

Hepatic colorectal metastases: methods of improving resectability

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Liver metastases are found in 40% to 70% of patients with a colorectal cancer. In nearly one third of cases, the liver is shown to be the only site of cancer spread at autopsy. The frequency of synchronous colorectal liver metastases is 15% to 30% [1–3]; metachronous metastases develop in the same percentage of patients, usually within a period of 3 years [3,4]. There is no spontaneous long-term survival in untreated patients, and the median survival time ranges from 6 to 18 months [5–8].

Factors associated with decreased patient survival are multiple liver metastases [9], presence of metastatic lymph nodes [10], presence of extrahepatic metastases [11,12], increased carcinoembryonic antigen levels [9], and high grade of malignancy of the primary tumor. Among all these factors, liver involvement is the most important one.

At present it is well established that the only treatment resulting in long-term survival for patients with colorectal liver metastases is hepatic resection. However, at time of diagnosis, the majority of patients who have colorectal liver metastases present unresectable tumors. Using current criteria, resection can be performed in only 10% to 20% of all patients who have colorectal liver metastases [13–15].

The main cause of unresectability is the impossibility of removing the entire tumor while leaving a sufficient residual amount of functional liver parenchyma (at least 30% of initial liver volume). In this situation, resection should not be performed because of the high risk of postoperative severe liver failure. Oncologic reasons may also contraindicate resection as the presence of extra hepatic tumor.

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In all cases, surgical treatment should aim for complete tumor removal because the outcome of patients who have been incompletely resected is similar to that of nonoperated patients [16]. This article describes the authors' experience and results with the application of different methods used to improve the resectability of hepatic colorectal metastases. Different strategies are proposed in relation to the initial cause of unresectability.

Definition of unresectable hepatic metastases

Before describing the methods that improve resectability of hepatic colorectal metastases, it is important to clarify the definition of unresectability. Many factors, such as number and size of metastases, resection margins, and presence of extrahepatic disease have an impact on resectability and on long-term survival probability. At present, the only absolute contraindication for hepatic resection is the impossibility to resect all the tumoral tissue while leaving enough functional hepatic parenchyma to avoid postoperative liver insufficiency.

The authors' proposed classifications of unresectability are as follows:

Unresectability “de principe”

Owing to lower survival rates, some subgroups of patients with negative prognostic factors, such as high number and large size of metastases, have been historically recommended to be excluded from resection [17]. For example, patients with multinodular metastases have a worse prognosis than those with single metastasis [9,18], and having 4 or more metastases has been considered a contraindication for resection. However, recent studies suggest that the number should not be an argument to contraindicate resection, provided that a complete resection can be performed [19–23]. The size of metastases follows the same criteria, and recent studies fail to identify size as an independent prognostic factor [21], although metastases larger than 5 cm used to be associated with poorer outcome [24].

Carcinological unresectability

Concerns the presence of extrahepatic disease and the impossibility to respect disease-free resection margins. Resection margins of at least 1 cm have been considered as a rule for hepatic resection of metastases. However, recent studies show that the predominant prognostic factor for long-term survival is a disease-free resection margin, independently from its width, which can be more limited than 1 cm [9,19,25,26]. Overall, resection margins of at least 1 cm have to be respected; however, when multinodularity or close proximity to vessels does not allow such a margin, hepatectomy need not be contraindicated provided that it is macroscopically complete.

Extrahepatic disease is usually associated to unfavorable outcome [18,24]. Nevertheless, long-term survival is reported in a significant number of patients when complete resection of extrahepatic disease is performed, especially in the case of pulmonary metastases [27–31]. Long-term prognosis is unfavorable in patients with metastatic lymph nodes [10,26,32,33]. However, hepatic resection combined with lymphadenectomy could be proposed to patients whose tumoral disease is downstaged by chemotherapy and could be completely resected.

Technical unresectability

Technical unresectability is the main cause of unresectability and is usually due to the extent of hepatic resection needed to achieve radicality. Three main causes could be responsible of this situation: number of metastases, multinodularity, and location of tumors.

Methods to improve resectability

The strategy of facing primarily unresectable hepatic metastases should include the objectives of downstaging tumoral disease and treating hepatic metastases with an R0 resection, saving at least 30% of functional remnant liver. For surgeons, the aim is to individualize the reasons of unresectability for each patient, determine the conditions of reversibility, and formulate an adapted onco-surgical strategy.

Many treatments and surgical tools are currently available to be used either alone or combined to each other to target the objective of resection. This article briefly describes these different options independently and proposes a strategy to face the difficult cases of primarily unresectable colorectal hepatic metastases.

Chemotherapy

Novel chemotherapeutic regimens combining 5-FU, folinic acid, and either oxaliplatin or irinotecan have been proved to increase both patient survival and quality of life [15,34–38]. However, they do not allow eradication of the metastatic disease with the corresponding chance of long-term survival. Nevertheless, these chemotherapeutic regimens have been shown to downstage liver disease in patients with previously unresectable metastases [15].

Tumoral downstaging can make surgery possible in patients previously considered unresectable—mainly by reducing the size of liver metastases—thus switching them from an expected poor prognosis to one with a chance of long-term survival (Figs. 1, 2).

Chronomodulation, which consists of timing the administration of individual drugs to coincide with circadian rhythms that influence their effectiveness, allows neoadjuvant chemotherapy regimens to be more



Fig. 1. Initially unresectable, centrally located colorectal liver metastasis before chemotherapy.

effective, better tolerated, and delivered at higher doses [39]. In our series, using this type of chemotherapy regimen, a high response rate was observed and resection became possible in 95 of 701 (13.5%) patients initially considered unresectable [15]. The overall 5-year survival rate of patients who could be submitted to a potentially curative resection after neoadjuvant chemotherapy was 34% and was highest in patients whose tumor was large (60%) and lowest in those with extrahepatic spread (18%). After a mean follow-up of 4.2 years, 39 of 95 patients were alive (41%); 25 of them were recurrence-free (26%).

Hepatic resection after tumor response to chemotherapy can provide a hope of long-term survival similar to that of primarily resected patients; as a matter of fact, the survival curve for patients with secondary resection is similar to that of primary resection (Fig. 3). Because chemotherapy for colorectal cancer is constantly evolving, future developments should allow an increasing proportion of patients to be considered for surgery.



Fig. 2. Downstaging after chemotherapy in the case of Fig. 1 enabled further hepatectomy.

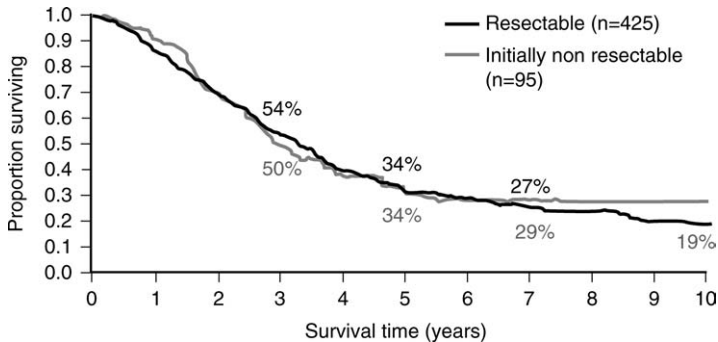


Fig. 3. Survival of liver resection for initially unresectable colorectal metastases downstaged by chemotherapy versus primary resection.

Portal vein embolization

Liver resection should not be performed when the proportion of remnant liver is less than 30% of the total liver parenchyma. In this condition there is indeed a high risk of postoperative liver failure, which is the main cause of postoperative mortality. It is also important to estimate the proportion of functional liver by excluding the tumor, which is considered nonfunctional. Allowance should also be paid to possible hepatic damage resulting from preoperative chemotherapy [40].

Three levels of postoperative hepatic failure risk can be categorized according to the remnant liver volume: (1) low risk when it is 40% or greater; (2) medium risk when it is 25% to 40%; and (3) high risk when functional remnant liver parenchyma it is 25% or less.

Preoperative portal venous embolization (PVE) of the liver to be resected induces a compensatory hypertrophy of the future remnant liver, enabling more confident resection of tumors with clear margins. It permits an increase in the extent of resection and reduces the risk of postoperative hepatic failure [41–43]. The technique of percutaneous PVE is reported in detail elsewhere [41].

In our center, PVE is routinely performed when the estimated rate of functional remnant liver parenchyma is 30% or less in the absence of chemotherapy or 40% or less in case of prolonged preoperative chemotherapy. Hepatic resection is considered when hypertrophy of the future remnant liver has reached a plateau on CT scan hepatic volumetric assessment, which occurs usually within 4 to 6 weeks from PVE. In our experience, the mean estimated volume of functional remnant liver parenchyma has increased from 26% to 37% of total liver volume after PVE ($P < 0.001$) [43].

Preoperative PVE in patients with initially unresectable tumors, permitted to increase by 19% the number of large hepatectomies (liver resection of more than three Couinaud's segments [44]). Their 5-year survival rate was 40%, similar to that following hepatic resection without

PVE [43]. Other series of preoperative PVE confirm that it does not only increase resectability, but it also allows increasing safety of large hepatic resections [45–47].

Local destructive therapies

Cryotherapy and radiofrequency are efficient methods to locally destroy tumors that cannot be surgically resected. The limits of these treatments are mainly the size of the tumor, which should not exceed 30 mm, and the contact with major biliary or vascular structures. In case of multinodularity, local tumor destruction could be used as an adjunct to resection, with a curative intent, and applied to tumors that turn out to be unresectable at laparotomy. As suggested in a preliminary experience [48], our current experience in 35 patients with unresectable colorectal liver metastases treated by cryosurgery combined to resection suggest that a benefit exists, similar to that of resection alone, with a 5-year survival rate of 30% (unpublished data). Radiofrequency of unresectable colorectal metastases combined with resection is currently in use and similarly increases the resectability of patients primarily unfit for a complete surgical resection.

The use of local destructive therapy methods are particularly useful in complement to large hepatectomy for bilateral multinodular involvement, resecting surgically the maximal amount of metastases, and “ablating” by local treatment few nonresectable nodules in the remnant liver. Those remnant metastases must be, at best, three or less in number with a size not exceeding 3 cm in diameter to be optimally treated by radiofrequency or cryotherapy. Cryotherapy and radiofrequency have similar complication rates and similar initial success, but the local tumor recurrence rate seems lower with radiofrequency than with cryotherapy (19% versus 71%) [49]. However, no randomized treatment has clearly stated the superiority of one treatment over the other.

Local destructive treatments can also be used in association with PVE to prevent the tumoral progression of a metastatic nodule located in nonembolized liver segments, as it has been described that the growth rate of metastases is more rapid than that of the liver parenchyma [50,51].

Two-stage hepatectomy

Two-stage hepatectomy consists of a sequential strategy whose overall intention is curative. This option is usually applied to multinodular metastases involving both lobes of the liver that are impossible to resect in a single procedure (Fig. 4). The first hepatic resection is intended to remove the highest possible number of metastases and has as main objective of making the second hepatectomy potentially curative. After the first resection procedure, the remnant liver hypertrophies and systemic chemotherapy limits the growth and spread of the remaining tumor deposits. Postoperative chemotherapy, which usually uses the same drug protocol as

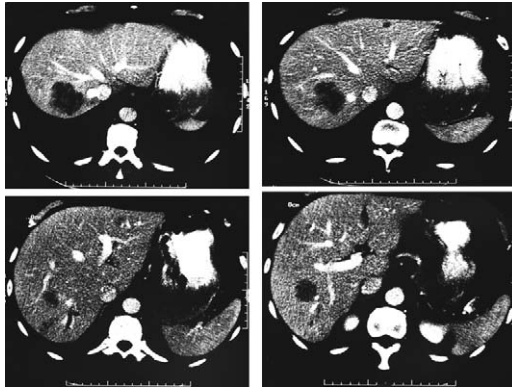


Fig. 4. Multinodular bilobar metastases needing a right hepatectomy and a left lobectomy managed by two-stage hepatectomy.

before surgery, is begun 3 weeks after liver resection so that it does not interfere with early liver regeneration. The second stage is performed only if it is potentially curative in the absence of significant tumor progression and only when adequate parenchyma hypertrophy has reduced the risk of postoperative liver failure. The objective of a two-stage strategy is, of course, to avoid posthepatectomy liver failure; in addition, there must be a clear idea of the type of second stage at the time of first operation. The application of this strategy is limited to selected patients.

An example of two-stage hepatectomy is given in Figs. 4, 5, and 6, in which a first-stage left lobectomy is associated with a right PVE (Fig. 5) and is followed in a second stage by a right hepatectomy, thus leaving a disease-free remnant liver made up of segments 1 and 4 (Fig. 6). As reported in the

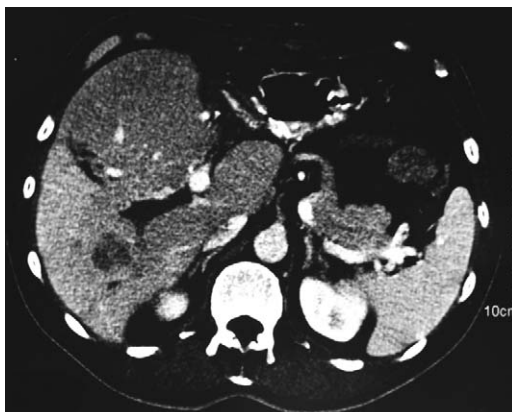


Fig. 5. Abdominal CT scan after first-stage hepatectomy: left lobectomy associated with a right PVE.

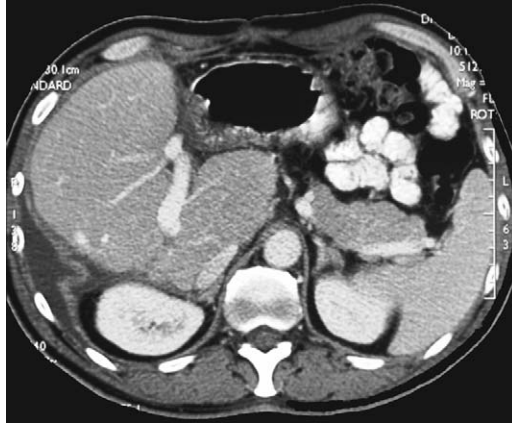


Fig. 6. Abdominal CT scan after second-stage hepatectomy (right hepatectomy). The remnant liver parenchyma consisted of hypertrophied segments 1 and 4.

authors' own recent series of 13 patients undergoing a two-stage hepatectomy, the 3-year survival rate was 35% [52]. Long-term results of this new strategy in a larger number of patients are to be awaited for a true evaluation of this option.

Repeat hepatectomies

Despite the attempt of surgery to be as curative as possible, 60% to 70% of patients undergoing liver resection for colorectal liver metastases will develop recurrence of the disease, one third of which isolated to the liver [9,24,53]. Even if repeat liver resections are technically more demanding and difficult, most series report comparable morbidity and mortality and overall similar long-term survival rates as that of first hepatectomy [54,55].

In the authors' initial experience of repeat hepatectomies, patients undergoing a second hepatic resection with curative intent have a long-term survival rate similar to that of patients with only one hepatectomy. Similarly, a third hepatectomy offers the same survival benefit as first or second hepatectomy [56].

Strategy

The management of initially unresectable colorectal liver metastases is an example of a clinical problem for which a multidisciplinary approach is fundamental. The main objective is to render the maximum number of patients resectable. There are two complementary ways to reach feasibility of resection depending on the reason of unresectability: neoadjuvant chemotherapy and application of specific surgical techniques.

The principal cause of hepatic colorectal metastasis unresectability is technical, needing the resection of more than 70% of functional liver parenchyma, with a consequent risk of postoperative liver failure.

Multinodularity represents the more frequent cause of technical unresectability. Schematically, three clinical situations can be faced for multinodular metastases, each with an adapted surgical solution depending on their number, size, and location (Fig. 7):

1. Multinodular unilobar metastases needing a hepatectomy larger than 60% to 70% of functional liver parenchyma should benefit from a preoperative PVE. The hypertrophy induced on the future remnant liver parenchyma further allows a curative resection with a minimized risk of postoperative hepatic insufficiency (Fig. 7a).
2. Multinodular bilobar metastases for which resection leaves three or fewer nodules of 3 cm or less in the remnant liver may benefit from a multimodal approach consisting of hepatic resection associated with radiofrequency or cryotherapy of the nonresected nodules (Fig. 7b).
3. Multinodular bilobar metastases for which resection leaves three or more nodules of 3 cm or more in the remnant liver may benefit from a two-step hepatectomy according to the heretofore mentioned criteria of selection (Fig. 7c).

Tumor involvement with major hepatic veins or the inferior vena cava is the second cause of technical unresectability. This represents a surgical challenge because of the high intraoperative bleeding risk. Many techniques exist for surgeons who face the technical problems of these high-risk resections, ranging from the intermittent portal triad clamping (Pringle maneuver) to the total hepatic vascular exclusion with or without

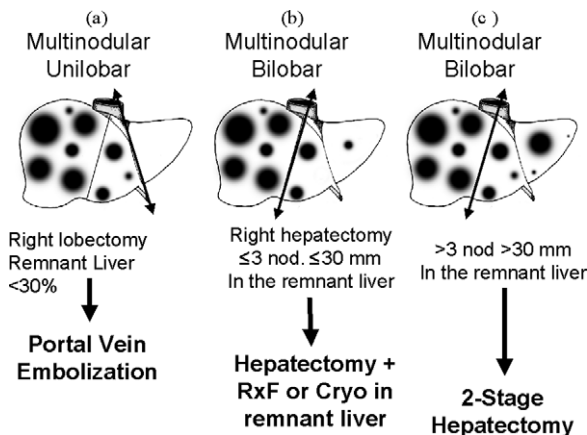


Fig. 7. Proposed strategy for primarily unresectable multinodular liver metastases depending on size, number, and location.

preservation of caval flow. The choice of type of vascular control depends on the complexity and the presumed time length of resection, with the objective to minimize blood loss and avoid prolonged ischemia time. Other methods, such as extracorporeal veno-venous bypass, hypothermic perfusion of the liver, and hepatic vein reconstruction, can also be used to extend surgical indications. These methods undeniably improve feasibility of complex hepatic resections and thus increase resectability of ill-located colorectal liver metastases.

Although all these techniques are separately described, it is important to understand that they could be combined depending on the clinical situation. Thus management of colorectal hepatic metastases should be multimodal, incorporating chemotherapy, portal venous embolization, surgery, local destructive treatments, and adequate methods of vascular occlusion. Accordingly, surgical strategies in patients with unresectable liver metastases who have been downstaged by chemotherapy seldom involve a single straightforward hepatectomy. In the authors' experience [15,57], many patients underwent associated procedures that included the following: repeat liver resections (28%), local ablative treatments (15%), planned two-stage hepatectomies (9%), PVE (9%), and resection of pulmonary metastases (6%).

Summary

Surgery is the best treatment modality for colorectal liver metastases. When initially unresectable, hepatic resection of metastases after downstaging by chemotherapy can provide a hope of long-term survival similar to that of primarily resected patients.

Definitions of resectability have evolved with the emerging principle that if metastases can be completely resected regardless of their size and number, resection should be performed as the sole mean of achieving long-term survival.

Specific surgical techniques can be combined to improve resectability. If the tumor is considered unresectable, recent developments make possible to render some tumors surgically resectable. Depending on the tumor size, number and location, neoadjuvant treatments, mainly chemotherapy, can be used, followed by resection.

Resection may be contraindicated if the residual volume of liver is inadequate to avoid liver failure. This may be changed either by PVE or two-stage hepatectomy, both of which use the natural regenerative capacity of the liver. Local destructive therapies such as cryosurgery and radio-frequency can also be used in conjunction with resection for patients in whom all metastases are not surgically resectable. The present use of these ablative techniques is improving the percentages of unresectable patients considered for surgery.

All of the above-described methods can be combined to achieve a surgical strategy that is as curative as possible, increasing the number of patients primarily unresectable, with a long-term survival hope similar to that of primarily resectable patients. To achieve this objective, a close collaboration between oncologists, radiologists, and surgeons is mandatory, with routine re-evaluation of patients for an adequate timing of each treatment.

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