



GUIDELINES

United Kingdom criteria for liver transplantation in the setting of isolated unresectable colorectal liver metastases

Jamie Murphy^{1,2}  | Raj Prasad³ | Krishna Menon⁴ | on behalf of the NHS Blood and Transplant Liver Transplantation for Colorectal Liver Metastases Fixed Term Working Unit

¹Department of Surgery and Cancer, Imperial College London, London, UK

²Digestive Diseases and Surgery Institute, Cleveland Clinic London, London, UK

³Liver Transplantation and HPB Surgery, Leeds Teaching Hospitals NHS Trust, Leeds, UK

⁴Institute of Liver Studies, King's College Hospital, London, UK

Correspondence

Jamie Murphy, Academic Surgical Unit, 10th Floor Queen Elizabeth Queen Mother Building, St Mary's Hospital, London W2 1NY, UK.
Email: jamie.murphy2@nhs.net

Abstract

Aim: Studies have demonstrated that liver transplantation may be an effective treatment for isolated unresectable colorectal cancer liver metastases (CRCLM). Published data suggest that 5-year survival may be as high as 80%; however, recurrent disease is commonplace. Consequently, the Liver Transplantation for Unresectable Colorectal Liver Metastases Fixed Term Working Unit recommended to the NHS Blood and Transplant Liver Advisory Group that while CRCLM is an appropriate indication for transplantation, selection criteria should be conservative and that it should be undertaken within a clinical service evaluation programme. The aim of this work is to outline the proposed UK selection criteria and follow-up process for CRCLM transplantation.

Method: Consensus statement by colorectal cancer/liver transplantation patient representatives, experts in colorectal cancer surgery/oncology, liver transplantation surgery, hepatology, hepatobiliary radiology, hepatobiliary pathology and nuclear medicine.

Results: This study provides a comprehensive outline of the inclusion/exclusion criteria for referral in the UK. Furthermore, the referral framework is also explained. Pretransplant assessment criteria for listing/delisting are outlined. Finally, the oncology-specific outcome measures posttransplant are described.

Conclusion: It is anticipated this service will begin in December 2022. A series of educational events for the referrers and transplant units will be arranged throughout 2023 to highlight CRCLM as a newly accepted UK indication for transplantation. A national audit will be undertaken to identify patients currently on treatment who meet the criteria for transplant. Data will be collected in a national registry and reviewed on an ongoing basis to confirm the safety of this treatment and to determine if the inclusion criteria require revision.

Liver Transplantation for Colorectal Liver Metastases Fixed Term Working Unit Members: Ms Anya Adair, consultant transplant/hepatobiliary surgeon, Royal Infirmary, Edinburgh, UK; Ian Parker, liver transplant patient representative; Mrs Lindy Berkman, colorectal patient representative; Dr William Gelson, consultant hepatologist, Cambridge Liver Unit, Addenbrooke's Hospital, Cambridge, UK; Mr John Isaac, consultant hepatobiliary and liver transplant surgeon, Queen Elizabeth Hospital, Birmingham; Dr Rebecca Jones, consultant hepatologist, The Leeds Teaching Hospitals NHS Trust, Leeds, UK; Professor Derek Manas, consultant hepatobiliary and transplant surgeon, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK; Professor Gary Middleton, consultant oncologist, Queen Elizabeth Hospital, Birmingham; Professor Jamie Murphy, consultant surgeon, Imperial College London, London, UK; Dr Praveen Peddu, consultant hepatobiliary radiologist, King's College Hospital, London, UK; Mr Thamara Perera, consultant transplant/hepatobiliary surgeon, Queen Elizabeth Hospital Birmingham, UK; Mr Raj Prasad, consultant transplant/hepatobiliary surgeon, Leeds Teaching Hospitals NHS Trust, Leeds, UK; Professor Joerg-Matthias Pollok, consultant transplant/hepatobiliary surgeon, Royal Free Hospital, London, UK; Professor Andrew Scarsbrook, consultant radiologist and nuclear medicine physician, Leeds Teaching Hospitals, Leeds, UK; Professor Yoh Zen, consultant hepatobiliary histopathologist, King's College Hospital, London, UK.

[Correction added on 4 February 2023, after first online publication: In the preceding sentence, Professor Joerg-Matthias Pollok's name has been corrected to include his middle name.]

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2022 The Authors. *Colorectal Disease* published by John Wiley & Sons Ltd on behalf of Association of Coloproctology of Great Britain and Ireland.

KEYWORDS

colorectal cancer, liver metastases, transplant

INTRODUCTION

The liver is the most common site of colorectal cancer (CRC) metastases due to colonic venous drainage via the hepatic portal system. Approximately 20% of patients will present with primary CRC and synchronous liver metastases at the time of diagnosis, with a further 50% of patients developing metachronous liver metastases within 3 years of diagnosis [1–4]. While surgical resection of CRC liver metastases (CRCLM) offers a potential 10 year survival for 26% of patients [5], only 20% of patients undergo surgery with curative intent, with considerable variability between centres regarding what constitutes resectable disease [6, 7]. Unresected CRCLM are associated with a median survival of 22 months when treated with cytotoxic chemotherapy and targeted agents alone [8]. Consequently, additional treatment strategies are needed to improve the life expectancy of patients with unresectable CRCLM.

Unsuccessful attempts at liver transplantation for unresectable CRCLM were first described as early as 1963. However, the first published study demonstrating a potential role for this treatment reported that long-term survival of 10 years or more was possible when patients who had no evidence of lymph node involvement in their primary CRC were selected for transplantation [9, 10]. A more general appreciation of liver transplantation as a viable treatment option for patients with unresectable isolated CRCLM occurred when prospective studies of well-selected patients were reported from Oslo University Hospital. SEcondary CAncer-1 (SECA-1) was the first study to be published from Norway and reported a 60% 5-year survival for a cohort of 21 patients; however, recurrence rates were high, with a 1-year disease free survival (DFS) rate of 35% [11]. Thirteen patients experienced recurrence in the lung while seven patients developed metastases in the transplanted graft. Notably, none of the patients received chemotherapy after transplantation. Given the significant rate of early relapse the second study published from Norway applied more stringent selection criteria and recruited 15 patients. SECA-II required patients to have a 10% RECIST criteria response to systemic chemotherapy, no evidence of extrahepatic disease as determined by fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography–computed tomography (PET-CT) and an interval of 1 year between the original CRC diagnosis and transplantation [6]. The more stringent selection criteria were associated with an increased 5-year survival of 83%; nevertheless recurrent disease predominantly in the lung remained challenging. A DFS of 53% was reported at 1 year, with six of the eight patients who suffered recurrence developing pulmonary metastases as the first or only site of disease. The data from Norway are supported by a separate multicentre retrospective cohort study assessing 12 patients [12]. A lower 5-year survival rate of 50% was reported by the study authors, which may possibly be explained by the heterogeneous nature of the selection criteria; however, the 1-year DFS of 56% was in keeping with the results of SECA-II.

What does this paper add to the literature?

This study outlines the inclusion/exclusion criteria for referring patients with colorectal cancer liver metastases to be considered for liver transplantation in the UK. This study also explains the UK referral framework. Pretransplant assessment criteria for listing/delisting are outlined and oncology-specific outcome measures posttransplant are described.

PROPOSED STRATEGY IN THE UNITED KINGDOM

In light of the published literature the Liver Advisory Group of NHS Blood and Transplant established a fixed-term working unit (FTWU) to outline the criteria that would be used to initiate a liver transplantation programme for isolated unresectable CRCLM in the UK. The FTWU recommended that this should be conducted as a NHS service evaluation and anticipated that approximately 20–30 patients would undergo transplantation for this indication over a 2-year period. It is important to highlight that although the eligibility criteria established by the FTWU differ from those used by the SECA-I and SECA-II studies these did form the basis for establishing the UK selection criteria. The UK criteria are conservative and will be kept under review to ensure they are not overly restrictive, and that enough patients are assessed for this intervention. The outcome measures listed below will be audited at a national level with specific reference to safety and oncological data.

PATIENT SELECTION**Inclusion criteria**

Patients will be considered as being eligible to be assessed for liver transplantation by meeting the following inclusion criteria:

1. The patient must have undergone a microscopically margin negative (R0) resection of the primary CRC, and this must have been histopathologically confirmed as an adenocarcinoma.
2. The presence of liver metastases must be confirmed by CT, MRI with Primovist and diffusion weighting imaging (DWI) or FDG PET-CT and documented by either the local colorectal cancer or hepatobiliary metastasis multidisciplinary team (MDT) meeting. The liver disease burden must be assessed using MRI with Primovist and DWI and be documented as unresectable by the local specialist hepatobiliary metastasis MDT.

3. Patients will have been treated with systemic chemotherapy and demonstrated to have a $\geq 30\%$ reduction in disease volume as assessed by RECIST 1.1 criteria (based on CT or MRI with Primovist) at either the 3- or 6-month time points after commencement of chemotherapy [13]. The best treatment response on MRI with Primovist and DWI will be used to fulfil this criterion. Metabolic tumour volume as determined by PET-CT will be recorded as a variable of interest for the registry but will not be used to make this assessment.
4. After induction chemotherapy has produced the required response in the disease burden, patients will need to demonstrate stable disease on any standard of care imaging modalities for a minimum of 2 years from commencing systemic chemotherapy, prior to being considered for transplantation assessment.
5. In cases where disease progression occurs and the systemic chemotherapy regimen changes, the patient may again be re-considered for transplantation eligibility but only after a $\geq 30\%$ reduction in disease volume is again achieved and the response is sustained for a period of 2 years.

Exclusion criteria

Those who meet the following criteria will be excluded from assessment for liver transplant:

1. Patients who were diagnosed with nonepithelial colorectal malignancies will not be considered eligible.
2. Patients who have had a complete clinical response in the primary CRC must have had a radical resection of the primary tumour site 3 months or more prior to assessment for transplant.
3. At no point during treatment must there be any evidence of extrahepatic metastatic disease on any imaging modality. This will preclude eligibility for transplant assessment until such time as there is histopathological evidence that extrahepatic imaging abnormalities are benign processes.
4. Sequentially increasing serum carcinoembryonic antigen (CEA) assays even in the absence of any evidence of extrahepatic metastases on all imaging modalities will preclude eligibility for transplant assessment.
5. Those who have undergone prior liver resection of CRLM and then developed unresectable disease burdens will not be considered for liver transplantation.
6. Patients with a second primary tumour will be excluded for assessment except for histologically confirmed nonmelanoma skin cancers.

The following factors will not be used as exclusion criteria: mucinous differentiation, signet ring cell morphology, tumour differentiation status, nodal metastases, extramural/lymphovascular/perineural invasion, N/K-RAF or BRAF status, mismatch repair protein status or right sided tumours. The FTWU considered that the requirement for a $\geq 30\%$ reduction in disease volume followed

by disease stability during a 2-year period before being eligible for transplant assessment allowed the biology of the cancer to be tested by time.

PATHWAY FOR TRANSPLANTATION ASSESSMENT

All patients identified as meeting eligibility criteria by colorectal MDTs will be referred to the local hepatobiliary metastasis MDT. The hepatobiliary metastasis MDT will assess whether the disease is unresectable and suitable for transplantation. The MDT will establish that the eligibility criteria outlined above have been met. If onward referral to the regional liver transplant service is deemed appropriate, then the local hepatobiliary metastasis MDT will provide the relevant documentation as part of their referral: relevant histopathology, imaging (CT chest/abdomen/pelvis, MRI with Primovist and DWI, FDG PET-CT), clinic letters outlining surgical and medical oncology treatment with confirmation the CRCLM are not technically resectable. For some colorectal MDTs the local hepatobiliary metastasis MDT will be co-located with the regional liver transplant centre. In that instance the colorectal MDT will refer to the hepatobiliary metastasis MDT which will again confirm eligibility, and when the decision to refer for liver transplant assessment is made the patient will be discussed by the liver transplant service in the national transplantation MDT. Where there is a lack of agreement between the referring hepatobiliary metastasis MDT and the regional liver transplant service the final decision rests with the transplant service, which will liaise with the referring team regarding future management options. When approval is granted by the quality assurance panel the patient will be informed and prepared for listing via the transplant assessment pathway as per the protocol of the liver transplant centre. Formal transplant assessment will then be undertaken, and when completed the liver transplant MDT will ratify the decision to proceed, the patient's registration will be activated on the national transplant waiting list and systemic chemotherapy will be stopped. [Figure 1](#) outlines the referral pathway for patients with unresectable CRCLM who are being considered for liver transplantation. Further details regarding transplant assessment and organ allocation are outside the scope of this protocol and reported elsewhere by our group [14]; however, as patients will have to stop systemic treatment it is anticipated that transplantation will occur within a 3-month period.

ONCOLOGICAL ASSESSMENT PRIOR TO LISTING

In addition to the standard assessment pathways conducted by the relevant regional liver transplant centre, additional oncological assessments will be necessary prior to patients being listed for graft allocation. A colonoscopy within the past year will be required to exclude luminal local recurrence or a metachronous second CRC

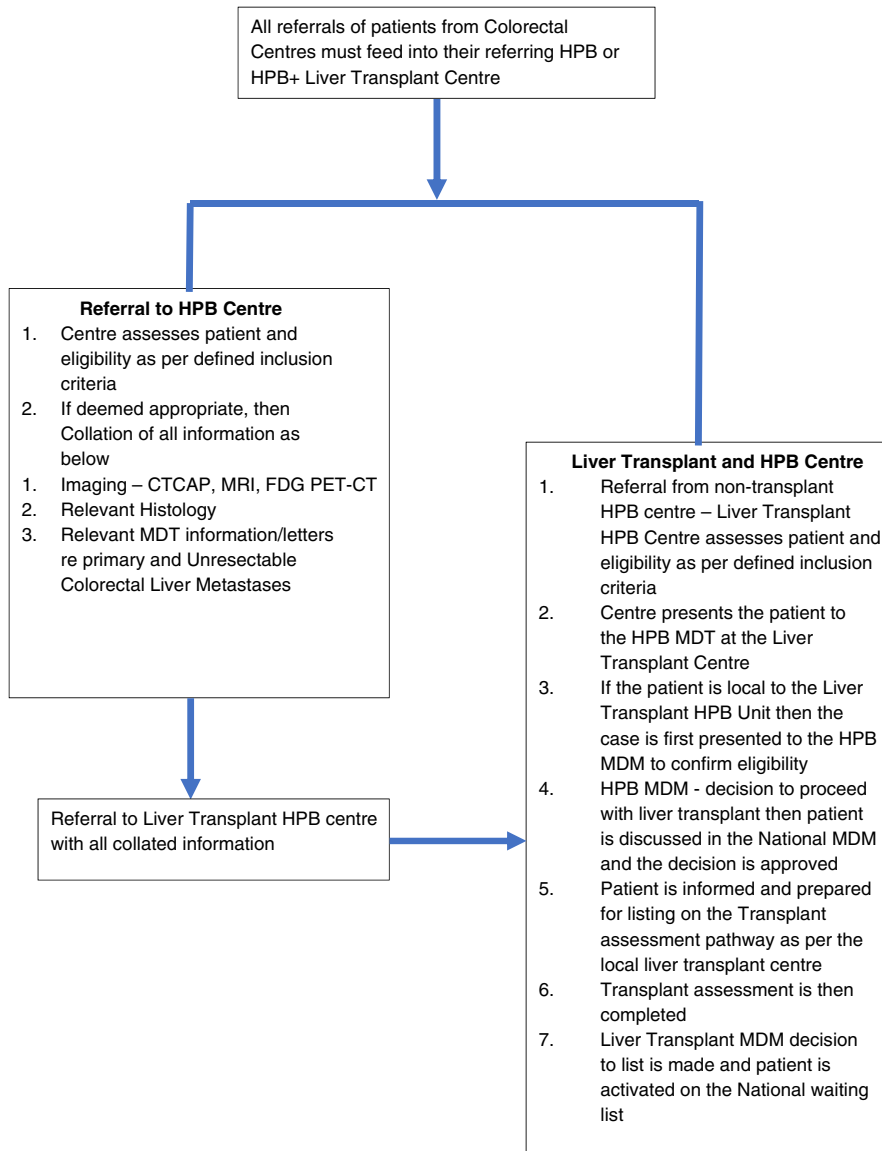


FIGURE 1 Referral pathway for patients with unresectable colorectal cancer liver metastases who are being considered for liver transplantation (CTCAP, CT chest abdomen and pelvis; HPB, hepatobiliary; FDG PET-CT, fluorine-18 fluorodeoxyglucose positron emission tomography-computed tomography; MDM, multidisciplinary meeting; MDT, multidisciplinary team)

primary tumour. For patients with CEA-excreting tumours a total of three CEA serum assays approximately 4 weeks apart will have been undertaken over the prior 3 months and the values must not have been sequentially increasing. Patients will require restaging imaging within 6 weeks of being listed for transplant, which will take the form of CT chest/abdomen/pelvis, MRI of the liver with Primovist and DWI and FDG PET-CT. Any suspicion of extrahepatic disease on imaging must be biopsied to exclude malignancy before continuing, but it is not anticipated that liver metastases will be routinely biopsied as part of transplantation assessment. For patients previously diagnosed with rectal cancer a pelvic MRI with DWI will be undertaken within 4 weeks of being listed for transplant to confirm there is no radiological evidence of local recurrence. In cases where patients were previously diagnosed with pT3 or pT4 colon cancers a staging laparoscopy performed by the local colorectal service will be necessary to exclude any visual evidence of peritoneal disease, and where abnormalities are detected these will be biopsied to confirm they are benign processes. Where laparoscopy is not thought to be

technically possible, for example with known significant adhesions or failed access to the abdomen at attempted laparoscopy, then an MRI of the abdomen and pelvis with DWI in two planes will be accepted as a substitute [15]. It is appreciated that expertise is limited in this form of imaging and it may be necessary to refer patients to national centres with the relevant expertise to exclude the presence of colorectal peritoneal metastases (e.g. Basingstoke North Hampshire Hospital, Christie Hospital, Ninewells Hospital, Birmingham Good Hope Hospital, Imperial College Healthcare NHS Trust, St Mark's Hospital) before approval for transplant listing is granted.

ONCOLOGICAL REASONS RESULTING IN DELISTING

While the transplant listing algorithm outlined elsewhere is designed to result in patients receiving grafts in a timely fashion it is appreciated that for most patients restaging imaging will be necessary while on

the transplantation list to confirm disease stability [14]. Unless indicated for urgent clinical reasons this will occur every 6 weeks and take the form of CT chest/abdomen/pelvis, MRI of the liver with Primovist and DWI and FDG PET-CT. Identification of extrahepatic disease will result in the patient being removed from the transplantation list, and the patient would only be reinstated if biopsies from abnormalities on imaging were demonstrated by histopathological assessment to be benign. It is appreciated that some growth of the liver metastases will occur after patients stop chemotherapy and await transplantation; however, if there is a $\geq 30\%$ increase in disease volume as assessed by RECIST 1.1 criteria the patient will no longer be considered eligible for transplantation and will recommence systemic chemotherapy.

OUTCOME MEASURES

In addition to conventional transplant outcome measures [14] a number of CRC specific metrics will also be monitored [16]. Recorded oncological data will include the following:

1. Overall survival, disease free survival.
2. Disease recurrence sites and volume, and the number and type of oncological interventions posttransplant.
3. Quality of life will also be assessed using the validated EORTC QLQ-C30 and EORTC QLQ-LMC21 questionnaires at certain defined points, namely listing for transplantation, at each of the 6-week re-staging points while awaiting graft allocation, 6 weeks after discharge from hospital having received a transplanted liver and at 3-monthly intervals up to the 2 year follow-up point posttransplantation.
4. A national registry will be instituted to record the variables outlined above and these outcome measures will be compared with those of patients who were considered for transplantation but deemed not suitable or fit enough for surgery. Patients initially considered for transplant but who may end up undergoing a resection will also be included within the registry.

CONCLUSION

This paper has outlined inclusion/exclusion criteria for referring patients with unresectable CRCLM for transplantation in the UK, the UK referral framework, transplant assessment criteria for listing/delisting and the oncology-specific outcome measures posttransplant. It is anticipated this service will begin in December 2022. A programme of educational events will be arranged by the FTWU and the Liver Advisory Group throughout 2023 to highlight CRCLM as a newly accepted UK indication for transplantation. Prior to this clinical service evaluation beginning, a national audit will be undertaken to identify patients on systemic chemotherapy who meet the criteria for transplantation described above. The data generated by this service evaluation will be collected in a national registry and reviewed on an ongoing basis to confirm the safety of transplantation for CRCLM and to determine if inclusion criteria are too conservative and require revision.

CONFLICT OF INTEREST

The authors declared no conflict of interest for this article.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Jamie Murphy  <https://orcid.org/0000-0003-0519-9031>

REFERENCES

1. Donadon M, Ribero D, Morris-Stiff G, Abdalla EK, Vauthey JN. New paradigm in the management of liver-only metastases from colorectal cancer. *Gastrointest Cancer Res.* 2007;1(1):20–7.
2. Valderrama-Treviño AI, Barrera-Mera B, Ceballos-Villalva JC, Montalvo-Javé EE. Hepatic metastasis from colorectal cancer. *Euroasian J Hepatogastroenterol.* 2017;7(2):166–75.
3. Hugen N, van de Velde CJH, de Wilt JHW, Nagtegaal ID. Metastatic pattern in colorectal cancer is strongly influenced by histological subtype. *Ann Oncol.* 2014;25(3):651–7.
4. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. *Br J Surg.* 1990;77(11):1241–6.
5. Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol.* 2012;4:283–301.
6. Dueland S, Syversveen T, Solheim JM, Solberg S, Grut H, Bjørneth BA, et al. Survival following liver transplantation for patients with nonresectable liver-only colorectal metastases. *Ann Surg.* 2020;271(2):212–8.
7. Homayounfar K, Bleckmann A, Helms HJ, Lordick F, Rüschoff J, Conradi LC, et al. Discrepancies between medical oncologists and surgeons in assessment of resectability and indication for chemotherapy in patients with colorectal liver metastases. *Br J Surg.* 2014;101(5):550–7.
8. Franko J, Shi Q, Meyers JP, Maughan TS, Adams RA, Seymour MT, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the analysis and research in cancers of the digestive system (ARCAD) database. *Lancet Oncol.* 2016;17(12):1709–19.
9. Mühlbacher F, Huk I, Steininger R, Gnatt M, Götzinger P, Wamser P, et al. Is orthotopic liver transplantation a feasible treatment for secondary cancer of the liver? *Transplant Proc.* 1991;23(1 Pt 2):1567–8.
10. Kappel S, Kandioler D, Steininger R, Längle F, Wrba F, Ploder M, et al. Genetic detection of lymph node micrometastases: a selection criterion for liver transplantation in patients with liver metastases after colorectal cancer. *Transplantation.* 2006;81(1):64–70.
11. Hagness M, Foss A, Line PD, Scholz T, Jørgensen PF, Fosby B, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. *Ann Surg.* 2013;257(5):800–6.
12. Toso C, Pinto Marques H, Andres A, Castro Sousa F, Adam R, Kailil A, et al. Liver transplantation for colorectal liver metastasis: survival without recurrence can be achieved. *Liver Transpl.* 2017;23(8):1073–6.
13. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228–47.
14. Menon K, Vijayashanker A, Murphy J, Line P, D., Isaac J, Prasad R, et al. Liver transplant for isolated unresectable colorectal liver metastases—protocol for a service evaluation in the United Kingdom - UKCoMET study; 2022. Submitted.

15. Garcia Prado J, González Hernando C, Varillas Delgado D, Saiz Martínez R, Bhosale P, Blazquez Sanchez J, et al. Diffusion-weighted magnetic resonance imaging in peritoneal carcinomatosis from suspected ovarian cancer: diagnostic performance in correlation with surgical findings. *Eur J Radiol.* 2019;121:108696.
16. Brustia R, Dechartres A, Scatton O. A methodological review of clinical outcomes reported in liver transplantation trials. *HPB (Oxford).* 2020;22(6):833–44.

How to cite this article: Murphy J, Prasad R, Menon K, United Kingdom criteria for liver transplantation in the setting of isolated unresectable colorectal liver metastases. *Colorectal Dis.* 2023;25:489–494. <https://doi.org/10.1111/codi.16446>