Surgical resection including peri-operative chemotherapy (adjuvant and neoadjuvant)

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Introduction

Liver metastases develop in nearly 20% of patients with stage II and 50% of patients with stage III colorectal cancer and represent the major cause of death in this disease. Unlike many other types of cancer, the presence of distant metastases from colorectal cancer does not preclude curative treatment. Surgical resection remains the only treatment that can, to date, ensure long-term survival and cure in some patients. However, only a minority of patients with liver metastases are amenable to surgery. Recent progress (including new chemotherapeutic regimens, ablative techniques, and interventional radiology) could result in an increase in the number of patients that can be treated with a curative intent. Recurrences are still observed in two-thirds of patients after resection of liver metastases. Here again, various attempts have been made to reduce this risk with the use of adjuvant intravenous and/or intra-arterial chemotherapies, or to provide curative treatments in case of recurrence with either surgery or ablative techniques.

Surgical resection of liver metastases: the state of the art

In the absence of treatment, the median survival rarely exceeds 9 months. In a large prospective study, conducted from 1980 to 1990 and including 484 patients with untreated hepatic metastases from colorectal cancer, the median survival was 31% at 1 year, 7.9% at 2 years, 2.6% at 3 years and 0.9% at 4 years. Factors that independently influenced survival were: the volume of the liver involvement, the presence of extra-hepatic disease, metastatic lymph nodes in the mesentery, carcino-embryonic antigen (CEA) level, and the age of the patient. According to the presence or the absence of these criteria, the median survival varied from 3.8 months to 21 months [1]. A few retrospective studies have compared the survival of patients whose potentially resectable metastases were left untreated with the survival of patients whose metastases were resected [2,3]. In these studies, 25% to 30% of patients survived 5 years after complete resection of metastases, whereas there were no five-year survivors in untreated patients. Although the benefit of surgical resection of liver metastases has not been demonstrated by any randomised trial, it is now accepted that resection of colorectal liver metastasis improves long-term survival and therefore should be considered whenever possible. Only liver transplantation has been abandoned for this indication because immunosuppression has been associated with relapse of cancer in all patients [4].

Pre-operative assessment

The decision to perform surgery and the extent of surgical resection for liver metastases are based upon the patient's condition, the extent of the disease, and liver function. Patients are only candidates for surgery if they have no non-resectable extra-hepatic disease, if all liver deposits can be resected with a tumour-free margin, and if sufficient liver parenchyma can be preserved to avoid post-operative liver insufficiency. Therefore, the goals of pre-operative assessment are: to determine the ability of the patient to tolerate hepatic resection, to exclude the presence of non-resectable extra-hepatic disease, and to delineate the anatomy of metastases. The patient's condition should be suitable for a general anaesthesia and a potentially haemorrhagic surgery. Special attention is given to the cardiocirculatory status, because of the possibility of clamping manoeuvres, and to the coagulation profile. Furthermore, the hepatic functional reserve should be sufficient to allow a sufficient post-operative liver function.

If remnant liver parenchyma is normal, up to 6 of the 8 anatomical segments (75% of the volume of the liver) can be resected without inducing post-operative liver failure. Such major resections cannot be performed safely if remnant liver parenchyma is abnormal. Many patients receive pre-operative chemotherapy, which may alter liver parenchyma. It is unclear whether the risk of post-operative liver insufficiency is increased in these conditions. The functional capacity of the liver can be assessed by the Child–Pugh classification, hepatic biological blood tests, and in some cases by the indocyanin green (ICG) retention tests. The volume of the non-tumorous parenchyma that will be left in place after hepatic resection can be evaluated by computerised tomography (CT) scan volumetry. Post-operative liver function will not be altered if the residual liver volume/body weight is greater than 0.5%.

The pre-operative assessment of the control of primary and extra-hepatic sites and the extent of hepatic involvement will be covered in another chapter.

Surgical treatment

Intra-operative assessment

The exact role of laparoscopy used alone or in combination with laparoscopic ultrasound has not yet been fully evaluated, but recent studies have suggested that it could be helpful in some cases either to avoid unnecessary laparotomy or to adapt abdominal incision to the extent of resection [5].

During laparotomy, a careful exploration of the abdominal cavity is performed. The presence of metastatic lymph nodes in the porta hepatis and the celiac region worsens the prognosis considerably, but should not be considered as an absolute contraindication to resection if the nodes can be completely removed, because five-year recurrence-free surviving patients have been reported in such cases [6]. Intraoperative ultrasound (IOUS) should be performed in every case. It can provide a precise mapping of the anatomical relations of the metastases to the main intra-parenchymatous vascular pedicles and can help in selecting the type of resection to be performed. IOUS can detect small intra-parenchymatous lesions and thereby modify the extent of the initially planned operation [7]. It may also guide the fine needle biopsies that can be necessary to precisely determine the nature of the detected lesions.

Different types of liver resections

Anatomically, the liver can be divided in 8 entities called segments (I to VIII). Each segment is vascularised by a portal pedicle. Liver resections can be divided in two groups: anatomical resections removing one or several segments; and atypical or wedge resections removing a portion of liver parenchyma surrounding a hepatic lesion. Resections removing 3 or more continuous segments are defined as major hepatic resections. Three types of major liver resections are commonly performed: right hepatectomy (segments V, VI, VII, VIII), left hepatectomy (segments II, III, IV), and extended right hepatectomy — also called right lobectomy (segments IV, V, VI, VII, VIII). Other types of anatomical resections can be performed: extended left hepatectomy (left trisegmentectomy) extending a left hepatectomy to segments V and VIII, central hepatectomy (segments IV, V, VIII), left lateral lobectomy (segments II, III), or bi-segmentectomies (V–VI, VII–VIII, VI–VII) [8,9].

Choice of operation

The goal of carcinological surgery for liver metastases is to remove all the metastatic sites, if possible with a free clearance margin of 1 cm. The extent of liver resection is not by itself a prognostic factor. The type of liver resection depends on the size, the number, and the location of the metastases; their relation to the main vascular and biliary pedicles; and the volume of the liver parenchyma that can be left in place after surgery. Small metastases located near the liver capsule can be resected by wedge resections, while larger lesions often require major resections.

In some cases, the choice is between performing several wedge resections or a major liver resection removing all the deposits at once. The first solution preserves more healthy liver parenchyma, but the cut section of the liver may be larger, increasing the risk of post-operative haemorrhage or fluid collections. The second solution, a major liver resection, allows a better clearance between tumour deposits and the cut section of the liver, a better control of peri-operative haemorrhage, and recognition of main intra-hepatic vessels; but it removes more parenchyma with a risk of post-resectional hepatic failure and the theoretical risk of promoting the development of dormant liver metastases by the mechanisms involved in liver regeneration. In addition, a large resection may preclude further treatment in case of intra-hepatic recurrence.

In case of synchronous metastases discovered at the same time as the primary metastasis, a wedge resection of an isolated easily accessible metastasis can be performed. In other cases, it appears preferable to delay the hepatic resection for 2 to 3 months, for several reasons: first, the incision required to ensure a good exposure is usually different for the colorectal and the liver resection; second, bowel section and subsequent peritoneal contamination can favour the

infection of an intra-abdominal or subphrenic fluid collection; third, haemodynamic changes and portal hypertension subsequent to vascular clamping can be detrimental to the viability of digestive sutures; and finally, a 2 to 4 month delay can be helpful to appreciate the natural behaviour of the metastatic disease. During this period, a systemic chemotherapy is usually performed, but the results of such an approach have not been prospectively assessed to date. Although combined resection of both primary and liver metastases have been reported by specialised centres [10], combined resection including major liver resections are associated with an increased mortality and morbidity [6].

Results of liver resection for colorectal metastases

Operative mortality and morbidity rates (Table 1)

In most recent studies, in-hospital mortality varies from 0% to 5% and is strongly influenced by peri-operative blood loss, pre-operative liver function, and extent of liver resection. Post-operative complications are observed in 25% to 40% of patients. Morbidity after hepatic resection is usually due to transient liver failure, haemorrhage, sub-phrenic abscesses, or biliary fistula. The mean hospital stay after liver surgery averages 10 to 15 days in the absence of complication.

Long-term results

Liver resection of colorectal metastases is associated with 3- and 5-year survival rates close to 40% and 25%, respectively (Table 2). After resection, recurrences are observed in 2/3 of the patients and involve the liver in 50% of cases. In a large retrospective study, 5-year survival was 28% in 1588 patients who had a resection of isolated colorectal liver metastases, and 15% in 250 patients who had resected liver and extra-hepatic metastases. None of the 77 patients who had a palliative resection survived the 5-year mark [6].

Table 1

Operative mortality and morbidity rates after liver resection for colorectal liver metastases

Authors [Ref.]	Year	No. of patients	Mortality (%)	Morbidity (%)
Nordlinger et al. [11]	1987	80	5	13
Doci et al. [12]	1991	100	5	39
AFC[a] [6]	1992	1818	2	24
Sheele et al. [13]	1995	469	4	–
Jamison et al. [14]	1997	280	4	–
Fong et al. [15]	1999	1001	3	–
Minagawa et al. [16]	2000	235	0	–

[a] Multi-centre trial.

Table 2

Overall survival after surgical resection of liver metastases from colorectal cancer

Authors [Ref.]	Year	No. of patients	3-year survival (%)	5-year survival (%)
Nordlinger et al. [11]	1987	80	40	25
AFC[a] [6]	1992	1818	41	26
Gayowski et al. [17]	1994	204	–	32
Sheele et al. [13]	1995	469	41	33
Nordlinger et al. [18]	1996	1569	41	26
Jamison et al. [14]	1997	280	–	27
Fong et al. [15]	1999	1001	57	37
Minagawa et al. [16]	2000	235	51	38

[a] Multi-centre trial.

Several studies have looked at factors influencing survival. The gender of the patient and the site of the primary tumour do not seem to influence the outcome. The stage of the primary tumour is associated with 5-year survival rates of 70% in stage I or II colorectal cancers and of 33% in stage III [6]. Prognosis seems better in cases of metachronous metastases, small lesions, and when there are less than 4 lesions; but the involvement of one or both lobes does not influence the outcome. CEA level is strongly correlated to recurrence-free survival. A free margin of at least 1 cm offers a better chance of avoiding recurrence, but several series have shown that a smaller margin did not affect survival [19]. The type of resection does not seem to influence the prognosis, provided that a clear margin is obtained. Blood transfusions could be associated with an adverse outcome but may reflect the surgical difficulties faced with large and numerous lesions. In large retrospective series of 1568 patients with resected liver metastases from carcinoma, a multivariate analysis showed that age, size of the largest metastasis, CEA level, stage of the primary tumour, disease-free interval, number of liver nodules, and resection margin > 1 cm or < 1 cm were the only independent prognosis factors [18].

Repeat liver resections for metastases

Recurrence limited to the liver following previous hepatic resection occurs in 25% to 50% of cases and may be amenable to repeat resection [20,21]. Post-operative mortality and morbidity after a repeat resection do not differ from those reported after a first resection, and the mean survival approaches 2 years. In a recent series including 146 patients with intrahepatic recurrence following hepatectomy treated by repeat liver resection, the actuarial survival rates were 78% at 1 year, 30% at 3 years, 16% at 5 and 10 years,

comparable to that observed following primary liver resections [20]. Hepatic recurrences should therefore be resected whenever possible.

Surgical resection of liver metastases: new promises

How to increase resectability?

No existing treatment other than surgery can result in long-term survival, but only 10% to 20% of patients with liver metastases fulfill standard selection criteria and so are amenable to surgery. As a consequence, the trend is to be more aggressive and to increase the indication for surgical resection. Portal vein embolisation, ablative techniques and chemotherapy may render "amenable-to-surgery" those patients who would have been refused some years ago.

Portal vein embolisation

Although a tumour is technically resectable, resection can be contra-indicated if the future remnant liver is too small to provide sufficient post-operative liver function. In such cases, pre-operative selective portal vein embolisation has been proposed to induce ipsilateral atrophy and controlateral compensatory hypertrophy of the remnant liver, thus preventing post-operative liver failure [22]. Portal vein embolisation can be considered when the estimated rate of remnant functional liver parenchyma is less than 1% of the body weight (i.e. less than two segments of the liver). In patients with non-cirrhotic livers, pre-operative portal vein embolisation can be expected to induce a 40–60% increase in the size of the non-embolised portion. However, if liver metastases are present in the non-embolised portion of the liver, induced liver regeneration or hypertrophy is associated with accelerated increase in the size of metastases [23]. Portal vein embolisation is usually performed by percutaneous ultrasonographically-guided puncture of a portal vein radicle through tumour-free liver. Following embolisation, a liver resection, judged primarily impossible, is feasible in 60% of cases with a mortality and a morbidity rate comparable to those observed following primary liver resections. In a recent study, actuarial survival rates after hepatectomy with ($n = 19$) or without ($n = 88$) portal vein embolisation were comparable: 81%, 67%, and 40% versus 88%, 61%, and 38% at 1 year, 3 years, and 5 years, respectively [22].

Local destruction

New methods of ablation of liver metastases have been developed in recent years, such as cryotherapy, radio frequency ablation, and laser hyperthermia. The details of these techniques and their impact on the management of liver metastases from colorectal cancers will be outlined in another chapter.

Neoadjuvant chemotherapy

Systemic chemotherapy is used when liver metastases are not amenable to surgical resection. Clinical trials have shown that palliative chemotherapy is better than symptomatic treatment alone, if administered before symptoms occur, with improvement in both survival and quality of life [24]. In terms of tumour response, associations of 5-fluorouracil (5FU) and folinic acid are effective in about 20% of cases. When associated with new drugs such as oxaliplatin or irinotecan (CPT-11, Campto®), response rates approach 60% [25]. The shrinkage of liver metastases may have several consequences: small metastases may become no longer visible with conventional imaging techniques, major vascular pedicles of the liver may become free from tumour, large lesions may become accessible to ablative techniques or resection. As a consequence, some patients with initially non-resectable disease may become candidates for surgery. In one study, systemic chemotherapy permitted surgical resection of liver metastases in 16% of patients previously considered as non-resectable because of the location, the size, and/or the number of the hepatic deposits, or because of the association with extra-hepatic disease. The cumulative 3- and 5-year survival rates were comparable to those observed after resection of resectable lesions [26]. Some chemotherapeutic regimens using both 5FU Oxaliplatin and CPT-11, aiming at increasing resectability rates, are currently under evaluation, and may increase the rate of surgical resections for metastases in the near future.

Chemotherapy for non-resectable lesions can no longer be considered as palliative and the clear distinction between resectable and unresectable metastases may very soon become obsolete with the emergence of a new third group of patients: patients with metastases that become resectable after response to chemotherapy. Will these patients be moved prognostically from an expectation of a very low 5-year survival rate to a 30% 5-year survival rate, or will they show recurrence rapidly after resection and have the same prognosis as if they had not undergone resection? Time will tell.

How to decrease post-operative recurrence?

Despite progress in surgical technique and improved surgical skill, recurrences are unfortunately still observed in two-thirds of patients after resection of liver metastases. Various attempts are being made to reduce this risk.

Better selection of the candidates for liver resection

One way would be to improve the selection of patients for whom surgery is considered. In this setting, a simple prognostic scoring system has been developed to evaluate the chances of cure of patients after resection of liver metastases [15,18]. If these prognosis scoring systems are very useful for the stratification of patients in randomised series, they are not routinely used to exclude candidates for surgical resection. Indeed, even in patients with high risk of recurrence, no existing treatment other than surgery can result in long time survivals and the trend is to be more aggressive and to increase the indication for surgical resection of liver metastases.

Adjuvant chemotherapy

The benefit of adjuvant chemotherapy after resection of colorectal metastases has not yet been clearly proven. A few studies have been published, mainly testing hepatic arterial infusion (HAI) of the drugs. The rationale for HAI relies both on the dual blood supply of the liver and on the fact that liver metastases larger than 1 mm are supplied mainly by the hepatic artery. Intra-arterial therapy may result in a significant increase of exposure of tumour to the drug with reduced systemic side effects. HAI also has limitations, including the risks of extra-hepatic progression, severe side effects including biliary toxicity, and technical problems precluding the use of the intra-hepatic catheter. Three recently published series have evaluated the potential benefit of hepatic arterial infusion as an adjuvant treatment after resection of colorectal liver metastases. A German multi-centre trial failed to demonstrate any survival benefit of HAI with 5-FU (5-fluorouracil) and folinic acid without systemic treatment over surgery alone, with a significant toxicity in the patients receiving chemotherapy [27]. A study from the Memorial Sloan–Kettering Cancer Center compared HAI plus systemic 5-FU and folinic acid to systemic 5-FU and folinic acid only, and concluded that combined treatment resulted in a decrease in the hepatic recurrence rate and an improved overall survival only at 2 years [28]. A third study organised by the Eastern Cooperative Oncology Group evaluated HAI with floxuridine and intravenous continuous infusion of 5-FU, and concluded that HAI combined with intravenous 5-FU reduced the risk of recurrence when compared with surgery alone, but resulted in no benefit in overall survival [29]. The message we can deduce from these studies is that HAI alone is not sufficient as adjuvant treatment for liver metastases. HAI associated with systemic chemotherapy can reduce the risk of recurrences after surgery, but increase the risk of side effects. These studies are not sufficient to convince physicians that HAI administered after surgery should be the standard, but do constitute an important step towards the validation of the principle of combined chemotherapy and surgery to treat liver metastases from colorectal cancers.

The role of systemic chemotherapy after complete resection of metastases has only been evaluated in two recent trials. A French study organised by the Federation Francophones de Cancerologie Digestive and a European–Canadian study have tested 5-FU and folinic acid over no treatment. Both series have similar results with a survival benefit in the treated arm, but the difference was not significant [30,31].

The beneficial effect of chemotherapy after complete surgical resection of colorectal metastases is likely, but not proven, and several questions remain unanswered: Should the chemotherapy be administered intravenously or through the hepatic artery? Should it be given before or after the surgery? Should the best regimen include oxaliplatin or irinotecan? It is important that medical oncologists and surgeons participate in large prospective trials evaluating new regimens and new treatment modalities that would be feasible in most institutions. Because of the difficulty in organising such trials, it is likely that only multi-centre trials, possibly with international cooperation, will help solve these questions. An international Intergroup study organised by the European Organisation for Research and Treatment of Cancer (EORTC) is comparing surgery with or without neoadjuvant and adjuvant oxaliplatin, 5-FU, and folinic acid in patients with resectable liver metastases. Studies evaluating irinotecan-based regimens are also in preparation. One hopes that these studies will help to clarify the exact role of peri-operative chemotherapy to decrease recurrence and improve survival.

Conclusions

In the treatment of liver metastases from colorectal cancer, surgery remains the standard treatment of resectable metastases and should be proposed whenever possible (Fig. 1). However, surgery is feasible in

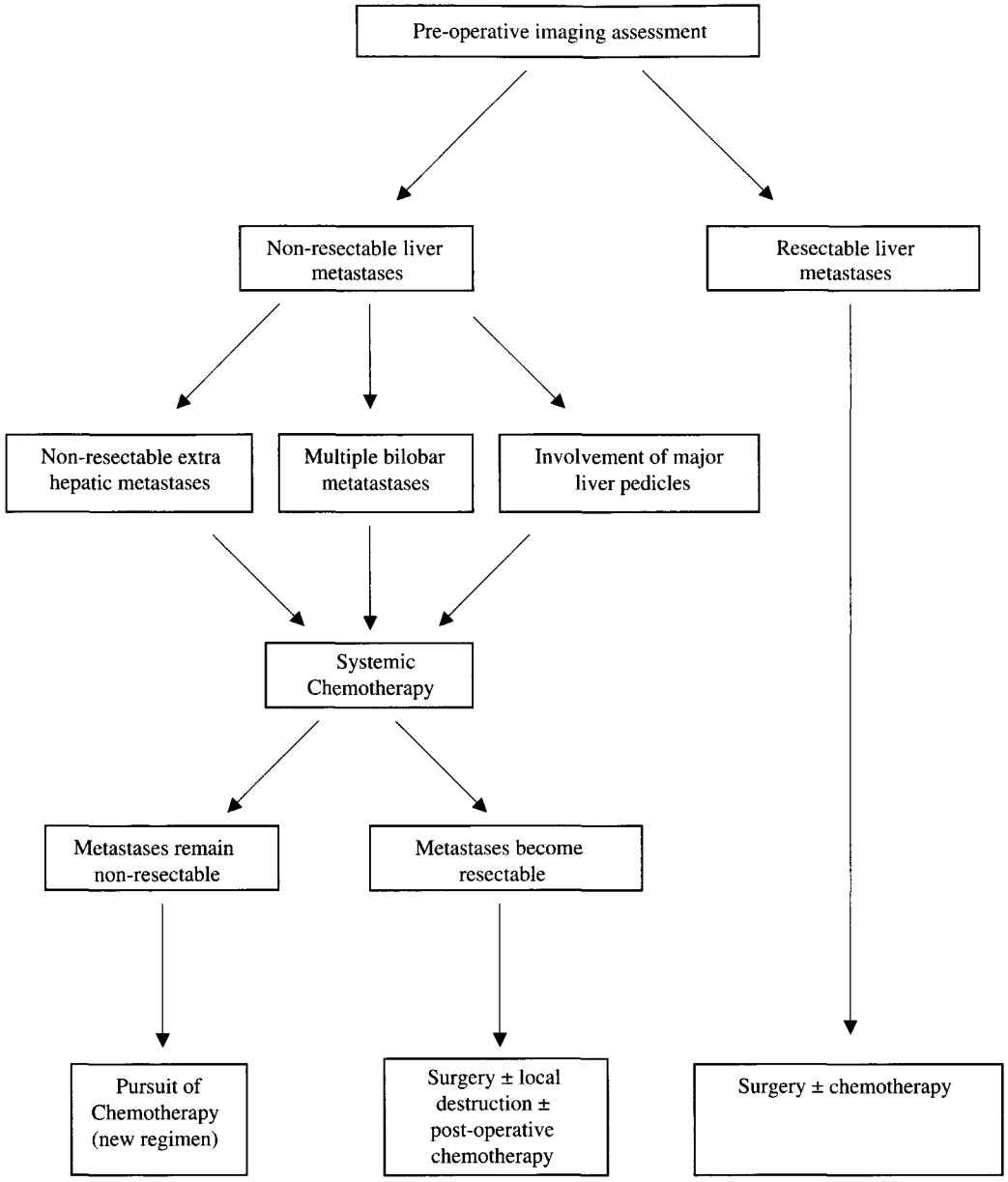

Fig. 1. Decision tree for the management of liver metastases from colorectal carcinoma.

only 10–20% of these patients. Others benefit from chemotherapy. Recent progress in chemotherapy and the development of ablative techniques increases the number of operable patients with curative intent. It is likely that a combination of surgery and chemotherapy will be validated in the near future.

For resectable metastases, it is urgent to determine, by prospective randomised trials, whether pre- or post-operative chemotherapeutic regimens using new drugs could decrease recurrence after surgical resection. For non-resectable metastases, the benefit of new ablative techniques and neoadjuvant chemotherapy needs further evaluation. One thing is certain: only a multidisciplinary approach and enrolment in randomised trials can offer patients the best chance for cure.

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