World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v3.i12.183

World J Gastrointest Surg 2011 December 27; 3(12): 183-196
ISSN 1948-9366 (online)

EDITORIAL

Current state of surgical treatment of liver metastases from colorectal cancer

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Received: October 12, 2010 Revised: October 23, 2011
Accepted: November 1, 2011
Published online: December 27, 2011

Abstract

Hepatic resection is the procedure of choice for curative treatment of colorectal liver metastases (CLM). Objectives of surgical strategy are low intraoperative blood loss, short liver ischemic times and minor postoperative morbidity and mortality. Blood loss is an independent predictor of mortality and compromises, in common with postoperative complications, long-term outcome after hepatectomy for CLM. The type of liver resection has no impact on the outcome of patients with CLM; wedge resections are not inferior to anatomical resections in terms of tumor clearance, pattern of recurrence or survival. Despite the lack of proof of survival benefit, routine lymphadenectomy has been advocated, allowing the detection of microscopic lymph node metastases and with prognostic value. In experienced hands, minimally invasive liver surgery is safe with acceptable morbidity and mortality and oncological results comparable to open hepatic surgery, but with reduced blood loss and earlier recovery. The European Colorectal Metastases Treatment Group recommended treating up front with chemotherapy for patients with both resectable and unresectable CLM. However, neoadjuvant chemotherapy can induce damage to the remnant liver, dependent on the number of chemotherapy cycles. Therefore, in our opinion, preoperative chemotherapy should be reserved for patients whose CLM are marginally resectable or unresectable. A meta analysis of randomized trials dealing with perioperative chemotherapy for the treatment of resectable CLM demonstrated a benefit of systemic chemotherapy but did not answer the question of whether a neoadjuvant or adjuvant approach should be preferred. Analysis of the literature demonstrates that the results of specialized centers cannot be attained in the reality of comprehensive patient care. Reasons behind the commonly poorer results seen in cancer networks as compared with literature-based data are, on the one hand, geographical disparities in access to specialized surgical and medical care. On the other hand, a selection bias in the reports of the literature may be assumed. Studies of surgical resection for CLM derive almost exclusively from case series generally drawn from large academic centers where patient selection or surgical expertise is superior to what is found in many communities. Therefore, we may conclude that the comprehensive propagation of the standards outlined in this paper constitutes a major task in the near future to reduce the variations in survival of patients with CLM.

Key words: Liver metastases; Colorectal cancer; Surgery; Chemotherapy; Outcome

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Grundmann RT. Current state of surgical treatment of liver metastases from colorectal cancer. *World J Gastrointest Surg* 2011; 3(12): 183-196 Available from: URL: http://www.wjgnet.com/1948-9366/full/v3/i12/183.htm DOI: http://dx.doi.org/10.4240/wjgs.v3.i12.183

INTRODUCTION

The objective of this article is to give an overview of surgical treatment of patients with colorectal liver metastases (CLM), on the basis of a workflow that has been elaborated recently by an expert group[1]. The present update will focus on hepatic resection only as the procedure of choice for curative treatment of CLM. Hepatectomy allows 10 year survival rates of 16%[2] to 23%[3]. The efficacy of ablative procedures such as radiofrequency ablation (RFA) will not be considered since the results of a panel of the American Society of Clinical Oncology (ASCO) demonstrate a compelling need for more research to determine the efficacy and utility of RFA to increase local recurrence-free, disease-free and overall survival (OS) for patients with CLM[4].

METHODOLOGY

Literature search strategy

The PubMed/MEDLINE literature database was selectively searched for articles with the keywords "colorectal liver metastases", "surgery" and "chemotherapy". Particular attention was devoted to studies and review articles that were published in the years 2008-2010 as the former published data are enclosed in the previous publication[1]. The literature search was limited to articles in English, German and human patients.

PATIENT SELECTION/PREDICTORS OF OUTCOME

Selection criteria for hepatic resection in patients with CLM are as follows[1,5]: (1) General operability of the patient in consideration of concomitant diseases; (2) Attainability of an R 0-situation: (a) In combination with ablative procedures where required; (b) Preoperative (neoadjuvant) chemotherapy where required; and (c) Curability of extrahepatic colorectal metastases; (3) Adequate liver functional reserve after R0 resection: Preoperative portal vein embolization or two stage hepatectomy where required; (4) At least two contiguous hepatic sectors with adequate inflow, outflow and biliary; drainage can be obtained; and (5) Experience of the surgeon/center.

The clinical risk score (CRS)[6] is frequently recommended for the selection of patients who may benefit from hepatic resection for CLM. It assigns one point to each of the following criteria: (1) Nodal status of primary; (2) Disease-free interval from the primary to discovery of the liver metastases of < 12 mo; (3) Number of tumors > 1; (4) Preoperative carcinoembryonic antigen (CEA) level > 200 ng/mL; and (5) Size of the largest tumor > 5 cm.

The 5 year actuarial survival rate for patients with 0 points was 60%, whereas that for patients with 5 points was 14%. In fact, no patient with 5 points survived 5 years. Fong *et al*[6] concluded that patients with a CRS of 0, 1 or 2 have a highly favorable outcome and surgical resection is undoubtedly rational therapy for such patients. Patients with scores of 3 or 4 have a much more guarded prognosis and resection should be planned in the context of adjuvant therapies. Rees *et al*[7] presented another multifactorial model for the evaluation of long-term survival after hepatic resection for CLM. They identified 7 risk factors as independent predictors of poor survival: number of hepatic metastases > 3, node positive primary, poorly differentiated primary, extrahepatic disease, tumor diameter ≥ 5 cm, CEA level > 60 ng/mL and positive resection margin. Patients with the worst postoperative prognostic criteria had an expected median cancer-specific survival of 0.7 years and a 5 year cancer-specific survival of 2%. Conversely, patients with the best prognostic postoperative criteria had an expected median cancer-specific survival of 7.4 years and a 5 year cancer-specific survival of 64%. However, the utility of prognostic models on general populations is inconsistent, as a review revealed of six scoring systems and fourteen prognostic factors[8]. Neither of these risk factors can reliably exclude the patient in a given case from hepatic resection. This demonstrates, too, the experience of the Mayo Clinic[9]. In this analysis of specific predictors of outcome, perioperative blood transfusion and positive hepatoduodenal lymph nodes were the only significant correlates of both survival and recurrence; neither variable is identifiable preoperatively. Thus, hepatic resection may be undertaken if all gross disease can be addressed.

SURGICAL STRATEGY

Objectives of surgical strategy are low intraoperative blood loss, short liver ischemic times and minor postoperative morbidity and mortality. Blood loss is an independent predictor of mortality[10] and compromises, in common with postoperative complications, long-term outcome after hepatectomy for CLM[11]. Ito *et al*[12] mentioned 5 year disease-free survival (DFS) rates of 25% for patients who had complications, compared with 33% for patients without complications. Similar results have been indicated by others, especially in the event of postoperative infective complications[13].

Minimum requirements for the amount of the future liver remnant (FLR) after hepatectomy are 25% of the healthy liver in patients with otherwise normal liver parenchyma, 40% in patients with preoperative chemotherapy, fibrosis, fatty liver or diabetes, and 50%-60% in patients with cirrhosis (Child A)[1,14]. Wedge resections have become more common in an attempt to preserve liver parenchyma but non-anatomical resections as compared to anatomical resections are supposed to be associated with a higher incidence of positive margins (R1 resection)[15]. In fact, the type of liver resection has no impact on the outcome of patients with CLM[16]; wedge resections are not inferior to anatomical resections in terms of tumor clearance, pattern of recurrence or survival. Zorzi *et al*[17] reported 5 year actuarial survival rate of 61% for wedge resection and 60% for anatomical resection, respectively. 5 year survival rates with no significant difference (29% for wedge resection *vs* 27% for anatomical resection) were also indicated by Guzzetti *et al*[18]. In addition, segmental resections have been described combined with less blood loss and fewer complications but no difference in survival as compared to more extended resections[19,20].

The Pringle maneuver should not be used routinely but may be required if massive bleeding is encountered during no-clamp hepatectomy[21]. A prospective randomized study reported no difference in terms of blood loss, rate of blood transfusion, mortality or morbidity for liver resection with or without hepatic pedicle clamping[22]. A Pringle maneuver of more than 30 min may result in ischemic insult to the remnant liver; besides, prolonged portal triad clamping during liver surgery for CLM is suspected to be associated with decreased time to hepatic tumor recurrence[23]. An alternative is ischemic preconditioning, in which a brief period of ischemia and reperfusion is applied prior to the prolonged ischemic insult[24]. Ischemic preconditioning reduces the blood transfusion requirements in patients undergoing liver resection; however, there is no evidence to suggest a protective effect of ischemic preconditioning in non-cirrhotic patients[25]. A further randomized trial demonstrated that intermittent occlusion is as effective as ischemic preconditioning to minimize postoperative liver injury. In this trial, intermittent portal triad clamping was performed by cycles of a 15 min inflow occlusion followed by 5 min reperfusion. The length of the transection determined the number of repeated cycles[26]. More recently, Fu *et al*[27] suggested choosing hemihepatic vascular inflow occlusion over the Pringle maneuver in terms of earlier recovery of postoperative liver function.

Perihepatic lymph node status is an important prognostic factor for patients undergoing hepatic resection for CLM[28], with location of metastatic regional lymph nodes strongly influencing survival. Adam *et al*[29] observed 5 year OS of 25% for pedicular, 0% for celiac and 0% for para-aortic regional lymph nodes. Nevertheless, Grobmyer *et al*[30] assessed that routine lymphadenectomy or routine sampling at the time of hepatic resection is unnecessary, particularly in patients without any clinical or radiological evidence of disease. Gurusamy *et al*[31] accomplished a systematic review of the literature to determine the role of lymphadenectomy in resection of CLM. They found no evidence of survival benefit for routine or selective lymphadenectomy. Beyond that, in a more recent Cochrane review, these authors concluded that there is no evidence in the literature to assess the role of surgery versus other treatments [(neo-adjuvant) chemotherapy or RFA] for patients with CLM and hepatic node involvement[32]. Despite the lack of proof of survival benefit, routine lymphadenectomy has been advocated by others[33-35]. They argue that systematic lymphadenectomy allows the detection of microscopic lymph node metastases (the frequency was 18%[35]) and is of prognostic value, particularly when the ratio of involved/total resected lymph nodes is verified. Furthermore, this information may potentially influence post resection chemotherapy recommendations.

MINIMALLY INVASIVE SURGERY

In experienced hands, minimally invasive liver surgery is safe with acceptable morbidity and mortality and oncological results comparable to open hepatic surgery, but with reduced blood loss and earlier recovery[36-38]. The laparoscopic approach can be recommended for peripheral lesions requiring limited hepatectomies or left lateral sectionectomies. Laparoscopic major hepatectomies, however, need further evaluation[39]. An international consensus conference defined solitary lesions, 5 cm or less, located in liver segments 2 to 6 as acceptable indications and considered left lateral laparoscopic sectionectomies standard practice[40]. Quite recently, a survey was published on the current state of laparoscopic hepatic surgery in Germany in the year 2008[41]. All in all, 551 laparoscopic hepatic resections were reported for benign and malignant liver lesions, respectively. Atypical resections were the primary indication, followed by left lateral resections. This corresponds with a world review of laparoscopic liver resection in 2804 patients[42], indicating wedge resection or segmentectomy (45%) followed by left lateral sectionectomy (20%) as the most common liver resections. Nguyen *et al*[43] reported a multicenter international series of 109 patients with CLM undergoing minimally invasive liver resection, with no perioperative deaths and 12% morbidity. Minimally invasive approaches included totally laparoscopic (56%) and hand-assisted laparoscopic (41%). Major liver resections ($\geqslant$ 3 segments) were performed in 45% of the patients. Negative margins were achieved in 94.4% of patients; the actuarial 5 year survival rate was 50%. Comparable oncological results of laparoscopic hepatectomy *vs* open hepatectomy for patients with CLM were stated by Castaing *et al*[44] (5 year patient survival 64% *vs* 56%). Nevertheless, laparoscopic surgery has not been tested by controlled trials for efficacy or safety. A bias in patient selection in the so far reported series favoring laparoscopic surgery cannot be excluded[45]. In addition, when propagating laparoscopic surgery for CLM, the substantial learning curve has to be kept in view. Vigano *et al*[46] mentioned 60 mandatory cases, which is a considerable case load for a hospital and means that this kind of surgery can only be performed in high volume centers.

TUMOR SIZE/RESECTION MARGIN

Fong *et al*[6] and others[7,47,48] refer to the largest size of metastasis $\geqslant$ 5cm as a negative prognostic factor but tumor size should not be an exclusion criterion of hepatectomy as long as R0 resection can be achieved. In this context, the width of the negative resection margin has been debated. Muratore *et al*[49] found a positive resection margin, associated with an increased risk of resection margin recurrence, but the width of the negative resection margin (⩽ 1 cm *vs* > 1 cm) was not a prognostic factor of worse recurrence-free survival. Hamady *et al*[50] also suggested that the former "1 cm rule" should be abandoned. Nuzzo *et al*[51] suggested that a resection margin less than or equal to 5 mm is associated with a greater risk of recurrence on the surgical margin, with a lesser rate of overall and disease-free survival. Are *et al*[52] analyzed the impact of margin width on long-term outcome after hepatic resection for CLM in a total of 1019 patients. The 5 year survival rates were 29% (margin < 1 mm), 35% (margin 1-5 mm), 40% (margin 5-10 mm) and 45% (margin > 10 mm). They concluded that, in patients undergoing hepatic resection for colorectal metastasis, a > 1 cm margin should be attempted whenever possible. However, inability to achieve this should not preclude hepatic resection. Pawlik *et al*[47] came to slightly different conclusions. In their study, the 5 year survival rate was 17.1% for patients with a positive margin compared with 63.8% for patients with a negative surgical margin. The width of the negative surgical margin did not affect the 5 year survival rate (1 mm to 4 mm: 62.3%; 5 mm to 9 mm: 71.1%; at least 1.0 cm: 63.0%). Based on these data, a margin of at least 1 mm appears to be the minimal requirement to reduce margin-related recurrences. Even this rule has been questioned by de Haas *et al*[53]. In their study, the 5 year DFS was 29% in the R0 group versus 20% in the R1 group. R1 resection was not an independent predictor of poor OS, which could mean that R1 resection might be revisited in the current era of effective chemotherapy. In contrast, Welsh *et al*[54] comment on a 5 year cancer-specific survival for R0 and R1 hepatic resections of 39.7% and 17.8%, respectively. Furthermore, Tomlinson *et al*[55] reported no patients who survived 10 years who had a positive margin. It should be concluded that complete resection and not millimeters defines outcome.

TUMOR NUMBER

A number of hepatic metastases > 3 was an independent predictor of poor survival in the multifactorial predictive model described by Rees *et al*[7]. This concurs with a systematic literature review of tumor number and outcome, including 46 studies with 9934 patients, reporting median 5 year survival for patients with four or more CLM being as few as 17.1%[56]. Better outcome in patients with four or more CLM was seen by Pawlik *et al*[57] (5 year OS 50.9%) and Kornprat *et al*[58] (5 year survival 33%). Indeed, these results could be achieved in a high percentage of cases (89.9% in[57]) only in combination with neoadjuvant chemotherapy, suggesting that with the introduction of potent new protocols of chemotherapy, higher tumor numbers should not be used to deny patients a potentially curative resection[14]. Vice versa, it may be argued that patients with tumor progression while on chemotherapy are predominantly not candidates for resection. Adam *et al*[59] mentioned an OS of merely 8% in patients with multiple (⩾ 4) CLM under these conditions, even after potentially curative hepatectomy.

BILOBAR METASTASES

Hepatic resection is also effective in the case of bilobar metastases. Tomlinson *et al*[55] reported 5 and 10 year survival rates of 29% and 25% in patients with bilateral resections. Figueras *et al*[60] described 259 patients with so called expanded indications (liver metastasis > 10 cm, ⩾ 4 liver metastases, extrahepatic disease), including 194 patients with bilateral deposits. The actuarial 5 and 10 year survival rates were 34% and 24%, respectively, compared with 45% and 36% for patients with "classic" indications.

EXTRAHEPATIC DISEASE

Reviewing the published data, Carpizo and D´Angelica[61] concluded that there is a role for surgery in highly selected patients with a single site of extrahepatic disease (EHD) amenable to complete resection. However, the goals of surgery must not be viewed as potentially curative as recurrence occurs in most patients. In 127 patients with hepatectomy for CLM and concurrent resection of EHD, the 5 year survival was 26%, compared with 49% for those without EHD[62]. Patients with portal lymph node metastases had worse survival than those with lung or ovarian metastases. Among patients who had a complete resection of all disease, 95% recurred. Elias *et al*[63] described a 5 year OS rate of 29% for patients with R0 resection of CLM and simultaneous resection of EHD. Most favorable results could be obtained if the number of liver metastases was < 6 and if the metastases responded to preoperative chemotherapy.

Prerequisites for hepatic and pulmonary resection in patients who present with a synchronous or metachronous combination of liver and lung metastases are[64]: (1) The primary tumor and/or the local recurrence are controlled or controllable; (2) The liver and/or the lung are the only site of metastasis; (3) Removal of all the liver and lung tumors is technically feasible (R0 resection); and (4) The patient is considered likely to tolerate surgery well.

In these cases concomitant or sequential hepatic and pulmonary resection may be performed, with an expected 5 year survival rate of about 30%[65-68] to 40%[64], determined after simultaneous resection or after last organ resection for metastases. An analysis of prognostic factors revealed that survival was significantly longer when the disease-free interval between the development of the first and second sites of metastases exceeded 1 year, in patients with a single liver metastasis and in patients younger than 55 years old[68]. Patients with lung as the first site of metastatic disease had a worse outcome than patients with metastases primarily confined to the liver[67]. Prognosis was also better in patients with metachronous disease than in those with synchronous disease[64], but this was not confirmed by others[67,69]. The relatively low patient numbers reported so far prove the extraordinary indication.

Table 1 Simultaneous *vs* staged resection of colorectal cancer and synchronous colorectal liver metastases

Author	Patients (*n*)		Morbidity		Comment
	Sta	Sim	Sta	Sim	
Martin *et al*[73]	160	70	55%	56%	Major hepatectomy rate: Sta 32 % *vs* Sim 33 %
Slupski *et al*[74]	61	28	13%	14%	Major hepatectomy rate: Sta 48 % *vs* Sim 28 %
Moug *et al*[75]	32	32	59%	34%	Case matched study
Reddy *et al*[77]	475	135	17.6%	36.1%	Major hepatectomy
			10.5%	14.1%	Minor hepatectomy
de Haas[78]	173	55	25.4%	11%	3-year recurrences: Sta 63.6% *vs* Sim 85%

Sim: Simultaneous resection; Sta: Staged resection. The lower patient numbers in the simultaneous resection group compared with the staged resection group demonstrate a bias in patient selection. Simultaneous patients often had fewer and smaller metastases and less often underwent major hepatectomy.

SYNCHRONOUS DISEASE

The optimal surgical strategy for patients with synchronous CLM is still unclear, as long as all recommendations are based on observational studies; randomized controlled trials cannot be identified[70]. Traditionally, the standard therapy for most patients with colorectal cancer and synchronous CLM consists of colorectal resection first to prevent bleeding, perforation or obstruction, followed 6 weeks later by staged liver resection[71]. Whether patients with synchronous CLM alternatively should undergo simultaneous resection of colorectal primary and the hepatic metastases is a pending question. From a systematic review of the literature, Hillingso and Wille-Jorgensen[70] argued that synchronous resections can be undertaken in selected patients, provided that surgeons specialized in colorectal and hepatobiliary surgery are available (grade C recommendation). A second review and meta analysis[72] remarked that simultaneous resection is safe and efficient while avoiding a second major operation and might be considered as the preferred treatment, although caution is needed in interpretation of the results due to the heterogeneity of the groups (Table 1). At least in patients with smaller liver tumors and (right sided) colon cancer, simultaneous colon and hepatic resection reduces overall hospital stay, with no differences in morbidity and mortality rates compared with staged resection[73-75]. Restraint is advised in older patients and left sided (colo) rectal cancer, especially if major hepatic resections are necessary, due to an increased risk of severe morbidity and mortality[71,76]. In a multi-institutional analysis[77], simultaneous colorectal resection raised mortality from 1.4% to 8.3% and severe morbidity from 15.1% to 36.1% for major hepatectomy, but not for minor hepatectomy (mortality 0.5% *vs* 1.0%; severe morbidity 12.5% *vs* 14.1%). De Haas *et al*[78] found combining colorectal resection with a limited hepatectomy safe in patients with synchronous CLM (mortality rate 0%-0.6%); however, in their patients, the combining strategy had a negative influence on progression-free survival: three-year overall and progression-free survival rates were 74% and 8%, respectively, in the simultaneous group, compared with 70.3% and 26.1% in the delayed group.

A further therapeutic option for patients with synchronous CLM consists of the "liver-first approach"- firstly starting with chemotherapy, secondly doing the liver surgery and lastly, performing the colorectal resection[79,80]. Mentha *et al*[80] treated 35 patients with a liver first protocol but 5 patients could not complete the program. Median survival of the remaining 30 patients undergoing R0 hepatic resections was 44 mo, with an overall 5 year survival of 31%. Another small series of 16 (from 23) patients completing the full treatment protocol was reported by Verhoef *et al*[81]. The rationale of this approach is the reflection that, in patients with advanced or technically doubtful resectable synchronous liver metastases from colorectal cancer, CLM might progress during treatment of the primary, precluding curative treatment in a second stage. Since the curability of liver metastases in this situation but not the primary tumor decides the prognosis of the patient, resection of the primary should be postponed. Neoadjuvant chemotherapy first allows initial control and downsizing of liver metastases and delivery of preoperative radiotherapy for rectal cancer. Furthermore, in patients with incurable metastatic disease, useless colorectal surgery can be avoided. The risk of major complications that involve the primary tumor and which require surgery is low in patients with asymptomatic colorectal cancer and upfront chemotherapy. In a retrospective analysis of 233 patients receiving combination chemotherapy without surgery as initial treatment of stage IV colorectal cancer (of them 221 with CLM), 93% never required surgical intervention for primary tumor symptomatology[82]. A systematic review of the literature confirms this attitude. Scheer *et al*[83] found resection of the primary tumor provided only minimal palliative benefit for patients with stage IV colorectal cancer. As a consequence, most patients with asymptomatic primary tumors and unresectable synchronous CLM should be treated first with chemotherapy[84]. In addition, hepatic resection should be performed before bowel resection in patients with resectable synchronous CLM, especially if a potential increase in hepatic tumor size might interfere with the planned surgical approach[71].

RECURRENT HEPATIC METASTASES

De Jong *et al*[85] reported on 1669 patients treated with surgery (resection +/- RFA) for CLM. 947 (56.7%) patients developed recurrence with a median recurrence-free survival of 16.3 mo. First recurrence site was intrahepatic only (43.2%), extrahepatic only (25.8%) and intra- and extra-hepatic (21.0%). This data demonstrates the large potential of repeat liver surgery for CLM, with the selection criteria for the second hepatic resection being the same as for the first approach. Because repeat liver resections are technically more demanding and difficult, there was concern that re-resections might be associ-

Table 2 Survival after repeat liver resection for recurrent colorectal liver metastases

Author	Yr	Patients (*n*)	5-year survival
Petrowsky *et al*[87]	2002	126	34%[a]
Thelen *et al*[88]	2007	94	38%[a]
Brachet *et al*[89]	2009	62	40%[b]
de Jong *et al*[91]	2009	246	32.6%[c]
Mise *et al*[92]	2010	60	39%[d]
		21	37%[e]
		9	20%[f]

[a]From time of second liver resection; [b]From time of first liver resection; [c]From time of second "curative intent surgery" (hepatic resection and RFA included); [d]From time of repeated resection for isolated hepatic recurrence; [e]From time of repeated resection for isolated pulmonary recurrence; [f]From time of repeated resection for hepatic + pulmonary recurrence.

ated with higher rates of death and complications than first resections. However, studies show a similar range of death rates and morbidity of repeat liver resection compared with those of primary hepatic resection. Yan *et al*[86] found an overall perioperative morbidity rate ranging between 7% and 30% and mortality rate ranging from 0 to 5% when reviewing 17 observational studies on repeat hepatectomy published before January 2007. The 30 d death rates were 1.6% in 126 patients undergoing second liver resection[87], 3/94 patients (3%)[88] and 0/62 patients[89]. Adam *et al*[90] described no perioperative death in 60 patients, even after a third hepatic resection for liver recurrences following a second hepatectomy. The 5 year DFS after repeat hepatectomy ranged from 16% to 48% in the above mentioned review[86]. Thus, further resection of the liver can provide prolonged survival in well-selected patients with recurrent CLM (Table 2) and is justified if a R0 resection can be achieved, at least as long as there is a lack of evidence for effective alternative treatments.

STRATEGIES FOR IMPROVING RESECTABILITY

Portal vein embolization

Selective portal vein embolization (PVE) or portal vein ligation (PVL)[93] of the right (more often) or left portal vein homolateral to the tumor induces homolateral hepatic atrophy and contralateral hepatic hypertrophy. This approach is an effective means of creating hypertrophy of the FLR and should be considered in patients in whom an extended hepatectomy is planned and who have a predicted (post resection) FLR volume less than 25% of total liver volume[94]. A meta-analysis of the literature involving 1088 patients described an overall morbidity rate of 2.2% without mortality for PVE. Four weeks following PVE, 85% patients underwent the planned hepatectomy. Reasons for non resection following PVE included severe progression of liver metastases (4%), extrahepatic spread (3.2%), altered treatment to transcatheter embolization or chemotherapy (2.2%), and inadequate hypertrophy of remnant liver (1.7%)[95]. The increase in remnant liver volume after PVE averages 12% of the total liver[96]; with reference to the FLR volume, an increase of 37% has been observed[97]. The increase depends on the condition of the liver parenchyma. Farges *et al*[98] found, 4 to 8 wk after PVE, a mean increase of remnant liver volume of 16% of the total liver for patients with normal liver and 9% for those with chronic liver disease. In this study, PVE had no beneficial effect on the postoperative course in patients with normal liver and elective right hepatectomy. In contrast, in patients with chronic liver disease, the hypertrophy of the FLR induced by PVE significantly decreased the rate of postoperative complications.

Whether PVE might be an oncological risk factor has been queried. Azoulay *et al*[99], Elias *et al*[100] and Mueller *et al*[101] reported long-term survival after PVE comparable to that after resection without PVE. In contrast, Pamecha *et al*[97] observed long-term survival as less in patients requiring PVE before major hepatectomy for CLM. In this study, the 5 year survival after liver resection with PVE was 25%, compared with 50% without PVE. This might be ascribed to accelerated tumor growth after PVE, as was seen by Kokudo *et al*[102], but also to patient selection. Wicherts *et al*[103] reported overall 3 year survival rates of 44% with PVE and 61% without PVE in patients who underwent hepatectomy for CLM. Patients treated by PVE presented with more than three metastases more often and more frequently with bilobar metastases. Nevertheless, stimulation of tumor growth after PVE is a major concern[104] and requires further investigation with regard to the need of (neo-) adjuvant chemotherapy, which was received by all 30 PVE patients described by Azoulay *et al*[99].

Two stage hepatectomy

Two stage hepatectomy is a surgical modality recommended for patients with primarily unresectable and especially bilobar metastases[105]. The initial stage of the hepatic resection is intended to remove the highest possible number of metastases but not all of them due to the risk of postoperative liver failure. The timing of the second hepatectomy is selected as a function of liver regeneration, control of remnant liver tumor by chemotherapy, and the probability that the second hepatectomy can be curative. The first results were not particularly satisfying. The 15% perioperative death rate of the two stage hepatectomy strategy was higher than the 1% observed in patients undergoing primary resection during the same period[105]. Meanwhile, two stage hepatectomy combined with PVE has been reported with acceptable morbidity and no operative mortality[106]. Because of concern that metastases in the FLR may progress after PVE, metastases located in the FLR should be ideally resected before PVE in a first stage hepatectomy. PVE was performed 2 to 5 wk after the first stage hepatectomy; the mean time between PVE and second stage hepatectomy ranged between 4 and 6 wk[106]. The clinical assessment of this approach should keep in mind the small patient numbers reported, even by exceptionally experienced centers, pointing to the relevance of patient selection for the achievement of the reported 5 year survival rates (Table 3). The second stage

Table 3 Two stage hepatectomy in patients with colorectal liver metastases

Author	Yr	Patients (*n*)		Survival
		Planned	Feasible	
Adam *et al*[105]	2000	16	13[a]	35% 3-year OS
Jaeck *et al*[106]	2004	33	25	54.4% 3-year OS
Togo *et al*[108]	2005	11	11	45 % 3-year OS
Wicherts *et al*[109]	2008	59	41	42% 5-year OS
				13% 5-year DFS
Tsai *et al*[107]	2010	45	35	58% 3-year OS
Karoui *et al*[110]	2010	33	25[b]	48% 5-year OS
				22% 5-year DFS

OS: Overall survival; DFS: Disease-free survival. [a]Patients are included in Wicherts *et al*[109]; [b]Bilobar synchronous metastases-combined colorectal resection and clearance of one liver lobe as the first stage procedure.

will not be feasible in 20%-25% of patients, mainly due to disease progression[107].

Combined resection and radiofrequency ablation

Pawlik *et al*[111] described hepatic resection combined with RFA as a novel option in patients with multifocal hepatic lesions that were otherwise unresectable. 172 patients (124 of them with CLM) with 737 tumors were included in this study. 387 tumors were resected and 350 ablated, respectively. The average size of the lesions treated with RFA ranged to 1.8 cm × 1.6 cm × 1.5 cm. The postoperative complication rate was 19.8% with a mortality rate of 2.3%. Median actuarial survival time for patients with CLM averaged 37.3 mo, comparable with the cancer specific 3-year survival rate of 38% for resection + RFA in a further study[112]. According to these results, combining hepatic resection with RFA expands the number of patients suited for surgical therapy, particularly as larger lesions that are less effectively treated with ablation can be resected and smaller lesions can be ablated[14]. Survival following this combined approach is difficult to interpret due to a bias in patient selection. The results depend on the definition of "unresectability". Besides, the disease extent in the existing observational studies determined the modality of treatment-less extensive lesions were treated by resection, the more extensive by resection + RFA and the most extensive by chemotherapy alone[113]. Abdalla *et al*[114] found a survival advantage for resection +RFA compared with chemotherapy alone in patients with unresectable CLM. However, the patient groups were not comparable and tumor number was most predictive of poor survival. Whether the survival benefit with resection +RFA compared with chemotherapy alone would be sustained using newer systemic chemotherapy regimens and comparing unresectable lesions of identical size is an unresolved issue. Kornprat *et al*[115] observed a 3-year DFS of only 8% in 39 patients with CLM treated by intraoperative thermoablation (RFA or cryosurgical ablation) combined with hepatic resection, although actuarial survival was 47% at 3 years. 85% of patients received neoadjuvant therapy and nearly all received adjuvant chemotherapy. These investigators concluded that the longer survival seen in their study, despite the presence of recurrent disease, was probably a reflection of improved systemic chemotherapy. They had to leave the question of whether the results of their study reflected improved systemic chemotherapy or the effect of the extended combined surgical approach unanswered.

ACCOMPANYING CHEMOTHERAPY

Neoadjuvant chemotherapy in patients with initially unresectable CLM

Preoperative chemotherapy allows 15% to 30% of patients with initially unresectable or marginally resectable CLM to be rescued by liver surgery, offering 5 year survival rates of 30%-35%, and is therefore highly recommended under these circumstances[116,117]. Adam *et al*[118] reported an overall 5 year survival of 33% with this approach compared with 48% in patients who underwent primary resection without downsizing chemotherapy within the same period. The lower survival relied on the more extensive tumor spread of patients that were initially unresectable. Negative prognostic factors of survival following surgery were: rectal primary, ≥ 3 metastases, CA19-9 > 100 UI/L and maximum tumor diameter > 10 cm. The 5 year survival expectancy was 59% for patients without any risk factors, 30% for 1 factor, 7% for 2 factors, and 0% to 1% for 3 and 4 factors. The same study group gave account of the long-term outcome of 148 patients with initially unresectable CLM who underwent rescue surgery after downsizing chemotherapy[119]. 24 patients (16%) were considered cured after mean follow-up of 118.6 mo. Independent predictors of cure included maximum size of metastases less than 30 mm at diagnosis, number of metastases at hepatectomy ≤ 3 and complete pathological response. For neoadjuvant chemotherapy, the most effective regimen, in terms of response rate and progression-free survival, which the patient can tolerate should be used, coupled with the recommendation that surgery should be conducted as early as possible to minimize the effects of chemotherapy on the liver[117]. Standard combination chemotherapy regimens comprise folic acid plus 5-fluorouracil (5-FU) in combination with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX)[120]; these regimens plus a biologic[121] or triple cytotoxic drug therapy (FOLFOXIRI)[122] in patients with good performance status[117]. A further option to increase resectability of CLM consists of the use of hepatic artery infusion chemotherapy plus systemic chemotherapy[123]; however, randomized trials are needed to prove whether this approach might be superior to systemic chemotherapy alone. Remarkably enough, hepatic arterial infusion of oxaliplatin followed by radical surgery enabled removal of initially unresectable isolated CLM in 21 of 87 patients (24%) after failure of previous systemic chemotherapy[124]. In this study, 5-year OS was 56% in the surgery group versus none in the non surgery group.

Neoadjuvant chemotherapy in patients with resectable CLM

The European Colorectal Metastases Treatment Group recommended that patients with both resectable and unresectable CLM should be treated up front with chemotherapy. Only patients with a 2-cm solitary metastasis and good prognostic features should go straight to surgery[117]. This recommendation is based on the results of the EORTC 40983 trial where the progression-free survival (PFS) in all randomly assigned patients at 3 years was 28.1% with surgery alone and 35.4% in those patients who received perioperative chemotherapy (FOLFOX4) (P = 0.058)[125]. In patients in whom hepatic resection was actually achieved after study entry, the rate of PFS at 3 years was increased by 9.2% from 33.2% to 42.4% with chemotherapy (P = 0.025). Data on OS are still unavailable. Postoperative complications occurred more often in patients who had received preoperative chemotherapy (25%) than in those who had received surgery alone (16%), but operative mortality was 1% in both treatment groups. Whether most patients with resectable CLM should start with chemotherapy as proposed by Benoist and Nordlinger[126] may be challenged as long as further studies are lacking and retrospective data do not support this insight[127]. Neoadjuvant chemotherapy can induce damage to the remnant liver[128-130], dependent on the number of chemotherapy cycles[131,132]. Hepatic steatosis, a mild manifestation of non-alcoholic fatty liver disease (NAFLD), may occur after treatment with 5-FU and is associated with increased postoperative morbidity. Chemotherapy associated steatohepatis (CASH) can appear after treatment with irinotecan, especially in obese patients. It is associated with an increased morbidity and possibly mortality following hepatic resection as a result of the development of liver failure. Hepatic sinusoidal obstruction syndrome (SOS) can emerge in patients treated with oxaliplatin but does not appear to be associated with an increased risk of perioperative mortality; however, it may be associated with an increased morbidity. Besides, SOS can lead to early recurrence and decreased survival in the long-term[133]. Another impact of preoperative chemotherapy is that metastases that respond to treatment may be no longer visible on computed tomography (CT) or at surgery. Patients should be carefully monitored during chemotherapy and receive surgery before metastases disappear[126]. The timing between chemotherapy and surgery is a key parameter for optimal outcome of patients. The longer chemotherapy is administered and the higher the number of treatment lines, the lower the survival after resection[134]. Thus, the side-effects of preoperative chemotherapy have to be balanced against its potential benefit. In our[1] and others'[135] opinion, preoperative chemotherapy should remain reserved, at least for now, for patients whose CLM are marginally resectable or unresectable. For the remainder, adjuvant chemotherapy should be considered as long as the additional benefit of preoperative chemotherapy over effective postoperative chemotherapy in patients with resectable CLM is not proven. Adjuvant chemotherapy combined with surgery yielded comparable results to neoadjuvant treatment in patients with resectable CLM[136]. A meta analysis of randomized trials dealing with perioperative chemotherapy for the treatment of resectable CLM demonstrated a benefit of systemic chemotherapy but could not answer the question of whether a neoadjuvant or adjuvant approach should be preferred[137]. Another systematic review of randomized and non randomized trials dealing with neoadjuvant chemotherapy for resectable CLM suggested that a prospective randomized trial of neoadjuvant therapy versus adjuvant therapy after liver resection is required to determine the optimal perisurgical treatment regimen[138].

Adjuvant chemotherapy

The first multicenter randomized trial comparing adjuvant 5 FU and folinic acid with surgery alone after resection of CLM reported a 5-year DFS of 33.5% for treated patients *vs* 26.7% in the control group[139]. There was also a trend to increased OS in those patients receiving chemotherapy. Further support of a 5-FU-based adjuvant chemotherapy regimen can be derived from a retrospective cohort study comprising of 792 patients. Parks *et al*[140] reported a median survival time of 47 mo in the treatment group compared with 36 mo in the control group. In addition, the results of a pooled analysis of two randomized trials suggest the use of systemic adjuvant chemotherapy after potentially curative resection of CLM[141]. In this evaluation, the median OS was 62.2 mo in the surgery + chemotherapy arm compared with 47.3 mo in the surgery alone arm. The European expert panel therefore considered adjuvant chemotherapy following liver resection an option in resected patients, particularly for those patients who did not receive preoperative chemotherapy[117].

CONCLUSION AND PERSPECTIVES FOR THE FUTURE

At present, 10%-20% of all patients with CLM can be assumed to be candidates for resective surgery. Hepatic resection can be performed safely with a mortality rate of 1%-2% and a survival rate of more than 40% after 5 years[135]. The results, however, depend on patient selection and require a specialized team experienced in hepatic surgery. High hospital procedure volume is an important predictor of low perioperative mortality after hepatic resection[142] and is also associated with improved long-term prognosis after hepatectomy for CLM[143]. In contrast to this, Cummings *et al*[144] reported on 13 599 patients aged ≥ 65 years with colorectal cancer and synchronous or metachronous liver metastases, identified from a Medicare database. Only 833 patients (6.1%) in this cohort underwent hepatic resection and their 30 d mortality rate was 4.3%, distinctly higher than that given in the literature for surgical case series[7,145]. The 5-year survival was 32.8% in resected patients compared with 10.5% in patients who did not undergo liver surgery. This analysis demonstrates strikingly that patients profit from surgical treatment but apart from that, the results of specialized centers could not be attained in the reality of comprehensive patient care. This applies to resection rate as well as to perioperative mortality and long-term outcome and is confirmed by the subsequent analysis of 3957 Medicare beneficiaries who underwent hepatic resection for CLM between January 1, 2000 and December 31, 2004[146]. In this national study, crude 30 day and 90 d mortality were 4.0% and 8.2%, respectively; the 5-year survival rate was 25.5%. Reasons behind the commonly poorer results seen in cancer networks as compared with literature-based data are, on the one hand, geographical disparities in access to specialized surgical and medical care[147,148]. On the other hand, a selection bias in the reports of the literature may be assumed. Asiyanbola *et al*[149] conducted a systematic MEDLINE review on mortality after hepatectomy for hepatocellular carcinoma and metastatic disease. The literature-based mortality rate was 3.6% (US centers only, 2.8%). The Nationwide Inpatient Sample (NIS) dataset, however, stated the perioperative mortality rate for hepatectomy as 5.6%, 1.6-fold higher compared to reports from the literature. Studies of surgical resection for CLM derive almost exclusively from case series generally drawn from large academic centers where patient selection or surgical expertise is superior to what is found in many communities. This may lead to an overly optimistic estimate of the benefits derived from hepatic resection for CLM in general. It might be argued that the results described by Cummings *et al*[144] and Robertson *et al*[146] reflect the experience in patients ≥ 65 years of age only. However, more than two-thirds of colorectal cancer incidents occur in this age group. Furthermore, younger but not older age was a risk factor for long-term outcome after hepatic resection for CLM in the studies described by de Haas *et al*[150] and Adam *et al*[151]. Therefore, we may conclude that the comprehensive transfer of the standards outlined in this paper constitutes a major task in the nearer future to reduce the variations in the use of liver resection and survival in patients with CLM.

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