REVIEW

Multisciplinary management of patients with liver metastasis from colorectal cancer

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Abstract

Colorectal cancer (CRC) is one of the leading causes of cancer-related death. Surgery, radiotherapy and chemotherapy have been till now the main therapeutic strategies for disease control and improvement of the overall survival. Twenty-five per cent (25%) of CRC patients have clinically detectable liver metastases at the initial diagnosis and approximately 50% develop liver metastases during their disease course. Twenty-thirty per cent (20%-30%) are CRC patients with metastases confined to the liver. Some years ago various studies showed a curative potential for liver metastases resection. For this reason some authors proposed the conversion of unresectable liver metastases to resectable to achieve cure. Since those results were published, a lot of regimens have been studied for resectability potential. Better results could be obtained by the combination of chemotherapy with targeted drugs, such as anti-VEGF and anti-EGFR monoclonal antibodies. However an accurate selection for patients to treat with these regimens and to operate for liver metastases is mandatory to reduce the risk of complications. A multidisciplinary team approach represents the best way for a proper patient

management. The team needs to include surgeons, oncologists, diagnostic and interventional radiologists with expertise in hepatobiliary disease, molecular pathologists, and clinical nurse specialists. This review summarizes the most important findings on surgery and systemic treatment of CRC-related liver metastases.

Key words: Liver metastases; Colorectal cancer; Liver resection; Multidisciplinary team; Chemotherapy

Core tip: Approximately 25% of colorectal cancer patients have liver metastases at the initial diagnosis and almost half develop liver metastases later. Although unresectable liver metastases can be converted into resectable disease with the help of combination chemotherapy with targeted therapy, patients should be accurately selected. Multidisciplinary teams including health professional with expertise in hepatobiliary disease is needed to decide the best way to manage these patients' treatment.

INTRODUCTION

Globally, colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females[1]. Moreover, CRC is the second leading cause of cancer mortality in the United States, accounting for 9% of cancer deaths[2]. In Europe, it caused nearly 204000 deaths in 2004[3]. The liver is the most common metastatic site[4], probably due to tumor spread *via* the portal system[5]. Twenty to twenty-five percent of patients have clinically detectable colorectal liver metastases (CLM) at the initial diagnosis and approximately 50% of the patients develop CLM during their disease course[6]. Resection of the CLM, sometimes in combination with other local treatment modalities such as radiofrequency ablation (RFA), has become the standard of care, despite lack of evidence from randomized controlled trials, and offers the only potential for cure[7,8]. The natural history of metastatic colorectal cancer (mCRC) is variable, however, untreated CLM have a poor prognosis with median survival rates of less than 8 mo[6,9]. Only 20%-30% patients with mCRC have disease that is confined to the liver[6]. Patients presenting with CLM can generally be divided into three groups: those with

initially resectable disease; those with metastases that may become resectable following treatment ("conversion" therapy); and patients whose liver metastasis never will be resectable[10]. Unfortunaly, only a minority of patients (10%-20%) with CLM are considered eligible for resection, while about 85% of them have liver disease considered unresectable at presentation[11,12]. Recent data suggest that of those undergoing resection of CLM, around one out of three patients will be still alive after 5 years from diagnosis. A single center 5-years survival now approaches 60% following hepatectomy, with 10 years survival in excess of 25%; about half of them will be alive after 10 years, so considered as cured[13]. A systematic review and meta-analysis of 142 studies published in 1999-2010 has also confirmed these data, showing 5-year survival rates of 16%-71%, for patients with CRC, after surgical resection of liver metastases[14]. Even more, long-term survival rates for those patients with initially unresectable metastases treated with chemotherapy prior to surgery are similar to those of patients whose metastases were considered to be resectable[15-21]. Indeed, since there is a strong correlation between tumor response and resection rate[3,22], this has led to an increased use of chemotherapeutic and biological agents as "conversion therapies" in patients with mCRC. Indeed, these strategies can facilitate downsizing of CLM and convert initial unresectable metastases to resectable. Hence, the percentage of patients potentially eligible for curative liver resection is increasing. This has been due to advances in surgical and perioperative management, the use of more effective chemotherapies and combination therapies, the incorporation of targeted therapies and new local treatment approaches (*e.g.,* hepatic intra-arterial chemotherapy, RFA, stereotactic radiotherapy)[23]. Nonetheless, difficulties remain in deciding who is a candidate for resection, and often underestimated since many patients with liver metastasis never were referred to a hepatobiliary surgeon[24].

Therefore, the goal for patients with metastatic colorectal disease is a multidisciplinary treatment approach, in order to decrease peri-operative morbidity and mortality, as well as long-time survival by increasing the number of patients undergoing potential curative liver resections.

RESECTION OF CLM - CURRENT EVIDENCES

Surgical treatment

Hepatectomy remains the standard of care for CLM. In the past, post-operative mortality was high but nowadays it has decreased to around 1%[25-27] allowing more extended hepatic resections by more advanced surgical techniques. Nevertheless, liver failure after hepatectomy remains the major concern for the hepatobiliary surgeon. Resection, even partial, can

Table 1 Response and resection rates from trials with first-line chemo/biologic therapy

Study	Selection	Treatment	Response	Resection
Van Cutsem *et al*[88] 2009	Unselected	Bevacizumab + chemotherapy (FOLFOX/FOLFIRI)	NA	11.8%
				6% (R0)
Okines *et al*[89] 2009	Unselected	Bevacizumab + Oxaliplatin-based chemotherapy	38%	6.3%
Wong *et al*[90] 2011	Unselected	Bevacizumab + XELOX	68%	48.0%
Loupakis *et al*[91] 2013	Unselected	Bevacizumab + FOLFOXIRI	64%	15.0%
Martin *et al*[92] 2014	Unselected	Bevacizumab + FOLFOX + DEBIRI	78%	35.0%
Bokemeyer *et al*[94] 2009	*KRAS* WT	Cetuximab + FOLFOX	57%	7.3%
				4.7 (R0)
Van Cutsem *et al*[95] 2011	*KRAS* WT	Cetuximab + FOLFIRI	57%	16.0%
				7% (R0)
Folprecht *et al*[22] 2010	*KRAS* WT	Cetuximab + chemotherapy (FOLFOX/FOLFIRI)	68%	43.0%
				34% (R0)
Garufi *et al*[96] 2010	*KRAS* WT	Cetuximab + FOLFOXIRI	79%	60.0%
Ye *et al*[97] 2013	*KRAS* WT	Cetuximab + FOLFOXIRI	57%	25% (R0)
Köhne *et al*[100] 2012	*KRAS* WT	Panitumumab + FOLFIRI	56%	15.0%
Douillard *et al*[101] 2010	*KRAS* WT	Panitumumab + FOLFOX	57%	27.0%
				5.2% (R0)
	NRAS WT	Panitumumab + FOLFOX		31.0%

NA: Not available.

result in a small postoperative remnant liver function, hence increasing the risk of postoperative liver failure and subsequent very high mortality. In 2006, a national multicenter study by the group of Schroeder *et al*[28] showed an overall mortality rate after hepatectomy of 8.5% in the perioperative period. This mortality rate increases up to 16% when performing an hepatectomy of 3 segments or more.

Below a critical liver volume, the remnant liver cannot sustain metabolic, synthetic, and detoxifying functions[29]. However liver volume is not the best surrogate for liver function, in particular for patients with concomitant liver disease[30,31]. Based on data from the transplantation literature, it has been postulated empirically that each percent increase in fat content, either microvesicular or macrovesicular, decreases the functional mass of a donor liver by 1%[32]. In patients with cirrhosis, with non-alcoholic steatohepatitis, with obstructing jaundice due to a tumor or livers after chemotherapy regeneration capacity may be impaired (Table 1).

Major partial hepatectomy in combination with underlying parenchymal disease correlate well with increased morbidity and mortality rates[33-37]. In several series, the overall liver failure rate leading to death ranges from 25% to 100% following hepatic resection for hepatocellular carcinoma (HCC)[38-42]. However patients with HCC mostly have underlying cirrhosis as an etiologic factor for their tumors. Instead mortality rates after resection for CRC have a wide range, with up to 50% of deaths from liver failure[43,44]. Prolonged recovery and also mortality can also occur for the same reason as for patients with HCC, further indicating the importance of liver reserve in recovery from hepatic surgery in patients who received chemotherapy[45]. Most chemotherapeutic agents, even 5-fluorouracil, can cause liver damage[15]. Some studies suggest that patients who receive chemotherapy develop steatosis[35,46-48] whereas others show no correlation between any chemotherapy regimen and severe steatosis[49]. Others found that irinotecan is associated with the development of steatohepatitis in some patients[49,50]. Therefore, successful liver resection implicates correct recognition of remnant liver function. The group of Van Gulik could nicely show that pre-operative measurement of 99mTc-mebrofenin uptake in the future remnant liver on functional hepatobiliary scintigraphy proved more valuable than measurement of the volume of the future remnant in the assessment of the post-hepatectomy risk of liver failure and liver failure-related mortality[30,31,51,52].

In addition, sparing residual liver parenchyma should be of considerable importance in patients who received neo-adjuvant chemotherapy for CLM. The definition of what are resectable lesions is extremely variable and it depends on the experience and aggressiveness of the surgical team. A study of Lalmahomed *et al*[53], showed that patients treated with liver sparing resections, had to undergo more interventions for local recurrence than patients undergoing anatomical resections. Another population-based study in England showed that of 115 patients undergoing surgery for CRC between 1998 and 2004, 2.7% had minimum 1 hepatic resection. Another disadvantage of liver sparing resections was reported in the literature by DeMatteo *et al*[54] finding higher incidence of positive resection margins when performing liver sparing resections. Indeed, 50% to 75% of patients develop disease recurrence after initially curative resection of CLM. Anatomical resections may not offer the same advantage for these lesions as for HCC, which arise within a segment of the liver and might benefit from the removal of the complete functional liver unit. Indeed, several studies in patients with CLM have been reported in which no significant difference in morbidity, mortality, recurrence rate, or survival according to resection type and liver

sparing resections has been observed[55-57]. Moreover, the cure rate by initial hepatectomy is only 20% to 30% of cases[58,59]. Several studies in patients with CLM reported no significant difference in morbidity, mortality, recurrence rate, or survival according to resection type[60-62]. Karanjia *et al*[63] showed that patients who underwent right and extended right hepatectomy had a poorer short-term outcome, with a higher incidence of operative morbidity and mortality, compared to patients, undergoing other types of surgical treatment for the same disease. The degree of hepatic resection seems to influence tumor growth. Indeed, growth factors such as hepatocyte growth factor, epidermal growth factor, and insulin-like growth factor are generally upregulated early in liver regeneration, producing a mitogenic response and resulting in rapid hepatocyte cell proliferation[64,65]. Some other studies with less than 50% hepatectomies showed no tumor growth stimulation[66,67]. A larger resection causes the liver to express higher levels of growth factors and cytokines to restore the liver to its functional size in approximately the same time as for a smaller hepatectomy[68-71]. A number of studies have found that the larger the percentage of resection, the higher the incidence and volume of recurrence[72,73]. In addition, as mentioned before, although neoadjuvant chemotherapy increases resectability for CLM, it is associated with hepatic changes, such as hepatic sinusoidal obstruction, periportal inflammation, and steatohepatitis, which can affect patient outcome[74] and which might increase the risk of progressive hepatic failure and death after major liver resection. An extensive resection can be tolerated with virtually no risk related if the underlying liver is normal. In contrast, even a minor hepatectomy can be dangerous in patients with severely compromised livers[46]. Actually, the assessment of the underlying liver function is critical for the type of surgery.

Given the implications of these recent advances that have extended the indications for hepatectomy in the treatment for CRC metastases, as well as the positive and negative effects of an extended liver resection, there is need of a multimodality approach to treat patients with metastatic liver disease.

Chemotherapy treatment
In the last years the role of chemotherapy in the management of CLM is considerably increased. Nowadays, it may be considered for both unresectable and resectable CLM. For patients with unresectable CLM, "conversion chemotherapy" aims to convert unresectable, to resectable disease, often representing the initial treatment choice. Standard regimens comprising 5-FU/LV plus either irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) can facilitate resection in 7%-40% of patients[24]. In 1999 the group of Giacchetti reported that 5-FU/LV plus oxaliplatin treatment could reduce the size of liver metastases by > 50% in 59% of the patients with unresectable CLM and complete resection

was achieved in 38% of patients[75]. Treatment with 5-FU/LV, oxaliplatin and irinotecan (FOLFOXIRI) regimens permitted R0, curative-intent resections, in 15% of patients, and 36% of patients with liver metastases only[76]. Recently, a randomized, phase II trial, comparing intensified chemotherapy regimens (high-dose FOLFIRI, FOLFOX7, FOLFIRINOX) with standard chemotherapy regimens (FOLFOX4, FOLFIRI), for initially unresectable mCRC, has shown that FOLFIRINOX appears more active than other regimens (conversion rate to resectability: 67%; mOS > 48 mo; all others < 30 mo). Furthermore, this trial has confirmed that patients who undergo R0/R1 resections do much better than non-operated, or R2 (R0/R1: mOS > 65.2 mo; not-operated/R2:mOS: 18.3 mo, $P < 0.001$)[77].

For patients with resectable disease, "perioperative chemotherapy" has become an attractive option, in order to reduce the incidence of cancer relapse, occurring in up to 50%-70% of them after resection, through the eradication of occult disease[78,79]. Recently, the randomized, phase III trial, EORTC 40983, comparing peri-operative (both neoadjuvant and adjuvant) FOLFOX4 chemotherapy with surgery alone in 364 patients with resectable CLM, has shown a significant increment of PFS, in favour of perioperative treatment, but no significant differences in long term OS between the two treatment arms[80]. In addiction, the risk of post-operative complications has been shown to be significantly more frequent in the chemotherapy arm compared with surgery alone, and also to correlate with the duration of perioperative treatment. Several trials currently ongoing, such as the EORTC trial 40091 (NCT01508000) are investigating the combination of targeted agents such as Bevacizumab and Panitumumab with FOLFOX-chemotherapy regimen in perioperative treatment of patients candidate for resection of CLM, but results are not available yet.

Targeted biological treatment
Our increased understanding of the biology of CRC has led to the development of biologic therapies targeting two different mechanisms, angiogenesis (bevacizumab) and epidermal growth factor receptors (EGFRs) (cetuximab and pantumumab)[81]. One strategy to further increase the number of candidates eligible for surgery is the addition of active targeted agents to standard chemotherapy. In general, response rates appear to be highest with the EGFRIs, therefore these agents may potentially also lead to greater resection rates.

Resection rates with anti-angiogenesis agents: Bevacizumab
Addition of bevacizumab to first and second line chemotherapy for mCRC improves progression-free survival[82-85] and in some studies overall survival[83,84]. However, data on the role of bevacizumab added to chemotherapy in the perioperative setting are limited,

perhaps as a result of concerns about potential wound healing complications[86,87]. The Bevacizumab Expanded Access Trial showed that resection of hepatic metastasis after first-line bevacizumab plus chemotherapy was feasible and curative-intent hepatic resection of metastasis was performed in (11.8%) of patients overall (R0 in 6%)[88]. However, resection rates were higher in patients treated with bevacizumab plus Oxaliplatin chemotherapy (16.1%), than in those treated with bevacizumab plus Irinotecan chemotherapy (9.7%).

In a further first-line trial comparing oxaliplatin based chemotherapy plus bevacizumab or placebo, 6.3% of patients with bevacizumab and 4.9% of those treated with placebo underwent R0 resection of the metastasis ($P = 0.24$)[89]. Another study of neoadjuvant CAPOX plus bevacizumab allowed 12 out of 30 (40%) patients with initially unresectable CLM to be converted to resectable[90]. Loupakis *et al*[91] have recently reported a RR of 64% and a resection rate of 15%, in patients treated with FOLFOXIRI plus bevacizumab, as compared with respectively 53% and 12%, of those treated with FOLFIRI plus bevacizumab. Finally, the combination of intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI), with the FOLFOX plus Bevacizumab regimen, led to a 78% RR, and 35% of downsizing to resection, in patients with unresectable, liver-limited CRC, representing a new, promising, treatment strategies in this subset of patients[92].

Resection rates with anti-EGFR agents: Cetuximab and panitumumab

Anti-EFGR agents, cetuximab and panitumumab, are active both as single agents as well as in combination with chemotherapy in mCRC, with activity is confined to patients with RAS (both *KRAS* and *NRAS*) wild type tumors[93]. Five key randomized trials have evaluated the effects of cetuximab in patients with unresectable liver metastasis: (1) OPUS (Oxaliplatin and cetuximab in first-line treatment of MCRC)[94]. Addition of cetuximab to FOLFOX-4 almost doubled the R0 resection rate from 2.4% (FOLFOX-4 alone) to 4.7% (cetuximab plus FOLFOX-4); (2) CRYSTAL (cetuximab combined with irinotecan in first-line therapy for MCRC)[95]. Addition of cetuximab to FOLFIRI led an increase in the R0 resection rate from 3.7% to 7.0%; (3) colorectal Liver Metastases (CELIM)[22]. Patients received neoadjuvant treatment with cetuximab plus either FOLFIRI or FOLFOX6 and resections were performed in 43% of patients overall; 34% had RO resections; (4) POCHER (Cetuximab plus chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin as neoadjuvant chemotherapy in CLM)[96]; and (5) a Randomized Controlled Trial of Cetuximab Plus Chemotherapy for Patients With *KRAS* Wild-Type, Unresectable, Colorectal Liver-Limited Metastases, has recently shown that the addiction of Cetuximab to chemotherapy, significantly improved the R0 resection rate (25.7% *vs* 7.4%, *P* = 0.01)[97].

We need to discuss the reasons for the discrepancies in secondary liver resection rates in KRAS WT liver limited disease between these five studies following CT + Cetuximab. Overall RR was 60%-79% across these 5 studies but hepatectomy rates after CT + Erbitux was 9% in OPUS; 16% in CRYSTAL, 43% (33%R0) in CELIM, 60% in POCHER, and 25% in the recent Chinese trial. In the latter studies, resectability was detected by a multidisciplinary team, including a liver surgeons, while in CRYSTAL and OPUS, it was detected by non-specialist oncologists.

Two other randomized trials (COIN[98] and NORDIC VII[99]), have recently shown that Cetuximab adds no benefit to the Oxaliplatin chemotherapy regimen, in first-line treatment of mCRC, irrespectively of K-RAS status, even if in the COIN study cetuximab resulted in a higher response rate in patients with wild-type *KRAS* tumors[98].

Resection rates have also been reported in first-line panitumumab trials in patients with mCRC. Indeed, in a phase Ⅱ single-arm study, panitumumab plus FOLFIRI treatment resulted in resection rates of 15% *vs* 7% in the *KRAS* WT and mutant (MT) groups, respectively[100]. In a large, randomized phase Ⅲ study, of the 16% of patients with liver-limited disease, R0 resections were achieved in 32% of patients receiving FOLFOX4 plus panitumumab *vs* 28% of those receiving FOLFOX4 alone[101]. Baseline resectability was not recorded and so conversion rates could not be assessed. However, in a subsequent post-hoc analysis of the PRIME study, including RAS WT (both *KRAS* and *NRAS*) patients with liver metastasis only, Panitumumab plus FOLFOX resulted in conversion of about one-third of initially unresectable patients, enabling metastasectomy in 31% and complete resection in 29%, compared with 22% metastasectomy and 17% complete resection in the chemotherapy arm[102]. Recently, a retrospective-prospective analysis of PRIME study has shown that NRAS mutations predicted a lack of response to anti-EGFR Panitumumab. Infact, the subgroup of patients reporting NRAS mutations, representing 17% of non-mutated KRAS population, reported inferior outcomes, which were consistent with the outcomes of the KRAS mutated patients[93]. This highlights the importance for detecting other RAS mutations to better select a subgroup of patients most likely to benefit from anti-EGFR Mabs.

USE OF RESECTION IN CLINICAL PRACTICE

Patient selection

Difficulties remain in deciding who is resectable in clinical practice. Most liver surgeons accept the current AHPBA consensus on definition of resectability[103]. Until recently, CLM resection was mostly offered to those patients with liver-only disease that was (ideally)

detected metachronously after curative resection of the primary tumor, confined to one lobe of the liver, had less than 3 metastases, the largest of which was smaller than 5 cm in diameter. These patients need to have a margin of healthy liver tissue of more than 1 cm[104,105]. This would restrict CLM resection to < 10% of patients with liver-limited disease. Although the definition of resectable disease is broadening, patient selection guidelines for resection of CLM remain controversial, with an increase in aggressive management approach being used in recent years[8]. The criteria for CLM resectability are not standardized and are related to the experience of the surgeon and of the multidisciplinary team (MDT). Different teams and surgeons might approach the same patient differently. Current guidelines state that resection should be considered for solitary or confined liver metastases[24]. The remaining liver also needs to be healthy (viable vascular inflow and biliary and vascular outflow) and represent 20%-25% of liver volume at presentation[106]. Extra-hepatic disease is no longer an absolute contraindication for CLM resection[27]. This means that at least 20% of patients with liver-only disease are now considered candidates for resection. Multiple resections can also be safely performed if there is sufficient healthy remnant liver[12] and the risks of surgery are not too great. Survival benefit following repeat resection appears similar to that following the first liver resection[107,108]. General factors that influence safe liver resection include patient age, performans status, and concurrent parenchymal liver disease. Contraindications include unresectable extrahepatic disease, significant parenchymal liver disease, or patient unfit to undergo the procedure[12]. As difficulties remain in deciding who is resectable, many studies have examined potential prognostic factors for outcome following resection, with the aim of developing preoperative criteria for the selection of patients who may benefit from resection of CLM. Many clinical and pathological factors have been evaluated as potential prognostic determinants of survival after surgical resection of CLM. Such as: age, sex, primary tumor stage, synchronous or metachronous hepatic metastases, extrahepatic distant metastases, surgical margin, tumor size, number and distribution of CLM; carcinoembryonic antigen level, type of hepatectomy, and adjuvant chemotherapy. In Japan, Fong et al evaluated clinical, pathologic and outcome data for 1001 patients with mCRC undergoing resection[109]. Seven criteria were identified that predicted for worse prognosis after resection. Five of these were subsequently chosen for a preoperative scoring system (the Clinical Risk Score). These were: node-positive primary, disease-free interval from primary to metastases < 12 mo, number of hepatic tumors > 1, largest hepatic tumor > 5 cm, and carcinoembryonic antigen level > 200 ng/mL. Patients with a score less than 2 had favorable prognostic characteristic after resection, scores of 3-4 were considered candidates for resection

followed by adjuvant therapy. Prognosis was poor for those with scores of 5. This Clinical Risk Score has subsequently been validated and found to be highly predictive of patient outcome and survival[110]. More recently another scoring system was developed in Japan[111,112]. This, included six variables which showed overlap with those used in the Clinical Score (multiple tumors, the largest tumor > 5 cm in diameter, resectable extrahepatic metastases, serosa invasion, local lymph node metastases of primary cancers, and postoperative disease free interval of less than 1 year including synchronous hepatic metastasis). In line with the criteria mentioned above, a recent population-based study of patients with isolated CLM, increasing age, poor performance status, and high initial tumor burden were all associated with a decreased rate of referral to a hepatobiliary surgeon[8]. Novel qualitative morphologic criteria by CT evaluation have also been identified to predict the response to bevacizumab-containing chemotherapy in patients with CLM[113]. Moreover, the optimal response to preoperative treatment according to these morphologic criteria translated into a survival benefit following hepatic resection. Finally, a recent study by Karagkounis *et al*[114], consistently with the findings of other 3 studies[115-117], has shown that both RAS and BRAF mutations are associated with a worse prognosis after resection of CLM. These interesting evidences support the introduction of new treatment decision models in the management of CRC patients with liver metastatic disease, taking into account the new molecular factors as indicators of "biological resectability", together with the other clinical-pathological factors, in order to predict the outcomes of patients undergoing resection of CLM, and select good candidates for surgery.

MDT APPROACH TO PATIENT MANAGEMENT

Patients with cancer have complex needs and so their care cannot be addressed optimally by a single specialty or discipline. To ensure the optimal management and treatment of patients with mCRC throughout their treatment history, a MDT approach is now the norm in most European countries. Colorectal MDTs should also identify/establish a specialised hepatobiliary MDT that can provide the required additional expertise and facilities for patients with CLM[6]. Some studies in patients with liver-only metastases have showed improved survival among patients undergoing resection who are managed by a MDT including a liver surgeon[118,119]. The MDT would normally comprise two or more specialist surgeons with a high level of skills and training in liver resection surgery. Other team members may include an oncologist, diagnostic and interventional radiologists with expertise in hepatobiliary disease, a histopathologist, and clinical nurse specialist[6]. There should be regular interaction

and discussion within the MDT to ensure that resection is utilized where appropriate and to ensure that patients not initially considered resectable are brought into the resectable category wherever possible. For example the MDT should be consulted regarding choice of combination chemotherapy and targeted agents, duration of chemotherapy break before/after surgery, care choices and follow-up screening *etc*.

Thus, patients with mCRC may see a colorectal surgeon, a liver surgeon, and a medical oncologist to define optimal therapy. Medical oncologists should use the most active treatment for the shortest time by combination of chemotherapeutic regimens and targeted drugs to achieve tumor shrinkage without harming the normal liver. Defining the acceptable residual functioning liver volume may require assessment by a radiologist working with a liver surgeon[6]. Resection can be useful even at later lines of therapy and so it is important that the MDT is consulted at each stage of a patient's treatment. Repeat resection can be safely and effectively performed with survival races similar to those following initial resection[107,108,120]. Throughout the patient's disease course, the clinical nurse specialist/nurse practitioner is key to providing them with advice, support and information.

CONCLUSION

Patients with pretreated mCRC have few treatment options available, resection of metastatic disease is the only potentially curative strategy. Criteria for resectability have changed in recent years leading to an increased use of resection in patients with mCRC. No OS differences between simultaneous resection and staged resection of the primary tumour and resectable synchronous liver metastases. Increasing data suggest that biological agents (alone of combined with chemotherapy)-especially those targeting the EGFR-may be particularly useful in facilitating resection of liver metastases. Molecular biomarkers (first KRAS, and more recently NRAS), influences dramatically the anti-EGFR Mab activity and their identification have become mandatory for proper treatment planning in oncology. No OS benefit to adding perioperative chemotherapy to surgery for resectable liver metastases. Patients with mCRC should be managed by a MDT to ensure optimal treatment choices are made over their disease course, including optimizing opportunities for potentially curative resection of metastatic disease.

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