**Name of journal:** ***World Journal of*** ***Gastroenterology***

**ESPS Manuscript NO: 25402**

**Manuscript Type: REVIEW**

**Multisciplinary management of patients with liver metastasis from colorectal cancer**

De Greef K *et al*. Liver metastasis in CRC management

Kathleen De Greef, Christian Rolfo, Antonio Russo, Thiery Chapelle, Giuseppe Bronte, Francesco Passiglia, Andreia Coelho, Konstantinos Papadimitriou, Marc Peeters

**Kathleen De Greef, Thiery Chapelle,**Hepatobiliary, Transplant and endocrine surgery Department, Antwerp University Hospital, 2650 Edegem, Belgium

**Christian Rolfo, Francesco Passiglia, Andreia Coelho,** Phase I – Early Clinical Trials Unit, Oncology Department and Multidisciplinary Oncology Center Antwerp, Antwerp University Hospital, 2650 Edegem, Belgium

**Antonio Russo, Giuseppe Bronte, Francesco Passiglia,** Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, University of Palermo, 90133 Palermo, Italy

**Christian Rolfo, Andreia Coelho,** Oncology Department, Centro Hospitalar de Trás-os-Montes e Alto Douro, 5000-508 Vila Real, Portugal

**Konstantinos Papadimitriou, Marc Peeters,** Oncology Department and Multidisciplinary Oncology Center Antwerp, Antwerp University Hospital, 2650 Edegem, Belgium

**Author contributions:** De Greef K and Rolfo C wrote the manuscript; De Greef K, Rolfo C, Russo A, Chapelle T, Bronte G, Passiglia F, Coelho A, Papadimitriou K and Peeters M contributed to the content of the manuscript, revision and final manuscript approval; De Greef K, Rolfo C and Peeters M conceived the idea and manuscript format; De Greef K and Rolfo C contributed equally to this work.

**Conflict-of-interest statement:** The authors declare no conflict of interest for this paper.

**Open-Access:** This article is an open-access article, which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Correspondence to: Christian Rolfo**, **MD, PhD, Professor,** Head of Phase I, Early Clinical Trials Unit**,** Oncology Department,Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem, Belgium. christian.rolfo@uza.be

**Telephone**: +32-3-8213646

**Received:** March 7, 2016

**Peer-review started:** March 8, 2016

**First decision:** May 12, 2016

**Revised:** June 21, 2016

**Accepted:** July 31, 2016

**Article in press:**

**Published online:**

**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

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

De Greef K, Rolfo C, Russo, Chapelle T, Bronte G, Passiglia F, Coelho A, Papadimitriou K, Peeters M. Multisciplinary management of patients with liver metastasis from colorectal cancer. *World J Gastroenterol* 2016; In press

**INTRODUCTION**

Globally, colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females[[1](#_ENREF_1)]. Moreover, colorectal cancer (CRC) is the second leading cause of cancer mortality in the United States, accounting for 9% of cancer deaths[[2](#_ENREF_2)]. In Europe, it caused nearly 204000 deaths in 2004[[3](#_ENREF_3)]. The liver is the most common metastatic site[[4](#_ENREF_4)], probably due to tumor spread via the portal system[[5](#_ENREF_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](#_ENREF_6)]. Resection of the colorectal liver metastasis, 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 (RCT), and offers the only potential for cure[[7](#_ENREF_7),[8](#_ENREF_8)]. The natural history of metastatic colorectal cancer is variable, however, untreated CLM have a poor prognosis with median survival rates of less than 8 mo[[6](#_ENREF_6),[9](#_ENREF_9)]. Only 20%-30% patients with metastatic CRC (mCRC) have disease that is confined to the liver[[6](#_ENREF_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](#_ENREF_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](#_ENREF_11),[12](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_15)]. Indeed, since there is a strong correlation between tumor response and resection rate[[3](#_ENREF_3),[22](#_ENREF_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 colorectal liver metastases 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 (HIAC), radiofrequency ablation, stereotactic radiotherapy)[[23](#_ENREF_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](#_ENREF_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 COLORECTAL LIVER METASTASIS– CURRENT EVIDENCES

# *Surgical treatment*

Hepatectomy remains the standard of care for colorectal liver metastasis. In the past, post-operative mortality was high but nowadays it has decreased to around 1%[[25-27](#_ENREF_25)] 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 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](#_ENREF_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](#_ENREF_29)]. However liver volume is not the best surrogate for liver function, in particular for patients with concomitant liver disease[[30](#_ENREF_30),[31](#_ENREF_31)]. Based on data from the transplantation literature, it has been postulated empirically that each per cent increase in fat content, either microvesicular or macrovesicular, decreases the functional mass of a donor liver by 1%[[32](#_ENREF_32)]. In patients with cirrhosis, with non-alcoholic steatohepatitis (NASH), 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](#_ENREF_33)]. 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](#_ENREF_38)]. However patients with HCC mostly have underlying cirrhosis as an etiologic factor for their tumors. Instead mortality rates after resection for colorectal cancer have a wide range, with up to 50% of deaths from liver failure[[43](#_ENREF_43),[44](#_ENREF_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](#_ENREF_45)]. Most chemotherapeutic agents, even 5-fluorouracil, can cause liver damage[[15](#_ENREF_15)]. Some studies suggest that patients who receive chemotherapy develop steatosis[[35](#_ENREF_35),[46-48](#_ENREF_46)] whereas others show no correlation between any chemotherapy regimen and severe steatosis[[49](#_ENREF_49)]. Others found that irinotecan is associated with the development of steatohepatitis in some patients[[49](#_ENREF_49),[50](#_ENREF_50)]. Therefore, successful liver resection implicates correct recognition of remnant liver function. The group of Van Gulik *et al*[[30](#_ENREF_30),[31](#_ENREF_31),[51](#_ENREF_51),[52](#_ENREF_52)] could nicely show that preoperative 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.

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](#_ENREF_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](#_ENREF_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](#_ENREF_55)]. Moreover, the cure rate by initial hepatectomy is only 20% to 30% of cases[[58](#_ENREF_58),[59](#_ENREF_59)]. Several studies in patients with CLM reported no significant difference in morbidity, mortality, recurrence rate, or survival according to resection type[[60-62](#_ENREF_60)]. Karanjia *et al*[[63](#_ENREF_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](#_ENREF_64),[65](#_ENREF_65)]. Some other studies with less than 50% hepatectomies showed no tumor growth stimulation[[66](#_ENREF_66),[67](#_ENREF_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](#_ENREF_68)]. A number of studies have found that the larger the percentage of resection, the higher the incidence and volume of recurrence[[72](#_ENREF_72),[73](#_ENREF_73)]. In addition, as mentioned before, although neoadjuvant chemotherapy increases resectability for colorectal liver metastasis, it is associated with hepatic changes, such as hepatic sinusoidal obstruction, periportal inflammation, and steatohepatitis, which can affect patient outcome[[74](#_ENREF_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](#_ENREF_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 colorectal cancer 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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_78),[79](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_82)] and in some studies overall survival[[83](#_ENREF_83),[84](#_ENREF_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](#_ENREF_86),[87](#_ENREF_87)]. The Bevacizumab Expanded Access Trial (BEAT) 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](#_ENREF_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](#_ENREF_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](#_ENREF_90)]. Loupakis *et al*[[91](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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 colorectal liver metastases)[[96](#_ENREF_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](#_ENREF_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](#_ENREF_98)] and NORDIC VII[[99](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_104),[105](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_106)]. Extra-hepatic disease is no longer an absolute contraindication for CLM resection[[27](#_ENREF_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](#_ENREF_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](#_ENREF_107),[108](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_110)]. More recently another scoring system was developed in Japan[[111](#_ENREF_111),[112](#_ENREF_112)]. This, included six variables which showed overlap with those used in the Clinical Score (multiple tumors, the largest tumor > 5 crn in diameter, resectable extrahepatic metastases, serosa invasion, local lymph node metastases of primary cancers, and postoperative disease free interval of less than1 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](#_ENREF_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](#_ENREF_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](#_ENREF_114)], consistently with the findings of other 3 studies[[115-117](#_ENREF_115)], 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.

**MULTIDISCIPLINARY TEAM 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 multidisciplinary team (MDT) approach is now the norm in most European countries. Colorectal MDTs should also identify/establish a specialised hepatotiliary MDT that can provide the required additional expertise and facilities for patients with CLM[[6](#_ENREF_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](#_ENREF_118),[119](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_107),[108](#_ENREF_108),[120](#_ENREF_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.

**REFERENCES**

1 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]

2 Society AC. Cancer facts and figures 2010. Available from: URL: http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2010/

3 **Van Cutsem E**, Nordlinger B, Adam R, Köhne CH, Pozzo C, Poston G, Ychou M, Rougier P. Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. *Eur J Cancer* 2006; **42**: 2212-2221 [PMID: 16904315 DOI: 10.1016/j.ejca.2006.04.012]

4 **Adam R**, Hoti E, Folprecht G, Benson AB. Accomplishments in 2008 in the management of curable metastatic colorectal cancer. *Gastrointest Cancer Res* 2009; **3**: S15-S22 [PMID: 20011559]

5 **Weiss L**, Grundmann E, Torhorst J, Hartveit F, Moberg I, Eder M, Fenoglio-Preiser CM, Napier J, Horne CH, Lopez MJ. Haematogenous metastatic patterns in colonic carcinoma: an analysis of 1541 necropsies. *J Pathol* 1986; **150**: 195-203 [PMID: 3806280 DOI: 10.1002/path.1711500308]

6 **Garden OJ**, Rees M, Poston GJ, Mirza D, Saunders M, Ledermann J, Primrose JN, Parks RW. Guidelines for resection of colorectal cancer liver metastases. *Gut* 2006; **55** Suppl 3: iii1-iii8 [PMID: 16835351 DOI: 10.1136/gut.2006.098053]

7 **Chiappa A**, Makuuchi M, Lygidakis NJ, Zbar AP, Chong G, Bertani E, Sitzler PJ, Biffi R, Pace U, Bianchi PP, Contino G, Misitano P, Orsi F, Travaini L, Trifirò G, Zampino MG, Fazio N, Goldhirsch A, Andreoni B. The management of colorectal liver metastases: Expanding the role of hepatic resection in the age of multimodal therapy. *Crit Rev Oncol Hematol* 2009; **72**: 65-75 [PMID: 19147371 DOI: 10.1016/j.critrevonc.2008.11.003]

8 **Ksienski D**, Woods R, Speers C, Kennecke H. Patterns of referral and resection among patients with liver-only metastatic colorectal cancer (MCRC). *Ann Surg Oncol* 2010; **17**: 3085-3093 [PMID: 20839067 DOI: 10.1245/s10434-010-1304-9]

9 **Bengtsson G**, Carlsson G, Hafström L, Jönsson PE. Natural history of patients with untreated liver metastases from colorectal cancer. *Am J Surg* 1981; **141**: 586-589 [PMID: 7223955 DOI: 10.1016/0002-9610(81)90057-X]

10 **Adam R**, Bhangui P, Poston G, Mirza D, Nuzzo G, Barroso E, Ijzermans J, Hubert C, Ruers T, Capussotti L, Ouellet JF, Laurent C, Cugat E, Colombo PE, Milicevic M. Is perioperative chemotherapy useful for solitary, metachronous, colorectal liver metastases? *Ann Surg* 2010; **252**: 774-787 [PMID: 21037433 DOI: 10.1097/SLA.0b013e3181fcf3e3]

11 **Van den Eynde M**, Hendlisz A. Treatment of colorectal liver metastases: a review. *Rev Recent Clin Trials* 2009; **4**: 56-62 [PMID: 19149763 DOI: 10.2174/157488709787047558]

12 **Poston GJ**, Figueras J, Giuliante F, Nuzzo G, Sobrero AF, Gigot JF, Nordlinger B, Adam R, Gruenberger T, Choti MA, Bilchik AJ, Van Cutsem EJ, Chiang JM, D'Angelica MI. Urgent need for a new staging system in advanced colorectal cancer. *J Clin Oncol* 2008; **26**: 4828-4833 [PMID: 18711170 DOI: 10.1200/JCO.2008.17.6453]

13 **Chua TC**, Saxena A, Chu F, Zhao J, Morris DL. Predictors of cure after hepatic resection of colorectal liver metastases: an analysis of actual 5- and 10-year survivors. *J Surg Oncol* 2011; **103**: 796-800 [PMID: 21246567 DOI: 10.1002/jso.21864]

14 **Taylor A**, Kanas G. Survival after surgical resection of hepatic metastases from colorectal cancer: A systematic review and meta-analysis. *Ann Oncol* 2010; **21**(suppl 8): 632P

15 **Scheele J**, Stangl R, Schmidt K, Altendorf-Hofmann A. [Recurrent tumor after R0 resection of colorectal liver metastases. Incidence, resectability and prognosis]. *Chirurg* 1995; **66**: 965-973 [PMID: 8529448]

16 **Scheele J**, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. *World J Surg* 1995; **19**: 59-71 [PMID: 7740812 DOI: 10.1007/BF00316981]

17 **Figueras J**, Valls C, Rafecas A, Fabregat J, Ramos E, Jaurrieta E. Resection rate and effect of postoperative chemotherapy on survival after surgery for colorectal liver metastases. *Br J Surg* 2001; **88**: 980-985 [PMID: 11442531 DOI: 10.1046/j.0007-1323.2001.01821.x]

18 **Bismuth H**, Adam R, Lévi F, Farabos C, Waechter F, Castaing D, Majno P, Engerran L. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg* 1996; **224**: 509-20; discussion 520-2 [PMID: 8857855]

19 **Nordlinger B**, Benoist S. Benefits and risks of neoadjuvant therapy for liver metastases. *J Clin Oncol* 2006; **24**: 4954-4955 [PMID: 17075112]

20 **Nordlinger B**, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, Jaeck D. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Française de Chirurgie. *Cancer* 1996; **77**: 1254-1262 [PMID: 8608500 DOI: 10.1002/(SICI)1097-0142(19960401)77]

21 **Fong Y**, Salo J. Surgical therapy of hepatic colorectal metastasis. *Semin Oncol* 1999; **26**: 514-523 [PMID: 10528899 DOI: 10.3322/canjclin.49.4.231]

22 **Folprecht G**, Gruenberger T, Bechstein WO, Raab HR, Lordick F, Hartmann JT, Lang H, Frilling A, Stoehlmacher J, Weitz J, Konopke R, Stroszczynski C, Liersch T, Ockert D, Herrmann T, Goekkurt E, Parisi F, Köhne CH. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol* 2010; **11**: 38-47 [PMID: 19942479 DOI: 10.1016/S1470-2045(09)70330-4]

23 **Nordlinger B**, Van Cutsem E, Rougier P, Köhne CH, Ychou M, Sobrero A, Adam R, Arvidsson D, Carrato A, Georgoulias V, Giuliante F, Glimelius B, Golling M, Gruenberger T, Tabernero J, Wasan H, Poston G. Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group. *Eur J Cancer* 2007; **43**: 2037-2045 [PMID: 17766104 DOI: 10.1016/j.ejca.2007.07.017]

24 **Van Cutsem E**, Nordlinger B, Cervantes A. Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. *Ann Oncol* 2010; **21** Suppl 5: v93-v97 [PMID: 20555112 DOI: 10.1093/annonc/mdq222]

25 **Adam R**, Chiche L, Aloia T, Elias D, Salmon R, Rivoire M, Jaeck D, Saric J, Le Treut YP, Belghiti J, Mantion G, Mentha G. Hepatic resection for noncolorectal nonendocrine liver metastases: analysis of 1,452 patients and development of a prognostic model. *Ann Surg* 2006; **244**: 524-535 [PMID: 16998361 DOI: 10.1097/01.sla.0000239036.46827.5f]

26 **Adams RB**, Haller DG, Roh MS. Improving resectability of hepatic colorectal metastases: expert consensus statement by Abdalla et al. *Ann Surg Oncol* 2006; **13**: 1281-1283 [PMID: 16964448 DOI: 10.1245/s10434-006-9149-y]

27 **Isoniemi H**, Osterlund P. Surgery combined with oncological treatments in liver metastases from colorectal cancer. *Scand J Surg* 2011; **100**: 35-41 [PMID: 21482503]

28 **Schroeder RA**, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. Predictive indices of morbidity and mortality after liver resection. *Ann Surg* 2006; **243**: 373-379 [PMID: 16495703 DOI: 10.1097/01.sla.0000201483.95911.08]

29 **Breitenstein S**, Apestegui C, Petrowsky H, Clavien PA. "State of the art" in liver resection and living donor liver transplantation: a worldwide survey of 100 liver centers. *World J Surg* 2009; **33**: 797-803 [PMID: 19172348 DOI: 10.1007/s00268-008-9878-0]

30 **Bennink RJ**, Dinant S, Erdogan D, Heijnen BH, Straatsburg IH, van Vliet AK, van Gulik TM. Preoperative assessment of postoperative remnant liver function using hepatobiliary scintigraphy. *J Nucl Med* 2004; **45**: 965-971 [PMID: 15181131]

31 **Dinant S**, de Graaf W, Verwer BJ, Bennink RJ, van Lienden KP, Gouma DJ, van Vliet AK, van Gulik TM. Risk assessment of posthepatectomy liver failure using hepatobiliary scintigraphy and CT volumetry. *J Nucl Med* 2007; **48**: 685-692 [PMID: 17475954 DOI: 10.2967/jnumed.106.038430]

32 **Marcos A**, Ham JM, Fisher RA, Olzinski AT, Shiffman ML, Sanyal AJ, Luketic VA, Sterling RK, Posner MP. Emergency adult to adult living donor liver transplantation for fulminant hepatic failure. *Transplantation* 2000; **69**: 2202-2205 [PMID: 10852626 DOI: 10.1097/00007890-200005270-00044]

33 **Jarnagin WR**, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, Corvera C, Weber S, Blumgart LH. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg* 2002; **236**: 397-406; discussion 406-7 [PMID: 12368667]

34 **Poon RT**, Fan ST, Wong J. Selection criteria for hepatic resection in patients with large hepatocellular carcinoma larger than 10 cm in diameter. *J Am Coll Surg* 2002; **194**: 592-602 [PMID: 12022599 DOI: 10.1016/S1072-7515(02)01163-8]

35 **Belghiti J**, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. *J Am Coll Surg* 2000; **191**: 38-46 [PMID: 10898182 DOI: 10.1016/S1072-7515(00)00261-1]

36 **Nagino M**, Kamiya J, Uesaka K, Sano T, Yamamoto H, Hayakawa N, Kanai M, Nimura Y. Complications of hepatectomy for hilar cholangiocarcinoma. *World J Surg* 2001; **25**: 1277-1283 [PMID: 11596890 DOI: 10.1007/s00268-001-0110-8]

37 **Das BC**, Isaji S, Kawarada Y. Analysis of 100 consecutive hepatectomies: risk factors in patients with liver cirrhosis or obstructive jaundice. *World J Surg* 2001; 25: 266-272; discussion 272-263

38 **Nagasue N**, Yamanoi A, el-Assal ON, Ohmori H, Tachibana M, Kimoto T, Kohno H. Major compared with limited hepatic resection for hepatocellular carcinoma without underlying cirrhosis: a retrospective analysis. *Eur J Surg* 1999; **165**: 638-646 [PMID: 10452257 DOI: 10.1080/11024159950189681]

39 **Nagasue N**. Liver resection for hepatocellular carcinoma: indications, techniques, complications, and prognostic factors. *J Hepatobiliary Pancreat Surg* 1998; **5**: 7-13 [PMID: 9683747 DOI: 10.1007/PL00009954]

40 **Tsao JI**, DeSanctis J, Rossi RL, Oberfield RA. Hepatic malignancies. *Surg Clin North Am* 2000; **80**: 603-632 [PMID: 10836009 DOI: 10.1016/S0039-6109(05)70203-6]

41 **Tsao JI**, Loftus JP, Nagorney DM, Adson MA, Ilstrup DM. Trends in morbidity and mortality of hepatic resection for malignancy. A matched comparative analysis. *Ann Surg* 1994; **220**: 199-205 [PMID: 8053742 DOI: 10.1097/00000658-199408000-00012]

42 **Nonami T**, Nakao A, Kurokawa T, Inagaki H, Matsushita Y, Sakamoto J, Takagi H. Blood loss and ICG clearance as best prognostic markers of post-hepatectomy liver failure. *Hepatogastroenterology* 1999; **46**: 1669-1672 [PMID: 10430318]

43 **Fortner JG**, Fong Y. Twenty-five-year follow-up for liver resection: the personal series of Dr. Joseph G. Fortner. *Ann Surg* 2009; **250**: 908-913 [PMID: 19855260 DOI: 10.1097/SLA.0b013e3181b59491]

44 **Nordlinger B**, Benoist S. [Recent advances in the case management of colorectal cancer liver metastases]. *Bull Acad Natl Med* 2003; **187**: 899-904 [PMID: 14979055]

45 **Schneider PD**. Preoperative assessment of liver function. *Surg Clin North Am* 2004; **84**: 355-373 [PMID: 15062650 DOI: 10.1016/S0039-6109(03)00224-X]

46 **Zorzi D**, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. *Br J Surg* 2007; **94**: 274-286 [PMID: 17315288 DOI: 10.1002/bjs.5719]

47 **Peppercorn PD**, Reznek RH, Wilson P, Slevin ML, Gupta RK. Demonstration of hepatic steatosis by computerized tomography in patients receiving 5-fluorouracil-based therapy for advanced colorectal cancer. *Br J Cancer* 1998; **77**: 2008-2011 [PMID: 9667683 DOI: 10.1038/bjc.1998.333]

48 **Kooby DA**, Stockman J, Ben-Porat L, Gonen M, Jarnagin WR, Dematteo RP, Tuorto S, Wuest D, Blumgart LH, Fong Y. Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. *Ann Surg* 2003; **237**: 860-89; discussion 860-89; [PMID: 12796583 DOI: 10.1097/01.SLA.0000072371.95588.DA]

49 **Vauthey JN**, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, Xiong HQ, Eng C, Lauwers GY, Mino-Kenudson M, Risio M, Muratore A, Capussotti L, Curley SA, Abdalla EK. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 2006; **24**: 2065-2072 [PMID: 16648507 DOI: 10.1200/JCO.2005.05.3074]

50 **Fernandez FG**, Ritter J, Goodwin JW, Linehan DC, Hawkins WG, Strasberg SM. Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases. *J Am Coll Surg* 2005; **200**: 845-853 [PMID: 15922194 DOI: 10.1016/j.jamcollsurg.2005.01.024]

51 **Dinant S**, Gerhards MF, Rauws EA, Busch OR, Gouma DJ, van Gulik TM. Improved outcome of resection of hilar cholangiocarcinoma (Klatskin tumor). *Ann Surg Oncol* 2006; **13**: 872-880 [PMID: 16614876 DOI: 10.1245/ASO.2006.05.053]

52 **Erdogan D**, Heijnen BH, Bennink RJ, Kok M, Dinant S, Straatsburg IH, Gouma DJ, van Gulik TM. Preoperative assessment of liver function: a comparison of 99mTc-Mebrofenin scintigraphy with indocyanine green clearance test. *Liver Int* 2004; **24**: 117-123 [PMID: 15078475 DOI: 10.1111/j.1478-3231.2004.00901.x]

53 **Lalmahomed ZS**, Ayez N, van der Pool AE, Verheij J, IJzermans JN, Verhoef C. Anatomical versus nonanatomical resection of colorectal liver metastases: is there a difference in surgical and oncological outcome? *World J Surg* 2011; **35**: 656-661 [PMID: 21161655 DOI: 10.1007/s00268-010-0890-9]

54 **DeMatteo RP,** Palese C, Jarnagin WR, Sun RL, Blumgart LH, Fong Y.. Anatomic segmental hepatic resection is superior to wedge resection as an oncologic operation for colorectal liver metastases. *J Gastrointest Surg* 2000; **4:** 178-184 [PMID: 10675241 DOI: 10.1016/S1091-255X(00)80054-2]

55 **Hasegawa K**, Kokudo N, Imamura H, Matsuyama Y, Aoki T, Minagawa M, Sano K, Sugawara Y, Takayama T, Makuuchi M. Prognostic impact of anatomic resection for hepatocellular carcinoma. *Ann Surg* 2005; **242**: 252-259 [PMID: 16041216 DOI: 10.1097/01.sla.0000171307.37401.db]

56 **Wakai T**, Shirai Y, Sakata J, Kaneko K, Cruz PV, Akazawa K, Hatakeyama K. Anatomic resection independently improves long-term survival in patients with T1-T2 hepatocellular carcinoma. *Ann Surg Oncol* 2007; **14**: 1356-1365 [PMID: 17252289 DOI: 10.1245/s10434-006-9318-z]

57 **Ueno S**, Kubo F, Sakoda M, Hiwatashi K, Tateno T, Mataki Y, Maemura K, Shinchi H, Natsugoe S, Aikou T. Efficacy of anatomic resection vs nonanatomic resection for small nodular hepatocellular carcinoma based on gross classification. *J Hepatobiliary Pancreat Surg* 2008; **15**: 493-500 [PMID: 18836803 DOI: 10.1007/s00534-007-1312-8]

58 **Yokoi Y**, Suzuki S, Nakamura S. [The impact of hepatic resection on metastatic colorectal cancer]. *Gan To Kagaku Ryoho* 2002; **29**: 848-855 [PMID: 12090034]

59 **Suzuki S**, Sakaguchi T, Yokoi Y, Kurachi K, Okamoto K, Okumura T, Tsuchiya Y, Nakamura T, Konno H, Baba S, Nakamura S. Impact of repeat hepatectomy on recurrent colorectal liver metastases. *Surgery* 2001; **129**: 421-428 [PMID: 11283532 DOI: 10.1016/S0039-6060(01)83158-5]

60 **Zorzi D**, Mullen JT, Abdalla EK, Pawlik TM, Andres A, Muratore A, Curley SA, Mentha G, Capussotti L, Vauthey JN. Comparison between hepatic wedge resection and anatomic resection for colorectal liver metastases. *J Gastrointest Surg* 2006; **10**: 86-94 [PMID: 16368496 DOI: 10.1016/j.gassur.2005.07.022]

61 **Gold JS**, Are C, Kornprat P, Jarnagin WR, Gönen M, Fong Y, DeMatteo RP, Blumgart LH, D'Angelica M. Increased use of parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. *Ann Surg* 2008; **247**: 109-117 [PMID: 18156930 DOI: 10.1097/SLA.0b013e3181557e47]

62 **Stewart GD**, O'Súilleabháin CB, Madhavan KK, Wigmore SJ, Parks RW, Garden OJ. The extent of resection influences outcome following hepatectomy for colorectal liver metastases. *Eur J Surg Oncol* 2004; **30**: 370-376 [PMID: 15063889 DOI: 10.1016/j.ejso.2004.01.011]

63 **Karanjia ND**, Lordan JT, Quiney N, Fawcett WJ, Worthington TR, Remington J. A comparison of right and extended right hepatectomy with all other hepatic resections for colorectal liver metastases: a ten-year study. *Eur J Surg Oncol* 2009; **35**: 65-70 [PMID: 18222623 DOI: 10.1016/j.ejso.2007.12.002]

64 **Harun N**, Nikfarjam M, Muralidharan V, Christophi C. Liver regeneration stimulates tumor metastases. *J Surg Res* 2007; **138**: 284-290 [PMID: 17254608 DOI: 10.1016/j.jss.2006.06.024]

65 **Jiang WG**, Hiscox S. Hepatocyte growth factor/scatter factor, a cytokine playing multiple and converse roles. *Histol Histopathol* 1997; **12**: 537-555 [PMID: 9151142]

66 **Castillo MH**, Doerr RJ, Paolini N, Cohen S, Goldrosen M. Hepatectomy prolongs survival of mice with induced liver metastases. *Arch Surg* 1989; **124**: 167-169 [PMID: 2916937 DOI: 10.1001/archsurg.1989.01410020037005]

67 **Doerr R**, Castillo M, Evans P, Paolini N, Goldrosen M, Cohen SA. Partial hepatectomy augments the liver's antitumor response. *Arch Surg* 1989; **124**: 170-174 [PMID: 2464982 DOI: 10.1001/archsurg.1989.01410020040006]

68 **Fausto N**, Campbell JS, Riehle KJ. Liver regeneration. *Hepatology* 2006; **43**: S45-S53 [PMID: 16447274 DOI: 10.1002/hep.20969]

69 **Fausto N.** Growth factors in liver development, regeneration and carcinogenesis. *Prog Growth Factor Res* 1991; **3:** 219-234 [PMID: 1667366 DOI: 10.1016/0955-2235(91)90008-R]

70 **Fausto N**, Webber EM. Mechanisms of growth regulation in liver regeneration and hepatic carcinogenesis. *Prog Liver Dis* 1993; **11**: 115-137 [PMID: 8272507]

71 **Mangnall D**, Smith K, Bird NC, Majeed AW. Early increases in plasminogen activator activity following partial hepatectomy in humans. *Comp Hepatol* 2004; **3**: 11 [PMID: 15617575 DOI: 10.1186/1476-5926-3-11]

72 **Ikeda Y**, Matsumata T, Takenaka K, Sasaki O, Soejima K, Sugimachi K. Preliminary report of tumor metastasis during liver regeneration after hepatic resection in rats. *Eur J Surg Oncol* 1995; **21**: 188-190 [PMID: 7720894 DOI: 10.1016/S0748-7983(95)90468-9]

73 **Mizutani J**, Hiraoka T, Yamashita R, Miyauchi Y. Promotion of hepatic metastases by liver resection in the rat. *Br J Cancer* 1992; **65**: 794-797 [PMID: 1616850 DOI: 10.1038/bjc.1992.170]

74 **Vauthey JN**. Colorectal liver metastases: treat effectively up front and consider the borderline resectable. *J Clin Oncol* 2007; **25**: 4524-4525 [PMID: 17925547 DOI: 10.1200/JCO.2007.13.1136]

75 **Giacchetti S**, Itzhaki M, Gruia G, Adam R, Zidani R, Kunstlinger F, Brienza S, Alafaci E, Bertheault-Cvitkovic F, Jasmin C, Reynes M, Bismuth H, Misset JL, Lévi F. Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. *Ann Oncol* 1999; **10**: 663-669 [PMID: 10442188 DOI: 10.1023/A: 1008347829017]

76 **Falcone A**, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, Crinò L, Benedetti G, Evangelista W, Fanchini L, Cortesi E, Picone V, Vitello S, Chiara S, Granetto C, Porcile G, Fioretto L, Orlandini C, Andreuccetti M, Masi G. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007; **25**: 1670-1676 [PMID: 17470860 DOI: 10.1200/JCO.2006.09.0928]

77 **Ychou M**, Rivoire M, Thezenas S, Quenet F, Delpero JR, Rebischung C, Letoublon C, Guimbaud R, Francois E, Ducreux M, Desseigne F, Fabre JM, Assenat E. A randomized phase II trial of three intensified chemotherapy regimens in first-line treatment of colorectal cancer patients with initially unresectable or not optimally resectable liver metastases. The METHEP trial. *Ann Surg Oncol* 2013; **20**: 4289-4297 [PMID: 23955585 DOI: 10.1245/s10434-013-3217-x]

78 **Nathan H**, de Jong MC, Pulitano C, Ribero D, Strub J, Mentha G, Gigot JF, Schulick RD, Choti MA, Aldrighetti L, Capussotti L, Pawlik TM. Conditional survival after surgical resection of colorectal liver metastasis: an international multi-institutional analysis of 949 patients. *J Am Coll Surg* 2010; **210**: 755-64, 764-6 [PMID: 20421045]

79 **House MG**, Ito H, Gönen M, Fong Y, Allen PJ, DeMatteo RP, Brennan MF, Blumgart LH, Jarnagin WR, D'Angelica MI. Survival after hepatic resection for metastatic colorectal cancer: trends in outcomes for 1,600 patients during two decades at a single institution. *J Am Coll Surg* 2010; **210**: 744-52, 752-5 [PMID: 20421043]

80 **Nordlinger B**, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Mauer M, Tanis E, Van Cutsem E, Scheithauer W, Gruenberger T. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; **14**: 1208-1215 [PMID: 24120480 DOI: 10.1016/S1470-2045(13)70447-9]

81 **Peeters M**, Price T. Biologic therapies in the metastatic colorectal cancer treatment continuum--applying current evidence to clinical practice. *Cancer Treat Rev* 2012; **38**: 397-406 [PMID: 21899955 DOI: 10.1016/j.ctrv.2011.08.002]

82 **Kabbinavar FF**, Schulz J, McCleod M, Patel T, Hamm JT, Hecht JR, Mass R, Perrou B, Nelson B, Novotny WF. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. *J Clin Oncol* 2005; **23**: 3697-3705 [PMID: 15738537 DOI: 10.1200/JCO.2005.05.112]

83 **Hurwitz H**, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350**: 2335-2342 [PMID: 15175435 DOI: 10.1056/NEJMoa032691]

84 **Giantonio BJ**, Levy DE, O'dwyer PJ, Meropol NJ, Catalano PJ, Benson AB. A phase II study of high-dose bevacizumab in combination with irinotecan, 5-fluorouracil, leucovorin, as initial therapy for advanced colorectal cancer: results from the Eastern Cooperative Oncology Group study E2200. *Ann Oncol* 2006; **17**: 1399-1403 [PMID: 16873427 DOI: 10.1093/annonc/mdl161]

85 **Saltz LB**, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F, Cassidy J. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008; **26**: 2013-2019 [PMID: 18421054 DOI: 10.1200/JCO.2007.14.9930]

86 **Gordon CR**, Rojavin Y, Patel M, Zins JE, Grana G, Kann B, Simons R, Atabek U. A review on bevacizumab and surgical wound healing: an important warning to all surgeons. *Ann Plast Surg* 2009; **62**: 707-709 [PMID: 19461291 DOI: 10.1097/SAP.0b013e3181828141]

87 **Tamiya A**, Yamazaki K, Boku N, Machida N, Kojima T, Taku K, Yasui H, Fukutomi A, Hironaka S, Onozawa Y. Safety of bevacizumab treatment in combination with standard chemotherapy for metastatic colorectal cancer: a retrospective review of 65 Japanese patients. *Int J Clin Oncol* 2009; **14**: 513-517 [PMID: 19967487 DOI: 10.1007/s10147-009-0911-6]

88 **Van Cutsem E**, Rivera F, Berry S, Kretzschmar A, Michael M, DiBartolomeo M, Mazier MA, Canon JL, Georgoulias V, Peeters M, Bridgewater J, Cunningham D. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. *Ann Oncol* 2009; **20**: 1842-1847 [PMID: 19406901 DOI: 10.1093/annonc/mdp233]

89 **Okines A**, Puerto OD, Cunningham D, Chau I, Van Cutsem E, Saltz L, Cassidy J. Surgery with curative-intent in patients treated with first-line chemotherapy plus bevacizumab for metastatic colorectal cancer First BEAT and the randomised phase-III NO16966 trial. *Br J Cancer* 2009; **101**: 1033-1038 [PMID: 19789532 DOI: 10.1038/sj.bjc.6605259]

90 **Wong R**, Cunningham D, Barbachano Y, Saffery C, Valle J, Hickish T, Mudan S, Brown G, Khan A, Wotherspoon A, Strimpakos AS, Thomas J, Compton S, Chua YJ, Chau I. A multicentre study of capecitabine, oxaliplatin plus bevacizumab as perioperative treatment of patients with poor-risk colorectal liver-only metastases not selected for upfront resection. *Ann Oncol* 2011; **22**: 2042-2048 [PMID: 21285134 DOI: 10.1093/annonc/mdq714]

91 **Loupakis F,** Cremolini C. FOLFOXIRI plus bevacizumab (bev) versus FOLFIRI plus bev as first line treatment of metastatic colorectal cancer (mCRC): Results of the phase III randomized TRIBE trial. *J Clin Oncol* 2013; **30**: 2012

92 **Martin RC**, Scoggins CR, Schreeder M, Rilling WS, Laing CJ, Tatum CM, Kelly LR, Garcia-Monaco RD, Sharma VR, Crocenzi TS, Strasberg SM. Randomized controlled trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizamab for patients with unresectable colorectal liver-limited metastasis. *Cancer* 2015; 121: 3649-3658[PMID: 26149602 DOI: 10.1002/cncr.29534]

93 **Douillard JY**, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocákova I, Ruff P, Błasińska-Morawiec M, Šmakal M, Canon JL, Rother M, Williams R, Rong A, Wiezorek J, Sidhu R, Patterson SD. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med* 2013; **369**: 1023-1034 [PMID: 24024839 DOI: 10.1056/NEJMoa1305275]

94 **Bokemeyer C**, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, Donea S, Ludwig H, Schuch G, Stroh C, Loos AH, Zubel A, Koralewski P. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2009; **27**: 663-671 [PMID: 19114683 DOI: 10.1200/JCO.2008.20.8397]

95 **Van Cutsem E**, Köhne CH, Láng I, Folprecht G, Nowacki MP, Cascinu S, Shchepotin I, Maurel J, Cunningham D, Tejpar S, Schlichting M, Zubel A, Celik I, Rougier P, Ciardiello F. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol* 2011; **29**: 2011-2019 [PMID: 21502544 DOI: 10.1200/JCO.2010.33.5091]

96 **Garufi C**, Torsello A, Tumolo S, Ettorre GM, Zeuli M, Campanella C, Vennarecci G, Mottolese M, Sperduti I, Cognetti F. Cetuximab plus chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin as neoadjuvant chemotherapy in colorectal liver metastases: POCHER trial. *Br J Cancer* 2010; **103**: 1542-1547 [PMID: 20959822 DOI: 10.1038/sj.bjc.6605940]

97 **Ye LC**, Liu TS, Ren L, Wei Y, Zhu DX, Zai SY, Ye QH, Yu Y, Xu B, Qin XY, Xu J. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. *J Clin Oncol* 2013; **31**: 1931-1938 [PMID: 23569301 DOI: 10.1200/JCO.2012.44.8308]

98 **Maughan TS**, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, Idziaszczyk S, Harris R, Fisher D, Kenny SL, Kay E, Mitchell JK, Madi A, Jasani B, James MD, Bridgewater J, Kennedy MJ, Claes B, Lambrechts D, Kaplan R, Cheadle JP. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet* 2011; **377**: 2103-2114 [PMID: 21641636 DOI: 10.1016/S0140-6736(11)60613-2]

99 **Tveit KM**, Guren T, Glimelius B, Pfeiffer P, Sorbye H, Pyrhonen S, Sigurdsson F, Kure E, Ikdahl T, Skovlund E, Fokstuen T, Hansen F, Hofsli E, Birkemeyer E, Johnsson A, Starkhammar H, Yilmaz MK, Keldsen N, Erdal AB, Dajani O, Dahl O, Christoffersen T. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. *J Clin Oncol* 2012; **30**: 1755-1762 [PMID: 22473155 DOI: 10.1200/JCO.2011.38.0915]

100 **Köhne CH**, Hofheinz R, Mineur L, Letocha H, Greil R, Thaler J, Fernebro E, Gamelin E, Decosta L, Karthaus M. First-line panitumumab plus irinotecan/5-fluorouracil/leucovorin treatment in patients with metastatic colorectal cancer. *J Cancer Res Clin Oncol* 2012; **138**: 65-72 [PMID: 21960318 DOI: 10.1007/s00432-011-1061-6]

101 **Douillard JY**, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocákova I, Ruff P, Błasińska-Morawiec M, Šmakal M, Canon JL, Rother M, Oliner KS, Wolf M, Gansert J. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010; **28**: 4697-4705 [PMID: 20921465 DOI: 10.1200/JCO.2009.27.4860]

102 **Peeters M**, Tabernero J. Resection Rates and Survival in Patients with Wild-Type KRAS/NRAS Metastatic Colorectal Cancer and Liver Metastases: Data from the PRIME Study. In: Markers in cancer - ASCO, EORTC and NCI meeting, 2013.

103 **Vauthey JN**, Choti MA, Helton WS. AHPBA/SSO/SSAT Consensus Conference on hepatic colorectal metastases: rationale and overview of the conference. January 25, 2006. *Ann Surg Oncol* 2006; **13**: 1259-1260 [PMID: 16952025 DOI: 10.1245/s10434-006-9017-9]

104 **Stangl R**, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. *Lancet* 1994; **343**: 1405-1410 [PMID: 7515134 DOI: 10.1016/S0140-6736(94)92529-1]

105 **Rees M**, Plant G, Bygrave S. Late results justify resection for multiple hepatic metastases from colorectal cancer. *Br J Surg* 1997; **84**: 1136-1140 [PMID: 9278662 DOI: 10.1002/bjs.1800840828]

106 **Vauthey JN**, Nordlinger B, Kopetz S, Poston G. Sequenced chemotherapy and surgery for potentially resectable colorectal liver metastases: a debate over goals of research and an approach while the jury remains out. *Ann Surg Oncol* 2010; **17**: 1983-1986 [PMID: 20232164 DOI: 10.1245/s10434-010-1007-2]

107 **Nordlinger B**, Vaillant JC, Guiguet M, Balladur P, Paris F, Bachellier P, Jaeck D. Survival benefit of repeat liver resections for recurrent colorectal metastases: 143 cases. Association Francaise de Chirurgie. *J Clin Oncol* 1994; **12**: 1491-1496 [PMID: 8021741]

108 **Ruiz-Tovar J**, López Hervás P. Repeated liver resection for recurrence of colorectal cancer metastases. *Clin Transl Oncol* 2010; **12**: 634-638 [PMID: 20851805 DOI: 10.1007/s12094-010-0569-6]

109 **Fong Y**, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; **230**: 309-18; discussion 318-21 [PMID: 10493478 DOI: 10.1097/00000658-199909000-00004]

110 **Mann CD**, Metcalfe MS, Leopardi LN, Maddern GJ. The clinical risk score: emerging as a reliable preoperative prognostic index in hepatectomy for colorectal metastases. *Arch Surg* 2004; **139**: 1168-1172 [PMID: 15545561 DOI: 10.1001/archsurg.139.11.1168]

111 **Nagashima I**, Takada T, Nagawa H, Muto T, Okinaga K. Proposal of a new and simple staging system of colorectal liver metastasis. *World J Gastroenterol* 2006; **12**: 6961-6965 [PMID: 17109517 DOI: 10.3748/wjg.v12.i43.6961]

112 **Nagashima I**, Takada T, Adachi M, Nagawa H, Muto T, Okinaga K. Proposal of criteria to select candidates with colorectal liver metastases for hepatic resection: comparison of our scoring system to the positive number of risk factors. *World J Gastroenterol* 2006; **12**: 6305-6309 [PMID: 17072953 DOI: 10.3748/wjg.v12.i39.6305]

113 **Chun YS**, Laurent A, Maru D, Vauthey JN. Management of chemotherapy-associated hepatotoxicity in colorectal liver metastases. *Lancet Oncol* 2009; **10**: 278-286 [PMID: 19261256 DOI: 10.1016/S1470-2045(09)70064-6]

114 **Karagkounis G**, Torbenson MS, Daniel HD, Azad NS, Diaz LA, Donehower RC, Hirose K, Ahuja N, Pawlik TM, Choti MA. Incidence and prognostic impact of KRAS and BRAF mutation in patients undergoing liver surgery for colorectal metastases. *Cancer* 2013; **119**: 4137-4144 [PMID: 24104864 DOI: 10.1002/cncr.28347]

115 **Nash GM**, Gimbel M, Shia J, Nathanson DR, Ndubuisi MI, Zeng ZS, Kemeny N, Paty PB. KRAS mutation correlates with accelerated metastatic progression in patients with colorectal liver metastases. *Ann Surg Oncol* 2010; **17**: 572-578 [PMID: 19727962 DOI: 10.1245/s10434-009-0605-3]

116 **Stremitzer S**, Stift J, Gruenberger B, Tamandl D, Aschacher T, Wolf B, Wrba F, Gruenberger T. KRAS status and outcome of liver resection after neoadjuvant chemotherapy including bevacizumab. *Br J Surg* 2012; **99**: 1575-1582 [PMID: 23027075 DOI: 10.1002/bjs.8909]

117 **Vauthey JN**, Zimmitti G, Kopetz SE, Shindoh J, Chen SS, Andreou A, Curley SA, Aloia TA, Maru DM. RAS mutation status predicts survival and patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. *Ann Surg* 2013; **258**: 619-26; discussion 626-7 [PMID: 24018645]

118 **Lordan JT**, Karanjia ND, Quiney N, Fawcett WJ, Worthington TR. A 10-year study of outcome following hepatic resection for colorectal liver metastases - The effect of evaluation in a multidisciplinary team setting. *Eur J Surg Oncol* 2009; **35**: 302-306 [PMID: 18328668 DOI: 10.1016/j.ejso.2008.01.028]

119 **Adam R**, Haller DG, Poston G, Raoul JL, Spano JP, Tabernero J, Van Cutsem E. Toward optimized front-line therapeutic strategies in patients with metastatic colorectal cancer--an expert review from the International Congress on Anti-Cancer Treatment (ICACT) 2009. *Ann Oncol* 2010; **21**: 1579-1584 [PMID: 20219759 DOI: 10.1093/annonc/mdq043]

120 **Ruiz-Tovar J**, López Hervás P. Value of third metastasectomy of colorectal adenocarcinoma. *Clin Transl Oncol* 2007; **9**: 56-58 [PMID: 17272232 DOI: 10.1007/s12094-007-0011-x]

 **P-Reviewer:** Eefsen RL **S-Editor:** Qi Y **L-Editor: E-Editor:**

**Specialty Type:** Gastroenterology and Hepatology

**Country of Origin:** Belgium

**Peer-Review Report Classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**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 plus chemotherapy (FOLFOX/FOLFIRI) | NA | 11.8% 6% (R0) |
| Okines *et al*[89] 2009  | Unselected | Bevacizumab plus Oxaliplatin-based chemotherapy | 38% | 6.3% |
| Wong *et al*[90] 2011 | Unselected | Bevacizumab plus XELOX | 68% | 48% |
| Loupakis *et al*[91] 2013 | Unselected | Bevacizumab plus FOLFOXIRI  | 64% | 15% |
| Martin *et al*[92] 2014 | Unselected | Bevacizumab plus FOLFOX plus DEBIRI | 78% | 35% |
| Bokemeyer *et al*[94] 2009 | KRAS WT | Cetuximab plus FOLFOX | 57% | 7.3%4.7(R0) |
| Van Cutsem *et al*[95] 2011 | KRAS WT | Cetuximab plus FOLFIRI | 57% | 16%7%(R0) |
| Folprecht *et al*[22] 2010 | KRAS WT | Cetuximab plus chemotherapy (FOLFOX/FOLFIRI) | 68% | 43%34% (R0) |
| Garufi *et al*[96] 2010 | KRAS WT | Cetuximab plus FOLFOXIRI | 79% | 60% |
| Ye *et al*[97] 2013 | KRAS WT | Cetuximab plus FOLFOXIRI | 57% | 25% (R0) |
| Kohne *et al*[38] 2012 | KRAS WT | Panitumumab plus FOLFIRI | 56% | 15% |
| Douillard *et al*[101] 2010 | KRAS WTNRAS WT | Panitumumab plus FOLFOXPanitumumab plus FOLFOX | 57% | 27%5.2%(R0)31% |