

# Adjuvant and neoadjuvant treatment in resectable and non-resectable metastatic colon cancer

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## Introduction

The major cause of death in colorectal cancer is liver metastases, which affects 20% of patients with stage II and 50% with stage III cancer. The presence of liver or lung metastases from colorectal cancer does not preclude curative treatment. Even though only a minority of patients with liver metastases is amenable to surgery, surgical resection remains the only treatment that can, to date, ensure long-term survival and cure in some patients. Recent progress, including new chemotherapeutic regimens, ablative techniques and interventional radiology, may permit an increase in the number of patients that can be treated with a curative intent. Unfortunately, recurrences are still observed in two-thirds of patients after resection of liver metastases. To reduce this risk, new therapeutic management regimes are tested using adjuvant intravenous and/or intra-arterial chemotherapies or, to provide curative treatments in case of recurrence, with either surgery or ablative techniques.

## Resection of liver metastases: update

With no treatment the median survival of patients rarely exceeds 1 year. 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. The volume of liver involvement, the presence of extrahepatic disease, metastatic lymph nodes in the mesentery, carcinoembryonic antigen (CEA) level and the age of the patient all influenced the survival rate. Depending on the presence or absence of these criteria, median survival varied from 3.8 to 21 months [1]. In the absence of any randomised trials, few retrospective studies have compared the survival of patients with potentially resectable metastases that were left untreated with survival of patients after resection of

colorectal metastases [2,3]. There were no 5-year survivors in untreated patients, whereas 25–30% of patients survived 5 years after complete resection of metastases. The benefit of surgical resection for liver metastases is now well-recognised, and complete resection with intent to cure is, to date, the only treatment that can ensure long-term survival. 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 surgical resection for liver metastases and the extent of resection are based on the patient's condition, the extent of the disease and liver function. Surgery should be considered only with curative intent if liver metastases can be totally resected with tumour-free margins and sufficient postoperative remnant liver to avoid liver failure. Patients must not have non-resectable extrahepatic disease. The goals of pre-operative assessment are to determine whether the patient's condition will permit hepatic resection (i.e. general anaesthesia, clamping manoeuvres requiring a correct cardiovascular status). It should exclude the presence of non-resectable extrahepatic disease and delineate the anatomy of metastases. If remnant parenchyma is normal, 75% of the volume of the liver can be resected. However, many patients receive pre-operative chemotherapy, which may alter liver parenchyma. Liver function can be assessed by the Child-Pugh classification, hepatic biochemical blood tests and, in some cases, by the indocyanin green (ICG) retention tests. The volume of the non-tumourous parenchyma that will be left in place after hepatic resection should be evaluated by computed tomography (CT) scan volumetry.

## Surgical treatment

### *Intra-operative assessment*

The exact place of laparoscopy in liver surgery is not clearly determined [5]. Surgery should start with a careful exploration of the abdominal cavity to rule out peritoneal carcinosis or an unexpected bi-lobar involvement of the liver by metastases, which could be a contraindication for resection. The presence of metastatic lymph nodes in the porta hepatis and the coeliac region considerably worsens the prognosis, but should not be considered as an absolute contraindication to resection if they can be completely removed, because 5-year recurrence-free surviving patients have been reported in such cases [6]. Intra-operative ultrasound (IOUS) should be performed in every case because it allows a precise mapping of the anatomical relations of the metastases to the main intra parenchymatous vascular pedicles and help to select the type of resection. IOUS can detect small intraparenchymatous lesions and thereby modify the extent of the initially planned operation [7]. It may also be used to guide the fine needle biopsy of doubtful lesions or to evaluate the degree of destruction of a metastasis treated by radiofrequency ablation.

### *Types of liver resection*

If remnant liver parenchyma is normal, up to 6 of the 8 anatomical segments can be resected without inducing postoperative liver failure. 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 three or more continuous segments are defined as major hepatic resections: 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) [8,9].

### *Surgical strategy*

The aim of carcinological surgery for liver metastases is to remove or destroy with ablation procedures all the metastatic sites with a free clearance margin. 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. Superficial small metastases can be resected with wedge resections. Larger lesions often require major resections.

It should also be kept in mind that a large resection may preclude further surgery in case of intrahepatic recurrence.

If synchronous metastases are discovered at the same time as the primary cancer, it is usually preferable to perform the bowel resection during a first procedure, since combined resection of both primary and liver metastases is associated with an increased mortality and morbidity rate (intra-abdominal fluid infection, vascular clamping deleter for the viability of digestive sutures) when hepatic resection is a major resection [6]. Usually, surgical resection of the liver metastases is delayed for 2–4 months after bowel resection, allowing observation of the response of liver metastases to systemic chemotherapy, which is often administered during the interval, and constitutes an important prognostic factor.

## Results of liver resection for colorectal metastases

### *Complications of surgery (Table 1)*

In most recent studies, in-hospital mortality varies from 0% to 5% and is strongly influenced by per-operative blood loss, pre-operative liver function and extent of liver resection. Postoperative complications are observed in 25–40% 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 ranges from 10 to 15 days in the absence of complications.

Table 1  
Mortality and morbidity rates after liver resection for colorectal liver metastases

Reference	Year	Patients (n)	Mortality (%)	Morbidity (%)
Nordlinger et al. [10]	1987	80	5	13
Doci et al. [11]	1991	100	5	39
AFC <sup>a</sup> [6]	1992	1818	2	24
Sheele et al. [12]	1995	469	4	–
Jamison et al. [13]	1997	280	4	–
Fong et al. [14]	1999	1001	3	–
Minagawa et al. [15]	2000	235	0	–

<sup>a</sup> AFC: Association Française de Chirurgie.

<sup>b</sup> Multicentre trial.

### *Long-term results*

Liver resection of colorectal metastases is associated with 3- and 5-year survival rates close to 40%

and 30%, respectively (Table 2). After resection, recurrences are observed in two-thirds of 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 extrahepatic metastases. None of the 77 patients who had a palliative resection survived for 5 years [10].

Table 2  
Overall survival after surgical resection of liver metastases from colorectal cancer<sup>a</sup>

Reference	Year	Patients (n)	Survival	
			3-year (%)	5-year (%)
Nordlinger et al. [10]	1987	80	40	25
AFC <sup>a</sup> [6]	1992	1818	41	26
Gayowski et al. [16]	1994	204	–	32
Sheele et al. [12]	1995	469	41	33
Nordlinger et al. [17]	1996	1569	41	26
Jamison et al. [13]	1997	280	–	27
Fong et al. [14]	1999	1001	57	37
Minagawa et al. [15]	2000	235	51	38

<sup>a</sup> AFC: Association Française de Chirurgie.

<sup>b</sup> Multicentre trial.

Several studies have assessed factors influencing survival. Gender 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 rate of 70% in stage I or II colorectal cancers and 33% in stage III [6]. Prognosis seems better in cases of metachronous metastases, small lesions and when there are less than four lesions, but the involvement of one or both lobes does not influence the outcome. CEA level is strongly correlated with recurrence-free survival. A free margin of at least 1 cm offers better chances of avoiding recurrence, but several series have shown that a smaller margin did not affect survival [18]. The type of resection does not seem to influence prognosis, provided that a clear margin is obtained. Blood transfusions could be associated with an adverse outcome but may reflect the surgical difficulties for the resection of 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 > or <1 cm were only independent prognosis factors [10].

### Control of extrahepatic metastatic sites

Pre-operative chest radiograph combined with a CT scan is performed to detect lung metastases. Synchronous liver and lung metastases should not be considered a contraindication to hepatic resection, provided that both sites can be completely resected. The carcinological principle for resection of lung metastases is similar to that for liver metastases. The primary tumour should have been totally resected with no evidence of local recurrence or other unresectable metastases. In a recent study, 239 patients were operated for lung metastases of colorectal cancer, 43 (18%) had previously had synchronous liver metastases surgically resected. Seven patients (16%) underwent subsequent lung resection for recurrences and the median survival from lung resection was 19 months [11]. Similar results were reported by the Metastatic Lung Tumour Study Group of Japan, with 47 patients who underwent pulmonary and hepatic resection with 3-, 5- and 8-year survivals of 36%, 31% and 23%, respectively [12]. Surgical resection of lung metastases can significantly prolong survival. Prognostic factors are similar to those associated with resection of liver metastases but age, sex and type of resection have not been shown to have an impact on survival. After resection of lung metastases, the lung is the first site of recurrence in 50–70% of cases, followed by loco-regional recurrences at the site of the primary metastasis, and brain and liver metastases. Repeat lung resections can be considered in some cases, because 5-year actuarial survival rates of 30% have been reported [13]. Exploration of other sites of possible metastasis, such as brain by CT scan or bone by scintigraphy is performed only if there is a clinical suspicion. Their presence is an absolute contraindication to liver or lung resection, since the prognosis depends on evolution of these unresectable metastases.

### Repeat liver resections for recurrent metastases

Recurrence limited to the liver following previous hepatic resection occurs in 25–50% of cases and may be amenable to repeat resection [14,15]. Postoperative mortality and morbidity 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 intra-hepatic recurrence following hepatectomy treated by repeat liver resection, the actuarial survival rates was 78% at 1 year, 30% at 3 years, 16% at 5 and 10 years; comparable to that observed following primary liver resections [14].

Hepatic recurrences should therefore be resected whenever possible.

## Progress in surgery of liver metastases

### *Increase in resectability*

Only 10–20% of patients with liver metastases fulfil standard selection criteria and are amenable to surgery. 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 patients who would have been refused some years ago.

### *Portal vein embolisation*

If the future remnant liver after liver resection is too small to provide sufficient postoperative liver function, pre-operative selective portal vein embolisation has been proposed to induce ipsilateral atrophy and contralateral hypertrophy of the remnant liver, thus preventing postoperative liver failure [16]. 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 an accelerated increase in the size of metastases [17]. Following embolisation, a liver resection judged primarily impossible is feasible in 60% of cases, with mortality and morbidity rates comparable to those observed following liver resections without embolisation. 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, 3 and 5 years, respectively [16].

### *Local destruction*

New methods of ablation of liver metastases have been developed in recent years, such as cryotherapy, radiofrequency ablation and laser hyperthermia, but these fall outside the scope of the present article.

### *Neoadjuvant chemotherapy*

Systemic chemotherapy is used when liver metastases are not amenable to surgical resection. Clinical trials have shown that palliative chemotherapy is better for quality of life than symptomatic treatment alone, if administered before symptoms occur. Associations of

5-FU and folinic acid are associated with a tumour response rate close to 20% of cases. When associated with new drugs, such as oxaliplatin or CPT-11, response rates approach 50% [19]. With active chemotherapy regimens (irinotecan or oxaliplatin + 5-FU/leucovorin) alone survival rate is less than 5% at 5 years.

A phase III randomised trial evaluating the benefit of an anti-angiogenic agent (Bevacizumab) combined with chemotherapy using irinotecan shows that the rates of overall survival, progression-free survival and tumour response were improved in the combination-therapy group. The addition of anti-angiogenic agents to chemotherapy could be considered in the near future as a new standard for the treatment of unresectable metastatic colorectal cancer [20].

After shrinkage of the tumours, neoadjuvant chemotherapy can be used to downstage previously unresectable metastases. Large lesions may also become accessible to ablative techniques, which are known to allow safe liver resection up to 3–5 cm in diameter or resection. In one study, systemic chemotherapy permitted surgical resection of liver metastases in 16% of patients previously considered non-resectable because of the location, the size, the number of the hepatic deposits, or because of the association with extrahepatic disease. The cumulative 3- and 5-year survival rates were comparable to those observed after resection of resectable lesions [21].

New studies suggest the importance of neoadjuvant chemotherapy. The outcomes of patients referred for resection of synchronous colorectal liver metastases with or without previous neoadjuvant chemotherapy were compared. Patient- and tumour-related variables were similar in both groups. Five-year survival was similar in both groups (43% versus 35%,  $P=0.4$ ), but the subgroup of patients with stable disease or disease responding to chemotherapy had a better survival when compared with patients who did not receive chemotherapy (85% versus 35%,  $P=0.03$ ) [22].

In a recent study comparing the outcome of patients with multiple bi-lobar hepatic metastases from colorectal cancer, receiving or not neoadjuvant chemotherapy before hepatectomy, patients who had received neoadjuvant chemotherapy had a better 3- and 5-year survival (67% and 38.9% versus 51.8% and 20.7%) [23].

Finally, a retrospective study suggests that tumour progression while on chemotherapy is a poor prognostic factor and could be considered as a contraindication for liver resection for multiple metastases. A total of 131 patients who underwent liver resection for multiple metastases after systemic neoadjuvant

chemotherapy (5-FU, leucovorin, oxaliplatin or irinotecan) were divided into three groups according to response to chemotherapy: patients with an objective response; with tumour stabilisation; and with tumour progression. All patients had a liver resection with intent to cure. Patients with a tumour progression had a lower 5-year survival compared with those with objective response and stabilisation (8% versus 37% and 30%) [24]. Response to neoadjuvant chemotherapy appears to be an important prognostic factor for survival of patients after resection of liver colorectal metastases.

The clear distinction between resectable and unresectable liver metastases is becoming obsolete with the emergence of new groups of patients: those whose metastases become resectable after response to chemotherapy. In addition, patients with progression during chemotherapy may not be good candidates for liver resection.

#### *How to decrease postoperative recurrence?*

Unfortunately, recurrences are still observed in most patients after resection of liver metastases despite progress in surgical technique and improved surgical skill. Various attempts are being made to reduce this risk.

#### *Selection of candidates for liver resection*

One way to reduce the risk of recurrence would be to improve selection of patients in whom surgery is considered. In this setting, simple prognostic scoring systems have been developed to evaluate the chances of cure of patients after resection of liver metastases [10,25].

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. Some studies have been published, mainly testing hepatic arterial infusion (HAI) of the drugs. HAI delivers high concentrations of cytotoxic drugs direct to malignant tissue. The technique is based on the understanding that metastases derive their blood supply largely from the hepatic artery, whereas

healthy hepatocytes are supplied mainly by the portal vein. 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 extrahepatic progression, severe side-effects including biliary toxicity, and technical problems precluding the use of the intrahepatic catheter. Results from three randomised trials, which evaluated the potential benefit of hepatic arterial infusion as adjuvant treatment after resection of colorectal liver metastases, are available. A German multicentre trial failed to demonstrate any survival benefit of HAI with 5-FU and folinic acid without systemic treatment over surgery alone, with a significant toxicity in the patients receiving chemotherapy and an increased risk of death [26]. A study from the Memorial Sloan-Kettering Cancer Centre compared HAI + systemic 5-FU and folinic acid with 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 (86% versus 72%,  $P=0.03$ ) [27]. 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 (46% versus 25%,  $P=0.03$ ), but resulted in no benefit in overall survival [28]. 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 at the expense of an increase in side-effects. These studies are not sufficient to convince physicians that HAI administered after surgery should be the standard, but constitute an important step toward the validation of the principle of combined chemotherapy and surgery to treat liver metastases from colorectal cancers.

Adjuvant systemic chemotherapy following hepatic resection has been evaluated in two phase III randomised trials. A French study organised by the Federation Francophones de Cancerologie Digestive and a European-Canadian study have compared systemic administration of 5-FU and folinic acid for 6 months after surgery versus surgery alone. Although there was no statistically significant difference between the groups, these studies show a trend towards a benefit for adjuvant chemotherapy [29,30].

These regimens have some side-effects, with grade 3/4 toxicity in about one-quarter of the patients (neutropaenia, thrombocytopaenia, stomatitis, vomiting, diarrhoea). Chemotherapeutic regimens are being

investigated in phase III randomised trials, in particular combination of irinotecan and 5-FU/FA, following complete resection of hepatic metastases.

The beneficial effect of chemotherapy after complete surgical resection of colorectal metastases is likely, but is not yet formally proven, and several questions remain unanswered: should the chemotherapy be administered intravenously or through the hepatic artery? Should it be given before or after surgery? Should the best regimen include oxaliplatin or irinotecan, and biological agents? Therefore, it is urgent that medical oncologists and surgeons participate in large prospective trials evaluating new regimens and new treatment modalities feasible in most institutions. Because of the difficulty in organising such trial, it is likely that only multicentre trials, possibly with international co-operation, will help solve these questions. An international intergroup study organised by the European Organisation for Research and Treatment of Cancer (EORTC) has compared surgery with or without neoadjuvant and adjuvant oxaliplatin, 5-FU and folinic acid in patients with resectable liver metastases. A total of 363 patients have been entered in this large study, and survival data are expected in 2006. It is hoped that these studies will help to clarify the exact role of peri-operative chemotherapy in decreasing recurrence and improving survival.

## Conclusion

The standard treatment for resectable hepatic metastases is complete surgical resection (Fig. 1). Surgery is feasible in only 10–20% of patients. The benefits of chemotherapy are being increasingly recognised, especially in facilitating the resection of initially unresectable liver metastases. In fact, 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 vital to determine, by prospective randomised trials, whether pre- or post-operative chemotherapeutic regimens, using new drugs decrease recurrence after surgical resection and improve survival. For non-resectable metastases, the benefits of new ablative techniques and neoadjuvant chemotherapy need to be formally demonstrated. The management of patients with hepatic metastases requires a multidisciplinary approach. Participation in randomised trials is of paramount importance to validate the different proposed therapeutic strategies.

## Conflict of interest statement

None declared.

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