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Hot Topic

Managing synchronous liver metastases from colorectal cancer: A multidisciplinary international consensus

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ABSTRACT

An international panel of multidisciplinary experts convened to develop recommendations for managing patients with colorectal cancer (CRC) and synchronous liver metastases (CRCLM). A modified Delphi method was used. CRCLM is defined as liver metastases detected at or before diagnosis of the primary CRC. Early and late metachronous metastases are defined as those detected ⩽12 months and >12 months after surgery, respectively. To provide information on potential curability, use of high-quality contrast-enhanced computed tomography (CT) before chemotherapy is recommended. Magnetic resonance imaging is increasingly being used preoperatively to aid detection of subcentimetric metastases,

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Multidisciplinary team management
Surgery
Synchronous colorectal liver metastases
Systemic therapy

and alongside CT in difficult situations. To evaluate operability, radiology should provide information on: nodule size and number, segmental localization and relationship with major vessels, response after neoadjuvant chemotherapy, non-tumoral liver condition and anticipated remnant liver volume. Pathological evaluation should assess response to preoperative chemotherapy for both the primary tumour and metastases, and provide information on the tumour, margin size and micrometastases. Although the treatment strategy depends on the clinical scenario, the consensus was for chemotherapy before surgery in most cases. When the primary CRC is asymptomatic, liver surgery may be performed first (reverse approach). When CRCLM are unresectable, the goal of preoperative chemotherapy is to downsize tumours to allow resection. Hepatic resection should not be denied to patients with stable disease after optimal chemotherapy, provided an adequate liver remnant with inflow and outflow preservation remains. All patients with synchronous CRCLM should be evaluated by a hepatobiliary multidisciplinary team.

Introduction

Colorectal cancer (CRC) has become the third most common malignancy worldwide in terms of incidence and fourth for cancer mortality [1]. At CRC diagnosis, 20–25% of patients have stage IV disease [2–5], in which synchronous CRC liver metastases (CRCLM) are present in 15–25% of cases [6] and metastases are confined to the liver in 70–80% of these cases [7]. Surgical resection is the most effective treatment approach for CRCLM, but only a minority of patients are suitable for upfront surgery [8]. Although data from the population-based Burgundy registry have to be interpreted with caution as they are from the period 1976 to 2000, they show that resection for cure of CRCLM is performed significantly less often in cases of synchronous metastases than for metachronous metastases (6.3% vs 16.9%, respectively) [7]. The prognosis for patients with untreated CRCLM is poor; in the Burgundy registry, fewer than 30% of patients with untreated disease were alive after 1 year and fewer than 5% survived 5 years after diagnosis [7]. Data from this registry also showed that 5-year survival rates were shorter with synchronous than with metachronous CRCLM (3.3% vs 6.1%, respectively) [7], although some studies have shown no significant difference [9]. The reported percentage of synchronous CRCLM is increasing compared with metachronous metastases [10], probably due to improved imaging techniques leading to earlier diagnosis. However, different definitions of synchronous metastases can be found in the literature and adoption of a standardized definition is needed to clarify future reporting.

An international multidisciplinary group of experts in managing liver metastases (LM) from CRC (the EGOSLIM group) convened to discuss synchronous metastases and their management. In the absence of data from randomized controlled trials (RCTs) to guide decisions, the aims of the meeting were to agree: a definition for synchronous CRCLM; imaging for their detection; pathological evaluation and reporting; resectability of CRCLM; timing for surgery of the primary tumour and CRCLM; chemotherapy and treatment regimens; postoperative management; and the multidisciplinary approach to management. Through dissemination of the consensus decisions reached, it is hoped that the management of patients with synchronous CRCLM will be optimized.

Methods

The international consensus panel comprised experts from the USA, Europe and Asia in the treatment of patients with CRCLM and included one coordinator, five medical oncologists (including two gastroenterologists), five hepatic surgeons, one colorectal surgeon, two radiologists, one pathologist and one molecular gastrointestinal oncologist. All important aspects of multidisciplinary team (MDT) management of synchronous CRCLM were identified before the meeting by the coordinator and referred to experts for presentation at the meeting. Meta-analyses, RCTs and studies evaluating clinical practice in the management of synchronous CRCLM were identified and reviewed before, and discussed during, the meeting. A modified Delphi method was used to aid achievement of a consensus (see Appendix 1) [11]. Recommendations were formulated when approved by all or a large majority of the panel members and are summarized in Table 1. Strength of recommendations was attributed based on the Strength of Recommendation Taxonomy [12]. For all recommendations, there is an assumption that all imaging, surgery and therapy are optimal. Some panel members were not present for the whole meeting and some members chose to abstain from voting on some questions not in their area of expertise.

Definition and prognosis of synchronous LM

Different definitions of synchronous CRCLM exist. Although, by definition, all metastases are synchronous (occult or detectable at diagnosis), most definitions include detection at or before diagnosis or surgery of the primary tumour [13], whilst some also include metastases detected up to 3 [14,15], 4 [16] or 6 months [17,18] following diagnosis.

With regard to prognosis of resected synchronous LM, a disease-free interval from the primary to discovery of the LM of less than 12 months has been associated with a hazard ratio of 1.3 for disease recurrence [19]. The majority of the panel (14/15, 93%) agreed that synchronicity is a sign of poor prognosis, irrespective of the treatment. In the ongoing LiverMetSurvey international registry, an international registry of patients undergoing surgery for CRCLM, [20], available current data show a significant difference in survival when metastases are detected at or 1 month before diagnosis vs 0–3 months after diagnosis ($p < 0.0001$); 5-year survival is 39% vs 44%, respectively (Fig. 1). Survival rates are not significantly different between patients in whom metastases are detected at or 1 month before vs up to 6 months or 6–12 months after diagnosis (Fig. 1). However, survival rates are significantly different between patient groups when metastases are detected at or within 1 month before diagnosis vs more than 12 months after the primary diagnosis ($p < 0.0001$). Although lacking confirmatory molecular biological information, these data support the division of LM into those diagnosed at the following time points: at or before the time of diagnosis; 0–12 months following diagnosis; and more than 12 months following diagnosis.

Consensus recommendations

- Synchronous CRCLM have less favorable cancer biology and expected survival than metachronous, particularly late metachronous, metastases.

Table 1
Questions and subquestions addressed by the participants before and at the meeting, and a summary of the recommendations.

Question	Subquestion/options	Recommendation	Strength of recommendation[a]
What would you consider to be the correct definition of 'synchronous' LM?	1. LM diagnosed strictly at the same time as the colorectal primary 2. LM diagnosed up to 3 months after the colorectal primary 3. LM diagnosed up to 6 months after the colorectal primary 4. LM diagnosed up to 12 months after the colorectal primary	• Synchronous CRCLM should be termed 'synchronously detected liver metastases'. This is defined as LM detected at or before diagnosis of the primary tumour • Early metachronous metastases are considered to be those detected within 12 months of diagnosis or surgery of the primary • Late metachronous metastases are considered to be those detected more than 12 months after surgery	A
2. Is synchronicity of LM a sign of poor prognosis regarding the outcome, irrespective of the treatment?	1. Yes 2. No	• Synchronicity is a sign of poor prognosis	B
3. Clinical scenario 1: patients with resectable LM and asymptomatic CRC	A. Would you mainly consider: 1. Chemotherapy first, OR 2. Resection of the primary first, OR 3. Resection of the primary and LM in a one-stage procedure?B. In this setting, if you have to choose, what do you consider to be the most important timing for chemotherapy? 1. Preoperative 2. Postoperative 3. Both pre- and postoperative a. Is this true for all cases? C. In this setting, do you think that the chemotherapy regimen should be: 1. The same as for patients with more advanced disease 2. Different and probably alleviated (e.g. without targeted therapy)?	• Chemotherapy should be given preoperatively unless surgery of the primary and LM is considered easy • For rectal tumours, preoperative radiotherapy is a standard of care, but not for high rectal tumours or T2 tumours, and one-stage surgery should not be performed • For colonic primary tumours, one-stage surgery is not advocated for tumours needing complex surgery, in high-risk patients or when hepatectomy would be major • A total of 6 months of chemotherapy is recommended, independently of whether given pre- or postoperatively • Postoperative chemotherapy can be different to preoperative chemotherapy and may be less intense	B
4. Clinical scenario 2: patients with non-resectable LM and asymptomatic CRC	A. Would you mainly consider: 1. Chemotherapy first, OR 2. Resection of the primary first?B. Do you consider, in this setting, the use of a reverse strategy (beginning with liver resection) 1. A good rationale 2. A poor rationale?	• Chemotherapy should be administered initially with the aim of achieving resectability of CRCLM • If CRCLM become resectable, a reverse strategy should be advocated • For rectal cancer, radiotherapy may be given before chemotherapy, or after resection of LM	A B
5. Clinical scenario 3: patients with resectable LM and symptomatic CRC	A. Would you mainly consider: 1. Chemotherapy first, OR 2. Radiotherapy, OR 3. Resection of the primary first, OR 4. Resection of the primary and LM in a one-stage procedure?B. Would you investigate using a stent, if technically possible? 1. Yes, sometimes 2. No, never	• For bleeding CRC, following transfusions, preoperative chemotherapy should be advocated • For perforations, resection of the primary to remove the tumour (right colon) or suture or creating a stoma (left colon) is advocated • For proven occlusion with distended evidence of obstruction, resection of the primary should be performed first • For occlusions, stents are an option but results have been poor	A
6. Clinical scenario 4: patients with non-resectable LM and symptomatic CRC	A. Would you mainly consider: 1. Chemotherapy first, OR 2. Resection of the primary first?B. Would you investigate using a stent, if technically possible? 1. Yes, sometimes 2. No, never	• The aim of management is to make LM resectable; patients would be managed as for scenario 3 • Stents are not recommended unless there is a chance for cure	B
7. What is your opinion of one-stage resection of both the primary tumour and LM?	1. Favorable in all possible cases 2. Reserved for limited hepatectomies 3. Reserved only for easy-to-operate colonic cancers (excluding rectal)	• One-stage resection is not appropriate in all cases • When both the primary tumour and metastases are resectable, simultaneous resection can be performed in selected patients undergoing limited hepatectomy	A
8. Compared with separate resections, do you consider a one-stage procedure	1. Overall, more risky 2. No more risky?	• A one-stage procedure is considered more risky than separate resections	A
9. Would your chemotherapy regimen be different for resectable and unresectable synchronous metastases?	1. No, the same (doublets or doublets with targeted therapy) 2. Stronger (e.g. triple or triple with targeted therapy) for unresectable 3. Stronger for resectable	• The same chemotherapy regimen can be used for resectable and unresectable synchronous LMs	A
10. After R0 surgery of both colorectal and liver tumours, would you consider chemotherapy?	1. Yes, routinely 2. No, never 3. Yes, in selected cases	• A total of 6 months of chemotherapy is recommended, whether given preoperatively or postoperatively	B

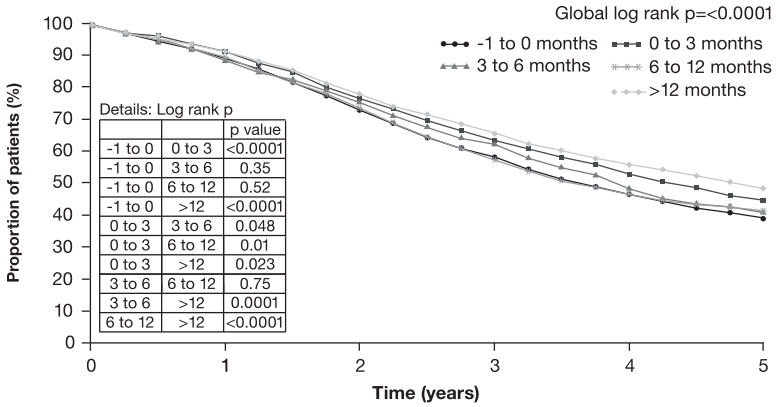
(*continued on next page*)

Table 1 (*continued*)

Question	Subquestion/options	Recommendation	Strength of recommendation[a]
11. After R0 surgery of both colorectal and liver tumours, would you consider associated targeted therapy?	1. Yes, routinely 2. No, never 3. Only in patients responding to preoperative targeted therapy	• The use of targeted therapy (anti-EGFR and VEGF monoclonal antibodies) following R0 surgery is not advocated	A

CRC, colorectal cancer; EGFR, epidermal growth factor receptor; LM, liver metastases; VEGF, vascular endothelial growth factor.

[a] Attributed based on the Strength of Recommendation Taxonomy [12]: 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.



		p value
-1 to 0	0 to 3	<0.0001
-1 to 0	3 to 6	0.35
-1 to 0	6 to 12	0.52
-1 to 0	>12	<0.0001
0 to 3	3 to 6	0.048
0 to 3	6 to 12	0.01
0 to 3	>12	0.023
3 to 6	6 to 12	0.75
3 to 6	>12	0.0001
6 to 12	>12	<0.0001

Survival %

Diagnosis of metastases	1 year	2 years	3 years	4 years	5 years
-1 to 0 months	89%	73%	58%	46%	39%
0 to 3 months	91%	77%	64%	53%	44%
3 to 6 months	89%	75%	62%	48%	41%
6 to 12 months	90%	74%	57%	46%	41%
>12 months	92%	78%	66%	56%	48%

Number of exposed patients

	Total	1 year	2 years	3 years	4 years	5 years
-1 to 0 months	5272	3456	2259	1429	896	572
0 to 3 months	2783	1901	1294	840	542	341
3 to 6 months	1339	871	581	382	220	151
6 to 12 months	1913	1256	832	525	327	229
>12 months	4912	3346	2282	1550	1028	704

Fig. 1. Survival after liver resection for synchronous metastases in relation to the timing of diagnosis of the liver metastases.

- Synchronous CRCLM should be termed 'synchronously detected liver metastases'. This is defined as LM detected at or before diagnosis of the primary tumour.
- Early metachronous metastases are considered to be those detected within 12 months after diagnosis or surgery of the primary.
- Late metachronous metastases are considered to be those detected more than 12 months after diagnosis or surgery of the primary.

The role of imaging in the detection of synchronous CRCLM

Imaging is used to detect and characterize liver nodules and evaluate resectability. Imaging modalities include ultrasound, contrast-enhanced ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET)-CT. The best methods for staging are CT and MRI. A review of the literature indicates that MRI is more sensitive than CT for subcentimetre liver lesions [21] and after neoadjuvant chemotherapy [22], and that a thoraco-abdominal CT is the best option for initial staging [12]. Appraisal of published methods shows that a quadri/triphasic technique, optimal contrast administration and scanning parameters providing high spatial and contrast resolution show superior CT accuracy than generally reported in the literature [23–25,22]. Regardless of the technique, the need for high-quality baseline imaging before any chemotherapy cannot be stressed enough. Lesions are easier to see before chemotherapy and treatment response helps in characterization. MRI should be performed when characterization is difficult (e.g. when there are many small nodules including both metastatic and benign lesions) and when the liver is fatty [26]. Given the current state of technical development and experience, high-quality MRI and CT can be used for preoperative imaging.

In an RCT of patients with resectable CRCLM (not specifically synchronous), the use of PET-CT compared with CT alone did not result in significant changes in surgical management [27]. A role

for PET-CT has been suggested for detecting distant metastases [28,29]. Contrast-enhanced intraoperative ultrasound has been shown to improve both the sensitivity of intraoperative ultrasonography to detect LM and the rate of complete resection of hepatic metastases in patients undergoing surgery for CRCLM after chemotherapy [30].

Consensus recommendations

- The panel was unanimous that initial CT has to be performed before and after injection of iodine contrast, and that the use of a low dose to decrease irradiation exposure is not appropriate.
- If synchronous CRCLM are initially resectable, liver MRI may be performed in addition to the initial high-quality CT, depending on local expertise and the clinical scenario.
- PET-CT may be useful for the detection of extrahepatic disease, particularly in patients with recurrent disease or high tumour load (multinodular and/or large metastases) or for whom difficult hepatic resections are planned.

Role of imaging in evaluating response to preoperative treatment

Assessing the response to preoperative treatment (chemotherapy with or without targeted agents) can be judged on tumour size [31,32], morphologic changes unrelated to size [33–35] and metabolic activity [36,37]. Change in size is a key indicator of response, but limitations encountered with the Response Evaluation Criteria In Solid Tumors (RECIST) have led investigators to explore alternative measures of the impact of chemotherapy on tumour size [38,39] and to define new parameters such as early tumour shrinkage and depth of response [40,41]. It has been shown that when treatment includes biological agents, such as bevacizumab, size is a poor predictor of outcome compared with non-size-based morphological criteria [35,34]. PET-CT is increasingly used to measure response in oncology, but its role when added to cross-sectional imaging to assess response in CRC metastases needs to be further explored [36,37].

Consensus recommendations

- The following information should be provided by the radiologist for evaluating the response to treatment based on CT imaging:
  - Response based on size criteria.
  - Response based on morphological criteria.
  - Assessment of steatosis and signs of portal hypertension.
  - Evaluation of the predicted future liver remnant in the preoperative setting.
- Liver MRI is useful in patients with steatosis and to characterize unclear liver lesions, but the value of routine repeat MRI to evaluate response remains unclear.

Pathology and molecular biology

The role of pathology in the management of CRCLM, including synchronous CRCLM, is important in: diagnosing the specific tumour type; assessing the completeness of resection and tumour response; determining non-tumoral injury or reaction to preoperative chemotherapy; and defining tumour behavior in terms of lymphovascular invasion. Thereby, it provides an estimate of prognosis based on the tumour biology coupled with specific identification of biomarkers, such as epidermal growth factor receptor (EGFR, *KRAS* wild-type expression), vascular endothelial growth factor (VEGF) and the VEGF receptor. As yet, no biological marker has been identified that distinguishes synchronous metastases from metachronous metastases. *RAS* (*NRAS* and *KRAS)* mutations have been associated with worse disease-free and overall survival following CRCLM resection, independent of anti-EGFR therapy [42–44].

Identifying patterns of pathological tumour response to chemotherapy is a standard assessment and may guide surgery. The degree of pathological tumour response to chemotherapy is used as a surrogate marker of chemotherapy efficacy and of biological behavior of the tumour, recurrence and survival outcomes. It can also identify adverse effects of chemotherapy, such as chemotherapy-associated sinusoidal injury [45] or steatohepatitis [46]. A complete pathological response is reported in only about 10% of cases [47–50]. Tumour regression grade [49], percentage of viable tumour cells [47] and the thickness of the tumour's peripheral rim ('dangerous halo') [50] have all been used to evaluate pathological response. These criteria have been validated in multicentre studies associating response and survival. All but halo thickness have been shown to be prognostic for overall survival [47,50,48,49,51]. Safe resection margins are a goal of therapy but the optimal margin width remains to be determined; however, most studies indicate a minimal margin of 1 mm [52]. Intrahepatic micrometastases are only visible under a microscope and represent tumour invasion of sinusoids, the portal vein, the hepatic vein, and lymphatic and bile ducts [53,54]. Micrometastases are separated from CRCLM by a thin rim of normal parenchyma. Their incidence and distance from the tumour seem to increase with the size of CRCLM [53,55–57], but they are usually located within 1 cm of CRCLM. Micrometastases have been less frequently detected in patients receiving preoperative chemotherapy (25%) than in untreated patients (60%), but preoperative chemotherapy does not significantly reduce the distribution of micrometastases [53]. Several studies have shown micrometastases to have a negative impact on outcomes [58,57,54].

It has been hypothesized that metachronous CRCLM have a different biology after failure of FOLFOX compared with after 5-fluorouracil or no chemotherapy. Adjuvant FOLFOX has been associated with a high rate of somatic mutations in CRCLM and inferior outcomes after hepatectomy, including shorter disease-free survival and overall survival, than in the other two groups [59].

Consensus recommendations

- A standardized pathological evaluation report should include information on: the size of the tumour and margin size; toxic effects of therapy on non-tumour tissue; and the presence of micrometastases and a 'dangerous halo' (may indicate worse overall disease biology).
- Safe resection margins are still a goal of therapy; a minimal surgical clearance margin of 1 mm has been suggested as sufficient.
- No biological marker has yet been identified that distinguishes the biology and prognosis of synchronous from metachronous CRCLM.
- Tumour response to preoperative therapy is evaluated using tumour regression grade and/or pathological response (percentage viable tumour cells). Other scoring systems are available and have prognostic value.
- Molecular evaluation of LM is playing an increasing role in the evaluation of the biology of CRCLM. *RAS* (*NRAS* and *KRAS*) mutations have been associated with worse disease-free and overall survival after CRCLM resection, independent of anti-EGFR therapy.

Chemotherapy regimens for synchronous resectable metastases

Preoperative chemotherapy for synchronous metastases was advocated by all but one panel member. It was recognized that more evidence is needed to support this non-surgical strategy [60,61]. It has been suggested that preoperative chemotherapy has the benefit of downsizing unresectable metastases and increasing resectability of originally unresectable metastases, but not of resectable metastases [61]. It might also be useful for assessing tumour sensitivity to chemotherapy in patients with advanced disease. Elevated levels of carcinoembryonic antigen have been shown to be a marker of response to perioperative FOLFOX in patients with resectable CRCLM, regardless of the number of metastatic lesions [62]. One panel member favored liver resection first when disease is initially easily resectable.

Chemotherapy regimens for synchronous unresectable metastases

Chemotherapy regimens in mCRC are now achieving high response rates (>50%) and long median survival (~30 months). Any of the regimens used for the first-line management of advanced CRC are indicated in cases of synchronous LM, including FOLFOXFIRI with or without bevacizumab or anti-EGFR therapy, and doublets plus bevacizumab or anti-EGFR therapy [63–66]. In patients not responding to first-line chemotherapy, second-line therapy for mCRC with FOLFIRI plus panitumumab can still elicit a treatment response [67]. Resection is possible but not common following second-line treatment [68,69]. Although there are no evidence-based data to support the use of targeted therapies after resection, if a regimen is effective in the preoperative setting, many teams use the same regimen postoperatively.

Although upfront surgery of the primary tumour is advocated by some [70], studies have shown that preoperative chemotherapy can delay surgery of an asymptomatic primary tumour in patients with synchronous CRCLM without compromising survival [71–73].

Data from the GERCOR database, and also from the Crystal and OPUS studies, suggest that in patients with unresectable disease, the response rate is higher in patients with liver-limited metastases than in those with non-liver-limited metastases (personal communication, Aimery de Gramont) [74]. GERCOR data also suggest that response to second-line therapy does not depend on response to first-line therapy (personal communication, Aimery de Gramont).

With longer overall and median survival rates, indications for surgery are increasing, with R1 surgery (complete tumour resection without safe margins) being justified for patients with a response to preoperative chemotherapy [75,76]. Following preoperative chemotherapy and resection, adjuvant chemotherapy should be considered. The panel considered the optimal timing for assessment of response to chemotherapy to be every 2 months. These recommendations are in keeping with those from the European Society for Medical Oncology for mCRC, which recommend cytotoxic doublet plus targeted therapy for patients with potentially resectable and unlikely resectable mCRC [77], and those of the National Institute for Health and Care Excellence (NICE) in England and Wales [78]. Overall, a total duration of 6 months of perioperative (preoperative and adjuvant) chemotherapy is recommended.

Consensus recommendations

- All but one panel member favored first-line optimal chemotherapy for patients with potentially resectable synchronous metastatic disease.
- Optimal chemotherapy regimens for synchronous CRCLM include doublets (e.g. FOLFOX, FOLFIRI) combined with targeted therapy (e.g. bevacizumab, cetuximab, panitumumab, depending on RAS status), triplets (FOLFOXIRI) and triplets combined with targeted therapy. However, there was a consensus that chemotherapy without targeted therapy could be used for patients with resectable CRCLM in the absence of evidence for biological agents being useful in this setting.
- As advocated in earlier recommendations for synchronous CRCLM, at least four courses of first-line chemotherapy should be given and, if progression occurs during first-line therapy or only stable disease is achieved after 4 months, second-line treatment should be considered if conversion from borderline or non-resectable metastases to resectability is still the goal [79].
- A sequential treatment approach (e.g. adding a third agent to a doublet) may be used to treat patients who are unresponsive to first-line therapy.
- The optimal timing for assessing response to chemotherapy is considered to be every 2 months.
- These recommendations are in line with those from the European Society for Medical Oncology for mCRC, which recommends cytotoxic doublet plus targeted therapy for patients with potentially resectable and unlikely resectable mCRC [77], and those of NICE in England and Wales [78].
- Overall, a total duration of 6 months of perioperative (preoperative and adjuvant) chemotherapy is recommended.

Surgery of the primary tumour

Colorectal surgery should be performed by a specialist colorectal surgeon. The quality of surgery is as important for tumours of the rectum as it is for those of the colon and requires total mesocolon/mesorectal excision, lymph node clearance and a good margin of resection. Based on preoperative staging, the surgeon must be aware of the tumour margins before surgery. For rectal cancer, most patients with synchronous CRCLM will have a local tumour burden that requires radiotherapy.

When both the primary tumour and the metastases are resectable, simultaneous resection can be performed in selected patients undergoing limited hepatectomy with similar outcomes to sequential surgery [80,81,13]. Simultaneous resection should be discouraged when the hepatectomy would be major (involving three or more segments) or when complex rectal surgery is to be performed, due to significantly higher postoperative mortality and morbidity [82].

Delaying hepatic resection does not impair survival and may help select those patients most likely to benefit from hepatic resection [83]. When CRC is asymptomatic, the decision for surgery depends on the resectability of CRCLM. When CRCLM are non-resectable, the benefit of resection of the primary tumour without liver resection is debatable, although the results of a meta-analysis have shown a survival benefit [84]; however, data from this meta-analysis of non-randomized trials are questionable due to potential publication biases. Several RCTs have been started but most have not recruited a sufficient number of patients, and have been stopped prematurely [85].

Laparoscopy is increasingly being used and is generally feasible for the colon and rectum, but is more difficult if the tumour has invaded adjacent organs or perforated the visceral peritoneum (T4). Compared with conventional surgery, laparoscopy is associated with less pain, better pulmonary function, reduced fatigue, shorter hospital stay and better quality of life [86,87]. Laparoscopic surgery for colon and rectal cancer provides similar overall and disease-free survival to open surgery [88]. In addition, the incidence of sexual dysfunction and micturition symptoms

following rectal cancer surgery by laparoscopy has been reported to be similar to that following open surgery [89].

Consensus recommendations

- Colorectal surgery should be performed by a specialist colorectal surgeon.
- Laparoscopy is generally feasible for the colon and rectum, with similar outcomes to open surgery, but is more difficult if the tumour has invaded adjacent organs or perforated the visceral peritoneum (T4).
- For synchronous rectal LM, preoperative radiotherapy is recommended for mid or low rectal tumours, but chemotherapy remains an adequate treatment for LM.
- When both the primary tumour and the metastases are resectable and uncomplicated, simultaneous resection can be performed in selected patients undergoing limited hepatectomy.
- When synchronous CRCLM are non-resectable, resection of the asymptomatic primary without liver resection might have benefits.

Surgery of the liver

The classical approach to surgery of synchronous CRCLM has been to perform primary surgery on the primary CRC followed by resection of LM 2–3 months later, with or without chemotherapy in the interval between surgeries. Currently, preoperative chemotherapy is increasingly being used and, if the CRC is asymptomatic, may be administered before surgery of the primary tumour with the aim of downsizing the metastases and improving resectability rates. As mentioned above, simultaneous resections for CRC and synchronous LM have been shown to be favorable in a number of studies, although caution should be exercised for major combined resections or in patients with comorbid conditions, due to the higher risk of mortality and complications related to simultaneous surgery in this setting [80,81,13,82].

When the primary CRC is asymptomatic, and in particular for those patients requiring neoadjuvant radiotherapy for rectal cancer, liver surgery might be performed first (reverse approach). If both primary rectal cancer radiation and CRCLM chemotherapy are required, initial short-course (5×5 Gy) radiation followed by chemotherapy is recommended. Preoperative chemotherapy is advised to downsize synchronous CRCLM for resection, to minimize the risk of synchronous CRCLM progressing beyond the possibility of cure and to minimize the occurrence of new metastases [90]. Resection of CRCLM should be performed as soon as it appears feasible after tumour shrinkage [91]. When patients receive more than 6 months of aggressive chemotherapy, the risk associated with surgery is increased [92]. Similar outcomes have been reported for patients undergoing a classic (CRC first), combined or reverse (liver-first) surgical strategy for synchronous CRCLM [93].

Hepatic resection should not be denied to patients with stable disease after optimum chemotherapy, provided there is adequate liver remnant with inflow and outflow preservation. This may be achieved, for example, through advanced techniques such as portal and/or hepatic venous embolization or two-stage hepatectomy [94–96]. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) to induce growth of the future liver remnant before liver resections is being investigated, but results to date indicate increased complications and mortality [97]. Data on overall and long-term survival with ALPPS are needed.

In Asia, resectable synchronous CRCLM are more likely to be indicated for upfront simultaneous resection (before chemotherapy) [98], whereas in Westernized countries, chemotherapy first is the preferred option [78,77]. One-stage surgery is more frequently performed in Asia, with acceptable short-term outcomes.

Consensus recommendations

- Simultaneous surgery of the primary tumour and CRCLM should be reserved for selected patients with both resectable lesions and requiring limited surgical procedures.
- Preoperative chemotherapy is usually advised to control the metastatic disease and to downsize synchronous CRCLM for resection.
- The reverse approach (i.e. liver surgery performed first) may be used after preoperative chemotherapy when the CRCLM tumour burden is large and combined resection is not possible.
- Hepatic resection should not be denied to patients with stable disease after optimum chemotherapy, provided there is adequate liver remnant with vascular inflow and outflow preservation.
  - o This may be achieved through specific techniques aimed to increase resectability.

Multidisciplinary teams

The last few years have seen a greater awareness of the importance of MDTs. Results from a first prospective study to evaluate the MDT discussion process and its effects on treatment approaches for a variety of gastrointestinal cancers at a US cancer centre have recently been published [99]. Despite 84% of clinicians being certain of their original plan, a change was recommended in 36% of cases, 72% of which involved major changes; there was 77% adherence to the recommended treatments. The potential advantages of an MDT include better patient care and survival outcomes, and improved consistency, continuity, coordination and cost-effectiveness of care [100–102]. Same-centre management also has benefits over referred-patient management, including a reduced number of interventions, shorter delays in care, better control of chemotherapy and decreased postoperative mortality [103–105]. This could be of utmost importance in patients with synchronous metastases.

Non-adherence to MDT decisions has been shown to result in a trend toward lower survival rates in lung cancer [106]. A UK study of non-adherence to MDT decisions (15.1% of decisions were not implemented) in gastrointestinal surgery showed the main reasons for non-adherence to be comorbid conditions (43.9%), patient choice (34.2%) and more information becoming available (19.5%) [107].

Consensus recommendations

- A proficient MDT consisting of at least a colorectal surgeon, liver surgeon, medical/gastrointestinal and radiation oncologist, radiologist, nuclear medicine physician and pathologist optimizes the treatment of CRCLM.
- The treatment should be considered as a whole, from diagnosis to the last treatment at the same centre.
- It is important to evaluate and analyze the outcomes from MDTs to assess improvements in treatment goals.

The critical impact of the expertise of the team for patient management

Following the mandatory legal requirement for MDT management of all cancer patients in the UK, France, Belgium, Spain and a number of other European countries over the last 10–15 years, there has been a significant overall improvement in outcomes for all patients with stage IV CRC [108,109]. A specialized MDT

dedicated to the management of stage IV CRC is superior to that of a general CRC MDT [110,111] and should include surgeons specializing in colorectal surgery, hepatobiliary surgery and thoracic surgery, dedicated CRC medical and radiation oncologists, both imaging and interventional radiologists, and dedicated CRC surgical pathologists.

Clinical scenario recommendations for synchronous CRCLM

In clinical practice, the main determinants of the decision-making process are the tumour statuses of both the primary tumour and metastases and, more precisely, the need for emergency surgery of a complicated primary tumour and the resectability of both tumour sites.

Asymptomatic CRC and resectable synchronous CRCLM

This is the most favorable clinical scenario. A panel consensus (10/11, 91%) was reached for chemotherapy to be given preoperatively. Four or six cycles of chemotherapy were recommended. However, data from the LiverMetSurvey show that 5-year survival is not better with chemotherapy first than with surgery of the primary tumour first (42% vs 47%, respectively) (Fig. 2). It is, however, likely that surgery of the primary tumour first could have been reserved for selected patients with less widespread disease compared with those treated with chemotherapy first.

For mid and low rectal primary tumours, radiotherapy is often needed and one-stage surgery should not be performed. For colonic and upper rectal primary tumours, one-stage surgery is not advocated for complex colonic tumours, for high-risk patients or when hepatectomy is major ($\geqslant$3 segments). Data from the LiverMetSurvey show that irrespective of the status of the primary tumour, one-stage resection of both the primary tumour and metastases is associated with worse 5-year survival (40%) compared with liver-first surgery (47%) or primary-first surgery (44%) (Fig. 3).

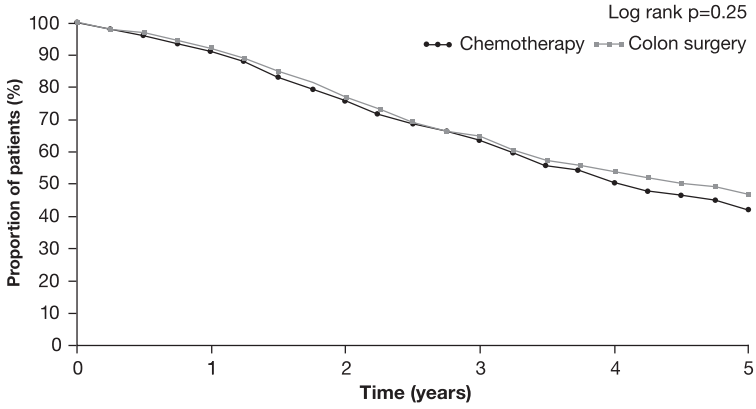
Most panel members (8/12, 67%) considered pre- and postoperative chemotherapy to be equally important; 3/12 (25%) considered preoperative chemotherapy and 1/12 (8%) considered postoperative chemotherapy to be most important. Most participants (9/11, 82%) considered that postoperative chemotherapy could be different to preoperative chemotherapy, and probably less intensive.

In summary, the recommended management is for chemotherapy first, with or without radiotherapy, followed either by surgery in a one-stage procedure (for patients with limited hepatic disease and easy-to-resect primary tumours) or by staged surgery (for other patients). No strong evidence exists, however, to support this expert recommendation of chemotherapy first, as opposed to colon resection first.

Asymptomatic CRC and non-resectable synchronous CRCLM

This second scenario is one of the most frequently observed, and has traditionally been managed with resection of the primary tumour followed by chemotherapy and then surgery of metastases when resectability can be obtained. Treatment has since evolved, and the entire panel agreed that chemotherapy should be administered initially with the aim of achieving resectability of CRCLM. For potentially resectable disease, all were in favor of optimal chemotherapy (doublets plus biologics, or triplets plus biologics). Data from the LiverMetSurvey show no difference in 5-year survival rates between patients receiving chemotherapy first and those undergoing colectomy first, before resection of CRCLM (31% vs 33%, respectively) (Fig. 4). However, colectomy first may have been reserved for patients with the best prognosis, introducing a bias into the analysis. Three ongoing trials are comparing the management strategies of colectomy first vs chemotherapy first.

All of the panel experts agreed that simultaneous surgery should not be attempted. If CRCLM become resectable, all recommended the reverse approach to surgery (i.e. liver first). Data from the LiverMetSurvey, although not significantly different between strategies, support this approach; 5-year survival rates were 42% for the reverse approach compared with 33% for colon first surgery and 28% for one-stage surgery (Fig. 5). For rectal cancer, alternative approaches are to begin with short-course radiotherapy for the primary cancer and then chemotherapy for downsizing CRCLM or to administer primary optimal chemotherapy, then radiotherapy



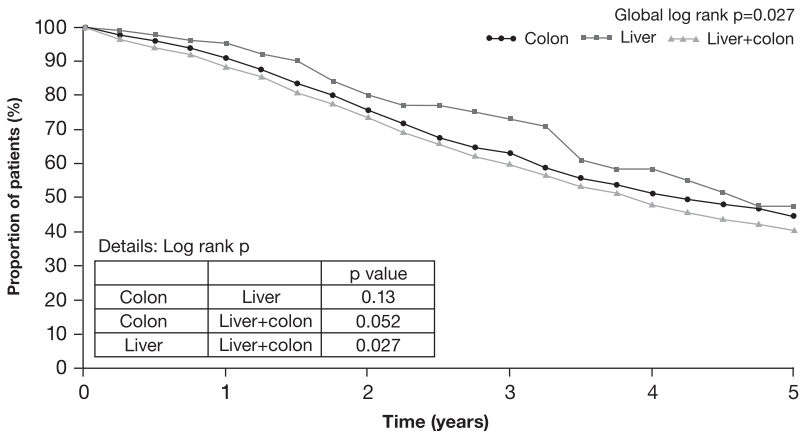
Survival %

First treatment	1 year	2 years	3 years	4 years	5 years
Chemotherapy	91%	76%	63%	50%	42%
Colon surgery	92%	77%	65%	54%	47%

Number of exposed patients

	Total	1 year	2 years	3 years	4 years	5 years
Chemotherapy	798	540	324	198	123	75
Colon surgery	1554	1058	707	465	312	221

Fig. 2. Survival following liver resection for synchronous resectable metastases in relation to first treatment (colon surgery or chemotherapy).



		p value
Colon	Liver	0.13
Colon	Liver+colon	0.052
Liver	Liver+colon	0.027

Survival %

First surgery	1 year	2 years	3 years	4 years	5 years
Colon	91%	76%	63%	51%	44%
Liver	95%	80%	73%	58%	47%
Liver+colon	89%	73%	60%	48%	40%

Number of exposed patients

	Total	1 year	2 years	3 years	4 years	5 years
Colon	1813	1222	811	531	353	246
Liver	150	99	54	34	18	11
Liver+colon	1181	816	541	350	225	134

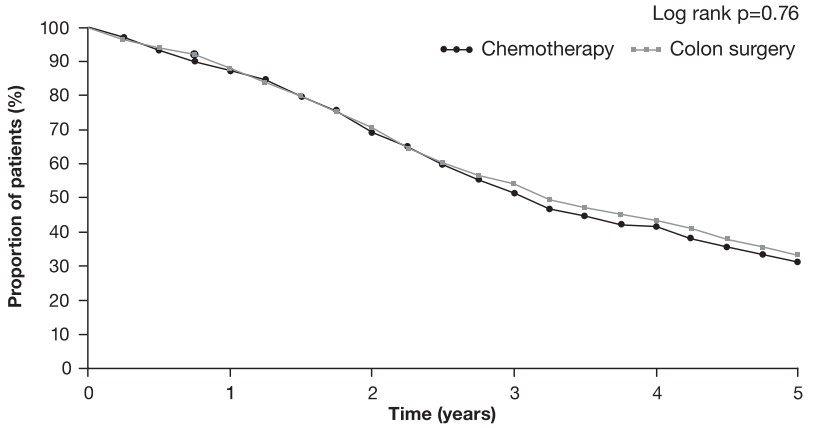
Fig. 3. Survival after liver resection for synchronous resectable metastases in relation to the first surgery (colon, liver or colon plus liver).

and, in the window between irradiation and rectal cancer surgery, resection of CRCLM. For primary colon or rectal tumours that appear unresectable or borderline resectable, in the UK, NICE guidance is that preoperative chemotherapy should not be offered solely to facilitate sphincter-sparing surgery to patients with rectal cancer [78].

In summary, the consensus is for optimal chemotherapy first, with the aim of making LM resectable. This should then be followed by hepatic surgery and resection of the primary tumour.

Symptomatic CRC and resectable synchronous CRCLM

Patients with symptomatic CRC may have bleeding, obstruction or perforation. Generally, bleeding can be managed with blood transfusions and will often stop after chemotherapy treatment. Most of the expert panel (9/12, 75%) were in agreement that patients with bleeding should undergo preoperative chemotherapy; the others (3/12, 25%) considered that resection of the primary tumour should be undertaken first.



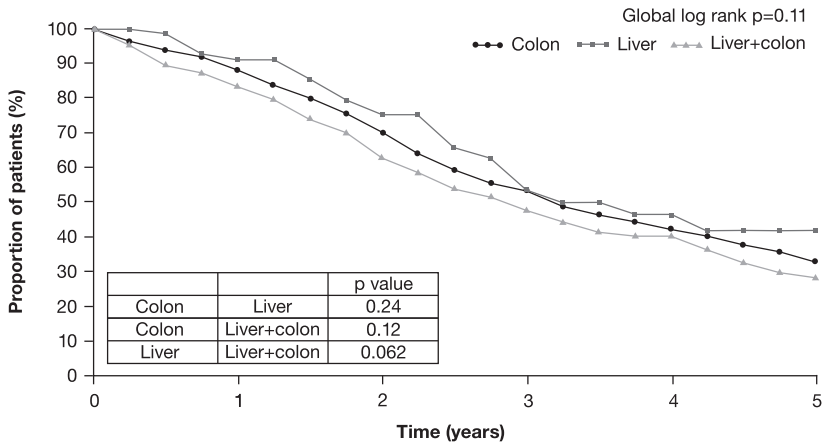
Survival %

First treatment	1 year	2 years	3 years	4 years	5 years
Chemotherapy	87%	69%	52%	42%	31%
Colon surgery	88%	71%	54%	43%	33%

Number of exposed patients

	Total	1 year	2 years	3 years	4 years	5 years
Chemotherapy	470	280	169	88	52	28
Colon surgery	705	460	293	180	105	61

Fig. 4. Survival following liver resection for synchronous unresectable metastases in relation to first treatment (colon surgery or chemotherapy).



Survival %

First surgery	1 year	2 years	3 years	4 years	5 years
Colon	88%	70%	53%	42%	33%
Liver	91%	75%	53%	46%	42%
Liver+colon	83%	63%	47%	40%	28%

Number of exposed patients

	Total	1 year	2 years	3 years	4 years	5 years
Colon	855	553	348	210	123	74
Liver	82	55	35	16	11	4
Liver+colon	328	187	113	58	33	17

Fig. 5. Survival following liver resection for synchronous unresectable metastases in relation to first surgery (colon, liver or colon plus liver).

For bowel perforation, surgery is required either to remove the tumour when it is easily resectable, such as right hemicolectomy for right-sided colon lesions or sigmoid colectomy for sigmoid lesions, or to create a stoma (left colon) in cases requiring more technical surgery, such as low anterior resection syndrome and total mesorectal excision. The panel was in complete agreement that, if possible, resection of the primary tumour should be performed first under these circumstances.

Stents are an option for colorectal obstruction, but the results have been poor and the panel recommended reserving them only for easily resectable cases, particularly in elderly patients, and not for right colon or rectal surgery or when anti-angiogenic agents are used. This guidance is in line with that provided by the Endoscopy and Cancer Committee of the French Society of Digestive Endoscopy and the French Federation of Digestive Oncology [112] and with UK NICE guidance [78]. For clinically and radiologically proven complete occlusion with distended evidence of obstruction, the panel was in complete agreement that resection of the primary tumour should be performed first; 9/11 (82%) would perform surgery and use a stoma, whilst 2/11 (18%) would use a stent.

In summary, recommendations are for resection of the primary tumour for perforated or occlusive tumours (but not for tumours with bleeding causing anaemia), followed by chemotherapy and then surgery of LM.

Symptomatic CRC and non-resectable synchronous CRCLM

The expert panel considered that the aim of management for patients with symptomatic CRC and non-resectable synchronous CRCLM is to make the LM resectable. The use of stents is not recommended in most patients owing to the high risk of complications (e.g. perforation, migration bleeding, pain). As in the previous clinical scenario, surgery of the primary tumour should be reserved for cases of bowel perforation or occlusion, with systemic chemotherapy used to downsize both metastases and the primary tumour in other scenarios.

In summary, recommendations are for resection of the primary tumour for perforated or occlusive tumours, followed by chemotherapy and then surgery of LM if tumour shrinkage is achieved. For tumours with bleeding causing anaemia, induction chemotherapy is recommended to downsize both the primary tumour and LM, followed by surgery of the site with the most significant tumour load (usually the liver; i.e. reverse approach).

Conclusions

Synchronous CRCLM should be termed 'synchronously detected liver metastases'. This is defined as LM detected at or before the diagnosis of the primary tumour. Synchronous CRCLM may have less favorable cancer biology and be associated with lower expected survival compared with metachronous metastases. Initial high-dose contrast-enhanced CT of the abdomen is recommended to provide information on whether synchronous CRCLM are resectable.

Recommendations have been made for the management of four different clinical scenarios

1. For asymptomatic CRC and resectable synchronous CRCLM, the recommended management is for chemotherapy first, with or without radiotherapy, followed either by surgery in a one-stage procedure (for patients with limited hepatic disease and easy-to-resect primary tumours) or by staged surgery (for other patients). No strong evidence exists, however, to support

this expert recommendation of chemotherapy first, as opposed to colon resection first; ongoing trials may provide such evidence.
2. For asymptomatic CRC and non-resectable synchronous CRCLM, the consensus is for optimal chemotherapy first, with the aim of making LM resectable. This should then be followed by hepatic surgery and resection of the primary tumour.
3. For symptomatic CRC and resectable synchronous CRCLM, recommendations are for resection of the primary tumour for perforated or occlusive tumours (but not for tumours with bleeding causing anaemia), followed by chemotherapy and then surgery of LM.
4. For symptomatic CRC and non-resectable synchronous CRCLM, recommendations are for resection of the primary tumour for perforated or occlusive tumours, followed by chemotherapy and then surgery of LM if tumour shrinkage is achieved. For tumours with bleeding causing anaemia, induction chemotherapy is recommended to downsize both the primary tumour and LM, followed by surgery of the site with the most significant tumour load (usually the liver; i.e. reverse approach).

At least four courses of first-line optimal chemotherapy (doublets with targeted therapy or triplets with or without targeted therapy) are recommended for potentially resectable metastatic disease, with assessment of response every 2 months and a total (preoperative and adjuvant) duration of 6 months' systemic therapy. Intra-arterial chemotherapy may be an alternative option and has been associated with good response rates.

It is hoped that the recommendations provided and the treatment plans for the four different clinical scenarios should help to raise the standard of care for patients with synchronous CRCLM.

Author contributions

All authors met the International Committee for Medical Journal Editors criteria for authorship, were fully involved in manuscript development, and assume responsibility for the direction and content. All authors have approved the manuscript for submission.

Disclosures

RA discloses advisory roles for Amgen, Merck Serono and Sanofi-Aventis, and has participated in presentations sponsored by Amgen, Merck Serono, Roche and Sanofi-Aventis. AdG discloses advisory roles for Roche, Sanofi, Lilly and Sirtex, and has participated in presentations sponsored by Roche and Sanofi. JF discloses an advisory role for Roche, and has participated in presentations sponsored by Roche, Merck Serono and Sanofi. NK discloses research funding from Dainippon Sumitomo Pharma, Merck Serono, Bristol-Meyers Squibb, Chugai, Taiho Yakuhin and Bayer. FK has no conflicts of interests to disclose. EL discloses a consulting agreement with Novartis Pharma AG and has participated in presentations sponsored by Roche. GP discloses advisory roles for Biocompatibles, Merck Serono, Pfizer and Sanofi-Aventis, and has participated in presentations sponsored by Biocompatibles, Merck Serono, Pfizer and Sanofi-Aventis. PR discloses advisory roles for Keocyt, Merck Serono, Sanofi and Sirtex, and research funding from Roche and Servier, and has participated in presentations sponsored by Amgen, Merck Serono, Pfizer and Sanofi. LR-B has no conflicts of interests to disclose. AS discloses advisory roles for Amgen, Bayer, Merck Serono, Roche and Sanofi, and has participated in presentations sponsored by Amgen, Merck Serono, Roche and Sanofi. CT discloses participation in presentations sponsored by Merck Serono. ST has no conflicts of interest to disclose. EVC discloses research funding from Amgen, Bayer, Boehringer, Eli-Lilly, Merck Serono, Pfizer, Roche and Sanofi. J-NV discloses honoraria and research funding from Roche and Sanofi-Aventis. LP has no conflicts of interest to disclose.

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