieved conversion after chemotherapy are candidates to this type of treatment.

In our service, we recommend starting these patients' management with chemotherapy, aiming at the immediate treatment of both the liver metastases and the micrometastatic systemic disease. The main concerns regarding this approach are the possibility of complications related to the primary tumor (pain, bleeding or obstruction) or the progression of liver metastases during the CT period. However, the first is a rare event, not different from the rates of complications or bridle obstructions in patients submitted to surgery[61,62], whereas the latter represents such a poor prognosis that these patients would hardly have benefited from any initial surgical treatment[63].

Treatment outcomes

Even considering the increase in surgical indications for larger tumors, multiple nodules, synchronous bilobar lesions and extrahepatic disease, one can observe an increase in survival throughout the last decades, going in a period of five years from 30% in the oldest series to more than 50% in the current ones (Table 1).

A published analysis of 70 patients submitted to surgery in our institution between January 1999 and June 2005 showed a five-year-survival of 51%[64]. A more recent reassessment of our series, taking into account 142 surgeries in 121 patients in recent years, showed a global survival of 66.2% in five years and 54.9% in seven years (data not published).

Conclusion

The perfecting of surgical techniques together with safer procedures, as well as the improvement in chemotherapy regimens have allowed doctors to offer patients with liver metastasis the possibility of curative treatment or long-term survival. Factors that were previously considered contraindications for the surgery, such as number of metastases, synchronous metastases and even the presence of extrahepatic disease, must be considered only as prognostic factors and must not prevent the patient from having the opportunity of being treated.

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Table 1 – Outcomes of liver resection for metastatic colorectal cancer

Author (year)	Mortality %	Mean survival (months)	Five-year survival
Hughes *et al.* (1986) - Multicêntrico	–	–	33%
Gayowski *et al.* (1994) - Pittsburg Medical Center	0	33	32%
Jamison *et al.* (1997) - Mayo Clinic	4	33	27%
Fong *et al.* (1999) - Memorial Sloan Katering	3	42	36%
Choti *et al.* (2002) - Johns Hopkins	1	46	40%
Fernandez *et al.* (2004) - Washington University	1	–	59%
Pawlik *et al.* (2005) - M.D. Anderson	1	74	58%
Hospital A.C. Camargo (2005)	0	–	51%
Hospital A.C. Camargo (2010)	0.9 (30 days) 1.8 (90 days)	–	66.2%

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