Neoadjuvant chemotherapy for non-/resectable metastases

Gunnar Folprecht

University Hospital Carl Gustav Carus,
University Cancer Center/Medical Department I, Dresden, Germany

Introduction

The prognosis of patients with metastatic colorectal cancer has been improving over the last two decades due to increasing options for systemic treatment, but also because liver metastases were resected more frequently. Resection of metastases that can provide the option of long term survival or even cure [1] was uncommon in the 1990s and has since become more frequent. In the Netherlands, hepatic surgery due to liver metastases increased from 4% (1995–99) to 10% (2004–07) [2]. In specialised centres, it reached nearly 20% of patients with metastatic colorectal cancer [3]. One indicator of the new view on potential metastasectomies is the 2010 updated TNM classification dividing stage M1 into M1a (metastases in one organ, "only") from metastases in more than one organ or the peritoneum (stage M1b) [4].

In clinical practice, the decision to resect metastases is influenced by several factors, of which technical resectability is a necessary precondition. A main criterion for surgical resectability is the remaining functional liver tissue (including sufficient perfusion and bile drainage) of ca. 30%. Other factors influencing the decision are the experience of the centre and the individual surgeon, the presence of extrahepatic disease [5], prognostic factors after resection (i.e. number of metastases, primary tumour stage [6], and disease-free interval [7]) and co-morbidities (Fig. 1).

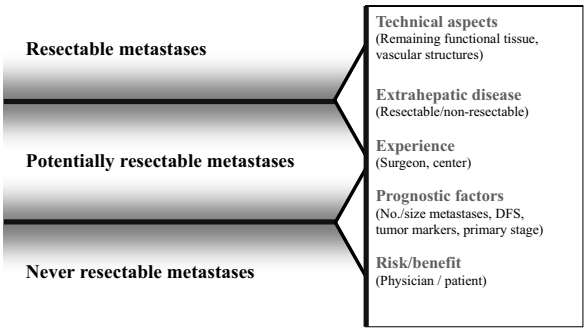

Fig. 1. Clinical situations regarding resectability and influencing factors.

Especially in situations with high risk for early recurrence, the views on the risk/benefit ratio – both of the patient and of the treating physician(s) – influence the actual procedure and contribute to the lack of a general agreement on criteria for resectability. The lack of investigations on whether there is a benefit also in short disease-free intervals after liver resection (six, nine, or twelve months) contributes to the uncertainty regarding uniform criteria for metastasectomies in high risk situations. Even so, three treatment situations can be distinguished: (1) patients with upfront resectable metastases, (2) patients with potentially resectable metastases, and (3) patients who are very unlikely to become resectable, even after chemotherapy.

In patients with multiple metastases that will never be resectable, improving overall survival with a good quality of life is regarded as the aim of palliative chemotherapy, and progression-free survival the most common surrogate parameter. If patients have resectable disease, there is the typical question of adjuvant/neoadjuvant therapy and disease-free survival is the usual surrogate. In the situation of potentially resectable disease, the prognosis is improved when a liver resection can be performed after chemotherapy which justifies a slightly different approach including other surrogate parameters for therapy as discussed below.

Furthermore, patients with limited metastatic disease are classical candidates for multidisciplinary treatment and multidisciplinary treatment decision making. Although from a strong evidence based point of view, chemotherapy is the only method with a survival benefit proven in randomised controlled trials, there are alternatives to achieve resectability, such as two staged resections and portal vein embolisation, further local treatment options such as (radiofrequency) ablation or intra-arterial therapies. Patients will benefit if the full spectrum is used in an appropriate way.

Patients with potentially resectable disease

Most reports of resection of initially non-resectable liver metastases were published after more active schedules for treatment of metastatic colorectal cancer had been introduced into clinical practice. The first small collection describing patients with successful liver resection of initially non-resectable metastases was published nearly 20 years ago – after neoadjuvant treatment with 5-FU/folinic acid [8]. With the higher efficacy of – mostly oxaliplatin based – combination therapies, larger series reporting successful liver resection after chemotherapy in initially non-resectable patients with colorectal liver metastases were published. Giacchetti and co-workers in 1999 described in the resected patients a five-year survival of 50% compared to a median overall survival of 15 months in patients without resection [9]. This improved prognosis was confirmed by a later publication on the observational cohort. A five- and ten-year survival of 33% and 25% was observed in patients with initially non-resectable liver metastases who underwent successful liver resection after chemotherapy [1]. Similar results were published by other groups [10,11].

These improved long term results changed the treatment strategy in patients with metastases limited to the liver. In contrast to palliative treatment, less the balance between toxicity and progression-free survival as surrogate endpoint, but tumour shrinkage (usually measured as response rate according to RECIST or WHO criteria) as *conditio sine qua non* for resection in non-resectable patients became an aim for chemotherapy. The hypothesis that tumour response is associated with the rate of liver resection was confirmed in a retrospective overview on published studies [12].

Further confirmation that neoadjuvant treatment can actually improve resectability comes from a retrospective review of the CT-/MRI-images of a randomised trial. These scans were evaluated by a group of surgeons blinded to the information whether the images were recorded before or after chemotherapy. According to imaging criteria, resectability was increased after systemic chemotherapy [13].

Chemotherapy doublets such as FOLFOX or FOLFIRI are associated with response rates of 40–50% [14–16]. Recent studies have shown that the efficacy of systemic therapy can be improved when chemotherapy doublets are combined with antibodies, or a combination of all chemotherapeutical drugs is used.

Resectability after chemotherapy

After retrospective reports of successful resection following chemotherapy of initially non-resectable liver metastases were published, several phase II trials investigated prospectively different chemotherapy regimens in the setting of non-resectable liver metastases. Non-resectability was not uniformly defined in the trials, which increases the problems with a cross-trial comparison of these studies. Some retrospective analyses for the conversion of non-resectable to resectable liver metastases report mostly oxaliplatin based therapy [9]. An Italian group demonstrated that irinotecan/5-FU/FA (FOLFIRI) also can be used as neoadjuvant treatment for liver metastases. Achieving a response rate of 48%, twenty-eight per cent of patients were R0 resected [17]. In a prospective multicentre trial with FOLFOX as chemotherapy 14/17 patients (33%) were resected [18]. In this trial, resection was performed after tumour response occurring within a median duration of 6 months.

Chemotherapy triplet combinations

With the combination oxaliplatin, irinotecan and 5-FU in one regimen (i.e. "FOLFIRINOX", "FOLFOXIRI"), high response rates have been observed in phase II trials [19,20]. Two randomised trials compared the triple combination to FOLFIRI in a general patient population with metastatic colorectal cancer [21,22]. The Greek trial, using lower doses of irinotecan and oxaliplatin than the Italian trial as well as a more bolus driven 5-FU schedule, found non-significant trends towards a higher efficacy with the triple combination therapy (Table 1) [21]. The Italian GONO group reported found significantly improved response rates, progression-free survival and overall survival – as well as a higher rate of liver resections in the FOLFOXIRI arm (15% vs. 6%, $P = 0.033$) [22] and a better long term survival [30]. As expected, toxicity was higher, but manageable [22].

A French study group investigated the standard doses of oxaliplatin (85 mg/m^2), irinotecan (180 mg/m^2) and 5-FU (same doses as in doublet regimen) and described in a phase II trial in patients with liver limited disease a high response rate of 71% [95% CI: 53–85%] and a rate of R0 liver resection of 27% [20].

Chemotherapy in combination with EGFR antibodies

The epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab have been shown to

Table 1
Phase III trials comparing chemotherapy triplets or antibody combinations to doublets

Schedule	n	Response rate	R0 resections	PFS (mo)	OS (mo)
FOLFOXIRI vs. FOLFIRI					
FOLFOXIRI [22] 85 mg/m^2 OX, 165 mg/m^2 IRI, 3200 mg/m^2 5-FU (46 h), 200 mg/m^2 l-FA	122	60%***	15%*	9.8 ***	22.6 *
FOLFIRI	122	34%	6%	6.9	16.7
HR				*0.63*	*0.70*
FOLFOXIRI [21] 65 mg/m^2 OX, 150 mg/m^2 IRI, 2×400 mg/m^2 5-FU bolus, 2×600 mg/m^2 5-FU (22 h)	137	43%	6.6%	8.4	21.5
FOLFIRI	146	34%	1.4%	6.9	19.5
Chemotherapy doublets +/– EGFR antibodies (k-ras wild type patient data)					
"CRYSTAL" [23]					
Cetuximab+FOLFIRI	316	59%***	5.1%*	9.9 **	23.5 **
FOLFIRI	350	40%	2.0%	8.4	20.0
HR				*0.70*	*0.80*
"OPUS" [24,25]					
Cetuximab+FOLFOX	82	57%**	7.3%	8.3 **	22.8
FOLFOX	97	34%	3.1%	7.2	18.5
HR				*0.57*	*0.86*
"COIN" [26]					
Cetuximab/fluoropyrimidine/oxaliplatin	362	59%*		8.6	17.0
Fluoropyrimidine/oxaliplatin	367	50%		8.6	17.9
HR				*0.96*	*1.04*
"PRIME" [27]					
FOLFOX + panitumumab	325	55%	8.3%	9.6 *	23.9
FOLFOX	331	48%	7.0%	8.0	19.7
HR				*0.80*	*0.83*
Chemotherapy doublets +/– bevacizumab					
IFL + bevacizumab [28]	402	45%**	<2%	10.6***	20.3***
IFL	401	35%		6.2	15.6
HR				*0.54*	*0.66*
"NO16966" [29]					
Bevacizumab/fluoropyrimidine/oxaliplatin	699	38%	8.4%[a]	9.4**	21.3
Fluoropyrimidine/oxaliplatin	701	38%	6.1%[a]	8.0	19.9
HR				*0.83*	*0.89*

FA, folinic acid; IFL, irinotecan–folinic acid–fluorouracil; IRI, irinotecan; PFS, progression-free survival; OS, overall survival, OX, oxaliplatin.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
[a] All resections.

be active if activating k-ras mutations are absent in the tumour [31,32].

The CRYSTAL trial comparing FOLFIRI with or without cetuximab as palliative first line therapy for metastatic disease described an increased response rate (57% vs. 40%, $P < 0.001$) that was associated with a higher rate of R0 metastasectomies (5.1% vs. 2.0%, $P = 0.026$) in patients with k-ras wild type tumours [23]. Similar results were found in the smaller OPUS trial studying FOLFOX +/– cetuximab (Table 1) [24]. Both studies were not designed for investigation of neoadjuvant therapy and the frequency of liver resections was relatively was low in both arms.

The multicentre randomised CELIM trial compared neoadjuvant chemotherapy with FOLFOX/cetuximab or FOLFIRI/cetuximab in patients with liver limited, non-resectable disease. The response rate was 70%

[95% CI 58–81%] in k-ras patients. In total, 34% of patients were R0 resected after neoadjuvant treatment [13]. The unplanned subgroup analyses of the CRYSTAL and OPUS study for patients with liver limited metastases and k-ras wild type found similar response rates of 71% with FOLFIRI/cetuximab (compared to 44% with FOLFIRI alone, $P = 0.002$) and 76% vs. 39%, $P = 0.02$, with FOLFOX +/– cetuximab [25].

In the British COIN trial (oxaliplatin/fluoropyrimidine +/– cetuximab, third arm: early termination of oxaliplatin/fluoropyrimidine) that was negative for the primary endpoint overall survival, a significantly higher response rate was reported for patients treated with cetuximab. The trial results might have been influenced by a negative interaction between capecitabine/oxaliplatin and cetuximab. Interestingly, the unplanned sub-subgroup analysis demonstrated a significantly better progression-free survival for k-ras wild type patients with liver metastases only and FOLFOX as chemotherapy when cetuximab was added [26].

The progression-free survival was significantly longer with panitumumab in the PRIME trial (FOLFOX +/– panitumumab). For response rates, a non-significant trend was observed (55% vs 48%, $P = 0.07$, Table 1) [27]. Both trials, COIN and PRIME, found similar resection rates in both treatment arms. Difficult to interpret is the not yet fully published NORDIC VII trial (Nordic FLOX regimen +/– cetuximab) which has shown an improved efficacy in patients with k-ras mutations but not in patients with k-ras wild type [33]. In addition to the above mentioned discussion on an interaction between CapOx vs. FOLFOX and cetuximab activity, there are speculations whether the different results for CRYSTAL and the COIN/NORDIC VII trial can be explained by different interactions between oxaliplatin or irinotecan and EGFR antibodies. However, at least basing on the few studies with direct comparison of irinotecan and oxaliplatin in combination with fluoropyrimidine and cetuximab, there was no clear difference regarding efficacy with either combination [13,34,35].

Chemotherapy and the VEGF antibody bevacizumab

Adding bevacizumab to the irinotecan/5-FU bolus regimen IFL or to the 5-FU/folinic acid resulted in a significant prolongation of the progression-free survival and the overall survival. Although statistically significant, the response rates increased rather moderately with these schedules (45% vs. 35% and 34% vs. 25%) [28,36]. Both regimens are unusual in neoadjuvant treatment of liver metastases.

In the NO16966 trial, the contribution of bevacizumab was in combination with FOLFOX or capecitabine/oxaliplatin. In this trial, the response rates were equal (38% vs. 38%) in both treatment arms with similar resection rates (8.4 vs 6.1%, Table 1). Although the primary endpoint progression-free survival was met, an added value of bevacizumab in downsizing liver metastases (measured by the response rate) was not demonstrated in this trial [29]. Given the above cited treatment alternatives, FOLFOXIRI or cetuximab based combinations (the latter for k-ras wild type patients) might perhaps be more appropriate regimens if tumour response for later resectability is the primary treatment aim.

Toxicity of neoadjuvant treatment

In trials for patients with metastatic colorectal cancer investigating palliative chemotherapy doublets with or without antibodies, side effects are frequent. In randomised phase III trials, grade $\geqslant 3$ toxicities occur in 60–85% of patients; the rate of treatment-associated mortality is <2%. [27–29,37]. In the neoadjuvant situation, higher rates of toxicity temporarily influencing the quality of life might rather be accepted in the light of a potentially curative treatment. Furthermore, patients qualifying for later resections will have a rather good performance status and might tolerate side effects better than their counterparts with more advanced disease.

With the background of planned resection, not only the general toxicity but also a potential influence of chemotherapy on the liver function and the morbidity of resection has to be considered.

Oxaliplatin is associated with a sinusoidal obstruction of the liver, inducing a macroscopically "blue liver" [38]. For irinotecan, a steatosis/steatohepatitis ("yellow liver") is described. Both steatohepatitis and sinusoidal obstruction were found in ~20% of irinotecan and oxaliplatin treated patients, respectively, but only in <10% of patients with 5-FU alone or the opponent drug, and infrequent in untreated patients [39]. Sinusoidal obstruction was associated with increased morbidity [40], steatohepatitis with increased mortality [39], but it was not definitely clarified whether the latter relationship was regarding irinotecan-induced steatohepatitis or steatohepatitis from other causes.

Generally, the methodology for studies investigating the impact of liver directed toxicity on perioperative

morbidity is limited by the fact that the resecting surgeon will consider liver damage and adapt his treatment strategy on the macroscopic findings. One of the few controlled reports of the actual influence on postoperative complications is the randomised EORTC study 40983 comparing neoadjuvant treatment (FOLFOX) with surgery alone in patients with resectable metastases. The postoperative morbidity was increased from 16% to 25% if the patients were pre-treated ($P = 0.04$). The mortality was equal in both groups (1%). At least in this trial with 3 months of FOLFOX treatment, only 1 patient (out of 182 with neoadjuvant treatment) was not resected because of liver toxicity [41].

However, the morbidity is associated with the number of preoperative chemotherapy cycles. The perioperative morbidity of liver resection increases from 14% and 19% (no chemotherapy and $\leqslant$5 cycles, respectively) to 45% with 6–9 cycles and 62% with $\geqslant$10 cycles [42]. Similar findings were published by other groups [43,44]. Reducing the risk associated with resection is a reason to maintain the neoadjuvant chemotherapy as short as possible in patients with non-resectable metastases.

A special aspect is the influence of bevacizumab on wound healing and liver toxicity. Wound healing is after surgery is impaired if bevacizumab treatment is ongoing [45]. Therefore, an interval of at least 6 weeks (3 half-times) between end of bevacizumab treatment and resection is recommended. For planned liver surgery, a major impact of bevacizumab on perioperative morbidity is not measurable [46–48]. Some authors found that sinusoidal obstruction is reduced in patients with bevacizumab treatment [49,50]. These comparisons refer to cohorts of patients treated in different time periods and clinical relevance may be questionable; confirmatory investigations would be preferable.

Duration of therapy in non-resectable studies

Duration of neoadjuvant treatment is not clarified by randomised studies. For the above mentioned reasons, a time as short as possible is currently the mostly recommended strategy.

In the multicentre study with FOLFOX, it was reported that the median duration until response before resection was 6 months [18]. In the more recent CELIM study, the median time of neoadjuvant treatment was slightly shorter – four months: Eighteen per cent of resected patients were operated after the first staging CT (2 months), in most patients who were actually resected, this decision was made after the 4-month CT scan, and in some additional patients after the 6-month imaging. Longer neoadjuvant treatments did very seldom result in a decision to operate a patient (4% of resected pts) [13]. It might be concluded that re-discussion in the multidisciplinary team should be scheduled at least at three and six months during neoadjuvant chemotherapy (or at 2, 4 and 6 months), and that the treatment strategy should be reconsidered if resectability is not achieved within the first six months. As a neoadjuvant treatment (with FOLFOX) of three months is widely regarded as indicated even in resectable patients [41], major efforts to shorten the neoadjuvant treatment below three months will not be absolutely necessary in non-resectable patients.

Patients with resectable metastases

Adjuvant systemic chemotherapy in patients with resected liver metastases was investigated in two studies using 5-FU/folinic acid. Both studies were closed early due to poor recruitment. In one of these studies, chemotherapy had significant influence on disease-free survival although the primary analysis was negative [51]. A metaanalysis of both trials demonstrated a strong trend to a better disease-free survival (HR 1.32 [95% CI 1.0–1.76, $P = 0.058$) and a trend to a better overall survival (HR 1.32 [0.95–1.82], $P = 0.095$) but failed significance [52]. A comparison between adjuvant FOLFIRI and 5-FU/FA in patients with resected liver metastases found no difference between both arms [53].

The EORTC 40983 trial randomised patients with resectable metastases (defined as technically resectable and $\leqslant$4 metastases) to perioperative chemotherapy (3 months FOLFOX pre- and 3 months FOLFOX postoperatively) or to surgery alone. In the intention-to-treat analysis the trial was negative, even though a strong trend for a better disease-free survival was observed (HR 0.79 [0.62–1.02], $P = 0.058$) [41]. Because an analysis according to the usually definition for progression-free survival, as well as the analysis for patients actually resected, were positive [41], a common interpretation is that a benefit for the resectable patients was shown. To clarify this situation, which is unsatisfying from a strictly evidence based point of view, a literature based meta-analysis was performed that compared liver surgery alone with surgery plus any perioperative or postoperative therapy. As this metaanalysis found a significant benefit regarding disease-free survival for surgery plus chemotherapy [54], it is difficult to regard surgical treatment alone as standard of care.

Uncertainty remained whether patients with resectable metastases actually need a neoadjuvant therapy or whether adjuvant treatment is sufficient. While neoadjuvant treatment increases perioperative morbidity (see above), the rate of 24% of patients in the EORTC study not receiving adjuvant therapy [41] underlines one advantage of neoadjuvant therapy – that all patients receive at least three months of chemotherapy. A NSABP study (NCT01189227) and a German AIO trial (NCT01266187) are randomising patients to a perioperative vs. adjuvant chemotherapy with bevacizumab/FOLFOXIRI or cetuximab/FOLFOX.

While ESMO recommends a perioperative therapy [55], the German guidelines, among others, recommend considering neoadjuvant or adjuvant treatment without clear recommendation of any chemotherapy [56]. At first glance, more balanced recommendations to adjuvant therapy for "easily" resectable metastases (⩽2 metastases, metachronous) and to neoadjuvant therapy for "less favourable" metastases have the counterargument that in the EORTC study most patients had single metastases and metachronous metastases.

Complete response

Macroscopically complete response

Treatment until macroscopically complete remission is not the current aim of treatment, because (1) metastases should probably be resected despite CR, (2) to find the metastases will become more difficult during resection and (3) the longer treatment increases morbidity. However, despite close follow up, aiming for complete remission of metastases cannot always be avoided. This applies especially to smaller metastases if larger metastases limit the resection and require a longer treatment.

Stephan Benoist and co-workers reported a retrospective cohort of patients who had liver metastases "disappearing" on CT-scans. Out of 66 disappeared metastases, 55 (88%) were not regarded as "cured": 20 metastases were macroscopically visible at resection, 12 had viable tumour when the segment was resected, and 23 metastases recurred during the first year of follow up [57]. In contrast to these data, in a small cohort described at the Institute Gustav Roussy, out of sixteen patients with disappearing liver metastases (mostly treated with intra-arterial therapy), ten patients (62%) had no recurrence at the site of former metastases [58]. Furthermore, a North American group described 118 disappearing liver metastases in 39 patients. "Only" 44% of these patients developed an intrahepatic recurrence with a median follow-up of >40 months. Significantly associated with "true complete response" – defined as no recurrence during follow-up or pathological CR – were normal CEA, no BMI >30, no steatosis, intra-arterial therapy and confirmation of disappearance by MRI [59]. In the presence of these factors, close follow-up of disappearing liver metastases is an option, especially if resection of the former metastatic region would require additional major surgery.

Microscopically complete response

Microscopically complete response (pathologic complete response, pCR) is known to be associated with better prognosis in different tumour entities. Similar findings – a 5 year overall survival of 75–76% compared to 33–56% without pCR – were published for colorectal liver metastases with complete response after neoadjuvant therapy [60,61].

In a publication of Adam and co-workers, age (⩽60 y), size (⩽3 cm), low CEA (⩽30 ng/ml) and response according to RECIST criteria were significantly associated with pCR [60]. Blazer et al found CEA (⩽5 ng/ml), size (⩽3 cm), and chemotherapy with oxaliplatin/bevacizumab/fluoropyrimidine independently associated with pathological response. Regarding pathological *complete* response, there was no difference in frequency related to chemotherapy (irinotecan vs. oxaliplatin, with/without bevacizumab) [61].

However, the low frequency of pCR – 29/767 patients (3.8%/9%) [60,61] – may limit the importance of pCR in the daily clinical practice and even its practicability as a primary endpoint of a clinical trial.

Treatment intensification

Different approaches have been investigated to increase efficacy of medical treatment. As the combination of VEGF- and EGFR-antibodies has shown disappointing results in first-line therapy [62,63], discussion will focus on FOLFOXIRI-like combinations plus antibodies and on intra-arterial therapy.

Chemotherapy triplets and antibodies

The GONO group performed a phase II study with bevacizumab plus FOLFOXIRI and found a promising activity (response rate 77%, progression-free survival 13 months) with a R0 resection rate of 20% in the selected patient group without increased toxicity.

In the POCHER study, a chronomodulated oxaliplatin/irinotecan/5-FU schedule was explored in combination with cetuximab. The relatively high activity (response rate of %, progression-free survival 12 months, overall survival 37 months) was associated with a R0 resection of 60%. However, doses of all cytotoxic drugs were reduced during the study due to toxicity [64]. A French group used the FOLFORINOX regimen – high standard doses of irinotecan (180 mg/m^2), oxaliplatin (85 mg/m^2) and 5-FU (400/2400 mg/m^2) – for a study with the primary endpoint of complete response. CR rate was 12%, the overall response rate 81%, progression-free survival 10 months, but the toxicity higher than in other studies for colorectal cancer (e.g., diarrhoea grade $\geqslant$3 in 52%). A phase I study on FOLFOXIRI in a schedule similar to that of Falcone and co-workers [22] has shown feasibility at reduced irinotecan doses (125 mg/m^2) and response rates of 75%, progression-free survival 14 months [65].

With current knowledge, randomised trials should be the context of FOLFOXIRI-like regimens plus antibodies.

Intra-arterial regimens

With the availability of newer drugs, interest in intra-arterial therapy has decreased as better efficacy can be achieved with a less complex, systemic combination therapy. Some publications from highly specialised centres have demonstrated that the combination of intraarterial and systemic therapy induces high response rates [66,67] and might improve efficacy even in the era of new systemic drugs.

Summary

The identification of patients with resectable and potentially resectable metastatic disease is important. For resectable patients, the superiority of a combined approach has been shown. Mostly, perioperative chemotherapy with FOLFOX as established in the EORTC 40983 trial is recommended; postoperative chemotherapy might be an alternative and is being compared to perioperative treatment in randomised trials. In patients with non-resectable (liver) metastases, response followed by resection is mostly the treatment aim, which can be achieved by multiple regimens. In phase III trials, especially FOLFOXIRI [22] and cetuximab plus doublet (e.g. FOLFIRI [37]) have shown high response rates and increased resection rates compared to the control arm. More intensive schedules are under investigation.

Re-evaluation for resectability should be performed at least at three and six months during chemotherapy. Resection is currently recommended as soon as resectability is assumed from imaging, as longer chemotherapy is associated with increased morbidity and complete remission is not generally regarded as the treatment aim.

Conflict of interest statement

G. Folprecht received a study grant from Merck KGaA, honoraria for ad-hoc advisory boards from Roche, Bristol-Myers-Squibb and Merck KGaA, and lecture honoraria from Merck KGaA, Roche, Novartis and Amgen.

References

1 Adam R, Wicherts DA, de Haas RJ, et al. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? *J Clin Oncol* 2009 Apr 10;**27**(11):1829–35.

2 van der Pool AE, Damhuis RA, Ijzermans JN, et al. Trends in incidence, treatment and survival of patients with stage IV colorectal cancer; a population-based series. *Colorectal Dis* 2010 Dec 22.

3 Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol* 2009 Aug 1;**27**(22):3677–83.

4 Sobin LH, Gospodarowicz MK, Wittekind C. *TNM classification of malignant tumours*, 7th edn. Wiley-Blackwell; 2009.

5 Adam R, Aloia TA. Is hepatic resection justified after chemotherapy in patients with colorectal liver metastases and lymph node involvement? *J Clin Oncol* 2009 Mar 10; **27**(8):1343–5.

6 Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. *Ann Surg* 2008 Jan;**247**(1):125–35.

7 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 Sep;**230**(3):309–18.

8 Fowler WC, Eisenberg BL, Hoffman JP. Hepatic resection following systemic chemotherapy for metastatic colorectal carcinoma. *J Surg Oncol* 1992 Oct;**51**(2):122–5.

9 Giacchetti S, Itzhaki M, Gruia G, et al. Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. *Ann Oncol* 1999 Jun;**10**(6):663–9.

10 Masi G, Loupakis F, Pollina L, et al. 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 Mar;**249**(3):420–5.

11 Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007 Oct 10;**25**(29):4575–80.

12 Folprecht G, Grothey A, Alberts S, Raab HR, Köhne CH. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol* 2005 May 3;**16**(8):1311–9.

13 Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol* 2010 Jan 1;**11**(1):38–47.

14 Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000 Mar 25;**355**(9209):1041–7.

15 Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004 Jan 15; **22**(2):229–37.

16 de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000 Aug;**18**(16):2938–47.

17 Pozzo C, Basso M, Cassano A, et al. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. *Ann Oncol* 2004 Jun;**15**(6):933–9.

18 Alberts SR, Horvath WL, Sternfeld WC, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol* 2005 Dec 20;**23**(36):9243–9.

19 Falcone A, Masi G, Allegrini G, et al. Biweekly chemotherapy with oxaliplatin, irinotecan, infusional fluorouracil, and leucovorin: a pilot study in patients with metastatic colorectal cancer. *J Clin Oncol* 2002 Oct 1;**20**(19):4006–14.

20 Ychou M, Viret F, Kramar A, et al. Tritherapy with fluorouracil/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX): a phase II study in colorectal cancer patients with non-resectable liver metastases. *Cancer Chemother Pharmacol* 2008;**62**(2):195–201.

21 Souglakos J, Androulakis N, Syrigos K, et al. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). *Br J Cancer* 2006 Feb 27;**94**(6):798–805.

22 Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007 May 1;**25**(13):1670–6.

23 Van Cutsem E, Köhne CH, Lang I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol* 2011 Apr 18.

24 Bokemeyer C, Bondarenko I, Hartmann JT, et al. 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**(7):1535–46.

25 Van Cutsem E, Bokemeyer C, Heeger S, Sartorius U, Rougier P, Kohne C. Outcome according to metastatic site in patients with KRAS wild-type tumors: Analysis from the CRYSTAL and OPUS studies. *J Clin Oncol (Meeting Abstracts)* 2011 Feb 3;**29**(4 suppl):472.

26 Maughan T, Adams RA, Smith CG, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy (CT) for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet* 2011;**377**:2103–14.

27 Douillard JY, Siena S, Cassidy J, et al. Randomized, phase iii trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010 Nov 1; **28**(31):4697–705.

28 Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004 Jun 3;**350**(23):2335–42.

29 Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008 Apr 20;**26**(12):2013–9.

30 Masi G, Vasile E, Loupakis F, et al. Randomized trial of two induction chemotherapy regimens in metastatic colorectal cancer: an updated analysis. *J Natl Cancer Inst* 2011 Jan 5;**103**(1):21–30.

31 Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008 Oct 23;**359**(17):1757–65.

32 Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008 Apr 1;**26**(10):1626–34.

33 Tveit K, Guren T, Glimelius B, et al. Randomized phase III study of 5-fluorouracil/folinate/oxaliplatin given continuously or intermittently with or without cetuximab, as first-line treatment of metastatic colorectal cancer: the Nordic VII Study (Nct00145314), by the Nordic Colorectal Cancer Biomodulation Group. *Ann Oncol* 2010;**21**:9.

34 Moosmann N, von Weikersthal LF, Vehling-Kaiser U, et al. Cetuximab plus capecitabine and irinotecan compared with cetuximab plus capecitabine and oxaliplatin as first-line treatment for patients with metastatic colorectal cancer: AIO KRK-0104 – a randomized trial of the German AIO CRC study group. *J Clin Oncol* 2011 Mar 10;**29**(8):1050–8.

35 Ocvirk J, Brodowicz T, Wrba F, et al. Cetuximab plus FOLFOX6 or FOLFIRI in metastatic colorectal cancer: CECOG trial. *World J Gastroenterol* 2010 Jul 7;**16**(25):3133–43.

36 Kabbinavar FF, Hambleton J, Mass RD, Hurwitz HI, Bergsland E, Sarkar S. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol* 2005 Jun 1;**23**(16):3706–12.

37 Van Cutsem E, Köhne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009 Apr 2;**360**(14):1408–17.

38 Rubbia-Brandt L, Audard V, Sartoretti P, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. *Ann Oncol* 2004 Mar;**15**(3):460–6.

39 Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 2006 May 1;**24**(13):2065–72.

40 Nakano H, Oussoultzoglou E, Rosso E, et al. Sinusoidal injury increases morbidity after major hepatectomy in patients with

colorectal liver metastases receiving preoperative chemotherapy. *Ann Surg* 2008 Jan;**247**(1):118–24.

41 Nordlinger B, Sorbye H, Glimelius B, et al. 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 Mar 22;**371**(9617):1007–16.

42 Karoui M, Penna C, Amin-Hashem M, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Ann Surg* 2006 Jan;**243**(1):1–7.

43 Aloia T, Sebagh M, Plasse M, et al. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. *J Clin Oncol* 2006 Nov 1;**24**(31):4983–90.

44 Kishi Y, Zorzi D, Contreras CM, et al. Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. *Ann Surg Oncol* 2010 Nov;**17**(11):2870–6.

45 Scappaticci FA, Fehrenbacher L, Cartwright T, et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. *J Surg Oncol* 2005 Sep 1; **91**(3):173–80.

46 Wicherts DA, de Haas RJ, Sebagh M, et al. Impact of bevacizumab on functional recovery and histology of the liver after resection of colorectal metastases. *Br J Surg* 2011;**98**(3):399–407.

47 Kesmodel SB, Ellis LM, Lin E, et al. Preoperative bevacizumab does not significantly increase postoperative complication rates in patients undergoing hepatic surgery for colorectal cancer liver metastases. *J Clin Oncol* 2008 Nov 10;**26**(32):5254–60.

48 Gruenberger B, Tamandl D, Schueller J, et al. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. *J Clin Oncol* 2008 Apr 10;**26**(11):1830–5.

49 Klinger M, Eipeldauer S, Hacker S, et al. 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 May;**35**(5):515–20.

50 Rubbia-Brandt L, Lauwers GY, Wang H, et al. Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. *Histopathology* 2010 Mar;**56**(4):430–9.

51 Portier G, Elias D, Bouche O, et al. 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 Nov 1;**24**(31):4976–82.

52 Mitry E, Fields AL, Bleiberg H, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. *J Clin Oncol* 2008 Oct 20;**26**(30):4906–11.

53 Ychou M, Hohenberger W, Thezenas S, et al. A randomized phase III study comparing adjuvant 5-fluorouracil/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer. *Ann Oncol* 2009 Dec;**20**(12):1964–70.

54 Wieser M, Sauerland S, Arnold D, Schmiegel W, Reinacher-Schick A. Peri-operative chemotherapy for the treatment of resectable liver metastases from colorectal cancer: A systematic review and meta-analysis of randomized trials. *BMC Cancer* 2010;**10**:309.

55 Van Cutsem E, Nordlinger B, Cervantes A. Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. *Ann Oncol* 2010 May;**21**(Suppl 5):v93–7.

56 Schmiegel W, Reinacher-Schick AC, Adler G, et al. S3-Leitlinie „Kolorektales Karzinom“ Ergebnisse evidenzbasierter Konsensuskonferenzen am 6./7. Februar 2004 und am 8./9. Juni 2007. S3-Guideline “Colorectal Cancer” 2004/2008. *Z Gastroenterol* 2008;**46**:1–73.

57 Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? *J Clin Oncol* 2006 Aug 20;**24**(24):3939–45.

58 Elias D, Goere D, Boige V, et al. Outcome of posthepatectomy-missing colorectal liver metastases after complete response to chemotherapy: impact of adjuvant intra-arterial hepatic oxaliplatin. *Ann Surg Oncol* 2007 Nov;**14**(11):3188–94.

59 Auer RC, White RR, Kemeny NE, et al. Predictors of a true complete response among disappearing liver metastases from colorectal cancer after chemotherapy. *Cancer* 2010 Mar 15; **116**(6):1502–9.

60 Adam R, Wicherts DA, de Haas RJ, et al. Complete pathologic response after preoperative chemotherapy for colorectal liver metastases: myth or reality? *J Clin Oncol* 2008 Apr 1;**26**(10):1635–41.

61 Blazer DG, III, Kishi Y, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. *J Clin Oncol* 2008 Nov 20;**26**(33):5344–51.

62 Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med* 2009 Feb 5;**360**(6):563–72.

63 Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol* 2009 Feb 10;**27**(5):672–80.

64 Garufi C, Torsello A, Tumolo S, et al. Cetuximab plus chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin as neoadjuvant chemotherapy in colorectal liver metastases: POCHER trial. *Br J Cancer* 2010 Nov 9; **103**(10):1542–7.

65 Folprecht G, Schuette K, Stoehlmacher J, Goekkurt E, Trarbach T. Cetuximab and FOLFOXIRI: Dose-escalation study in previously untreated patients with metastatic colorectal cancer. *Proc Gastrointest Canc Symp* (ASCO/AGA/ASTRO/SSO) 2010, abstract 480.

66 Malka D, Paris E, Caramella C, et al. Hepatic arterial infusion (HAI) of oxaliplatin plus intravenous (iv) fluorouracil (FU), leucovorin (LV), and cetuximab for first-line treatment of unresectable colorectal liver metastases (CRLM) (CHOICE): A multicenter phase II study. *J Clin Oncol (Meeting Abstracts)* 2010 Jun 14;**28**(15 suppl):3558.

67 Kemeny NE, Melendez FDH, Capanu M, et al. Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2009 Jul 20; **27**(21):3465–71.