REVIEW Libri Oncol., Vol. 41 (2013), No 1-3, 41 – 58

CURRENT SURGICAL TREATMENT FOR COLORECTAL LIVER METASTASES

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Summary

Approximately 50% of patients with colorectal cancer (CRC) will developduring 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 nowdays, 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 managment 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 algoritam 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, hepatekto-

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 neoadjuvanta 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 agensa, 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 kemoterapijske protokole, dokazano poboljšava preživljenje kod definitivno inoperabilnih 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 opcijakoja može produžiti život ovim bolesnicima. Prema tome, sva ova otvorena pitanja zahtijevaju suvremenionko-kirurškipristup svakom pojedinom bolesniku, u sklopu multidisciplinarnog tima, s kirurgomu glavnoj ulozi kod planiranja liječenja.

KLJUČNE RIJEČI: *kolorektalni karcinom, metastaze jetre, multidisciplinarno liječenje, R0 resekcija, kemoterpija, 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 wich 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 extrahepatic 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 annualy, but on the contrary, according to available data, in eight major Croatian hospitals only about 300 patients per year undergo resection for CLM(2). Substantially the question arises: where the other patients 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 recieve 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 rarly symptomatic and usualy diagnosed with follow up cross-sectional imaging, such as computed tomography (CT) or magnetic resonance imaging (MRI). Approximatly 80% of metastases are detected in the first 3 years after diagnosis of the primary tumour, 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 insuffi ciency. 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.

Ultrasonografy (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 biliar 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 tumour. US, however, is most useful as intraoperative tool. Scaife *et al* (14) reported that intraoperative ultrasonografy (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 isstill 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. Disadventages of MD-CTinclude 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 *at 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 subcentimeter 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 CTor 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 algoritham 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 noninvasively 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 forseveral 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, an inadequate resection margin of < 1 cm, 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(6,24). 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 nowdays 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 wherewedge 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 resectio. 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 pre-conditioning. 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 *at 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 *at al*. (38) discussed the most widely (above mentioned) used methodes 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 ascpet, 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 routinly 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 thephysician 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 tumour and CLM is associated with increased morbiditiy 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 tumour 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 resectionis 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 forpatients 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 planed 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 periopertive chemotherapy is often used, but it still draws controversy among liver suregons. 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 %, p0.04), 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 a 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 doesnot 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 sistemic 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 agenst 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 allpatients with CLM should be seen by a liver surgeon who is in charge of multidiscplinary team before chemotherapy, is gaining in importance. The goal of such multidisciplinary strategy is reducingchemotherapy 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 *at 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 catheter-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 fewrather unanswered questions: which protocol should be applied; how many cycles before surgical intervention and finally, when we should start palliative tretament ?

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 vol-ume 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 remant 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 pateint completely tumour-free.The new strategy offers two adavantages: first, it elegantly addresses the most feared complication following major hepatectomies, i.e. postoperative hepatic insufficiency. The dieseased 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 ofall, 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 moality. 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). Nowdays, 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 pani- tumumab 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 sig-nificantly 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 onlychance to prolong life for these patients. In most cases, repeated resecion 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 hepaticresection 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 conlusion, the bestcandidates 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 purposeof 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 *el 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). Nowdays, 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.

REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer statistics, CA Cancer J Clin. 2008;58(2):71–96.
2. Cancer RCN. CANCER INCIDENCE IN CROATIA. 2013;(Bulletin no. 36).
3. Steele G, Ravikumar TS. Resection of hepatic metastases from colorectal cancer. Biologic perspective. Ann Surg. 1989 Aug; 210(2):127–38.
4. Blumgart LH, Allison DJ. Resection and embolization in the management of secondary hepatic tumors. World J Surg. 1982 Jan; 6(1):32–45.
5. Jatzko G, Wette V, Müller M, Lisborg P, Klimpfinger M, Denk H. Simultaneous resection of colorectal carcinoma and synchronous liver metastases in a district hospital. Int J Colorectal Dis. 1991 May; 6(2):111–4.
6. Altendorf-Hofmann A, Scheele J. A critical review of the major indicators of prognosis after resection of hepatic metastases from colorectal carcinoma. Surg Oncol Clin N Am 2003 Jan; 12(1):165–92, xi.
7. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999 Sep; 230(3):309–18; discussion 318–21.
8. Abdalla EK, Vauthey J-N, Ellis LM, Ellis V, Pollock R, Broglio KR, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg. 2004 Jun;239(6):818–25; discussion 825–7.
9. Choti MA, Sitzmann J V, Tiburi MF, Sumetchotimetha W, Rangsin R, Schulick RD, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg. 2002 Jun; 235(6):759–66.
10. Abdalla EK, Hicks ME, Vauthey JN. Portal vein embolization: rationale, technique and future prospects. Br J Surg. 2001 Feb; 88(2):165–75.
11. Adam R, Wicherts DA, de Haas RJ, Ciacio O, Lévi F, Paule B, et al. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? J Clin Oncol. 2009 Apr 10; 27(11):1829–35.
12. Wicherts D a., de Haas RJ, Adam R. Bringing unresectable liver disease to resection with curative intent. Eur J Surg Oncol. 2007 Dec; 33(SUPPL. 2):S42–51.
13. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer [Internet]. 2014. Available from: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
14. Scaife CL, Ng CS, Ellis LM, Vauthey JN, Charnsangavej C, Curley SA. Accuracy of preoperative imaging of hepatic tumors with helical computed tomography. Ann Surg Oncol. 2006 Apr; 13(4):542–6.
15. Frankel TL, Gian RK, Jarnagin WR. Preoperative imaging for hepatic resection of colorectal cancer metastasis. J Gastrointest Oncol. 2012 Mar; 3(1):11–8.
16. Bipat S, van Leeuwen MS, Comans EFI, Pijl MEJ, Bossuyt PMM, Zwinderman AH, et al. Colorectal liver metastases: CT, MR imaging, and PET for diagnosis--meta-analysis. Radiology. 2005 Oct; 237(1):123–31. A
17. Kong G, Jackson C, Koh DM, Lewington V, Sharma B, Brown G, et al. The use of 18F-FDG PET/CT in colorectal liver metastases--comparison with CT and liver MRI. Eur J Nucl Med Mol Imaging. 2008 Jul; 35(7):1323–9.
18. Lubezky N, Metser U, Geva R, Nakache R, Shmueli E, Klausner JM, et al. The role and limitations of 18-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan and computerized tomography (CT) in restaging patients with hepatic colorectal metastases following neoadjuvant chemotherapy: comparison with operative and. J Gastrointest Surg. 2007 Apr; 11(4):472–8.
19. Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. Radiology. 2010 Dec; 257(3):674–84.
20. Potter MW, Shah SA, McEnaney P, Chari RS, Callery MP. A critical appraisal of laparoscopic staging in hepatobiliary and pancreatic malignancy. Surg Oncol. 2000 Nov; 9(3):103–10.
21. Rodgers MS, Collinson R, Desai S, Stubbs RS, McCall JL. Risk of dissemination with biopsy of colorectal liver metastases. Dis Colon Rectum. 2003 Apr; 46(4): 454–8; discussion 458–9.
22. Elias D, Liberale G, Vernerey D, Pocard M, Ducreux M, Boige V, et al. Hepatic and extrahepatic colorectal metastases: when resectable, their localization does not matter, but their total number has a prognostic effect. Ann Surg Oncol. 2005 Nov; 12(11):900–9.
23. Malik HZ, Hamady ZZR, Adair R, Finch R, Al-Mukhtar A, Toogood GJ, et al. Prognostic influence of multiple hepatic metastases from colorectal cancer. Eur J Surg Oncol. 2007 May; 33(4):468–73.
24. Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg. 2005 May; 241(5): 715–22, discussion 722–4.
25. De Haas RJ, Wicherts DA, Flores E, Azoulay D, Castaing D, Adam R. R1 resection by necessity for colorectal

liver metastases: is it still a contraindication to surgery? Ann Surg. 2008 Oct; 248(4):626–37.
26. Miller G, Biernacki P, Kemeny NE, Gonen M, Downey R, Jarnagin WR, et al. Outcomes after resection of synchronous or metachronous hepatic and pulmonary colorectal metastases. J Am Coll Surg. 2007 Aug; 205 (2):231–8.
27. Ferrero A, Viganò L, Polastri R, Muratore A, Eminefendic H, Regge D, et al. Postoperative liver dysfunction and future remnant liver: where is the limit? Results of a prospective study. World J Surg. 2007 Aug; 31(8):1643–51.
28. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. Oncologist. 2008 Jan; 13(1):51–64.
29. Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Française de Chirurgie. Cancer. 1996 Apr 1; 77(7):1254–62. A
30. Couinaud C. [The anatomy of the liver]. Ann Ital Chir.;63(6):693–7.
31. Pang YY. The Brisbane 2000 terminology of liver anatomy and resections. HPB 2000; 2:333-39. HPB (Oxford). 2002 Jan; 4(2):99; author reply 99–100.
32. Welsh FKS, Tekkis PP, O'Rourke T, John TG, Rees M. Quantification of risk of a positive (R1) resection margin following hepatic resection for metastatic colorectal cancer: an aid to clinical decision-making. Surg Oncol. 2008 Jul; 17(1):3–13.
33. Zorzi D, Mullen JT, Abdalla EK, Pawlik TM, Andres A, Muratore A, et al. Comparison between hepatic wedge resection and anatomic resection for colorectal liver metastases. J Gastrointest Surg. 2006 Jan; 10(1):86–94.
34. Hata S, Imamura H, Aoki T, Hashimoto T, Akahane M, Hasegawa K, et al. Value of visual inspection, bimanual palpation, and intraoperative ultrasonography during hepatic resection for liver metastases of colorectal carcinoma. World J Surg. 2011 Dec; 35(12): 2779–87.
35. Abdalla EK, Noun R, Belghiti J. Hepatic vascular occlusion: which technique? Surg Clin North Am. 2004 Apr; 84(2):563–85.
36. Melendez JA, Arslan V, Fischer ME, Wuest D, Jarnagin WR, Fong Y, et al. Perioperative outcomes of major hepatic resections under low central venous pressure anesthesia: blood loss, blood transfusion, and the risk of postoperative renal dysfunction. J Am Coll Surg. 1998 Dec; 187(6):620–5.
37. Lesurtel M, Selzner M, Petrowsky H, McCormack L, Clavien P-A. How should transection of the liver be performed?: a prospective randomized study in 100 consecutive patients: comparing four different transection strategies. Ann Surg. 2005 Dec; 242(6):814–23.
38. Aragon RJ, Solomon NL. Techniques of hepatic resection. J Gastrointest Oncol. 2012 Mar; 3(1):28–40.
39. Nguyen KT, Geller DA. Laparoscopic liver resection--current update. Surg Clin North Am. 2010 Aug; 90(4):749–60.
40. Reddy SK, Barbas AS, Gan TJ, Hill SE, Roche AM, Clary BM. Hepatic parenchymal transection with vascular staplers: a comparative analysis with the crush-clamp technique. Am J Surg. 2008 Nov; 196(5):760–7.
41. Martin R, Paty P, Fong Y, Grace A, Cohen A, DeMatteo R, et al. Simultaneous liver and colorectal resections are safe for synchronous colorectal liver metastasis. J Am Coll Surg. 2003 Aug; 197(2):233–41; discussion 241–2.
42. Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. Lancet. 1994 Jun 4; 343 (8910):1405–10.
43. Jaeck D, Bachellier P, Weber JC, Mourad M, Walf P, Boudjema K. [Surgical treatment of synchronous hepatic metastases of colorectal cancers. Simultaneous or delayed resection?]. Ann Chir. 1996 Jan; 50(7):507–12; discussion 13–6.
44. Fujita S, Akasu T, Moriya Y. Resection of synchronous liver metastases from colorectal cancer. Jpn J Clin Oncol. 2000 Jan; 30(1):7–11.
45. Chua HK, Sondenaa K, Tsiotos GG, Larson DR, Wolff BG, Nagorney DM. Concurrent vs. staged colectomy and hepatectomy for primary colorectal cancer with synchronous hepatic metastases. Dis Colon Rectum. 2004 Aug; 47(8):1310–6.
46. Hillingsø JG, Wille-Jørgensen P. Staged or simultaneous resection of synchronous liver metastases from colorectal cancer--a systematic review. Colorectal Dis. 2009 Jan]; 11(1):3–10.
47. Aloia TA, Vauthey J-N. Management of colorectal liver metastases: past, present, and future. Updates Surg. 2011 Mar]; 63(1):1–3.
48. Reddy SK, Pawlik TM, Zorzi D, Gleisner AL, Ribero D, Assumpcao L, et al. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. Ann Surg Oncol. 2007 Dec]; 14(12):3481–91.
49. Brouquet A, Mortenson MM, Vauthey J-N, Rodriguez-Bigas MA, Overman MJ, Chang GJ, et al. Surgical strategies for synchronous colorectal liver metastases in 156 consecutive patients: classic, combined or reverse strategy? J Am Coll Surg. 2010 Jun; 210(6):934–41.
50. Verhoef C, van der Pool AEM, Nuyttens JJ, Planting AST, Eggermont AMM, de Wilt JHW. The "liver-first approach" for patients with locally advanced rectal cancer and synchronous liver metastases. Dis Colon Rectum. 2009 Jan; 52(1):23–30.
51. Mentha G, Roth AD, Terraz S, Giostra E, Gervaz P, Andres A, et al. "Liver first" approach in the treatment of colorectal cancer with synchronous liver metastases. Dig Surg. 2008 Jan; 25(6):430–5.
52. Poultsides GA, Servais EL, Saltz LB, Patil S, Kemeny NE, Guillem JG, et al. Outcome of primary tumor in

patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. J Clin Oncol. 2009 Jul 10; 27 (20):3379–84.

53. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2013 Nov; 14(12):1208–15.
54. Adam R, Wicherts D a, de Haas RJ, Aloia T, Lévi F, Paule B, et al. Complete pathologic response after preoperative chemotherapy for colorectal liver metastases: myth or reality? J Clin Oncol. 2008 Apr 1; 26 (10):1635–41.
55. Chua TC, Saxena A, Liauw W, Kokandi A, Morris DL. Systematic review of randomized and nonrandomized trials of the clinical response and outcomes of neoadjuvant systemic chemotherapy for resectable colorectal liver metastases. Ann Surg Oncol. 2010 Feb; 17(2):492–501.
56. Benoist S, Brouquet A, Penna C, Julié C, El Hajjam M, Chagnon S, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? J Clin Oncol. 2006 Aug 20; 24(24):3939–45.
57. Van Vledder MG, de Jong MC, Pawlik TM, Schulick RD, Diaz LA, Choti MA. Disappearing colorectal liver metastases after chemotherapy: should we be concerned? J Gastrointest Surg. 2010 Nov; 14(11):1691–700.
58. Adam R, Avisar E, Ariche A, Giachetti S, Azoulay D, Castaing D, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. Ann Surg Oncol. 2001 May; 8(4):347–53.
59. Pawlik TM, Choti MA. Surgical therapy for colorectal metastases to the liver. J Gastrointest Surg. 2007 Aug; 11(8):1057–77.
60. Adam R, Pascal G, Castaing D, Azoulay D, Delvart V, Paule B, et al. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? Ann Surg. 2004 Dec; 240(6):1052–61; discussion 1061–4.
61. Gallagher DJ, Zheng J, Capanu M, Haviland D, Paty P, Dematteo RP, et al. Response to neoadjuvant chemotherapy does not predict overall survival for patients with synchronous colorectal hepatic metastases. Ann Surg Oncol. 2009 Jul; 16(7):1844–51.
62. Neumann UP, Thelen A, Röcken C, Seehofer D, Bahra M, Riess H, et al. Nonresponse to pre-operative chemotherapy does not preclude long-term survival after liver resection in patients with colorectal liver metastases. Surgery. 2009 Jul; 146(1):52–9.
63. Kishi Y, Zorzi D, Contreras CM, Maru DM, Kopetz S, Ribero D, et al. Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. Ann Surg Oncol. 2010 Nov; 17(11):2870–6.
64. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005 Jun; 41(6):1313–21.
65. Fernandez FG, Ritter J, Goodwin JW, Linehan DC, Hawkins WG, Strasberg SM. Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases. J Am Coll Surg. 2005 Jun; 200(6):845–53.
66. Vauthey J-N, Pawlik TM, Ribero D, Wu T-T, Zorzi D, Hoff PM, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol. 2006 May; 24(13):2065–72.
67. Aloia T, Sebagh M, Plasse M, Karam V, Lévi F, Giacchetti S, et al. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. J Clin Oncol. 2006 Nov; 24(31):4983–90.
68. Bismuth H, Adam R, Lévi F, Farabos C, Waechter F, Castaing D, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. Ann Surg. 1996 Oct; 224(4):509–20; discussion 520–2.
69. Masi G, Loupakis F, Pollina L, Vasile E, Cupini S, Ricci S, et al. Long-term outcome of initially unresectable metastatic colorectal cancer patients treated with 5-fluorouracil/leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) followed by radical surgery of metastases. Ann Surg. 2009 Mar; 249(3):420–5.
70. Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg. 2004 Oct; 240(4):644–57; discussion 657–8.
71. Nuzzo G, Giuliante F, Ardito F, Vellone M, Pozzo C, Cassano A, et al. Liver resection for primarily unresectable colorectal metastases downsized by chemotherapy. J Gastrointest Surg. 2007 Mar; 11(3):318–24.
72. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004 Jul 3; 350(23):2335–42.
73. Kopetz S, Abbruzzese JL, Eng C et al. Preliminary results from a phase II study of infusional 5-FU, leucovorin, and irinotecan (FOLFIRI) plus bevacizumab as first-line treatment for metastatic colorectal cancer (mCRC). J Clin Oncol. 2006; ASCO Annua(24):Abstract 3579.
74. Bertolini F, Malavasi N, Scarabelli L, Fiocchi F, Bagni B, Del Giovane C, et al. FOLFOX6 and bevacizumab in non-optimally resectable liver metastases from colorectal cancer. Br J Cancer. 2011 Mar; 104(7):1079–84.
75. Kesmodel SB, Ellis LM, Lin E, Chang GJ, Abdalla EK, Kopetz S, et al. Preoperative bevacizumab does not significantly increase postoperative complication rates in patients undergoing hepatic surgery for colorectal

cancer liver metastases. J Clin Oncol. 2008 Nov; 26(32):5254–60.
76. Folprecht G, Gruenberger T, Bechstein WO, Raab H-R, Lordick F, Hartmann JT, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol. 2010 Jan; 11(1):38–47.
77. Kemeny MM, Adak S, Gray B, Macdonald JS, Smith T, Lipsitz S, et al. Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy--an intergroup study. J Clin Oncol. 2002 Mar; 20(6):1499–505.
78. Shimonov M, Hayat H, Chaitchik S, Brener J, Schachter P, Czerniak A. Combined systemic chronotherapy and hepatic artery infusion for the treatment of metastatic colorectal cancer confined to the liver. Chemotherapy. 2005 May; 51(2-3):111–5.
79. Kelly RJ, Kemeny NE, Leonard GD. Current strategies using hepatic arterial infusion chemotherapy for the treatment of colorectal cancer. Clin Colorectal Cancer. 2005 Sep; 5(3):166–74.
80. Di Stefano DR, de Baere T, Denys A, Hakime A, Gorin G, Gillet M, et al. Preoperative percutaneous portal vein embolization: evaluation of adverse events in 188 patients. Radiology. 2005 Feb; 234(2):625–30.
81. Azoulay D, Raccuia JS, Castaing D, Bismuth H. Right portal vein embolization in preparation for major hepatic resection. J Am Coll Surg. 1995 Sep; 181(3):266–9.
82. Azoulay D, Castaing D, Smail A, Adam R, Cailliez V, Laurent A, et al. Resection of nonresectable liver metastases from colorectal cancer after percutaneous portal vein embolization. Ann Surg. 2000 Apr; 231(4):480–6.
83. Adam R, Laurent a, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. Ann Surg. 2000 Dec; 232(6):777–85.
84. Wicherts DA, Miller R, de Haas RJ, Bitsakou G, Vibert E, Veilhan L-A, et al. Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases. Ann Surg. 2008 Dec; 248(6):994–1005.
85. Jaeck D, Pessaux P. Bilobar colorectal liver metastases: treatment options. Surg Oncol Clin N Am. 2008 Jul; 17(3):553–68, ix.
86. Schnitzbauer AA, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg. 2012 Mar; 255(3):405–14.
87. Donati M, Stavrou G a, Oldhafer KJ. Current position of ALPPS in the surgical landscape of CRLM treatment proposals. World J Gastroenterol. 2013 Oct]; 19(39):6548–54.
88. Khatri VP, Chee KG, Petrelli NJ. Modern multimodality approach to hepatic colorectal metastases: solutions and controversies. Surg Oncol. 2007 Jul; 16(1):71–83.
89. Buscarini L, Rossi S. Technology for Radiofrequency Thermal Ablation of Liver Tumors. Semin Laparosc Surg. 1997 Jun; 4(2):96–101.
90. Iwatsuki S, Dvorchik I, Madariaga JR, Marsh JW, Dodson F, Bonham AC, et al. Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. J Am Coll Surg. 1999 Sep; 189(3):291–9.
91. Amersi FF, McElrath-Garza A, Ahmad A, Zogakis T, Allegra DP, Krasne R, et al. Long-term survival after radiofrequency ablation of complex unresectable liver tumors. Arch Surg. 2006 Jun; 141(6):581–7; discussion 587–8.
92. Moran MR, Rothenberger DA, Lahr CJ, Buls JG, Goldberg SM. Palliation for rectal cancer. Resection? Anastomosis? Arch Surg. 1987 Jun; 122(6):640–3.
93. Temple LKF, Hsieh L, Wong WD, Saltz L, Schrag D. Use of surgery among elderly patients with stage IV colorectal cancer. J Clin Oncol. 2004 Sep; 22(17): 3475–84.
94. Van Cutsem E, Rivera F, Berry S, Kretzschmar A, Michael M, DiBartolomeo M, et al. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. Ann Oncol. 2009 Nov; 20(11):1842–7.
95. Van Cutsem E, Köhne C-H, Hitre E, Zaluski J, Chang Chien C-R, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009 Apr; 360(14):1408–17.
96. Giusti RM, Shastri K, Pilaro AM, Fuchs C, Cordoba-Rodriguez R, Koti K, et al. U.S. Food and Drug Administration approval: panitumumab for epidermal growth factor receptor-expressing metastatic colorectal carcinoma with progression following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Clin Cancer Res. 2008 Mar; 14(5):1296–302.
97. Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol. 2007 Oct; 25(29):4575–80.
98. Shaw IM, Rees M, Welsh FKS, Bygrave S, John TG. Repeat hepatic resection for recurrent colorectal liver metastases is associated with favourable long-term survival. Br J Surg. 2006 Apr; 93(4):457–64.
99. Pessaux P, Lermite E, Brehant O, Tuech J-J, Lorimier G, Arnaud J-P. Repeat hepatectomy for recurrent colorectal liver metastases. J Surg Oncol. 2006 Jan; 93(1):1–7.
100. Adam R, Bismuth H, Castaing D, Waechter F, Navarro F, Abascal A, et al. Repeat hepatectomy for colorectal liver metastases. Ann Surg. 1997 Jan; 225(1):51–60; discussion 60–2.
101. Adam R, Pascal G, Azoulay D, Tanaka K, Castaing D, Bismuth H. Liver resection for colorectal metastases:

the third hepatectomy. Ann Surg. 2003 Dec; 238(6):871–83; discussion 883–4.

102. Small R, Lubezky N, Ben-Haim M. Current controversies in the surgical management of colorectal cancer metastases to the liver. Isr Med Assoc J. 2007 Oct; 9(10):742–7.
103. Portier G, Elias D, Bouche O, Rougier P, Bosset J-F, Saric J, et al. Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. J Clin Oncol. 2006 Nov; 24(31):4976–82.
104. Mitry E, Fields ALA, Bleiberg H, Labianca R, Portier G, Tu D, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. J Clin Oncol. 2008 Oct; 26(30):4906–11.
105. Rahbari NN, Reissfelder C, Schulze-Bergkamen H, Jäger D, Büchler MW, Weitz J, et al. Adjuvant therapy after resection of colorectal liver metastases: the predictive value of the MSKCC clinical risk score in the era of modern chemotherapy. BMC Cancer 2014 Jan; 14:174.

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