10 Colorectal Liver Metastases

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- *The liver is the most common site of metastases from colorectal cancer, and complete resection of colorectal liver metastases (CLM) is the only potentially curative treatment.*
- *Resection of CLM is associated with low operative mortality and long-term survival has improved, with 5-year survival rates exceeding 50%.*
- *Besides a potential effect on survival, preoperative chemotherapy can increase the resection rate and improve patient selection. Despite no clear benefits for initially resectable CLM, neoadjuvant chemotherapy has a crucial role in initially unresectable disease.*
- *Surgical strategies, such as preoperative portal vein embolization, two-stage hepatectomy and resection combined with ablation, have enabled surgical resection of multiple bilateral CLM.*
- *Selected patients with extrahepatic disease, mainly lung metastases, have been considered for curative resection with substantial increases in overall survival.*
- *Synchronous CLM can be resected after, simultaneously with, or before resection of the primary cancer, according mainly to location, symptoms, and extent of colorectal cancer and hepatic metastases. Simultaneous resection should be avoided if major resections are required for both primary and hepatic diseases.*
- *Surgery for hepatic recurrence of CLM results in similar overall survival to that associated with first hepatic resection, and curative surgery should be considered for each relapse.*

INTRODUCTION

Colorectal cancer is among one of the most common malignancies worldwide, with over 1.2 million new cancer cases and more than 600,000 deaths per year.[1] Among those patients with advanced disease, more than 50% will develop hepatic metastases (nearly 1/3 synchronous and 2/3 metachronous) and many will have disease apparently confined to the liver, the most common site of metastases from colorectal cancer.

Resection of all evident metastases offers the only potential for definitive cure, with reported 5-year survival rates exceeding 50%, compared to a typically poor prognosis for those not undergoing resection.[2,3] While in earlier years only patients with very limited liver metastases were considered for surgical therapy, the number of patients thought to be eligible for surgical therapy has increased based on encouraging results in patients with more extensive disease. In spite of this increasingly aggressive approach, only about 30% of patients with liver-only metastases can be considered surgical candidates.[4–6]

Silvio Marcio Pegoraro Balzan and Vinicius Grando Gava (Eds.)

Improved systemic chemotherapeutic regimens including oxaliplatin and irinotecan have improved survival and response rates.

The addition of biological therapies such as bevacizumab, cetuximab, panitumumab, aflibercept, and regorafinib have further improved the efficacy of combined-modality therapies for advanced colorectal cancer.[7] Also, strategies including preoperative hepatic preconditioning, staged liver resections, and resection combined with tumor ablation have expanded the ability to safely treat patients with more extensive disease.[8,9]

Multidisciplinary team evaluation is necessary in the management of metastatic colorectal liver patients. A periodical re-appraisal with the hepatic surgeon should be done even in initially non-resectable cases.

This chapter reviews advances in the surgical treatment of colorectal liver metastases (CLM).

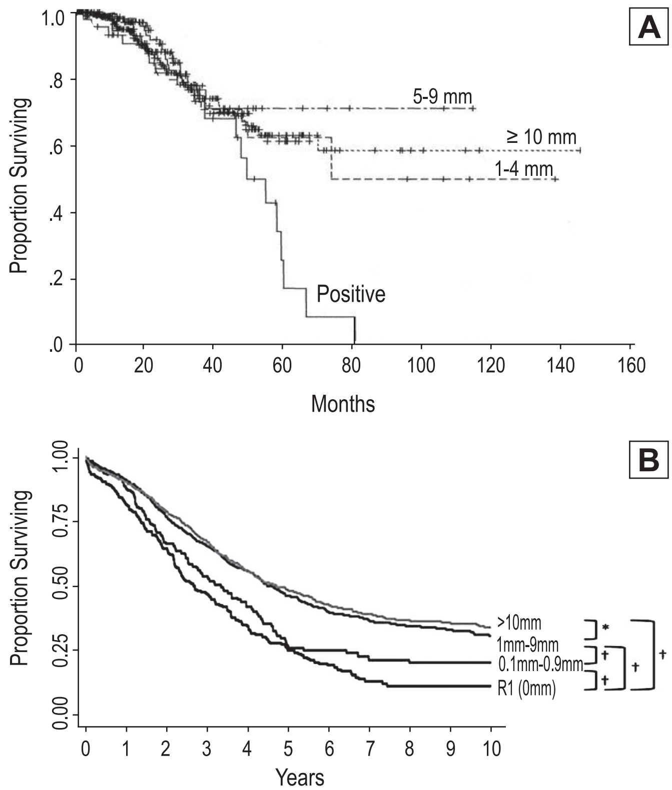

Figure 1. Survival stratified by margin status. Two major series evaluating the influence of surgical margin status on overall survival following colorectal liver metastases resection. **A**) No significant difference in survival in patients with a negative surgical margin, regardless of the width of the margin. Adapted from Pawlik et al.[12] **B**) No significant difference in survival in patients with a negative surgical margin of more than 1 mm. * P not significant; † P< 0.05. (Adapted from Sadot et al.[13])

LIVER RESECTION FOR COLORECTAL METASTASES

DEFINING RESECTABILITY

The decision to pursue surgical resection should be made based on the ability of the surgeon to locally treat all disease with negative pathological surgical margins, as well as the absence of any extrahepatic disease.

In the past, only patients with very limited disease were considered to be candidates for liver resection, often excluding patients with more than three or bilateral metastases.[5] However, more recent studies have shown that high survival rates can be achieved even in patients with more extensive disease, and a high tumor number or the proximity of major vessels are no longer contraindications for surgical resection, as long as complete eradication of gross disease can be obtained.[6]

The role of surgical margins has evolved over the years, and a predicted margin of less than 1 cm is no longer a contraindication to resection. The width of a negative surgical margin (≥1 mm) does not seem to affect survival, recurrence risk, or site of recurrence.[10–12] A large retrospective series including more than 2,000 CLM resections found similar overall survival (OS) for surgical margins of more than 1 mm and of more than 10 mm (**Figure 1**), better than for positive margins.[13] Also negative margins of less than 1 mm resulted in better OS than positive margins.[13] However, in the era of modern chemotherapy regimens, even R1 procedures performed by necessity in subjects initially deemed unresectable or marginally resectable might be beneficial in a selected group of patients, mainly those with optimal response to chemotherapy.[14–20] In fact, positive margins may be a surrogate indicator of the biology of tumor rather than an independent predictor of survival, as demonstrated by multivariate analysis in some recent studies.[15,17] Nonetheless, the need of extensive procedures, such as vascular and/or contiguous organs resections, should not preclude patients from a potentially curative surgery (R0 resection) when feasible.

Standard requirements for the resection of hepatic colorectal metastases comprise the excision of all lesions (combined or not with ablation techniques) with sufficient functional remnant liver parenchyma. Sufficient remnant liver volume with adequate i) blood inflow, ii) blood outflow, and iii) biliary drainage is necessary. The remnant liver volume depends on the parenchymal features. Patients with diseased parenchyma require a larger remnant volume. Thus, cirrhosis, steatosis, and chemotherapy-associated liver injury (CALI) must be considered to accomplish a safe resection **(Table 1)**. Further information can be found in **Chapter 4** (Underlying Liver Disorders in Hepatic Surgery) and **Chapter 22** (General Technical Aspects of Liver Resections) of this textbook.

Such changes have led to the development of new strategies to achieve complete CLM resection. Frequently used strategies aim to increase the proportion of liver parenchyma free of metastases through portal flow modulation (embolization or ligation), or to reduce the burden of metastatic disease (chemotherapy). Local ablative technologies (including radiofrequency and microwave) can be associated in the clearance of the remnant hepatic parenchyma. Portal vein embolization and ablative technologies, including technical issues, are detailed in **Chapter 7** (Portal Vein Embolization, Transarterial Chemoembolization, and Local Ablation of Hepatic Tumors). Technical aspects of liver resections are outlined in chapters in **Section 4** (Technical Aspects of Liver Resections).

Concerning anatomical and non-anatomical resections, no oncological benefit has been proven for one over another. However, a potential advantage of a non-anatomical resection is the sparing of liver parenchyma, probably making patients more suitable to repeat hepatectomies in case of liver recurrence.

The paradigm towards complete resection of all disease has also shifted towards the management of patients with liver metastases and concomitant extrahepatic metastases. Recent studies have shown that long-term survival can be obtained in patients with concomitant lung metastases or even periportal lymph node metastases, although prognosis is generally poorer. However, the presence of aortocaval lymph node metastases or multiple extrahepatic metastatic sites portends a poor prognosis, and surgical resection should generally not be performed in these patients.[21,22]

PREOPERATIVE STAGING OF PATIENTS WITH COLORECTAL LIVER METASTASES

In order to assess the extent of tumor burden, every patient that presents with potentially resectable liver metastases should be subject to careful preoperative evaluation.

To perform *a la carte* procedures, avoiding futile and/or extensive resections, accurate information concerning both intra- and extrahepatic disease must be obtained. Improved preoperative assessment, including positron emission tomography (PET) imaging, has been responsible for a decrease in the rate of non-therapeutic laparotomies over the years.[23]

Table 1. Current Criteria Defining Resectability for Surgical Resection of Colorectal Liver Metastases.

Criteria
1. Macroscopic and microscopic (R0) treatment of the disease is feasible with either resection alone or resection combined with local ablation.
2. Sufficient remnant liver volume (staged procedures should be considered). 2a. 20% if normal liver 2b. 30% if chemotherapy-associated liver injury 2c. 40% if cirrhosis
3. Vascular inflow, outflow, and biliary drainage can be preserved.

Hepatic assessment

Contrast-enhanced high quality cross-sectional imaging is routinely used to evaluate intrahepatic metastases. The role of cross-sectional imaging is to define the number, location, distribution, and relation of hepatic tumors to vascular and biliary structures.[24] This information is useful to determine resectability and to plan the best surgical approach. In addition, radiologists reviewing images should be familiar with the amount of previous chemotherapy. Changes such as sinusoidal congestion and fatty replacement are frequent in patients undergoing preoperative chemotherapy and can lead to alterations in the appearance of the liver, resulting in false positive and negative studies.

Computed tomography (CT) and magnetic resonance imaging (MRI) are the most frequently used cross-sectional methods. CT is the most often used, but emerging data suggests that MRI have a greater sensitivity.[25,26]

Triphasic contrast-enhanced CT scan has a sensitivity of 80-90% to identify liver metastases.[27–29] However, CT

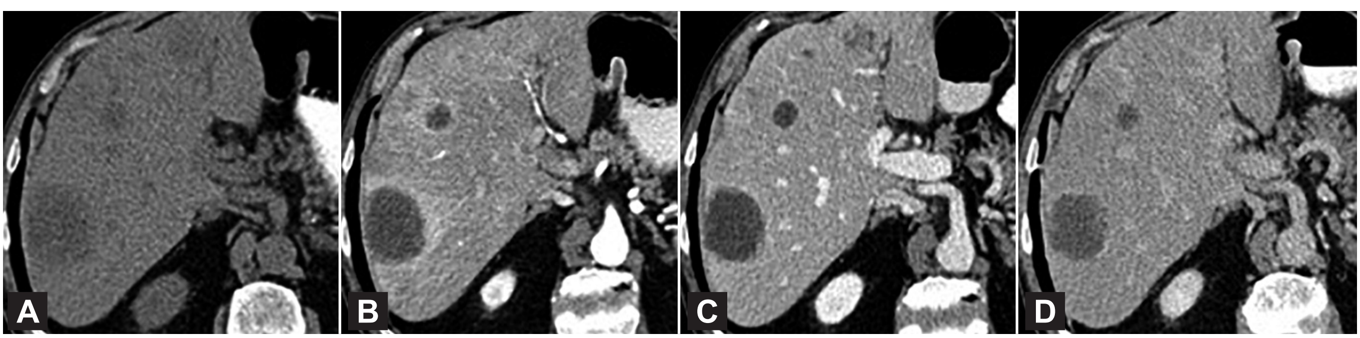

Figure 2. Colorectal liver metastases (CLM) aspect on dynamic computed tomography (CT). Lesions are poorly visualized on unenhanced CT (**A**) and demonstrate less enhancement than surrounding parenchyma on arterial (**B**), portal (**C**), and venous (**D**) phases. (*Courtesy of Dr Gustavo F Luersen, Department of Radiology, Hospital Moinhos de Vento, Brazil*)

lacks the sensitivity and ability to characterize lesions of less than 1 cm. The arterial phase is useful to define arterial anatomy and identify co-existing benign lesions. Colorectal metastases are best identified on the CT portal phase, when they usually appear as hypodense lesions (**Figure 2**). Nonetheless, CT scan is the preferred method to perform volumetric assessment.

Contrast-enhanced MRI has an accuracy of 80-90% to assess the extent of liver disease.[30–32] Compared to CT scan, MRI has the ability to potentially differentiate indeterminate lesions.[33,34] It also has a greater sensitivity for the detection of sub-centimeter hepatic tumors, especially when using liver-specific contrast agents (such as Gd-EOB-DTPA, Primovist® in Europe, and Eovist® in the USA) and/or diffusion-weighted imaging (DWI).[35–40] Like CT, detailed anatomy and volumetric data can be obtained, but without ionizing radiation exposure. Furthermore, MRI has a notable capacity to detect focal lesions in patients with hepatic steatosis. This ability makes it a particularly useful method for patients submitted to previous chemotherapy (CALI), as well as for those who are obese and/or diabetic.

Despite the potential benefits of MRI over CT, the latter is the cross-section imaging modality most frequently used for intrahepatic assessment, mostly due to its lower cost and broader availability. Moreover, the actual superiority of MRI over conventional multi-detector CT imaging in the management of these patients is still controversial, and most centers will use MRI scans selectively. A recent study with modern imaging modalities suggests that thoraco-abdominal CT provides adequate baseline evaluation, while MRI is the most rational approach to the subset of patients that will need staging and re-staging after neoadjuvant chemotherapy.[41]

The exact role of PET imaging in the assessment of intrahepatic disease remains controversial, since its sensitivity remains poorer than other imaging methods.[41–43] Importantly, it is preferable to obtain PET imaging prior to any preoperative chemotherapy since this decreases the sensitivity of F-fluorodoxyglucose (FDG) PET. Inflammatory tissues have increased FDG uptake and may result in false positive findings.

Extrahepatic assessment

A tailored work-up, according to the chance of additional metastatic disease being found and potentially change the patient management, should be performed.

Chest CT is usually indicated on preoperative assessment of colorectal cancer; however, preoperative CT scan detects sub-centimeter or indeterminate pulmonary nodules in approximately one third of patients submitted to CLM resection. Of these nodules, nearly one quarter are ultimately proven to be metastases, but they do not impact 3-year disease-specific survival after CLM resection. Thus, indeterminate or sub-centimeter pulmonary nodules seen on CT scans should not be considered a contraindication for liver resection.[44–48]

Assessment of pulmonary and other extrahepatic metastatic sites can be done by additional whole-body imaging modalities such as PET-CT and DWI MRI.

Positron emission tomography with 18-fluorodeoxyglucose (FDG PET) more recently has been introduced in the preoperative evaluation of patients with hepatic colorectal metastases. While cross-sectional imaging relies on anatomical and vascular changes in the liver parenchyma as a result of tumor growth, FDG PET imaging visualizes the increased uptake of glucose in tumor cells and is thus a form of functional imaging. When combined with CT imaging (PET-CT), FDG PET can provide an even more accurate depiction of disease spread.[49] Several studies have shown that PET imaging detects occult sites of extrahepatic disease in up to one third of patients, significantly altering clinical management in the majority of these cases.[42,43] Response to chemotherapy can be evaluated by a decrease in the standard uptake values (SUV) on PET. However, changes in SUV can lead to a decrease in the sensitivity of FDG PET. This stresses the importance of performing PET imaging before starting chemotherapy.

Diffusion-weighted MRI (DWI) is a rapidly evolving functional imaging modality for whole-body evaluation. DWI derives its image contrast from differences in the motion of water molecules between tissues. Recent comparisons with PET indicate a similar diagnostic ability of whole-body DWI (WB-DWI) in the work-up of oncological patients.[50,51] In the near future, WB-DWI will probably be performed before a PET-CT is done. WB-DWI is free of ionizing radiation and of contrast media, making it a suitable tool to optimize medical imaging workflow in metastatic patients.

In summary, often more than one imaging modality is required to gather the preoperative information needed. While CT, PET, and MRI have a comparable sensitivity for detection of large liver metastases, MRI excels at detection of sub-centimeter liver metastases and re-staging after chemotherapy. PET scan can alter clinical management in up to a third of patients, mostly due to the detection of occult sites of extrahepatic disease.

Further details on radiology of the liver can be found in **Chapter 2** (Radiological Anatomy of the Liver).

INTRAOPERATIVE ASSESSMENT AND INTRA-OPERATIVE ULTRASOUND

Before liver resection is begun, a careful intraoperative assessment of the liver and abdominal cavity should be performed to evaluate the extent of intrahepatic disease and potential presence of unexpected extrahepatic intra-abdominal disease. To prevent patients from undergoing a non-therapeutic laparotomy, some have advocated a laparoscopic assessment prior to open surgery, including intraoperative ultrasound.[52] However, with increasing accuracy of preoperative staging modalities, the rate of non-therapeutic laparotomies has dramatically decreased over recent years and is currently as low as 4.7%. Therefore, the yield of routine staging laparoscopy is considered to be low.[23]

Intraoperative ultrasound (IOUS) is an important addition to the operative evaluation of patients undergoing planned liver surgery. Not only does it provide valuable information to aid the surgeon in the planning and executing the hepatectomy, IOUS can also detect additional intrahepatic metastases as small as 3-4 mm in size. Studies have found that, even in the era of modern high quality preoperative imaging, IOUS has detected additional metastases in 1.4-10% of patients and can change the surgical strategy.[33,53–56] IOUS should always be performed using a dedicated intraoperative probe and experienced operator. Additional liver metastases are more likely to be detected in patients with multiple and hypoechoic tumors.[33,55] Moreover, the use of contrast-enhanced intraoperative ultrasonography (CE-IOUS) for patients with colorectal metastases seems to improve the sensitivity of intraoperative ultrasonography.[57] CE-IOUS may be helpful in identifying disappearing liver metastases from colorectal carcinoma after chemotherapy.[58]

Detailed techniques of IOUS can be found in **Chapter 3** (Intraoperative Assessment of the Liver).

OUTCOMES OF LIVER RESECTION FOR COLORECTAL METASTASES

Perioperative outcomes

The perioperative mortality of liver resection for colorectal metastases has decreased in recent decades, currently 1% or less in most high-volume centers (**Table 2**).[59] Complication rates remain similarly low, even following major resections. In a randomized controlled trial comparing outcomes following preoperative chemotherapy, overall mortality and morbidity was 1% and 20%, respectively.[60] One of the most important factors having an impact on the risk of adverse postoperative outcome is the presence of associated comorbidity. In one study, Breitenstein et al.[61] found that the presence of multiple comorbidities was associated with a 1.5 times increased risk of major postoperative complications. Selecting the appropriate patient for surgical therapy is important in order to minimize perioperative risk. In addition, the potential for adverse outcome and the complexity of these operations justifies the recommendation that major liver resection be performed at major centers and by experienced surgeons.[62]

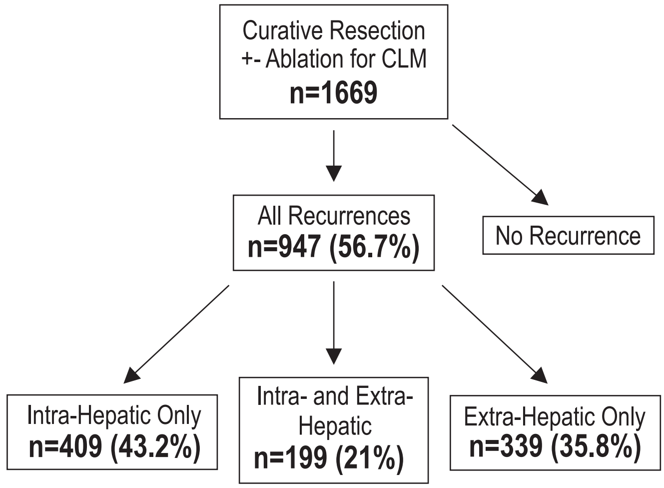

Figure 3. First site of recurrence after 1,669 curative intent surgeries for CLM with a median follow-up of 30 months. 608 (64.2%) patients presented with intrahepatic disease as a component of the first pattern of recurrence, while 409 had only intrahepatic disease. CLM: Colorectal Liver Metastases. (Adapted from de Jong et al.[72])

Further information on evaluation of risk factors and complications after liver resection can be found in **Chapter 9** *(*Morbidity and Mortality after Liver Surgery*)*.

Long-term outcomes

With increasing safety, improved imaging, and more active chemotherapy, long-term outcomes of patients undergoing resection of liver metastases has markedly improved over the years, with a median survival of up to 46 months and corresponding 5-year survival rates exceeding 50% **(Table 2)**. The actual 10-year survival rate after resection of CLM is 17-36%.[63–70] Nathan et al.,[71] using a model of conditional survival, determined that the probability of surviving an additional five years, given that the patient had already survived three or five years after liver resection, is 40% and 50%, respectively. Considering that prolonged survival can be achieved in palliative settings with modern systemic

Table 2. Studies investigating long-term and short-term outcomes after curative intent liver resection for colorectal liver metastases.

Author and year of publication	Number of patients included	Mortality	Morbidity	5-year disease-free survival	5-year overall survival
Nordlinger, 1992	1568	2%	23%	15%	28%
Fong, 1999	1001	3%	31%	Not reported	37%
Malik, 2007	700	3%	29.5%	31%	45%
De Jong, 2009	1669	Not reported	Not reported	30%	47%

chemotherapy, cure should be considered after a 5-year disease-free survival or a 10-year overall survival.

In spite of these encouraging results, approximately two thirds of patients will still develop recurrent disease after liver resection. In a large cohort of 1,669 liver resections for CLM,[72,73] recurrence was observed in 947 cases (57%) after a median follow-up of 30 months, most of them intrahepatic only. Patterns of recurrence are depicted in **Figure 3**. Of the 947 patients who experienced recurrence, 197 patients (21%) underwent repeat curative intent surgery. Extrahepatic sites of recurrence included the lung, lymph nodes, peritoneum, bone, brain, adrenal, and ovary. Another study, based on 6,025 patients from the LiverMetSurvey registry, reported a recurrence rate of 45.4% after liver resection. Recurrence occurred within six months after hepatectomy in a quarter of cases and was mainly hepatic. Outcomes were poorer in early recurrence compared to late recurrence; however, re-hepatectomy was able to restore better survival, in both early and late relapse.[74]

Several clinical risk scores have been introduced in an attempt to stratify patients by their risk of recurrence and death prior to surgical intervention. In 1999, the Memorial Sloan Kettering Cancer Center group published their *clinical risk score* based on a retrospective review of 1,001 patients.[75] Five clinical variables were used to stratify patients: i) largest tumor size >5 cm, ii) more than one hepatic tumor, iii) disease free interval <12 months, iv) node-positive primary, and v) carcinoembryonic antigen (CEA) > 200 ng/ml). The greater the number of factors, the worse the prognosis. Similarly, Nordlinger et al. proposed a slightly different scoring system, which also incorporated surgical margin status and primary tumor stage.[76] While these and other risk scores offer some guidance to the clinician, and may help in the selection of patients for perioperative management, long-term survival can be achieved even among those with poor prognostic factors, and therefore should not be used to exclude patients from being offered surgical treatment. In addition, these risk scores do not incorporate more direct measures of tumor biology, such as the preoperative chemotherapy response or other biomarkers that may be more powerful predictors of long-term outcome.[77–79]

COMBINING CHEMOTHERAPY WITH HEPATIC SURGERY

NEOADJUVANT AND ADJUVANT CHEMOTHERAPY IN INITIALLY RESECTABLE PATIENTS

Currently, first-line chemotherapeutic regimens for advanced colorectal cancer usually include 5-fluorouracil and leucovorin or capecitabine in combination with either irinotecan (FOLFIRI or XELIRI) or oxaliplatin (FOLFOX or XELOX). Response rates of approximately 40% are seen, with median survival rates in unresectable patients of approximately 20 months. While the benefit of adjuvant chemotherapy in patients with stage III colon cancer is evident, the role and optimal sequencing of chemotherapy in patients with resectable stage IV disease is less clear.

Chemotherapy can be either administered preoperatively as a neoadjuvant regimen, postoperatively as an adjuvant treatment, or pre- and postoperatively as a split regimen. In this scenario, the goal for the administration of chemotherapy is to eradicate micrometastatic disease and prevent early recurrence, and thus prolong survival. However, level 1 evidence to support this strategy is not abundant, and no data is available to compare the efficacy of preoperative versus postoperative chemotherapy. A randomized controlled trial from France (EORTC 40983) investigating the impact of perioperative FOLFOX on long-term outcome in patients with resectable liver metastases showed an improved 3-year recurrence-free survival in the surgery plus chemotherapy group, when compared to the surgery-only group (42% vs. 33%, respectively), although no benefit in overall survival was shown in this trial.[60,80] Another trial investigating the added value of adjuvant 5-fluorouracil and folinic acid showed an increase in 5-year disease-free survival in the chemotherapy group (33.5% vs. 26.7%), although no significant difference in overall survival was detected and the trial was widely criticized for using a relatively inferior chemotherapeutic regimen.[81] On the other hand, the addition of cetuximab to standard chemotherapy (oxaliplatin or irinotecan based) for patients with KRAS exon 2 wild-type tumor genotype with resectable colorectal liver metastases was evaluated in the New EPOC. This randomized trial failed to find benefits for progression-free survival with the addition of cetuximab; in fact, progression-free survival was shorter with this association (14.1 months vs. 20.5 months, p=0.03).[82]

While the precise value of neoadjuvant chemotherapy with regard to overall survival might not be clear, the application of preoperative chemotherapy may be associated with other benefits in terms of increased resection rates and improved preoperative patient selection. First, occult lesions might become apparent while on chemotherapy, thus allowing for timely alteration of patient management and preventing futile surgical intervention. In addition, progression of tumor growth while on chemotherapy is a powerful predictor of worse prognosis. A French study showed that radiologic tumor progression of multiple metastases while on chemotherapy was associated with poor outcome, reporting a 5-year survival of only 8%.[83] In addition, a major or even complete pathological response to preoperative chemotherapy seems to be an extremely powerful predictor of good survival.[79,84,85] However, predicting the pathological response based on post-chemotherapy imaging can be challenging, and many studies have shown vast discrepancies between the observed radiological response and the actual pathological response.

Despite these potential advantages, preoperative chemotherapy has also been associated with several potential disadvantages. First, patients might have disease progression to a point that their disease becomes unresectable. In addition, perioperative chemotherapy has been associated with increased complication rates. In the EORTC 40983 trial, surgical morbidity increased from 16% to 25% when preoperative chemotherapy was administered, compared to surgery alone. Other studies have also described an association between preoperative chemotherapy and postoperative morbidity, most likely mediated by chemotherapy-associated liver injury (CALI), further defined as chemotherapy-associated steatosis or steatohepatitis and sinusoidal obstructive syndrome.[86–88] For further details on the effects of chemotherapy on liver surgery, please refer to **Chapter 4** (Underlying Liver Disorders in Hepatic Surgery). For these reasons, it is generally recommended that no more than six cycles (three months) of preoperative chemotherapy should be administered in patients with resectable disease, since little oncological benefit is to be expected when chemotherapy is continued beyond this point, but the risk of liver injury and associated morbidity will continue to increase.[89]

CONVERTING UNRESECTABLE TO RESECTABLE DISEASE

High response rates with active cytotoxic chemotherapy regimens have afforded the opportunity to downsize patients initially considered unresectable. The addition of biological agents, such as those directed to vascular endothelial growth factor (bevacizumab, aflibercept, or regorafenib) or epidermal growth factor receptor (cetuximab or panitumumab) have further increased response rates and overall survival, even in patients with disease refractory to conventional first line chemotherapy. Folprecht et al.[90] reported that up to 30% of patients with initially unresectable disease and non-mutated KRAS became surgical candidates after first line cetuximab combined with either FOLFOX or FOLFIRI. Recently, in a multi-institutional trial from Japan including initially unresectable patients receiving upfront FOLFOX plus cetuximab or bevacizumab (and switch to FOLFIRI if still unresectable after six cycles), R0 resection was reached in 47% of cases (50% and 42% in the wild and mutant KRAS group, respectively, P=0.36).[91]

The goal of tumor downsizing is to be able to remove the gross residual disease from all original sites. Liver metastases located near major vascular pedicles that need to be salvaged are ideal candidates (**Figure 4**). In such cases, patients with unresectable liver metastases who would have a poor prognosis without surgery can be offered salvage resection of initially unresectable disease. In a study by Adam et al.[7] investigating the outcome of patients who underwent liver resection of initially unresectable disease, they found the overall 5-year survival was 33%, which compared favorably to those who were initially resectable (**Figure 5**). Patients that become more rapidly resectable (fast responders) seem to present better outcomes than those who need long treatment (slow responders).[92]

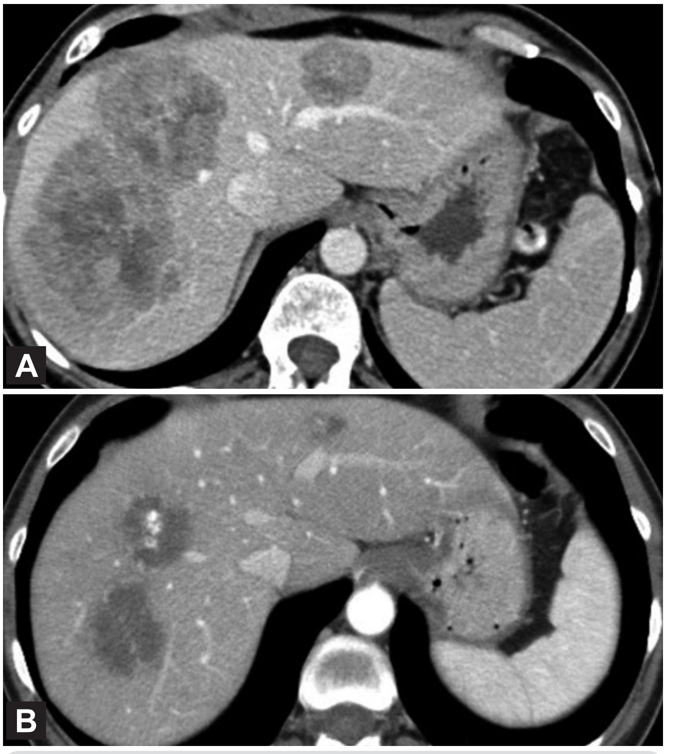

Figure 4. A) CT images of a patient with initially unresectable disease (left lesion abutting left portal pedicle); **B**) converted into resectable disease following preoperative chemotherapy. Following chemotherapy this patient was resected with a two-staged approach.

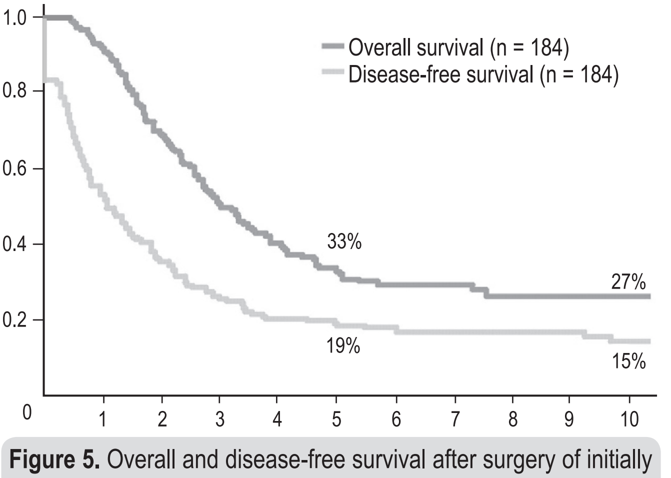

Figure 5. Overall and disease-free survival after surgery of initially unresectable metastases that underwent downsizing chemotherapy. (Adapted from Adam et al.[7])

DISAPPEARING METASTASES FOLLOWING CHEMOTHERAPY

An additional potential disadvantage of preoperative chemotherapy is related to the impact of chemotherapy on the accuracy of preoperative imaging. For example, chemotherapy-associated steatosis can significantly affect the sensitivity of preoperative CT scanning in the detection of colorectal metastases. Moreover, small liver metastases can shrink and disappear while on chemotherapy, further complicating the management of these patients (**Figure 6**). Benoist et al.[93] found that while these lesions might become completely invisible on post-chemotherapy CTscans, viable tumor cells are present in over 80% of these disappearing metastases. Other studies confirmed this discrepancy. Another study by van Vledder et al.[94] showed that viable tumor cells were present in approximately half of all disappearing lesions. In this study, disappearing metastases were common in patients undergoing preoperative chemotherapy, with approximately 25% of patients having at least one lesion disappear. Patients with multiple and small lesions were more likely to have lesions disappear. Importantly, when carefully assessed intraoperatively, approximately 50% of these lesions were detected with IOUS. Moreover, overall survival was not significantly affected if some of these disappearing liver metastases were left surgically untreated, possibly due to the opportunity of these patients to undergo repeat surgical intervention when a recurrence in these untreated lesions was observed during follow-up. In general, it is recommended to completely resect or ablate all known disease sites prior to chemotherapy, to prevent early recurrence and the need for re-operation. In selected cases, small metastases likely to disappear in the future remnant liver after preoperative chemotherapy may be marked with coils before chemotherapy.[95]

EXPANDING THE ROLE OF SURGICAL THERAPY FOR COLORECTAL LIVER METASTASES

MULTIPLE BILATERAL DISEASE

The resectability of multiple hepatic metastases that are not likely to be resected by wedge resections could be increased by using surgical options such as portal vein embolization, two-stage hepatectomy, and resection combined with ablation.[9]

Portal Vein Embolization

Portal vein embolization (PVE) is a well-established strategy to optimize the volume and function of the future remnant liver (FRL) before hepatectomy, reducing the risk of postoperative liver failure. More commonly, preoperative right portal vein embolization (with or without segment 4 portal branch embolization) is performed three to six weeks before right trisectionectomy in patients with FRL less than 30% of total liver volume in patients with CLM (**Figure 7**). Liver metastases (in both embolized and non-embolized lobes) usually have an increased growth rate following PVE and contralateral lesions can developed; however, the impact on recurrence and on overall survival after liver resection is not clear.[96–101] Chemotherapy before PVE or between PVE and hepatectomy seems to reduce tumor progression, improve long-term survival, and does not impede liver hypertrophy.[102–104] About one third of patients requiring preoperative PVE do not reach resection due to disease progression. For further details on PVE, please refer to **Chapter 7** (Portal Vein Embolization, Transarterial Chemoembolization, and Local Ablation of Hepatic Tumors).

Two-Stage Hepatectomy

Another approach in patients with bilateral metastases is a two-stage approach, in which partial resection is performed in the first stage, followed by a second resection after hypertrophy to complete the disease resection (**Figure 8**). Using this

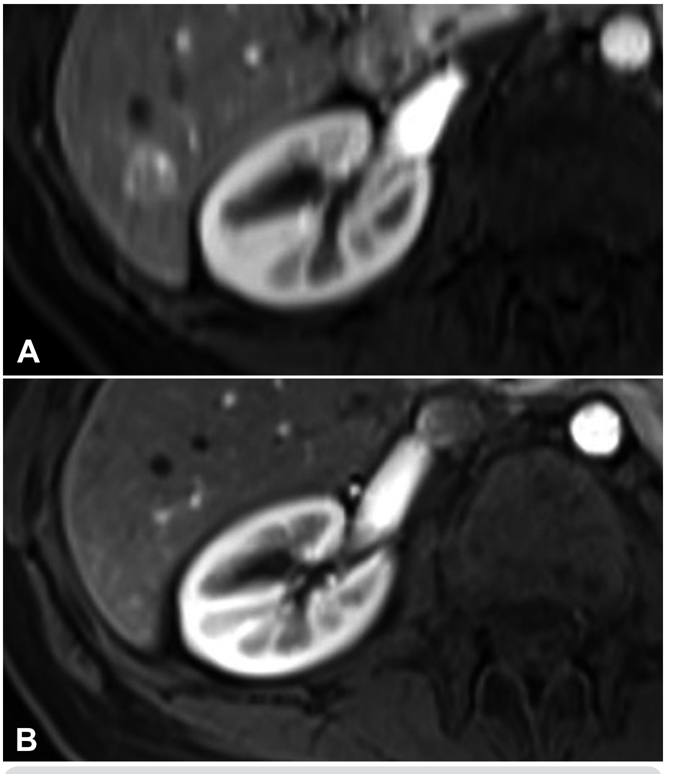

Figure 6. Missing colorectal liver metastases (CLM). **A**) T1-weighted magnetic resonance imaging (MRI) showing a CLM on segment 6 (arrow). **B**) After two months of oxaliplatin-based chemotherapy, the lesion is no longer visible. (*Courtesy of Dr Gustavo F Luersen, Department of Radiology, Hospital Moinhos de Vento, Brazil*)

technique, one hemiliver is cleared of all macroscopic disease during a first operation by either resection or ablation. Most commonly, the minor resection is performed first (usually resection of all metastases from the FRL) followed by the major contralateral resection, in order to avoid gross disease present in the hypertrophying liver. In some cases, the first operation can be combined with portal vein ligation (or postoperative PVE) of the contralateral liver that will be resected later (**Figure 9**).[105] Several studies haveshown that approximately two thirds of patients will be able to complete both stages of the resection without disease progression, and that prognosis of those patients is comparable to one-stage resections.[106]

The associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) procedure is an alternative to PVE for increasing the FRL, in which right portal vein ligation and in situ splitting of the liver parenchyma is performed during the first stage, and after one to two weeks resection is completed. This procedure can be used after ineffective PVE. ALPPS presents high rates of morbidity and mortality, and future studies are required to clarify the benefits of this approach.[107,108]

In general, two-stage procedures allow selection of patients with favorable biology.

Resection Combined with Ablation

In some cases of unresectable disease, surgical resection can be combined with local ablative therapies to achieve complete local therapy of liver metastases. While a wide variety of ablative methods are available, radiofrequency ablation (RFA) is the most commonly used ablation method. More recently, microwave tumor ablation is gaining in popularity. In both approaches, direct tissue heating at the tumor site results in tissue denaturation and cell death. As with resection alone, a curative-intent strategy that utilizes RFA requires the goal of complete ablation in order to achieve durable local control at the site. A preponderance of evidence is emerging that RFA is most successful in small tumors (<3 cm) and those located away from major vascular structures.[109] Yet, it is often such situations in which the disease cannot be resected. Local recurrence rates after ablation vary significantly in reported series, ranging from 4% to 40%. A systematic review and meta-analysis investigating factors associated with local recurrence after RFA found an overall local recurrence rate of 14.7% for colorectal liver metastases treated with RFA.[110]

Outcomes regarding overall and disease-free survival following ablation, with or without resection, are difficult to compare to resection alone given the significant differences in patient selection and other biases. Indeed, de Jong et al. found that, although long-term survival was lower in patients undergoing ablation versus resection (**Figure 10**), oncological characteristics were significantly different, clearly impacting the ability to compare groups in any cohort study.[8,111]

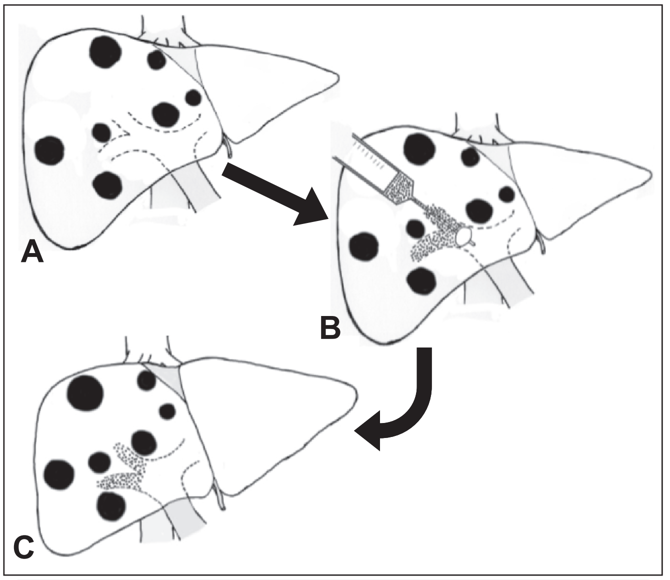

Figure 7. Portal vein embolization. **A**) Schematic representation of multiple colorectal liver metastases and a small future remnant liver (left lobe). **B**) Percutaneous right portal vein embolization (with or without segment 4 portal branch embolization) is performed. **C**) Future remnant liver hypertrophy usually occurs 4-6 weeks after portal embolization and right trisectionectomy is possible.

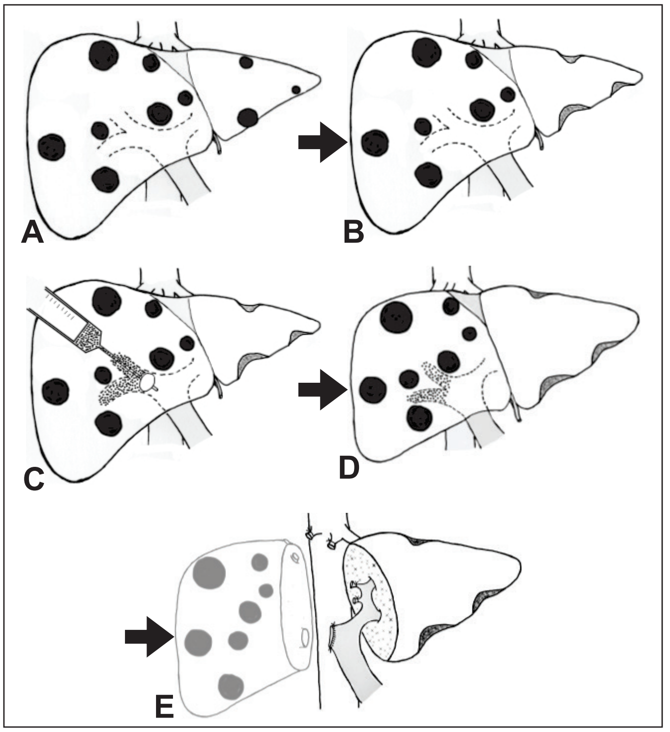

Figure 8. MSchematic representation of two-stage hepatectomy. **A**) Multiple bilateral colorectal liver metastases; **B**) enucleation of CLM of segments 2 and 3 (occasionally, deep located lesions may be ablated); **C**) Right portal vein embolization (with or without segment 4 portal branches embolization) or right portal vein ligation; **D**) Hypertrophy of non-embolized segments (future remnant liver); and E) Extended hepatectomy, usually 4-6 weeks after portal vein occlusion.

HEPATIC RESECTION AND EXTRAHEPATIC DISEASE

Extrahepatic disease commonly includes portal lymph node metastases, peritoneal metastases, and lung metastases, but other sites can be involved. Until recently, the simultaneous presence of hepatic and extrahepatic disease was considered an absolute contraindication to resection due to poor survival. However, recent studies have reported 5-year overall survival rates of up to 42% for selected patients with extrahepatic disease undergoing R0 resection.[21,112–114] These results suggest that surgery could have a role in highly selected patients with limited extrahepatic disease, i.e. with a single extrahepatic site and/or few metastases. Despite acceptable long-term results, recurrence occurs in the vast majority of these patients and this approach should not be considered curative. A recent review suggested that extrahepatic tumors limited to the lung and associated with little extension of hepatic disease (fewer than three lesions) resulted in the best outcomes in the setting of extrahepatic disease.[114] In fact, isolated lung metastasis was the only significant predictor of survival in the evaluation of a prognostic model for concomitant extrahepatic disease.[115]

Lymph node metastases

Microscopic lymph node involvement is present in approximately 15% of patients with liver metastases. It is associated with poor prognosis and generally represents a contraindication to liver resection.[116] However, some challenging points should be considered. First, prediction of metastatic lymph nodes in the hepatic pedicle can be difficult, preoperatively or even intraoperatively. Second, complete hepatic pedicle lymphadenectomy can result in long-term survival if nodal involvement is limited to the hepatic pedicle. However, it is unclear if these results can be extrapolated to patients with grossly enlarged nodes. Thus, hepatic pedicle nodal involvement may not be an absolute contraindication to surgery in selected cases. But there is no evidence that routine portal lymphadenectomy improves oncological outcomes.[117,118] On the other hand, celiac and/or para-aortic nodal involvement is rarely associated with long-term survival.[119–121]

Lung metastases

Retrospective data suggest that simultaneous resection of limited pulmonary and hepatic metastases in selected patients results in long-term survival.[122] Recurrence is frequent in this group of patients, but re-resection allows for adequate overall long-term survival.[123–128] Synchronous hepatic and pulmonary resection can be safely performed, especially if no extended resections are needed. Staged approach could be preferred if liver or lung surgery is likely to be complex, and in this situation the more severely involved organ is treated first. Thus, the presence of pulmonary metastases should not preclude hepatic resection in selected cases if lung disease can be resected or ablated.[129,130]

Peritoneal metastases

Peritoneal metastases is often observed in patients with advanced stage primary tumors. Limited peritoneal disease alone (without other metastatic sites) treated by

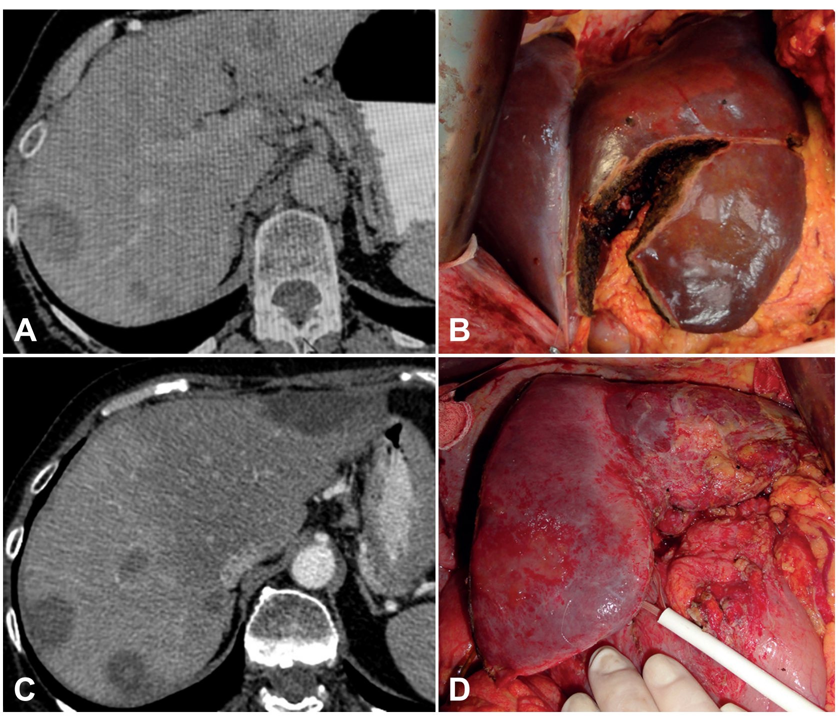

Figure 9. Two-stage hepatectomy for bilateral colorectal liver metastases (CLM). **A**) Preoperative computed tomography (CT) in a patient with multiple CLM in right hemiliver and two lesions in segment 3 (bigger lesion showed). **B**) Intraoperative view during first stage (segmentectomy 3 and right portal vein ligation). **C**) CT 6 weeks after the first stage. Note the hypertrophy of the left liver, arterialization of the right hemiliver (higher density than left hemiliver during arterial phase) and the area of resection of segment 3 (arrow). **D**) Intraoperative view after the second stage (right hepatectomy).

cytoreduction and intraperitoneal chemotherapy has resulted in favorable long-term survival, similar to patients with liver-only metastases undergoing R0 resection. The presence of concomitant but limited extent peritoneal and hepatic disease should not be an absolute contraindication to radical synchronous surgery in selected patients, since 3-year survival rates can reach 55%.[131–133]

In summary, the site of extrahepatic disease, the number of tumors, the ability to undertake a complete resection, responsiveness of disease to chemotherapy, and favorable tumor biology might guide a careful selection of patients that can benefit from radical surgery.

MANAGEMENT OF SYNCHRONOUS LIVER METASTASES AND PRIMARY TUMOR

Synchronous CLM are thought to have less favorable cancer biology and are associated with poorer long-term outcomes.[134] Particular consideration should be given to the patient with synchronous resectable liver metastases and a primary tumor that is still in place, as the options regarding management can be many. Current treatment strategies include various sequences and timing for therapeutic modalities. As with metachronous metastases, the management goals remain the same – complete resection of all macroscopic metastatic disease and integration of systemic therapy, as well as resection of the primary tumor.

Colorectal-first approach. In the past, patients with synchronous metastases traditionally underwent a resection of their primary tumor first, followed by a period to recuperate and potentially undergo systemic chemotherapy, followed by a subsequent staging and liver resection to address their metastases three to six months after colorectal resection. More recently, systemic chemotherapy has often been employed first in order to define the biology before embarking on surgical therapy, particularly in the asymptomatic patient. The main disadvantage of this strategy is the progression of CLM beyond resectability during the primary tumor resection, especially in case of postoperative complications after colorectal surgery. In fact, only a minority of patients with synchronous disease complete the planned treatment using a colorectal-first approach.[135]

Simultaneous resection. Combined liver and bowel resection, with or without preoperative chemotherapy (or chemoradiation for rectal primary) has been shown to be safe in many cases.[136–141] Perioperative morbidity and mortality rates are similar when a bowel resection is associated with a minor hepatectomy.[139,142,143] In general, it is acceptable to perform a major colorectal procedure and a minor hepatic resection and vice-versa. However, simultaneous major colorectal and major hepatic resections should be avoided or limited to experienced centers.[144] During simultaneous resection, the liver is usually approached first to avoid congestion with increased risk for the digestive anastomosis. Data regarding oncological outcomes after simultaneous versus staged resections for stage IV colorectal cancer are more limited. Despite this, possible equivalent overall and disease-free survival rates, regardless of timing of resection, have been suggested.[145]

Liver-first (or chemotherapy-first) approach. A reversed or liver-first staged approach can be taken.[146] The liver-first approach comprises initial preoperative chemotherapy followed by liver resection and subsequent colorectal resection, with chemotherapy or chemo-radiation between surgeries. The rationale for the liver-first approach is to provide early systemic treatment for patients with stage IV colorectal cancer and to prevent progression of the liver disease while surgery of the primary tumor is undertaken.[146–148] As complications of digestive surgery can delay systemic treatment and enable progression of hepatic tumors, this strategy is particularly useful if digestive anastomosis is risky in patients with extensive liver disease (potentially resectable or initially unresectable). Also, preoperative chemotherapy may reduce the size of CLM, allowing for more conservative liver surgery or resection of initially unresectable disease. Thus, patients with unresectable or marginally resectable synchronous CLM and asymptomatic primary tumors could be initially treated by first-line chemotherapy, followed by liver resection if technically possible. Also, in some symptomatic patients, the primary tumor can be left *in situ* and managed endoscopically (i.e. by stent) or with a diverting ostomy to allow early initiation of systemic chemotherapy. Long-term survival outcomes with this approach are variable.[148,149]

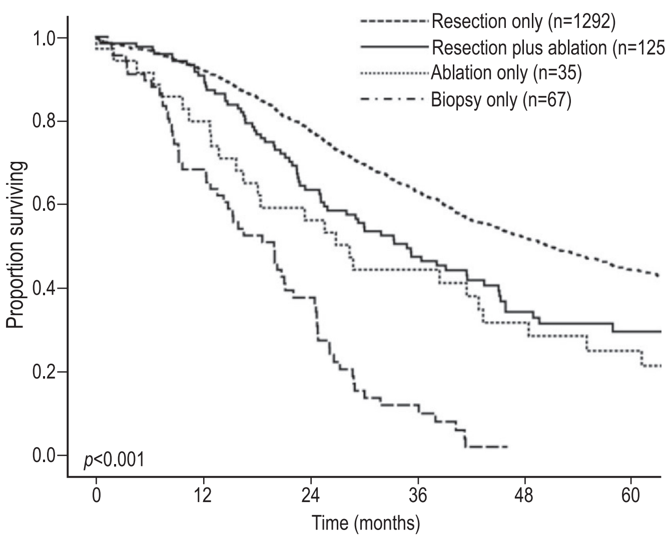

Figure 10. Kaplan Meyer curve showing overall survival in patients undergoing resection only, resection combined with ablation, or ablation only. (Adapted from de Jong et al.[8])

Up-front hepatectomy. Patients with resectable synchronous CLM may undergo liver resection prior to chemotherapy. This strategy has the potential advantage of avoiding the risks related to chemotherapy-associated liver injury and the challenging management of missing liver metastases. Moreover, the oncological benefits for initially resectable CLM are not clear.[80,150–153] On the other hand, neoadjuvant chemotherapy would allow for proper selection of patients, avoiding unnecessary surgery in chemoresistant disease. Such a strategy may be particularly useful in patients with resectable liver metastases and an asymptomatic primary rectal tumor, especially when chemoradiation therapy is being considered prior to proctectomy.

Although no well-defined guidelines are present regarding the optimal management of patients with synchronous disease, any one of the aforementioned strategies can be considered, based on multidisciplinary evaluation.[154] Individual treatment should consider multiple factors, including the presence of symptoms, location of primary tumor and liver metastases, extent of tumor (both primary and metastatic), dominant disease (colorectal or liver), patient performance status, and underlying comorbidities.

In summary, the general directions for the approach of synchronous CLM include: colorectal-first or simultaneous resection for patients with symptomatic primary tumor; chemotherapy-first for initially unresectable or marginally resectable CLM, followed by liver resection if feasible; and up-front hepatectomy or neoadjuvant chemotherapy for patients with initially resectable CLM.

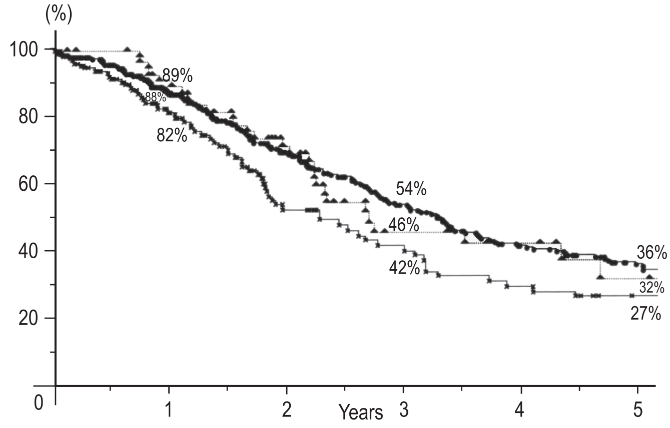

Figure 11. MCumulative survival after the last hepatectomy in patients with only 1 (–•–), only 2 (–×–), or 3 (–▲–) hepatectomies. (Adapted from Adam et al.[156])

REPEAT LIVER RESECTION

Among the two-thirds of patients who will develop recurrence following apparently complete resection of colorectal liver metastases, approximately 50% will develop isolated recurrences again within the liver.[72,73] For these patients, repeat resection can be considered. As with the evaluation for initial resection, defining resectability should be based on the ability to achieve complete removal of macroscopic disease with preservation of sufficient functional liver parenchyma. If these criteria are followed, repeat hepatectomy (second, third, fourth) is associated with comparable perioperative outcomes to that after primary liver surgery.[155] Several studies have shown that long-term outcomes and patterns of recurrence of repeat resection are comparable to initial resection (**Figure 11**)[53, 156] Clearly, patients offered repeat resection are typically those with favorable biology and few comorbid conditions. In such cases, major resection is performed less commonly and tumor ablation is performed more frequently. The favorable outcomes following repeat surgical therapy support the need to consider a local strategy in patients with recurrent colorectal liver metastases (**Figure 12**).[157,158]

LAPAROSCOPIC APPROACH

Laparoscopic hepatectomy has been increasingly performed in specialized centers. Laparoscopic approach for CLM seems to result in short-term benefits regarding surgical blood loss and operative transfusion rate, hospitalization time, and surgical morbidity.[159–163] Regarding oncological outcomes, laparoscopic resection provides similar benefits to open surgery, with 5-year overall survival rates of 36-

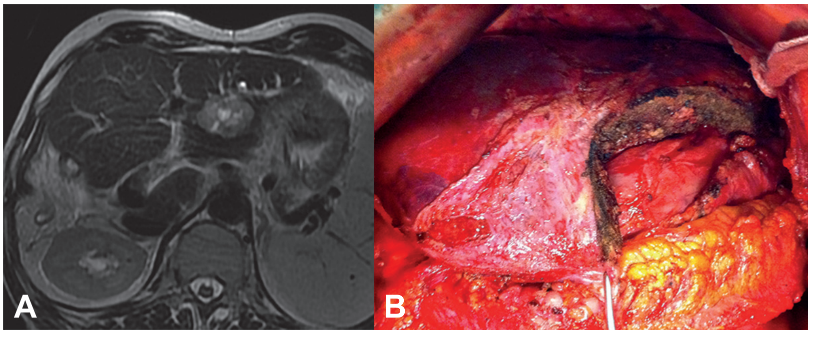

Figure 12. Second hepatectomy for hepatic recurrence 5 years after right hepatectomy for colorectal liver metastases. **A**) T2-weighted magnetic resonance imaging reveals lesion on segment 3 (arrow) in the remnant liver; **B**) Intraoperative aspect of the second hepatectomy (segmentectomy 3). Patient is alive and free of recurrence 3 years after re-hepatectomy.

64%.[162–168] Laparoscopic simultaneous resection of the primary tumor and liver metastases is also an option in selected cases.[169,170] Technical and oncological aspects of laparoscopic liver resections are discussed in **Chapter 27** (Principles of Laparoscopic Liver Resections).

FINAL CONSIDERATIONS

Surgical therapy for colorectal liver metastases has been shown to be increasingly effective. Preoperative staging and intraoperative assessment are important to achieve safe and complete resection of all sites of disease. Current methods for increasing the ability to offer liver resection include preoperative chemotherapy, staged resection, and ablative strategies. In the future, one can anticipate an increasing use of local therapies of colorectal metastases, particularly as systemic chemotherapy improves. The use of minimally invasive approaches, including laparoscopic and robotic resection, will likely increase, in addition to other non-resectional techniques.

SUGGESTED READING

Choti, M. a. *et al.* Trends in Long-Term Survival Following Liver Resection for Hepatic Colorectal Metastases. *Ann. Surg.* **235**, 759–766 (2002).

A large single-center study in hepatic resection for colorectal liver metastases showing a recent improvement in overall survival. Predictors of long-term survival are identified.

Wicherts, D. a *et al.* Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases. *Ann. Surg.* **248**, 994–1005 (2008).

This large series of two-stage hepatectomy demonstrates the feasibility and usefulness of this technique for selected patients with extensive bilobar colorectal liver metastases. Overall five-year survival was 42% for 41 patients that completed a second hepatectomy (69% of patients planned for a two-stage procedure).

Pawlik, T. M. *et al.* Effect of Surgical Margin Status on Survival and Site of Recurrence After Hepatic Resection for Colorectal Metastases. *Ann. Surg.* **241**, 715–724 (2005).

This paper evaluates the effect of margin status on long-term survival and recurrence after resection of colorectal liver metastases. This large series shows that a margin of 1 mm to 4 mm results in similar margin recurrence to wider margins.

Nathan, H. *et al.* Conditional survival after surgical resection of colorectal liver metastasis: an international multi-institutional analysis of 949 patients. *J. Am. Coll. Surg.* **210**, 755–64 (2010).

Multi-institutional study including almost 1,000 patients that underwent colorectal liver metastasis resection. Prognostic scoring systems are evaluated and another method of prognostic information (conditional survival) is proposed to estimate the survival after hepatectomy for colorectal liver metastases.

de Jong, M. C. *et al.* Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. *Ann. Surg.* **250**, 440–8 (2009).

This large multi-institutional series found recurrence after resection of colorectal liver metastases in more than half of patients. Most recurrences were intrahepatic only, allowing for repeated resection in selected patients, with similar recurrence-free survival.

Pulitanò, C. *et al.* Liver resection for colorectal metastases in presence of extrahepatic disease: results from an international multi-institutional analysis. *Ann. Surg. Oncol.* **18**, 1380–8 (2011).

A large multi-institutional study including 171 patients that underwent resection of colorectal liver metastases and extrahepatic disease.

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