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CONSENSUS STATEMENT

The multi-societal European consensus on the terminology, diagnosis and management of patients with synchronous colorectal cancer and liver metastases: an E-AHPBA consensus in partnership with ESSO, ESCP, ESGAR, and CIRSE

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Abstract

Background: Contemporary management of patients with synchronous colorectal cancer and liver metastases is complex. The aim of this project was to provide a practical framework for care of patients with synchronous colorectal cancer and liver metastases with a focus on terminology, diagnosis and management.

Methods: This project was a multi-organisational, multidisciplinary consensus. The consensus group produced statements which focused on terminology, diagnosis and management. Statements were refined during an online Delphi process and those with 70% agreement or above were reviewed at a final meeting. Iterations of the report were shared by electronic mail to arrive at a final agreed document comprising twelve key statements.

Results: Synchronous liver metastases are those detected at the time of presentation of the primary tumour. The term "early metachronous metastases" applies to those absent at presentation but detected

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within 12 months of diagnosis of the primary tumour with "late metachronous metastases" applied to those detected after 12 months. Disappearing metastases applies to lesions which are no longer detectable on MR scan after systemic chemotherapy. Guidance was provided on the recommended composition of tumour boards and clinical assessment in emergency and elective settings. The consensus focused on treatment pathways including systemic chemotherapy, synchronous surgery and the staged approach with either colorectal or liver-directed surgery as first step. Management of pulmonary metastases and the role of minimally invasive surgery was discussed.

Conclusions: The recommendations of this contemporary consensus provide information of practical value to clinicians managing patients with synchronous colorectal cancer and liver metastases.

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Introduction

In 2020, the European Commission estimated that colorectal cancer accounted for 12.7% of all new cancer diagnoses and 12.4% of all deaths due to cancer making this the second most frequently occurring cancer.[1] About one-fifth of patients with colorectal cancer have metastases either exclusively or predominantly in the liver at the time of presentation.[2] Hepatic metastases may also be detected later in the course of the disease.[2]

Current guidelines for the management of colorectal cancer are provided by the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) in addition to other organisations/societies.[3–7] The relative absence of high-quality evidence in relation to surgical aspects of the management of patients with synchronous colorectal cancer and liver metastases results in these guidelines providing only broad recommendations in this area. For example, neither the NCCN nor the ESMO guidelines address definitions of synchronous/metachronous disease or "disappearing" metastases and the focus on management is relatively limited in terms of guidance on selection of surgical treatment pathways.[3,4]

Recognising this information gap, the Expert Group on OncoSurgery management of Liver Metastases (EGOSLIM) produced a report in 2015 on the management of patients with colorectal cancer and synchronous liver metastases.[8] Almost a decade later, diagnostic options have increased and treatment pathways have become more complex.[9]

Consensus methodology is a valuable option to find concordance in current practice considering both the difficulty in conducting high quality surgical randomised trials in patients with synchronous colorectal cancer and liver metastases and the persisting evidence of variation in the use of definitions for synchronous disease.[10–12] This project was a major, multi-organisational, multidisciplinary collaborative consensus to provide a practical framework for care of patients with synchronous colorectal cancer and liver metastases with a focus on terminology, diagnosis and management.

Methods

Overview and scope

This project was a multi-organisational, multidisciplinary consensus to produce a practical document to guide clinicians involved in the care of patients with synchronous colorectal cancer and liver metastases. The scope of the project was to review and where necessary, update terminology and to describe current management pathways.

The MEDLINE®, EMBASE, Web of Science and Cochrane databases were queried in July 2022. The search terms 'colon cancer', 'rectum cancer' and 'liver metastases'were used in combinations. A search was carried out to inform the construction of each statement prior to circulation. Separate searches were undertaken for terminology, diagnosis, composition of multidisciplinary team, considerations for "upfront" synchronous surgery, chemotherapy for synchronous metastases, the "bowel-first" and "liver-first" approaches.

The final recommendations are based on expert consensus. Thus, the project report should not be considered a comprehensive evidence review. Further, although the consensus addresses integration of chemotherapy and (where appropriate) radiotherapy with surgery, the reader is referred to guidelines such as those of NCCN or ESMO for details on specific systemic chemo (radio) therapy regimens.[3,4]

Participants

This consensus project was commissioned by the executive committee of the European-African Hepato-Pancreato-Biliary Association (E-AHPBA) in September 2021. Formal submissions to participate in this project were accepted by the executive

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boards of the European Society of Surgical Oncology (ESSO), the European Society of Coloproctology (ESCP), the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) and the Cardiovascular and Interventional Radiology Society of Europe (CIRSE). The European Society for Medical Oncology (ESMO) did not formally participate but oncologists affiliated with this organisation participated in the exercise. Consensus participants were selected through two routes; first, those who had published work in areas relevant to the consensus and second, those who were invited to participate by their respective specialist societies. Participants in the consensus comprised 123 clinicians as follows: Hepato-Pancreato-Biliary (HPB) surgeons (including individuals with expertise in liver transplantation), colorectal surgeons, oncologists, radiologists (including individuals with expertise in magnetic resonance [MR scan] radiology and interventional radiology), cancer nurse specialists, histopathologists and surgeons in training. Prior to the consensus, a series of qualitative interviews was undertaken with patients who had synchronous colorectal cancer and liver metastases and their relatives/carers in order to ascertain their views on management.[13] These patients' views were utilized to inform the design of the questions and the subsequent statements of this consensus.

Design and content of statements for consensus

A subgroup of the consensus participants representing surgical, oncological and radiological specialties met in a series of online meetings to produce statements covering the scope of the project. Eighteen statements addressed definitions and clinical pathways. Specifically, these statements addressed terminology for synchronous and metachronous liver metastases, recommendations on the composition of a specialist multidisciplinary team and tests required for diagnosis and management in both the emergency and elective settings. Management of patients with a synchronous presentation included statements on selection for systemic chemotherapy as first intervention, synchronous surgery and the staged approach. Finally, there were specific statements on the term "disappearing metastases", the role of minimally invasive surgery and the management of pulmonary metastases. For each of the eighteen statements there were a series of qualifying sentences and a document with all statements was sent to all members of the consensus (see appendix 1).

Consensus process

The consensus process took place between June 2022 and December 2022 and consisted of two rounds of a Delphi process followed by a final face-to-face meeting in Zaragoza, Spain.[14,15] The Delphi process used SurveyMonkey (www.surveymonkey.com/mp/audience). The first round took place in September 2022. Results were collated and a threshold of 70% was set for consensus. Statements for which there was less than 70% support were removed or modified with respondents' feedback and used to produce a second round of the Delphi process. The third component was a final face-to-face meeting held in Zaragoza, Spain on 2nd and 3rd December 2022. The second-round statements, together with the results of the second round of Delphi voting were then individually discussed, followed by an audience vote.

Assembly of consensus report

All involved in the consensus process were invited to participate in the writing process. Results from the two Delphi rounds together with information from the face-to-face meeting were integrated into a final series of twelve statements. Iterations were shared by electronic mail to arrive at a final agreed document comprising twelve statements. Areas of persisting disagreement (lack of consensus) were also noted and acknowledged in the final document. As the recommendations were by consensus, grading of evidence was not used.[16] The eighteen statements used at the outset were compressed to twelve key statements after discussion. Research proposals generated during the consensus process were collated and will take the form of a separate manuscript.

Prior to submission, the final document was reviewed by a validation committee drawn up of experts on this topic (William Jarnagin, Jean-Nicholas Vauthey, Norihiro Kokudo and Sabine Tejpar).

Role of sponsors in consensus process

Multiple sponsors contributed to support the face-to-face consensus meeting. None had any role in the design of the statements or in the recommendations made in the final report.

Ethics

The E-AHPBA Scientific and Research Committee reviewed and approved this study. Although the project involves a collaboration between E-AHPBA, ESSO, ESCP, ESGAR and CIRSE, the responsibility for the views expressed in this manuscript rests with the consensus authors and this document does not represent an official position statement of any organisation.

Planned review and renewal

It is the intention to update this consensus document approximately five years after publication.

Results

i. terminology for description of synchronous and metachronous liver metastases (Table 1)

Synchronous liver metastases are defined as those detected at the time of presentation of the primary tumour (colon or rectal cancer). Use of this term is unchanged from the EGOSLIM consensus.[8] Evidence of differential survival between patients with liver metastases detected in the first 12 months after diagnosis of the primary compared to those detected after the first year is recognised by retention of the terms "early" and "late"

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Table 1 E-AHPBA/ESSO/ESCP/ESGAR/CIRSE Consensus terminology for synchronous and metachronous liver metastases

i. Liver metastases detected at the time of diagnosis of the primary are termed "synchronous".
ii. The definition of synchronous liver metastases also includes patients with incidental liver metastases detected intra-operatively.
iii. To be termed "metachronous" disease, liver metastases should have been excluded on cross-sectional imaging at the time of diagnosis of the primary tumour.
iv. Liver metastases detected up to 12 months after diagnosis of the primary tumour - but absent at presentation - are termed "Early Metachronous" metastases.
v. Liver metastases detected more than 12 months after diagnosis of the primary are termed "Late metachronous" metastases.

metachronous metastases respectively.[8] In order to be termed "metachronous" disease, liver metastases should be excluded on cross-sectional imaging at the time of diagnosis of the primary tumour.

Consideration was given to extending the time interval for the use of the term "synchronous" to either 3 or 6 months after diagnosis of the primary tumour.[17] Evidence from a literature review indicating similar survival for patients with synchronous liver metastases was also considered as the recommendations contradict the EGOSLIM recommendations.[17] However, from a practical perspective, management of the primary tumour will likely have taken place prior to the 3 or 6 month "extended" cut-offs and thus treatment of liver metastases discovered at these later time points is in effect the management of early metachronous disease. Therefore, this consensus does not recommend these extended time intervals for use of the term "synchronous".

ii. Scope and constitution of a multidisciplinary team (MDT; tumour board) for management of patients with synchronous colorectal cancer and liver metastases

The consensus recommends that all patients with liver metastases from colorectal cancer should have their care reviewed at a specialist MDT with expertise in the management of liver metastases.[18,19]

The consensus recommends that such an MDT should include the following core specialties: radiology (with expertise in gastrointestinal imaging), hepatobiliary (liver) surgery, colorectal surgery, gastrointestinal oncology, histopathology, cancer nurse specialist and MDT co-ordinator (case manager). In addition to this core group extended membership could comprise (but not be restricted to) interventional radiology, radiation oncology/radiotherapy, thoracic surgery, liver anaesthesiology and gastroenterology. The consensus acknowledges that the role and availability of cancer nurse specialists varies between healthcare systems. The consensus also accepts that in practice the composition of an MDT represents a compromise between an "ideal" arrangement, including both core and extended members and a pragmatic acknowledgement that logistics and workforce issues often restrict the ability of all specialties to be present in a single meeting.

iii. Diagnostic tests

The consensus recommendations broadly follow those of NCCN and ESMO and state the following.[3,4]

1) Contrast-enhanced computed tomography (CT) of the thorax, abdomen and pelvis should be undertaken at the time of presentation.
2) Liver MRI with hepatobiliary contrast agents should be undertaken at the time of presentation (and prior to any chemotherapy).[20] If hepatobiliary contrast agents are not available standard liver agents (not hepatocyte-specific) may be used.
3) There should be histological confirmation of diagnosis from biopsy of the primary tumour but not ordinarily from liver metastases.
4) Consideration should be given to undertaking a complete endoscopic examination of the colon and rectum at the time of diagnosis. CT colonography can be undertaken if complete endoscopy cannot be performed.[21]
5) Where available, MR for low and mid rectal primary tumours (within 12 cm proximal to the anal verge) should be undertaken at the time of presentation.[20] Trans rectal ultrasound (TRUS) may be an alternative although MR is preferred.[22]
6) Determination of mutation status for RAS, BRAF and HER2 amplifications either individually or as part of a next-generation sequencing (NGS) panel together with determination of MMR (mismatch repair) status should be performed from the primary tumour.[5,23,24]
7) Lesional liver biopsy may need to be considered in some specific settings – for example if there is a prior history of a different malignancy.
8) The tumour marker carcino-embryonic antigen (CEA) should be measured at baseline presentation for disease monitoring/surveillance.[25]

The consensus acknowledges the value of ^{18}fluorodeoxyglucose positron emission tomography (FDG-PET) in decision making in patients with stage IV colorectal cancer but does not recommend this test to be routinely used in the diagnosis of patients with synchronous colorectal cancer and liver metastases.[3,26]

The consensus also acknowledges that mutation analysis is currently not available in many healthcare systems.

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iv. Clinical management of the patient with synchronous colorectal cancer and liver metastases and an emergency presentation

The consensus recommends that surgery aimed at addressing the emergency complications of the primary tumour should be considered after appropriate resuscitation in patients with a performance status that permits active treatment.[27] There should be no intervention directed at the liver metastases during the emergency presentation.

The consensus recommends consideration of an endoluminal stent (for left-sided obstructing tumours), defunctioning stoma or resectional surgery for patients with intestinal obstruction depending on the circumstances and available expertise.[27,28]

In selected patients presenting with bleeding from rectal tumours, radiotherapy or interventional radiology techniques can be considered.[29,30]

After recovery from the acute episode, complete diagnostic staging should be undertaken.

v. further clinical assessment of the patient with synchronous colorectal cancer and liver metastases and an elective presentation

In addition to the diagnostic tests above, assessment of fitness for intervention is recommended. For patients of Eastern Co-operative Oncology Group staging (ECOG) zero status, additional fitness tests are not routinely recommended.[31] The consensus recommends that where available, dynamic cardiopulmonary exercise testing could be considered prior to surgery with selection depending on performance status.[32] A pre-habilitation programme could also be considered, depending on availability and time to surgical intervention.[33] The consensus acknowledges the limited evidence for pre-habilitation programmes at the present time.

Accurate documentation of disease stage and distribution is recommended as part of detailed clinical assessment after completion of diagnostic tests and the consensus recommends documentation (which could be on a standardized proforma) as follows.

1) In relation to the primary tumour, sidedness and radiological assessment of T stage (including circumferential margin involvement) and nodal status should be recorded.
2) The presence or absence of extra-hepatic metastases should be specified together with site.
3) In relation to thoracic metastases, number, laterality and definite or "indeterminate" should be noted.
4) In relation to liver metastases, the size, number and distribution within Couinaud segments should be specified. The consensus acknowledges that although documentation of extent, size and distribution of liver metastases is an important component of assessment this can be challenging in the situation of patients with multiple liver metastases. In this situation, the consensus acknowledges that relevant practice would be to document the segments involved at baseline as this could have practical implications for any potential surgical treatment after induction systemic therapy.[34,35] The consensus does not define a threshold number of metastases above which the benefit of documenting the number and size of lesions is limited.

During the Delphi rounds, statements were also included on describing the location of liver metastases in relation to important inflow/outflow structures and the vena cava. Although these were not retained in the final recommendations, the consensus notes that there may be situations where description of critical structures adjacent to a tumour would be valuable.

vi. Considerations for "upfront" synchronous resection of liver tumour(s) and bowel primary tumour in patients with resectable synchronous colorectal cancer and liver metastases

In this consensus, the term "upfront" applies to a proposed intervention when it is the first treatment. Synchronous resection of synchronous disease is defined as resection of liver metastases and primary bowel tumour under a single general anaesthetic (single surgery).

This consensus acknowledges the practical distinction between the management of colonic and rectal primary tumours including in relation to the use of neoadjuvant radiotherapy.[36,37] The consensus acknowledges the evidence of differential biological behaviour according to the sidedness or laterality of colon cancer but notes that at the present time this information is not widely integrated into treatment planning.[38]

The consensus makes the following recommendations in relation to undertaking synchronous hepatectomy with colectomy in patients with colonic tumours.

1. Although synchronous resection of liver and colonic tumours as a first step is supported by the consensus, it is emphasised that for most patients with colorectal cancer and synchronous liver metastases, systemic chemotherapy and not surgery will be the preferred first treatment.[3,4]
2. The consensus recommends that for patients considered for synchronous hepatectomy and colectomy there should be a combination of an adequate functional volume in the future liver remnant and a primary colon tumour not requiring neoadjuvant systemic treatment. The consensus does not define adequate future liver remnant beyond emphasising that there must be adequate biliary drainage, portal and arterial inflow, adequate venous drainage and sufficient parenchymal volume in the future remnant liver.[39,40]
3. The consensus recommends that when upfront synchronous liver resection is to be undertaken together with colectomy, the liver resection component should be a minor hepatectomy.[41]

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No consensus was reached on whether to support upfront synchronous major hepatectomy with colectomy although it is acknowledged that this combination can be safely undertaken.[11,42]

For patients with a rectal primary tumour, the consensus does not recommend upfront, synchronous liver resection together with rectal surgery. These patients normally require non-surgical treatments as a first step including radiotherapy, chemo-radiotherapy/total neoadjuvant therapy.[43,44]

The consensus acknowledges that the results of the ongoing COLLISION and NEW COMET trials comparing ablation to resection may influence a change towards the use of the term "locally treatable" rather than exclusively "resectable".[45,46] The options for local treatment by ablation should be evaluated at MDT.

vii. Considerations for "upfront" systemic chemotherapy in patients with synchronous colorectal cancer and liver metastases

The consensus recommends systemic chemotherapy as a first treatment in patients with a performance status which precludes surgery (but not systemic chemotherapy), in those with extra-hepatic disease at presentation (M_{1b} status) and in patients with peritoneal metastases at presentation (M_{1c} status).[3,4] The consensus refers clinicians to the current NCCN and ESMO guidelines for decision making around choice of chemotherapy agents, use of combination chemotherapy, biologic agent(s) and treatment regimens.[3,4]

viii. Considerations for a "bowel-first" approach in patients with synchronous colorectal cancer and liver metastases

The consensus supports the bowel-first approach in two settings; first, the patient with a symptomatic primary tumour and/or imminent intestinal obstruction or perforation,[21] second, as part of a staged approach (bowel-first; liver-second) to tumour clearance in patients with synchronous disease treated by systemic chemotherapy.[47] The consensus recommends re-staging with repeat cross-sectional imaging of the thorax, abdomen and pelvis and further MDT discussion between surgical stages. Resection of an asymptomatic primary colorectal tumour is not recommended in the presence of non-resectable liver metastases.[48,49]

ix. Considerations for a "liver-first" approach after systemic chemotherapy in patients with synchronous colorectal cancer and liver metastases

The term "liver-first" is defined in this consensus as liver resection as the first surgical intervention in patients with synchronous colorectal cancer and liver metastases.[50]

The consensus supports the "liver-first" approach in the following situations.

1) When there are specific liver-related criteria such as borderline resectability which favour hepatectomy first after systemic chemotherapy[51,52].
2) Patients with rectal tumours with a response to chemo-radiotherapy. Liver resection can be undertaken in the window between completion of chemo (radio)therapy of the rectal cancer and the ensuing evaluation of treatment response before surgical treatment of the rectal primary tumour.[52,53] This is the most widely accepted indication for the liver-first approach. Attention should be given to avoid the liver-first approach in patients with locally-advanced, surgically unresectable primary tumours.
3) Patients with rectal cancer and resectable synchronous liver metastases who have a clinical complete response of the primary tumour to neoadjuvant treatment.[54,55] In this setting, it is possible that the liver-first approach may evolve into a "liver surgery-only" approach for the patient.

x. terminology and management of "disappearing" liver metastases

The consensus first addresses the terminology in this situation. This can be seen in Table 2. The consensus recommends hepatobiliary contrast-enhanced MR scan before and after systemic chemotherapy to assess for disappearing lesions as this is in keeping with current state-of-the-art liver imaging.[56,57] It is accepted that this 2022 consensus terminology is dependent on MR and not all clinicians have access to this. There was no consensus to state that complete response on CT alone could justify the term "disappearing" metastases.

No consensus was reached on the use of an observation policy in patients with a complete radiological response to systemic chemotherapy in liver metastases as assessed on MRI. Carcino-embryonic antigen (CEA) measurement (i.e. a relevant biochemical response/decline in serum values) can be used to augment clinical decision making in patients who have a response to treatment – provided that baseline, pre-treatment values are available for comparison.[25]

xi. Management of synchronous pulmonary metastases in patients with synchronous colorectal cancer and liver metastases

The consensus regards the presence of definite pulmonary metastases on cross sectional imaging (M_{1b} disease) to be an indication for systemic treatment as first line rather than surgery.[3,4]

Table 2 E-AHPBA/ESSO/ESCP/ESGAR/CIRSE consensus definitions of "disappearing" liver metastases

i. The term disappearing metastases is defined in this study as lesions present on baseline contrast MR which are no longer visible on hepatobiliary contrast MR after systemic chemotherapy.
ii. The presence of a "scar" on cross-sectional imaging is termed "evidence of treatment response" but if visible on hepatobiliary contrast MR, the lesion is not regarded as "disappearing".

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The consensus does not support resection of pulmonary metastases at the same time as resection of liver tumours and/or the colonic primary tumour.

The consensus recommends that the opinion of a thoracic MDT about the potential locoregional treatment of pulmonary metastases should be sought before embarking on liver or bowel surgery in patients with suspected or confirmed pulmonary metastases.

xii. The role of minimally invasive surgery in the management of colorectal cancer with synchronous liver metastases

The consensus regards minimally invasive approaches for both primary tumour and liver metastases as appropriate options.[58–60] The consensus acknowledges that to date, the published literature focuses predominantly on minimally invasive hepatectomy rather than on the management of patients with synchronous colorectal cancer and liver metastases using laparoscopic or robotic approaches.

Discussion

This consensus represents arguably the most comprehensive exercise undertaken to date to address the management of patients with synchronous colorectal cancer and liver metastases. It is the first to bring together multiple professional societies to address this topic. Despite the scope and extent of this consensus there are important factors that could have influenced the recommendations and introduced bias and these should be discussed.[61] First, composition of the consensus group was predominantly surgical with hepatobiliary surgeons constituting the largest individual group. Although this was necessary to have sufficient expertise and depth to address complex surgical pathways this could introduce bias towards operative interventions. Second, the consensus does not address the likely impact of the molecular genetics of colorectal cancer on surgical decision-making, for example, the evidence of poor outcome after hepatectomy in patients who carry the $BRAF^{v600E}$ mutation.[62] However, mutation analysis may not be available at the outset of management and is not available at all for many patients in a global context. Third, some aspects of the recommendations of this consensus are biased against healthcare systems with limited access to MR. For example, the decision to use MR for definition of disappearing liver metastases could restrict the utility of this definition.

Having reviewed these limitations, what can be gained from this consensus? The focus towards standardizing the definitions of synchronous and metachronous disease is an important cornerstone of this project.

The terminology around the use of the terms synchronous, early and late metachronous is retained because of evidence favouring these descriptors. This terminology should be universally adopted for disease description and comparison of outcomes.

The definition of "disappearing" metastases takes an important step towards integration of modern imaging by relying on MR.

The consensus then follows the treatment pathway of a patient with colorectal cancer and synchronous liver metastases, starting with a focus on the composition of the MDT. Here, the recommendations on core and extended members do not differ substantially from those described in both NCCN and ESMO guidelines. Similarly, as would be expected, the consensus recommendation on diagnostic tests closely follow both NCCN and ESMO recommendations.

In terms of management, the consensus provides guidance on the use of systemic chemotherapy as first treatment, synchronous surgery (as a first intervention) and staged surgery.

The lack of consensus about the role of major hepatectomy combined with colonic surgery is highlighted. Although major hepatectomy can be combined with colonic resection the evidence is predominantly based on case series or retrospective data and insufficient to make a recommendation.[11,63,64]

The consensus regarded minimally invasive approaches or open surgery to either the primary tumour or liver metastases as equivalent. It is of note that the literature on minimally invasive liver surgery does not focus on patients with synchronous disease. To this extent, the forthcoming Internationally Validated European Guidelines Meeting on Minimally Invasive Liver Surgery (IEGUMILS) 2024 will have a specific focus on this area and on current research in patients with synchronous colorectal cancer and liver metastases (Abu Hilal M personal communication).

Setting the findings in the context of current evidence and guidelines, the consensus approach permitted the flexibility to focus on important practical aspects of management. For example, although the importance of accurate documentation of disease distribution is discussed, this is thought to be the first document to address the situation of the patient with multiple liver metastases in all segments where the distribution of the disease is more relevant to future management than a numerical or volume-based description of tumour burden.

In summary, this multi-society, multi-disciplinary consensus provides information of practical value to clinicians treating patients with synchronous colorectal cancer and liver metastases. The clarifications of terminology can be generally adopted and would help in future comparison of outcomes. The clinical recommendations emphasise the importance of comprehensive staging, the need to integrate systemic treatments with surgery and current areas of equipoise and limitations in knowledge. Incorporation of knowledge on the cancer biology of colorectal cancer into management together with an understanding of the genetic heterogeneity of metastatic colorectal cancer will likely help to rationalise future management.[65,66]

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APPENDIX 1. STATEMENTS FOR FIRST ROUND OF DELPHI VOTING

SECTION 1: TERMINOLOGY.

Question 1: What is the optimal definition of the term "synchronous" liver metastases?

(Current concepts of the cancer biology of liver metastasis in colorectal cancer indicate that all metastases may be synchronous but present clinically at variable time points in the disease course. Thus, the definition of synchronous disease should be clinical and help to focus optimal management).

A. Liver metastases present at the time of diagnosis of the primary.
B. The definition should also include patients with incidental liver metastases detected intra-operatively.
C. Alternatively, the timeframe of "synchronous" should be increased from that of the EGOSLIM consensus 2015 to include liver metastases discovered up to 6 months after diagnosis of the primary tumour.

Question 2: What are the optimal definitions of "metachronous" liver metastases?

A. To be termed "metachronous" disease, liver metastases should ideally have been excluded on cross-sectional imaging at the time of diagnosis of the primary tumour.
B. Liver metastases detected up to 12 months after diagnosis of the primary tumour (but absent at presentation) should be termed "Early Metachronous" metastases.
C. Alternatively, if the 6-month timeframe for the term synchronous is to be adopted then "early metachronous" refers to lesions discovered after 6 months and before 12 months.
D. Liver metastases detected more than 12 months after diagnosis of the primary are termed "Late metachronous metastases."

SECTION 2: DIAGNOSIS.

Question 3: What tests are required at the time of diagnosis of a patient with colorectal cancer and synchronous liver metastases?

A. There should be biopsy confirmation from the primary tumour.
B. A complete endoscopic examination of the colon and rectum should be performed at the time of diagnosis. A CT (virtual) colonoscopy could be undertaken if complete endoscopy cannot be performed.
C. Molecular profiling including RAS and MSI as a minimum should be performed from the primary tumour in all patients where feasible to aid in further management.
D. Biopsy of liver metastases to confirm diagnosis is not ordinarily required.
E. Lesional liver biopsy may need to be considered in some specific settings – for example if there is a prior history of a different malignancy.
F. Contrast-enhanced computed tomography (CT) of the thorax, abdomen and pelvis should be undertaken at time of presentation.
G. Where available, hepatobiliary contrast-enhanced magnetic resonance scan (MR) of the liver should be undertaken at the time of presentation (and prior to any chemotherapy).
H. Where available, MR for low and mid rectal primary tumours (below 12 cm from the anal verge) should be undertaken at the time of presentation. Trans rectal ultrasound (TRUS) may be an alternative. A structured reporting template for MR scans and TRUS of the rectum should be used.
I. ^{18}Fluoro-deoxyglucose positron emission tomography (FDG-PET) should be undertaken at the time of presentation in patients with colorectal cancer and synchronous liver metastases.
J. The tumour marker carcino-embryonic antigen (CEA) should be measured at baseline presentation for disease monitoring/surveillance.
K. The tumour marker carbohydrate antigen CA 19-9 should be measured at baseline presentation for disease monitoring/surveillance.

SECTION 3: INITIAL MANAGEMENT - THE URGENT PRESENTATION.

Question 4: When a patient presents as an emergency (with perforation, obstruction or life-threatening bleeding) with colorectal cancer and synchronous liver metastases and a performance status which permits active treatment (with resuscitation) what should be the initial management?

A. Surgery aimed at addressing the emergency complication of the primary tumour should be considered.
B. Intra-operatively detected liver metastases should NOT be biopsied.
C. There should be no intervention directed at the liver metastases during the urgent presentation.
D. A diverting stoma (with no resection of the primary) or resectional surgery can both be considered for patients with intestinal obstruction, depending on the tumour location, available expertise and patient status.
E. Bowel stenting could be performed as a bridge to surgery in selected patients if expertise is available, but perforation can potentially worsen long-term outcomes.
F. Patients with rectal tumours who present with bleeding may be treated with radiotherapy.
G. Patients with colorectal tumours who present with bleeding may be treated with interventional radiological procedures.

SECTION 4: ELECTIVE MANAGEMENT OF SYNCHRONOUS DISEASE. LIVER METASTASES SPECIALIST MULTIDISCIPLINARY TEAM.

Question 5: Should all patients with liver metastases from colorectal cancer have their care reviewed at an MDT with expertise in the surgical management of liver metastases?

A. Yes – all patients with liver metastases from colorectal cancer should have their care reviewed at a specialist MDT with expertise in the surgical management of liver metastases.
B. No – patients should only be referred if they have M1a disease and if their performance status permits active treatment.

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SECTION 4: ELECTIVE MANAGEMENT OF SYNCHRONOUS DISEASE. LIVER METASTASES SPECIALIST MULTIDISCIPLINARY TEAM.

Question 6: Which specialties should (ideally) be represented in a specialist liver metastases multidisciplinary team/tumour board?

A. Radiologist with an expertise in gastrointestinal imaging.
B. Interventional Radiologist.
C. Hepatobiliary Surgeon.
D. Colorectal Surgeon.
E. Thoracic Surgeon.
F. Liver transplant Surgeon.
G. Liver anaesthesiologist.
H. Gastrointestinal oncologist.
I. Radiation oncologist.
J. Gastrointestinal physician.
K. Cancer specialist nurse.
L. Dietitian.
M. Palliative care physician.
N. MDT co-ordinator (case manager).

SECTION 5: INITIAL CLINICAL ASSESSMENT IN PATIENTS WITH POTENTIALLY RESECTABLE SYNCHRONOUS DISEASE WITH AN ELECTIVE PRESENTATION.

Question 7: In addition to detailed history, physical examination, baseline blood tests (including tumour marker assays as appropriate) and cross-sectional imaging for diagnosis what additional assessments should be undertaken in patients with colorectal cancer and synchronous liver metastases?

NOTE: This consensus does not address preoperative liver functional assessment prior to hepatectomy as this is discussed in detail in the Surg-Innsbruck consensus meeting.

A. For patients of Eastern Co-operative Oncology Group staging (ECOG) 0–1, additional fitness tests are not required.
B. Patients should be selectively enrolled in a formal pre-habilitation programme depending on performance status.
C. Patients should selectively undergo dynamic cardiopulmonary exercise testing depending on performance status.
D. Consider the use of a validated frailty score where appropriate.
E. Nutritional status should be assessed for patients with potentially treatable metastatic colorectal cancer.

SECTION 6: INITIAL TREATMENT PLANNING IN PATIENTS WITH POTENTIALLY RESECTABLE SYNCHRONOUS DISEASE WITH AN ELECTIVE PRESENTATION.

Question 8: The following aspects are important in terms of assessment of the extent and distribution of the disease at presentation.

A. Presence or absence of extra-hepatic metastases should be specified.
B. In relation to thoracic metastases, number, laterality and definite or "indeterminate" should be noted.
C. In relation to liver metastases, the number of lesions should be specified.
D. In relation to liver metastases, the size of lesions should be specified.
E. In relation to liver metastases, the location within Couinaud segments should be specified.
F. Additionally, the term "juxta inflow" should be used for lesions in contact with the liver inflow.
G. Additionally, the term "juxta outflow" should be used for lesions in contact with hepatic veins.
H. Additionally, the term "juxta caval" should be used for lesions in contact with the vena cava.
I. In relation to a primary colon or rectal tumour, a radiological assessment of T and N stage should be recorded.
J. In patients with a rectal primary tumour there should be a radiological assessment of lateral lymph nodes and whether the circumferential margin is at risk.

SECTION 7: TREATMENT – CONSIDERATIONS FOR "UPFRONT" SYNCHRONOUS SURGERY IN PATIENTS WITH POTENTIALLY RESECTABLE SYNCHRONOUS DISEASE WITH AN ELECTIVE PRESENTATION.

Question 9: It is accepted that there is not robust evidence to guide selection of patients with synchronous disease for synchronous surgery. Patients with colorectal cancer and synchronous liver metastases may be considered for upfront synchronous resection of primary and liver metastases in some clinical settings.

A. In addition to resectable liver tumour(s) there must be a resectable primary tumour not requiring neoadjuvant systemic treatment or radiotherapy (as assessed on cross-sectional imaging).
B. If "up-front" synchronous hepatic surgery is to be considered, there must be an adequate future liver remnant (extent not specified).
C. Upfront synchronous surgery can be considered if the liver disease burden is resectable by minor hepatectomy (not otherwise specified) ± metastasectomy in addition to resection of the primary tumour.
D. Upfront synchronous surgery can be considered if the liver disease burden is resectable by major hepatectomy (hemi-hepatectomy or beyond) ± metastasectomy in addition to resection of the primary tumour.
E. Major hepatectomy should not be combined with total mesorectal excision for rectal tumour.
F. Ablative techniques (otherwise not specified) can be directed at the liver (±resection) as first-line up-front treatment.

SECTION 7: TREATMENT – CRITERIA AGAINST UPFRONT SYNCHRONOUS SURGERY IN PATIENTS WITH SYNCHRONOUS DISEASE WITH AN ELECTIVE PRESENTATION.

Question 10: Criteria against upfront synchronous surgery for patients with an elective presentation of colorectal cancer and synchronous liver metastases include the following.

A. Significant co-morbidity (method of assessment not specified).
B. Extrahepatic disease at presentation (M_{1b} status).
C. Peritoneal metastases at presentation (M_{1c} status).
D. (Radiological) T4 status of the primary tumour.
E. (Radiological) N1 (or beyond) status of the primary tumour.
F. Rectal tumour requiring radiotherapy, chemoradiotherapy or primary chemotherapy.
G. Rectal tumour requiring total mesorectal excision

SECTION 7: TREATMENT – CONSIDERATIONS FOR SYSTEMIC CHEMOTHERAPY AS FIRST TREATMENT IN PATIENTS WITH AN ELECTIVE PRESENTATION OF COLORECTAL CANCER AND SYNCHRONOUS LIVER METASTASES.

Question 11: Criteria favouring systemic chemotherapy as first treatment. This consensus refers clinicians to the current ESMO guidelines for decision making around choice of chemotherapy agent, use of combination chemotherapy, biologic agent(s) and treatment intervals. Note that this question complements question 10.

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A. Performance status which precludes synchronous surgery.
B. Extrahepatic disease at presentation (M_{1b} status).
C. Peritoneal metastases at presentation (M_{1c} status).
D. Bi-lobar hepatic metastases (not otherwise specified).
E. (Radiological) T4 status of the primary tumour.
F. (Radiological) N1 (or beyond) status of the primary tumour.

SECTION 7: TREATMENT – SYSTEMIC CHEMOTHERAPY AS FIRST TREATMENT IN PATIENTS WITH SYNCHRONOUS DISEASE AND RESECTABLE LIVER METASTASES AT PRESENTATION.

Question 12: The type and duration of systemic treatment are discussed in detail in the ESMO and NCCN guidelines, but key aspects are discussed here. Chemotherapy backbone should be FOLFOX or FOLFIRI or FOLFOXIRI chemotherapy or (oral 5-FU equivalent) depending upon previous treatment, residual toxicity, patient preference and Performance score.

A. Standard backbone chemotherapy without monoclonal antibody should be considered.
B. Alternatively, a biologic agent (Epidermal Growth Factor Receptor Inhibitor [EGFRi]) should be added to standard chemotherapy in patients with extended RAS wild type primary tumour (left sided tumours only)
C. Or, Alternatively, a biologic agent (Epidermal Growth Factor Receptor Inhibitor [EGFRi]) should be added to standard chemotherapy in patients with extended RAS wild type primary tumour regardless of sidedness.
D. Bevacizumab may be added to the standard chemotherapy backbone
E. Only patients with a response to chemotherapy (partial response or stable disease) should proceed to liver resection.

SECTION 7: TREATMENT – CONSIDERATIONS FOR THE BOWEL-FIRST APPROACH IN PATIENTS WITH AN ELECTIVE PRESENTATION OF COLORECTAL CANCER WITH SYNCHRONOUS LIVER METASTASES AFTER SYSTEMIC CHEMOTHERAPY.

Question 13: Criteria favouring a bowel-first approach after systemic chemotherapy for patients with colorectal cancer and synchronous liver metastases include.

A. Symptomatic primary tumour.
B. Imminent endoscopic or radiologic obstruction
C. Resectable primary tumour with unresectable liver metastases.
D. Resection of primary tumour only in a setting where there is no availability of liver surgery.

SECTION 7: TREATMENT – RE-STAGING AFTER INITIAL SYSTEMIC CHEMOTHERAPY IN PATIENTS WITH AN ELECTIVE PRESENTATION OF SYNCHRONOUS DISEASE.

Question 14: Re-staging after systemic chemotherapy.

A. Re-evaluation should be considered after 8–12 weeks of treatment with systemic chemotherapy.
B. The liver disease should be re-evaluated by contrast-enhanced CT.
C. The liver disease should be re-evaluated by hepatobiliary contrast-enhanced liver MR where available.
D. In patients initially regarded as unresectable and treated with systemic chemotherapy ^{18}FDG-PET scan should be considered before undertaking surgery in addition to CT and/or MR.
E. In patients with rectal tumours treated by chemotherapy or chemoradiotherapy, consider re-staging the primary tumour before considering hepatic resection.

SECTION 7: TREATMENT – CONSIDERATIONS FOR THE LIVER-FIRST APPROACH AFTER SYSTEMIC CHEMOTHERAPY IN PATIENTS WITH AN ELECTIVE PRESENTATION.

Question 15: The liver-first approach after systemic chemotherapy can be considered in the following situations.

A. When there are specific hepatic criteria such as borderline resectability
which favour hepatectomy first in patients with synchronous disease.
B. This approach can be considered in patients with response after total neoadjuvant treatment including long-course chemoradiotherapy for patients with rectal tumours.
C. This approach can be used in the rare instance of patients with rectal cancer and resectable synchronous liver metastases who have a clinical complete response of the primary tumour to neoadjuvant treatment.

SECTION 7: TREATMENT – MANAGEMENT OF "DISAPPEARING METASTASES" IN PATIENTS WITH AN ELECTIVE PRESENTATION.

Question 16: "Disappearing metastases" are defined as liver lesions which were noted on cross-sectional imaging at baseline and are no longer noted on imaging after systemic chemotherapy.

A. The term disappearing metastases is defined in this study as lesions present on baseline contrast MR which are no longer visible on hepatobiliary contrast MR after systemic chemotherapy.
B. The presence of a "scar" on cross-sectional imaging is termed "evidence of treatment response" but if visible on hepatobiliary contrast MR, the lesion is not regarded as "disappearing".
C. Intra-operative assessments such as ultrasound (with or without contrast) are not included in the definition of disappearing liver metastases.
D. Hepatic resection should plan to resect all sites where disease was present at baseline.
E. A "watch and wait" policy may be adopted in those patients who have a complete radiological hepatic response (disappearing metastases).
F. A bowel-first approach should be adopted in patients who have a radiological complete hepatic response to systemic chemotherapy.

SECTION 7: TREATMENT – MANAGEMENT OF SYNCHRONOUS THORACIC METASTASES IN PATIENTS WITH AN ELECTIVE PRESENTATION OF SYNCHRONOUS DISEASE.

Question 17: The management of thoracic metastases in a patient presenting with colorectal cancer and synchronous liver metastases.

A. The presence of definite pulmonary metastases on cross sectional imaging is M_{1b} disease and is an indication for systemic treatment as first line rather than surgery.
B. In addition to the oncologic status of M_{1b} disease, the physiologic injury consequent upon pulmonary, hepatic and bowel surgery under a single anaesthetic precludes synchronous lung, liver and bowel resection.
C. Alternatively, in specific settings, synchronous thoracic, liver and bowel surgery can be considered (if this question is answered

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affirmatively, please provide additional information in the comments section).

D. The opinion of a thoracic MDT about the potential locoregional treatment of pulmonary metastases should be sought before embarking on liver or bowel surgery.

SECTION 7: TREATMENT – MINIMALLY INVASIVE SURGERY IN PATIENTS WITH AN ELECTIVE PRESENTATION OF SYNCHRONOUS DISEASE.

Question 18: Minimally invasive surgery.

A. Minimally invasive approaches for both primary tumour and liver metastases are regarded as equivalent to the open approach.

B. Currently, there is no evidence to favour the minimally invasive approach over open surgery in the synchronous setting.

C. If a minimally invasive approach to liver resection is to be adopted, a liver resection complexity score should be used to guide selection of approach.

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