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Current Perspective

Towards a pan-European consensus on the treatment of patients with colorectal liver metastases

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ABSTRACT

Colorectal cancer (CRC) caused nearly 204,000 deaths in Europe in 2004. Despite recent advances in the treatment of advanced disease, which include the incorporation of two new cytotoxic agents irinotecan and oxaliplatin into first-line regimens, the concept of planned sequential therapy involving three active agents during the course of a patient's treatment and the integrated use of targeted monoclonal antibodies, the 5-year survival rates for patients with advanced CRC remain unacceptably low. For patients with colorectal liver metastases, liver resection offers the only potential for cure. This review, based on the outcomes of a meeting of European experts (surgeons and medical oncologists), considers the current treatment strategies available to patients with CRC liver metastases, the criteria for the selection of those patients most likely to benefit and suggests where future progress may occur.

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1. Introduction

Colorectal cancer (CRC) is fourth in the league of cancer deaths worldwide with nearly 204,000 deaths in Europe alone each year.[1] Approximately 25% of CRC patients present with overt metastases, and an additional 25–35% of patients will develop metastases during the course of their disease.[2] Significantly between 20% and 30% of patients with advanced CRC have liver only metastases,[3] while approximately 50% of recurrences following resection of the primary tumour are confined to the liver.[4]

Despite the recent advances in first-line chemotherapy strategies for the treatment of patients with advanced CRC,[5–9] liver resection offers the only chance of cure for patients with colorectal liver metastases.[10] Five-year survival rates following resection range between 25% and 40% compared with between 0% and 5% for patients from the same institute who did not undergo liver resection,[4,10–15] and are consistent with the 5-year survivals reported for most large series where liver resection has been performed.[16–19] However, approximately 85% of patients with stage IV CRC, referred to specialist centres, have metastatic liver disease which is considered to be unresectable at presentation.[20]

Over the last five years, there has been a recognition that the improved combination chemotherapy regimens, namely 5-fluorouracil/folinic acid (5-FU/FA) in combination with either irinotecan or oxaliplatin,[5–9] routinely used in the treatment of patients with advanced CRC, can facilitate the downsizing of colorectal liver metastases and render initially unresectable metastases resectable.[18,20–23] Consequently, the percentage of patients potentially eligible for curative liver resection is increasing. Significantly also, the long-term survival rates for those patients with initially unresectable metastases treated with chemotherapy prior to surgery[18] are similar to those of patients whose metastases were considered to be resectable (Fig. 1).[13,17,19,24] The results of a recent study, however, suggest that the recurrence rate may be quite high for these patients.[25]

However, despite these advances the selection criteria for the resection of CRC liver metastases are not well documented. Consequently, the possibility of resection of CRC liver metastases is often underestimated, and currently even

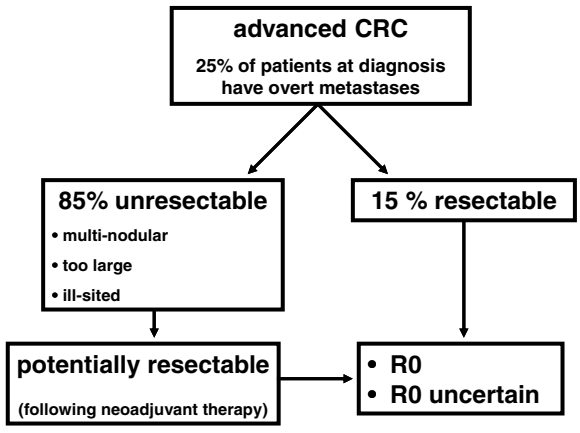

Fig. 1 – Treatment schema for patients with advanced CRC.

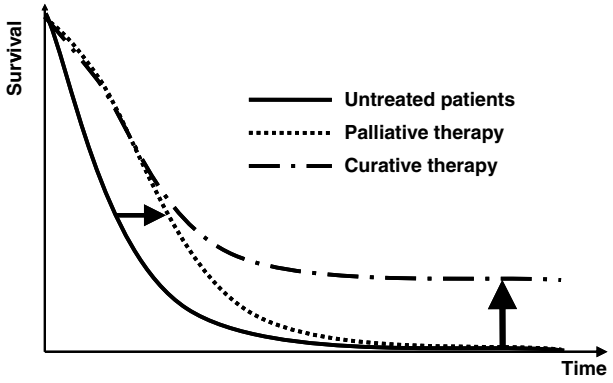

Fig. 2 – Effective curatively intentioned therapy displaces the survival curve in time, and also alters its shape, reflecting a degree of long-term survival (reproduced with the kind permission of Professor C.-H. Kohne).

in Europe, we have the situation where away from specialist centres, many patients with liver metastases are considered to be incurable and many patients with curable liver metastases are never referred to a surgeon.[26] Conversely, in centres that specialise in liver resection we can have the situation where some patients who are incurable undergo resection.

The goal of a multidisciplinary treatment approach in this context is to increase cost-effectively the number of patients with long-term survival by increasing the number of patients undergoing potentially curative liver resections (Fig. 2). The first question that we need to address is: 'How do we establish guidelines that will facilitate this process and that can be readily adopted by the surgeons and medical oncologists, across Europe, working both inside and outside of specialist centres?' Specifically, how do we prepare generally applicable guidelines to optimise the chances of survival of CRC patients with liver metastases?

2. Current status

Although there are several published clinical scoring systems,[15,19,24,27–30] the French recommendations for clinical practice with regard to the 'Therapeutic management of liver metastases from colorectal cancer' published in March 2003,[31] are by far the most comprehensive. Already in 2005–2006 we have moved on from the French recommendations,[31] in terms not only of what is considered to be surgically resectable disease but also in terms of the recognition of the potential efficacy of planned, preoperative (neoadjuvant) chemotherapy, in selected patients, in facilitating an increase in the number of patients who can undergo liver resection.[23]

Based on the considerable evidence that liver resection either alone or in conjunction with preoperative chemotherapy in selected patients offers a chance for long-term survival,[10,12,13,15,17–19] the aim of this review is to outline the new areas of consensus among European surgeons and medical oncologists in the treatment of patients with colorectal liver metastases, achieved at a meeting of the European Colorectal Metastases Treatment Group held in Paris, November 2005, and identify the emerging areas for discussion.

3. The role of surgery

Historically, surgical resection of CRC liver metastases has been the sole treatment modality to achieve long-term survival in patients with stage IV CRC, with approximately 25–40% of patients who undergo R_0 liver resection (*i.e.* rendered macroscopically disease free) alive at five years (Fig. 1).[13,19,30,32] However, only approximately 15% of patients with liver metastases are resectable at presentation (Fig. 1).

Until recently, the classic contraindications for resection of CRC liver metastases have been: ⩾4 metastases, disease outside the liver, metastatic nodes in the liver pedicule, a resection margin of <1 cm, the presence of co-morbid disease and an incomplete resection.[33,34] However, these limitations for resectability are changing.

Initially, based on the French Recommendations, four categories of resectability could be defined: (i) potentially resectable Class I, (ii) potentially resectable Class II, (iii) initially unresectable that may become resectable and (iv) definitely unresectable. However, the terms Class I and Class II[31] were only introduced to distinguish between those resectable metastases that were easy to resect and those that were more difficult to resect and therefore had a less certain outcome; with no evaluation made of long-term clinical outcome. Today, it is clear that European experts in the field consider that liver metastases should be classified quite simply as either resectable or unresectable, irrespective of how their resectable status has been arrived at.

In addition, advances in surgical techniques have increased the number of patients who can be considered candidates for liver resection, in terms of number of metastases (Fig. 3), resection margin, and the presence of disease outside of the liver.[11–13,19,24,33,35–38] The results of a recent retrospective multivariate analysis suggest that the total number of resectable metastases, inside or outside the liver, has a greater prognostic value than the location of the metastases.[39] Consequently, the presence of disease outside the liver should no longer be considered a strict contraindication for liver resection provided that the disease outside the liver is resectable.[39–41] Although, the number and size of metastases are important, when considering liver resection, it is the size of the liver remnant that is now considered critical. Preoperative portal vein embolisation which results in hypertrophy of the remaining liver can increase the normal liver reserve and facilitate extensive liver resections,[42,43] although the precise benefit is uncertain.

A margin of 1 cm or more between the cut section of the liver and the tumour has long been considered a prerequisite for resection. Then a 2 mm margin of resection was considered appropriate.[38] Experts now consider that resections should be performed whatever the margin, rather than no resection. Indeed in the opinion of the authors (European Colorectal Metastases Treatment Group), resection is only contraindicated when all the metastases cannot be cleared or in the presence of celiac lymph nodes and the presence of non-resectable disease at the outside of the liver. The group also acknowledged that regional ablative techniques such as cryotherapy[44] and radiofrequency ablation (RFA)[44–46] can be used in conjunction with conventional surgery for small poorly located lesions. However, it should be made clear that RFA cannot be considered equivalent to, and cannot substitute for, surgical resection.[47]

It was also proposed that there should be a new staging system for patients with stage IV CRC, which would allow stratification of patients from the outset as follows:

- Stage IVa: easily resectable liver metastases.
- Stage IVb: resectable liver metastases.
- Stage IVc: liver metastases that may become resectable after downsizing.
- Stage IVd: liver metastases that are unlikely to become resectable.
- Stage Va and b: resectable and unresectable disease, respectively, outside of the liver.

However, perhaps the most striking realisation was that not all patients with favourable prognostic indices appear to be suitable for liver resection. There is a clear recognition among experts that some patients with resectable metastases and favourable prognostic indices actually do extremely badly following resection (Fig. 4), and that clinical factors are not

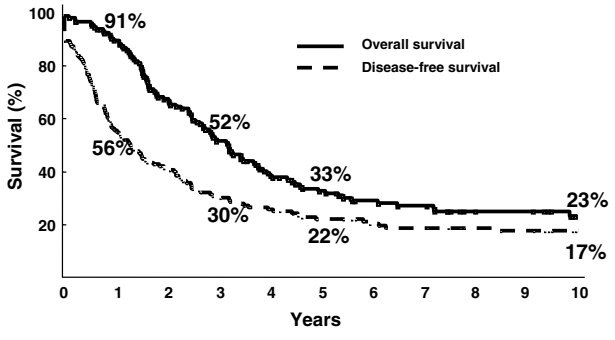

Fig. 3 – Survival after resection of unresectable colorectal liver metastases following systemic chemotherapy. Data for 138 patients (April 1988–July 1999). (Adapted from Adam *et al.*[30] and reproduced with the kind permission of Professor R. Adam.)

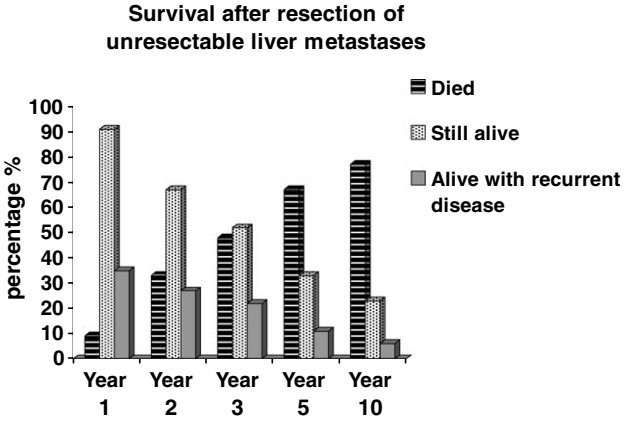

Fig. 4 – Patient outcome after resection of initially unresectable colorectal liver metastases. Data for 138 patients (1988–1999).[30]

always sufficient to predict patient outcome after resection. There is therefore an urgent need to develop indicators of the biology of the disease.

4. The role of perioperative chemotherapy

The use of perioperative chemotherapy in patients with liver only metastases is used in two clearly defined treatment settings. The first of these is in the preoperative, neoadjuvant setting to render initially unresectable metastases resectable and the second in either the adjuvant or neoadjuvant settings to reduce the risk of recurrence in patients with resectable metastases.

4.1. *Preoperative chemotherapy*

A retrospective study in France was the first to specifically address the possible role of preoperative, neoadjuvant chemotherapy in the treatment of CRC patients with unresectable metastases,[18] and reported a resection rate of 16% (53/330 patients) and a 5-year survival rate after resection of 40%.[16,18] Although, there were few reports of resection rates prior to the advent of the new first-line combination therapy regimens, the advances made in combination therapy, the advent of three-drug therapy (irinotecan/oxaliplatin/5-FU/FA)[48,49] and the use of new targeted therapies[50–52] have all led to improved first-line response rates and further reports of initially unresectable liver metastases being rendered resectable following chemotherapy. The majority of the available data for the use of preoperative chemotherapy still come from retrospective studies. However, a recent analysis of all published and presented trials and retrospective studies that have reported objective response rates and rates of resection of initially unresectable liver metastases has demonstrated a strong correlation between response rate (RR) and resection rate in selected patients with isolated liver metastases.[23]

This analysis showed both RR and preoperative chemotherapy to be strong predictors of resectability for CRC liver metastases in selected patients, *i.e.* those patients with no metastases at the outside of the liver (Fig. 5).[23] The authors argued that the correlation between RR and resection rate was essentially what one might predict as a response to chemotherapy is almost a prerequisite of liver resection. Such a correlation supports a treatment approach that uses the most active regimen particularly in potentially curable (*i.e.* selected) patients.[23] The resection rates for recent studies in selected patients with isolated liver metastases are summarised in Table 1.

However, the correlation between tumour response and resection in the selected patients[23] was based on only a few studies[21,25,53–56] in only three of which[25,54,55] resection was chosen as the primary endpoint. The correlation between tumour response and resection in non-selected patients was based on data from a large number of studies and over 2900 patients.[23] Thus, the correlation although less strong was highly significant ($P < 0.001$). However, the interpretation of the data for both patient populations may have been influenced by access to liver surgery, differences in the definitions of resectability between the different studies and an absence of clear reporting of the quality (*i.e.* R_0/R_1) of the resections carried out.

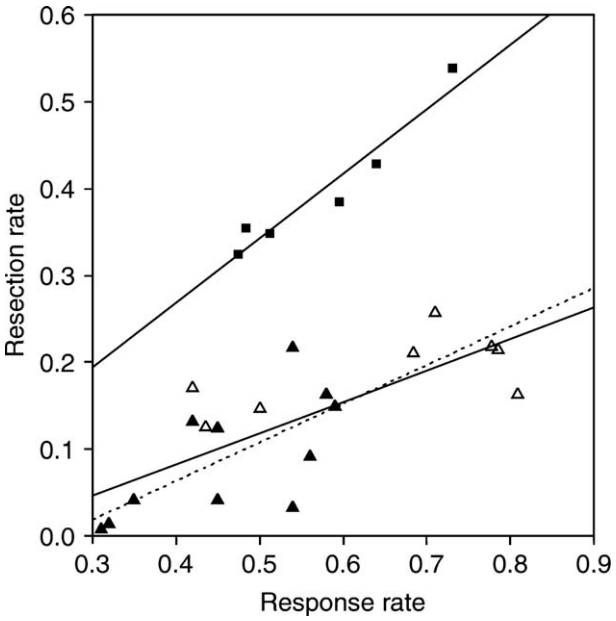

Fig. 5 – The rate of liver resection following chemotherapy plotted against response rate.[23] Squares represent patients in studies/retrospective analyses with non-resectable metastases confined to the liver: $r = 0.96$, $P = 0.002$). Studies with non-selected patients with colorectal cancer are shown as triangles.

Table 1 – A comparison of response and resection rates in selected patients (no extra-hepatic disease) with initially non-resectable liver metastases

Regimen	*N*	Response rate (%)	Resection (R_0 and R_1) (%)	Reference
FOLFOX	43	51	40	Alberts *et al.*[25]
FOLFIRI	40	48	33	Pozzo *et al.*[54]
FOLFIRI (+HAI)	31	48	35	Zelek *et al.*[56]
FOLFIRI	28	54	11	Ho *et al.*[89]
FOLFOXIRI	21	64	43	de la Camara *et al.*[53]
FOLFOXIRI	26	73	54	Quenet *et al.*[55]

There is, therefore, an urgent need for carefully planned, prospective trials that specifically investigate the role of preoperative chemotherapy in the treatment of patients with initially unresectable liver metastases, starting with clearly defined criteria for resectability and clear reporting of the number of patients who undergo R_0 resection *versus* R_1 or R_2 resection. A prospective single-centre trial of neoadjuvant irinotecan/5-FU/FA therapy in selected patients, with clearly defined criteria of unresectability, achieved an RR of 48% and a liver resection rate of 33%.[54] A recent prospective multicentre trial of the efficacy of FOLFOX4 in patients with liver-only CRC metastases, deemed not to be optimally resectable using predefined criteria for unresectability, reported 25 out of 42 eligible patients to have experienced a reduction in their

tumour burden, after a median of 10 cycles of treatment.[25] Of these, 17 (40%) went on to have surgery, 14 of whom (33%) underwent R_0 resections.[25] Although the 3-year survival rate was 71%, the recurrence rate was also high (71%) for those patients undergoing R_0 resection.[25] In another prospective study, of irinotecan, oxaliplatin and 5-FU/FA in 26 patients with unresectable liver metastases, with clearly defined criteria of unresectability, an RR of 73% and an R_0 resection rate of 34.6% were achieved.[55] Thus, neoadjuvant chemotherapy for the treatment of liver metastases has the potential to render initially unresectable metastases resectable, increase the number of complete R_0 resections, facilitate sparing of the liver parenchyma, and presumably minimise micrometastatic disease. It may also provide a measure of tumour responsiveness facilitating the optimisation of postoperative chemotherapy.

The role of preoperative chemotherapy in the case of resectable metastases is essentially unknown and the question is 'Should surgery be delayed for this?' especially as concerns have been raised regarding the effects of chemotherapy on the liver particularly in the case of oxaliplatin.[57,58] In the randomised EORTC 40983 trial of pre and postoperative FOLFOX4 chemotherapy *versus* surgery alone in patients with resectable liver metastases, surgery was performed within the planned timelines (median 114 d) in those patients randomised to receive preoperative chemotherapy.[59] Complete R_0 resections were achieved in 96.7% and 88.5% of operated patients in the chemotherapy and surgery alone arms, respectively, and the surgical morbidity and mortality rates were low.

The data for the influence of preoperative chemotherapy on the survival of these patients with potentially resectable liver metastases are not yet available, but are eagerly awaited. However, in a separate study, Adam *et al*. demonstrated that response to preoperative therapy is predictive of long-term outcome.[60]

So, what is the optimal chemotherapy regimen and method of delivery for downsizing potentially resectable metastases? Infusional, systemic 5-FU/FA in combination with either irinotecan or oxaliplatin achieves high and similar response rates and facilitates resection.[21–23,54] As stated previously, a few small studies have reported high response and resection rates with the combinations of the three cytotoxic agents, but with increased[48,49,53,55] and manageable[55] toxicity. A randomised comparative trial of triple-drug oxaliplatin/irinotecan/5-FU/FA (FOLFOXIRI) versus two-drug irinotecan/5-FU/FA (FOLFIRI) therapy in this setting achieved RRs of 66% and 41% ($P = 0.0002$) and R_0 resection rates of 15% and 6%, respectively, with an acceptable toxicity profile for the triple-drug combination.[49]

In a few small studies the approach of combination chemotherapy administered systematically and intrahepatically is being evaluated in patients with unresectable liver metastases. There is currently no evidence of a survival advantage for regional over systemic combination chemotherapy, although a few studies have reported a survival advantage for regional chemotherapy when compared to intravenous 5-FU.[61–64] A phase I trial of systemic oxaliplatin combination therapy together with regional hepatic arterial infusion (HAI) chemotherapy of floxuridine and dexamethasone in patients with unresectable liver metastases previously treated with chemotherapy has reported an extremely high response rate.[65] In a French study, oxaliplatin was administered intra-arterially, together with intravenous 5-FU/FA, and achieved higher response rates than in the pivotal combination therapy trials.[66] Similarly high response rates were observed for triple-drug therapy delivered intra-arterially in heavily pretreated patients.[67] However, these approaches have to be evaluated in larger multicentre studies. Achieving a high response rate is not the primary goal of palliative therapy. Patients who have multiple organ metastases that are unlikely to become resectable should ideally be treated with palliative therapies that prolong progression-free and overall survival with the minimum of toxicity while maintaining quality of life. While patients who have metastases that may be rendered resectable by chemotherapy should be preferentially treated with a chemotherapy regimen that achieves a high tumour response rate. A major consideration when discussing the use of the most active regimen in the treatment of patients with the potential for liver resection following downsizing of their tumour is that the surgeons do not need, and indeed do not want, a patient to reach the stage of achieving a complete response prior to resection. A complete response makes it difficult for the surgeon to identify where the resection margins should be. It is highly likely however that the regimens for the two patient categories will be the same or in large part the same, except for considerations given to patient tolerability.

There is a clear need to identify which patients will respond to which preoperative therapies and to exclude from particular treatments those that might experience severe toxicity. In the future, pharmacogenetic analyses may help to predict the likelihood of response and toxicity for 5-FU, irinotecan and oxaliplatin. Low levels of thymidylate synthetase, encoded by the TYMS gene,[68,69] and dihydropyrimidine dehydrogenase, encoded by the DPYD gene (coupled with low levels of thymidine phosphorylase), predict good response and survival[70] to 5-FU/FA. However, low levels of DPYD expression have also been correlated with severe 5-FU toxicity.[71,72] TYMS promoter polymorphism status has also been shown to predict 5-FU toxicity.[72] CDKN1A (p21), BCL2 and ICE gene expression levels may predict response to irinotecan along with microsatellite instability.[73,74] UGT1A1 polymorphism is predictive of irinotecan toxicity.[71,75] In the case of oxaliplatin, particular polymorphisms: XPD-751, GSTP1-105, and ERRC1-118 may predict survival, [73,76] and a reduced Fas/Fas ligand ratio is predictive of intrinsic and acquired oxaliplatin resistance.[77] Age however is not an issue for patients with good performance status as demonstrated by data from retrospective analyses.[78,79] Physiological age is clearly more important than chronological age. The results of prospective studies are eagerly awaited.[80]

4.2. *Postoperative adjuvant therapy*

The aim of postoperative adjuvant therapy is to reduce the risk of recurrence, and postoperative adjuvant chemotherapy is an accepted component of treatment for those patients who receive preoperative chemotherapy to render their CRC liver metastases resectable. Even patients with initially resectable liver metastases can be expected to benefit from adjuvant

therapy in much the same way as patients undergoing resection of their primary colorectal tumour. The rationale behind the use of postoperative adjuvant chemotherapy following liver resection is the high failure rate observed with surgery alone, coupled with the fact that prospective studies of adjuvant therapy show a trend towards increased survival.[81–83]

Adjuvant therapy can be delivered either systemically, intra-arterially or by both routes. However, currently, there is no clear evidence that delivery by HAI is vastly superior to systemic therapy. There are two trials of adjuvant systemic 5-FU/FA compared to surgery alone after resection of liver metastases.[81,84] Both trials were closed prematurely because of poor accrual. Both showed a trend for improved disease-free and overall survival associated with adjuvant treatment, but these differences were not significant probably because of low patient numbers. A meta-analysis of these data are currently underway. The FFCD adjuvant trial randomised 167 patients to either chemotherapy (5-FU/FA) or observation following surgery. The results suggested an advantage in terms of the 5-year disease-free survival rate (33% *versus* 24%) for those patients who received chemotherapy. The advantage was also maintained for 5-year overall survival but it was less marked (51% *versus* 44%).[81] The EORTC NCIC, GIVIO trial randomised 129 patients, following resection of their liver metastases, between postoperative intravenous 5-FU/FA and surgery alone and reported, respectively, a 4-year disease-free survival of 45 % *versus* 35% and a 4-year overall survival of 57% *versus* 47% (not statistically significant).[84]

No benefit has been shown for 5-FU/FA delivered via HAI over surgery alone ($n = 226$).[85] In another smaller study, however, HAI fluorodeoxyuridine (FUdR) plus systemic 5-FU was shown to be superior to surgery alone ($n = 109$) in terms of 4-year disease-free survival (46% *versus* 25%, [$P = 0.04$]).[86] While HAI FUdR plus systemic chemotherapy improved the 2-year survival rate over systemic chemotherapy alone, the difference at five years was not statistically significant.[87] Unfortunately, to date, most of the trials in this treatment setting have been inconclusive because of the low numbers of evaluable patients as a consequence of both methodological and technical complications associated with the method of delivery. Also, the problems of feasibility, toxicity and cost make it difficult to propose HAI as a standard regimen in Europe.

5. Conclusions

This meeting of the European Colorectal Metastases Treatment Group provided clear evidence that the field of liver resection for CRC liver metastases is progressing rapidly and that an ever-increasing number of patients can either be considered, or rendered eligible, for liver resection. However, there was also the recognition that despite this progress many patients with metastases are considered to be incurable and are not recommended for surgery. There needs therefore to be an insistence on a multidisciplinary approach to the treatment of these patients with an improved appraisal of their status and improved workup.

Within the European Colorectal Metastases Treatment Group there was an agreement (Table 2) that surgical techniques now allow resection right up to the tumour margin. Also, that there is no longer a need for the surgeon to consider four categories of metastases. Metastases can be classified as either resectable or unresectable. In fact, the consensus was to look at the introduction of a new staging system for stage IV CRC to allow clear stratification of patients prior to treatment.

However, for trials designed to assess the conversion of initially unresectable metastases to the status of resectability, a clear definition of initial unresectability is critical. There was full agreement that liver surgery is contraindicated when less than 30% of the liver would remain post surgery. Otherwise, resection should always be considered except in patients where involved coeliac lymph nodes are present or where there is evidence of disease outside of the liver, or the liver deposits cannot be cleared. Other criteria for unresectability are invasion of one branch of the liver pedicle and contact with the contra-lateral branch, contact with the inferior vena cava and invasion of the three hepatic veins.

There was also the clear recognition that there is a need to improve preoperative workup to minimise the number of

Table 2 – Summary of consensus recommendations on the treatment of patients with CRC liver metastases and identification of issues to be resolved at the next meeting

Consensus recommendations	Issues for the future
1. Multidisciplinary teams are essential. No patient should be operated on without multidisciplinary team discussion	1. Definition of new staging system
2. Surgical resection should be considered wherever possible.	2. Resectability as a new clinical endpoint
3. Improved preoperative workup required: High quality CAT scan/FDG-PET	3. The role of chemotherapy in the treatment of synchronous metastases
4. Clear definition of unresectability established	4. The role of chemotherapy (pre- and/or postoperatively) in the treatment of resectable liver metastases
5. Surgical resection can take place right up to the margin	5. Determination of whether or not combining cytotoxic chemotherapy with targeted therapies will increase the number of patients eligible for resection
6. Need to develop new staging system to stratify patients from the start of treatment: Stages IV a–d Stages V a and b	6. Development of markers for tumour biology and genetic modifiers of response/toxicity and integration of pharmacogenetic discriminators into clinical trial protocols

patients who are operated on unnecessarily. This can be accomplished by increased use of high-quality computed axial tomography (CAT) scans of the abdomen and chest and also, if possible, through the use of fluorodeoxyglucose-positron emission tomography (FDG-PET).[88] It was also recognised that there is a need for preoperative monitoring during chemotherapy to avoid eliciting a complete tumour response, which would make the task of the surgeon more difficult.

Thus, while it is clear that active neoadjuvant chemotherapy can shift patients with colorectal liver metastases from the category of non-curable to one where there is the potential for cure, there remain many challenges for the treatment of these patients in the future. Firstly, CRC is clearly not a single disease, with uniform mechanistic causes. There is therefore a need to develop markers of tumour biology to facilitate the identification of not only those patients with highly-aggressive tumours who fail on standard chemotherapy, but also those who fail rapidly after potentially curative liver resection (Fig. 4). In addition, essential steps forward are the development of the proposed new staging system, the preparation of clear guidelines for essential workup and surveillance practices, the resolution of the issues surrounding the choice of resectability as a new clinical endpoint in the treatment of stage IV CRC patients and the integration of the analysis of disease markers and predictors of response into clinical trial protocols (Table 2).

The critical message however is that no patient with advanced CRC should be operated on for liver metastases without a multidisciplinary team discussion. The recognition that a subset of patients with initially unresectable liver disease can now be rendered eligible for resection requires increased flexibility in our thinking, particularly with regard to the management of those patients treated initially with palliative intent. Surgeons clearly think in terms of cure and macroscopic clearance of disease, whereas the medical oncologist tends to think in packages of benefit. Going into the future, this difference in thinking raises the question of 'what is a meaningful endpoint for trials of preoperative therapy?'.

Conflict of interest statement

None declared.

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