

Surgery of liver metastases from colorectal cancer: new promises

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For a long time, patients with liver metastases from colorectal cancer were considered to be incurable. Over the last 30 years, the benefits of surgical resection and systemic chemotherapy have been established. Actually, surgical resections are feasible with a very low mortality and a 5-year survival that approaches 40%, but only 10–20% of patients are candidates for surgery. The others gain benefit from chemotherapy with increasingly active drugs. To improve this overall picture, efforts have been made to increase the number of patients that could be candidates for surgery and to decrease the risk of recurrence after surgical resection. Shrinkage of tumours after administration of pre-operative chemotherapy and the availability of ablative techniques now allow the treatment, with curative intent, of metastases initially considered as non-resectable. Chemotherapeutic regimens have been developed to decrease the risk of postoperative recurrence.

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 is amenable to surgery. 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 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.

In the first part of this paper, we will review standard practice and the results of surgery for metastatic colorectal cancer. Then, we will discuss new treatments which, in the near future, may allow the cure of more patients with metastases.

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Surgical resection of liver metastases: the state-of-the-art

Natural history of unresected metastases

In the absence of treatment, median survival rarely exceeds 9 months. In a large prospective study conducted from 1980–1990 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 extrahepatic disease, metastatic lymph nodes in the mesentery, CEA level and the age of the patient. According to the presence or absence of these criteria, the median survival varied from 3.8 to 21 months¹.

Patients selected for surgical resection of liver metastases represent a subset with more limited disease. Few retrospective studies have compared the survival of patients with potentially resectable metastases that were left untreated with survival of resected patients. Wilson *et al* found no 5-year survivors in patients with untreated, but potentially resectable, liver metastases compared with 28% for those who had undergone resection of their metastases². Wanebo *et al*³ found that patients with an untreated solitary liver metastasis had a median survival of 19 months with no patient surviving 5 years, while patients with a resected single liver metastasis had a median survival of 36 months with 25% of patients surviving 5 years.

Although these studies are retrospective and methods for assessment of extent of disease have improved, it is now accepted that resection of colorectal liver metastasis improves long-term survival and, therefore, should be discussed whenever possible.

Selection of patients for surgery

The decision and the extent of surgical resection for liver metastases are based upon the patient's condition, extent of the disease, and liver function. Surgical resection should only be performed with a curative intent leaving no macroscopic residual disease. The goals of pre-operative assessment are, therefore, to determine the ability of the patient to tolerate hepatic resection, to exclude the presence of non-resectable extrahepatic disease, and to delineate the anatomy of metastases.

Patient's condition

The patient should be suitable for a general anaesthesia and a potentially haemorrhagic surgery. Special attention must be given to the cardiocirculatory status because of the possibility of clamping manoeuvres and to the coagulation profile.

Liver function

The hepatic functional reserve should be sufficient to allow adequate postoperative 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 postoperative liver failure. Such major resections cannot be performed safely if remnant liver parenchyma is abnormal. Many patients will have received pre-operative chemotherapy, which may alter liver parenchyma. It is unclear whether the risk of postoperative 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-tumourous parenchyma that will be left in place after hepatic resection can be evaluated by CT scan volumetry. It is admitted that postoperative liver function will not be altered if the residual liver volume/body weight is greater than 0.5%.

Control of primary and extra-hepatic sites

Local control of the primary tumour: In case of metastases discovered during the follow-up after resection of a colorectal cancer (metachronous metastases), adequate control of the site of the primary tumour should be assessed. This is usually done by rectal digital examination and colonoscopy to eliminate anastomotic recurrence or a new colic cancer, and a CT scan to verify the absence of locoregional spread. Endorectal ultrasonography can be helpful after primary rectal cancer excision and low anterior anastomosis. Magnetic resonance imaging (MRI) seems to be useful when local recurrence is suspected after abdominoperineal excision.

Control of other metastatic sites: Chest X-ray with or without thoracic CT scan is performed to rule out lung metastases. Lung metastases do not constitute a contra-indication to hepatic resection providing that they can be entirely resected by a simultaneous or delayed resection. Recent studies have shown that, in patients with liver metastases from colorectal cancer and no evidence of lung metastases on chest X-ray, chest CT could be avoided⁴. Brain CT scan and bone scintigraphy are performed only if there is a clinical suspicion of brain or bone metastasis. Their presence usually contra-indicate liver resection.

Pre-operative assessment of the hepatic involvement

Liver resections leaving behind untreated intrahepatic metastases do not prolong survival^{5,6} and should not be performed. It is, therefore, of major relevance to localize accurately all intrahepatic lesions before performing surgical resection. It is also important to plan an adequate type of resection. Transabdominal ultrasound and spiral CT scan with

portal phase or MRI are usually sufficient to detect small metastases, to determine their location from the main hepatic pedicles precisely, and to calculate the volume of the non-tumourous liver parenchyma that will be left in place after resection – all the information that will help to determine which type of resection can be performed.

Intra-operative assessment

The exact role of laparoscopy used alone or in combination with laparoscopic ultrasound has not 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 resection⁷.

During laparotomy, a careful exploration of the abdominal cavity is performed. 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 contra-indication to resection if they can be completely removed because 5-year recurrence-free surviving patients have been reported in such cases⁵. Intra-operative ultrasound (IOUS) should be performed in every case. It can provide a precise mapping of the anatomical relations of the metastases to the main intraparenchymatous 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. It may also guide fine needle biopsies that may be necessary to identify precisely the nature of the detected lesions.

Surgical treatment

Based upon pre- and peri-operative assessment, patients are candidates for surgery if they have no non-resectable extrahepatic disease, all liver deposits can be resected with tumour-free margins, and sufficient liver parenchyma can be preserved to avoid postoperative liver insufficiency. Surgical resection is, to date, the only potentially curative treatment of colorectal metastases. Liver transplantation has been abandoned for this indication because immunosuppression has been associated with relapse of cancer in all patients. In a collective review of 43 cases of orthotopic liver transplantation for metastases, the 2-year survival was 14% and there were no surviving patients at 5 years⁸.

Different types of liver resections

Anatomically, the liver can be divided in 8 entities called segments (I–VIII). Each segment is vascularised by a portal pedicle. Liver resections can be divided into two groups: (i) anatomical resections removing one or several segments; and (ii) atypical or wedge resections removing a portion of liver parenchyma surrounding an hepatic lesion. Resections removing 2 or more continuous segments are defined as major hepatic resections.

Four types of major liver resections are commonly performed: left lateral lobectomy (segments II, III), 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) or bisegmentectomies (V–VI, VII–VIII, VI–VII)^{9–12}.

Choice of operation

The goal of 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, as well as 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, larger lesions often require major resections.

In some cases, the choice between performing several wedge resections or a major liver resection removing all the deposits at once can be difficult. The first solution preserves more healthy liver parenchyma, but the cut section of the liver may be larger increasing the risk of postoperative haemorrhage or fluid collection. On the other hand, 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 the recognition of main intrahepatic vessels, but 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 intrahepatic recurrence.

In the case of synchronous metastases discovered at the same time as the primary, a wedge resection of an isolated, easily accessible metastasis can be performed. In the other cases, it appears preferable for several reasons to delay the hepatic resection for 2–3 months: (i) the incision required to ensure good exposure is usually different for the colorectal and the liver resection; (ii) bowel section and subsequent peritoneal contamination can favour infection of an intra-abdominal or subphrenic fluid collection; (iii) haemodynamic changes and portal hypertension subsequent to vascular clamping can be detrimental to the viability of digestive sutures; and (iv) appreciation of the natural behaviour of the metastatic disease. During this period, systemic chemotherapy is usually performed, but the results have not been prospectively assessed to date. Although combined resection of both primary and liver metastases has been

reported by specialized centres^{6,13}, combined resection including major liver resections are associated with increased mortality and morbidity⁵.

Results of liver resection for colorectal metastases

Postoperative complications

In most recent studies, in-hospital mortality varies from 0–5% and is strongly influenced by peri-operative blood loss, pre-operative liver function and extent of liver resection. Postoperative complications are observed in 25% of patients^{5,14–16}. Morbidity after hepatic resection is usually due to transient liver failure, haemorrhage, subphrenic abscesses or biliary fistula (Table 1). The mean hospital stay after liver surgery averages 10–15 days in the absence of complications.

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 two-thirds of the patients and involve the liver in 50% of the 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 5 years⁵.

Prognostic factors

In order to improve prognosis and provide a potential selection of the patients before surgery or for postoperative adjuvant treatment, numerous studies have looked at factors influencing survival. They are summarized in Table 3. The sex and the site of the primary tumour do

Table 1 Complications of liver resection

Liver-related complications	Peri-hepatic fluid collection or abscess	5–10%
	Bile leak	3%
	Liver failure	1–5%
	Haemorrhage	1–2%
Infections	Wound	1–3%
	Intra-abdominal sepsis	1–3%
General complications	Pleural effusion	2–5%
	Pneumonia	2–5%
	Deep vein thrombosis/pulmonary embolism	1–2%
	Cardiac failure, myocardial infarction	1%

Data compiled from Scheele *et al*¹⁶, Doci *et al*¹⁴, Fong *et al*¹⁵, and Nordlinger *et al*⁵.

Table 2 Results of surgical resection of liver metastases from colorectal cancer

Study	n	Operative mortality (%)	Postoperative morbidity (%)	Survival			
				1 Year (%)	2 Years (%)	3 Years (%)	5 Years (%)
Nordlinger <i>et al</i> ²² 1987	80	5	13	–	51	40	25
Scheele <i>et al</i> ⁶ 1991	207	5	22	–	–	41	31
Doci <i>et al</i> ¹⁴ 1991	100	5	39	–	–	–	30
*AFC ⁵ 1992	1818	2	24	–	–	41	26
Gayowski <i>et al</i> ¹⁷ 1994	204	0	–	91	–	–	32
Scheele <i>et al</i> ¹⁶ 1995	469	4	–	83	–	–	33
Fong <i>et al</i> ¹⁵ 1995			–	85	–	–	35
Jenkins <i>et al</i> ²⁰ 1997			–	81	–	–	25
Jamison <i>et al</i> ¹⁹ 1997	280	4	–	84	–	–	27
Minagawa <i>et al</i> ²¹ 2000	235	0	–	–	–	51	38

*Multicentre trials.

not seem to influence the outcome. The stage of the primary tumour is associated with 5-year survival rate of: 70% in stages I or II and of 33% in stage III colorectal cancers⁵. Prognosis seems better in cases of meta-chronous metastases, small lesions, and when there are less than 4 lesions,

Table 3 Predictive factors associated with tumour recurrence and survival following surgical resection of liver metastases

	No. of patients	Sex	Site of primary tumour	Type of resect.	Pre-op CEA level	Dis.-free inter.	Age	Tumour size	Stage of the primary	Syn./meta.	No. of metas.	Tumour-free margin	ITR	Lymph node metas.
Doci <i>et al</i> ¹⁴ 1991	100	No	No	No	No	–	No	–	Yes	No	No	–	–	–
*Hughes <i>et al</i> ¹⁸ 1988	859	No	–	–	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–	–
Scheele <i>et al</i> ¹⁶ 1995	469	No	No	Yes	No	–	No	Yes	Yes	Yes	No	Yes	–	–
*Nordlinger <i>et al</i> ⁵ 1996	1568	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–
Jamison <i>et al</i> ¹⁹ 1997	280	–	–	–	–	–	–	No	No	–	No	No	–	Yes
Cady <i>et al</i> ²³ 1998	244	–	–	–	Yes	No	–	No	No	–	Yes	Yes	–	–
Minagawa <i>et al</i> ²¹ 2000	235	No	No	No	No	No	No	No	Yes	No	Yes	No	–	Yes
Rate of positivity (%)		0	0	25	33	40	40	43	75	50	50	57	100	100

*Multicentre trials.

Resect = resection; Dis.-free inter. = Disease-free interval; Syn./meta. = Synchronous/metachronous; Metas. = Metastases ;

ITR = Incomplete tumour removal

but the involvement of one or both lobes does not influence the outcome. The CEA level is strongly correlated with recurrence-free survival. A free margin of at least 1 cm offers the best chance of avoiding recurrence, but several series have shown that a smaller margin did not affect survival^{23,24}. In a retrospective study including more than 1500 patients, 5-year survival was 30% when the margin was greater than 1 cm, 15% when it was less than 1 cm and 0% when resection was incomplete⁵. 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.

Uni- and multivariate analysis of the prognostic value of different factors has led to the proposal of a simple prognostic scoring system to evaluate the chances of cure of patients after resection of liver metastases. One of these scoring systems was developed from a retrospective series of 1568 patients with resected liver metastases from carcinoma²⁵. Two- and 5-year survival rates were 64% and 28%, respectively, and were affected by 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. Giving one point to each factor, the population was divided into three risk groups with different 2-year survival rates: 0–2 (79%), 3–4 (60%), and 5–7 (43%).

Repeat liver resections for metastases

Recurrence limited to the liver following previous hepatic resection occurs in 25–50% of the cases and may be amenable to repeat resection^{26–28}. 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 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 years and 10 years, comparable to those observed following primary liver resections²⁷. Hepatic recurrences should, therefore, be resected whenever it is 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 10–20% of patients with liver metastases fulfil standard selection criteria and are amenable to surgery. As a consequence, the trend is to be more aggressive and to increase the

indications for surgical resection. Portal vein embolization, ablative techniques and chemotherapy may render amenable to surgery patients that would have been refused some years ago.

Portal vein embolization

Although a tumour is technically resectable, resection can be contraindicated if the future remnant liver is too small to provide sufficient postoperative liver function. In such cases, pre-operative selective portal vein embolization has been proposed to induce ipsilateral atrophy and contralateral compensatory hypertrophy of the remnant liver, thus preventing postoperative liver failure²⁹. Portal vein embolization 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 embolization can be expected to induce a 40–60% increase in the size of the non-embolized portion. However, if liver metastases are present in the non-embolized portion of the liver, induced liver regeneration or hypertrophy is associated with an accelerated increase size of metastases³⁰. Portal vein embolization is usually performed by percutaneous, ultrasonographically guided puncture of a portal vein radicle through tumour-free liver. Following embolization, a liver resection, judged primarily impossible, is feasible in 60% of cases with mortality and morbidity rates 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 embolization were comparable: 81%, 67%, and 40% *versus* 88%, 61%, and 38% at 1, 3 and 5 years, respectively³¹.

Local destruction

Local ablative methods such as cryotherapy or radiofrequency ablation (RFA) have been proposed to destroy tumours *in situ*. The efficacy of these new treatment modalities has not been tested in randomized trials and their use should be restricted to the treatment of otherwise non-resectable liver deposits.

Cryotherapy involves the freezing and thawing of liver tumours by means of a cryoprobe inserted into the tumour. During freeze/thaw cycles, ice formation occurs in an area termed iceball, leading to tumour destruction. Cryosurgery is feasible for tumours up to 6 or 8 cm even if located near the main vascular pedicles. The size of the probe renders percutaneous utilisation difficult. Complications include haemorrhage, subphrenic or hepatic abscess, bile collection or fistula, myoglobinuria.

Radiofrequency ablation involves percutaneous or intra-operative insertion of an electrode into the lesion under ultrasonic guidance. Radiofrequency energy is emitted through the electrode and generates

heat leading to coagulative necrosis. RFA is feasible for tumours of less than 3 cm and some strategies can increase the treatment area up to 5 cm (multi-probe arrays, internal cooling of the electrode, vascular clamping, *etc.*). The complication rate is low, usually below 2%.

The effectiveness of cryotherapy and RFA in destroying liver metastases has been demonstrated in several retrospective studies, but the long-term results and the beneficial effects on survival are not yet proven. Regional therapies can be used as palliative treatment for non-resectable lesions or can be associated with surgical resection. In a prospective, non-randomised study, RFA was used in 123 patients with histologically confirmed, unresectable hepatic malignancies without extrahepatic disease. The mortality and morbidity rates were 0 and 2.4%, respectively. With a median follow-up of 15 months, secondary lesions recurred in the site of local destruction in only 3% of patients. New hepatic or extrahepatic disease developed in 30% of patients and the liver was the first site of recurrence in 80% of them³².

Pre-operative chemotherapy

Systemic chemotherapy is used when liver metastases are not amenable to surgical resection. Palliative chemotherapy has been shown to increase survival and enhance quality-of-life³³. In terms of tumour response, co-treatment with 5-fluorouracil (5-FU) and folinic acid is effective in about 20% of cases. When associated with new drugs such as oxaliplatin or CPT-11, response rates approach 60%³⁴. The shrinkage of liver metastases may have several consequences: (i) small metastases may become no longer visible with conventional imaging techniques; (ii) major vascular pedicles of the liver may become free from tumour; and (iii) large lesion 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, the number of 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 lesions³⁵. Some chemotherapeutic regimens using 5-FU, oxaliplatin and CPT-11 aimed 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 distinction between resectable and unresectable metastases is becoming an evolving concept that may change over time. The possibility of surgical resection with or without the help of ablative techniques has, therefore, to be discussed regularly between surgeons and

medical oncologists. As a result of this close co-operation and with the help of these new techniques, surgery will be proposed for an increasing number of patients who were initially considered as non-resectable. 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 recur rapidly after resection and have the same prognosis as if they had not undergone resection? Only the future will tell.

How to decrease postoperative recurrence?

The benefit of adjuvant chemotherapy after resection of colorectal metastases has not yet been clearly proven. 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 in exposure of the tumour to the drug with reduced systemic side-effects. However, HAI has limitations including the risks of extrahepatic progression, severe side-effects including biliary toxicity, and technical problems precluding the use of the intrahepatic catheter. Three recently published series have evaluated the potential benefit of hepatic arterial infusion as adjuvant treatment after resection of colorectal liver metastases. 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 chemotherapy³⁶. A study from the Memorial Sloan-Kettering Cancer Center compared HAI + 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 years³⁷. A third study organized 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 survival³⁸. 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. The role of systemic chemotherapy after complete resection of

metastases has been evaluated in a single trial which tested 5-FU and folinic acid over no treatment. Here again there was a survival benefit in the treated arm, but the difference was not significant.

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 imperative that medical oncologists and surgeons participate in large prospective trials aimed at answering these questions. An international intergroup study organised by the European Organisation for Research and Treatment of Cancer (EORTC) is comparing surgery with or without neo-adjuvant and adjuvant oxaliplatin, 5-FU, and folinic acid in patients with resectable liver metastases. Studies evaluating irinotecan-based regimens are also in preparation. Hopefully, these studies will clarify the exact role of peri-operative chemotherapy to decrease recurrence and improve survival.

Summary and conclusions

In the treatment of liver metastases from colorectal cancer, complete surgical resection is associated with a very low mortality and can give 5-year survival approaching 40%. Best candidates for resection are those with less than 4 lesions, less than 5 cm in size, without extrahepatic disease, that appeared more than 2 years after the resection of a stage I or II colorectal cancer and whose CEA level is less than 5 ng/ml. However, surgery is feasible in only 10–20% of the patients. Others benefit from chemotherapy. Recent progress in chemotherapy and the development of ablative techniques increases the number of operable patients with a curative intent. The benefits of these new tools used to improve resectability and of adjuvant peri-operative chemotherapy used to decrease recurrence needs further evaluation.

References

- 1 Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. *Lancet* 1994; **343**: 1405–10
- 2 Wilson SM, Adson MA. Surgical treatment of hepatic metastases from colorectal cancer. *Arch Surg* 1976; **111**: 330–3
- 3 Wanebo HJ, Semoglou C, Attiyeh F *et al.* Surgical management of patients with primary operable colorectal cancer and synchronous liver metastases. *Am J Surg* 1978; **135**: 81–5
- 4 Kronawitter U, Kemeny NE, Heelan R, Fata F, Fong Y. Evaluation of chest computed tomography in the staging of patients with potentially resectable liver metastases from colorectal carcinoma. *Cancer* 1999; **86**: 229–35

- 5 Nordlinger B, Jaeck D, Guiguet M, Vaillant JC, Balladur P, Schaal JC. Surgical resection of hepatic metastases. Multicentric retrospective study by the French Association of Surgery. In: Nordlinger B, Jaeck D. (eds) *Treatment of Hepatic Metastases of Colorectal Cancer*. Paris: Springer, 1992; 129–46
- 6 Scheele J, Stangl R, Altendorf-Hofmann A, Gall FP. Indicators of prognosis after hepatic resection for colorectal secondaries. *Surgery* 1991; **110**: 13–29
- 7 Timothy GJ, Greig JD, Crosbie JL, Miles WFA, Garden OJ. Superior staging of liver tumors with laparoscopy and laparoscopic ultrasound. *Ann Surg* 1994; **6**: 711–9
- 8 Pichlmayr R. Is there a place for liver grafting for malignancy? *Transpl Proc* 1988; **20**: 478–82
- 9 Bismuth H, Houssin D, Castaing D. Major and minor segmentectomies ‘régérées’ in liver surgery. *World J Surg* 1982; **6**: 10–24
- 10 Makuuchi M, Hasegawa H, Yamasaki S, Hasegawa H. Four new hepatectomy procedures for resection of the right hepatic vein and preservation of the inferior right hepatic vein. *Surg Gynecol Obstet* 1987; **164**: 69–73
- 11 Starzl TE, Bell RH, Beart RW, Putnam CW. Hepatic trisegmentectomy and other liver resections. *Surg Gynecol Obstet* 1975; **141**: 429–37
- 12 Starzl TE, Iwatsuki S, Shaw B. Left hepatic trisegmentectomy. *Surg Gynecol Obstet* 1982; **155**: 21–7
- 13 Elias D, Detroz B, Lasser P, Plaud B, Jerbi G. Is simultaneous hepatectomy and intestinal anastomosis safe? *Am J Surg* 1995; **169**: 254–60
- 14 Doci R, German L, Bigmani P, Montallo F, Moranito A, Bozzetti F. One hundred patients with hepatic metastases from colorectal cancer treated by resection: analysis of prognostic determinant. *Br J Surg* 1991; **78**: 797–801
- 15 Fong Y, Cohen AM, Fortner JG *et al*. Liver resection for colorectal metastases. *J Clin Oncol* 1997; **15**: 938–46
- 16 Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. *World J Surg* 1995; **19**: 59–71
- 17 Gayowski TJ, Iwatsuki S, Madariaga JR *et al*. Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. *Surgery* 1994; **116**: 703–10
- 18 Hughes KS, Rosenstein RB, Songhorabodi S *et al*. Resection of the liver for colorectal carcinoma metastases. A multi-institutional study of long-term survivors. *Surgery* 1988; **103**: 278–88
- 19 Jamison RL, Donohue JH, Nagorney DM *et al*. Hepatic resections for metastatic colorectal cancer. Results in cure for some patients. *Arch Surg* 1997; **132**: 505–11
- 20 Jenkins LT, Milikan KW, Bines SD *et al*. Hepatic resection for metastatic colorectal cancer. *Am Surg* 1997; **63**: 605–10
- 21 Minagawa M, Makuuchi M, Torzilli G *et al*. Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer. *Ann Surg* 2000; **231**: 487–99
- 22 Nordlinger B, Quilichini MA, Parc R, Hannoun L, Delva E, Huguet C. Hepatic resection for colorectal liver metastases. Influence on survival of pre-operative factors and surgery for recurrence in 80 patients. *Ann Surg* 1987; **205**: 256–63
- 23 Cady B, Jenkins RL, Steele Jr GD *et al*. Surgical margin in hepatic resection for colorectal metastasis: a critical and improvable determinant of outcome. *Ann Surg* 1998; **227**: 566–71
- 24 Yamamoto J, Shimada K, Kosuge T, Yamasaki S, Sakamoto M, Fukuda H. Factors influencing survival of patients undergoing hepatectomy for colorectal metastases. *Br J Surg* 1999; **86**: 332–7
- 25 Nordlinger B, Guiguet M, Vaillant J-C *et al*. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. *Cancer* 1996; **77**: 1254–62
- 26 Huguet C, Bona S, Nordlinger B *et al*. Repeat hepatic resection for primary and metastatic carcinoma of the liver. *Surg Gynecol Obstet* 1990; **171**: 398–402
- 27 Lange JF, Leese T, Castaing D, Bismuth H. Repeat hepatectomy for recurrent malignant tumors of the liver. *Surg Gynecol Obstet* 1989; **169**: 119–26
- 28 Nordlinger B, Vaillant JC, Guiguet M *et al*. Repeat liver resections for recurrent colorectal metastases: prolonged survivals. *J Clin Oncol* 1994; **12**: 1491–6
- 29 Kawasaki S, Maakushi M, Kasaku T *et al*. Resection for multiple metastatic liver tumors after portal embolization. *Surgery* 1994; **115**: 674–7

- 30 Elias D, De Baere T, Roche A, Ducreux M, Leclerc J, Lasser P. During liver regeneration following right portal embolization the growth rate of liver metastases is more rapid than that of the liver parenchyma. *Br J Surg* 1999; **86**: 784–8
- 31 Azoulay D, Castaing D, Smail A *et al.* Resection of non-resectable liver metastases from colorectal cancer after percutaneous portal vein embolization. *Ann Surg* 2000; **231**: 480–6
- 32 Curley SA, Izzo F, Delrio P *et al.* Radiofrequency ablation of unresectable primary and metastatic hepatic malignancies: results in 123 patients. *Ann Surg* 1999; **230**: 1–8
- 33 Nordic Gastrointestinal Tumor Adjuvant Therapy Group. Expectancy of primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomized trial. *J Clin Oncol* 1992; **10**: 904–11
- 34 Douillard JY, Cunningham D, Roth AD *et al.* Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomized trial. *Lancet* 2000; **355**: 1041–7
- 35 Bismuth H, Adam R, Lévi F *et al.* Resection of non resectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg* 1996; **224**: 509–20
- 36 Lorenz M, Rossion I. Adjuvant and palliative regional therapy of liver metastases in colorectal tumors. *Dtsch Med Wochenschr* 1995; **120**: 690–7
- 37 Kemeny N, Huang Y, Cohen A *et al.* Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; **341**: 2039–48
- 38 Kemeny MM, Sudeshna A, Gray B *et al.* Combined modality treatment for resectable metastatic colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy – an intergroup study. *J Clin Oncol* 2002; **20**: 1499–505 Outcome following surgery for colorectal cancer