Multidisciplinary treatment of resectable liver metastases (including chemotherapy associated liver damage)

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Introduction

The major cause of death in colorectal cancer is due to liver metastases which occur in 20% of patients with stage II and 50% with stage III disease. The presence of liver or lung metastases from colorectal cancer does not preclude curative treatment. If only a minority of patients with liver metastases are amenable to surgery, surgical resection remains the only treatment that can, to date, ensure long-term survival and cure in some patients. Recent progress including new chemotherapeutic regimens, ablative techniques and interventional radiology may increase the number of patients that can be treated with a curative intent. Unfortunately, recurrences are still observed in two thirds of patients after resection of liver metastases. New therapeutic managements are tested using adjuvant intravenous and/or intra arterial chemotherapies to reduce this risk or to provide curative treatments in case of recurrence with either surgery or ablative techniques.

Resection of liver metastases: Update

In the absence of treatment the median survival of the patients rarely exceeds 1 year. In a large prospective study conducted from 1980 to 1990 and including 484 patients with untreated hepatic metastases from colorectal cancer, the median survival was 31% at 1 year, 7.9% at 2 years, 2.6% at 3 years and 0.9% at 4 years. The survival rate was influenced by the volume of the liver involvement, the presence of extra hepatic disease, metastatic lymph nodes in the mesentery, CEA plasma level and the age of the patient. According to the presence or the absence of these criteria, the median survival varied from 3.8 to 21 months [1]. In the absence of randomised trials, only few retrospective studies have compared the survival of patients with potentially resectable metastases that were left untreated with survival of patients after resection of colorectal metastases [2,3]. There were no 5-year survivors in untreated patients whereas 25 to 30% of patients could survive 5 years after complete resection of metastases. The benefit of surgical resection for liver metastases is now well recognised and complete resection with intent to cure is, to date, the only treatment that can ensure a long term survival. Liver transplantation has been abandoned in this indication because immunosuppression has been associated with relapse of cancer in all patients [4].

Preoperative assessement: Definition of resectability

The decision and the extent of surgical resection for liver metastases are based upon the patient's condition, extent of the disease and liver function. Surgery should be considered only with curative intent if liver metastases can be totally resected with tumour free margins and sufficient post operative remnant liver to avoid liver failure. Patients must not have non-resectable extra-hepatic disease. The goals of preoperative assessment are to determine if the patient's condition will permit hepatic resection (i.e. general anaesthesia, clamping manoeuvres requiring a correct cardiovascular status). It should exclude the presence of non resectable extra-hepatic disease and delineate the anatomy of metastases. Liver metastases will be considered as resectable if all liver deposits can be safely removed with clear margins leaving a remnant liver parenchyma accounting for at least 25% of non tumourous liver along with its arterial/portal inflow and hepatic vein outflow. In summary, liver metastases are non resectable if there is invasion of the two main portal pedicles, if there is invasion of a portal pedicle and of the contralateral hepatic vein, if the three major hepatic veins are invaded or if the total removal of liver deposits will leave less than

25% of functional liver. Resectable lesions are usually divided into two subtypes. Liver metastases that can be resected with an anatomical liver resection removing less than four segments and leaving more than 40% of healthy liver parenchyma are referred as type I resectability. Resection which necessitates the removal of more than four segments (major hepatectomy) with a complex and hazardous procedure, because some lesions are ill located in the vicinity of major hepatic vessels or biliary pedicles, are referred to as type II resectability.

Liver function can be assessed by the Child–Pugh classification, hepatic biochemical blood tests and in some cases by the indocyanin green (ICG) retention tests. The volume of the non tumourous parenchyma that will be left in place after hepatic resection should be evaluated by CT scan volumetry or by the remnant liver volume to body weight ratio with a cut-off of 0.5% [5].

Surgical treatment

Intra-operative assessment

The exact place of laparoscopy in liver surgery is not clearly determined. Its interest would be to avoid unnecessary laparotomies. It could influence the type of surgical procedure in a substantial proportion of patients [6]. Surgery should start with a careful exploration of the abdominal cavity to rule out peritoneal carcinomatosis or an unexpected bilobar involvement of the liver by metastases which could be a contraindication for resection. The presence of metastatic lymph nodes in the porta hepatis and the celiac region considerably worsens the prognosis but should not be considered an absolute contraindication for resection if the nodes can be completely removed and combined with a type 1 hepatectomy, as 5-year recurrence free survival has been reported in such cases [7]. However, a type II hepatectomy should not be performed in the presence of celiac metastatic nodes [8]. Intra-operative ultrasound (IOUS) should be performed in every case because it allows a precise mapping of the anatomical relations of the metastases to the main intra parenchymatous vascular pedicles and helps to select the type of resection. IOUS can detect small intraparenchymatous lesions and thereby modify the extent of the initially planned operation [9,10]. It may also be used to guide fine needle biopsies of doubtful lesions or to evaluate the degree of destruction of a metastasis treated by radiofrequency ablation.

Types of liver resections

If remnant liver parenchyma is normal, up to six of the eight anatomical segments can be resected without inducing post-operative liver failure. Liver resections can be divided into two groups: anatomical resections removing one or several segments and atypical or wedge resections removing a portion of liver parenchyma surrounding an hepatic lesion. Resections removing three or more continuous segments are defined as major hepatic resections: right hepatectomy (segments V,VI,VII,VIII), left hepatectomy (segments II,III,IV) and extended right hepatectomy also called right lobectomy (segments IV,V,VI,VII,VIII) [11,12].

Surgical strategy

The aim of surgery for liver metastases is to remove or destroy with ablative procedures all the metastatic sites with a free clearance margin. The type of liver resection depends on the size, the number and the location of the metastases, their relation to the main vascular and biliary pedicles and the volume of the liver parenchyma that can be left in place after surgery. Superficial small metastases can be resected with a wedge resection. Larger lesions often require major resections. It should also be kept in mind that a large resection may preclude further surgery in case of intrahepatic recurrence.

Synchronous hepatic metastases are found in 15 to 20% of patients undergoing an operation for primary colorectal cancer. Resection of primary tumour and liver metastases can be either simultaneous or delayed. In the majority of cases it seems preferable to delay the liver resection [7]. The abdominal wall incision is usually different for the colorectal and the liver resection, bowel resection and subsequent peritoneal contamination can lead to seeding of a peri-hepatic or sub-phrenic fluid collection, haemodynamic changes and portal hypertension subsequent to vascular clamping can be detrimental to the viability of digestive sutures. In a large multicentric survey the postoperative morbidity was significantly increased when both resections were performed simultaneously (6.1% versus 2.4%). However, some have reported one-stage procedures without added morbidity and no difference in 5-year survival in selected cases [13,14]. The most common attitude is to remove, simultaneously, metastases if they require a minor hepatectomy and are accessible through the same incision. In the other cases, the liver resection is postponed 2 to 4 months later allowing the observation of the response of liver metastases to systemic chemotherapy which is often

Table 1
Operative mortality and morbidity rates after liver resection for colorectal liver metastases

Authors	Year	No. of patients	Mortality	Morbidity
Nordlinger *et al.* [23]	1987	80	5%	13%
Doci *et al.* [24]	1991	100	5%	39%
AFC* [7]	1992	1818	2%	24%
Sheele *et al.* [25]	1995	469	4%	–
Jamison *et al.* [26]	1997	280	4%	–
Fong *et al.* [27]	1999	1001	3%	–
Minagawa *et al.* [28]	2000	235	0%	–
Ercolani *et al.* [29]	2002	245	0.8%	15%
Choti *et al.* [30]	2002	226	0.9%	19%
Pawlik *et al.* [31]	2005	557	0.9%	–

∗ Multicentre trial.

administred during the interval and is an important prognostic factor for survival [15].

Only 10 to 20% of patients with liver metastases fulfil standard selection criteria and are directly amenable to surgery. The trend is to be more aggressive and to increase the indication for surgical resection. Surgical and invasive radiological techniques including portal vein embolisation, and intraoperative ablative techniques may render patients who would not have been considered some years ago to become amenable to surgery.

If the future remnant liver after liver resection is too small to provide sufficient postoperative liver function, preoperative selective portal vein embolisation has been proposed to induce ipsilateral atrophy and controlateral hypertrophy of the remnant liver, thus preventing postoperative liver failure [16]. In patients with non cirrhotic liver, preoperative portal vein embolisation can be expected to induce a 40–60% increase in the size of the non embolised portion that would be preserved during liver resection. However, if there are also liver metastases in one segment of the non embolised portion of the liver, the risk is to induce hypertrophy of metastases [17]. Following embolisation, a liver resection, judged primarily impossible, has proved feasible in up to 60% of cases with a mortality and a morbidity rate comparable to those observed following liver resections without embolisation [16]. In a recent study, actuarial survival rates after hepatectomy with ($n = 19$) or without ($n = 88$) portal vein embolisation were comparable: 81%, 67%, and 40% versus 88%, 61%, and 38% at 1, 3 and 5 years respectively [16]. More recently, a retrospective study suggested that portal vein embolisation before hepatectomy could reduce the intrahepatic recurence after surgery [18].

In patients with a limited number of bilobar metastases that are not totally resectable due to their location in the liver, liver resection can be combined with intraoperative radiofrequency ablation [19]. In such a situation, resection of a large tumour in one lobe can be combined with radiofrequency ablation of small deposits in the opposite lobe. Radiofrequency ablation should be reserved for lesions up to 3 cm because local recurrence rate at the site treated is reported to be over 30% for larger lesions [20,21]. Another potential indication for radiofrequency ablation is to combine it with resection to allow R0 resection when it is not feasible with resection alone [22]. Radiofrequency ablation is safe and effective to induce necrosis of liver metastases up to 3 cm in diameter, but is not a substitute for resection, based on available survival data.

Results of liver resection for colorectal metastases

Complications of surgery (Table 1)

In most recent studies, in-hospital mortality is less than 5% and is strongly influenced by intra operative blood loss, preoperative liver function and extent of liver resection. Post operative complications are observed in 25 to 40% of patients. Morbidity after hepatic resection is usually due to transient liver failure, haemorrhage, sub-phrenic abscesses or biliary fistula. The mean hospital stay after liver surgery ranges from 10 to 15 days in the absence of complication.

Long term results

Liver resection of colorectal metastases is associated with 3 and 5-year survival rates close to 50% and 35%

Table 2
Overall survival after surgical resection of liver metastases from colorectal cancer

Authors	Year	No. of patients	Overall survival	
			3-year	5-year
Nordlinger *et al.* [23]	1987	80	40%	25%
AFC* [7]	1992	1818	41%	26%
Sheele *et al.* [25]	1995	469	41%	33%
Nordlinger *et al.* [32]	1996	1569	41%	26%
Jamison *et al.* [26]	1997	280	–	27%
Fong *et al.* [27]	1999	1001	57%	37%
Minagawa *et al.* [28]	2000	235	51 %	38%
Ercolani *et al.* [29]	2002	245	53%	34%
Choti *et al.* [30]	2002	226	–	40%
Pawlik *et al.* [31]	2005	557	74%	58%

*Multicentre trial.

respectively (Table 2). After resection, recurrences are observed in 2/3 of the patients and involve the liver in 50% of the cases. In a large retrospective study, 5-year survival was 28% in 1588 patients who had a resection of isolated colorectal liver metastases and 15% in 250 patients who had resected liver and extra-hepatic metastases. None of the 77 patients who had a palliative resection survived 5 year [32].

Several studies have assessed factors influencing survival. The interval between colorectal and hepatic surgery, the number of hepatic tumours (usually $\geqslant 4$), the size of the hepatic tumour (usually $\geqslant 5$ cm), preoperative CEA level, and the status of the primary colorectal cancer are considered the most important preoperative predictors of outcome. The gender and the site of the primary tumour do not seem to influence the outcome. The stage of the primary tumour affects 5 year survival rates after resection of metastases: 70 % in stage I or II colorectal cancers and 33% in stage III [7]. The involvement of one or both lobes of the liver does not influence the outcome. Many authors include factors such as surgical margin and the hepatic lymph node involvement in their assessment of survival risks. A free margin of at least 1 cm offers the better chance of avoiding recurrence but a recent multicentric series has shown that a smaller margin did not affect survival [31]. An estimated margin of <1 cm on CT scan before resection of hepatic colorectal metastases should not be considered as contraindication. The importance of the involvement of the liver pedicle lymph nodes has been recently investigated by a prospective study with 156 patients and shows a very poor 5-year survival (5%) [8]. The extent of liver resection (major anatomic resesection versus wedge resection) is not per se a prognostic factor [33]. Amount of blood transfusions could be associated with an adverse outcome but this may reflect the surgical difficulties faced with resection of large and numerous lesions.

Uni- and multivariate analysis of the prognostic value of different factors has permitted the proposal of a simple prognostic scoring system to evaluate the chances for cure of patients after resection of liver metastases. One of these scoring systems was developed from a retrospective series of 1568 patients with resected liver metastases from carcinoma [32]. Two- and 5-year survival rates were 64% and 28%, respectively, and were affected by age, size of the largest metastasis, CEA level, stage of the primary tumour, disease free interval, number of liver nodules and resection margin $>$ or <1 cm [32].

Repeat liver resections for recurrent metastases

Recurrence limited to the liver following previous hepatic resection occurs in 25% to 50% of the cases and may be amenable to repeat resection [34,35]. Post-operative mortality and morbidity do not differ from those reported after a first resection and the mean survival approaches 2 years. In a series including 146 patients with intra-hepatic recurrence following hepatectomy treated by repeat liver resection, the actuarial survival rates were 78% at 1 year, 30% at 3 years, 16% at 5 and 10 years, comparable to that observed following primary liver resections [34]. Recently, it has been reported that third hepatectomy is safe and provides an additional benefit of survival similar to that of first and second liver resections [36]. Hepatic recurrences should therefore be resected whenever it is possible.

Adjuvant chemotherapy

Unfortunately, recurrences are still observed in most patients after resection of liver metastases despite progress in surgical technique and improved surgical skill.

In order to improve these results, adjuvant chemotherapy has been tested in several randomised studies but its benefit after resection of colorectal metastases has not yet been clearly proven. A first trial failed to demonstrate any survival benefit of hepatic arterial infusion (HAI) with 5 FU and folinic acid without systemic treatment over surgery alone, with a significant toxicity in the patients receiving chemotherapy and an incresased risk of death [37]. A second study from the Memorial Sloan-Kettering Cancer Center showed that the addition of HAI with floxuridine to systemic 5-FU and folinic acid resulted in a decrease in the hepatic recurrence rate and an improved overall survival only at 2 years (86% versus 72%, $P = 0.03$) [38]. A third study organised by the Eastern Cooperative Oncology Group concluded that HAI with floxuridine combined with intravenous 5-FU reduced the risk of recurrence when compared with surgery alone (46% *versus* 25%, $P = 0.03$) but resulted in no benefit in overall survival [39]. The message we can deduce from these studies is that HAI alone is not sufficient as adjuvant treatment for liver metastases. HAI associated with systemic chemotherapy can reduce the risk of recurrences after surgery at the expense of an increase in side effects. These studies are not sufficient to convince physicians that HAI administered after surgery should be the standard but constitute an important step toward the validation of the principle of combined chemotherapy and surgery to treat liver metastases from colorectal cancers.

Adjuvant systemic chemotherapy following hepatic resection has been evaluated in two phase III randomised trials. A French study organised by the Federation Francophone de Cancerologie Digestive and a European-canadian study have compared systemic administration of 5 FU and folinic acid for 6 months, after surgery versus surgery alone. Although there was no statistically significant difference between the groups, these studies show a trend towards a benefit for adjuvant chemotherapy [40,41]. A metaanalysis of the two studies showed that adjuvant CT with a 5FU bolus based regimen tends to improve survival after complete resection of CRC metastases but the observed improvement in overall survival was not statistically significant [42].

Several other chemotherapy regimens using irinotecan or oxaliplatin are being investigated in phase III randomised trials.

In summary, the beneficial effect of chemotherapy after complete surgical resection of colorectal metastases is likely but not yet formally proven.

Neoadjuvant chemotherapy

The rationale for and against neoadjuvant chemotherapy in patients with resectable liver metastases

Because the beneficial effect of adjuvant chemotherapy after resection of liver metastases is uncertain, new approaches are needed to improve outcomes. In this setting, the administration of chemotherapy on a neoadjuvant basis has several potential advantages in patients with resectable liver metastases.

- It can serve to test the chemoresponsiveness, which can be useful to determine which treatment should be given after resection [43].
- Neoadjuvant chemotherapy can in theory eliminate micrometastatic disease and allow eradication of dormant cancer cells in the liver.
- If tumour shrinkage is observed during neoadjuvant chemotherapy, the rate of complete resection and of less extended liver resections may be increased [44].
- Finally, two recent studies have shown that response to neoadjuvant chemotherapy appears to be an important prognostic factor and may thus enable selection of good candidates for surgical resection [15,45].

In one study [15], the outcomes of patients referred for resection of synchronous colorectal liver metastases with or without previous neoadjuvant chemotherapy were compared. Patient and tumour related variables were similar in both groups. Five-year survival was similar in both groups, but the subgroup of patients with stable disease or disease responding to chemotherapy had a better survival when compared to patients who did not receive chemotherapy (85% versus 35%, $P = 0.03$). In another study [45], 131 patients who underwent liver resection for multiple metastases after systemic neoadjuvant chemotherapy (5-FU, leucoverin, oxaliplatin or irinotecan) were divided into three groups according to response to chemotherapy: patients with an objective response, tumour stabilisation or with tumour progression. Patients with tumour progression had a lower 5-year survival when compared with patients with objective response and stabilisation (8% versus 37%

and 30%), suggesting that tumour progression while on chemotherapy is a poor prognostic factor and could be considered as a contraindication for surgery.

However, neoadjuvant chemotherapy also has drawbacks:

– As will be discussed in detail later in this review, chemotherapy administered before liver resection may induce hepatic damage and affect postoperative outcome.
– When some liver metastases disappear during administration of chemotherapy, the so called complete response, there is still uncertainty on what to do next.

A major question is to know whether the sites of metastases that have disappeared on CT scan, should be resected or if they can be left in place. This is particularly important when the disappearance of lesions allows the surgeon to perform a minor instead of a major resection with a lower operative risk. In a recently published study [46], cancer persisted in more than 80% of the initial site of liver metastases, that had disappeared on imaging, suggesting that resection of the sites of initial metastases was necessary. In such cases, it may be difficult or impossible for the surgeon to identify the precise site in the liver where the metastases were located and thus decide what to resect with a sufficient resection margin. Thus one risk of neoadjuvant chemotherapy is to render inoperable some patients with initially resectable liver metastases because of the absence of residual visible tumour. These patients with resectable liver metastases should be referred to surgeons before liver metastases have completely disappeared.

Feasibility and benefits of neoadjuvant chemotherapy in patients with resectable liver metastases

The feasibility and the benefits of neoadjuvant chemotherapy have been evaluated in phase II studies. In a first study [47], 20 patients with initially resectable liver metastases received three cycles of combination neoadjuvant chemotherapy with weekly high-dose 5-fluorouracil as 24-h infusion, folinic acid and oxaliplatin. The curative resectability rate was 80%, the operative mortality and morbidity rates were 0 and 25% and toxicity grade 3–4 was observed in 30% of patients. The 2-year disease-free survival rate was 52% and the 2-year cancer-related survival rate 80%. In a second study [48], liver resection was performed after six cycles of FOLFOX-7 and followed by six cycles of FOLFIRI in 22 patients. The curative resection rate was 91% and grade 3–4 toxicity was observed in 30% of patients. The 2-year overall and disease-free survival rates were 89% and 47% respectively. Other phase II studies evaluating neoadjuvant chemotherapy with irinotecan- or bevacizumab-regimens for resectable liver metastases are also ongoing.

Progression-free and overall survival rates reported in these phase II studies are promising, but survival benefit of neoadjuvant chemotherapy for resectable colorectal liver metastases can only be demonstrated by a phase III clinical trial. The European Organisation for Research and Treatment of Cancer (EORTC) has completed accrual of a phase III trial comparing pre- and postoperative oxaliplatin based chemotherapies versus no chemotherapy in patients with resectable liver metastases [49]. Three hundred and sixty four patients with potentially resectable liver metastases were entered in this study. The interim analysis has shown that neoadjuvant chemotherapy was safely administered and timing of surgery was not affected; neoadjuvant chemotherapy has allowed resection of smaller tumours and mortality and morbidity rates were low [49,50]. Survival data will be presented at ASCO 2007. Thus, to date, the benefit of neoadjuvant chemotherapy is not yet formally proven for patients with resectable disease and its routine use can not be recommended in all patients.

Complication of neoadjuvant chemotherapy: The chemotherapy-associated liver injury

Recently, the enthusiasm over the potential positive effects of neoadjuvant chemotherapy has been cooled down somewhat by the awareness of toxicity to the remnant liver caused by preoperative treatment, which could increase the risks of surgery and even preclude liver resection. It is particularly important in patients with resectable liver metastases, since the benefits of neoadjuvant chemotherapy in such patients are not yet clearly proven.

There are now accumulating data showing that preoperative chemotherapy is associated with pathologic changes of liver parenchyma [51–58].

Two main types of chemotherapy-associated liver injuries have been reported: vascular changes and chemotherapy-associated steatohepatitis (CASH). The vascular changes include sinusoidal dilation with erythrocytes congestion, occasionally accompanied by perisinusoidal fibrosis and fibrotic venular occlusion, which could result in severe cases in sinusoidal obstruction syndrome as observed in venoocclusive disease [51]. Steatohepatitis is defined by the association of severe steatosis, lobular inflammation and ballooning [56]. Few studies have evaluated the

correlation between the type of liver injury and the neoadjuvant chemotherapy regimen. The liver damage that can result from systemic therapy is not restricted to the current generation of chemotherapies and it has been reported that even 5-fluorouracil can be associated with an increased risk of severe steatosis but not of steatohepatitis [59]. Oxaliplatin-based combination regimen is associated with an increased risk of vascular lesions of the liver [51,56,57]. In other reports, irinotecan-containing regimens have also been associated with increased risks of steatosis and steatohepatitis [52,53,56]. Steatohepatitis is observed more frequently after chemotherapy in patients with a higher body mass index [53]. This could explain why CASH is more frequently reported in US studies [54] whereas vascular lesions are more often reported in studies from Europe [51,55,57]. It is possible, therefore, that specific chemotherapy regimens do not automatically predispose to steatosis, but can aggravate it when it already exists [54].

That chemotherapy can be associated with liver injury is now well recognised. The main question is whether collective damages to the liver induced by preoperative chemotherapy have any clinical significance. The safety data of EORTC study 40983, comparing perioperative chemotherapy with 5FU, leucovorin and oxaliplatin (six cycles before surgery and six cycles after) to surgery alone in 364 patients, were presented at ASCO 2005 [49]. The results showed that mortality rate was very low (close to 1%) in the two treatment arms and the rate of reversible complications was acceptable. Thus, administration of six cycles of FOLFOX before surgery appears feasible. Another report from our institution brought another insight into the relation between duration of preoperative chemotherapy and perioperative morbidity, and showed that administration of more than six cycles of neoadjuvant systemic chemotherapy increased morbidity after major liver resection but did not increase mortality [55]. Furthermore, it has been reported that patients with more than 12 cycles of preoperative chemotherapy had a higher risk of reoperation and a longer hospital stay [57].

Some studies have looked at the relation between the type of lesions induced by chemotherapy and their potential clinical consequences. Steatosis is associated with increased overall and infective complications but does not have a significant impact on mortality [58]. Sinusoidal injury increases the risk of operative bleeding but does not increase perioperative morbidity and mortality [56,57]. Finally, steatohepatitis is the most severe injury since it increases overall postoperative mortality and specifically death from postoperative liver failure [56]. Consequently, the use of neoadjuvant therapy including the choice of chemotherapy regimens and the duration of treatment should be carefully considered because the risk of hepatoxicity is significant. Preoperative liver biopsy has been suggested in patients who have received prolonged systemic chemotherapy to evaluate the degree of chemotherapy-induced liver injury [54]. The interest of such an approach is uncertain, given the problems with intra- and inter-observer variations in the evaluation of CASH [56] and the heterogeneity of lesions due to chemotherapy in the liver. Using such information to deny resection of resectable liver metastases, based only on the results of biopsies, may not prove easy. The best alternative would be the ability to identify other factors which could predict, before start of treatment, which patients are at risk of developing chemotherapy-induced liver injury.

Concerning targeted agents, there are only few data describing the potential toxicity of anti-vascular endothelial growth factor (VEGF) therapy such as bevacizumab. Bevacizumab has been considered responsible for increased risk of organ perforation, bleeding and decreased wound healing [59]. Because VEGF plays a critical role in liver regeneration, it is also possible that hepatic regeneration could be impaired in patients who undergo surgery after having received VEGF blockers. Until further evidence is obtained, it is reasonable to allow a 6 to 8-week interval between the last administration of bevacizumab and surgery [59]. New clinical studies are necessary to determine if and how surgery is feasible after administration of novel systemic targeted agents. Such a study has been organised by EORTC, and will evaluate the feasibility and safety of liver surgery for metastases in patients who had received neoadjuvant chemotherapy with 5FU, oxaliplatin and cetuximab, with or without bevacizumab.

Conclusions

Surgery is the standard treatment of resectable metastases and should be proposed whenever possible. We have now learned that chemotherapy, as with all other treatment procedures, has both positive and negative impacts, and we must deal with both. Thus, both the choice of drugs and the duration of treatment must be decided with care. For patients with resectable metastases, neoadjuvant chemotherapy can be considered pending the results of EORTC 40983, but these patients also should not be overtreated to avoid chronic and progressive chemotherapy-induced liver damage,

which could preclude curative surgery. In the fast-moving field of combined treatment of patients with colorectal cancer liver metastases, multidisciplinary discussion and repeated evaluations are more indispensable than ever. If neoadjuvant chemotherapy is well chosen and well monitored and surgery is planned at the right moment, liver metastases can be resected safely.

Conflict of interest statement

None declared.

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