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REVIEW ARTICLE

Neoadjuvant chemotherapy and targeted therapy in patients with liver metastases from colorectal cancer; medical oncologist's point of view

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Summary

Colorectal cancer (CRC) is one of the most frequent malignancies, with more than 1,000,000 new cases annually worldwide and more than 4,000 new cases annually in Bulgaria. Liver metastases (LM) occur in more than 50% of CRC patients, but curative liver resection is possible only in 15% of them, resulting in 5-year survival rates of 30% on average. Improving resectability rates and hopefully patient's prognosis by adding upfront active chemotherapy and biological agents in metastatic CRC is a challenging opportunity for both medical and surgical oncologists. This review encompasses clinical trials of modern chemotherapy combinations in metastatic CRC and their application as neoadjuvant therapy before liver surgery. The different surgical methods for improving resectability of LM in patients with CRC are also discussed. In the neoadjuvant setting an emerging concern about chemotherapy-induced liver toxicity gained further attention. The recent data of liver injury following upfront systemic chemotherapy are revealed. The impact of anti-angiogenesis agents on liver regeneration and wound healing, which is not yet fully understood, is being discussed, focusing on patient-to-patient individualized decision by multidisciplinary team.

Key words: bevacizumab, cetuximab, liver resection, liver toxicity, neoadjuvant chemotherapy, unresectable liver metastases

Introduction

World statistics for CRC reveals 1,025,152 new cases annually and 528,978 deaths each year from this disease [1]. CRC morbidity and mortality in Bulgaria account for 27.8 and 16.1/100,000, respectively, with 3,983 new cases diagnosed in 2004 [2]. LM are present in 25% of patients at the time of diagnosis, and other 50% will develop LM within 3 years after primary tumor resection. Unfortunately liver resection is possible in approximately only 20% of those patients, which results in more than 30% (60% in selected cases) 5-year survival rates [3,4]. Chemotherapy regimens for metastatic CRC have improved dramatically over the past 10 years and resections of initially unresectable LM following neoadjuvant chemotherapy have been reported. Improvement in surgical approaches for LM resection has also been made in recent years. However, despite these advances, the criteria for CRC LM resection, even recently well documented [5,6], are not applied in a proper manner in routine clinical practice. Thus, the possibility of resection of LM from CRC is often underestimated, and currently many patients away from specialized centres are considered to be incurable and many patients with resectable LM are never referred to a surgeon [6]. Conversely, in centres specialized in liver resections some patients who are incurable undergo resection [6]. The goal of multidisciplinary treatment approach is to apply in clinical practice professional decisions in order to increase cost-effectively the number of patients with long-term survival who have undergone potentially curative and safe liver resections. The impact of chemotherapy-induced liver toxicity and upfront applied targeted therapy on liver regeneration are very important issues which require careful evaluation [7]. A multidisciplinary approach is essential for the optimal selection and monitoring of these patients.

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Neoadjuvant/adjuvant therapy in patients with CRC LM

5-fluorouracil (5-FU) has been the exclusive treatment for metastatic CRC for more than 40 years, resulting in tumor response of 15% and the modulation with leucovorin (LV) increased the response rate up to 25% [8,9]. These results made the combination 5-FU/LV standard treatment for metastatic CRC from the 1980s till 2002. In the last 5 years the combinations of FU/LV with oxaliplatin (FOLFOX) and with irinotecan (ILF, FOLFIRI) have been shown to be superior to FU/LV in terms of both response rate (56% FOLFIRI and 54% FOLFOX) and survival, resulting for the first time in median survival of 20 months [10,11]. Recently, the monoclonal antibody against vascular endothelial growth factor (VEGF) bevacizumab in combination with chemotherapy yielded median survival of 25 months [12]. The results of phase I and II studies of combination chemotherapy with cetuximab, another monoclonal antibody which blocks epidermal growth factor receptor (EGFR), increased the response rate up to 80% [13]. Recently, results from a phase III study published only in abstract form revealed that the addition of cetuximab to FOLFIRI significantly prolonged progression free survival (PFS) compared to treatment with chemotherapy alone (hazard ratio/HR=0.85, $p<0.05$) [14].

The high response rates achieved with modern chemotherapy in metastatic CRC offer a good rationale for its application in the neoadjuvant setting. Attempts are focused on obtaining higher resectability rates through effective downstaging in patients with initially unresectable disease. There are several advantages of neoadjuvant systemic therapy. First, the positive impact on micrometastatic disease with full-dose drugs administration before any operation when patient compliance is not impaired. Second, preoperative therapy represents also a reliable test of chemosensitivity of the tumor which can be evaluated radiologically and pathologically showing the efficacy of a specific drug or combination of drugs and hopefully determining the choice of postoperative (adjuvant) therapy. Third, during neoadjuvant therapy it is possible to distinguish patients with rapidly progressing disease for which liver surgery might not be beneficial [15,16]. Fourth, neoadjuvant chemotherapy in patients with resectable LM increases the number of radical resections and, by preserving liver parenchyma, improves the postoperative recovery [17,18]. Recently published final results from the randomized EORTC phase III study 40983 prove the benefit in terms of disease free survival (DFS) of perioperative chemotherapy to surgery alone in patients with initially resectable LM [19].

Neoadjuvant chemotherapy in primarily unresectable liver metastases

A strong correlation has been demonstrated between response rates in preoperative chemotherapy and resectability rates in retrospective trials analyses of neoadjuvant chemotherapy, making response to therapy a prerequisite for liver resection [15,16]. Objective response and resection rates in the retrospective and prospective studies of patients with liver metastases only are shown in Figure 1. Even that the rates of liver resection correlated highly with response to chemotherapy (r=96; p=0.002), the rates of R0 resections (without residual disease) did not correlate significantly with response rates [16]. The information for most active chemotherapy regimens which might be used in neoadjuvant settings came from reported tumor response rates in phase II and III clinical trials in metastatic CRC. Results from phase II trials in selected patients with liver metastases only are shown in Table 1. Tournigand et al. [11] reported tumor response of 54% with FOLFOX and 56% with FOLFIRI with infusional 5-FU, while Goldberg et al. [20] found tumor response rates for FOLFOX (45%) much higher compared with those received from IFL (31%) with bolus 5-FU and

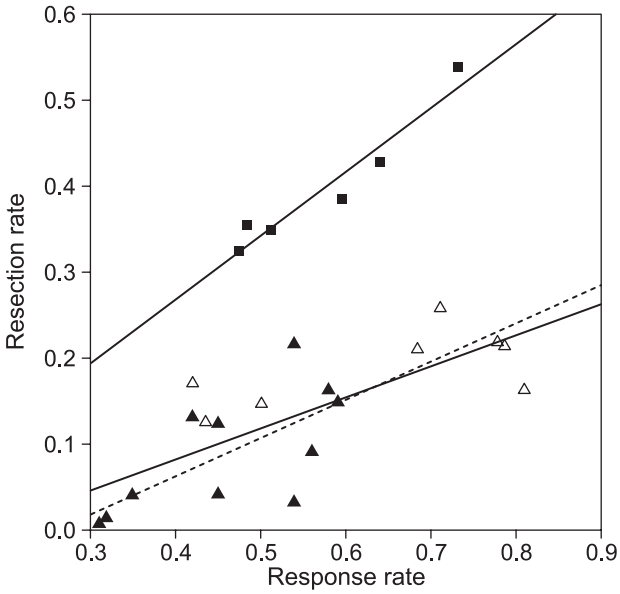

Figure 1. Rates of liver resection following chemotherapy [16].

■ Studies including selected patients (liver metastases only, non extrahepatic disease; r=0.96, p=0.002)
△ Studies including non-selected patients with mCRC (solid line) (r=0.74; p <0.001)
Due to high heterogeneity of these studies, the observed correlation is less strong.
▲Phase III studies including non-selected patients with mCRC (dashed line) (r=0.67; p <0.024).

Table 1. Resection of liver metastases after neoadjuvant chemotherapy (phase II studies) [16]

First author	*Schedule*	*Patients n*	*Response rate (%)*	*Resection rate R0 n (%)*	*Resection rate R0+R1 n (%)*	*DFS (mo)*
Alberts [28]	FOLFOX	44	62	14 (33)	17 (50)	18.0
Pozzo [29]	FOLFIRI	40	48	13 (33)	13 (33)	14.3
De la Camara [21]	Oxaliplatin/Irinotecan/5-FU/FA*	212	64	9 (43)	13 (43)	32.8
Quenet [22]	FOLFIRINOX§	26	73	9 (35)	14 (54)	NR
Giacchetti et al. [27]	Oxaliplatin/5-FU (chronomodulated)†	151	60	48 (32)	58 (38)	17.0

*oxaliplatin 120 mg/m^2, D1; irinotecan 150 mg/m^2 D1 and 14; 5-FU 2600 mg/m^2 D1nd 14; FA 500 mg/m^2 D1 and 14
§oxaliplatin 85 mg/m^2; irinotecan 180 mg/m^2; FA 400 mg/m^2; 5-FU 2400 mg/m^2 (46 h)
†retrospective analyses in patients with non-resectable liver metastases

DFS: disease free survival, mo: months, 5-FU: 5-fluorouracil, FA: folinic acid, FOLFIRINOX: 5-FU, folinic acid, irinotecan, oxaliplatin, FOLFOX: 5-FU/folinic acid, oxaliplatin, NR: not reported

with IROX (35%), a combination of irinotecan and oxaliplatin. Although the optimal combination of all effective drugs against advanced CRC is still unclear, it is reasonable now that optimal treatment should also include a third agent because chemotherapy triplets may produce higher response rates when compared with doublets [21,22]. Thus the triplet combination FOLFOXIRI resulted in significantly better response rate (60 vs. 34%, p<0.0001) and survival (PFS 9.8 vs. 6.9 months) compared to the doublet FOLFIRI, with radical liver resection rate of 36 vs. 12% in the phase III study of G.O.N.O. [23]. In the second randomized trial published to date of triplet combinations, Greek investigators did not find any statistical significant difference between FOLFOXIRI and FOLFIRI arms in terms of response rate (43 vs. 33.6%, respectively, p<0.168), and median overall survival (21.5 vs. 19.5 months, respectively, p<0.337) [24]. Even negative, those results do not preclude the use of triplet combinations in selected cancer patients like those with potentially resectable metastatic disease.

The retrospective trial of Bismuth et al. [25] was the first to particularly address the role of neoadjuvant chemotherapy in patients with unresectable LM. Reviewing 434 patients with LM, it was considered impossible to perform a complete macroscopic resection in 330 patients because of large lesions, multiple nodules, ill locations, or extra hepatic disease. The unresectable patients were treated with chronomodulated oxaliplatin/5-FU/LV and 53 (16%) patients proceeded to liver resection without postoperative mortality. A repeat hepatectomy was possible in 44% of the patients with hepatic recurrence. The 5-year survival rate after liver resection was 40%. Adam et al. [26] updated these results 5 years later and identified 701 patients with unresectable LM treated with neoadjuvant chemotherapy; 95 (13.6%) patients underwent a potentially curative liver resection with 5-year survival rate of 34%. In the retrospective study by Giacchetti et al. [27] a total of 389 patients with unresectable LM from CRC enrolled in 6 trials were evaluated. Unlike Bismuth/Adam trials, they assessed patients with liver-only metastases and identified 151 patients who were initially considered unresectable because of large tumor size (> 5 cm), multinodular (> 4 nodes), or ill-located metastases. Those unresectable patients were treated with neoadjuvant chemotherapy of oxaliplatin and FU/LV, resulting in 59% response and in 38% resection rates. The median survival was 48 and 15.5 months, respectively, for resected and non-resected patients.

Subsequent trials confirmed the ability of neoadjuvant chemotherapy to render patients resectable. Alberts et al. [28] reported a 62% response rate in 42 patients treated with FOLFOX 4 with resection rates of 41%, reaching a median survival of 31.4 months. In 40 patients with unresectable LM, defined as such because of unfavorable location of metastases, number of metastases, size of metastases, insufficient liver reserve, and the presence of extra hepatic disease, neoadjuvant FOLFIRI resulted in 47.5% response and 40% resection rates. Among 16 resected patients, 13 had R0 liver resections [29].

Neoadjuvant chemotherapy in primarily resectable liver metastases

In a prospective non-randomized study of 47 patients with resectable liver metastases the pre-and postoperative intensive chemotherapy consisting of 6 cycles FOLFOX 7 followed by 6 cycles FOLFIRI attained 89% 2-year survival rate [30]. In the randomized EORTC 40893 study of pre- and postoperative

FOLFOX 4 chemotherapy vs. surgery alone in patients with resectable LM complete resection was achieved in 96.7 vs. 88.5% ($p<0.05$) of operated patients in the chemotherapy and surgery alone arms, respectively. Recently published final results from this study show benefit in terms of DFS of perioperative chemotherapy compared to surgery alone in patients with initially resectable LM [19].

Adjuvant therapy after resection of liver metastases

The high relapse rates after curative liver resection and the positive survival results of adjuvant chemotherapy in resected patients with Dukes C disease support the use of the same active regimens after radical resection of LM. Patients with resectable LM can be expected to benefit from adjuvant therapy in the same way as CRC patients undergoing resection of their primary tumors [31]. Adjuvant intra-arterially chemotherapy is not superior to systemic chemotherapy and is connected with many problems regarding its feasibility, toxicity and cost [6]. There are 2 trials of adjuvant systemic chemotherapy with 5-FU/LV compared to surgery alone after LM resection. Both of them closed prematurely because of low patient accrual but they showed a trend for improved DFS and overall survival in favor of adjuvant systemic chemotherapy [31,32].

Blocking VEGF – the combination of chemotherapy and bevacizumab in the neoadjuvant setting

VEGF, known as a VEGF-A, a key mediator of angiogenesis is expressed in approximately 50% of colorectal cancers. Increased VEGF expression as well as VEGF serum levels are significantly correlated with lymph node status, tumor aggressiveness, microvessel density, high relapse rates and poor prognosis [33-35]. VEGF receptors were found to be highly expressed in human LM from primary CRC [34]. In preclinical mouse models bevacizumab inhibited VEGF by preventing binding of all VEGF A isoforms to all VEGFRs, blocked the growth of human tumor xenografts, and dramatically reduced (more than 90%) the size and number of liver metastases [36].

The mechanism by which bevacizumab enhances the activity of chemotherapy is not fully understood, but the reduction of tumor vasculature permeability may reduce interstitial pressure and the relative normalization of tumor blood flow improves drug delivery [37].

In a phase III study, adding bevacizumab 5 mg/kg every 2 weeks to first-line chemotherapy significantly improved median survival – from 15.6 months in patients treated only with IFL to 20.3 months for the combination arm bevacizumab/ILF ($p<0.05$) [12]. Combining bevacizumab with FOLFOX or XELOX resulted also in improved median survival (11.1 vs. 8.6 months ($p<0.05$)) in comparison with chemotherapy-alone arms [38].

Pooled analysis of the results from 3 randomized clinical trials (2 phase II studies and 1 phase III) for combined treatment of bevacizumab and chemotherapy in 1236 patients with metastatic CRC confirmed the improved outcomes of the treated patients with acceptable toxicity [39]. The half-life of bevacizumab is relatively long; the mean half-life is approximately 20 days (range 11-50) and is typically accepted to wait for a period of 2 half-lives before assuming that there is no effective drug concentration remaining [40]. Thus it is advisable to wait 8 weeks after the last dose of bevacizumab before performing liver resection [41]. Results from a recently published study (only in abstract form) for neoadjuvant XELOX+bevacizumab in 32 patients, 15 from whom underwent liver resection, showed lack of additional postoperative complications and impaired liver regeneration with safety application of bevacizumab 5 weeks before liver surgery [42].

Blocking EGFR – the combination of chemotherapy and cetuximab in the neoadjuvant setting

EGFR is a transmembrane glycoprotein encoded by the c-erbB-1 protooncogene and in normal and malignant cells it is involved in signalling pathways affecting cellular growth, differentiation, proliferation and angiogenesis [43]. The frequent expression of EGFR in CRC (up to 82%) [44] has been shown to be correlated with poor prognosis [45]. Cetuximab is a chimerical IgG1 MAB that binds to the extracellular domain of EGFR with high specificity and more than 10-fold higher affinity than its natural ligands, thus competitively inhibits phosphorylation of the intracellular tyrosine kinase domain and activation of the downstream signalling cascade [46]. Phase I and II studies of cetuximab and irinotecan- or oxaliplatin-based regimens as first-line treatments have shown very encouraging efficacy parameters [47]. Combination of cetuximab with FOLFIRI resulted in 43% partial responses with disease control rate (CR+PR+SD) of 88% [48]. A German study attained a response rate of 74% for the combination of cetuximab with irinotecan and the German Cooperative Group for Oncology (AIO) infusional regimen [49]. Cetuximab in combination with FOLFOX 4 showed an 81% overall response rate in 42 patients (confirmed response of 71%) with disease control rate of 98% [13]. In the last 3 studies the addition of cetuximab to the primary therapy facilitated

the resection of LM. Long-term follow-up will help determine the survival advantage of this treatment-facilitated resection of LM compared with patients receiving only cetuximab-based treatment without resection of their LM [50].

Recently published results from the first phase III study in first-line setting revealed that the addition of cetuximab to FOLFIRI significantly increases the response rates and reduces the relative risk of progression by 15% (HR=0.85, p<0.05) [14].

Surgical approaches for improving resectability of LMs from CRC

The highest risk from liver resection is postoperative liver insufficiency as a result of scant liver parenchyma. Postoperative morbidity and mortality are much more frequent in non-specialized surgical centres [51]. Even though there is no randomized clinical trial comparing the survival of patients with resected liver metastases to those treated only with systemic approach the large amount of data from retrospectives trials [15,16,52] proved survival advantage for radical liver resections. The hypothesis that patients with liver resection commonly have better prognostic factors such as performance status and/or small tumor volume in comparison with those treated only with chemotherapy is obviously false because of the survival data in patients with comparable performance status and tumor burden who refused surgery and were treated conservatively; the 5-year survival for the latter groups of patients was 0% compared with 40% for resected patients [3]. Similar data are shown on Figure 2, where Stangl et al.

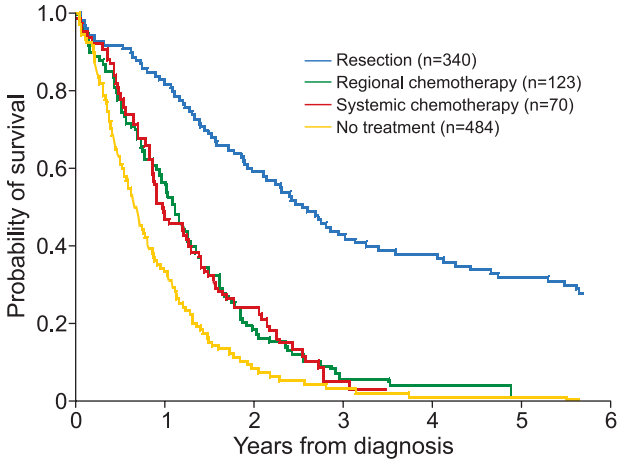

Figure 2. Overall survival in patients with colorectal liver metastases [53].

analysed the impact of various factors on survival of 1099 consecutive patients of whom 51.5% received no treatment for their hepatic metastases [53]. Recently the progress in surgical techniques and their combination in some cases can further improve the resectability of LM [54,55].

Intraoperative ultrasonography in comparison to preoperative imaging (CT, ultrasonography) discovers additional lesions in 10-50% of patients, thus improving the therapeutic value of liver resection in CRC patients [56].

The routine use of the so-called controlled parenchyma-sparing segmental liver surgery tailors the extend of resection to the extend of pathology and minimizes postoperative liver failure [57].

One of the classic contraindications of liver resection is the presence of portal lymph node metastases, but Jaeck et al. reported 19% 3-year survival rate in CRC patients undergoing complete pedicle lymphadenectomy. Patients with metastases limited to the portal triad had a better 3-year DFS than those with nodal metastases along the common hepatic artery and celiac axis (38 vs. 0%; p<0.05) [56].

In multiple unilobar disease, when the projected remnant liver is less than 30% of the total liver, portal embolization can induce hypertrophy of the healthy liver, leading to resectability [57].

In multiple bilobar disease, in situ destruction of residual non-resectable tumor by radiofrequency may be associated with liver resection to achieve potential radicality of the procedure [58].

Two-stage hepatectomy is also an alternative for those patients whose tumors could not be resected in a single procedure with residual non-resectable disease [59].

Surgical approaches for improving resectability in unresectable LM are successful in approximately 15% of the patients [60]. Classical contraindications for liver resection are the presence of ≥ 4 lesions, extra hepatic disease, resection margins < 1 cm, as well as presence of multilobar and ill-defined lesions [25]. Current strategy accepted in most specialized centres is to resect all lesions regardless of their size and number concerning adequate healthy liver parenchyma [61]. Recently a group of experts develop a therapeutic decision-making model for patients with CRC LM, called OncoSurge decision model. According to these guidelines unresectability is defined as the presence of extra hepatic disease, LM which encompass more than 70% of the liver parenchyma or more than 6 segments, liver failure and patients for whom surgical intervention is contraindicated [5]. Primary resection of LM is recommended if no metastatic lymph nodes *ad portam hepatis*

are present and with adequate radiologically defined resection margins. Resection was feasible post chemotherapy, independent of tumor response in the case of ≤ 4 metastases and unilobar liver involvement. For > 4 metastases or bilobar liver involvement resection was possible only after tumor shrinkage with chemotherapy. Although this model may be useful in helping medical and surgical oncologists determine the suitability and timing of multidisciplinary treatment of patients with CRC LM, it does not provide assistance in the timing of liver resection after regimens containing bevacizumab or other targeted agents, because the chemotherapy combinations considered in the OncoSurge model are FU/LV, FU/LV + oxaliplatin, FU/LV+ irinotecan, or FU/LV + oxaliplatin + irinotecan.

The European Colorectal Metastases Treatment Group consensus recommendations include the proposal for a new staging system of patients with stage IV CRC which are the following: Stage IVa - easily resectable LM; Stage IVb - resectable LM; Stage IVc - LM that can become resectable after downstaging; Stage IVd: LM that are unlikely to become resectable; Stage V - resectable and unresectable disease, respectively, outside of the liver [6]. According to the above mentioned recommendations liver resection is contraindicated when all the metastases cannot be removed or in the presence of celiac lymph nodes and the presence of extrahepatic non-resectable disease. This experts group also acknowledged that regional ablative techniques can be used in conjunction with conventional surgery for small poorly located lesions [6].

The neoadjuvant therapy-induced liver toxicity and its impact on hepatic regeneration after resection

The mortality rate associated with liver resection has declined to far below 5% during the last decade [62], correlating directly with preoperative liver function and resected tumor volume. Liver dysfunction might be only transient if the liver has the ability to regenerate, but it is prolonged when regeneration is impaired [63]. Severe steatosis had a negative impact on hepatocyte proliferation and on regeneration of the remnant liver mass after 70% partial hepatectomy and many studies suggest that chemotherapy can be associated with steatosis [64]. Based on data from the transplantation literature, it is postulated empirically that each 1% increase in fat content, either microvesicular or macrovesicular, decreases the functional mass of the donor liver by 1% [64]. However, whether steatosis following chemotherapy produces a similar decrease in the functional hepatic mass and a subsequent adverse outcome following hepatic resection is unknown. The study of Behrns et al. [65] was the first designed to evaluate outcomes following major hepatectomy (at least 4 hepatic segments) in patients with LM from CRC including 56 patients with mild and 7 with marked steatosis. In the 7 patients with marked steatosis, increased perioperative morbidity and mortality after hepatectomy were noticed, but the small patient number limits further interpretations. Subsequently, Parikh et al. [66] showed that perioperative treatment with irinotecan was associated with steatosis. The authors concluded that there were no perioperative deaths in patients with simple steatosis, even when severe. Vauthey et al. [67] reported a systemic analysis of the association between chemotherapy type, histopathological liver injury and postoperative outcome in 406 resected liver specimens from patients who underwent resection of LM from CRC after upfront chemotherapy. Similarly to previously published data, there was no increase in mortality after hepatic resection in patients with steatosis. Unlike steatosis, the pathological finding of steatohepatitis had important impact on postresection outcomes. Oxidative stress and the production of reactive oxygen species due to mitochondrial dysfunction appear to play central roles in the process of progression of steatosis to non-alcoholic steatohepatitis (NASH). According to the "two-hit theory" of NASH pathogenesis [68], the first hit is steatosis but the second is chemotherapy-induced production of reactive oxygen species [69]. Fernandez et al. [70] were the first to report an increased incidence of NASH in patients with LM from CRC treated with neoadjuvant chemotherapy. In the Vauthey et al. study [67], treatment with irinotecan was associated with steatohepatitis independent of body mass index (BMI) and patients with steatohepatitis had 90-day mortality rate of 15% compared with 2% for patients without steatohepatitis ($p=0.001$), and a higher risk for postoperative liver failure compared with all other patients ($p=0.01$). Based on these data caution is advised when using irinotecan in patients with known steatosis and steatohepatitis and in patients at known risk of steatosis. Rubbia-Brandt et al. [71] for the first time reported oxaliplatin-associated SOS (sinusoidal obstruction syndrome or veno-oclusive disease) in the non-tumor liver specimens of patients undergoing liver resection after therapy with oxaliplatin. The pathophysiology of SOS involves the depolymerization of F-actin in sinusoidal endothelium cells, the activation of metalloproteinases and the consequent induction of oxidative stress [72]. As mentioned above, several chemotherapeutic agents (5-FU, taxanes, and platinum derivatives) can induce oxidative stress [72]. Rubbia-Brandt et al. [71] found

perisinusoidal injuries, including dilatation and congestion with fibrosis and venous occlusion in 78% of the patients, but no correlation between cumulative dose of oxaliplatin and the presence and severity of sinusoidal injuries was noticed. In the study of Vauthey et al. [67] oxaliplatin was associated with sinusoidal dilatation nearly 5 times more than therapy with irinotecan (19 vs. 4%; $p<0.05$) and the risk did not increase with the number of chemotherapy courses, but most studied patients received preoperative chemotherapy for 3-4 months. The results regarding the degree of chemotherapy-induced injury are shown in Table 2 [67]. In order to avoid liver toxicity and to determine the proper time for liver resection it is advisable to evaluate resectability every 4-6 weeks and in the case of prolonged exposure to chemotherapy and of known or suspected liver parenchymal disease to perform a liver biopsy for evaluation of hepatotoxicity [7].

The enthusiasm generated from the use of bevacizumab-containing chemotherapy regimens as preoperative treatment for patients whose LMs have the potential for conversion to resectability should be tempered with caution because the potential toxic impact of this antiangiogenetic agent on liver regeneration and wound healing is not known [7]. In animal models it has been shown that VEGF plays a critical role in liver regeneration after partial hepatectomy [73]. Thus, VEGF not only regulates angiogenesis in the regenerating liver, but also mediates a paracrine pathway by which other cytokines can be upregulated. For example, activation of VEGFR1 on liver sinusoidal endothelial cells leads to induction of hepatocyte growth factor which in turn mediates liver repair [74]. It has been suggested that inhibition of VEGF impairs wound healing and might downregulate liver regeneration [75].

Advances in chemotherapy and in liver surgery have increased the number of patients with LM from CRC who will be candidates for potentially curative liver resection. This implies that patients should be evaluated by experienced hepatic surgeons and medical oncologists before starting therapy to avoid extensive and unnecessary treatment. The proper evaluation of response rates as well as the degree of liver parenchymal disease induced by chemotherapy in patients with known risk factors for steatohepatitis has gained further attention. In the neoadjuvant setting only the team work of medical, surgical oncologists and gastroenterologists, having the best knowledge of multimodality approach, will devise safe, rational and ontologically appropriate treatment to improve prognosis of CRC patients with LM.

Table 2. Chemotherapy-induced hepatic injury [67]

Chemotherapy	*Steatosis cases* %	*Steatohepatitis cases* %	*Sinusoidal dilatation cases* %
None	9	4	2
5-Fluorouracil	17	5	0
Irinotecan	11	20*	4
Oxaliplatin	4	6	20*

*chemotherapy vs. non-chemotherapy, $p< 0.05$

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