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REVIEW

Current treatment for colorectal liver metastases

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Abstract

Surgical resection offers the best opportunity for survival in patients with colorectal cancer metastatic to the liver, with five-year survival rates up to 58% in selected cases. However, only a minority are resectable at the time of diagnosis. Continuous research in this field aims at increasing the percentage of patients eligible for resection, refining the indications and contraindications for surgery, and improving overall survival. The use of surgical innovations, such as staged resection, portal vein embolization, and repeat resection has allowed higher resection rates in patients with bilobar disease. The use of neoadjuvant chemotherapy allows up to 38% of patients previously considered unresectable to be significantly downstaged and eligible for hepatic resection. Ablative techniques have gained wide acceptance as an adjunct to surgical resection and in the management of patients who are not surgical candidates. Current management of colorectal liver metastases requires a multidisciplinary approach, which should be individualized in each case.

Key words: Colorectal liver metastases; Multidisciplinary treatment

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INTRODUCTION

Colorectal cancer (CRC) is the fourth most common cancer in the West and the second most common cause of cancer related mortality after lung cancer in Europe and North America[1,2]. More than 50% of patients with CRC will develop liver metastases during their lifespan[2,3]. A quarter of patients with primary CRC are found to have synchronous hepatic secondaries[4]. Almost half of patients undergoing resection for primary CRC eventually develop metachronous liver secondaries[5].Despite improvements in chemotherapies and biological agents, survival is rarely longer than three years[6,7].

Evidence based on numerous retrospective and comparative studies indicates that hepatic resection is the only available treatment that allows long-term survival[8]. Experiences with liver resection is associated with a 25% to 51% 5-year survival[9,10]. By contrast, five-year survivors with chemotherapy alone are anecdotal. Historically, only 5%-10% of patients with colorectal liver metastases were resectable; currently, with the advances in diagnostic methods and new therapies, resectability rates have increased to 20%-25%[11].

Emerging strategies designed to increase the proportion of patients who are candidates for complete surgical resection have been introduced in clinical practice. Neoadjuvant chemotherapy[11], preoperative portal vein embolization[12], and the two-stage resection approach[13]

contribute to this aim. However, even with these new strategies, the majority of patients with colorectal liver metastases are not candidates for a curative resection.

In this review, the current data supporting the use of liver resection in the management of colorectal liver metastases are analyzed. For this purpose, the role of new imaging techniques for the preoperative evaluation and new staging systems to stratify the patients are extensively reported. Moreover, the most recently introduced chemotherapies and biological therapies to prevent recurrence after surgery or to downstage unresectable tumors are analyzed.

NATURAL HISTORY

Liver metastases from colorectal cancer carry a median survival of 5 to 20 mo if left untreated; two-year survival is unusual, and five-year survival is extremely rare[4-14]. Factors associated with a significant disadvantage in the unresected group include extent of liver disease, presence of extrahepatic disease, age of the patient, and carcinoembryonic antigen (CEA) level[14]. Prognosis is closely related to the extent of liver replacement by the tumor[4,15]. Indeed, Wood *et al*[15] in a retrospective study of 113 patients undertaken in the Glasgow Royal Infirmary, reported a one-year survival rate of 5.7% for patients with widespread liver disease, 27% for patients with metastases localized to one hepatic lobe, and 60% for patients with solitary metastases.

Even when hepatic resection is performed with curative intent[16], 60% to 70% of patients will develop local or distant recurrence[17]. Recurrence occurs equally at intrahepatic and extrahepatic sites; 80% of all recurrences occur within two years. The median survival of patients with recurrent disease is 8 to 10 mo without any treatment[14]. Repeat resection is feasible in 10% to 15% of these cases and may achieve a five-year overall survival rate of 15% to 40% in selected patients. Cure is considered after the achievement of 10-year disease-free survival[18].

Chemotherapy alone, whether administered systemically or regionally, has a palliative role and rarely results in prolonged survival. Several retrospective studies have reviewed the clinical outcome of patients with potentially resectable liver metastases treated with chemotherapy alone. An obvious survival advantage for patients undergoing curative resection compared to those treated with chemotherapy was noted[19]. Scheele *et al*[19]compared 183 patients with resected hepatic metastases with 62 patients with resectable lesions who did not undergo surgery and 920 patients with unresectable disease. The median survival for the three groups was 30 mo, 14.2 mo and 6.9 mo, respectively. Although the patients of the second group lived longer than those of the third group, no patient in either group survived more than five years.

These poor results in untreated hepatic metastases from colorectal cancer and the continuous improvements in hepatic surgery provided the rationale for increasingly aggressive hepatic resections for the treatment of this condition[20].

CURRENT CRITERIA OF HEPATIC RESECTION

During the past two decades the five-year survival rates for hepatic colorectal metastases patients have almost doubled, from 30% to 60%[14]. The introduction of new chemotherapeutic agents and the shift in the criteria of surgical resection were the main factors in this progress[21]. Previous absolute or relative contraindications to resection included the presence of extrahepatic disease[8], involvement of hepatic pedicle lymph nodes[22], and an inadequate resection margin of < 1 cm[23]. All above contraindications for hepatic resection have been challenged and have already lost their importance in patient selection for hepatectomy[24,25].

The current criteria focus on what should be left after hepatic resection. Previous criteria for resection, such as the size, location, number of intrahepatic metastases, and the presence of bilobar or extrahepatic disease have been largely abandoned[14,26,27]. Nowadays, the definition of resectability includes a complete resection with tumor-free surgical margins (R0 resection), sparing at least two liver segments having an independent inflow, outflow, and biliary drainage. The amount of the liver remnant after resection should not be less than 20% and 30% of the total liver volume in normal and cirrhotic patients, respectively. This can be accurately predicted by computed tomography (CT) or magnetic resonance imaging (MRI) during preoperative evaluation.

PREOPERATIVE EVALUATION

Preoperative investigations before resection of colorectal liver metastases are focused on: (1) determining the diagnosis; (2) anatomically defining the lesion in the liver parenchyma for surgical planning; and (3) meticulous staging to rule out extrahepatic disease[28].

Preoperative biopsy

Fine needle aspiration (FNA) cytology is a well established approach for diagnosis. The potential benefit of FNA in suspect cases is the cytological confirmation of diagnosis, although this can be effectively obtained by other examinations, together with the patient's history. However, there is a potential for false negative results. Nevertheless, the benefit of this examination may be outweighed by the serious risk of needle tract seeding[29,30]. For these reasons, FNA cytology has been virtually abandoned in the preoperative evaluation of colorectal liver metastases.

Preoperative investigation

Metastatic liver tumors can usually be differentiated by imaging modalities, including ultrasound, CT, MRI and positron emission tomography (PET). CT plays a pivotal role in selecting patients for hepatic resection. The use of multidetector helical CT scans has improved resolution and increased the previously low sensitivity (53%) of detecting colorectal liver metastases to 70%-90%[14,31,32]. Liv-

er metastases can be distinguished as hypodense lesions in the portal phase. A CT scan may provide information regarding the anatomical characteristics of the metastatic lesions and their relation to lobar architecture and major vascular structures. However, a CT scan cannot detect subcentimeter lesions[14]. Colorectal liver metastases usually respect the liver capsule and the intersegmental planes and push these structures away. Even large lesions that appear to involve the inferior vena cava or the diaphragm on a CT scan, often do not do so and such appearances should not preclude surgical exploration[28].

MRI is more useful than CT in detecting small metastatic lesions in a fatty liver, and in defining the relationship of the lesions to the hepatic vasculature and the biliary tree with MR cholangiopancreatography[28]. However, it has a sensitivity of 70% to 80% and it does not offer any significant advantage over a CT scan[14]. Furthermore, MRI angiography and CT angiography have gradually replaced the more invasive direct hepatic angiography.

Ultrasonography is an inexpensive test that may identify small metastatic lesions within the hepatic parenchyma. It can give information regarding the size of the metastatic tumor and the extent of liver involvement. Moreover, Duplex ultrasound can define the relation of the tumor to the hilar structures, the hepatic veins, and the inferior vena cava. Ultrasound may be used as a first-line modality in the diagnostic evaluation of hepatic metastases[28].

A new modality in the diagnosis of colorectal liver metastases is whole body PET. 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. A recent meta-analysis reported a sensitivity and specificity for FDG-PET of 88% and 96%, respectively, for the detection of hepatic metastases, and 90% to 95% for the detection of extrahepatic disease[33]. The combination of CT and FDG-PET increases sensitivity and allows the selection of surgical therapy for patients likely to gain the most benefit[34]. The main limitation of a PET scan is the reduced sensitivity in detecting subcentimeter lesions, mucinous lesions, and lesions that have been treated with neoadjuvant chemotherapy[35].

During the last two decades, laparoscopy has emerged as a new diagnostic modality for patients with liver malignancies. When laparoscopy is employed, unnecessary laparotomy can be avoided in 78% of patients with unresectable disease[35]. In these cases, laparoscopy can decrease the morbidity of surgery, and shorten the delay to systemic therapy[36]. Laparoscopy is indicated in cases in which the results of imaging studies are suspicious, but not diagnostic for extrahepatic tumor, such as enlarged lymph nodes or possible peritoneal dissemination.

PREOPERATIVE TREATMENT

Chemotherapy

Current chemotherapy regimens including oxaliplatin and irinotecan in addition to 5-fluorouracil (5-FU), and leucovorin (LV) have achieved improved response rates in colorectal liver metastases, with significant reduction in disease bulk in almost 50% of patients and a median survival approaching two years[37]. New biological agents, such as those targeting epithelial and vascular endothelial growth factor pathways (bevacizumab, cetuximab) have added a significant survival benefit in these patients[38,39].

The successful use of combination chemotherapy in colorectal liver metastases has led to the concept that these agents could also be used before hepatic resection. In fact, the use of neoadjuvant chemotherapy has the benefit of downstaging the tumor, rendering a previously unresectable tumor resectable. This approach may assess the responsiveness of the tumor to chemotherapy, as the initial response to chemotherapy is strongly predictive of a favorable long-term outcome[40,41]. The development of steatohepatitis is a complication of preoperative chemotherapy, which results in a significantly increased 90-d postoperative mortality[42].

Neoadjuvant chemotherapy

The use of preoperative chemotherapy may exert a downsizing effect on the metastatic tumors, so one may perform surgery as soon as resectability is technically feasible. According to the Paul Brousse experience[43], modern chemotherapeutic regimens allow 12.5% of patients with unresectable colorectal liver metastases to be rescued by hepatic resection. This strategy may offer a possibility of long-term survival (33% at five years and 22% at 10 years) with a low operative risk. It is noteworthy that this strategy involves the wide use of repeat hepatectomies and extrahepatic resections in an effort to eradicate all tumors. Currently most reports suggest that infusional FU/LV with oxaliplatin and/or irinotecan are the most effective protocols for this purpose[31,44]. However, although the response rates are very high when used as first-line therapy, the response rates for second-line therapy are very low[31,45]. Therefore, tumors that progress while on chemotherapy usually have a low likelihood of becoming resectable with second-line chemotherapy.

Neo-adjuvant chemotherapy can also be used *via* hepatic arterial infusion (HAI) with high response rates, as first or second-line therapies[46]. Patients with metastatic lesions confined to the liver, without severe ascites or jaundice, are ideal candidates[47]. Preliminary data from several clinical trials with oxaliplatin or irinotecan *via* HAI have been promising[48]. However, HAI is rarely used outside specialized treatment centers, because of limited expertise, high cost of infusion pumps, and ongoing concerns regarding the considerable morbidity due to catheter-related complications, particularly sclerosing cholangitis[49].

Portal vein embolization

Portal vein embolization (PVE) is another modality used preoperatively for patients where the extent of liver

resection is expected to result in less than the optimal functional liver volume of 25% to 40%, necessary to prevent postoperative liver failure[21,50]. This technique, which induces ipsilateral atrophy and contralateral hypertrophy, is used to expand the number of patients undergoing curative hepatectomy for colorectal liver metastases. The most commonly used agents for embolization include gelatin sponge particles (Gelfoam) with iodized oil (Lipiodol), cyanoacrylate, alcohol, fibrin glue, or gelatin sponge, and they are usually administered percutaneously[14,51]. The amount of liver tissue gained is about 15% of the total liver volume, and the time for maximum regeneration ranges from three to nine weeks[52].

Azoulay *et al*[51] have reported on a group of 30 patients who were deemed ineligible for liver resection because the estimated remnant liver was considered too small. These patients underwent PVE with minimal morbidity and no mortality. PVE substantially increased the remnant liver volume, rendering 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. In conclusion, PVE followed by hepatic resection represents a two-stage hepatectomy: progressive atrophy of the embolized area, which triggers compensatory hypertrophy of the future remaining parenchyma, followed by liver resection. Therefore, PVE increases the resectability of colorectal liver metastases with a survival benefit comparable to that obtained with primary liver resection.

Several disadvantages of PVE have emerged as more experience is collected. Thrombosis, and/or migration of the emboli to the contralateral hepatic lobe, hemobilia, hemoperitoneum, and transient liver insufficiency, are complications occurring in 10% of cases and can be easily managed[50]. Another adverse side effect is the possibility that PVE may stimulate the growth of tumors in the contralateral liver lobe, although this has yet to be clarified[53]. A way of counteracting this effect is the administration of concurrent chemotherapy soon after PVE, the so-called "interterm chemotherapy"[14].

LIVER RESECTION

Over the last two to three decades, an aggressive surgical approach has been followed for the treatment of colorectal hepatic metastases, based on the fact that the liver is the first isolated site of metastases for colorectal cancer. This direct treatment of hepatic metastases prevents dissemination of the disease from the liver to other sites[54].

The role of hepatic resection as an effective treatment for colorectal liver metastases was established in 1988 from the registry of hepatic metastases[9]. In a retrospective review on 859 patients with colorectal liver metastases who were surgically treated between 1948 and 1985, the five-year actuarial survival rate and the disease-free survival rate were 33% and 21%, respectively. Along with the gradual improvement in imaging techniques, better understanding of liver anatomy, recent refinements of surgical techniques, and the continuous progress in pre-and postoperative care, the postoperative mortality rate after hepatectomy has been reduced to < 3% and the five-year survival rate after resection of colorectal liver metastases has reached 26%-58%[10,25].

Initially, liver resection was based on the anatomic system described in the early 1950s by Couinaud[55], who defined the intrahepatic divisions of blood vessels and bile ducts. However, 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"[56] was based on the internal anatomy and described the several levels of division of the liver segments; today, it has gained wide acceptance 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. Hepatic resections have regularly been along the liver segmental anatomy planes[31]. An alternative approach is a non-anatomical or wedge resection, removing a smaller volume of liver with reduced postoperative morbidity and mortality. However, this carries a higher risk of positive resection margins[41]. However, in a recent series where wedge resections were performed for single rather than multiple lesions, the incidence of positive resection margins was equivalent for both wedge resection and segmental resection (8.3%), and the five-year survival was equivalent in both groups[57].

Intraoperative ultrasound can delineate the interior anatomy of the liver, including intrahepatic vessels, and allows hepatic resection to be performed more safely and anatomically. Moreover, intraoperative ultrasound may identify extrahepatic sites of the disease, such as infiltrated lymph nodes in the celiac axis and the liver hilum, or deposits in the peritoneal cavity[58]. Extrahepatic disease sites in the peritoneal cavity impart a significant disadvantage in prognosis, whereas an excellent five-year survival (20% to 48%) can be achieved with pulmonary metastases with an R0 resection[59].

There is a variety of techniques and devices used for hepatic resection, including the clamp crushing technique, Cavitron Ultrasonic Surgical Aspirator (CUSA, Covidien, Mansfield, MA, United States), Hydrojet (Hydro-Jet, Erbe, Tubingen, Germany), and bipolar sealing devices. Among these, the clamp crushing technique remains the most efficient in terms of reduced operation time, blood loss and total costs[60].

Synchronous disease

Synchronous hepatic metastases occur in about 20%-30% of newly diagnosed colorectal cancers, and they present a challenging problem in the management of these patients[9]. Consensus has not been reached as to the timing of surgical resection of the hepatic secondaries and the primary colorectal tumor. Traditionally, these patients

were managed by a second laparotomy 12-16 wk after the resection of the primary tumors[61]. The advantage of this approach is that it provides less surgical insult to the patient as the incision used in the two operations is different[14]. However, with advances in perioperative care and the continuous improvements regarding the postoperative morbidity and mortality rates after liver resection, most researchers today support simultaneous resection[62,63]. In fact, very few reports in the last decade still strongly oppose the simultaneous procedure.

Today, a simultaneous resection is preferred when there is a right colon primary, or when a single hepatic lesion is contemplated, whereas a staged resection is often done in case of rectal primaries, or multiple liver secondaries[31]. However, no real indications or contraindications exist for simultaneous resection of hepatic metastases, and it seems that the final decision depends on the surgeon's experience and the patient's physical status. In general, the results of simultaneous resection are comparable to staged resection in terms of morbidity, and mortality rates; 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[64].

Locally ablative modalities in combination with liver resection

Locally ablative modalities, such as radiofrequency ablation (RFA)[65], cryotherapy[66], or high intensity focused ultrasound[67], can be used in combination to hepatic resection, to offer curative treatment in patients with unresectable tumors. RFA is the most widely used modality. The goal of the combined approach is to resect the bulk of the metastatic load and to ablate the residual smaller lesions, to achieve a R0 status, preserving at the same time adequate liver parenchyma to avoid postoperative hepatic failure[68]. According to the MD Anderson Cancer Center' s experience[65] in the combined approach for advanced hepatic malignancies (72% were hepatic colorectal metastases), the perioperative mortality and morbidity rates were 2.3% and 19.8%, respectively. In addition, patients with colorectal secondaries had a median actuarial survival of 37.3 mo. The authors point out that the functional residual hepatic volume has to be accurately estimated to avoid fatal hepatic failure postoperatively, which is quite common in this combined approach.

The use of RFA in combination with surgical resection allows the hepatic surgeon to ablate small lesions while removing the large ones. RFA combined with hepatectomy is well tolerated by the patients and adds minimal complexity and morbidity to the operation. However, RFA is inferior for local control of metastatic lesions, systemic spread, and long-term survival. Indeed, there is a higher local recurrence rate associated with RFA than with resection, resulting in inferior disease-free survival rate[21]. Therefore, for the treatment of solitary hepatic metastases, the application of RFA cannot be primarily recommended[69]. On the other hand, RFA can be used as palliative treatment for unresectable metastases, as it achieves better survival than chemotherapy[21]. The only limitations in the use of RFA and other locally ablative modalities are the size of the lesion and its location close to major biliary or vascular structures[31].

Bilobar metastases

The management of bilobar liver metastases demonstrates the advantages of a multidisciplinary approach with a step-by-step strategy and restaging at regular intervals, to achieve a complete resection in most of these patients. The prognostic significance of bilobar distribution of multiple metastases is controversial. Some researchers report bilobar distribution as a poor prognostic factor[9], whereas others support the view that bilobar distribution does not affect overall patient survival[8,10]. In fact, the total tumor volume of liver metastases seems to have a stronger influence on survival than the number or location of metastatic lesions[70].

Surgical resection should be performed only if all the metastatic load of the liver can be removed (R0 resection). In case of involvement of lymph nodes in the hepatic pedicle, with frozen section confirmation, an extensive lymphadenectomy should be performed from the liver hilum to the celiac axis. Moreover, in patients who have more than three poorly differentiated metastatic lesions in segments IV and V, a routine extended lymphadenectomy of the hepatic pedicle seems justified[71,72].

In general, hepatic lymph node involvement is a poor prognostic factor affecting survival of these patients[9], but according to a multi-center study by the Association Francaise de Chirurgie, the five-year survival rate of patients with hepatic pedicle lymph node involvement who underwent lymphadenectomy was 12%, compared to the expected 0% to 2 % without resection[10].

The presence of extrahepatic disease is no longer a contraindication to hepatic resection. Recently, encouraging results have been reported in patients treated for liver metastases and peritoneal carcinomatosis[73]. However, this approach is suitable only for expert teams with experience in liver surgery and intraperitoneal chemotherapy[72].

Two-stage hepatectomy

The aim of this approach is to achieve in two steps a complete resection of the metastases in cases initially considered unresectable. In these cases, a single hepatectomy would have left too small a remnant liver after surgery, with a high risk of liver insufficiency after surgery[72]. In two-stage hepatectomy the highest possible number of tumors are resected first, and the remaining tumors are resected in a second procedure after a period of liver regeneration[13].

The aim of the first hepatectomy is to make the second hepatectomy potentially curative. Mapping permits the surgeon to achieve this by resecting the highest possible number of liver tumors or by clearing the metastatic load from the less invaded hepatic lobe, leaving

the other to be resected after regeneration. Neoadjuvant chemotherapy is given after the first operation, beginning three weeks postoperatively, so it does not interfere with initial liver regeneration. The usual interval between the two stages should be usually around 4 mo, (from 2 to 14 mo), depending on the progress of liver regeneration[13]. Patients with multiple bilobar liver metastases and too small a future remnant liver could be treated with a two-stage procedure with the use of portal vein embolization[72].

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 the colectomy, leaving the second major hepatectomy to be done in a second stage[72].

FOLLOW UP AFTER RESECTION

Patients who have undergone hepatic resection of colorectal metastases are monitored to identify early recurrence that may be amenable to repeat resection for cure. Most patients undergo serial physical examination, serum CEA level, chest X-ray, and CT 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[28]. Most patients surviving after liver resection present with recurrent disease at the liver or lung. The liver is the site of recurrence in 45% to 75% of cases after liver resection[5], and this explains the fact that most chemotherapeutic regimens address mainly the liver.

ADJUVANT CHEMOTHERAPY

Postoperative chemotherapy following complete resection of metastatic disease may lead to improvement in long-term prognosis. The past decade has been marked with significant changes in the options available for this group of patients. In addition to 5-FU, which has been used since 1996, several new drugs have been introduced on the market for the treatment of metastatic colorectal cancer (2006): irinotecan, oxaliplatin, capecitabine, benacizumab, and cetuximab. Therefore the efficacy of treatment regimens has substantially increased[28].

Adjuvant chemotherapy is used to increase survival and decrease the rate of recurrence. Recently, the first randomized clinical trial by Portier *et al*[74], which compared surgery alone to surgery plus adjuvant chemotherapy, provided clear evidence that adjuvant chemotherapy is beneficial for patients with colorectal liver metastases. In this study, 173 patients were randomly assigned to surgery and observation or surgery plus 6 mo of systemic adjuvant chemotherapy. The results showed a significantly improved five-year disease-free survival in the surgery plus chemotherapy group compared to surgery alone (33.5% *vs* 26.7%), with a trend towards improved overall five-year survival.

Adjuvant chemotherapy does not decrease the metastatic recurrence rate in the remnant liver after resection[75]. Indeed, according to another study[76], in patients with complete clinical response to chemotherapy according to CT imaging, in situ recurrence was observed in 78% one year after surgery, because of non-visible but viable tumor cells or microscopic disease.

REPEAT RESECTION

As mentioned in the natural history section, the majority of patients with colorectal liver metastases (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[17]. For these patients, the only chance to prolong life would be a repeat resection, usually combined with a locally ablative therapy (RFA). The results of repeat curative resection are comparable to the first one[14].

The only problem 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[27,77]. Therefore, repeat hepatectomy provides similar long-term survival to primary hepatectomy, without increasing perioperative morbidity and mortality[78]. Indeed, Pessaux *et al*[79] showed that overall five-year survival rates after the first, second and third hepatectomy are similar: 33%, 21% and 36%, respectively.

There are a number of 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 carcinoembryonic antigen levels, and the presence of extrahepatic disease[80,81]. 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[69]. 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.

CONCLUSION

There is an ongoing progress in the diagnostic imaging, chemotherapeutic regimens, and surgical techniques in the management of hepatic colorectal metastases. Hepatic resection has been recognized as the only treatment that could offer long-term survival. Traditional risk factors, indications, and contraindications have been abandoned. The present principle as to resectability is that resection should be performed if all metastases could be removed, while leaving a sufficient remaining liver parenchyma, regardless of their size, number, location and distribution.

Proper use of modern chemotherapy, PVE and/or two-stage hepatectomy and locally ablative modalities

might improve the resectability and prognosis in these patients. This review emphasizes the importance of a multidisciplinary approach for the optimal management of this disease. Moreover, decision making and patient care requires careful assessment of the risks and benefits for each individual, as well as balancing the technical feasibilities and oncological options for each case.

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