CURRENT SURGICAL TREATMENT FOR COLORECTAL LIVER METASTASES

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Summary

Approximately 50% of patients with colorectal cancer (CRC) will develop during their lifespan. Majority of colorectal liver metastases (CLM) patients will be unresectable at the time of diagnosis due to extensive intrahepatic and/or extrahepatic disease. R0 liver resection is still the only available treatment that allows long-term survival. In last two decades, the 5-year overall survival (OS) after curative liver resection of CLM has increased up to 58%. These improved outcomes are mainly due to multidisciplinary treatment of these patients. The definition of resectability has changed, so nowadays, the goal is the completion of R0 resection and normal liver function maintenance. Conversional (neoadjuvant) chemotherapy, portal vein embolization, two-stage hepatectomy, and tumour ablation are effective approaches to improve resectability for initially unresectable patients. The role of perioperative chemotherapy, for clearly resectable patients, still needs to be clarified. It results in longer disease-free survival (DFS) and OS times, but it is not clear whether it is the neoadjuvant or the adjuvant component that provides the benefit. Disadvantages of neoadjuvant chemotherapy are either progression or complete remission during treatment, and their management is challenging. According to available data the efficacy of adjuvant chemotherapy after CLM resection is questionable. However, the ideal chemotherapy and its optimal sequencing in the course of treatment are uncertain. Equally, the influence of chemotherapy-associated toxicity on the outcome of liver resection needs to be further explored. There is debate over whether the primary tumour and metastases should be removed at the same time or in a staged manner. Targeted therapy with novel biological agents such as bevacizumab and cetuximab, in addition to traditional chemotherapy, has been shown to improve the survival of unresectable CLM patients. The majority of patients will develop recurrent disease in the liver within the first two years after surgery, despite any mode of treatment that they have received. Therefore, a repeat resection is recommended as the only chance to prolong DFS and OS. Consequently, all of these issues demand an modern oncosurgical and multidisciplinary approach to the each individual with liver surgeon having a central role in treatment planning.

KEYWORDS: colorectal cancer, liver metastases, multidisciplinary treatment, chemotherapy; R0 resection, portal vein embolization

KIRURŠKO LIJEČENJE KOLOREKTALNIH METASTAZA U JETRI

Sažetak

Oko 50% bolesnika s rakom debelog crijeva razviti će metastaze u jetri tijekom svog životnog vijeka. Nažalost, većina bolesnika sa metastatskim kolorektalnim karicnomom će biti inoperabilna u vrijeme postavljanja dijagnoze zbog opsežne intrahepatičke i / ili ekstrahepatičke bolesti. R0 resekcija jetre je još uvijek jedini dostupni oblik liječenja koji omogućuje dugoročno preživljenje. U posljednja dva desetljeća, 5-godišnje preživljenje nakon kurativneresekcije jetre poraslo je na 58%. Ti poboljšani rezultati su uglavnom posljedica multidisciplinarnog liječenja tih bolesnika, iako je optimalnog algoritma još uvijek upitan. Definicija resektabilnosti se promijenila, pa se danas kao cilj liječenja postavlja mogućnost R0 resekcije uz normalno postoperativno održavanje jetrene funkcije. Neoadjuvantna kemoterapija, embolizacija poralne vene, hepatekt-
mija u dva akta ilokalna ablacija su učinkoviti pristupi u konverziji inicijalno inoperabilnih pacijenata u operabilne. Ulogu perioperativne kemoterapije, za evidentno operabilne bolesnike, još treba razjasniti. Perioperativna kemoterapija rezultira duljim periodom bez bolesti i ukupnim preživljenjem, ali nije jasno da li je neoadjuvantna ili adjuvantna komponenta ta koja pruža korist. Potencijalni nedostaci neoadjuvantne kemoterapije su ili napredovanje ili potpuna remisija tijekom liječenja, a liječenje tih bolesnika je izazov. Prema sadašnjim podacima iz literature, učinkovitost adjuvantne kemoterapije nakon resekcije metastatskog kolorektalnog karcinoma je upitna. Isto tako, idealni kemoterapijski protokol, sa ili bez bioloških agen-
sa, i njeno optimalno sekvenciranje u tijeku liječenja je upitno. Isto tako, utjecaj, s kemoterapijom povezane toksičnosti, na ishod kirurškog liječenja treba dodatno istražiti. Još uvijek se raspravlja o tome da li primarni tumor i metastaze treba ukloniti u isto vrijeme ili operacijama u dva akta. Za jasno inoperabilnog bolesnika, još je uvijek upitno da li primarni tumor treba resecirati. Ciljana terapija s novim biološkim agensima, kao što su bevacizumab i cetuksimab, uz tradicionalne kemo-
terapijske protokole, dokazano poboljšava liječenje kod definitivno operabilnih bolesnika. Većina bolesnika s metastatskim kolorektalnim karcinomom (55%-60%), će se razviti intrahepatalni recidiv unutar prve dvije godine nakon kirurškog zahvata, bez obzira na modalitet liječenja. Stoga se ponovljene resekcije jetre preporučuju kao jedina moguća opcija koja može produžiti život ovim bolesnicima. Prema tome, sva ova otvorena pitanja zahtijevaju suvremenionko-kirurški pristup svakom pojedinom bolesniku, u sklopu multidisciplinarnog tima, s kirurgomu glavnoj ulozi kod planiranja liječenja.

KLJUČNE RIJEČI: kolorektalni karcinom, metastaze jetre, multidisciplinarno liječenje, R0 resekcija, kemoterapija, embolizacija vene porte

INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy in the world, with an average of one million new cases and half a million deaths annually (1). Cancer of the colon and rectum is the second most common malignancy in Croatia (after lung cancer in men and breast cancer in women) and the second most common cause of death after lung cancer (2). According to the Croatian State Cancer Registry, in 2011, in Croatia were 2820 CRC cases; 1172 women and 1648 men, which means 13% of all newly diagnosed cancers in women and 15% in men, respectively (2). Approximately 50% of patients with CRC will develop liver metastases, whether synchronous or metachronous, during their lifespan (1,3). About 15%-25% of CRC patients have synchronous liver metastases which means presence of metastases at the time of diagnosis of the primary tumor or within 6 months of diagnosis (4,5). On the other hand, metachronous liver metastases will develop 20%-25% of patients with colorectal cancer (6). Data from numerous retrospective and comparative studies indicates that liver resection is still the only available treatment that allows long-term survival. In last two decades, the 5-year overall survival (OS) after curative liver resection of colorectal liver metastases (CLM) has increased to 35%-58% (7–9). Unfortunately, majority of CLM patients will be unresectable at the time of diagnosis due to extensive intrahepatic and/or extrahe-

patric disease. Initialy, about 10%-20% of patients with CLM are candidates for curative resection. However, modern oncosurgical strategies and multidisciplinary treatment including neoadjuvant chemotherapy, preoperative portal vein embolization (PVE) and two-stage hepatectomies, allows another 16%-37% of CLM patients previously considered unresectable, to be downsized and eligible for liver resection (10–12). Having in mind above information, in Croatia should be approximately 600-700 CLM patients resected annually, but on the contrary, according to available data, in eight major Croatian hospitals only about 300 pa-
tients per year undergo resection for CLM (2). Sub-
stantially the question arises: where the other pa-
tients with CLM end up ? The one of the goals of this paper is to try to answer to the question above by emphasizing the need that patients with CLM should be treated in high volume centers where they can receive high quality preoperative evaluation, imaging and multidisciplinary treatment. Current data presented in this paper support a central role of liver surgeon in the planning of individualized treatment and by that offering such patients the best chance for prolonged survival which is R0 resection with curative intent.

PREOPERATIVE EVALUATION

Preoperative evaluation before resection of CLM are focused on: determining the diagnosis;
anatomically defining the lesion in the liver parenchyma for surgical planning and accurate staging to rule out extrahepatic disease.

Clinical presentation

CLM are rarely symptomatic and usually diagnosed with follow-up cross-sectional imaging, such as computed tomography (CT) or magnetic resonance imaging (MRI). Approximately 80% of metastases are detected in the first 3 years after diagnosis of the primary tumor, annual CT/MRI is recommended by the National Comprehensive Cancer Network 3-5 years after primary resection (13). Occasionally, patients present with symptoms such as pain, abdominal distention, and liver insufficiency. These patients usually have advanced CLM with significant hepatic tumor burden and are less likely to be treated.

Preoperative imaging

Nowadays, ultrasound (US), helical CT, MRI and positron emission tomography/CT (PET/CT) are main options for imaging of CRC and CLM.

Ultrasonography (US)

US is widely used, inexpensive and reliable test, but has been replaced by cross-sectional imaging mainly due to user dependence and lower sensitivity for small lesions. It can give information regarding the size of the metastatic tumor and the extent of liver involvement. Besides, CD ultrasound can help defining the relation of the tumor to the vascular and biliary structures. Ultrasound may be used as a first line modality in the diagnostic of hepatic metastases during regular follow up after resection of the primary tumor. US, however, is most useful as intraoperative tool. Scaife et al (14) reported that intraoperative ultrasonography (IOUS) identified additional hepatic tumors in 27% of patients who underwent hepatic resection after state-of-the-art preoperative CT imaging. That study provides evidence that IOUS is still important modality in assessment of hepatic malignancies in patients who receive surgical treatment.

Cross-sectional imaging (CT, MRI and PET/CT)

So far, there is no gold standard of cross-sectional technique for identifying liver metastases or anatomic structures and much of it depends on institutional preferences. Computed tomography (CT) still plays central role in selecting patients for hepatic resection. Multi-detector helical computed tomography (MD-CT) is fast, relatively inexpensive, and with the addition of intravenous contrast and thin slices provides an adequate view of metastases which appear hypovascular to the surrounding liver tissue. Disadvantages of MD-CT include radiation exposure, toxicity of contrast and inability to characterize lesions less than 1 cm in size (15).

Magnetic resonance imaging (MRI) has recently been increasingly used as cross-sectional imaging modality to diagnose CLM. While the images can be of lower resolution than MDCT, they are capable to differentiate much better small liver lesions using the amount of water present. CLM appear hypointense to surrounding liver parenchyma on T1 images and hyperintense on T2 and diffusion weighted sequences. Compared with MDCT, MRI requires patient compliance because imaging lasts longer (although does not include radiation exposure), is relatively expensive with many contraindications (due to metallic implants) and typically only images the region of interest. A most important advantage of MRI over other imaging modalities is its ability to identify even small lesions, less than 1 cm in diameter (15). Such ability is useful in detecting smaller lesions in steatotic livers, especially after neoadjuvant treatment. MRI is also more useful than MDCT in defining the relationship of the lesions to the hepatic vasculature and the biliary tree with MR cholangiopancreatography (MRCP). Bipat et al. (16) in their meta-analysis concluded that MR imaging is preferred as the first-line modality for evaluating colorectal liver metastases, particularly in patients who have not previously undergone therapy; it provides anatomic details and has a high detection rate, even for lesions smaller than 10 mm.

Positron emission tomography (PET) relies on the propensity of hypermetabolic tissue to take up radioactive tagged glucose molecules. The most common tracer in PET scanning is fluoro-18-deoxyglucose (FDG)-PET, a glucose analog, which can proceed down the glycolytic pathway, and accumulate within the glucose-avid cancer cells. Commonly, it is performed in combination with CT to allow better localization of hypermetabolic foci. PET is not particularly useful in imaging in-
trahepatic tumors, because of the high physiologic metabolic activity of liver tissue. Main purpose is to help identify and characterize radiologically occult extra-hepatic disease in patients with e.g. elevated CEA level and normal or nonspecific CT/MRI findings (17). A basic limitation of a PET scan is the reduced sensitivity in detecting sub-centimeter lesions, mucinous lesions, and lesions that have been treated with neoadjuvant chemotherapy (18). In summary, multiple studies have compared the three modalities with regards to liver disease with most finding greatest sensitivity and specificity with MRI over CT or PET (19). At our institution, MRI is the imaging modality of choice due to its ease of acquisition and because we use it as standard modality in our algorithm of preoperative evaluation and clinical staging of patients with rectal and recently with colon cancer as well. We found MRI especially useful and better than CT in distinguishing metastases from benign entities such as cysts, adenomas, and hemangiomas.

Laparoscopy

Even we do not use laparoscopy as diagnostic tool at our institution, laparoscopy has emerged in recent years as a new diagnostic modality for patients with liver malignancies. The main advantage of laparoscopy is fact that unnecessary laparotomys can be avoided in 78% of patients with unresectable disease (20). In selected cases, laparoscopy can remarkably decrease the morbidity of surgery, and shorten the delay to systemic therapy. Laparoscopy is indicated in highly selected cases in which the results of imaging studies are suspicious and/or equivocal for extrahepatic tumor, such as enlarged lymph nodes or possible peritoneal dissemination.

Preoperative biopsy

Percutaneous needle biopsies and fine needle aspiration (FNA) cytology are well established approaches for diagnosis, although, both unnecessary when imaging identifies new lesions with characteristic imaging features for CLM in patients with well known history. Needle biopsy may be appropriate when a benign or non-CLM lesion is suspected and can’t be differentiated non-invasively with MRI/PET/CT and if would change the treatment plan eventually. Also, there is a potential for false negative results. Therewith, some authors reported that the benefit of this tool may be outweighed by the serious risk of needle tract seeding (21). For these reasons, needle biopsies and FNA cytology have been virtually abandoned in the preoperative evaluation of colorectal liver metastases. At our institution, we used needle biopsies for suspected non-CLM lesions on MRI for several patients with unknown primary cancer without any adverse outcomes.

SURGICAL TREATMENT

Definition of resectability and patient selection

The cornerstone of surgical treatment for CLM is proper patient selection. Patients with colorectal liver disease can be categorized into one of three major subtypes: clearly resectable, potentially resectable, or definitely unresectable. Liver metastases numbering more than three, the presence of extrahepatic disease, or involvement of hepatic pedicle lymph nodes used to be relative or absolute contraindications for CLM liver resection. According to this definition, as few as 20% of CLM patients were resectable (7,22). However, these criteria have changed in recent years. Malik et al (23) reported that significant number of patients with multiple metastases (>4) survive to 5 years or more and should not be denied surgery (patients with 4-7 lesions and >7 had 35% and 24% 5-year OS, respectively). Previously widely accepted resection margin of at least a 1-cm has been abandoned because several studies have indicated that the actual resection margin did not affect OS as long as R0 resection could be accomplished (24). In the era of modern perioperative chemotherapy, even R1 (microscopically positive margin) resections could benefit in selected patients who are good responders to therapy (25). Equally, the presence of extrahepatic disease is also no longer considered an absolute contraindication for hepatic resection. Some authors have reported that the 5-year OS after combined resection of lung and liver metastases is approximately 30% (26). In summary, resectability can be defined as ability to surgically remove all CLM with R0 (microscopically negative) margins while adequate future liver remnant (FLR) volume. Adequate FLR must have regenerative capacity and consist of at least
two liver segments with independent inflow/outflow and biliary drainage. The requirement for residual liver volume can be different for patients receiving chemotherapy. Although at least 20% of total liver volume should be preserved for a healthy liver, it is recommended that at least 30%–40% should be preserved for livers damaged by chemotherapy-associated steatosis or hepatitis (27,28).

Regarding the patients selection, many predictive models have been created based on retrospective review of large series data. Fong et al. (7) had reviewed results of 1,001 patients undergoing liver resection for CLM over a 13-year period. Multivariate analysis identified several factors associated with poor overall survival including: positive margin, number and size of tumors, high pre-operative CEA, lymph node positive primary, and disease-free interval from the primary to discovery of the liver metastases of < 12 months. Each clinical factor was assigned one point, and the total clinical risk score (CRS) was compared with the clinical outcome of each patient after liver resection. The total score was found to be highly predictive of long-term outcome (p<0.0001). The 5-year actuarial survival rate for patients with 0 points was 60%, whereas that for patients with 5 points was 14%. A similar scoring system was proposed by Nordlinger et al. (29) using data from 1,600 patients in Europe. We have to emphasize that while these scoring systems are able to stratify patients into high and low risk groups, they do not surely identify patients in whom cure is ruled out.

Some technical aspects of liver resection

Initially, liver resection was based on the anatomic system described in the early 1950s by Couinaud (30), who defined the intrahepatic divisions of blood vessels and bile ducts. Nevertheless, there was significant confusion regarding the description of liver anatomy and hepatic resections until the first universally accepted terminology system was introduced. The “Brisbane 2000 terminology of liver anatomy and resections” (31) was based on the internal anatomy and described the several levels of division of the liver segments. It is nowadays widely accepted among liver specialists.

The main purpose of liver resection is to resect the tumor with a sufficient tumor-free margin, while preserving as much normal parenchyma as possible. Previously, hepatic resections have been along the liver segmental anatomy planes and liver surgeons relied more on major resections (hemi-hepatectomies and trisectionectomies) because former data suggesting a higher positive margin rate with more limited, nonanatomical resections (32). The nonanatomical or wedge resection, by removing a smaller volume of liver is associated with reduced postoperative morbidity and mortality. Although, they carry a higher risk of positive resection margins, in a recent series where wedge resections were performed, the incidence of positive resection margins was equivalent for both wedge resection and segmental, anatomical resection (8.3%), and the five-year survival was equivalent in both groups (33).

As we mentioned before, intraoperative ultrasound (IOUS) is very important tool in modern liver surgery. It can delineate the interior anatomy of the liver, including intrahepatic vessels, and allows hepatic resection to be performed more safely and anatomically. Besides detecting additional intrahepatic nodules, IOUS is helpful in identifying extrahepatic sites of the disease, such as infiltrated lymph nodes in the celiac axis and the hepatic pedicle, or deposits in the peritoneal cavity (34). Please note that it is very important that liver surgeons is well skilled in intraoperative hepatic ultrasonography.

Blood loss is among the most important factors influencing postoperative outcome from hepatic resection. Control of the hepatic inflow at the hilum should be achieved in all liver resections so that a vascular occlusion can be performed if necessary. The variety of vascular occlusion techniques ranges from Pringle’s maneuver (i.e. portal triad clamping) to total hepatic vascular exclusion, including inflow occlusion (selective or total), hemi-hepatic clamping, and ischemic preconditioning. These methods can also vary with regards to timing and frequency (intermittent vs. continuous) with all their advantages and disadvantages (35). Additional tool in decreasing blood loss, postoperative morbidity and mortality is maintaining low central venous pressure (CVP) during hepatic resection. A study by Melendez et al. (36) showed a dramatic decrease in operative blood loss, morbidity, and mortality when liver resection is performed under low CVP conditions. Importantly, this study did not reveal any increase in
postoperative renal insufficiency and also emphasizes the importance of good collaboration between the anesthesiologist and the surgeon as key point in minimizing blood loss during resection.

There is a variety of techniques and devices used for parenchymal transection, including the clamp crushing technique, Cavitron Ultrasonic Surgical Aspirator (CUSA, Covidien, Mansfield, MA, United States), Hydrojet (Hydro-Jet, Erbe, Tubingen, Germany), The Harmonic Scalpel (Ethicon Endo-Surgery, Cincinnati, OH, USA) and bipolar sealing devices. The goal of all techniques is to quickly and safely divide the parenchyma while minimizing damage to inflow and outflow structures from the parenchyma to be left behind. Transection of the liver should be performed as a careful dissection with division of relevant vascular structures rather than blind coagulation. Among these, the clamp crushing technique remains the most efficient in terms of reduced operation time, blood loss and total costs (37). Also, appliance of each technique is in the domain of surgeon and institutional preferences. Aragon et al. (38) discussed the most widely (above mentioned) used methods at present and review the existing randomized data comparing them. They concluded that the use of one tool over the other will also vary according to the type of resection, and different techniques can be more advantageous in one setting than another. It is important to be familiar with many strategies and be able to apply them in the most appropriate setting.

How the role of laparoscopy in surgery is a growing field, it is now brought into liver resections in institutions experienced with minimally invasive surgical techniques. The majority of cases have been done total laparoscopic followed by hand assisted laparoscopic. The most common liver resections performed laparoscopically are wedge resections, followed by left lateral segmentectomy (39). Generally, tumors in the periphery of the liver are also considered amenable to resection. Major hepatectomies, whether left or right, are not as commonly performed. The technique involves using ultrasonic shears to dissect parenchyma with placement of clips on vessels or use of endo-GIA staplers for ligation of vasculature. In 2008 a consensus meeting at the University of Louisville established guidelines for minimally invasive liver surgery (39). Data currently shows the benefit of minimally invasive technique to be decreased blood loss, shorter hospital stay, and decrease use of pain medication. From oncological aspect, there should not be any concerns because reported negative margin is 94.4%, with overall survival of 50% at 5 years (39). In experienced centers, there does not appear to be any difference in DFS or OS between open versus laparoscopic liver surgery. However, the open surgical approach to liver resection will continue to grow and develop with technology. With growing interest in minimally invasive approach to liver resection, this adds an additional tool to the technology available for open surgery which will always be the gold standard.

At our institution, we routinely perform IOUS after liver mobilisation. For control of hepatic inflow we perform Pringle’s maneuver, whether in intermittent or continuous manner, depending on extent of liver tissue to be resected. For parenchymal transection we mostly use combination of crash/clamp technique, ultrasonic dissection and stapling devices. We use ultrasonic dissector as crash and clamp tool to first distinguish blood and bile structures and then ligate it (vibrating ultrasonic shears seal and divide blood vessels from 3 mm to 7 mm in diameter). We routinely use vascular stapling devices in major hepatectomies as they have become an accepted method of liver transection. Initially used primarily for division of major vessels, their use has been expanded to divide hepatic parenchyma. Staplers have the potential to be serially applied and fired in quick and efficient manner, thus decreasing overall operating time. As sort of validation for their use we found study by Reddy et al. (40) who published a retrospective series of 200 patients over 10 years who underwent partial hepatectomy with either the crush-clamp alone or vascular stapler techniques. Compared to crush-clamp, use of a vascular stapler was associated with less operative time, blood loss, and transfusion requirements.

Surgical treatment for clearly resectable colorectal liver metastases

Treatment of resectable synchronous CLM

Synchronous hepatic metastases occur in up to 25% of newly diagnosed CRC (41), and they present a challenging problem for the multidisciplinary team. The natural history of CLM suggests
that resection of an asymptomatic primary tumor without liver resection with curative intent offers poor long-term benefit (<5% 5-year OS) (42). The optimal timing of primary tumor and hepatic metastases resection in synchronous resectable CLM patients is somehow still controversial. Treatment sequencing can be simplified into the following three paradigms: classic (colorectal-first; staged), simultaneous (combined), or reverse approach (liver-first). The decision of whether to treat the CLM or CRC first depends on which site dominates both oncologically and symptomatically, which requires multidisciplinary discussions with liver surgeon playing a central role. Unilateral decision-making, often by the physician who first encounters the patient, can potentially limit a patient’s curative options. In the past, these patients were managed by classic, staged approach (i.e., liver resection following primary tumor resection and optional chemotherapy) based on observation that simultaneous resection of primary tumor and CLM is associated with increased morbidity and mortality (29,43,44). Simultaneous resection has been increasingly adopted in recent years due to novel reports that perioperative morbidity and mortality of simultaneous resection are comparable to those of staged resections (41,45). No significant difference in 5-year survival was found between these two groups in a systemic analysis. Actually, no real indications or contraindications exist for simultaneous resection of hepatic metastases. For patients needing minor hepatectomy, the extent of primary tumor resection prevails decision-making. For low-risk CRC resections, including low anterior resections, a simultaneous approach can be performed safely with minor hepatectomy, potentially decreasing length of stay, cost, and patient disability (46–48). For more extensive CRC resections, the classic (staged) approach is more suitable and safer. When indicated, patients with rectal cancer receive preoperative chemoradiation prior to resection. Additionally, simultaneous resection offers the advantage of completing the local control of the disease in a single procedure, allowing the use of adjuvant chemotherapy for systemic micrometastases (45). Still, Reddy et al. (48) have reported that patients undergoing simultaneous major hepatectomy (i.e., resection of three or more liver segments) had a significantly higher mortality (8.3% vs 1.4%) and severe morbidity (36.1% vs 17.6%) than those receiving staged resection.

Staged resection is recommended for the following cases: significant comorbidities precluding longer operative time for simultaneous resection, marginal/inadequate FLR, and/or complex operations needed at both sites such as major hepatectomy plus total colectomy with/ or proctectomy. When there is symptomatic CRC (bleeding or obstruction), priority in sequencing goes to primary.

A new modality has been proposed more recently, called the “liver-first” or reverse strategy, and involves first, liver resection, with or without preoperative chemotherapy, followed by optional chemotherapy after hepatectomy, and finally, primary tumour resection. This approach may be suitable for borderline resectable liver metastases, which may lose the precious time frame of surgical treatment if delayed and for patients with asymptomatic primary tumors and CLM requiring major hepatectomy. For properly selected patients, reverse approach is oncologically safe with good OS (49,50). The positive effect of this strategy is the fact that treating the liver first offers the ability to control metastatic disease early before potential progression beyond resectability (51). Once the metastatic disease is resected, locoregional control is the next priority. As well, if the patient’s disease systemically progresses after hepatectomy, then the patient is spared an unnecessary CRC procedure and potential ostomy. A potential disadvantage of this approach is that the primary tumour may progress and require emergency surgery during this process. Maybe that is why decision-making analysis has indicated that it is least probable to complete all planned sequential treatment for the liver-first approach among the above mentioned three treatment strategies. Thankfully, primary tumour progression during chemotherapy rarely (5–7 %) demands a strategy change (49,52).

**Treatment of resectable metachronous CLM**

At present, complete surgical resection is the primary therapy for patients with resectable metachronous CLM. Although the most fascinating benefit of preoperative chemotherapy is the conversion of unresectability to resectability, for initially resectable CLM patients perioperative chemotherapy is often used, but it still draws controversy among liver surgeons. The most serious
concern about preoperative (neoadjuvant) chemotherapy is whether it can bring about a survival benefit for these patients. Multiple studies on the treatment of primary CRC have encouraged discussions, if perioperative chemotherapy improves survival after resection of CRC liver metastases. The most relevant and the only published randomized prospective clinical trial to investigate the role of neoadjuvant chemotherapy in CLM patients, EORTC 40983 (53), indicated that patients with initially resectable CLM undergoing liver resection plus six cycles of preoperative FOLFOX4 and six cycles of postoperative FOLFOX4 chemotherapy had a better 3-year progression-free survival (PFS) compared to those receiving liver resection alone. There were more reversible postoperative complications in the chemotherapy patients (25 vs. 16%, p<0.04), but no increase in mortality (1% in each arm). Noteworthy, there was a significant defect in this study: patients in the control group did not undergo chemotherapy after hepatic resection. So, it is difficult to determine whether the reported PFS improvement is brought about by preoperative chemotherapy, postoperative chemotherapy or both.

Further, we have to emphasize several potential drawbacks of neoadjuvant chemotherapy in resectable CLM patients. First is possible missing the optimal timing of liver resection because of complete response of liver metastases during neoadjuvant chemotherapy. Approximately 4% of patients achieved a radiographic complete response (CR) to chemotherapy, and 9% had a pathological CR (54, 55). Radiographic CR mostly does not mean true liver metastases remission. Viable cancer cells can be pathologically found in 80% of patients with a radiographic CR and undergoing resection according to the prior sites (56). Approximately 60% of “disappeared metastases” will recur if are kept in place without resection (57). However, from surgical point of view, it is not always easy to perform hepatic resection according to the previous site of disappearing liver metastases. To avoid such scenario, it is recommended that the evaluation of liver lesions should be repeated every 2 months during preoperative chemotherapy (58, 59).

Afterward, a second potential drawback of neoadjuvant chemotherapy is progression of disease. In those patients, tumour progression can compromise their opportunity for resection and potentially good outcome. The previously mentioned EORTC 40983 clinical study (53), reported that 7% of initially resectable CLM patients had progressive disease (PD) during neoadjuvant chemotherapy, and 4% did not complete liver resection whether to prior liver disease progression or the presence of newly detected extrahepatic disease. After all, another issue concerning PD is whether they should be resected even if it is feasible. Adam et al. (60) have advocated that liver PD during chemotherapy indicates poor prognosis after resection and should be considered as a contraindication to liver resection. They reported a dismal 5-year OS (8%) and DFS (3%) after liver resection in patients with tumour progression during neoadjuvant chemotherapy. However, other studies have indicated that the response to neoadjuvant chemotherapy has no prognostic value (61, 62).

At last, chemotherapy-associated liver injury (CALI) is important drawback related to neoadjuvant systemic therapy. The majority of CLM patients are treated with chemotherapy prior to liver resection. Current most applied protocols are FOLFOX and FOLFIRI with addition of new biological agent such as Bevacizumab, Cetuximab and Panitumumab. Because of their efficacy, physicians have used above mentioned regimens to increase cure rates in resectable CLM, downsize borderline resectable cases, and attempt to convert unresectability to resectability. Consequently, that has led to extended systemic treatment before surgical referral. However, extended duration (>8 cycles) chemotherapy only increases the risk of CALI without improving pathologic response because the type of chemotherapy has more impact on pathologic response rather than the duration of chemotherapy (63). Thereby, assumption that all patients with CLM should be seen by a liver surgeon who is in charge of multidisciplinary team before chemotherapy, is gaining in importance. The goal of such multidisciplinary strategy is reducing chemotherapy to the point of resectability and thus avoiding overtreatment having on mind that further chemotherapy can be given postoperatively.

There are two types of CALI: non-alcoholic fatty liver disease (i.e., steatosis/steatohepatitis) and vascular sinusoidal obstruction. All three commonly used chemotherapeutic agents for CRC, 5-FU, oxaliplatin and irinotecan, can induce
steatosis with an incidence rate of 30%-40%. Approximately 3.6%-8% (59,64) of patients have chemotherapy induced steatohepatitis, which is relatively more common in patients receiving irinotecan as compared with those receiving 5-FU. On the other hand, irinotecan has been associated with both steatosis and steatohepatitis, especially in patients with clinical symptoms of metabolic syndrome (obesity and diabetes) (65). Macroscopically, the result is “yellow liver”. Irinotecan’s induced steatohepatitis is the only CALI associated with increased mortality from postoperative hepatic insufficiency (66). This is most important when choosing between FOLFOX and FOLFIRI. Oxaliplatin is associated with a spectrum of vascular injuries, macroscopically presenting as a friable “blue liver”. This type of hepatotoxicity has been associated with increased perioperative transfusions but not mortality (67).

Surgical treatment for unresectable CLM with potential convertibility

As we mentioned above, majority of CLM patients are initially unresectable (extensive and bilobar disease) but have the potential to become resectable through conversion therapeutic strategies including chemotherapy, embolization, two-staged operation or the combination of ablation therapy. The ability to treat patients with such extensive CLM depends on institutional resources (i.e., multidisciplinary teams and interventional radiology) besides well trained and experienced liver surgeons.

Conversion chemotherapy (“downsizing” of CLM)

When patients present with anatomically unresectable CLM (approximately 80%-90% of CLM patients at diagnosis), the first consideration should be the ability to downsize their lesions to resectability. Thanks to the development of new chemotherapy agents and targeted biological agents, chemotherapy can convert a considerable portion of initially unresectable CLM into resectable disease, which is called conversion chemotherapy (59,68,69). Effective chemotherapy may achieve this goal in 10–20 % of initially unresectable patients, and these patients who achieve resectability share long-term survival rates that are far superior to palliative chemotherapy and approach that of patients with initially resectable CLM (11,70). First, Bismuth et al. (68). in 1996 reported that preoperative chemotherapy, using oxaliplatin plus 5-FU/LV, enabled 16% (53/330) of initially unresectable CRLM patients to gain the chance of undergoing liver resection with a 5-year OS of 40%. In 2001, Adam et al. (58) reported that 13.6% (95/701) of initially unresectable CLM patients underwent hepatic resection after systemic neoadj. chemotherapy and achieved a 5-year OS of 34%. In one italian study, Nuzzo et al. (71) reported that in about one-third of the patients with primarily unresectable CLM, downsizing of the lesions by chemotherapy (FOLFIRI protocol) permitted a subsequent curative resection. In recent years, the addition of targeted agents such as bevacizumab and cetuximab to chemotherapy has been shown to further improve the conversion rates. The monoclonal antibody, bevacizumab, targeting vascular endothelial growth factor (VEGF), has shown promising results in the treatment of CLM. In a first-line setting, overall responses were between 45% and 70% when combined to 5-FU, LV and irinotecan (72,73). Present data suggests that liver resection should be performed at least 6-8 weeks after administration of the last dose of bevacizumab, because bevacizumab can cause bleeding, delayed wound healing, and bowel perforation (74,75). Cetuximab, on the other hand, is the anti-EGFR agent tailored for use in patients whose tumors express wild-type KRASmutation. In the CELIM study (76), 106 patients with initially unresectable CLM underwent cetuximab plus FOLFOX6 or cetuximab plus FOLFIRI and achieved an objective response rate of 68% and 57%, a liver resection rate of 40% and 38%, and a R0 liver resection rate of 38% and 30%, respectively.

Neoadjuvant conversional chemotherapy can also be used via hepatic arterial infusion (HAI) with high response rates, as first or second-line therapies. The ideal candidates are patients with lesions confined to the liver, without severe ascites or jaundice (77). Data from several clinical trials with oxaliplatin or irinotecan via HAI have been promising (78). However, HAI has several disadvantages such as limited expertise, high cost of infusion pumps and considerable morbidity due to cather-related complications, particularly sclerosing cholangitis. Therewith, HAI is rarely used outside specialized treatment centers (79).
In summary, conversion therapy has showed acceptable results despite potential drawbacks mentioned in chapter before, but still there are fe-
wrather unanswered questions: which protocol should be applied; how many cycles before surgical intervention and finally, when we should start palliative treatment?

Portal vein embolization (PVE)

Portal vein embolization (PVE) is another modality commonly used preoperatively for patients where the extent of liver resection is expected to result in less than the optimal functional liver volume of 20% to 40%, necessary to prevent postoperative liver failure (80). (PVE) can be helpful to induce ipsilateral atrophy and contralateral hypertrophy to fulfill the minimal liver volume requirement (10) and by that to expand the number of patients undergoing curative hepatectomy for CLM. PVE can be performed by a percutaneous transhepatic approach as well as by a transileocolic approach during laparotomy (81). The percutaneous method consists of accessing the portal vein via a transhepatic route under sonographic and fluoroscopic guidance (81). Venous portography then allows selective catheterization and embolization of one of the portal branches. The most commonly used agents for embolization include gelatin sponge particles (Gelfoam) with iodized oil (Lipiodol), cyanoacrylate, alcohol, fibrin glue, or gelatin sponge, but none of them emerged as superior to the others (10,82). After PVE, hepatic volume is routinely evaluated using computed tomography volumetric analysis. This imaging modality enables the surgeon to determine the degree of compensatory hypertrophy of the future remnant liver as well as to reevaluate metastatic disease. Generally, 4-6 weeks after embolization adequate hypertrophy has occurred to enable safe hepatic resection(10). Azoulay at al. (82) have reported on a group of 30 patients who were deemed unresectable because the estimated FLR was considered too small. These patients underwent PVE with minimal morbidity and no mortality. PVE substantially increased the FLR, providing liver resection feasible in 19 patients (63%), with low morbidity and mortality rates and survival rates similar to the patients who did not undergo PVE. As PVE is more used as treatment modality some disadvantages have emerged. Thrombosis, and/or migration of the emboli to the contralateral hepatic lobe, hemoperitoneum, hemobilia, and transient liver insufficiency, are complications occurring in 10% of cases and can be easily managed(80). Another potential drawback is the possibility that PVE may stimulate the growth of tumours in the contralateral liver lobe, although this has yet to be clarified. A way of counteracting this effect is the administration of concurrent chemotherapy 2-3 weeks after PVE, thus preventing interference with initial liver regeneration (83).

Two-staged hepatectomy

A two-stage procedure is indicated in some patients cannot become eligible for complete CLM resection through a single hepatectomy even after preoperative chemotherapy or PVE. These patients usually have multinodular, large metastases involving both liver lobes, which cannot be removed in a single hepatectomy owing to a too small volume of the FRL. The two-stage procedure consists of two subsequent hepatectomies, and takes advantage of physiological liver regeneration to accomplish radicality. The objective of the first hepatectomy is to make the second hepatectomy potentially curative (83). At the first hepatectomy, as much as possible of liver metastases is resected from the less-invaded hepatic lobe. After regeneration of the FLR, the remaining tumoral tissue in the opposite lobe is resected during a second operation. To control tumor growth between the two hepatectomies, chemotherapy is applied, generally starting 2-3 weeks after the first hepatectomy to prevent interference with liver regeneration. If the estimated FLR volume after the second hepatectomy is below 30% (40% for liver heavily treated with chemotherapy), PVE can be performed as additional procedure during the first operation.

In 2000, Adam et al. (83) first proposed the two-stage resection strategy when they reported the initial results from 13 patients undergoing two-stage hepatectomy with a 3-year survival rate of 35%. No perioperative deaths occurred at the first hepatectomy, compared to a perioperative mortality of 15% at the second hepatectomy. Morbidity rates were higher after the second hepatectomy compared to the first operation (45% versus 31%, respectively). An updated result of a 5-year OS of 42% in 41 patients receiving two-staged re-
section was reported in 2008 (84). This approach can also be used at the time of colectomy when multiple synchronous hepatic lesions preclude a single curative hepatectomy. In such cases, a limited resection of the metastatic load of one hemiliver could be done at the same time as resection of primary tumour, leaving the second major hepatectomy to be done in a second stage (85). For highly selected patients with multiple, bilobar colorectal liver metastases, a two-stage hepatectomy can offer long-term remission.

A novel method for extensive growth of FLR, as an efficient alternative to PVE, have been recently proposed. “ALPPS” stands for Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy (ALPPS). ALPPS is the most recent modification of the techniques developed for two-stage hepatectomies that allow resection of advanced CLM in two steps by making use of the regenerative capacity of the human liver. ALPPS was first described by Regensburg’s group from Germany (86). ALPPS allows to remove an extensive part of the liver in two steps. In the first step the liver parenchyma is transected along the intended line of resection and the future liver remnant cleaned by partial resections from all tumor tissue in the case of bilobar tumors. To this a portal ligation of the larger liver lobe that will have to be removed is added. The patient is then allowed to recover. After a waiting period of 1-2 weeks the second step is performed in which the deportalized liver is removed to make the patient completely tumour-free. The new strategy offers two advantages: first, it elegantly addresses the most feared complication following major hepatectomies, i.e. postoperative hepatic insufficiency. The diseased right hemiliver, left in place, acts as an auxiliary livere to assist the future liver remnant for the first and critical week after resection. Second this new operation induces an amount of hypertrophy that is unparalleled by other techniques. Schnitzbauer et al. (86) report a 74% volume increase of the remnant liver in a mean of 9 days. Although very promising, some considerations about this method have to be made. First of all, the technique has not yet been standardized. We should consider that the method has not yet been tested in an evidence based manner, only preliminary experience is available, very little data exist and mortality rates in initial reports are concerning (86,87).

Ablation therapy

Locally ablative modalities, such as radiofrequency ablation (RFA), cryotherapy or laser-induced interstitial thermo-therapy (LITT) can be added to hepatic resection, to offer curative treatment in patients with unresectable tumors. The goal of the combined approach is to resect the majority of metastases and to ablate the residual smaller lesions, to achieve a R0 status, preserving at the same time adequate FLR volume to avoid PHI (88). RFA is the most widely used modality. RFA is based upon the deliverance of a high-frequency (460e500 kHz) alternating current through a probe positioned in the tumour, which is turned into heat (>50°C) that causes tissue hyperthermia and cellular destruction (89). Although appealing as a less invasive treatment option, RFA is associated with higher local recurrence rates, especially for tumors >3 cm, multiple tumors, and tumors close to major vessels due to the heat sink effect. RFA plays a role in surgical therapy for highly selected patients with small tumors located away from major abdominal, biliary, and vascular structures but should be considered inferior to resection in terms of local control for CLM. However, RFA is inferior for local control of metastatic lesions, systemic spread, and long-term survival. There is a higher local recurrence rate associated with RFA than with resection, resulting in inferior disease-free survival rate (90). Therefore, for the treatment of solitary hepatic metastases, the application of RFA cannot be primarily recommended. On the other hand, RFA can be used as palliative treatment for unresectable metastases, as it achieves better survival than chemotherapy (90). There are three approaches for RFA, including percutaneous, open and laparoscopic. Ablation through the open approach seems to be superior to the percutaneous or laparoscopic methods in terms of local failure rate. Reported local recurrence rate is up to 43% (91).

Treatment for clearly unresectable CLM

Synchronous unresectable CLM – need of primary tumour resection

Generally, palliative primary tumour resection is required and advocated for patients with definitely unresectable metastatic colorectal cancer who have symptoms related to intestinal obstruction, perforation or intractable bleeding. Ne-
vertheless, for asymptomatic patients with unresectable CLM, the value of primary tumour resection is still questionable. In earlier studies, authors have suggested that primary tumour resection may have potential benefits in preventing tumor-related symptoms such as obstruction, which may require emergency operations with a high risk of surgical mortality (92). Nowadays, those claims are rather questionable with the application of novel chemotherapy agents that have ability to control intestinal symptoms. Thus, US National Comprehensive Cancer Network guidelines recommend that colon resection should be considered only for impending obstruction risk or intractable bleeding. Temple et al. (93) in study based on 9000 elderly CLM patients reported that 72% of them underwent resection of the primary tumour and 20% of them had symptoms of bowel obstruction, perforation or bleeding. It suggests that a majority of incurable CRC patients receive intestinal resection without a clear and reasonable indication. On the other hand, the study from Memorial Sloan-Kettering Cancer Center reported 233 metastatic CRC patients receiving chemotherapy without the primary tumour resection. Only 7% of the patients required palliative primary tumour resection during the disease course. Thus, the authors recommended chemotherapy without prophylactic primary tumour resection as a standard management of metastatic colorectal cancer without obstruction or bleeding symptom (52).

Novel therapeutic agents in combination with chemotherapy

Several randomized clinical trials has validated the survival benefit of adding targeted therapeutic agents such as bevacizumab, cetuximab and panitumumab to traditional chemotherapy in patients with clearly unresectable CLM. The BEAT study (94) indicated that bevacizumab-based combination chemotherapy is efficient in metastatic colorectal cancer. It included 1965 CLM patients undergoing bevacizumab combined with different types of chemotherapy as the first-line therapy, and demonstrated that the PFS in patients receiving bevacizumab plus FOLFIRI, FOLOFOX or Xelox was > 10 mo and the OS approached or exceeded 24 mo. The CRYSTAL study (95), which compared cetuximab plus FOLFIRI with FOLFIRI alone in the initial treatment of CLM patients, indicated that cetuximab improved the response rate (57.3% vs 39.7%, P < 0.0001), PFS (9.9 mo vs 8.4 mo, P = 0.0012) and OS (23.5 mo vs 20.0 mo, P = 0.0094) significantly in patients with wild-type KRAS. However, in a population subset with mutant KRAS, there was no significant difference in the response rate, PFS or OS between the two groups. In a phase III clinical trial(96), 463 CLM patients received either panitumumab plus best supportive care (BSC) or BSC alone after chemotherapy failure. Patients with panitumumab plus BSC had an objective response rate of 8% and a significantly better median PFS (96 d vs 60 d) than those who received BSC alone. In summary, from these trials we may conclude that targeted therapy, in addition to traditional chemotherapy, improves the survival of unresectable CLM patients. However, an important issue is how to accurately predict the tumor response to targeted therapy, and that should be further investigated, in consideration of its high cost.

Repeated resections

The majority of patients with CLM (55%-60%) will develop recurrent disease in the liver within the first two years after surgery, despite any mode of treatment that they have received (97). Therefore, a repeat resection would be the only chance to prolong life for these patients. In most cases, repeated resection is combined with a locally ablative therapy, mainly with RFA. The results of repeat curative resection are comparable to the first one. The only drawback with a second or third hepatectomy on the same patient is increased technical difficulty. Repeat resection carries perioperative morbidity and mortality rates of 5%-7% and 20%-39%, respectively (9). Thus, repeat hepatic resection provides similar long-term survival to primary hepatectomy, without increasing perioperative morbidity and mortality (98). Indeed, Pessaux et al. (99) indicated that overall five-year survival rates after the first, second and third hepatectomy are similar: 33%, 21% and 36%, respectively. Adam et al. (100,101) in their studies pointed out several prognostic factors determining patient eligibility and probable success after a third hepatectomy. These factors are: the curative nature of the first two hepatectomies, an interval of more than one year between the two procedures, the number of recurrent tumors, serum
CEA levels, and the presence of extrahepatic disease. In conclusion, the best candidates for repeat resection are patients with a low tumor load, no extrahepatic disease, and removal of all visible metastatic load during the second hepatectomy (102). However, the role of repeat liver resection in patients with intrahepatic recurrence still remains controversial, because of the disputable survival benefit and the additional risks of repeat surgery.

Follow up after resection

Patients who have undergone hepatic resection of CLM are followed up to identify early recurrence that may be amenable to repeat resection with curative intent. Most patients undergo serial physical examination, serum CEA level, chest X-ray, and CT/MRI of the upper and lower abdomen every 3 to 4 mo for the first two years and then every 6 mo for the following five years.

ADJUVANT CHEMOTHERAPY

Adjuvant chemotherapy for stage III CRC cancer patients has been widely accepted based on solid evidence for survival benefit. Therefore, postoperative chemotherapy after CLM resection is also accepted by many oncologists and has become common practice with main purpose of reducing high risk of recurrence after surgery. Still, considerable controversy exists regarding the role of adjuvant chemotherapy following complete resection of CLM. There have been few prospective randomized clinical studies that have investigated the adjuvant chemotherapy survival benefit after liver resection, and the sample size of these studies has been limited due to difficult accrual. In first study, by Portier et al. (103), after resection of CLM, adjuvant 5-FU–LV resulted in a significantly better 5-year DFS compared with the observation group (33.5% vs 26.7%, P = 0.028). There was also a trend toward better OS in the adjuvant chemotherapy group, although this was not statistically significant (51.1% vs 41.1%, P = 0.13). This study was prematurely stopped due to slow accrual. To improve the sample size and power, Mitry et al. (104) pooled results of this trial with a similar study (ENG (EORTC/NCIC CTG/GIVIO)). With a total of 278 patients in the combined analysis, authors showed a 9- and 15-month improvement in PFS and OS in multivariable analysis, respectively. Regardless the larger sample sizes, they were still unable to reach statistical significance leaving considerable doubt about the efficacy of adjuvant chemotherapy. Related to this subject, Rahbari et al. (105) in their recent study evaluated if patients’ clinical risk profile using the Memorial Sloan-Kettering Cancer Center clinical risk score (MSKCC-CRS) (7), which we mentioned before, may serve as a tool to predict the efficacy of adjuvant chemotherapy after resection of colorectal liver metastases. They concluded that adjuvant chemotherapy after potentially curative resection of CRC liver metastases is associated with favorable outcome in high-risk patients, but it offers no survival benefit in patients with low-risk features of disease. The MSKCC-CRS might thus offer a tool to tailor adjuvant therapy after resection of CLM.

CONCLUSION

Multidisciplinary treatment has become the standard practice for CLM management. In recent years we have witnessed the improvement in the diagnostic cross-sectional imaging, new chemotherapeutic regimens and agents, and surgical techniques in the management of CLM. Still, R0 liver resection has been recognized as the only treatment that could offer long-term survival. The cornerstone of surgical treatment for CLM is proper patient selection. Previous eligibility criteria for resection, indications, contraindications and risk factors have been abandoned. The present viewpoint is that resection should be performed if all metastases could be removed, while leaving a sufficient remaining liver parenchyma, regardless of their number, size, location and distribution (including extrahepatic disease as well). Nowadays, adequate use of novel chemotherapy, PVE and/or two-stage hepatectomy and locally ablative modalities, is able to improve the resectability range and prognosis in these patients. Although outcomes have improved, the risks of liver surgery such as bleeding and postoperative liver failure remain and these operations should be performed in experienced, high volume centers with appropriate auxilliary support. Even though commonly used, perioperative chemotherapy continues to be controversial and while reasonable to consider, its efficacy is largely questionable in pa-
tients with initially resectable disease. Preoperative/neoadjuvant chemotherapy is effective option for initially unresectable patients to be converted into resectable. The role of adjuvant chemotherapy after CLM resection still needs to be clarified. Therefore, this paper emphasizes the significance of a multidisciplinary approach in the careful assessment of the risks, benefits, technical issues and oncological options for each individual case.

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