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NEW STRATEGIES IN LIVER SURGERY FOR IV STAGE METASTATIC COLORECTAL CANCER

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ABSTRACT

With recent advances in chemotherapy, traditional clinicopathological factors should not be used to exclude otherwise resectable patients from surgery. Pathological or clinical response to chemotherapy has become valuable in determining the treatment for individual patients. Portal vein embolization and two-stage operation with ablative therapy and preoperative chemotherapy should be considered for unresectable liver metastases located in a liver remnant that is at the minimum volume required for survival. The recent E0RTC 40983 trials regarding preoperative chemotherapy for resectable CLM have failed to demonstrate a clear significant advantage. However, patients with a low clinical risk score for the recurrence, such as several metastases of less than 4 cm, and who are fit candidates for liver resection are often offered immediate surgery. Patients at high clinical risk should also be considered for neoadjuvant chemotherapy. One forthcoming and appealing strategy is to adapt postoperative treatment according to tumor response as evaluated by neoadjuvant chemotherapy or by the presence of individual tumor biomarker such as the Kras mutation or single-nucleotide polymorphisms. This could avoid the overtreatment of nonresponsive patients and enable a more tailored approach to treat an individual patient's disease. The treatment paradigm for CLM is rapidly changing with the development of newer anticancer chemotherapeutic agents.

Key words: colorectal cancer, liver metastases.

INTRODUCTION:

The second leading cause of cancer-related mortality worldwide is colorectal cancer. In the United States, more than 140,000 patients are diagnosed and 56,000 die of this disease on early basis.[1] At the time of diagnosis 85% of the patients are appropriate for resection at the time of diagnosis and the disease recurs in more than 50% of the patients in the first five years. Most frequently the metastases affect the liver (in 30% to 60% of cases), and the lung (in 20% to 30% of the cases). At presentation up to 25% of colorectal cancer patients have liver metastases, and a another 30% develop liver metastases usually until the second year after primary tumor resection.[2] Leaved without treatment the patients with colorectal liver metastases have median survival as 12 to 15 months and 5-year survival less than 5%. In spite of the introduction of a many new agents the median survival for patients with stage IV disease treated with the best chemotherapy remains only 25 months.[3, 4] Liver resection remains the best option for achieving long-term survival despite the new treatmen modalities. No consensus is available on if aggressive surgery is proper for CLM; there are some arguments the survival benefit after this procedure is due to better patient selection rather than of the treatment strategy. The tumor biology is probably prevailing no matter of the treatment applied. Therefore the only way to change the disease course for some patients is complete hepatic resection for CLM and integrated therapy with surgery and systemic chemotherapy is of increased importance. Patients with CLM previously considered as unresectable now have a chance for a curative resection because of the new development in multimodality treatment. Now the 5-year overall survival rate after surgery reaches 58%. [5–10]

EVALUATION OF LIVER SPREAD

A systematic and rigorous assessment of preoperative liver is the careful selection of patients for surgery. The detection of CLM has improved over the past decade, and various imaging techniques are now available for monitoring patients with colorectal cancer are available. In general, thin slice multiphase helical computed tomography (CT) is the preferred method of imaging for the detection of CLM, as it is the technique most widely used. It can be scan the chest, liver, abdomen and pelvis in the same exam, and through the various stages of analysis provides detailed anatomical associations of vascular tumors and in planning the resection liver. A similar alternative that is preferred by some centers is the magnetic resonance imaging (MRI) with a combination of gadolinium and contrast enhanced with superparamagnetic iron oxide.

Fluorodeoxyglucose positron emission tomography (FDG-PET) appears to be a useful for the detection of extrahepatic disease,[5] but is its ability to evaluate the liver itself is limited because the detection of intrahepatic lesions is poor, especially after chemotherapy.[11] A recent meta - analysis showed that FDG-PET has better sensitivity in detecting liver metastases of colorectal cancer (94.6%) than

helical CT (64.7%) or MRI 1.5T (75.8%).[12] The lower resolution of FDG-PET remains the disadvantage over CT or MRI, and its specificity, particularly in patients, with preoperative chemotherapy. Finally, FDG-PET provides no anatomical details required for surgical planning. In this way, the role of FDG-PET in patients with CLM can be determined. Although some authors claim diagnostic laparoscopy being beneficial to improving patient selection for hepatic resection of CLM,[13] the improved preoperative imaging gives the laparoscopic staging an inferior role. In addition to a careful evaluation of the liver and extrahepatic involvement, an accurate measurement of the liver is mandatory in the evaluation of candidate patients for major hepatectomy in order to evaluate the remnant liver and the need for preoperative portal vein embolization.[14] Volumetric data from are obtained from multiphasic CT imaging for the staging and surgical planning. The concept of the liver volume and the clinical significance are discussed later in this article.

Definition of resectability

The main oncological contraindications for surgery of the liver are the presence of unresectable liver disease and the presence of extrahepatic disease (Table 1).

Tab. 1. Contraindications to resection of colorectal liver metastases

Relative	Absolute
Extra hepatic metastases	Peritoneal carcinomatosis
Colonic recurrence	Multiple extrahepatic metastases
Solitary resectable peritoneal metastasis	Inability to perform hepatic RO resection
Hilar lymph nodes metastases	

In the past, resection of CLM has been performed in patients with more than three metastases, a negative resection margin expected less than 1 cm, or extrahepatic disease. However, recent studies have shown that long-term survival is possible even in patients with these clinical and pathological factors, and as such, the definition of resectability has evolved from tumor characteristics, such as tumor size and number to the possibility for complete resection of both extra- and intrahepatic (R0 resection). Another interpretation is that there is a shift away from focusing on the tumor to what will be left after resection (remnant liver). Currently, CLM should be considered resectable if the patient has no underlying liver disease and has at least two adjacent liver segments (not less than 20% of the remnant liver) that can be preserved with an adequate vascular flow, outputs and drainage of the bile ducts.[14, 15] The following sections are milestones in the discussion about contraindications, including a discussion of prognostic factors, selection factors and respectability.

Number of metastases

Multiple metastases and the presence of bilobar disease correlate with a worse prognosis, especially in cases where more than four metastases are involved, because this case is associated with an increased risk of extrahepatic disease and relapse after systemic surgery. In fact these patients generally take a broad pre-operative investigation. The use of FDG-PET may be particularly useful for detecting extrahepatic disease in patients at high risk. Pawlik et al.[5] recently reported on a cohort of 6 patients with more than four metastases treated with multimodal therapy, including preoperative chemotherapy. The 5-year disease-free survival and overall survival was 22% and 51% respectively after liver resection. Similarly, Kokudo et al,[16] reviewed patients from Tokyo with a high number of metastases, established that although the number of metastases is negative prognostic the surgery for CLM is still the only curative treatment. Up to 70% and 80% of the liver can be resected safely, and the mortality rate after liver resection is almost zero.[17] Therefore, the number of metastases should not be considered a contraindication for curative liver resection, but a prognostic factor, able to be overcome by surgery and systemic chemotherapy in selected patients

Surgical margin

Historically, at least 1 cm margin is required for safe surgical resection. Resections with an expected margin of less than 1 cm are often defined as “non radical” and sometimes considered as a contraindication for resection. Study of the real margin relapse showed that the margin of 1 cm is not beneficial to the probability of survival. In a series of 557 patients multicenter report by Pawlik et al, showed that although the positive surgical margin (R1) there is a slightly increased risk of local recurrence of the tumor (11%) and the width cannot predict the increased risk of margin recurrence or survival.[7] Similarly, other studies have shown that non-anatomic resections, which are usually associated with a minimum margin, are not associated with an increased risk of local recurrence after surgery.[18, 19] These studies have clearly shown that the expected minimum margin should not be considered as an contraindication against resection.

Hilar lymph nodes metastases

Whether resection of CLM is indicated in patients with hilar and perihepatic lymph node metastases is controversial. These lymph node metastases may predict a poor prognosis after surgery for CLM. Jaeck et al.[20] recently demonstrated that hilar and perihepatic lymph node metastases have strong negative influence on prognosis in comparison with multiple bilobar liver metastases, and that they are related with increased level of carcinoembryonic antigen, or even the presence of a solitary resectable peritoneal disease. Therefore, the presence of hilar lymph node metastases is usually a contraindication to resection of CLM and could be considered a good indicator of the need for preoperative chemotherapy in patients with unresectable disease at presentation. However, the precise role of lymphadenectomy during surgery for CLM needs to be clarified.[14]

Extrahepatic spread

Several authors have reported the long-term survival in patients with unresectable CLM and extrahepatic disease. Elias et al.[21] found survival rate of 28% in 5 years for patients with more than five metastases and extrahepatic sites of several diseases treated with radical surgery. Other studies have shown that long-term survival can be expected after complete resection of pulmonary metastases of colorectal cancer, even when metastases are detected in the same time as CLM. Selection criteria for patients for lung resection are under investigation. It is generally accepted, however, that the patient be considered for lung resection if it is technically feasible and there is no evidence of hilar or paracardiac engagement. With strict selection criteria, the operation of CLM with extrahepatic sites achieves survival rate of 78% after 3 years and 56% after 5 years.[22]

Surgical technique

Some attempts have been clarify the importance of anatomic and non-anatomic (limited) partial liver resection for CLM. A recent systematic review that compared the results after limited resection vs. anatomical CLM showed no difference in tumor clearance, relapse or long-term survival.[25] In other words, the anatomic resection is not superior to limited resection for CLM from an oncological point of view. Applying the principle that the outcome depends on complete resection of metastases both anatomical resection and non-anatomic (or a combination) should be used eradicate the disease. This analysis confirms the finding that the tumor biology and not the type of resection is important for the prognosis.

Intraoperative ultrasound

Since its introduction before 20 years, it is widely used by hepatobiliary surgeons.[26] Several studies have shown that this method complements the preoperative cross-sectional area. In experienced hands, IOU may show additional lesions in 10% to 15% of patients, although improvement of the preoperative studies can reduce of this advantage of the IOU. More importantly, IOU is much important for planning the parenchymal transection and the relationship between the tumor and vascular structures and intrahepatic bile to define the complete removal of the tumor and preservation to ensure that vasculobiliary essential structures.[27] The recent introduction of contrast-enhanced IOU may improve intraoperative staging.[28]

Hemostasis

One of the most powerful and independent prognostic factors after hepatic resection is the amount of blood loss during surgery.[29, 30] Maintenance of low central venous pressure, normally less than 5 mmHg has been shown to reduce blood loss from hepatic veins and liver parenchyma during liver transection.[31, 32] Different methods for reduction of the intraoperative bleeding have also been developed, such as continuous or intermittent pedicle clamping (Pringle maneuver), tightening hemi-liver and total vascular exclusion with or without clamping of the inferior vena cava[33] The majority of elective resection can be performed safely with intermittent pedicle clamping in general and the use of total vascular exclusion is rarely necessary and is usually[34-36] with hemodynamic changes resulting in increased in postoperative morbidity and mortality. Newly developed devices such as high frequency coagulants, saline-linked cautery and ultrasonic dissectors allow hemostatic parenchymal transection with minimal blood loss.[37] However a prospective randomized study showed no significant difference in blood loss when surgery was performed using new devices for dissection or traditional crush technique.[38] The contribution of postoperative anesthesia is also remarkable. The use of continuous epidural anesthesia provides optimal pain control so that the lung function is improving (used to be a problem in patients with upper abdominal incision), and leads to early mobilization of patients, which significantly reduces morbidity.

SHORT TERM AND LONG-TERM RESULTS

Hepatic resection is a well established procedure, with a mortality rate of less than 5% and morbidity less than 30% to 40%. Important factors for poor prognosis after liver resection are intraoperative bleeding, perioperative transfusions, insufficient remnant liver and infectious complications. These conditions can be devastating if lead to liver failure, which occurs in less than 4% of cases. Proper patient selection, meticulous technique and careful intraoperative and postoperative management are essential to minimize surgical complications. Table 2 shows the long-term results of several published series number of liver resection for CLM, and includes the most important predictors of relapse.[5, 7-9, 19, 39-48]

Tab. 2. Table 2. Predictors of recurrence and long-term survival after resection for colorectal liver metastases

Author, Year	Rl Status	Synchronous Presentation	Primary Nodes +	Size of Metastases	No. Metastases	Preoperatlve CEA	Extraliepatic Disease	5-Year Survival
Fernandez, 2004[5]		-	-	-	+	-		58%
Pawlik.2005[7]	+	-	-	+	+	+		58%
Abdalla, 2004[8]	+	-		+	+			58%
Choti.2002[9]	+	-	-	-	+	+		58%
Elias, 1998[19]	+	+	-	-	-	-	-	28%
Gayowski, 1994[39]	+	+	+	-	+	-	+	32%
Scheele, 199540	+	+	+	+	-	-	-	40%
Nordlinger, 1996[41]	+	+	+	+	+	+		28%
Jaeck, 1997[42]	+	+	+	+	+	+	-	26%
Jamison, 1997[43]	-			-	-			32%
Jenkins, 1997[44]	+			-	-		+	25%
Ambiru, 1999[45]	+	-	+		+	+		23%
Fong, 1999[46]	+		+		+	+	+	46%
Minagawa, 2000[47]	-		-	-	+	-	-	38%
Figueras, 2001[48]	+	-			+	+	+	53%

CEA, Carcinoembryonic antigen.

As reported despite the growing number of resections for CLM, the survival rate at 5 years is now over 51% to 58% in mono-and multi-institutional studies.[5-10] Interestingly, recent studies with patients with advanced multiple and bilateral disease, which was considered not suitable for resection until a few years, the preoperative systemic chemotherapy has proven to achieve long-term survival. The most important clinicopathological factors, which are useful for the prediction of prognosis after liver resection for CLM, are the margin status, the level of the colon tumor and primary location, preoperative carcinoembryonic antigen level, size and number of lesions and the presence or absence of extrahepatic metastases. These prognostic factors determined before the advent of effective systemic chemotherapy, but their relevance as prognostic indicators in this new era of management CLM is unknown. With advances in molecular biology techniques factors such as hTERT are potential prognostic indicators and emerging markers may become more accurate than clinical factors.[23]

New tactics to improve resectable cases

Advances in systemic chemotherapy combinations in conjunction with advances in surgical technique and patient selection has improved considerably the population of patients with potentially curative resection of CLM can be expanded. Examples of relatively new techniques include preoperative chemotherapy, portal vein embolization, two-stage hepatectomy for bilateral liver metastases, extended hepatectomy, and repeat hepatectomy. Many patients who were unsuitable for resection, only a few years ago would be classified, now with preoperative chemotherapy, cytoreductive surgery followed by liver treats.

Neoadjuvant chemotherapy

The development of new, more effective chemotherapeutic agents has led to a significant increase in survival benefit in patients with inoperable colon cancer stage IV. Oxaliplatin and irinotecan, which are usually used in conjunction with therapies based on 5-Fluorouracil/Folinic acid can shrink the liver metastases,control the potential sites of extrahepatic disease [49] and allow subsequent resection of residual disease. The indications for preoperative systemic chemotherapy are the risk factors for recurrence, such as tumor size, number of tumors, disease-free interval and the presence or absence of extrahepatic disease. The increased use of preoperative chemotherapy is a clinical dilemma, whether to prescribe or not a preoperative chemotherapy in patients with initially resectable disease. This dilemma is not only academic, because recent reports indicate an increased risk of adverse post-treatment excision events in patients with preoperative systemic chemotherapy. Liver damage such as steatosis and steatohepatitis in irinotecan-treated patients has been described and also intra-vascular damage, such as sinusoidal obstruction in patients treated with oxaliplatin have been reported.[50, 51] These chemotherapy-related liver injury reduce the ability of the hepatocytes to regenerate in response to major hepatectomy by changes in nuclear factors such as nuclear factor kappa B (NF-kB), which is crucial for the primal

stage of liver regeneration. This leads to an increased postoperative morbidity and even mortality. Although resection has proven to be safe after preoperative chemotherapy, the mortality rate is [52, 53] increased in certain types of liver damage associated with chemotherapy, specifically, steatohepatitis associated with irinotecan therapy.[54] The preoperative chemotherapy should be carefully applied in patients with resectable disease, because the development of intra-hepatic complications may require a change in surgical strategy or even exclude surgery as a treatment option at all. Faced with this clinical dilemma, molecular markers are needed to predict which patients will respond better to preoperative chemotherapy and which drugs or drug classes will be more effective and better tolerated by a particular patient.

Portal vein embolization

Portal vein embolization (PVE) in preparation for major hepatic resection has been shown to induce hypertrophy of the remnant liver and reduce the risk of postoperative liver failure after major hepatectomy.[55] PVE has become part of clinical practice in Japan for patients with primary liver cancer and helps to improve resectability rates of liver cancer.[56, 57] Ipsilateral PVE is usually performed through a percutaneous transhepatic approach by ultrasound-guided puncture of a portal branch embolization of the liver part planned for resection. There is a variety of substances used for embolization, e.g. absolute alcohol, ethiodized oil, cyanoacrylate with no clear difference between them.[58] PvE is a well tolerated procedure. In our series of 112 cases, the complication rate is 8.9% and includes hematoma, partial thrombosis of the portal vein, esophageal bleeding and migration of embolization agent. Only one patient was considered inoperable because of PVE complications, but he also had tumor progression, which presented as a contraindication to resection. Indications for PVE are based on the standardized future liver remnant (sFLR) and the presence or absence of underlying liver disease. The sFLR is measured by the ratio between the sFLR and the total liver volume (TLV). The sFLR calculated by volumetric CT of the liver and TLV is calculated using a formula for the correlation between TLV and body surface area, which accounts for individual liver metabolic demand.[59] The presence of underlying liver disease is important because a severely damaged liver is unable to regenerate. Both cirrhosis and severe steatosis are causing significantly impair of the liver regeneration after major hepatectomy. The use of PVE in these conditions allows enlargement of the free of metastases liver, although more slowly than in the healthy liver, reducing the risks from the subsequent hepatectomy. Liver enlargement is still followed by a nonlinear kinetic profile for the first 2 months of the POI. The largest increase in liver volume (75%) occurs within 3 weeks after PVE, after which a plateau phase is reached with minimal regeneration. It was recently shown that hypertrophy occurs to the rest of the liver after PVE by two complementary mechanisms - increased proliferation and hypertrophy of hepatocytes.[62] Thus, the optimal time to evaluate the hypertrophy after PvE is 3 to 4 weeks. Volumetric CT can be repeated at this time because it provides two key pieces of information: (1) if adequate liver volume has been reached; (2) growth rate, which is informative for the liver capacity for regeneration. We found that patients who had slower liver hypertrophy have much worse clinical outcome regardless of whether the target sFLR was achieved. The volume of the remnant liver significantly varies from patient to patient. In patients with an otherwise normal liver, PVE is indicated when the sFLR <20%. sFLR less than 20% leads to a significant increase in postoperative morbidity. Patients who received preoperative chemotherapy or with extensive steatosis, liver regeneration, a greater liver remnant more than 30% is proposed. Finally, in patients with liver cirrhosis, PVE is indicated when sFLR is <40%.[14] Contraindications for PVE include tumor invasion of the portal vein, portal vein thrombosis, coagulopathy incorrigible, dilated biliary the RPF, severe portal hypertension and renal failure.

Double-stage hepatectomy

Resection of multiple bilobar CLM can reduce excessive reduction of the FLR, which in turn can lead to liver failure postoperatively. In 2000, Adam et al.[63] proposed a new two-stage approach for initially resectable liver tumors. The maximum number of tumors removed in the first operation, and a second surgery is performed to remove the rest after a period of liver regeneration. The goal of the double-stage hepatectomy is to minimize the risk of liver failure after massive hepatectomy in patients with bilateral metastases. At our institute, we have reversed the approach to perform small resections at the first step usually in the remnant liver, and later extended resections at the second stage with or without PVE. This approach allows us to perform major surgery and resection of the primary tumor in the first phase, with low morbidity and subsequent major resection. The need for temporary chemotherapy or PVE can be evaluated before the following major resection. This approach was proposed by Jaeck et al.[64] who recently applied systematic approach based on two-stage hepatectomy with or without preoperative PVE for a curative resection for CLM. They reported 1- and 3-year survival rate of 70% and 54.4%. The two-step strategy for patients should not be entitled to an R0 resection in the process under consideration. However, it maintains the criteria for selection and use of preoperative chemotherapy in patients with multiple bilobar CLM and are clarified.

Repeat hepatectomy

Most patients who undergo liver resection for CLM have recurrence, and one third of these recurrences develop only in the liver. Selected patients with isolated hepatic recurrence may undergo repeat hepatectomy and achieve

long-term survival. After the third hepatectomy, survival rates at 5 years are estimated as 32% and postoperative morbidity and mortality are not higher than after the first hepatectomy.[65] As bilobar multiple CLM recurrence are very likely for recurrence, early diagnosis of the relapse is important to maximize the number of patiets appropriate for resection, and long-term survival can be achieved with this approach.

Radiofrequency ablation

Unfortunately, not all patients are suitable for liver resection for CLM and alternative therapies have been proposed. The most common alternative treatment for CLM is radiofrequency ablation (RFA). RFA involves placing an electrode into the liver tumor under radiological guidance (ultrasound [U.S.], CT or MRI), thermal (radio frequency) energy generated, which destroys the tumor and a margin of normal parenchyma. RFA can be performed percutaneously, laparoscopically or during laparotomy. The use of RFA of liver metastases was reported to be effective and safe by many authors. Larger follow-up data confirm the safety process, but suggest that RFA may not be equivalent to a local resection as a modality.[8] A study by Abdalla et al is comparing surgical resection vs RFA vs. a combined procedure (resection and ablation) for CLM, and found a 5-years recurrence rate after RFA to be higher compared to combined procedure or resection alone (84%, 64% and 52%). Limited hepatic recurrence after RFA is four times higher than after resection. Therefore, the long-term survival after resection is better then after local ablation (65% vs 22%) [8] The same group studied solitary CLM and showed that liver resection is associated with greater survival rates.[66] Local recurrence are significantly lower after resection (5%) compared to after RFA (37%) for solitary CLM and the rate of 5-year survival was significantly longer after resection (71%) compared to after RFA (27%). Baere et al. have been reported in a large study procedure-related death in West Germany around 2%.[67] Some authors have reported altered patterns of recurrence of growth after RFA, including sarcomatous and disseminated spread.[**68]** If such a recurrence is appropriate for resection, an aggressive approach is usually required, which increases postoperative morbidity and mortality. Based on previous experience with RFA, if a surgical resection is the treatment of choice for CLM, with RFA reserved only for patients excluded from surgery because of general contraindications like severe underlying liver disease, recovery after surgery, or technically unresectable limited disease. Because of poorer results with RFA and the availability of multiple modalities of resection, patients must always be submitted to the hepatobiliary surgeon for expertise to determine their suitability for resection before consideration of RFA.

CONCLUSION

Liver surgeons and oncologists should collaborate to evaluate patients with CLM in order to individualize treatment strategies and to optimize the chances of long-term survival. Today, using a multi-disciplinary and multi-modal and a variety of techniques available, it is possible for CLM to be managed successfully and provide many patients with long term survival. The increased acceptance of the hepatic resection in the management of CLM in the medical community and in the public undoubtedly leads to the development of standardized protocols for screening the population, patients, bowel resection, currently used in specialized units. Improving early detection of CLM will lead to increased respectability and improved results.

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