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ABSTRACT

An international panel of multidisciplinary experts convened to develop recommendations for the management of patients with liver metastases from colorectal cancer (CRC). The aim was to address the main issues facing the CRC hepatobiliary multidisciplinary team (MDT) when managing such patients and to standardize the treatment

patients receive in different centers. Based on current evidence, the group agreed on a number of issues including the following: (a) the primary aim of treatment is achieving a long disease-free survival (DFS) interval following resection; (b) assessment of resectability should be performed with high-quality cross-sectional imaging, staging the liver with magnetic resonance imaging and/or abdominal computed tomography (CT), depending on local expertise, staging extrahepatic disease with thoracic and pelvic CT, and, in selected cases, fluorodeoxyglucose positron emission tomography with ultrasound (preferably contrast-enhanced ultrasound) for intraoperative staging; (c) optimal first-line chemotherapy—doublet or triplet chemotherapy regimens combined with targeted therapy—is advisable in potentially resectable patients; (d) in this situation, at least four courses of first-line chemotherapy should be given, with assessment of tumor response every 2 months; (e) response assessed by the Response Evaluation Criteria in Solid Tumors (conventional chemotherapy) or nonsize-based morphological changes (antiangiogenic agents) is clearly correlated with outcome; no imaging technique is currently able to accurately diagnose complete pathological response but high-quality imaging is crucial for patient management; (f) the duration of chemotherapy should be as short as possible and resection achieved as soon as technically possible in the absence of tumor progression; (g) the number of metastases or patient age should not be an absolute contraindication to surgery combined with chemotherapy; (h) for synchronous metastases, it is not advisable to undertake major hepatic surgery during surgery for removal of the primary CRC; the reverse surgical approach (liver first) produces as good an outcome as the conventional approach in selected cases; (i) for patients with resectable liver metastases from CRC, perioperative chemotherapy may be associated with a modestly better DFS outcome; and (j) whether initially resectable or unresectable, cure or at least a long survival duration is possible after complete resection of the metastases, and MDT treatment is essential for improving clinical and survival outcomes. The group proposed a new system to classify initial unresectability based on technical and oncological contraindications. *The Oncologist* 2012;17: 1225–1239

INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer death in the world [1]. In 2008, >1.2 million new cases were recorded worldwide, with estimated age-standardized incidence and mortality rates, respectively, of 29.6% and 12.4% in Europe, 29.2% and 8.8% in the U.S., and 12.9% and 6.6% in Asia [1]. In some countries, the mortality rate from CRC is continuing to rise [1]. In Asia, many countries, including China, Japan, South Korea, and Singapore, have experienced a two- to fourfold increase in the incidence of CRC in the past couple of decades [2]. In many European Union countries, however, there has been a slight decrease in mortality from CRC [1], probably related to the introduction of screening programs but possibly also influenced by the greater efficacy of treatment and higher resection rates. In the U.K., following the introduction of screening, detection of stage I and II CRC increased compared with stage III/IV disease in the unscreened population. It is estimated that screening may reduce mortality from CRC by 40% and will also have the benefit of reducing treatment costs. Not all countries, however, currently have screening programs.

About 25% of patients present with stage IV CRC (synchronous metastases) and ∼50% of patients overall develop liver metastases. About 85% of patients with stage IV CRC have liver disease considered unresectable at presentation [3–5]. The 10-year survival rate for patients with stage I disease is ∼90%, but for patients with inoperable stage IV disease, it is currently only ∼5% [4]. For patients with liver metastases, the treatment strategy should be directed toward resectability [6]. A need has been recognized for a new staging system that acknowledges the improvements in surgical techniques for resectable metastases and the impact of modern chemotherapy on rendering initially unresectable liver metastases from CRC resectable while distinguishing between patients with a chance for cure at presentation and those for whom only palliative treatment is possible [5].

An international group of experts in managing liver metastases from CRC convened to discuss strategies to optimize treatment outcomes. The aims of this meeting were to address certain management issues that are currently under debate and to reach a consensus on the contraindications to initial liver resection so that patients presenting with such disease may be offered a similar standard of treatment wherever they are treated.

METHODS

The international consensus panel from the U.S., Europe, and Asia comprised one coordinator, five medical oncologists (including two hepatogastroenterologists), five hepatic surgeons, three radiologists, and a pathologist, with experience in the management of liver metastases from CRC. The coordinator selected the experts based on their experience. All important items related to multidisciplinary team (MDT) management of liver metastases from CRC were selected prior to the meeting by the coordinator and referred to an expert for presentation at the meeting. Meta-analyses, randomized controlled trials, and studies evaluating clinical practice in the management of liver metastases from CRC were identified and reviewed before and discussed during the meeting. After discussion, specific controversial issues were submitted to a vote of each expert to reflect the state of consensus. Recommendations were formulated when approved by all or a large majority of the panel members (Table 1). The strength of the recommendations was attributed based on the Strength of Recommendation Taxonomy [7]. The meeting was supported by Serono Symposia International Foundation, Rome, Italy.

Table 1. Questions about liver metastases from colorectal cancer addressed by the panel and recommendations from the discussions

Question	Subquestion	Recommendation	Strength of recommendation[a]
Should the prospect of surgery influence the choice of first-line chemotherapy?	Should the response to second-line chemotherapy be optimal before surgery is performed?	(1) The primary aim of treatment is resectability with R0 resection	A
	When should targeted therapies be used?	(2) Assessment of resectability should include liver MRI, abdominal and thoracic CT, and FDG-PET for preoperative imaging and US or preferably CEUS for intraoperative staging	B
		(3) Optimized first-line chemotherapy is advisable in potentially resectable patients	B
		(4) The use of doublet or triplet chemotherapy regimens combined with targeted therapy are most likely to induce maximum tumor shrinkage	B
Is there a minimum number of chemotherapy cycles before surgery and after what length of time should tumor response be assessed?		(5) When there is potential for resectability, at least four courses of first-line chemotherapy should be given, tumor response should be assessed every 2 months after starting chemotherapy; response is clearly correlated with outcome	B
		(6) The RECIST are the standard means to evaluate response to conventional chemotherapy, but for assessing response to antiangiogenic agents nonsized-based morphological changes correlate better with pathological response and survival outcomes than the RECIST; no imaging technique is currently able to accurately diagnose complete pathological response	B
		(7) Duration of chemotherapy should be as short as possible and resection achieved as soon as technically possible in the absence of tumor progression	B
Is there a maximum number of metastases for achieving potentially curative surgery?		(8) A large number of metastases or the age of the patient should not be an absolute contraindication to surgery combined with chemotherapy	C
How should potentially resectable synchronous metastases be managed?	Chemotherapy or surgery first? One- or two-stage surgical procedures? Is liver surgery first a valid approach?	(9) For synchronous metastases, major hepatic surgery during surgery for the primary CRC is controversial; the reverse surgical approach (liver first) produces as good an outcome as the conventional approach in selected cases	C
What is the recommended action to be taken when there is a complete clinical response (no metastases)?	Should resection be performed after chemotherapy or wait for appearance of metastases? Should chemotherapy be stopped or continued?	(10) Resection is best performed on the basis of the site of metastasis on the prechemotherapy CT or MRI scan; as an alternative, when disappearing metastases are deep and undetectable, even intraoperatively, a wait-and-see policy may be employed; the decision will depend on the initial extent of disease	B
Others		(11) For patients with resectable liver metastases from CRC, perioperative chemotherapy is associated with a better survival outcome	A
		(12) Whether initially resectable or unresectable, cure is possible after complete resection of the metastases	A
		(13) Multidisciplinary treatment is essential for improving clinical and survival outcomes	B

[a]Attributed based on the Strength of Recommendation Taxonomy [7]: A, recommendation based on consistent and good-quality patient-oriented evidence; B, recommendation based on inconsistent or limited-quality patient-oriented evidence; C, recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention or screening.
Abbreviations: CEUS, contrast-enhanced ultrasound; CRC, colorectal cancer; CT, computed tomography; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid Tumors; US, ultrasound.

ROLE OF IMAGING IN THE DIAGNOSIS OF LIVER METASTASES

In the management of liver metastases from CRC, imaging is used to detect and characterize liver lesions, to aid surgical decision making, and to help choose the best treatment option. Practice varies among institutions, but evidence suggests that the best methods for detection of liver metastases from CRC are computed tomography (CT) and magnetic resonance imaging (MRI) [8–10]. However, many teams alternate liver ultrasonography (US) and CT for detection to decrease irradiation resulting from repeated CT. A meta-analysis of 39 articles (3,391 patients) published in 2010 comparing CT, MRI, and ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) showed sensitivity estimates of 74.4%, 80.3%, and 81.4%, respectively, on a per lesion basis, and 83.6%, 88.2%, and 94.1%, respectively, on a per patient basis [9]. Data on FDG-PET–CT were too limited for comparison with other modalities. For lesions <10 mm, MRI was a more sensitive modality than CT. Similar results were reported in another meta-analysis published in 2010, which showed that MRI had better sensitivity than CT both in per patient (81.1% versus 74.8%; $p = .05$) and in per lesion (86.3% versus 82.6%; $p < .0001$) analyses [8]. However, these conclusions should be subject to caution because, as a result of the stringent inclusion criteria, only a few studies were derived from a large body of work. Many of the articles cited either did not indicate the CT technique or used suboptimal parameters. In general, meta-analyses reflect average practices and not state-of-the-art techniques; consequently, many of the technical parameters of the cited studies have been superseded.

For characterization of focal liver lesions, CT, contrast-enhanced ultrasound (CEUS), and MRI can be used [11]. MRI is the best technique for characterizing lesions and is often used as a means of additional imaging assessment. The serial change in liver lesions after neoadjuvant chemotherapy is also a very helpful means of tumor characterization. Resectability is dependent on multiple factors, including the number and location of metastases, volume of the future liver remnant (FLR), and quality of the nontumoral liver. All lesions identified on the prechemotherapy scan need to be accounted for on the presurgical scan to limit the risk for missed metastases. It is recognized that chemotherapy can induce toxic injury to the liver, primarily steatohepatitis and sinusoidal injury. Noncontrast CT and MRI may be used to assess steatosis [12–14], but steatohepatitis cannot be diagnosed with imaging. Sinusoidal injury can be judged by indirect signs of portal hypertension, particularly spleen size [15], or by using the liver-specific MRI contrast agent gadoxetic acid [16].

Complete resection is possible if liver vascularity can be preserved, the FLR is adequate with reference to body weight and total liver volume, and the quality of the remnant liver parenchyma is acceptable [17]. MRI and high-quality CT can be used for preoperative imaging; the choice of modality is dependent on the precise point in the clinical pathway and local expertise. US is indicated for intraoperative assessment of resectability [18]. When used intraoperatively, CEUS has been shown to reveal more lesions than conventional US [18], and

was significantly more sensitive ($p < .05$) than CT and/or MRI and conventional US in detecting liver metastases [19].

For the detection of extrahepatic metastases and local recurrence at the site of the initial colorectal surgery, CT and FDG-PET are available. Whereas high-quality CT can detect the majority of extrahepatic disease, FDG-PET may reveal additional disease or high metabolic activity of concern in indeterminate lesions. Initial studies showed a change in management in 10%–20% of patients following FDG-PET [20–23], whereas a recent prospective randomized trial evaluating high-quality CT and FDG-PET involving 263 patients showed only a 7.6% change in management following FDG-PET [24]. Thus, the size of the advantage of FDG-PET is uncertain, and the most cost-effective role for FDG-PET remains to be defined. It may be used for patients at higher risk for extrahepatic disease or as a problem-solving modality. It should be borne in mind that the sensitivity of FDG-PET is lower following neoadjuvant chemotherapy.

Consensus Recommendations

- The group recommended high-quality MRI and/or CT for mapping liver metastases preoperatively, depending on local expertise.
- US is useful for intraoperative staging and contrast-enhancement may improve the sensitivity of intraoperative US.
- High-quality CT of the chest and pelvis is recommended for detecting extrahepatic metastases.
- FDG-PET may provide additional information, mainly in patients with a high risk for extrahepatic disease, but there is currently no consensus as to the patient population with the most to gain, and current evidence is not considered strong enough to recommend its use in all patients.

OPTIMAL CHEMOTHERAPY

Chemotherapy may be used for both unresectable and resectable disease. Chemotherapy given to convert unresectable liver metastases to resectable is referred to as "conversion chemotherapy." The term "neoadjuvant chemotherapy" is reserved for chemotherapy for resectable and potentially resectable disease prior to surgery with or without adjuvant chemotherapy after surgery. One randomized trial demonstrated a higher progression-free survival (PFS) rate 3 years after liver resection using perioperative chemotherapy (i.e., before or after surgery) than with surgery alone [25], and it has been recommended that most patients with liver metastases from CRC be treated up front with chemotherapy, irrespective of the initial resectability of their metastases. However, in that study, all patients had resectable disease at the time of diagnosis and, although the results are encouraging, issues such as the true benefit of perioperative chemotherapy in terms of the overall survival (OS) time and its role in liver injury remain to be addressed. In addition, a recent multicentric retrospective study has not revealed any benefit in terms of OS or PFS of neoadjuvant chemotherapy in single metachronous liver metastases as opposed to a positive effect of adjuvant chemotherapy [26].

Without treatment, surgical resection is not possible in 70%–90% of patients with liver metastases from CRC. The prognosis of CRC patients is poor if metastases cannot be removed surgically; the aim of conversion chemotherapy is to achieve resectability rather than a complete response. When chemotherapy is initiated to achieve resectability, the aim should be for as short a treatment course as possible and surgery performed as soon as the metastases become resectable [27].

In the last 10 years, the overall survival (OS) times of patients with metastatic CRC have improved substantially [28] and largely reflect the increased number of available therapies. Before 2000, 5-fluorouracil (5-FU) was the only chemotherapeutic option. From 2000 onward, oxaliplatin and irinotecan became available and doublet cytotoxic regimens became standard therapy. Greater response rates have been reported with chemotherapy with doublet regimens than with single fluoropyrimidine-based regimens [4, 29], with complete resection (R0) rates of 11%–33% reported following chemotherapy with the leucovorin, 5-FU, and oxaliplatin (FOLFOX) or with leucovorin, 5-FU, and irinotecan (FOLFIRI) regimens [30–33]. Among 131 consecutive patients who underwent liver resection for multiple (four or more) liver metastases from CRC after systemic chemotherapy in 1993–2000, the 5-year survival rate of patients who received preoperative chemotherapy with 5-FU and leucovorin, combined with either oxaliplatin or irinotecan or both, was better in those achieving an objective response (37%) than in those with stable disease (30%) or disease progression (8%) [34]; 23% of patients in that study received two or three lines of chemotherapy and 24% had extrahepatic metastases. Similar results were observed in 4,851 patients from a prospective multi-institutional database—the LiverMetSurvey (Fig. 1). The use of triplet cytotoxic combinations with 5-FU plus both oxaliplatin and irinotecan (FOLFOXIRI) has translated into higher response rates and resectability rates, at least in one randomized study [35]. Hepatic arterial infusion (HAI) of chemotherapy may also provide a second chance to remove initially unresectable liver metastases from CRC [36, 37], even in patients heavily pretreated with chemotherapy [38].

More recently, treatment for metastatic CRC has moved toward more targeted therapy, with the availability of monoclonal antibodies targeting the epidermal growth factor receptor, for example, cetuximab and panitumumab, for which wild-type *KRAS* is a predictive biomarker, and vascular endothelial growth factor, for example, bevacizumab, which acts to inhibit angiogenesis. Studies (Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer and Oxaliplatin and Cetuximab in First-Line Treatment of mCRC) have shown that the addition of cetuximab to doublet cytotoxic chemotherapy results in a significantly higher response rate in patients with wild-type *KRAS* tumors [39–41], and it was associated with a relevant greater R0 resection rate [39] without a higher rate of surgical or postoperative complications. Although the Medical Research Council Continuous Chemotherapy plus Cetuximab or Intermittent Chemotherapy trial did not confirm a benefit of the addition of cetuximab to oxaliplatin

plus fluoropyrimidine chemotherapy in the first-line treatment of patients with advanced CRC, cetuximab resulted in a higher response rate in patients with wild-type *KRAS* tumors [42]. In the Cetuximab in Neoadjuvant Treatment of Non-Resectable Colorectal Liver Metastases trial, the rate of resectability was higher in patients with wild-type *KRAS* tumors when treated with the combination of FOLFOX or FOLFIRI plus cetuximab, although the R0 resection rates were similar in patients with wild-type *KRAS* and mutated *KRAS* tumors (34% versus 33%, respectively) [43]. According to a retrospective review, resectability rates in that study increased from 32% (22 of 68 patients) at baseline to 60% (41 of 68 patients) after chemotherapy with cetuximab ($p < .0001$) [43]. In the Preoperative Chemotherapy for Hepatic Resection study of FOLFOXIRI plus cetuximab in 41 patients with liver metastases from CRC, the overall response rate was 79% and resections were performed in 60% of patients [44]. Other recent studies, such as the NORDIC VII study, however, have shown less positive results with cetuximab as first-line therapy, even in patients with wild-type *KRAS* disease [45]. Studies with panitumumab have also shown slightly higher response rates with first- and second-line therapy, but the R0 resection rate was not higher [46–48].

Efficacy data on bevacizumab conversion treatment are also available. In the NO16966 trial, a slightly higher hepatic R0 resection rate (12.3% versus 11.6%) than with placebo was reported when bevacizumab was added to 5-FU or capecitabine plus oxaliplatin in patients with liver-only disease [49]. In the first Bevacizumab Expanded-Access Trial, the numbers of patients undergoing surgery with curative intent were 153 of 949 (16.1%) patients receiving oxaliplatin plus bevacizumab chemotherapy and 64 of 662 (9.7%) patients receiving irinotecan plus bevacizumab chemotherapy; R0 hepatic resection was performed in 76 of 949 (8.0%) and 34 of 662 (5.1%) patients, respectively [49]. In the Bevacizumab, Oxaliplatin, Xeloda® in Unresectable Liver Metastases study, in which bevacizumab was given with capecitabine plus oxaliplatin in patients with borderline, technically unresectable, liver-only metastases from CRC, 40% of patients were converted to resectability [50]. Furthermore, bevacizumab added to FOLFOXIRI achieved promising results in terms of the response rate and PFS interval, without unforeseen adverse events [51]. In addition, bevacizumab added to FOLFOX has been associated with a significantly higher frequency of complete or major response in patients undergoing hepatic resection following neoadjuvant chemotherapy [52].

Intra-arterial chemotherapy has been in use for some time, has clear efficacy, at least in tumor control [53, 54], and is associated with a lower risk for hepatic recurrence [55, 56]. In patients with unresectable liver metastases from CRC and a history of systemic chemotherapy failure, resection became possible in seven of 44 patients following bimonthly HAI of oxaliplatin combined with leucovorin and 5-FU [57]. After multidrug chronomodulated HAI as rescue treatment in heavily pretreated patients, resection became possible in four of 29 patients [38]. HAI may also be used as adjuvant therapy following resection [58]. However, HAI is not commonly used,
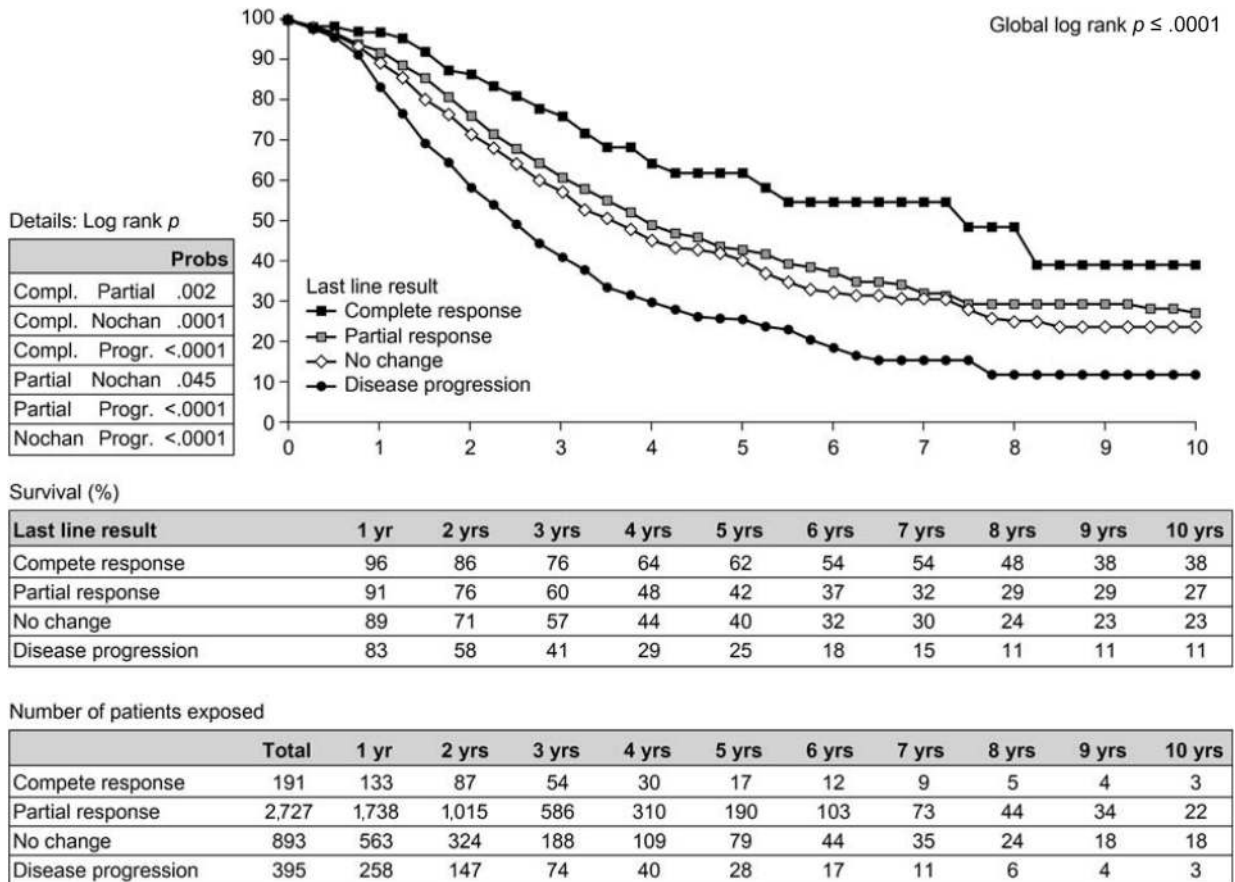
Details: Log rank p

		Probs
Compl.	Partial	.002
Compl.	Nochan	.0001
Compl.	Progr.	<.0001
Partial	Nochan	.045
Partial	Progr.	<.0001
Nochan	Progr.	<.0001

Survival (%)

Last line result	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Compete response	96	86	76	64	62	54	54	48	38	38
Partial response	91	76	60	48	42	37	32	29	29	27
No change	89	71	57	44	40	32	30	24	23	23
Disease progression	83	58	41	29	25	18	15	11	11	11

Number of patients exposed

	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Compete response	191	133	87	54	30	17	12	9	5	4	3
Partial response	2,727	1,738	1,015	586	310	190	103	73	44	34	22
No change	893	563	324	188	109	79	44	35	24	18	18
Disease progression	395	258	147	74	40	28	17	11	6	4	3

Figure 1. Overall survival probability in relation to response to preoperative chemotherapy in 4,851 patients undergoing a first resection of colorectal liver metastases from the LiverMetSurvey [78]. Reproduced with permission from http://www.livermetsurvey.org, June 2011.

and trials in progress will better define the place of HAI and, similarly, drug-eluting beads and radioembolization as bridges to surgery for liver metastases from CRC.

There is a need for further clinical trials studying the combination of targeted agents with effective triplet chemotherapy regimens. In addition, studies are warranted in patients with CRC and initially unresectable liver metastases that focus on different clinical presentations, such as patients with nonresectable disease that is potentially resectable if tumor shrinkage occurs, compared with those assessed as never resectable.

Following resection, in patients who have received a limited number of preoperative chemotherapy cycles, adjuvant chemotherapy should be considered. Because trials of adjuvant chemotherapy in patients with stage III CRC have not shown benefits of targeted agents [59–61] or irinotecan [62], such therapies cannot be recommended. Furthermore, there is no consensus for adjuvant chemotherapy in patients with resection of metachronous metastases following oxaliplatin-based adjuvant chemotherapy for the primary cancer.

Consensus Recommendations

- The group agreed that the aim of conversion chemotherapy is to achieve resectability rather than a complete response.

When there is a potential for resectability, at least four courses of chemotherapy should be given first line and, if progression occurs during first-line therapy or only stable disease is achieved after 4 months, second-line treatment should be considered.

- The optimal timing for assessment of response to chemotherapy was considered by the group to be every 2 months.
- The group agreed that preoperative treatment to induce resectability should be as short as possible and that postoperative chemotherapy should continue.
- Using oxaliplatin regimens is possible for patients who do not progress during adjuvant oxaliplatin-based treatment after resection of the primary CRC.
- Overall, a total duration of 6 months of perioperative (preoperative and adjuvant) chemotherapy is recommended.

ROLE OF IMAGING IN EVALUATION OF RESPONSE TO CHEMOTHERAPY

In the clinical setting, response to chemotherapy using imaging modalities can be judged from three perspectives: change in tumor size, morphological changes unrelated to size, and metabolic activity. Size-based criteria have included the World Health Organization criteria [63], original Response Evalua-

tion Criteria in Solid Tumors (RECIST) [64], and revised RECIST [65], which use unidimensional criteria to formulate a response rate. One of the shortcomings of the RECIST is the arbitrary choice of cutoff values that define a response [66]. Two recent studies in patients with liver metastases from CRC showed that an early decrease in size by 10% correlates better with outcome than the required 30% decrease using the RECIST [66, 67], suggesting that the cutoff value and optimal time for evaluation need to be reappraised. Of interest, a 10% decrease in size is also the cutoff value used for the Choi criteria in the evaluation of gastrointestinal stromal tumors [68].

Morphological changes that are nonsize-based have been described for assessing response to biological agents, which have a predominantly cytostatic mechanism of action. These observations form the basis of the Choi criteria and the recently described morphological response criteria for hepatic metastasis from CRC [69]. These new criteria are based on the subjective evaluation of changes in tumor texture and margins. Responding tumors evolve from a complex, heterogeneous solid mass to a pseudocystic mass, and response is classified as optimal, incomplete, or absent. In a study of 234 liver metastases from CRC from 50 patients who underwent hepatic resection after neoadjuvant chemotherapy that included bevacizumab, morphological criteria correlated with the pathological response and OS outcomes and were a better surrogate for pathological response than the RECIST [69]. In a validation cohort of 82 patients with unresectable diseases, an optimal morphological response was associated with a median OS duration of 31 months (95% confidence interval [CI], 26.8–35.2 months), compared with 19 months (95% CI, 14.6–23.4 months) in patients with an incomplete or no morphological response ($p = .009$), whereas the RECIST did not correlate with the survival outcome in either the surgical or the validation cohort [69].

Metabolic activity is currently evaluated primarily with FDG-PET–CT. Preliminary studies suggest that the degree of chemotherapy-induced change in tumor glucose metabolism is predictive of patient outcome, and that the use of FDG-PET for therapy monitoring is clinically feasible [70, 71]. The role of PET in monitoring the response to treatment for patients with liver metastases from CRC, however, remains to be further defined. Other biomarkers that can detect response to treatment prior to change in lesion size, such as perfusion CT and diffusion-weighted MRI, are also under evaluation for assessing treatment response of liver metastases from CRC [72].

The disappearance of metastases on CT and MRI scans qualifies as a complete radiographic response using the RECIST but is not an indication of a complete pathological response [73]. Similarly, the lack of FDG uptake or complete response using PET does not imply complete pathological response [74]. Because some lesions may disappear or may be hardly detectable with intraoperative ultrasonography (IOUS) following neoadjuvant chemotherapy, a technique to mark small lesions with coils before chemotherapy has been successful [75].

Consensus Recommendations

- Changes in tumor size (RECIST) adequately evaluate the efficacy of conventional chemotherapy, but morphological response criteria correlate better with pathological response and OS outcomes than the RECIST in patients who have received antiangiogenic agents. Factors that are important for the evaluation of response to chemotherapy and for preoperative staging include high-quality prechemotherapy imaging and careful comparison of prechemotherapy and presurgical scans.

Surgical Management

Resectable Patients

Surgical resection remains the only treatment associated with a long survival time in patients with liver metastases from CRC, with a 40% survival at 5 years and almost 25% of patients demonstrating a postoperative survival duration up to 10 years in specialized centers [76, 77]. Results from the LiverMetSurvey, involving 13,334 patients from 330 centers in 58 countries who underwent surgery for liver metastases, show a better survival outcome in patients who undergo first resection of liver metastases than in those who do not (Fig. 2) [78]. A recent systematic review of 142 studies published in 1999–2010 confirmed these results and revealed 5-year survival rates for patients with liver metastases in the range of 16%–71% (median, 38%) after liver resection [79]. Although advances in diagnostic techniques and treatment strategies have improved resectability rates and surgical outcomes over the past 10 years, most patients with hepatic metastases from CRC remain ineligible for potentially curative surgical resection [80].

Initially Unresectable Patients

Until relatively recently, patients with unresectable disease were treated with palliative chemotherapy [81]. A range of strategies has now been developed to render a patient's disease surgically resectable (e.g., portal vein embolization, neoadjuvant chemotherapy, hepatectomy combined with radiofrequency ablation, two-stage hepatectomy) [82, 83]. Portal vein embolization is indicated when the FLR as a proportion of total liver volume is 20%–30% in patients with a normal liver and ≤40% in patients who have had extensive chemotherapy [17, 84]. The efficacy of conversion chemotherapy has increased dramatically in recent years, and it has become the best means of downsizing tumoral disease and converting patients with unresectable disease to resectability [30]. Although survival times following conversion chemotherapy and surgery in patients with initially unresectable disease are lower than those in patients undergoing primary liver resection [30, 78] (Fig. 3), they are greater than when resection is not performed [30]. However, the tumor eradication process generally involves more than one procedure in the majority of patients [30].

The current definition of resectability includes the potential for complete resection with tumor-free margins (R0 resection), with preservation of at least two disease-free liver segments with viable vascular inflow, outflow, and biliary drainage and an FLR volume of 30% [85]. Some authors, how-
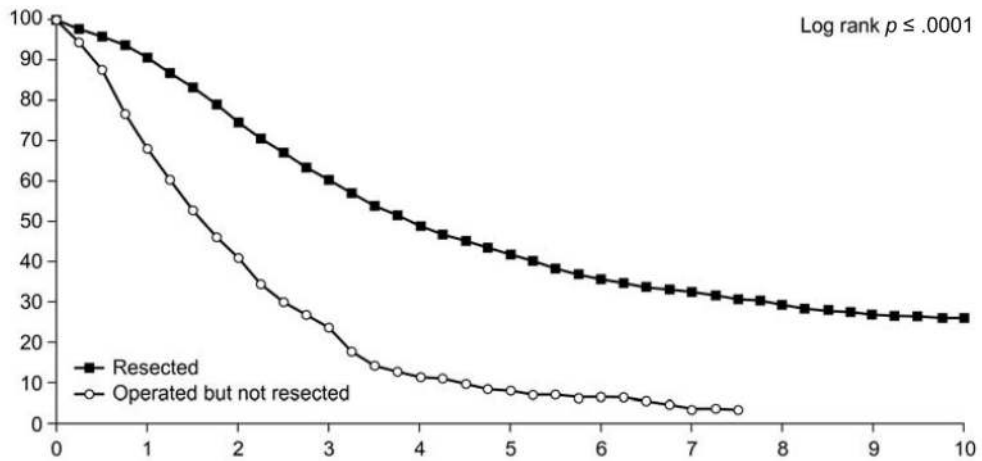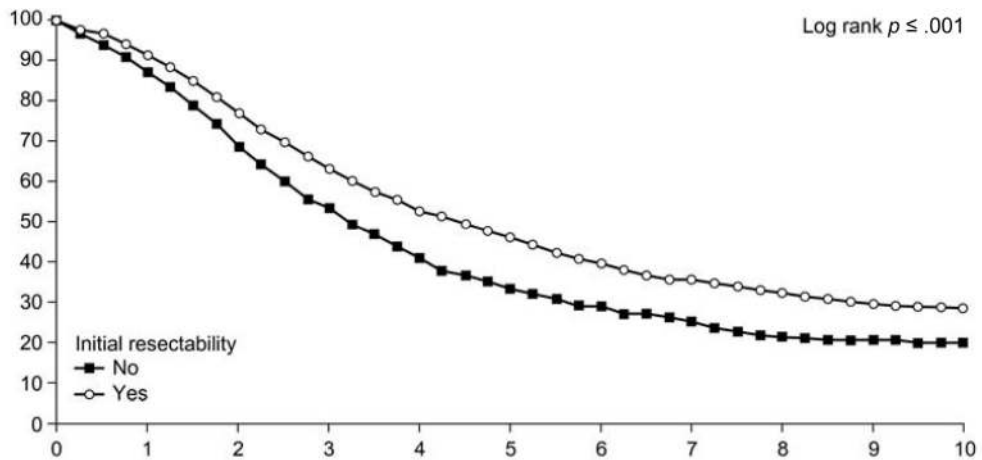
Survival (%)

Resected	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Resected	90	74	60	49	42	36	32	29	27	25
Not resected	68	41	24	11	8	6	4			

Number of patients exposed

	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Resected	13,893	9,451	6,159	3,893	2,464	1,642	1,095	798	578	429	324
Not resected	881	471	225	90	29	17	11	3	0	0	0

Figure 2. Overall survival probability after a first resection for colorectal liver metastases in 14,774 patients from the LiverMetSurvey [78]. Reproduced with permission from http://www.livermetsurvey.org, June 2011.

Survival (%)

Initial resectability	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
No	87	69	53	41	33	29	25	21	20	20
Yes	91	76	63	52	46	39	36	32	29	28

Number of patients exposed

	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
No	1,999	1,275	745	426	223	131	84	55	40	31	23
Yes	8,941	5,917	3,766	2,333	1,482	982	642	461	329	243	190

Figure 3. Overall survival probability after resection of initially unresectable versus nonresectable liver metastases. Data from 10,940 patients in the LiverMetSurvey [78]. Reproduced with permission from http://www.livermetsurvey.org, June 2011.

ever, set the safety limit to a 20%–25% FLR volume [80, 86]. Further clarification of categories of nonresectability is crucial; for example, differentiation between disease that is technically nonresectable and disease that is oncologically nonresectable (e.g., presence of other metastases in the lung). Furthermore, many patients with liver metastases from CRC who now satisfy the revised resection criteria are in high-risk groups associated with poor outcomes. As the number of high-risk patients undergoing liver resection continues to increase, a better understanding of the associated risk–benefit ratio is needed to prevent unnecessary surgery. Several independent prognostic risk factors have been identified, including the number of hepatic metastases, node-positive primary tumors, poorly differentiated primary tumors, extrahepatic disease, tumor diameter, carcinoembryonic antigen levels, and positive resection margins [77, 79]. However, none of these risk factors represents an absolute contraindication to hepatic resection provided that surgery is able to remove all the tumoral disease. In particular, a large number of liver metastases should not be a contraindication because resection of multiple bilobar hepatic metastases has demonstrated survival benefits in selected cases [87]. Increasing interest in predictive molecular markers, such as *KRAS* and *BRAF*, will also help stratify patient populations to targeted therapy [67, 88–91]. However, more data are needed before widespread use of such biomarkers is implemented.

Approximately 20%–30% of newly diagnosed cases of CRC have identifiable synchronous liver metastases [92]. There is currently no standard of care for treating synchronous liver metastases from CRC, and no consensus has been reached concerning the timing of primary and metastatic tumor resections. Although synchronous liver metastases from CRC are traditionally treated with a two-stage resection, recent improvements in perioperative care and postsurgical morbidity and mortality favor simultaneous resection in cases in which the primary tumor is in the colon and the number of hepatic metastases is limited. Resection of liver metastases first (reverse treatment) is considered the best option when hepatic disease is predominant and when the primary tumor is asymptomatic or symptoms are easy to manage [93, 94]. This approach can be performed with acceptable perioperative mortality and morbidity rates. Although this represents a highly selected group of patients with synchronous liver metastases from CRC, particularly when the primary tumor is predominantly in the rectum, requiring a neoadjuvant treatment strategy, a considerable OS benefit can be achieved [95].

Separate resections are generally favored in cases of rectal primary tumors and cases of multiple metastatic sites [96–98]. The surgical mortality rate is significantly higher when surgery of extensive hepatic resections is combined with colorectal resection [87].

In patients with extensive bilateral (bilobar) hepatic metastases with some parenchymal sparing, chemotherapy should be followed by consideration of two-stage hepatectomy, a procedure first described in 2000 [99]. With this approach, left liver metastases are usually resected separately (first-stage resection) with or without portal vein embolization followed by

right or extended right hepatectomy (second-stage resection) [100, 101]. Resection of the primary can be combined with the left hemiliver clearance during the first stage because the hepatectomy is usually limited to fewer than three segments. The two-stage approach has been shown to be associated with a better survival outcome than with chemotherapy without surgery in patients with liver-only disease and an objective response to chemotherapy: the 5-year OS rates were 51% versus 15%, respectively ($p = .005$) [102]. The surgical mortality rate is significantly higher when surgery of extensive hepatic resections is combined with colorectal resection [87, 103].

Increasingly more patients with unresectable liver metastases from CRC are being treated with a combination of systemic chemotherapy and radiofrequency ablation (RFA). A randomized phase II trial of 119 patients with liver-limited disease demonstrated a significantly longer median PFS interval with than without RFA ($p = .025$) [104]. However, the survival results with RFA or RFA combined with resection remain inferior to those with resection in patients with solitary or multiple liver metastases [105, 106].

Consensus Recommendations

- Surgery remains the best treatment option for a long survival duration when R0 resection can be achieved with preservation of a functioning liver remnant of 25%–30%.
- Conversion chemotherapy results in a higher resectability rate and greater survival probability in patients with initially unresectable tumors.
- Strategies to help achieve R0 resection include portal vein embolization, staged hepatectomies, and hepatectomies with RFA. The safety of major hepatic resection during surgery for the primary CRC is still controversial.
- Separate resections are favored over synchronous resections with rectal surgery because of the higher morbidity and mortality rates associated with the latter. The reverse surgical approach (liver first) produces as good an outcome as the conventional approach.
- A large number of liver metastases should not be an absolute contraindication to surgery combined with chemotherapy provided that resection can be complete.
- Surgery may be performed in more than one procedure (two-stage hepatectomy) when resection of all liver metastases cannot be achieved in a single procedure. Repeated hepatectomy or thermal ablation of liver recurrences can prolong the hepatic DFS interval.

PATHOLOGICAL RESPONSE

Pathological response to neoadjuvant chemotherapy has shown prognostic potential in patients with liver metastases from CRC, and consequently it has been integrated as an endpoint in several studies [107–109]. The degree of pathological response has been shown to vary depending on the chemotherapy regimen used [107, 108].

In addition to a pathological complete response, in which no residual tumor cells can be observed, other ways of scoring pathological response have been proposed, including tumor re-

gression grades [107, 110] and a pathological response grade [108, 111, 112]. The first evaluates the ratio of residual viable tumor cells to fibrous tissue within the tumor and has the advantage of being the same scoring system as the one used for primary colorectal tumors by the American Joint Committee on Cancer (the tumor–node–metastasis staging system), allowing easy comparison of response between the primary tumor and metastases. The latter is based on the percentage of viable tumor cells. Both scoring systems evaluate the amount of residual tumor cells rather than the change in tumor size; even if a tumor appears to shrink in size, the number of viable tumor cells may not decrease proportionally. Both scoring systems have shown prognostic value [107, 110–112].

Pathological examinations can also reveal the mechanisms underlying chemotherapy-associated liver injuries, which can potentially result in higher postoperative morbidity rates and, in rare cases, patient death [113]. For example, oxaliplatin-based regimens have been linked to toxic injury to endothelial cells, resulting in sinusoidal obstruction syndrome (SOS, formerly known as veno-occlusive disease), characterized by sinusoidal wall disruption, and can be complicated by fibrosis or nodular regenerative hyperplasia (NRH) and a greater risk for bleeding during surgery or poor liver function or reserve [114, 115]. The addition of bevacizumab has been associated with a lower incidence of oxaliplatin-induced SOS and NRH lesions [116]. Similarly, irinotecan has been linked to the development of steatohepatitis, a type of nonalcoholic fatty liver disease [117, 118], and 5-FU plus leucovorin and/or irinotecan are associated with a higher incidence of hepatic steatosis, particularly in patients with a body mass index >25 kg/m^2 [119, 120]. Many patients with liver metastases from CRC are only referred for surgical resection following numerous prior chemotherapy regimens, but accumulated hepatic toxicity may mean that curative surgery is no longer possible in some of these patients, highlighting the importance of coordinated efforts among medical oncologists, surgeons, and patients to optimize disease management [121].

Tumor margins for resection can be difficult to define. Most residual tumor cells after chemotherapy are seen in the periphery of the tumor at the interface between the tumor and non-neoplastic liver tissue [107]. A recent study of 22 patients with advanced bilateral liver metastases from CRC found that half of the patients had tumor regrowth at the periphery of the metastasis when neoadjuvant chemotherapy was interrupted, and this occurred regardless of tumor response. This peripheral tumor growth was found to be caused by a "dangerous halo" of proliferating tumor cells infiltrating the parenchyma surrounding the metastasis [122]. Tumor-specific DNA has also been detected up to 4 mm beyond the visible tumor margin [123]. However, surgical resection margins are currently selected using preoperative radiology, IOUS, and palpation, none of which take into account the possibility of a halo, increasing the risk for disease recurrence [122]. The use of two-stage hepatectomies may help to reduce the risk for recurrence by allowing pathological assessment between resections [102]. Lesions that have disappeared on imaging after chemotherapy have been found to contain viable tumor cells when resected [73].

The development of a fatty liver while being treated with chemotherapy may contribute to the disappearance of liver metastases on multidetector CT, particularly if a portal venous phase acquisition alone is obtained; in these circumstances, MRI is particularly advantageous [124]. Surgical oncologists are often faced with the dilemma of whether to resect all areas that previously contained definite metastases in order to prevent missing undetected metastases or to resect only those areas where metastatic lesions remain visible [121]. MRI, particularly with diffusion sequences, can currently detect small remnant metastases that are not visible with other imaging modalities. Although a consensus emerged to attempt resection of previous metastatic sites, recent experience in highly chemosensitive patients, especially after adjuvant HAI, showed that about two thirds of disappearing lesions did not recur [125]. When disappearing metastases occur, adjuvant intra-arterial chemotherapy is probably the best means to avoid them recurring [126].

Consensus Recommendations

- Resection is best performed on the basis of the site of metastasis on the prechemotherapy CT or MRI scan. As an alternative, when disappearing metastases are deep and undetectable even intraoperatively, a wait-and-see policy may be employed with follow-up every 2 months to see if the metastases become visible, and then resect. The management decision depends on the initial extent of the disease.
- Assessments should include histological evaluation of tumor margins, evaluation of the nontumoral liver parenchyma, and evaluation of the pathological response to preoperative chemotherapy.

Is Cure Possible?

The group discussed the definition of cure and agreed that a precise definition is needed. Cure is usually defined by a 10-year survival time because relapse is unusual after 10 years from an R0 resection [127]. However, a DFS duration of 3 or 5 years should be explored as a marker for potential cure. It was also agreed that, in patients with metastatic CRC, cure is only possible after hepatic resection [128]. In patients with initially unresectable disease, chemotherapy can convert 16% of patients to resectability [129].

Consensus Recommendations

- Cure is possible after complete resection regardless of whether the initial disease was resectable or unresectable.

MDTs

MDTs are an increasingly favored management approach for cancer care [130, 131], and it has been proposed that patients with liver metastases from CRC should be treated by an MDT whenever possible [27]. The MDT model is a patient-centered approach requiring a team of specialists, including at least surgeons, oncologists, radiologists, and pathologists, and depending on the institution size and availability of expertise, nurses, nutritionists, and a cancer coordinator may ideally form part of the MDT [132]. The team works together to identify appropri-

ate tests and the best treatment options available under the guidance of a nominated team leader in regularly scheduled MDT meetings [132, 133]. This model also allows communication between local and more specialized physicians, whether in the form of a second opinion or patient referral. An essential part of managing an MDT involves regular assessment of team effectiveness to help optimize patient care [134]. Although there are few published data on the barriers to an effective MDT, potential barriers may include: (a) a lack of (or conflict regarding) leadership and coordination, including ambiguous team roles; (b) insufficient administrative support and implementation; (c) limited resources (e.g., expertise, time, associated costs, availability of meeting facilities, data management, and a coordinator); and (d) a lack of commitment and/or interest from team members and hospital staff [133]. However, despite the obstacles facing MDTs, several important patient benefits have been reported, including greater accuracy of disease staging [135], fewer treatment and referral delays [136, 137], individualized evidence-based practice for patients, greater continuity of care [138], enhanced quality of life [139], and better clinical and survival outcomes [140–146]. In addition, health care professionals and health services may benefit from MDTs through strengthened awareness, communication, and relationships among members and disciplines, increasing the opportunities for knowledge sharing and professional development (e.g., review sessions providing learning opportunities for staff) [136, 147, 148]. Other advantages include facilitation of clinical trial recruitment [149], minimization of duplication of effort, opportunities to pool resources and encourage crosstraining [150], and the potential to alleviate regional disparities in health care services.

Consensus Recommendations

- Patients with liver metastases from CRC are best managed with a multidisciplinary approach. MDTs contribute many advantages and benefits in cancer care for the patient, health care professionals, and health care service providers. However, MDTs also involve several challenges.
- Although there is a fundamental need to establish specialized MDTs, universal guidelines on implementation, dynamics, and monitoring are currently lacking, and recommendations from scientific societies would prove particularly valuable to sustain a performing MDT.

Conclusions

Resectability and survival rates are better in specialized centers that employ multidisciplinary specialists, including radiologists, pathologists, oncologists, and liver surgeons, than in nonspecialized centers. Thus, it is recommended that all patients with liver metastases be managed by specialized hepatobiliary MDTs to decide the best strategy, the main objective of which is to achieve surgical resection. The group considered that multidisciplinary treatment is essential for better clinical and survival outcomes. It is hoped that the proposed new system for deciding whether or not a patient is eligible for resection described in Table 2 will help to simplify treatment

Table 2. Contraindications to hepatic resection in patients with colorectal cancer liver metastases

Category	Contraindication
Technical (A)	
1. Absolute	Impossibility of R0 resection with ≥25%–30% liver remnant
	Presence of unresectable extrahepatic disease
2. Relative	R0 resection possible only with complex procedure (portal vein embolization, two-stage hepatectomy, hepatectomy combined with ablation[a])
	R1 resection
Oncological (B)	
1.	Concomitant extrahepatic disease (resectable)
2.	Number of lesions ≥5
3.	Tumor progression

Any patient should be categorized as A1 or A2/B1, B2, or B3. This classification may help to clearly define the type of unresectable patients included in all clinical trials.
[a]Includes all methods, including radiofrequency ablation.

decisions and standardize treatment care across centers. In addition, the recommendations on a number of key issues—managing potentially resectable synchronous metastases, whether or not the prospect of surgery should influence the choice of first-line chemotherapy, whether or not there is a maximum number of metastases for achieving potentially curative surgery, the recommended action to be taken when there is a complete clinical response, guidance on the minimum number of chemotherapy cycles before surgery, and the respective role of preoperative and postoperative chemotherapy—should also help to raise the standard of care for patients with liver metastases from CRC.

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