TOPIC HIGHLIGHT

San-Jun Cai, MD, Professor, Director, *Series Editor*

Multi-modality treatment of colorectal liver metastases

Guo-Xiang Cai, San-Jun Cai

Guo-Xiang Cai, San-Jun Cai, Department of Colorectal Surgery, Fudan University Shanghai Cancer Center, Shanghai 200032, China
Guo-Xiang Cai, San-Jun Cai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China
Author contributions: Cai GX wrote the paper; Cai SJ was responsible for writing the outline and revising the paper.
Correspondence to: San-Jun Cai, MD, Department of Colorectal Surgery, Fudan University Shanghai Cancer Center, 270 Dong An Road, Shanghai 200032, China. caisanjun@tom.com
Telephone: +86-21-64175590-1108 Fax: +86-21-64035387

Abstract

Liver metastases synchronously or metachronously occur in approximately 50% of colorectal cancer patients. Multimodality comprehensive treatment is the best therapeutic strategy for these patients. However, the optimal pattern of multimodality therapy is still controversial, and it raises several significant concerns. Liver resection is the most important treatment for colorectal liver metastases. The definition of resectability has shifted to focus on the completion of R0 resection and normal liver function maintenance. The role of neoadjuvant and adjuvant chemotherapy still needs to be clarified. The management of either progression or complete remission during neoadjuvant chemotherapy is challenging. The optimal sequencing of surgery and chemotherapy in synchronous colorectal liver metastases patients is still unclear. Conversional chemotherapy, portal vein embolization, two-stage resection, and tumor ablation are effective approaches to improve resectability for initially unresectable patients. Several technical issues and concerns related to these methods need to be further explored. For patients with definitely unresectable liver disease, the necessity of resecting the primary tumor is still debatable, and evaluating and predicting the efficacy of targeted therapy deserve further investigation. This review discusses different patterns and important concerns of multidisciplinary treatment of colorectal liver metastases.

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INTRODUCTION

Colorectal cancer is one of the most commonly diagnosed cancers, and it is ranked the third most common globally and fourth in China. Approximately 40% of colorectal cancer patients die of cancer recurrence and metastasis. The liver is the most frequent metastatic site of colorectal cancer. Approximately 15%-25% of colorectal cancer patients have synchronous liver metastases[1-3], and 20%-25% of patients with colorectal cancer develop metachronous hepatic metastases[4-7].

In recent decades, the 5-year overall survival (OS) after curative liver resection of colorectal liver metastases (CRLM) has increased to 35%-58%[8-10]. This improvement is largely due to advancements in CRLM multimodality treatment. Generally, CRLM can be categorized into three subsets: clearly resectable, potentially resectable, or definitely unresectable. This review discusses patterns and key issues of multidisciplinary treatment of these three different CRLM subsets with a focus on the

interactive influence of different therapeutic approaches.

CLEARLY RESECTABLE COLORECTAL LIVER METASTASES

Shifting definition of CRLM resectability

Liver lesions numbering more than three, an estimated resection margin < 1 cm, the presence of extrahepatic disease, or no expected sufficient remnant liver volume used to be deemed as contraindications for CRLM liver resection. According to this definition, only 10%-20% of CRLM patients were resectable. However, this definition has changed in recent years. The report by Malik *et al*[11] has indicated that patients with 4-7 or > 7 CRLMs still had a favorable outcome after liver resection (5-year OS 34.8% and 24.2%, respectively). In the past, it was widely accepted that at least a 1-cm resection margin must be achieved for CRLM resection. However, several studies have indicated that the actual clearance margin did not affect survival as long as R0 resection could be achieved[5,12]. The presence of extrahepatic metastases is also no longer considered an absolute contraindication for liver resection. Some cancer centers have reported that the 5-year OS after combined resection of lung and liver metastases is approximately 30%[13,14]. The CRLM resectability criteria have shifted to focus on whether R0 resection for all tumors can be achieved and if a sufficient volume of residual liver can be preserved. The requirement for residual liver volume can be different for patients receiving intensive chemotherapy. Although at least 20% of total liver volume should be preserved for a healthy liver, it is recommended that at least 30%-60% should be preserved for livers impaired by chemotherapy-associated steatosis or hepatitis[15].

Advantages and disadvantages of perioperative chemotherapy

The combination of surgery and chemotherapy is the most effective multidisciplinary therapeutic paradigm for CRLM with a curative intent. There are two patterns of perioperative chemotherapy for resectable CRLM: preoperative and postoperative chemotherapy. Postoperative chemotherapy is also known as adjuvant chemotherapy, although it is still debatable whether the alternative term adjuvant therapy should be used instead. Postoperative chemotherapy has become a common practice and is intended to reduce the high risk of recurrence after resection of metastases. Preoperative chemotherapy is also called neoadjuvant chemotherapy in the setting of resectable liver metastases. The role of preoperative chemotherapy is more controversial than postoperative chemotherapy because it can give rise to major concerns. Generally, the paradigm of preoperative chemotherapy plus liver resection plus postoperative chemotherapy has become the most prevalent treatment modality in real practice.

Survival benefit of perioperative chemotherapy: Adju-

vant chemotherapy for stage III colorectal cancer patients has been widely accepted based on solid evidence for survival benefit. Although postoperative chemotherapy after liver metastases resection is also accepted by many oncologists, there have been few prospective randomized clinical studies that have investigated the adjuvant chemotherapy survival benefit after liver resection, and the sample size of these studies has been limited due to difficult accrual. In the Fédération Francophone de la Cancérologie Digestive (FFCD) ACHBTH AURC 9002 clinical trial, CRLM patients receiving adjuvant chemotherapy of 5-fluorouracil (5-FU) and leucovorin (LV) after R0 liver resection had a significantly better 5-year disease-free survival (DFS) compared with the observation group (33.5% *vs* 26.7%, *P* = 0.028). There was also a trend toward better OS in the adjuvant chemotherapy group, although this was not statistically significant (51.1% *vs* 41.1%, *P* = 0.13)[16]. This study was prematurely stopped due to slow accrual. A pooled data analysis combined with another study (i.e., European Organisation for Research and Treatment of Cancer/ National Cancer Institute of Canada Clinical Trials Group/ Interdisciplinary Group for Cancer Care Evaluation trial), which had a similar design and stopped ahead of schedule for the same reason, was performed but also could not demonstrate a statistically significant improvement in OS (*P* = 0.095)[17].

Although the most fascinating benefit of preoperative chemotherapy is the conversion of unresectability to resectability, the role of neoadjuvant chemotherapy in patients with initially resectable CRLM is still controversial. The most important concern about neoadjuvant chemotherapy is whether it can bring about a survival benefit. The only published randomized prospective clinical trial to investigate the role of neoadjuvant chemotherapy in CRLM patients, EORTC 40983[18], indicated that patients with initially resectable CRLM undergoing liver resection plus six cycles of preoperative FOLFOX4 and six cycles of postoperative FOLFOX4 chemotherapy had a better 3-year progression-free survival (PFS) compared to those receiving liver resection alone. However, there was a significant defect in this study: patients in the control group did not undergo chemotherapy after hepatic resection. Therefore, it is difficult to determine whether the PFS improvement is brought about by preoperative chemotherapy, postoperative chemotherapy or both. To investigate the exact role of neoadjuvant chemotherapy, we still need to wait for the results of ongoing clinical studies to compare survival directly in patients undergoing postoperative chemotherapy alone with those undergoing both preoperative and postoperative chemotherapy.

Management of disappearing CRLM: A potential drawback of neoadjuvant chemotherapy in resectable CRLM patients is missing the optimal timing of liver resection because of complete response of liver tumors during chemotherapy. Approximately 4% of patients achieved a radiographic complete response (CR) to chemotherapy, and 9% had a pathological CR[19,20]. Radiographic CR does

not always mean true hepatic metastases remission. Viable cancer cells can be pathologically found in 80% (12/15) of patients with a radiographic CR and undergoing resection according to the prior sites[21]. If these radiographically disappearing liver metastases are kept in place without resection, 41%-75% will have recurrence *in situ*[21,22]. Nevertheless, it is not always easy to perform liver resection according to the previous site of disappearing liver metastases. To avoid such an intractable condition, it is recommended that the evaluation of liver lesions be repeated every 2 mo during preoperative chemotherapy[7,23-25].

Resection of CRLM progressing during neoadjuvant chemotherapy: A second potential risk of neoadjuvant chemotherapy is disease progression. Liver tumor progression may add to the difficulty of liver resection and even deprive patients of the opportunity for hepatic resection. The EORTC 40983 clinical study[18] reported that 7% of initially resectable CRLM patients had progressive disease (PD) during neoadjuvant chemotherapy, and 4% did not complete liver resection due to prior liver disease progression or the presence of new extrahepatic metastases. Another issue concerning liver metastases progression is whether they should be resected even if it is possible. Adam *et al*[26] have suggested that liver PD during chemotherapy indicates poor prognosis after resection and should be considered as a contraindication to liver resection. They reported a dismal 5-year OS (8%) and DFS (3%) after liver resection in patients with tumor progression during neoadjuvant chemotherapy. However, other studies have indicated that the response to neoadjuvant chemotherapy has no prognostic value. Reports from Neumann *et al*[27] and Gallagher *et al*[28] have indicated no difference in survival after liver resection among three groups of CRLM patients with PD, stable disease (SD) or objective response to neoadjuvant chemotherapy.

Impact of chemotherapy-induced hepatotoxicity on the outcome of hepatic resection: Another important concern related to neoadjuvant chemotherapy is whether the hepatotoxicity caused by preoperative chemotherapy increases the perioperative morbidity and mortality of liver surgery. There are two types of chemotherapy-associated hepatotoxicity: non-alcoholic fatty liver disease (i.e., macrovesicular steatosis/steatohepatitis) and vascular sinusoidal obstruction. All three commonly used chemotherapeutic agents for colorectal cancer, 5-FU, oxaliplatin and irinotecan, can induce steatosis with an incidence rate of 30%-40%[29,30]. Steatohepatitis is less common in patients with chemotherapy. Approximately 3.6%-8%[7,31] of patients have chemotherapy-associated steatohepatitis, which is relatively more common in patients receiving irinotecan as compared with those receiving 5-FU[32]. Vascular sinusoidal obstruction is associated with the use of oxaliplatin, and is present in 10%-52% of patients undergoing preoperative oxaliplatin therapy[7,25,33].

The impact of chemotherapy induced hepatic toxicity on the short-term outcome of patients receiving liver resection is still uncertain. A slightly increased morbidity was noted in patients undergoing six cycles of preoperative FOLFOX4 chemotherapy as compared with those without preoperative chemotherapy in the EORTC 40983 study[18]. Nevertheless, there was no difference in the perioperative mortality between these two groups. The study of Kooby *et al*[34] has demonstrated an increase in infection-related complications associated with moderate to severe steatosis in patients undergoing hepatic resection after chemotherapy, but no association with major surgical complications or mortality for preoperative chemotherapy was shown. However, Vauthey *et al*[25] have reported that, after the use of irinotecan, patients with steatohepatitis had a significantly higher 90-d postoperative mortality compared with those without steatohepatitis (15% *vs* 2%, *P* = 0.001). Therefore, it is recommended that irinotecan should be used cautiously in patients with known steatosis or steatohepatitis or those with a high risk for steatosis, such as those with obesity, hypertension or diabetes.

Management of resectable synchronous CRLM

Optimal sequencing of colorectal surgery, liver resection and perioperative chemotherapy: Approximately 15%-25% of patients have synchronous liver metastases at the diagnosis of colorectal cancer[1-3]. The optimal timing of primary tumor and liver metastases resection in synchronous resectable CRLM patients is still controversial. There are three approaches for the sequence of surgical treatment for primary tumor and liver disease: (1) simultaneous resection of primary cancer and liver metastases; (2) resection of primary colorectal tumor first followed by liver resection; and (3) hepatectomy first followed by primary cancer resection. The clinical decision usually depends on many factors, including surgical exposure, colectomy and hepatectomy complexity, surgeon expertise and patient comorbidity[35].

Based on the observation of the possible increased morbidity and mortality using a combination of hepatectomy and colectomy[36-39], a staged approach (i.e., liver resection following primary tumor resection and optional chemotherapy) was widely performed in the past. However, simultaneous resection of the primary cancer and the liver metastases has been increasingly adopted in recent years due to more recent reports that perioperative morbidity and mortality of simultaneous resection are comparable to that of staged resection[40-42]. No significant difference in 5-year survival was found between these two groups in a systemic analysis[43]. However, Reddy *et al*[35] have reported that patients undergoing simultaneous major hepatectomy (i.e., resection of three or more liver segments) had a significantly higher mortality (8.3% *vs* 1.4%) and severe morbidity (36.1% *vs* 17.6%) than those receiving staged resection. Therefore, simultaneous major hepatectomy is not highly recommended at present due to the potentially increased risk of severe complications. A new paradigm has been proposed more recently that is called the "liver-first" strategy[44], and includes first, liver resection, with or without preoperative

chemotherapy, followed by optional chemotherapy after hepatectomy, and finally, primary tumor resection. This approach may be suitable for borderline resectable liver metastases, which may lose the time frame of resection if delayed. Mentha *et al*[44] have reported 20 CRLM patients undergoing such a sequential resection with a resection rate of 80% and 4-year OS of 56%. However, there are some potential defects in the design of this approach. For patients with obstructive symptoms caused by the primary tumor, primary-tumor-directed treatment is more urgent and should be performed first. Another potential disadvantage of this approach is that the primary tumor may progress and require emergency surgery during this process. A decision-making analysis has demonstrated that it is least probable to complete all intended sequential treatment for the liver-first approach among the above three treatment sequences[45].

The role of minimally invasive surgery: It is difficult to perform a one-stage resection of primary and liver disease for rectal cancer liver metastases due to surgical exposure and lengthy incisions. In such a condition, laparoscopic surgery, particularly robot-assisted laparoscopic surgery, is advantageous to perform a simultaneous resection of liver metastases and rectal cancer. This type of surgery has been reported to be safe and feasible in a pilot study by Patriti *et al*[46]. An important concern about the laparoscopic hepatic resection is the oncologic outcome. It has been reported that the laparoscopic approach had a positive resection margin rate (5.6%) and 5-year OS (50%); comparable with open surgery for CRLMs. In a French study[47] comparing CRLM patients undergoing laparoscopic hepatic resection or open resection, the 5-year OS and DFS were similar in these two groups, whereas the laparoscopic surgery group even had a lower rate of positive resection margin than the open surgery group (13% *vs* 28%, *P* = 0.04).

UNRESECTABLE COLORECTAL LIVER METASTASES WITH POTENTIAL CONVERTIBILITY

Some CRLM patients are initially unresectable but have the potential to become resectable through conversion therapeutic strategies including chemotherapy, embolization, two-staged operation or the combination of ablation therapy.

Conversion chemotherapy

It is estimated that 80%-90% of CRLMs are considered unresectable at diagnosis. Due to the development of new chemotherapy agents and targeted therapeutic agents, chemotherapy can convert a considerable portion of initially unresectable CRLM into resectable disease, which is called conversion chemotherapy[7,48-50]. It was first reported in 1996 by Bismuth *et al*[49] that preoperative chemotherapy, using oxaliplatin plus 5-FU/LV, enabled

16% (53/330) of initially unresectable CRLM patients to gain the chance of undergoing liver resection with a 5-year OS of 40%. In 2001, Adam *et al*[23] reported that 13.6% (95/701) of initially unresectable CRLM patients underwent liver metastases resection after systemic chemotherapy and achieved a 5-year OS of 34%. Intensified chemotherapy such as FOLFOXIRI (i.e., oxaliplatin, 5-FU/LV and irinotecan) has been shown to have high response and conversion rates (19%)[50]; however, it has not been generally recommended thus far due to its considerable toxicity. In recent years, the addition of targeted agents such as cetuximab to chemotherapy has been shown to further improve the conversion rate to 30%-40%[51]. In the CELIM study[51], 106 patients with initially unresectable CRLM underwent cetuximab plus FOLFOX6 or cetuximab plus FOLFIRI and achieved an objective response rate of 68% and 57%, a liver resection rate of 40% and 38%, and a R0 liver resection rate of 38% and 30%, respectively.

Portal vein embolization and two-stage operation

Preserving at least 20% of future liver remnant is a major obstacle when performing an extended hemihepatectomy for extensive liver metastases. In this situation, Portal vein embolization (PVE) can be helpful to induce hypertrophy of the contralateral liver to fulfill the minimal liver volume requirement[52]. Generally, PVE is usually used before extended right hepatectomy and is seldom used for extended left hepatectomy because the right posterior sector generally provides > 30% of the liver volume. Even after preoperative chemotherapy or PVE, some patients cannot become eligible for complete CRLM resection through a single hepatectomy. PVE combined with a two-stage resection may be helpful in such circumstances. In 2000, Adam *et al*[53] first proposed the two-stage resection strategy when they reported the initial results from 13 patients undergoing two-stage hepatectomy with a 3-year survival rate of 35%. An updated result of a 5-year OS of 42% in 41 patients receiving two-staged resection was reported in 2008[54]. However, > 30% (18/59) of patients could not complete the second hepatectomy, mostly because of disease progression (*n* = 17). Additionally, the second hepatectomy has a significant higher postoperative mortality (7%) and morbidity (59%) than the first hepatectomy (0% and 20%, respectively).

Ablation therapy

The most commonly used approach for ablation therapy is radiofrequency ablation (RFA). Most previous studies have indicated that RFA is inferior to liver resection for CRLM with a high local recurrence rate[55]. However, for patients who cannot undergo liver resection because of extensive liver metastases and inadequate remnant liver volume, RFA can play an important role when combined with liver resection. RFA is generally recommended for CRLM less than 3 cm[56-64]. The local recurrence rate after RFA increases with tumor size in liver lesions > 3 cm[65]. Several studies have reported a significantly higher local

failure rate after ablation for tumors > 5 cm when compared to those 3cm-5 cm[64,66].

There are three approaches for RFA, including percutaneous, open and laparoscopic. Ablation through the open approach seems to be superior to the percutaneous or laparoscopic methods in terms of local failure rate[57,67,68]. However, the reported local recurrence rate of each approach has actually varied and overlapped each other in a range of 6%-40% in different studies[69-77].

DEFINITELY UNRESECTABLE CRLMs

Necessity of primary tumor resection

For patients with incurable metastatic colorectal cancer who have symptoms related to intestinal obstruction, perforation or intractable bleeding, palliative primary tumor resection is generally required and advocated. However, for asymptomatic patients with unresectable metastases, the value of primary tumor resection is still questionable. Early studies have indicated that primary tumor resection may have potential benefits in preventing tumor-related symptoms such as obstruction, which may require emergency operations with a high risk of surgical mortality[78-80]. However, this opinion may become outdated with the application of new efficient chemotherapy agents that have the ability to control intestinal symptoms well. Therefore, the US National Comprehensive Cancer Network guidelines recommend that colon resection should be considered only for impending obstruction risk or intractable bleeding. It is estimated that only 20%-30% of metastatic colorectal cancer patients are eligible for curative resection. Nevertheless, data from the US Surveillance, Epidemiology, and End Results (SEER) database have demonstrated that 66% of stage IV colorectal cancer patients received primary tumor resection[81]. In another study based on 9000 elderly metastatic colorectal cancer patients, 72% underwent primary tumor resection, whereas only 3.9% received metastasectomy and 20% had symptoms of bowel obstruction, perforation or bleeding[82]. It suggests that a considerable portion of incurable colorectal cancer patients receive intestinal resection without a clear and reasonable indication. The Memorial Sloan-Kettering Cancer Center reported 233 metastatic colorectal cancer patients receiving chemotherapy with the primary tumor left in place[83]. Only 7% of the patients required palliative primary tumor resection during the disease course. Thus, the authors recommended chemotherapy without prophylactic primary tumor resection as a standard management of metastatic colorectal cancer without obstruction or bleeding symptoms.

Targeted therapy in combination with chemotherapy

The survival benefit of adding targeted therapeutic agents such as bevacizumab, cetuximab and panitumumab to traditional chemotherapy in patients with unresectable metastatic colorectal cancer has been validated by several randomized clinical trials. The BEAT study[84] collected 1965 metastatic colorectal cancer patients undergoing bevacizumab combined with different types of chemotherapy as the first-line therapy, and demonstrated that the PFS in patients receiving bevacizumab plus FOLFIRI, FOLOFOX or Xelox was > 10 mo and the OS approached or exceeded 24 mo. This study indicated that bevacizumab-based combination chemotherapy is efficient in metastatic colorectal cancer. The PFS and OS were 8.6 and 18.0 mo, respectively, in patients receiving bevacizumab plus 5-FU, which is also comparable to a regimen including 5-FU plus oxaliplatin or 5-FU plus irinotecan.

The efficacy of cetuximab greatly depends on the status of the *KRAS* gene. The CRYSTAL study[85], which compared cetuximab plus FOLFIRI with FOLFIRI alone in the initial treatment of metastatic colorectal cancer patients, indicated that cetuximab improved the response rate (57.3% *vs* 39.7%, $P < 0.0001$), PFS (9.9 mo *vs* 8.4 mo, $P = 0.0012$) and OS (23.5 mo *vs* 20.0 mo, $P = 0.0094$) significantly in patients with wild-type KRAS. However, in a population subset with mutant KRAS, there was no significant difference in the response rate, PFS or OS between the two groups. The OPUS study[86] even exhibited a worse response rate and PFS for the cetuximab plus FOLFOX4 group as compared with FOLFOX4 group in patients with mutant *KRAS*. The status of the *BRAF* gene is another efficient predictor of cetuximab efficacy. Di Nicolantonio *et al*[87] have reported that the *BRAF* gene mutation rate in patients with wild-type *KRAS* was approximately 14% (11/79). None of the *BRAF* mutant patients responded to cetuximab or panitumumab or cetuximab plus chemotherapy. The PFS of patients with wild-type *BRAF* was better than their counterparts ($P < 0.001$). A considerable defect in the *BRAF* gene as a predictor of treatment response is that the mutation rate is low. The incidence rate of mutant *BRAF* is only 6.4%-14% in patients with wild-type *KRAS*, and no *BRAF* mutation has been reported in those with *KRAS* mutations.

In the second or third-line treatment settings, the addition of cetuximab or bevacizumab to chemotherapy, or a single treatment with cetuximab, has also been proven to be effective[88,89]. In a phase III clinical trial[90], 463 metastatic colorectal cancer patients received either panitumumab plus best supportive care (BSC) or BSC alone after chemotherapy failure. Patients with panitumumab plus BSC had an objective response rate of 8% and a significantly better median PFS (96 d *vs* 60 d) than those who received BSC alone. In another clinical trial[91], the combination of panitumumab with FOLFIRI as a second treatment for metastatic colorectal cancer patients improved the PFS (5.9 mo *vs* 3.9 mo, $P = 0.004$) and objective response rate (35% *vs* 10%, $P < 0.001$) in patients with wild-type *KRAS* compared to the regimen of FOLFIRI alone.

CONCLUSION

Multidisciplinary treatment has become the standard practice for CRLM management. Nevertheless, the optimal paradigm of multimodality treatment still needs to be further investigated. As the most effective treatment

method, surgical CRLM resection has been rendered an expanded indication in recent years. CRLM patients can be categorized into three subtypes: clearly initially resectable, potentially resectable, or definitely unresectable. For patients with initially resectable CRLM, the survival benefit of neoadjuvant chemotherapy is still unclear. The management of CRLM disappearing or progressing during neoadjuvant chemotherapy is challenging and controversial. The influence of chemotherapy-related toxicity on the outcome of liver resection needs to be further clarified. The optimal sequencing of primary tumor resection and liver lesions and perioperative chemotherapy deserves further investigation in patients with resectable synchronous CRLM. For patients who are initially unresectable but potentially convertible, chemotherapy, PVE, two-staged operation and ablation therapy are effective methods to convert unresectability into resectability. How to utilize these methods in a reasonable and better way needs to be further explored. For definitely unresectable CRLMs, it is still being debated whether the primary tumor should be resected. Targeted therapy, in addition to traditional chemotherapy, has been shown to improve the survival of unresectable CRLM patients. How to accurately predict the tumor response to targeted therapy is an important issue that should be further investigated in consideration of its high cost. A better understanding of these issues will greatly improve the effect of multidisciplinary treatment of CRLM patients.

REFERENCES

1   **Blumgart LH**, Allison DJ. Resection and embolization in the management of secondary hepatic tumors. *World J Surg* 1982; **6**: 32-45

2   **Cady B**, Monson DO, Swinton NW. Survival of patients after colonic resection for carcinoma with simultaneous liver metastases. *Surg Gynecol Obstet* 1970; **131**: 697-700

3   **Jatzko G**, Wette V, Müller M, Lisborg P, Klimpfinger M, Denk H. Simultaneous resection of colorectal carcinoma and synchronous liver metastases in a district hospital. *Int J Colorectal Dis* 1991; **6**: 111-114

4   **Benjamin IS**, Blumgart LH. Occult hepatic metastases in colorectal carcinoma. *Br J Surg* 1986; **73**: 1046

5   **Altendorf-Hofmann A**, Scheele J. A critical review of the major indicators of prognosis after resection of hepatic metastases from colorectal carcinoma. *Surg Oncol Clin N Am* 2003; **12**: 165-192, xi

6   **Scheele J**, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. *World J Surg* 1995; **19**: 59-71

7   **Pawlik TM**, Choti MA. Surgical therapy for colorectal metastases to the liver. *J Gastrointest Surg* 2007; **11**: 1057-1077

8   **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**: 309-318; discussion 318-321

9   **Abdalla EK**, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, Hess K, Curley SA. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg* 2004; **239**: 818-825; discussion 825-827

10   **Choti MA**, Sitzmann JV, Tiburi MF, Sumetchotimetha W, Rangsin R, Schulick RD, Lillemoe KD, Yeo CJ, Cameron JL. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg* 2002; **235**: 759-766

11   **Malik HZ**, Hamady ZZ, Adair R, Finch R, Al-Mukhtar A, Toogood GJ, Prasad KR, Lodge JP. Prognostic influence of multiple hepatic metastases from colorectal cancer. *Eur J Surg Oncol* 2007; **33**: 468-473

12   **Pawlik TM**, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C, Curley SA, Loyer EM, Muratore A, Mentha G, Capussotti L, Vauthey JN. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg* 2005; **241**: 715-722, discussion 722-724

13   **Neeff H**, Hörth W, Makowiec F, Fischer E, Imdahl A, Hopt UT, Passlick B. Outcome after resection of hepatic and pulmonary metastases of colorectal cancer. *J Gastrointest Surg* 2009; **13**: 1813-1820

14   **Miller G**, Biernacki P, Kemeny NE, Gonen M, Downey R, Jarnagin WR, D'Angelica M, Fong Y, Blumgart LH, DeMatteo RP. Outcomes after resection of synchronous or metachronous hepatic and pulmonary colorectal metastases. *J Am Coll Surg* 2007; **205**: 231-238

15   **Pawlik TM**, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. *Oncologist* 2008; **13**: 51-64

16   **Portier G**, Elias D, Bouche O, Rougier P, Bosset JF, Saric J, Belghiti J, Piedbois P, Guimbaud R, Nordlinger B, Bugat R, Lazorthes F, Bedenne L. Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. *J Clin Oncol* 2006; **24**: 4976-4982

17   **Mitry E**, Fields AL, Bleiberg H, Labianca R, Portier G, Tu D, Nitti D, Torri V, Elias D, O'Callaghan C, Langer B, Martignoni G, Bouché O, Lazorthes F, Van Cutsem E, Bedenne L, Moore MJ, Rougier P. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. *J Clin Oncol* 2008; **26**: 4906-4911

18   **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, Collette L, Praet M, Bethe U, Van Cutsem E, Scheithauer W, Gruenberger T. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008; **371**: 1007-1016

19   **Adam R**, Wicherts DA, de Haas RJ, Aloia T, Lévi F, Paule B, Guettier C, Kunstlinger F, Delvart V, Azoulay D, Castaing D. Complete pathologic response after preoperative chemotherapy for colorectal liver metastases: myth or reality? *J Clin Oncol* 2008; **26**: 1635-1641

20   **Chua TC**, Saxena A, Liauw W, Kokandi A, Morris DL. Systematic review of randomized and nonrandomized trials of the clinical response and outcomes of neoadjuvant systemic chemotherapy for resectable colorectal liver metastases. *Ann Surg Oncol* 2010; **17**: 492-501

21   **Benoist S**, Brouquet A, Penna C, Julié C, El Hajjam M, Chagnon S, Mitry E, Rougier P, Nordlinger B. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? *J Clin Oncol* 2006; **24**: 3939-3945

22   **Tanaka K**, Takakura H, Takeda K, Matsuo K, Nagano Y, Endo I. Importance of complete pathologic response to prehepatectomy chemotherapy in treating colorectal cancer metastases. *Ann Surg* 2009; **250**: 935-942

23   **Adam R**, Avisar E, Ariche A, Giachetti S, Azoulay D, Castaing D, Kunstlinger F, Levi F, Bismuth F. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. *Ann Surg Oncol* 2001; **8**: 347-353

24   **Rivoire M**, De Cian F, Meeus P, Négrier S, Sebban H, Kaemmerlen P. Combination of neoadjuvant chemotherapy

with cryotherapy and surgical resection for the treatment of unresectable liver metastases from colorectal carcinoma. *Cancer* 2002; **95**: 2283-2292

25 **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

26 **Adam R**, Pascal G, Castaing D, Azoulay D, Delvart V, Paule B, Levi F, Bismuth H. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? *Ann Surg* 2004; **240**: 1052-1061; discussion 1061-1064

27 **Neumann UP**, Thelen A, Röcken C, Seehofer D, Bahra M, Riess H, Jonas S, Schmeding M, Pratschke J, Bova R, Neuhaus P. Nonresponse to pre-operative chemotherapy does not preclude long-term survival after liver resection in patients with colorectal liver metastases. *Surgery* 2009; **146**: 52-59

28 **Gallagher DJ**, Zheng J, Capanu M, Haviland D, Paty P, DeMatteo RP, D'Angelica M, Fong Y, Jarnagin WR, Allen PJ, Kemeny N. Response to neoadjuvant chemotherapy does not predict overall survival for patients with synchronous colorectal hepatic metastases. *Ann Surg Oncol* 2009; **16**: 1844-1851

29 **Sørensen P**, Edal AL, Madsen EL, Fenger C, Poulsen MR, Petersen OF. Reversible hepatic steatosis in patients treated with interferon alfa-2a and 5-fluorouracil. *Cancer* 1995; **75**: 2592-2596

30 **Moertel CG**, Fleming TR, Macdonald JS, Haller DG, Laurie JA. Hepatic toxicity associated with fluorouracil plus levamisole adjuvant therapy. *J Clin Oncol* 1993; **11**: 2386-2390

31 **Kleiner DE**, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, Liu YC, Torbenson MS, Unalp-Arida A, Yeh M, McCullough AJ, Sanyal AJ. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005; **41**: 1313-1321

32 **Brunt EM**, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. *Am J Gastroenterol* 1999; **94**: 2467-2474

33 **Klinger M**, Eipeldauer S, Hacker S, Herberger B, Tamandl D, Dorfmeister M, Koelblinger C, Gruenberger B, Gruenberger T. Bevacizumab protects against sinusoidal obstruction syndrome and does not increase response rate in neoadjuvant XELOX/FOLFOX therapy of colorectal cancer liver metastases. *Eur J Surg Oncol* 2009; **35**: 515-520

34 **Kooby DA**, Fong Y, Suriawinata A, Gonen M, Allen PJ, Klimstra DS, DeMatteo RP, D'Angelica M, Blumgart LH, Jarnagin WR. Impact of steatosis on perioperative outcome following hepatic resection. *J Gastrointest Surg* 2003; **7**: 1034-1044

35 **Reddy SK**, Pawlik TM, Zorzi D, Gleisner AL, Ribero D, Assumpcao L, Barbas AS, Abdalla EK, Choti MA, Vauthey JN, Ludwig KA, Mantyh CR, Morse MA, Clary BM. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. *Ann Surg Oncol* 2007; **14**: 3481-3491

36 **Jenkins LT**, Millikan KW, Bines SD, Staren ED, Doolas A. Hepatic resection for metastatic colorectal cancer. *Am Surg* 1997; **63**: 605-610

37 **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

38 **Jaeck D**, Bachellier P, Weber JC, Mourad M, Walf P, Boudjema K. [Surgical treatment of synchronous hepatic metastases of colorectal cancers. Simultaneous or delayed resection?]. *Ann Chir* 1996; **50**: 507-512; discussion 513-516

39 **Fujita S**, Akasu T, Moriya Y. Resection of synchronous liver metastases from colorectal cancer. *Jpn J Clin Oncol* 2000; **30**: 7-11

40 **Martin R**, Paty P, Fong Y, Grace A, Cohen A, DeMatteo R, Jarnagin W, Blumgart L. Simultaneous liver and colorectal resections are safe for synchronous colorectal liver metastasis. *J Am Coll Surg* 2003; **197**: 233-241; discussion 241-242

41 **Lyass S**, Zamir G, Matot I, Goitein D, Eid A, Jurim O. Combined colon and hepatic resection for synchronous colorectal liver metastases. *J Surg Oncol* 2001; **78**: 17-21

42 **Chua HK**, Sondenaa K, Tsiotos GG, Larson DR, Wolff BG, Nagorney DM. Concurrent vs. staged colectomy and hepatectomy for primary colorectal cancer with synchronous hepatic metastases. *Dis Colon Rectum* 2004; **47**: 1310-1316

43 **Hillingsø JG**, Wille-Jørgensen P. Staged or simultaneous resection of synchronous liver metastases from colorectal cancer--a systematic review. *Colorectal Dis* 2009; **11**: 3-10

44 **Mentha G**, Majno PE, Andres A, Rubbia-Brandt L, Morel P, Roth AD. Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary. *Br J Surg* 2006; **93**: 872-878

45 **Aloia TA**, Fahy BN. A decision analysis model predicts the optimal treatment pathway for patients with colorectal cancer and resectable synchronous liver metastases. *Clin Colorectal Cancer* 2008; **7**: 197-201

46 **Patriti A**, Ceccarelli G, Bartoli A, Spaziani A, Lapalorcia LM, Casciola L. Laparoscopic and robot-assisted one-stage resection of colorectal cancer with synchronous liver metastases: a pilot study. *J Hepatobiliary Pancreat Surg* 2009; **16**: 450-457

47 **Castaing D**, Vibert E, Ricca L, Azoulay D, Adam R, Gayet B. Oncologic results of laparoscopic versus open hepatectomy for colorectal liver metastases in two specialized centers. *Ann Surg* 2009; **250**: 849-855

48 **Rahman S**, Toogood GJ, Lodge PJ, Prasad KR. Role of neoadjuvant chemotherapy in the treatment of multiple colorectal metastases to the liver (Br J Surg 2003; 90: 963-969). *Br J Surg* 2003; **90**: 1453

49 **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**: 509-520; discussion 520-522

50 **Masi G**, Loupakis F, Pollina L, Vasile E, Cupini S, Ricci S, Brunetti IM, Ferraldeschi R, Naso G, Filipponi F, Pietrabissa A, Goletti O, Baldi G, Fornaro L, Andreuccetti M, Falcone A. Long-term outcome of initially unresectable metastatic colorectal cancer patients treated with 5-fluorouracil/leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) followed by radical surgery of metastases. *Ann Surg* 2009; **249**: 420-425

51 **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

52 **Abdalla EK**, Hicks ME, Vauthey JN. Portal vein embolization: rationale, technique and future prospects. *Br J Surg* 2001; **88**: 165-175

53 **Adam R**, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. *Ann Surg* 2000; **232**: 777-785

54 **Wicherts DA**, Miller R, de Haas RJ, Bitsakou G, Vibert E, Veilhan LA, Azoulay D, Bismuth H, Castaing D, Adam R. Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases. *Ann Surg* 2008; **248**: 994-1005

55   **Abdalla EK**. Commentary: Radiofrequency ablation for colorectal liver metastases: do not blame the biology when it is the technology. *Am J Surg* 2009; **197**: 737-739

56   **de Meijer VE**, Verhoef C, Kuiper JW, Alwayn IP, Kazemier G, Ijzermans JN. Radiofrequency ablation in patients with primary and secondary hepatic malignancies. *J Gastrointest Surg* 2006; **10**: 960-973

57   **Amersi FF**, McElrath-Garza A, Ahmad A, Zogakis T, Allegra DP, Krasne R, Bilchik AJ. Long-term survival after radiofrequency ablation of complex unresectable liver tumors. *Arch Surg* 2006; **141**: 581-587; discussion 587-588

58   **Chow DH**, Sinn LH, Ng KK, Lam CM, Yuen J, Fan ST, Poon RT. Radiofrequency ablation for hepatocellular carcinoma and metastatic liver tumors: a comparative study. *J Surg Oncol* 2006; **94**: 565-571

59   **Lermite E**, Lebigot J, Oberti F, Pessaux P, Aube C, Cales P, Arnaud JP. Radiofrequency thermal ablation of liver carcinoma. Prospective study of 82 lesions. *Gastroenterol Clin Biol* 2006; **30**: 130-135

60   **Abitabile P**, Hartl U, Lange J, Maurer CA. Radiofrequency ablation permits an effective treatment for colorectal liver metastasis. *Eur J Surg Oncol* 2007; **33**: 67-71

61   **Gillams AR**, Lees WR. Radio-frequency ablation of colorectal liver metastases in 167 patients. *Eur Radiol* 2004; **14**: 2261-2267

62   **Kosari K**, Gomes M, Hunter D, Hess DJ, Greeno E, Sielaff TD. Local, intrahepatic, and systemic recurrence patterns after radiofrequency ablation of hepatic malignancies. *J Gastrointest Surg* 2002; **6**: 255-263

63   **van Duijnhoven FH**, Jansen MC, Junggeburt JM, van Hillegersberg R, Rijken AM, van Coevorden F, van der Sijp JR, van Gulik TM, Slooter GD, Klaase JM, Putter H, Tollenaar RA. Factors influencing the local failure rate of radiofrequency ablation of colorectal liver metastases. *Ann Surg Oncol* 2006; **13**: 651-658

64   **Machi J**, Uchida S, Sumida K, Limm WM, Hundahl SA, Oishi AJ, Furumoto NL, Oishi RH. Ultrasound-guided radiofrequency thermal ablation of liver tumors: percutaneous, laparoscopic, and open surgical approaches. *J Gastrointest Surg* 2001; **5**: 477-489

65   **Dodd GD**, Frank MS, Aribandi M, Chopra S, Chintapalli KN. Radiofrequency thermal ablation: computer analysis of the size of the thermal injury created by overlapping ablations. *AJR Am J Roentgenol* 2001; **177**: 777-782

66   **Jiang HC**, Liu LX, Piao DX, Xu J, Zheng M, Zhu AL, Qi SY, Zhang WH, Wu LF. Clinical short-term results of radiofrequency ablation in liver cancers. *World J Gastroenterol* 2002; **8**: 624-630

67   **Kuvshinoff BW**, Ota DM. Radiofrequency ablation of liver tumors: influence of technique and tumor size. *Surgery* 2002; **132**: 605-611; discussion 611-612

68   **Hildebrand P**, Kleemann M, Roblick UJ, Mirow L, Birth M, Leibecke T, Bruch HP. Radiofrequency-ablation of unresectable primary and secondary liver tumors: results in 88 patients. *Langenbecks Arch Surg* 2006; **391**: 118-123

69   **Stippel DL**, Böhm S, Beckurts KT, Brochhagen HG, Hölscher AH. Intraoperative radiofrequency ablation using a 3D navigation tool for treatment of colorectal liver metastases. *Onkologie* 2002; **25**: 346-350

70   **Mutsaerts EL**, Van Coevorden F, Krause R, Borel Rinkes IH, Strobbe LJ, Prevoo W, Tollenaar RA, van Gulik TM. Initial experience with radiofrequency ablation for hepatic tumours in the Netherlands. *Eur J Surg Oncol* 2003; **29**: 731-734

71   **Chhabra DG**, Shah RC, Parikh V, Jagannath P. Radiofrequency ablation of liver tumors: experience with open and percutaneous approach. *Indian J Gastroenterol* 2006 **25**: 66-70

72   **Jakobs TF**, Hoffmann RT, Trumm C, Reiser MF, Helmberger TK. Radiofrequency ablation of colorectal liver metastases: mid-term results in 68 patients. *Anticancer Res* 2006; **26**: 671-680

73   **Tait IS**, Yong SM, Cuschieri SA. Laparoscopic in situ ablation of liver cancer with cryotherapy and radiofrequency ablation. *Br J Surg* 2002; **89**: 1613-1619

74   **Berber E**, Pelley R, Siperstein AE. Predictors of survival after radiofrequency thermal ablation of colorectal cancer metastases to the liver: a prospective study. *J Clin Oncol* 2005; **23**: 1358-1364

75   **Chen MH**, Yang W, Yan K, Gao W, Dai Y, Wang YB, Zhang XP, Yin SS. Treatment efficacy of radiofrequency ablation of 338 patients with hepatic malignant tumor and the relevant complications. *World J Gastroenterol* 2005; **11**: 6395-6401

76   **Chen MH**, Yang W, Yan K, Zou MW, Solbiati L, Liu JB, Dai Y. Large liver tumors: protocol for radiofrequency ablation and its clinical application in 110 patients--mathematic model, overlapping mode, and electrode placement process. *Radiology* 2004; **232**: 260-271

77   **Livraghi T**, Solbiati L, Meloni MF, Gazelle GS, Halpern EF, Goldberg SN. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. *Radiology* 2003; **226**: 441-451

78   **Bacon HE**, Martin PV. The rationale of palliative resection for primary cancer of the colon and rectum complicated by liver and lung metastasis. *Dis Colon Rectum* 1964; **7**: 211-217

79   **Longo WE**, Ballantyne GH, Bilchik AJ, Modlin IM. Advanced rectal cancer. What is the best palliation? *Dis Colon Rectum* 1988; **31**: 842-847

80   **Moran MR**, Rothenberger DA, Lahr CJ, Buls JG, Goldberg SM. Palliation for rectal cancer. Resection? Anastomosis? *Arch Surg* 1987; **122**: 640-643

81   **Cook AD**, Single R, McCahill LE. Surgical resection of primary tumors in patients who present with stage IV colorectal cancer: an analysis of surveillance, epidemiology, and end results data, 1988 to 2000. *Ann Surg Oncol* 2005; **12**: 637-645

82   **Temple LK**, Hsieh L, Wong WD, Saltz L, Schrag D. Use of surgery among elderly patients with stage IV colorectal cancer. *J Clin Oncol* 2004; **22**: 3475-3484

83   **Poultsides GA**, Servais EL, Saltz LB, Patil S, Kemeny NE, Guillem JG, Weiser M, Temple LK, Wong WD, Paty PB. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. *J Clin Oncol* 2009; **27**: 3379-3384

84   **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

85   **Van Cutsem E**, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pintér T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009; **360**: 1408-1417

86   **Bokemeyer C**, Bondarenko I, Hartmann JT, de Braud F, Schuch G, Zubel A, Celik I, Schlichting M, Koralewski P. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. *Ann Oncol* 2011; **22**: 1535-1546

87   **Di Nicolantonio F**, Martini M, Molinari F, Sartore-Bianchi A, Arena S, Saletti P, De Dosso S, Mazzucchelli L, Frattini M, Siena S, Bardelli A. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. *J Clin Oncol* 2008; **26**: 5705-5712

88   **Cunningham D**, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I, Van Cutsem E. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic

colorectal cancer. *N Engl J Med* 2004; **351**: 337-345

89   **Sobrero AF**, Maurel J, Fehrenbacher L, Scheithauer W, Abu-bakr YA, Lutz MP, Vega-Villegas ME, Eng C, Steinhauer EU, Prausova J, Lenz HJ, Borg C, Middleton G, Kröning H, Luppi G, Kisker O, Zubel A, Langer C, Kopit J, Burris HA. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol* 2008; **26**: 2311-2319

90   **Giusti RM**, Shastri K, Pilaro AM, Fuchs C, Cordoba-Rodriguez R, Koti K, Rothmann M, Men AY, Zhao H, Hughes M, Keegan P, Weiss KD, Pazdur R. U.S. Food and Drug Administration approval: panitumumab for epidermal growth factor receptor-expressing metastatic colorectal carcinoma with progression following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. *Clin Cancer Res* 2008; **14**: 1296-1302

91   **Peeters M**, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, André T, Chan E, Lordick F, Punt CJ, Strickland AH, Wilson G, Ciuleanu TE, Roman L, Van Cutsem E, Tzekova V, Collins S, Oliner KS, Rong A, Gansert J. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol* 2010; **28**: 4706-4713