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Review

# Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group

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ABSTRACT

Liver resection offers the only chance of cure for patients with advanced colorectal cancer (CRC). Typically, the 5-year survival rates following liver resection range from 25% to 40%. Unfortunately, approximately 85% of patients with stage IV CRC have liver disease which is considered unresectable at presentation. However, the rapid expansion in the use of improved combination therapy regimens has increased the percentage of patients eligible

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for potentially curative surgery. Despite this, the selection criteria for patients potentially suitable for resection are not well documented and patient management by multidisciplinary teams, although essential, is still evolving. The goal of the European Colorectal Metastases Treatment Group is to establish pan-European guidelines for the treatment of patients with CRC liver metastases that can be adopted more widely by established treatment centres and to develop more accurate staging systems and evaluation criteria.



## 1. Introduction

Despite the recent advances in first-line chemotherapy strategies for the treatment of patients with advanced colorectal cancer (CRC),[1–5] liver resection offers the only chance of cure for patients with colorectal liver metastases.[6] Until recently, the 5-year survival rates following liver resection typically ranged between 25% and 40% compared with between 0% and 5% for patients from the same institute who did not undergo liver resection.[6–12] These are consistent with the 5-year survival rates reported for most large series where liver resection has been performed.[13–16] The major challenge however comes from the fact that approximately 85% of patients with stage IV CRC, referred to specialist centres, have metastatic liver disease which is considered to be unresectable at presentation[17] (see Fig. 1).

Over the last 5 years there has been the recognition that preoperative, neoadjuvant, combination chemotherapy regimens, namely, 5-fluorouracil/folinic acid (5-FU/FA) in combination with either irinotecan or oxaliplatin, can facilitate the downsizing of colorectal liver metastases and render initially unresectable metastases resectable,[15,17–20] and that the addition of targeted therapies[21–26] and a third cytotoxic to these standard combination therapy regimens[27–30] might render them even more effective in this clinical setting (Table 1). Over the same time period, advances in surgical techniques have led to changes in the criteria for resectability. Today, the requirement for the remaining liver remnant to be equivalent to 30% of the original liver volume is considered to be the most critical factor.[31] Even the presence of disease outside the liver no longer automatically excludes surgery provided that it is also resectable.[32] As a consequence, the percentage of patients eligible for potentially curative liver resection is increasing. The published resection rates, however, are very much biased towards specialist treatment centres. The goal of the European Colorectal Metastases Treatment Group (ECMTG) has been to advocate a multidisciplinary treatment approach to patients with metastatic colorectal disease, confined principally to the liver, which can be adopted by all treatment centres. The first manuscript of the ECMTG focussing on current treatment strategies and on criteria for resection was published in the Eur J Cancer in 2006.[31] The intention of this expert group is to increase the number of patients who achieve long-term survival by increasing the number of

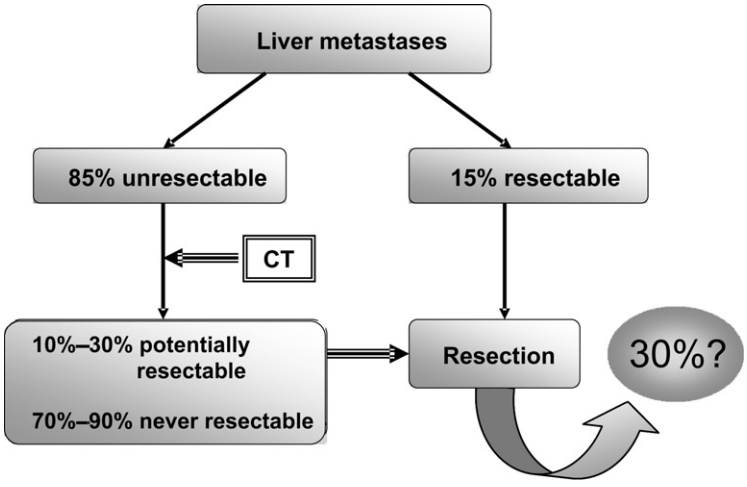


**Fig. 1 – Resectability of colorectal liver metastases in 2006.**

**Table 1 – Resection rates following first-line chemotherapy in patients with colorectal metastases**

| Study | Regimen | No. | Response rate (%) | Resection rate (all pts) % | Median survival/ 5-year survival (months/%) |
|---|---|---|---|---|---|
| Bismuth [15][NS] | 5-FU/FA ± oxaliplatin | 330 | – | 16 | –/40*** |
| Wein [62][NS] | 5-FU/FA | 53 | 42 | 17 | - |
| Giacchetti [18][S] | 5-FU/FA + oxaliplatin (cm) | 151 | 59 | 51(38) | 24/28 |
| | | | | | 48/50*** |
| Tournigand [19][NS] | FOLFIRI | 109 | 56 | 9 | 21.5/– |
| | FOLFOX6 | 111 | 54 | 22 | 20.6/– |
| Pozzo [44,45][S] | FOLFIRI | 40 | 48 | 33 | 30.1*/– |
| Ho [63][S] | Irinotecan/5-FU/FA | 40 | 55 | 10 | – |
| Alberts [33][S] | FOLFOX4 | 42 | 60 | 40 | 26/– |
| Tournigand [64,65][NS] | FOLFOX4 | 311 | 59 | 18 | –/32† |
| | FOLFOX7 | 309 | 59 | 15 | –/20† |
| Masi [66][NS] | FOLFOXIRI and simplified FOLFOXIRI | 74 | 72 | 26 | 36.8/37% at 4 years*** |
| Seium [30][NS] | 5-FU/FA and alternating oxaliplatin and irinotecan (OCFL) | 30 | 78 | 23 | 25.4/– |
| Falcone [28][NS] | FOLFOXIRI | 122 | 60 | 17 | >22.6/– |
| | FOLFIRI | | | (36**) | |
| | | 122 | 34 | 7 | >16.7/– |
| | | | | (12**) | |
| Abad [27][NS] | FOLFOXIRI | 47 | 69 | 26+ | >22/– |
| | | | | (40**) | |
| Quenet [29][S] | FOLFIRINOX | 25 | 72 | 56 | –/– |
| Folprecht [23][NS] | 5-FU/FA (AIO) + irinotecan + cetuximab | 21 | 67 | 19 | 33/– |
| Cervantes [21][NS] | FOLFOX4 + cetuximab | 43 | 79 | 23 | 30/– |
| Peeters [26][NS] | FOLFIRI + cetuximab | 42 | 45 | 21 | 23/– |
| Fisher [22][S] | FOLFOX4 + gefitinib | 27 | 78 | 22 | –/– |
| Kopetz [25] | FOLFIRI + bevacizumab | 23 | 74 | 17 | –/– |
| Hurwitz [24][NS] | IFL + bevacizumab | 402 | 45 | | 20.3/– |
| | IFL | 411 | 35 | <2% resection | 15.6/– |

* All patients; 24 months for non-resected patients; not reached for resected patients; ** resection rate in patients with liver mets only; ***resected patients only; + clearly defined criteria for resectability; † 3-year survival for R0/R1 patients; [S] selected patients (i.e. those with liver only mets); [NS] non-selected patients; NR = not reached.

patients who undergo resection of their liver metastases.[31] Today, resection rates in excess of 20% are not unusual in patients with initially unresectable liver metastases following neoadjuvant chemotherapy (Table 1), with 5-year survival rates of 50% now being reported. This manuscript reviews the current recommendations of the ECMTG resulting from their two recent workshops, in Paris in May 2006 and at the 31st ESMO Congress in September 2006.

## 2. Patient selection

A recent retrospective analysis of objective response rates and rates of resection for patients with initially unresectable liver metastases has demonstrated a strong correlation between the response rate (RR) to chemotherapy and the resection rate for liver metastases in patients with metastatic CRC (mCRC).[20] This correlation was stronger (0.96; $p = 0.002$) in selected patients, with isolated, liver-only metastases, than in non-selected patients (0.74; $p < 0.001$).[20] Indeed, the resection rate in selected patients following preoperative, 'neoadjuvant', chemotherapy ranged from 24% to 54% compared with 1% to 26% in non-selected patients.

The ECMTG members were unanimous in their recognition that there is an urgent need for improved patient work-up to facilitate improved patient selection for treatment with neoadjuvant chemotherapy, which in this clinical setting means chemotherapy administered with the aim of decreasing the size and stage of the liver tumour(s) and thereby increasing the potential for liver resection. The ECMTG recommended that the minimum patient work-up should include a good spiral computed tomography (CT) scan of the abdomen and thorax. A positron emission tomography (PET) scan was considered useful to rule out, the presence of metastases at other locations in the liver and the presence of extrahepatic disease.

Improved patient work-up should allow the early identification of those patients that are very unlikely to be candidates for resection and those that may, with the help of chemotherapy, be rendered resectable. Used in conjunction with a new staging system (see below), assessment of the general health status of the patient and predictors of clinical outcome, e.g. synchronous or metachronous metastases, these minimum work-up guidelines should permit a clearer classification/categorisation of patients and standardisation of treatment approaches across the different treatment centres.

## 3. New staging system

Currently stage IV is a 'catch all' classification/term that includes all colorectal tumours with liver metastases (and metastases outside of the liver), irrespective of the potential resectability of those metastases. A new staging system is

**Table 2 – Proposed new staging system for patients with CRC**

| ECMTG staging system subdividing patients according to their metastatic status |
|---|
| • M0 – no metastases |
| • M1a – resectable metastases |
| • M1b – potentially resectable liver metastases |
| • M1c – liver metastases that are unlikely to ever become resectable |

needed that acknowledges not only the improvements that have been made in surgical techniques for resectable metastases but also the impact that neoadjuvant chemotherapy has had on rendering initially unresectable CRC liver metastases resectable. It should distinguish clearly between patients with a chance of cure and those for whom only palliative treatment is possible. The current ECMTG definition of resectability with curative intent is the ability of the surgeon to remove the liver metastases leaving a clear resection margin (R0) and a liver remnant $\geqslant$30% of the original.[31] One of the aims of a new staging system will be to allow stratification of patients from the outset in terms of their potential resectability and use this to direct their therapeutic management. The development of such a staging system is already underway. The ECMTG have proposed a staging system that would subdivide the M from the TNM classification into M0 for patients with no known metastasis and M1 for patients with known metastases. The M1 patients would in turn be subdivided into three sub categories: M1a for patients with metastases that are resectable irrespective of site; M1b for patients with potentially resectable metastases, meaning that they are not resectable at the moment but may become resectable after response to chemotherapy and M1c for patients with metastases which are not resectable and are unlikely to become resectable after chemotherapy (Table 2). For both the M1a and the M1b patients who become resectable, resection offers the possibility of cure. Even in the third M1c subgroup, although unlikely, the possibility of doing a resection should not be excluded. All cases involving resection should be discussed in multidisciplinary team meetings. The advantage of this staging system is that it is simple and could be used for the every day care of patients with CRC liver metastases. It is likely that a more detailed and perhaps more sophisticated staging system should be used to stratify patients entered in clinical trials. This will be the objective of future workshops.

## 4. A new end-point for trials involving resection

Resectability could become a new end-point for assessing the efficacy of neoadjuvant (pre-operative) chemotherapy, prior to hepatic resection.[20] Overall survival, although the most objective end-point, is a long-way down the line from the neoadjuvant treatment setting for stage IV disease and can be influenced by many other factors. However, the indications for resection itself are also subjective, dependent not only on the patient and the metastases, but also on the skill and aggressiveness of the surgeon. Resectability as an end-point is also confounded by the fact that the best way to manage patients with unresectable liver metastases is to administer chemotherapy until the metastases become resectable and not until best response.[33,34] In addition, a 20% reduction in tumour size may render a metastasis resectable in one situation, whilst an 80% reduction in tumour volume might be insufficient to confer resectability in another. Also, the choice of initially unresectable patients influences both the resection rate and the assessment of efficacy in these trials.

It was because of issues such as these that the ECTMG felt that progression-free survival (PFS) rather than resection rate should be the primary end-point for trials of neoadjuvant chemotherapy regimens in CRC patients with initially unresectable liver metastases. The data show that few patients whose disease progresses during the course of neoadjuvant therapy are still alive at 5 years, even if they do undergo a complete and apparently curative resection.[35] Thus, the arguments in support of using PFS as a clinical end-point are analogous to those put forward by Sargent et al. for the use of disease-free survival (DFS) as the primary end-point in the adjuvant setting.[36,37] However, if PFS is to act as a surrogate end-point for overall survival in this clinical context, we need to establish a correlation between PFS in the neoadjuvant setting and overall survival. Relapse-free survival (RFS) was also proposed as a surrogate end-point because of the high rates of recurrence in those patients undergoing apparently curative surgery. However, if we elect to use PFS and RFS as surrogate end-points there need to be two clear definitions:

- PFS/RFS censored for those patients who undergo hepatic resection and
- PFS/RFS for all patients, choosing the time of recurrence as progression.

Before we can even begin to seriously explore the potential of resectability as an end-point it is clear that we need to define the criteria for resectability, or at least unresectabilty, and design new trials. The ECMTG were also unanimous in their view that there needs to be a clear demonstration of a correlation between complete resection (R0) rate and survival in future trials. There is also the question of whether there is a role for debulking surgery in this setting. In addition, radiofrequency ablation (RFA) is now used frequently for the local control of liver metastases, and although it is not considered equivalent to surgical resection,[38] it can be combined with surgery to increase the number of patients who are candidates for complete local treatment.[39] At this time however, there are no definitive studies regarding surgical resection in combination with RFA in the treatment of liver metastases.[40] Furthermore, RFA can be used when neoadjuvant chemotherapy induces the shrinkage of large liver metastases to $\leqslant$3 cm.[39]

## 5. Optimal neoadjuvant chemotherapy

Since the recognition that neoadjuvant therapy could render initially unresectable metastases resectable, the use of neoadjuvant chemotherapy has expanded rapidly. However this has highlighted a divergence in the treatment strategies for those patients with initially unresectable but potentially resectable metastases and those patients whose liver metastases will

never be resectable. Patients whose liver metastases may be rendered resectable by chemotherapy are looking for a chemotherapy regimen that offers a high RR and hopefully, as a consequence, a high resection rate. Conversely, patients whose liver metastases will never be resectable are looking for prolonged survival, balanced against a good quality of life and the opportunity for the maximum utilisation of second-line therapy. Thus, the treatment end-points are different, RR versus prolonged survival, the goals being liver resection and prolongation of survival, respectively.

The addition of biological agents to standard combination therapy regimens has been associated with increased RR and prolonged median survival times. Indeed, if we analyse the currently available data for standard first-line combination therapy regimens plus a biological, in those studies where resection rates have been reported, the suggestion from non-randomised studies[21–23,25,26] and the one randomised study of 5-FU/FA (IFL) ± bevacizumab,[24] is that the use of targeted therapies increases the RR by at least 10%. However, to date, there is no evidence that this translates into significantly increased resection rates (Table 1).[21–26,41] Currently, the only targeted agent approved first-line for the treatment of mCRC is bevacizumab, but it is not associated with high resectability (see Table 1).[24,25] In addition, there are concerns, due to the potential risks during surgery, associated with bevacizumab treatment. The recommendation is therefore, that patients should wait at least 6–8 weeks from the time of the last dose of bevacizumab before elective liver resection.[42] Although recent evidence suggests that a 5-week rest from bevacizumab therapy may be sufficient.[43]

In fact, one of the highest resection rates to date (33%) comes from a recent, prospective, phase II study of irinotecan/5-FU/FA (FOLFIRI) in a selected patient population in which the criteria for unresectability were clearly defined.[44] This translated into a median overall survival of 30.1 months with a median survival in unresected patients of 24 months, while the median survival in resected patients has not yet been reached.[44,45] Comparison of the post-operative and long-term results of FOLFIRI therapy in patients with initially unresectable liver metastases, with those of patients with initially resectable metastases, showed that about one-third of patients (35.7%) were eligible for curative resection following FOLFIRI therapy. In these patients, median survival (46 months) did not differ from that for those patients who were initially resectable (47 months) and, although DFS was lower and recurrence more frequent, re-resection showed itself to be a valid treatment option.[46] However, if we compare this with another prospective phase II study, this time of oxaliplatin/5-FU/FA (FOLFOX4) in a selected patient population, the observed 40% resection rate[33] only yielded a median survival of 26 months. Furthermore, after 22 months of follow-up, 73% of resected patients had a recurrence and the 2-year survival was 18%.[33]

So, increasing the resectability rate might not be the only answer? Certainly consistent with the observations above, Adam and colleagues[33] have reported that following an average of 10 cycles of chemotherapy with 5-FU/FA (12%) ± irinotecan (7%) or oxaliplatin (70%) or both (4%), 138 good responders out of 1104 CRC patients (12.5%) with initially unresectable liver metastases, underwent liver resection. However, after a mean follow-up of 49 months 80% of patients (111) had disease recurrence with evidence that over 50% (71) of the 138 resectable patients had disease that had spread beyond the liver at the time of their liver resection.[47] One might hope that targeted therapies would be more effective than chemotherapy alone at suppressing the micrometastases responsible for reports of rapid recurrence. This is supported in part by the emerging long-term survivals in phase II studies of ~30 months from first-line combinations involving cetuximab.[20,21] However, despite some of the high RRs achieved for targeted agents in combination with the standard cytotoxic regimens used in the first-line treatment of CRC it is clearly too early to establish whether targeted therapies significantly increase resection rates (Table 1).

There is also emerging evidence that the triple-drug combination 5-FU/FA /irinotecan/oxaliplatin (FOLFOXIRI) is achieving high response rates and high resection rates in selected patients with liver only metastases (Table 1).[27–29,48] The three-drug combination has been shown to exhibit a high efficacy without a significant impact on safety.[27] In a randomised study[28] the FOLFOXIRI regimen, although moderately more toxic than FOLFIRI, was shown not only to be feasible but also to be a very manageable combination. Response rate, prevention of early progression, progression-free survival, and radical surgical resection of CRC liver metastases were all significantly better following FOLFOXIRI combination therapy than they were following FOLFIRI. The quality of life (QoL) was also similar between patients receiving FOLFIRI and FOLFOXIRI. Overall survival, although it was not the primary endpoint of the study, also seemed to be substantially improved for those patients receiving FOLFOXIRI.[28] It remains however unclear whether unselected patients really benefit from the triple cytotoxic combination. A Greek study comparing FOLFIRI with FOLFOXIRI did not show a benefit for the triple combination of cytotoxics.[49] It might well be that the triplet of cytotoxics is especially suited for the treatment of patients with initially unresectable liver metastases with the aim of rendering their metastases resectable. Whether the combination of three cytotoxics or two cytotoxics plus a biological is the preferred option in this setting remains unclear.

Recently it has also been suggested that patients with initially resectable liver metastases may also benefit from preoperative chemotherapy.[50,51] Certainly, peri-operative chemotherapy was shown to increase the 3-year PFS of resected patients by 9.2% compared with surgery alone in the EORTC 40983 trial.[52]

Finally, since the aim of neoadjuvant chemotherapy plus surgery is cure, the side effects of chemotherapy and the resultant relatively short-term infringement of their quality of life are often perceived by patients to be minor when balanced against the increased hope of cure.

## 6. Monitoring patients during neoadjuvant therapy

The monitoring of patients during neoadjuvant therapy was identified as a major challenge, bearing in mind the limitations of spiral CT and ultrasound scans. From the surgeon's point of view a complete response is undesirable as they

can no longer locate tumors for resection, and there is already evidence from one study that 83% of patients (55 out of 66), assessed to be disease-free by CT scan, had either persistent disease or early recurrence.[53] FDG-PET scanning has been shown to detect unsuspected tumor in 25% of patients considered to have resectable hepatic metastasis by conventional staging, resulting in an improved 5-year survival (58% at 5 years) for patients undergoing hepatic resection.[54] Contrast ultrasound plus microbubbles and enhanced MRI might also represent alternative imaging techniques with high sensitivities. Thus, going forward the ECMTG recommendations for the more accurate selection of resectable patients following neoadjuvant chemotherapy are firstly that an initial screening with spiral CT, FDG-PET and PET/CT, if available, can contribute to the optimal selection of patients for resection. MRI can be useful in situations where there is some measure of doubt. It is important to avoid patients undergoing unnecessary laparotomies, and the incidence is decreasing as imaging techniques improve. In cases where metastatic sites have 'disappeared', these regions should be surgically removed, when feasible, to minimise recurrence, since the evidence suggests that for most patients a complete response on CT scan does not mean cure.[53]

## 7. Effects of chemotherapy on liver

Increasingly, concerns are being raised about the effects of long-term neoadjuvant therapy on the liver, especially chemotherapy-induced steatohepatitis (CASH).[34,55–58] However, this appears to be particularly related to obese patients.[55] A recent analysis of 45 patients who received preoperative, neoadjuvant chemotherapy and 22 who did not receive any chemotherapy prior to resection for colorectal liver metastases showed that although prolonged neoadjuvant chemotherapy changed the liver parenchyma and increased post-operative morbidity (38% vs. 13.5% [$p = 0.003$]), it did not increase post-operative mortality.[59] Furthermore, postoperative morbidity was correlated with the number of cycles of chemotherapy, but not the type of chemotherapy.[59] It is felt, however, amongst the experts, that the liver changes were on the whole not a major issue and that the benefits of liver resection far outweighed the disadvantages of liver changes. Trials and retrospective analyses are ongoing which will hopefully shed more light on this issue. However, the feeling of the ECMTG was that if patients were not overtreated with chemotherapy, there was little evidence of increased mortality or morbidity due to liver damage. In the future, more accurate measurement of steatohepatitis, using for example non-contrast CT scans, will be required.

## 8. Treatment of synchronous metastases

CRC liver metastases may present synchronously with the primary tumour or at a different (later) time (metachronous). Although only approximately 20% of patients present with synchronous metastases and only 15% of these are potentially resectable (accounting for approximately 3% of patients overall), these patients now have a better chance of long-term survival. Today, the question is one of timing of the surgical removal of the primary and the administration of adjuvant/neoadjuvant chemotherapy or the immediate resection of the corresponding liver metastases. Namely, should first-line resection of synchronous resectable metastases from a colonic primary be delayed for chemotherapy? Should resection of the primary and the metastasis(es) be carried out simultaneously or sequentially with resection of the metastasis or metastases delayed? The role of interval chemotherapy then has to be considered.

The general rule for CRC patients with unresectable metastases is to resect the primary if it is symptomatic, but to treat with chemotherapy initially if the primary is essentially asymptomatic. For patients with rectal primaries and unresectable metastases, again the recommendations are broadly the same, but to treat with chemoradiation or chemotherapy alone if the primary is asymptomatic. Delaying surgery in both these settings allows the rate of disease progression to be monitored, while the administration of chemotherapy provides an insight into the responsiveness of the tumour and, if the patient is chemosensitive, some protection from progression of their disease. A retrospective analysis of patients operated on for synchronous metastases showed that the 5-year survival for patients who received preoperative (neoadjuvant) 5-FU/FA therapy was superior to that of those patients who received no preoperative treatment (43% vs. 35%).[60] More significantly, however, the study reported 50% objective responses with those patients who did not progress on therapy experiencing a significantly improved 5-year survival [85% vs. 35%; ($p = 0.03$)].[60] Another prospective study in 20 patients with non-obstructive colorectal tumours involving chemotherapy with 5-FU/FA plus irinotecan or oxaliplatin followed by resection of the liver metastases and finally removal of the primary, resulted in overall survival rates at 1, 2, 3 and 4 years of 85%, 79%, 71% and 56% with a median survival of 46 months.[61] Sixteen out of the 20 patients had R0 resections.[61]

## 9. The consensus and position statement

1. The ECMTG propose that resectability should always be considered either directly or after neoadjuvant chemotherapy except when:
   - Less than 30% of the liver would remain post-surgery even after portal vein embolisation.
   - Involved coeliac lymph nodes are present or where there is evidence of disease outside of the liver or in the liver that cannot be cleared.
   - There is invasion of the two branches of the liver pedicle or of the inferior vena cava or invasion of the three hepatic veins.
2. The ECMTG recommend the continued development of a clear, simple and pragmatic new staging system.
3. Minimal patient work-up prior to any clinical intervention should include:
   - A spiral CT scan of the abdomen and thorax.
   - An FDG-PET or FDG-PET/CT scan; especially in patients with resectable and potentially resectable liver metastases if there is any doubt about the presence of extrahepatic disease.

4. RFS/PFS should be the primary end-point following preoperative neoadjuvant chemotherapy with resection rate a secondary end-point.
5. The most active regimen possible should be chosen in the neoadjuvant setting. The efficacy of three cytotoxic-containing (triple-drug) regimens needs to be compared with combinations of two cytotoxics plus a targeted agent (biologic) in this clinical setting.
6. Correlation between R0 resection and survival is needed.
7. In the case of synchronous metastases, the primary tumour must always be operated on if symptomatic, irrespective of the resectability of the metastases. If the primary is asymptomatic with resectable metastases chemotherapy might be considered but there are little available data. Standard practice remains to resect the primary and metastases together or resect the primary and the metastases in a stepwise fashion followed by adjuvant chemotherapy.

Overall, the message from the ECMTG is that liver metastases can be resected safely, provided that there is careful patient work-up, accurate staging, and if, in the case of patients receiving neoadjuvant chemotherapy, surgery is conducted as early as possible.

## Conflict of interest statement

None declared.

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