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Preoperative selection of patients with colorectal cancer liver metastasis for hepatic resection

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Abstract

Surgical resection of colorectal liver metastases (CRLM) has a well-documented improvement in survival. To benefit from this intervention, proper selection of patients who would be adequate surgical candidates becomes vital. A combination of imaging techniques may be utilized in the detection of the lesions. The criteria for resection are continuously evolving; currently, the requirements that need be met to undergo resection of CRLM are: the anticipation of attaining a negative margin (R0 resection), whilst maintaining an adequate functioning future liver remnant. The timing of hepatectomy in regards to resection of the primary remains controversial; before, after, or simultaneously. This depends mainly on the tumor burden and symptoms from the primary tumor. The role of chemotherapy differs according to the resectability of the liver lesion(s); no evidence of improved survival was shown in patients with resectable disease who received preoperative chemotherapy. Presence of extrahepatic disease in itself is no longer considered a reason to preclude patients from resection of their CRLM, providing limited extra-hepatic disease, although this currently is an area of active investigations. In conclusion, we review the indications, the adequate selection of patients and perioperative factors to be considered for resection of colorectal liver metastasis.

Key words: Colorectal cancer liver metastases; Liver resection; Hepatectomy; Patient selection; Preoperative selection

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Core tip: Resection of colorectal liver metastases has shown to prolong survival. Proper selection of patients who would benefit most from such a major procedure is crucial. Past contraindications are continuously being challenged. At present the only requirement is the anticipation of acquiring a negative margin and an adequate future liver remnant. Extrahepatic metastases are considered based on site and controllability. The use of preoperative chemotherapy in resectable disease remains an area of controversy. This article reviews the preoperative selection of patients for colorectal liver metastasectomy.

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INTRODUCTION

"Biology is King; selection of cases is Queen, and the technical details of surgical procedures are princes and princesses of the realm who frequently try to overthrow the powerful forces of the King and Queen, usually to no long-term avail, although with some temporary apparent victories^[1]." - by Blake Cady, MD.

Colorectal cancer remains one of the three most common cancers in many countries^[2,3]. Around two thirds of patients will develop distant metastases during the course of their illness^[4]. The liver, in addition to being the most common site of metastases^[4], is also the first and only area of spread in 30%-40% of patients^[5-7]. Survival of patients with colorectal liver metastases (CRLM) is dismal if left untreated, whether the metastases are synchronous (developed within 12 mo of diagnosis) or metachronous (developed after 12 mo of diagnosis), with a 5-year survival of merely 3.3% and 6.1% respectively^[8]. However, unlike many other types of cancer, the presence of distant metastases does not preclude curative treatment. With ongoing advancements in multidisciplinary management, surgical resection of CRLM has demonstrated improvement in long-term survival for a significant number of patients, reaching an overall 5-year survival of up to 50%-60%^[9-11]. Unfortunately, not all patients with CRLM are candidates for resection^[12], either due to the status of their hepatic or extrahepatic disease, or their overall functional condition. Nevertheless, the criteria for selection of patients for colorectal liver metastasectomy are undergoing continuous modification and expansion^[13]. To further improve survival, proper selection of patients who would benefit most from such an invasive procedure becomes vital^[14]. This article reviews the preoperative selection of patients for colorectal liver metastasectomy. All

authors declare that they have no competing interest in the publication of this manuscript.

GENERAL PATIENTS FACTORS

A number of patient related factors must be assessed before the decision to resect CRLM is taken prior to any surgical intervention such as age, comorbidities, and tolerance to anesthesia.

In Höhn's classification^[15], liver resection is considered a major abdominal surgery. The resection of CRLM is performed *via* an open or laparoscopic approach commonly under general anesthesia (GA) alone or in combination with epidural analgesia. In the past 2 years, some centers report the procedure being performed under epidural anesthesia alone^[16], in aim to reduce the requirement of systemic narcotic and to allow better postoperative bowel function and preservation of pulmonary function^[17]. This, however, has not been established amongst the surgical community and is not until now the general consensus^[18]. It is therefore vital that the patient's tolerability to GA be evaluated prior to the decision to operate. Intraoperative blood loss^[19] and transfusion requirements^[20] are major determinants of morbidity and mortality following liver resection. It was found that blood loss may be controlled by lowering the central venous pressure to 5 mmHg or less intraoperatively^[21]; Johnson *et al*^[22] observed an almost bloodless operating field when CVP was less than 6 mmHg. Hypoperfusion injury is the main concern in regards to this technique, mainly acute kidney injury (AKI); which has been observed in procedures that may compromise splanchnic and renal circulation^[23]. It was however found in a retrospective analysis of more than 2000 liver resections^[24], that although renal dysfunction was fairly common when lowering CVP, it was more importantly a transient event with limited clinical significance.

The presence of comorbidities is still being argued as a reason to preclude a patient from hepatic surgery. In the "Patient Safety in Surgery Study" by Virani *et al*^[25] it was reported that a history of previous cardiac operation, hypertension, diabetes, dyspnea, COPD, ascites, wound or wound infection, alcohol use, dialysis, or bleeding disorder was associated with or had a trend towards association with postoperative morbidity or mortality. However, the status of these comorbidities should be optimized preoperatively, and surgery should only be contraindicated in certain conditions; acute liver failure, acute renal failure, acute viral hepatitis, alcoholic hepatitis, cardiomyopathy, hypoxemia, and severe coagulopathy (despite treatment)^[26]. Major abdominal surgery, especially when performed in a cancer setting warrants medical venous thromboembolism (VTE) prophylaxis^[27]. However, it has generally been believed that the post hepatectomy phase carries a high risk of bleeding secondary to post-

operative liver dysfunction^[28], thus decreasing the need for VTE prophylaxis due to this “auto-anticoagulation” effect. Yet, the contrary has been proven; the post hepatectomy phase in fact carries an increased risk for VTE, which increases in proportion to the extent of resection^[29]. This would necessitate the use of VTE prophylaxis in hepatectomies. The exception to this would be patients with known preoperative bleeding disorders, in which case achieving adequate homeostasis is prioritized.

Laparoscopy has increasingly proved to be of use in liver surgery, as it is associated with less surgical stress^[30], decreased blood loss and pain, shorter hospital stay, and lower complication rates^[31,32]. Most importantly laparoscopy has comparable long-term survival as the open approach when resecting CRLM, with the added benefit of allowing a simpler procedure in the event of recurrence^[32]. The role of laparoscopy has been especially established in minor liver resections^[31], but is not as clear in major resections^[33].

Various multi-institution studies determined advanced age to be an independent risk factor for morbidity and mortality following major abdominal procedures^[34,35]. Nonetheless, other studies stated that advanced age in itself is no longer considered an exclusion criterion while entertaining the possibility of liver resection; comparable mortality, morbidity, and survival have been achieved in older age groups as appose to younger patient^[36]. This controversy may be explained by the latter’s group bias in patient selection and the limitations posed by the extent of the procedures performed on the older age group^[37]. In an attempt to provide a broader view, an analysis was performed of the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database including over 400 different hospitals, they compared patients ≥ 75 years old with those < 75 undergoing elective hepatectomies^[38]. It was found that elderly patients were more likely to experience severe complications, and given their lower physiological reserve were less likely to be rescued successfully, and in consequence contributing to the major increase in the rates of 30-d postoperative mortality. This should not discourage selection of elderly patients for resection, but warrants optimization of their preoperative status as aforementioned, while also balancing the risks and benefits by which guide the extent of the procedure to be taken. At present, there does not seem to be any literature evaluating patients of an older age group (> 80 years), except for 2 case reports demonstrating successful hepatectomies in patients over 90 years of age^[39]. Although the authors stated that no postoperative complications were encountered, neither the post-operative course nor survival was mentioned.

A standard blood workup should be performed preoperatively, and abnormalities ought to be corrected as possible before surgery is commenced. Virani *et al*^[25] reported that preoperative elevated

alkaline phosphatase, bilirubin, creatinine, aspartate aminotransferase (AST), and decreased sodium was associated with increased morbidity. They also observed that the mean albumin level was lower in patients that developed complications in contrast to those that didn’t. A baseline carcinoembryonic antigen (CEA) should also be obtained preoperatively. Although the result in itself does not affect preoperative selection of patients for resection, a trend of rising CEA post hepatectomy should alert the treating physician of an unfavorable prognosis^[40]. Serum CEA and C-reactive protein (CRP) are also used in various prognostic scoring system^[36,41], which will be discussed below, and thus should be obtained to aid in correct preoperative stratification of patients.

IMAGING FOR EVALUATION OF THE METASTASES

Preoperative imaging studies aim to: (1) delineate the extent of hepatic metastases, whether they are segmental or lobar; (2) determine their best management plan; and (3) identify extrahepatic disease, taking into account lymph node and peritoneal involvement, local or regional recurrence or residual, and other sites of hematogenous spread such as the lungs^[42]. Many imaging modalities are available; the choice is determined by availability and user experience, in addition to the purpose of each study and the limitation it may present, and finally, available imaging results^[43].

In the 2006 British guidelines for resection of colorectal liver metastases, Garden *et al*^[44] recommended that detection of colorectal metastases be done using contrast-enhanced CT scans of the abdomen, pelvis, and chest (chest x-ray would also be acceptable). Multidetector-row CT (MDCT) is the most commonly used imaging modality for detection and characterization of hepatic metastases^[45], with detection rates of 68% to 91% using contrast-enhanced CT (CECT) scans of the abdomen^[46]. Nonetheless, a limitation that cannot be overlooked, in addition to the need for a high radiation doses, is the inability of CT to sufficiently characterize sub-centimetric lesions^[47], as appose to the more expensive and not so readily available option; magnetic resonance imaging (MRI) with hepatobiliary contrast^[43]. A recent retrospective study proposed this be overcome intraoperatively by using intraoperative ultrasonography (IOUS) for patients who were scanned with CT preoperatively, thus preventing unnecessary waiting times prior surgery and at lower costs, whilst also providing adequately sensitive detection^[48]. CT, however, remains inferior to MRI in detecting hepatic lesions on a background of fatty infiltration^[49].

Fluorodeoxyglucose-positron emission tomography (¹⁸FDG-PET) is an imaging technique that provides unique molecular and metabolic information in regards to many oncological diseases^[50]. To provide optimal

results, PET is combined with CT (or CECT), to produce a whole body metabolic map of glucose uptake^[43,50]. PET continues to prove to be of benefit in preoperative imaging of CRLM. In a recent meta-analysis and systemic review of the published literature, Maffione *et al.*^[51] found the following: (1) ¹⁸FDG PET/CT was 93% accurate in the detection of liver lesions on a patient basis, but less accurate on a lesion basis (sensitivity = 60%, specificity = 79%); (2) When compared to both MRI and CT, PET was less sensitive but more specific; and (3) With its added advantage of delineating extrahepatic metastases^[52], extrahepatic disease identified by PET and not by other imaging techniques had a mean incidence of 32%, and subsequently the decision to operate was either aborted or modified in a substantial number of patients (24%). Nonetheless, when PET/CT was studied in randomized settings, its addition to the diagnostic workup showed no influence on survival^[53].

Regarding MRI (magnetic resonance imaging), the International Hepato-Pancreato-Biliary Association (IHPBA) stated in their most recent expert consensus statement that in optimal situations "MRI combining Gd-EOB-DTPA (a hepatocyte-specific contrast agent; gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid) delayed images and diffusion-weighted imaging has the best performance characteristics for detecting and characterizing liver lesions, particularly those < 1 cm in size^[43]." This is of increased value in patients with preexisting steatosis, or chemotherapy induced changes^[49].

Finally, despite its limited role in staging or patient selection prior to surgery, ultrasound has undergone major advances that has made it an indispensable tool^[54]. The role of intraoperative ultrasound (IOUS) remains vital for correct staging and operative planning. Though the percentage varies amongst reports, IOUS continues to prove to be of value in identifying new sub-centimetric liver lesions intraoperatively that were missed during preoperative imaging, thus changing the surgical strategy of resection^[55]. The development of contrast-enhanced ultrasound (CEUS) has dramatically increased the potential of sonography in the assessment of focal liver lesions. The use of US contrast agents permits real time demonstration of the parenchymal microvasculature and the enhancement patterns of liver lesions, unlike the predetermined time points of contrast circulation utilized in CECT and MRI^[56]. Safety is an additional advantage of US contrast agents^[57]; as no hepato-, nephro-, or cardiotoxicities have been reported. The combination of the above mentioned techniques produces contrast enhanced IOUS (CE-IOUS). Recent studies have shown it to be beneficial in delineating minute metastases that would otherwise be difficult to identify against chemotherapy-induced background parenchymal injury^[58]. Torzilli *et al.*^[59] suggested that CE-IOUS be reserved for patients with multiple and isoechoic liver lesions on IOUS.

HEPATIC FACTORS

Despite the fact being that resection of hepatic metastases remains the only curative option for CRLM, less than 25% of patients are candidates for surgery^[12]. In 1986, Hughes *et al.*^[14] analyzed their hepatic metastases registry; this was the first reported attempt to develop a criteria for indications and contraindications for resection. They regarded the presence of positive porta-hepatis node, extra hepatic metastases, or four or more hepatic metastases to be contraindications to liver resection. Patients with Duke's C primary tumor presenting with multiple metastases or synchronous metastatic disease were also considered to be inappropriate for liver resection. During the same year, Ekberg *et al.*^[60] required the following to be present to qualify for resection: a maximum of three liver lesions, the ability to achieve a 10 mm resection margin, and absence of extrahepatic metastases. Since then, most, if not all, of these prerequisites have been challenged; the criteria are continuously undergoing revision and expansion^[13].

Resectability of metastatic lesions

Currently, the only local requirements that need be met to undergo resection of CRLM are: the anticipation of attaining a negative margin (R0), whilst maintaining an adequate future liver remnant (FLR) with adequate vascular inflow, outflow and biliary drainage^[61]. Therefore, regardless of other associated clinical factors, patients are candidates for resection provided they have an acceptable functional capacity, with technically resectable metastases confined to the liver, regional lymph nodes and/or lungs^[36,62].

The resection margin has for long been debated; some authors stress that an optimal margin should be at least 10 mm^[63], though a sub-centimetric margin should not be a criterion of exclusion^[42]. In contrast, various others and large scale studies report that neither overall nor disease free survival nor recurrence is affected by the width of the margin^[64-68]. Widespread acceptance of margins as narrow as 1 mm or less emerges from the realization of the importance of preserving liver volume and function^[40]. This is also due to the fact that 58%-78% of patients develop recurrence after initial resection of CRLM, almost 50% being intrahepatic^[69-72]; it is therefore crucial to maintain as much liver volume as possible during the first hepatectomy to widen treatment options in the event of recurrence^[40]. Thus the main factor affecting the decision of resection is the FLR and resection potential is determined but what will be left of the liver rather than what is being resected.

Invasion into the biliary ducts though may seem aggressive, in fact signifies an indolent nature of the tumor, and surprisingly better prognosis following resection^[73]. Preoperative imaging should however be utilized to assure complete surgical clearance.

Future liver remnant

The ability to calculate the future liver remnant (FLR) is a crucial factor in patient selection, bearing in mind that inadequate FLR is major contributor to early post-hepatectomy liver failure^[74]. An otherwise healthy liver will tolerate reducing its volume all the way down to 20%. However one that has developed chemotherapy induced injury or cirrhosis will require a FLR of 30% and 40% or more respectively according to the severity of the disease^[75-77].

Both the volume and function of the future remnant provide invaluable information. Liver volumetry offers a quantitative means^[75]; this is commonly calculated *via* CT, which is both reproducible^[78] and accurate^[79]. Functional assessment of the regenerative capacity of the FLR can be measured by assessing the liver's response to portal vein embolization (PVE)^[75]. Despite the fact that the liver continues to hypertrophy over time after PVE, the majority of the hypertrophic response happens during the first 3 wk, where a minimum of 5% degree of hypertrophy is considered acceptable^[80]. Another less commonly used method of measuring the functional capacity of the FLR is indocyanine green (ICG) clearance, which is utilized widely in Southeastern countries^[81]. In spite of the inverse relationship between the number and size of hepatic metastases and patient survival^[36,82], it has become the general rule that if an adequate FLR can be achieved by resection, this relationship should not be considered a reason for exclusion^[62].

Concurrent liver pathologies

Asides from the presence of the metastatic lesion, the health of the liver itself must be taken into consideration. A small Chinese study reported that although viral hepatitis in itself did not influence post-operative liver injury, it however did contribute to poor liver regeneration following hepatectomy by halting the post-operative surge of IL-6^[83].

Nonalcoholic steatohepatitis (NASH), but not simple steatosis, has also been linked to the post-operative course, as it increases overall and hepatic related morbidity^[84,85]. This has been demonstrated in experimental models, where the association between fatty infiltration of the liver and the decreased regenerative capacity following occlusion of the portal vein, as well as the increased sensitivity to ischemia reperfusion injury and hepatocellular injury following liver resection has been shown^[86]. Many preventive strategies may be implemented to overcome this in hopes of improving the liver's tolerance to resection; characterizing the degree of involvement of the liver parenchyma using invasive and non-invasive measures, while also utilizing parenchymal sparing techniques and liver volume modulation *via* portal vein embolization ligation^[87]. Medical therapies, such as vitamin E and pioglitazone, have also been postulated to downstage NASH^[88]. However the prolonged time needed to

optimize the liver "medically" may not be applicable in the surgical setting, as patients presenting with liver cancer will most likely require prompt management^[87]. A recent experimental study brought to light the effect of a 2 wk preoperative course of omega-3 acids in decreasing severe steatosis, thus improving liver regeneration and functional recovery following liver resection^[89]. Administration of insulin and dextrose to maintain a perioperative state of hyperinsulinaemic normoglycaemia has shown to significantly decrease postoperative liver dysfunction^[90], while also decreasing systemic inflammation^[91]. This method is more time efficient in comparison to the prior mentioned medical strategies.

There is a low incidence of CRLM within cirrhotic/unhealthy livers^[92]. This in turn reflects the small number of resections performed in this setting. Ramia *et al*^[93] attempted to evaluate the experience of multiple centers in resection of CRLM on a background of cirrhotic livers; of 2364 patients, only 20 had unhealthy livers (of which 10 were cirrhotic). Although the number was small, they observed low morbidity, null postoperative mortality rates, and acceptable total and disease free survival rates. The main concern post resection is the impaired ability of the cirrhotic liver to recover^[94]. Various methods may be implemented to overcome this preoperatively. As aforementioned, an anticipated adequate FLR is crucial when planning for resection; a 40% FLR is acceptable in a cirrhotic liver, as a pose to 20% in a healthy liver^[75-77]. Portal vein embolization may be utilized in cirrhotic livers when the FLR is \leq 40%^[95]. If the liver then still does not hypertrophy, major resection should be contraindicated^[96]. The degree of portal hypertension should also be assessed preoperatively, as gradients greater than 10 mmHg were related to increased morbidity and decreased survival^[97].

TIMING OF LIVER RESECTION

Of patients presenting with colorectal cancer, 14.5%-24% present with synchronous hepatic metastases. An additional 8.1%-20% present later with metachronous lesions^[8,98,99]. Although the presence of synchronous metastases suggests a disease of more aggressive nature which has proven to be a negative prognostic factor, this in itself should not be considered a contraindication to resection of liver lesions if curative intent is to be achieved^[100], as survival rates of both resected synchronous and metachronous lesions are similar^[101]. Bova *et al*^[102] studied the impact of the timing of occurrence of liver metastases on early postoperative outcome and long-term survival of colorectal cancer patients; they found that there was no difference between patients who had underwent curative hepatic resection for synchronous and metachronous CRLM. The timing of resection of the synchronous liver lesion remains controversial. Multiple approaches exist:

the traditional primary first approach, the liver first approach, and simultaneous resection of the primary and metastatic liver disease.

The traditional approach to patients with synchronous CRLM has traditionally been to address the primary tumor first, then to resect the liver lesion(s) in a later setting^[103]. The rationale behind this arises from the necessity of achieving source control of the primary disease first^[104]. This has however become a controversial area of discussion. The alternative liver-first approach gains its popularity from its aim to prevent the time lost between resection of the primary tumor and oncological therapy^[105]. Patients with rectal cancer will most often require complex and lengthy neoadjuvant chemoradiotherapy, which if begun prior to hepatectomy would result in progression of the liver disease^[106]. It is in this setting, and with the knowledge of the influence of metastatic liver disease on survival more than the primary colorectal disease itself, that patients would be suitable candidates for the liver-first approach^[107]. A meta-analysis by Kelly *et al.*^[108] reviewing the conventional, reversed, and combined approach observed that the liver-first group had the highest percentage of bilobar disease. This is consistent with the goal of providing oncological downstaging leading to curative resections. In regards to survival, patients undergoing a liver-first procedure showed similar^[10,107] if not superior^[109] overall and disease free survival as those undergoing the conventional colon-first procedure. Thus this approach may be utilized to obtain favorable results in a selected population of patients that have a high burden of CRLM, in comparison to a lower risk of the primary tumor to cause complications^[10].

Multiple meta-analyses showed that resection of the colorectal cancer and liver metastases in one setting was equal or superior to a staged resection in means of postoperative mortality, morbidity, hospital stay, overall and disease free survival^[110,111]. This indicates that simultaneous resection is a reasonable strategy in CRLM that could spare the patient the burden of undergoing two major procedures. The opposing opinion argues that delaying the liver surgery allows for occult metastases to become apparent, thus enabling better tumor clearance^[112] and improving patient selection by avoiding futile operations in patients whom prove to have an unresectable disease^[113]. However according to the "cascade" theory, cancer cells would migrate from the liver to the lung during the waiting period between resection of the primary tumor and the synchronous liver metastases^[114]. This again puts forward the benefits of simultaneous resection in aims of preventing dissemination of malignant cells. Yin *et al.*^[111] in their meta-analysis, pinpointed factors that were to be considered selection criteria for patients to undergo a simultaneous liver resection directed against delayed resection: resection of a maximum of three liver segments, right colectomy, and patients younger than 70 years old with no coexisting severe illnesses.

CHEMOTHERAPY AND RESECTION

Although resection is curative for CRLM, not all patients are candidates for hepatectomy^[12]. Cytotoxic and biological agents may be used peri-operatively to decrease both the tumor volume and risk of relapse^[115]. There are two situations in which preoperative chemotherapy may be administered; first, when the hepatic lesions are unresectable, where in the chemotherapy is considered as "induction" therapy to render the unresectable disease to a resectable state^[116].

In the context of unresectable liver disease, chemotherapy presents itself as the only initial treatment option^[117]. While the goal of chemotherapy in the vast majority of these patients is confined to prolonging survival and improving quality of life, the proportion of those that show good response to treatment may later be considered resectable^[118]. Multiple retrospective series evaluated the outcome of patients undergoing resection after downstaging of initially unresectable CRLM; the 5 year survival reached 33%^[119,120]. Beppu *et al.*^[121] found several factors that were associated with successful conversion or induction therapy: left colon or rectal cancer, H1/H2 metastases based on the Japanese Society for Cancer of the Colon and Rectum categories (H1: ≤ 4 lesions with the largest ≤ 5 cm, H3: ≥ 5 lesions with the largest > 5 cm, H2: anything that is not H1 or H3)^[122], absence of extrahepatic metastases, and response to chemotherapy. The former three may be used prior to induction to stratify patients with initially unresectable disease who would benefit most from aggressive chemotherapy, as a pose to palliative care.

The second situation is when the hepatic lesions are resectable, in which we consider the chemotherapy to be "neoadjuvant"^[116]. The proposed benefits are: (1) treatment of micrometastases; (2) reduction of the tumor volume, thus allowing a simpler more radical resection; and (3) shedding light on those who progress while on chemotherapy, hence identifying patients with aggressive tumor biology to be precluded from surgery^[123,124]. Additionally, the progression of a resectable disease into an unresectable one while undergoing neoadjuvant chemotherapy raises concern^[104], although this only happens in a minority and would indicate poor prognosis, mandating a second-line of chemotherapy before considering resection^[125].

The controversy arises from the concerns in regards to the effects of preoperative chemotherapy on the liver parenchyma, which would in turn increase the risk of post-operative complications. Whilst also leading to disappearing metastases on imaging, which would result in a more difficult resection^[111]. Two sequel of chemotherapy have been described; sinusoidal obstructive syndrome (SOS), with the use of oxaliplatin^[126], previously known as veno-occlusive disease^[127], and chemotherapy-associated steatohepatitis (CASH), with the use of irinotecan^[128]. Both sequel have been reported to occur with 5-fluo-

ouracil (5-FU), but to a lesser extent^[127]. The development of SOS appears to be linked to the number of oxaliplatin cycles, as it develops when ≥ 6 cycles are administered^[129]. However, the overall cumulative dose does not seem to affect the severity of SOS^[130]. The importance of this seems evident in the fact that patients with SOS undergoing major hepatectomy were found to have higher rates of postoperative complications, although it did not contribute to increased mortality^[131]. Molecular studies suggest that activation of vascular endothelial growth factor (VEGF) and coagulation pathways lead to the development of SOS, and thus support the clinical observation of the preventive role of bevacizumab (an anti-VEGF)^[132] and aspirin^[133]. Despite bevacizumab being reported to delay healing, it can be used safely if discontinued 6 to 8 wk prior to surgery^[132]. Only a limited number of studies reported regression of SOS and fibrosis following concurrent administration of cetuximab, an anti-epidermal growth factor receptor (EGFR)^[134], with the added benefit of not increasing post resection morbidity and mortality^[134]. Its effect on hepatic regeneration, has not yet been studied. However it has been proven to contribute to the development of drug induced lung injury, especially during the initial 90 d of therapy, which throughout the patient should be monitored closely^[135]. Steatosis and CASH however, appear to be associated with both increased morbidity and mortality following hepatectomy^[128,136]. Post-operative mortality in those with CASH was related to the development of hepatocellular insufficiency^[128], especially in patients with a BMI of more than 35 kg/m²^[137].

In a systemic review by Nigri *et al.*^[138] of published data, there was no evidence of improved survival in patients who had received preoperative chemotherapy, as a pose to those who underwent surgery alone. Only one study found a superior survival in the neoadjuvant group^[139], this study was however exclusive to patients with extensive disease including five or more bilobar metastases. Furthermore, pairing pre- and postoperative chemotherapy fails to significantly improve long term survival as proven by the European Organization for Research and Treatment of Cancer Intergroup (EORTC) 40983 randomized controlled trial^[125,140], which had a fairly lengthy follow up duration (median of 8.5 years). This trial, however, was limited to the FOLFOX4 regimen (folinic acid, fluorouracil, and oxaliplatin).

In summary, this deems the data insufficient to consider neoadjuvant chemotherapy a standard of care in initially resectable CRLM, although many centers will favor this approach, in part to evaluate response to chemotherapy^[138]. The decision should therefore be individualized to each situation. A final point to consider if chemotherapy is to be administered preoperatively in a resectable disease, is that it is not recommended for more than 3 mo^[131], nor for more than 6 cycles to be used^[131], and should be discontinued at least 4 wk prior to surgery^[133].

EXTRAHEPATIC DISEASE

In the past, the presence of extrahepatic disease (EHD) was considered a contraindication to resection of CRLM^[14]. However, reports of increased survival following resection of liver lesions in the setting of EHD have put this theory to challenge^[141]. The main purpose of resecting colorectal cancer liver metastases is rendering the patient as disease free as possible aiming to prolong overall survival. A crucial consideration to be taken into account is the site of the EHD^[142].

An important factor influencing this decision is the presence of pulmonary metastasis, which represents the most common form of extrahepatic metastases in CRC^[143]. Synchronous liver and lung metastasis remains an area of controversy in regards to the aggressiveness of the treatment that should be attempted. Multiple studies reported improved overall survival when aggressive lung and liver resections were performed in fit patients, with a median of 24.2 mo^[144,145]. Large scale analyses by MD Anderson^[146] and of the LiverMetSurvey registry^[147] showed that patients who underwent both liver and lung metastasectomy had a significantly better survival than those who underwent resection of the liver but not the lung metastases. The resectability of lung metastases is outside of the context of our current discussion, but regardless of this debate, the presence of lung metastases does not contraindicate resection of CRLM, as the burden of the liver tumor itself, not the lung, is what poses a significant factor impacting survival^[142]. In a systemic review by Hwang *et al.*^[142] when resection of CRLM was performed in the presence of EHD, those with pulmonary metastases had the best outcome in comparison with all other sites of metastases.

An area in which no consensus exists yet, is indeterminate pulmonary nodules (IPN); lung nodules ≤ 1 cm without definitive diagnostic characteristics. Although IPN are present in a quarter of the population^[148], the main concern is that they may also represent lung metastases, which would in turn might alter the management plan. During workup of patients opted for resection of their CRLM, IPN are detected in 4%-43%^[149-152]. Of these, 10%-35% were found to be lung metastases on follow up^[149,150]. Downs-Canner *et al.*^[153] concluded that IPN in the setting of CRLM were more likely to represent metastases than in the setting of primary hepatobiliary or other cancers. This however should not preclude patients from resection of CRLM, as survival post liver resection does not seem to be effected by the presence IPN (regardless of what they turn out to be), but does warrant intensive surveillance^[154].

On the other hand, mediastinal lymph node involvement is a consistent poor prognostic factor^[155]. In one study comparing intrathoracic and mediastinal lymph node involvement of CRC metastasis in resected patients, a median survival of 34.7 mo was reported in the former, while zero patients achieved a 5-year

survival in the latter group^[155]. However, there is no uniform consensus regarding routine preoperative assessment or intraoperative sampling. In regards to lymph nodes metastases, its' site provides crucial information to guide management. For instance, patients with portal lymph nodes have a superior survival to those with aortic^[142,156] or celiac nodes^[156]. Adam *et al*^[156] reported a 0% survival in patients with celiac and para-aortic lymph node metastases, thus patients presenting with them should not be considered for resection of their CRLM^[157]. Extensive peritoneal seeding generally indicates poor survival. However, if limited disease may be controlled by means of cytoreduction and intraperitoneal chemotherapy in synchronicity with resection of the CRLM, a 3-year survival of 23%-55% may be achieved^[158-160].

In their expert consensus statement, the IHPBA stated that the decision to resect CRLM in the presence of EHD should only be entertained when the EHD is surgically resectable or is controllable on the long term with adjuvant therapies^[43]. It can be said however, that the presence of EHD in itself and the number of metastases (both hepatic and extrahepatic) influences prognosis^[161]. Even when the EHD is controlled, survival is still only around half of that of patients with resected CRLM without EHD^[161]. Thus only a select group of patients who would benefit from such intervention should be chosen.

PREOPERATIVE PROGNOSTIC SCORING SYSTEMS

Many authors have attempted to develop a preoperative score that would predict prognosis following resection of CRLM, aiming to correctly select patients that would maximally benefit from the procedure. Fong *et al*^[36] in their analysis of around 1000 cases devised a clinical risk score including 5 preoperative components that predicted poor outcome: a node-positive primary, < 12 mo disease free interval from primary to metastases, > 1 liver lesion, the largest liver lesion > 5 cm, and a CEA of >200 ng/mL. They proposed that patients with a score of 2 or less were likely to have a favorable outcome following resection. Whilst those with a score of 3-5 should be opted for other adjuvant options.

The Glasgow prognostic score (GPS) is another score that has been utilized widely to predict outcome in various cancers^[41]. It originally included 2 components: CRP > 10 mg/L, indicating an ongoing systemic inflammation, and serum albumin < 35 g/L. Their absence was assigned a score of 0, the presence of either or both was assigned a score of 1 or 2 respectively. The score was later modified (mGPS) such as hypoalbuminemia present in the absence of an elevated CRP was assigned a score of 0, as low albumin in itself showed to have no significant effect on cancer specific survival^[162]. Both GPS and mGPS

have shown to be useful in predicting survival for those undergoing metastasectomy of CRLM^[163,164]. Kobayashi *et al*^[165] later combined the GPS with CEA levels aiming to identify the group of patients who would be candidates for resection but would later on have poor survival.

MD Anderson devised and validated a radiological based system to predict response of patients with CRLM to bevacizumab-containing chemotherapy^[166]. It has been observed that histologically, tumor response in CRLM is characterized by fibrous replacement instead of tumor necrosis^[167]. The system utilized qualitative morphological CT criteria to assign lesions into three groups; group 1 metastasis was characterized as homogeneous attenuation with a thin, sharply defined tumor-liver interface. Group 3 metastasis was characterized by heterogeneous attenuation and a thick, poorly defined tumor-liver interface. Group 2 metastasis had characteristics that could not be rated as 1 or 3. Morphologic response was defined as: "optimal" if the metastasis changed from group 3 or 2 to 1, "incomplete" if it changed from group 3 to 2, "none" if it did not change or increased. If multiple metastases were present, the response of the majority was taken into consideration. This morphological CT criteria correlates with overall survival, as patients with optimal response showed significantly improved survival following hepatectomy.

Multiple other scores have been developed for this purpose: Nordlinger group's score^[82], Nagashima group's score^[168], Konopke group's score^[169], Rees preoperative and postoperative risk indices^[170], Iwatsuki group's score^[171], Zakaria group's DSS and DFS scores^[172], the Leed group's score^[173], Ueno group's score^[174], Schindl group's score^[175], and Lise group's score^[176].

Roberts *et al*^[177] assessed the ability of eight different scores to correctly predict disease free and disease specific survival using the concordance (C) statistic. A model is considered reasonable if the C-statistic exceeds 0.7, strong if it exceeds 0.8, and perfect when it scores 1^[178]. The only score they found to have a score higher than 0.7 was the Rees postoperative index, thus indicating that available scores are at their best "reasonable"^[177]. In summary, it can be said that scoring systems may guide patient selection and surveillance, but should not be depended upon fully, nor should they replace individual patient tailored management.

Studies have shown that 10 years of surveillance are required to label a patient as being "cured" after resection of CRLM, as no disease related deaths have been reported thereafter^[172,179-181]. First recurrence after resection occurs after 5 years in 4.8%-23%^[172,177,179-181]. Therefore some may argue that intensive follow up after 5 years is unjustified as a standard of care. While others would argue that repeat resection prolongs survival^[177], thus justifying intensive surveillance to allow early identification of recurrence, and thereby providing further curative intervention.

CONCLUSION

Resection of CRLM prolongs survival. Proper selection of patients who would benefit most from such a major procedure is crucial. The criteria for resectability expand continuously. The only local requirements that need be met are: the anticipation of attaining a negative margin (R0), whilst maintaining an adequate FLR. If extrahepatic metastases are controllable surgically or medically on the long-term, their presence is no longer a contraindication for resection of CRLM. Resection may occur simultaneously with the primary tumor, or at a later setting, or even before the primary. This depends mainly on the tumor burden. Chemotherapy may be used in the neoadjuvant setting, although this practice is not unanimously adopted by all centers in the case of initially resectable disease. The two feared consequences of chemotherapy are SOS with the use of oxaliplatin, and CASH with the use of irinotecan, although administering neoadjuvant chemotherapy provides an opportunity to assess disease response to treatment, which may be indicative of the tumor biology.

Finally, although many preoperative scoring systems have been developed, their use should not dictate patient selection. A strong multidisciplinary approach, with collaborations between medical and radiation oncologists, hepatobiliary and colorectal surgeons, radiologists, medical physicians and nursing is mandated in order to select adequate surgical candidates and coordinate the oncological treatment plan for these patients.

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