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Liver Transplantation for Isolated Unresectable Colorectal Liver Metastases - Protocol for a Service Evaluation in the United Kingdom - UKCoMET study

Krishna Menon[1], Aarathi Vijayashanker[1], Jamie Murphy[2,3], Pål-Dag Line[4,8], John Isaac[5], Raj Prasad[6], Douglas Thorburn[7] *on behalf of the NHS Blood and Transplant Liver Transplantation for Colorectal Liver Metastases Fixed Term Working Group*

1. Institute of Liver Studies, King's College Hospital, London, UK
2. Department of Surgery and Cancer, Imperial College London, UK.
3. Digestive Diseases and Surgery Institute, Cleveland Clinic London, UK.
4. Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway
5. Liver Unit, Queen Elizabeth Hospital, Birmingham, UK
6. Liver Transplantation and HPB Surgery, Leeds Teaching Hospitals NHS Trust, Leeds, UK
7. Sheila Sherlock Liver Centre and UCL Institute for Liver & Digestive Health, Royal Free Hospital, London, UK
8. Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Liver Transplantation for Colorectal Liver Metastases Fixed Term Working Group 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, Addenbrooke's Hospital, Cambridge, UK.
- 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.
- Prof 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 Pollok, Consultant Transplant/ Hepatobiliary Surgeon, Royal Free Hospital, London, UK.
- Professor Andrew Scarsbrook, Consultant Radiologist and Nuclear Medicine Physician, Leeds Teaching Hospitals NHS Trust, Leeds, UK.
- Professor Yoh Zen, Consultant Hepatobiliary Histopathologist, King's College Hospital, London, UK.

Corresponding Author

Mr. Krishna Menon

Consultant Liver Transplant and HPB Surgeon

Institute of Liver Studies

King's College Hospital, Denmark Hill

London SE5 9RS Email: krishna.menon@nhs.net

Abstract

Aim: Liver transplantation (LT) for unresectable colorectal liver metastases (CRCLM) has gained renewed interest in light of recent studies that have demonstrated good overall survival in selected patients. Published data suggest 5-year survival as high as 80% although recurrence is common. A Fixed Term Working Group (FTWG) was set up by NHS Blood and Transplant (NHSBT) Liver Advisory Group (LAG) to advise whether unresectable colorectal liver metastases should be developed as an indication for LT within the United Kingdom. The FTWG recommendation was that liver transplantation may be undertaken for isolated and unresectable CRCLM using strict selection criteria and within the scope of a national clinical service evaluation programme and this view was supported by the NHSBT LAG.

Method: To formulate the proposal for the service evaluation, opinion and consensus was sought from colorectal cancer / liver transplantation patient representatives, experts in colorectal cancer surgery / oncology, liver transplantation surgery, hepatology, hepatobiliary radiology, hepatobiliary pathology, and nuclear medicine, and appropriate inclusion and exclusion criteria of patients were identified, including the proper pathway for referral and transplant listing.

Results: This paper provides a summary of the selection criteria of patients with isolated and unresectable colorectal liver metastases that will be considered for Liver Transplantation in the United Kingdom. Furthermore, the referral framework and pre- transplant assessment

criteria for listing/ de- listing have been highlighted. Finally, the oncology- specific outcome measures that will be utilised to assess applicability of LT in this setting are described.

Conclusion: This service evaluation of unresectable CRCLM as an indication for LT represents a significant development for colorectal cancer patients in the UK and a meaningful step forward in the emerging field of transplant oncology. This paper details the protocol for that pilot including referring and listing patients with unresectable CRCLM for LT in the United Kingdom, scheduled to begin in the fourth quarter of 2022.

Background

Colorectal cancer (CRC) is the third most common cancer and cause of cancer-related death in Europe (1). The liver remains the most common site of CRC metastases (CRCLM), owing to the venous drainage of bowel through the hepatic portal circulation. For isolated CRCLM, liver resection is currently the only potential curative therapy, with median survival post- resection ranging between 1.8 to 4.8 years, and additional improvement in disease-free (DFS) and progression free-survival (PFS) with perioperative chemotherapy (CT) (2–8). However, only 20% patients undergo resection with curative intent and there is considerable discordance between centres with regards to eligibility, treatment, and subsequent outcomes. For most patients with unresectable metastases, palliative systemic chemotherapy (CT) or immunotherapy is the only option. Significant advances have been made in the last 20 years with newer and novel systemic therapies including antibody and immunotherapies that had a positive impact on overall (OS) and PFS with 5-year OS between 8 to 15% (9).

The use of LT to treat metastatic disease has been controversial, primarily due to concerns of disease recurrence and progression, or de novo malignancies in the context of immunosuppression (10,11). Moreover, historically the approach was reserved for large unresectable tumours without the benefits of modern chemotherapy, that led to dismal patient outcomes and poor utility of donor organs (10,12). When LT was initially instituted for hepatocellular carcinoma (HCC) patients, their overall actuarial survival were 15% (13,14). The introduction of Milan criteria in 1996 changed the entire landscape of the management of these patients and improved their overall 4-year actuarial survival to 75% and recurrence free survival to 83% (15,16).

A surplus of organs in Norway in the first decade of the 21st century resulted in the initiation of a prospective study (SEcondary CArcinoma - SECA-I) to re-assess the role of liver

transplantation for CRCLM in the new era of modern systemic therapies and refinements in post-transplant immunosuppression. In a heterogenous cohort of 21 patients with liver-only disease, who underwent prior total resection of lymph node negative primary CRC tumour, with Eastern Cooperative Oncology Group (ECOG) performance score 0 or 1, and received six weeks of neoadjuvant CT an estimated 5-year overall survival of 60% was achieved (17). However, disease recurrence was frequent with 60% occurring in the lungs and a 1-year DFS rate of 35%. Risk factors for death in this study were carcinoembryonic antigen (CEA) >80 µg/L, progressive disease on CT at the time of LT, size of largest lesion > 5.5 cm, and less than 2 years from resection of the primary tumour to transplantation. Assigning 1 point to each adverse factor led to the development of the Oslo Score for risk stratification. The same group demonstrated an improved outcome with LT compared to a contemporary group of patients who received systemic therapy as part of Nordic VII study (56% vs.9% at 5 years) (18). In view of these encouraging results, albeit with high recurrence rates, more stringent patient selection criteria were adopted in their subsequent study, SECA- II, where 15 patients with an Oslo score between 0 and 2 underwent LT between 2012-2016 (19). Pre-requisites for inclusion were CRC patients with unresectable liver-only metastases, with at least 10% response to neoadjuvant CT and a time from diagnosis to liver transplant of at least 1 year. The estimated 1- and 5-year OS in this group was 100% and 83%, with 1- and 3-year DFS of 53% and 35%. These data were reinforced by another retrospective study, and a systemic review and pooled analysis (20,21). Furthermore, prospective clinical trials are underway to compare LT to palliative chemotherapy (NCT03494946- SECA III, NCT02597348- TRANSMET) (22,23). Therefore, in selected patients with unresectable CRCLM, OS after liver transplantation is comparable to the outcome of patients undergoing LT for HCC (15).

Despite emerging evidence, the role of LT for unresectable CRCLM is unclear due to lack of international guidelines on patient selection and graft allocation for centres to follow. To address this urgent need, the International Hepato-Pancreato-Biliary Association (IHPBA) commissioned the Liver Transplantation for Colorectal Liver Metastases 2021 working group, who released their consensus statements, outlining the framework by which LT could be safely instituted to provide evidence- based practice for these patients in future (24).

Proposal for Liver Transplantation for CRCLM In the UK

Establishment of Fixed Term Working Group

In view of the recent prospective evidence and consensus guidelines from IHPBA supporting the utility of LT in CRCLM, the Liver Advisory Group (LAG) of NHS Blood and Transplant (NHSBT), the regulatory authority overseeing all donation and transplant related activity in the United Kingdom, established a Fixed Term Working Group (FTWG) to advise whether isolated, unresectable CRCLM should be developed as an indication for LT within the United Kingdom.

The interdisciplinary group consisted of colorectal cancer/ liver transplantation patient representatives, experts in colorectal cancer surgery/ oncology, liver transplantation surgery, transplant hepatology, hepatobiliary radiology, hepatobiliary pathology, and nuclear medicine. This paper details the recommendations of the FTWG with international contribution from the Oslo Group. These recommendations were discussed and approved by the LAG in November 2021 (17). The group recommended that LT as an intervention in CRCLM should be conducted as a pilot service evaluation in all seven adult LT units in the UK, rather than as a randomised controlled trial, given the clear evidence in literature to suggest survival advantage and the recent recommendation to accept CRCLM as a global indication for LT (24).

It is expected that approximately 20-30 NHS patients will undergo transplantation for this indication over a 2-year period, commencing in the fourth quarter of 2022. The eligibility criteria established by the FTWG differ slightly from existing selection criteria. The highly appraised Norwegian study benefited from a surplus of donor organs in their country, which allowed them to explore rarer indications for LT. The average waiting time for a LT in Norway was less than 1 month and is currently a median of 2 months. On the contrary, the same in the United Kingdom is about 5 months among first-time, adult recipients (25). Therefore, recognising the need to maintain access to LT for existing indications, the UK protocol has been formulated to be more conservative but will be kept under regular review by the National Expert Review Panel that will consist of members from the FTWG, to ensure that they are not overly restrictive and that enough patients are being assessed for this intervention. The outcome measures will be audited at a national level with specific reference to safety, graft and oncological outcome measures.

Patient selection criteria

The selection process will involve identifying patients with unresectable CRCLM with favourable tumour biology who would achieve the greatest survival benefit from LT, based on the following criteria

1. Patients will have stage IV, liver-only disease with no resection options, and have undergone standard oncological resection of primary colorectal adenocarcinoma with microscopically- negative (R0) resection margins (including a circumferential resection margin (CRM) of $\geq$1 mm), at least 3 months before the time of listing.
2. Patients should be of ECOG performance status 0 or 1 and have satisfactory blood tests (Hb >10g/dl, Serum Bilirubin < 5 x upper normal level (ULN), Serum Creatinine < 1.25 times ULN, albumin above lower range of normal).

3. All patients will have received first-line systemic CT and showed a 30% response to CT based on RECIST criteria that is sustained for 2 years on cross-sectional imaging (CT and liver MR with Primovist) before listing for transplantation, with no evidence of disease dissemination on FDG PET-CT (26).
4. Any disease progression during this 2-year observation period will result in de-listing and commencement of 2nd line CT, at which point the clock will be 'reset'.

Units would be advised to undertake surgery for the primary tumour at the latest around the 18th month of the 2 years wait-time prior to LT. This would ensure timely bowel surgery and recovery within the 2-year window prior to LT. Patients participating in the evaluation will be requested to give signed informed consent for the treatment and follow up and their cooperation will be documented according to Good Clinical Practice, and national/local regulations. It is anticipated that from the point of listing, the patient will undergo transplant within a median of 3 months, during which time the patient will not be on CT.

Diagnostic Imaging of choice

The diagnostic accuracy of contrast-enhanced liver MRI or thoraco-abdominal, thin- slice CT, or both, for CRCLM is well-established for assessing the resectability of disease (27). Meta-analyses have evaluated the performance of CT and MR in this setting and shown that MR with diffusion-weighted imaging (DWI) and liver-specific contrast agents provide the best performance, especially in the setting of CT induced intra-tumoral changesv(28–30). Therefore, in this service evaluation, the presence of isolated liver metastases will be confirmed with baseline imaging by both CT and contrast-enhanced liver MR with DWI which will be documented as being unresectable by the Hepatobiliary Multidisciplinary Team (MDT).

The same modalities will be utilised serially throughout the pathway to measure treatment response, characterize previously indeterminate lesions, and identify occult metastases.

FDG PET-CT detects widespread disease not characterised by CT alone (31,32). This technique has been used by the Oslo Group with incorporation of hepatic metabolic tumour volume on PET-CT at the time of listing < 70 cm^3 as an inclusion criteria (33). However, the UK FTWG recommendation was that the pre-transplant biological behaviour of the tumour, characterised by metabolic tumour volume and total lesional glycolysis on PET-CT will be recorded as a variable of interest for registry analysis but it would not be used for pre-operative assessment. Therefore, the FTWG supports the use of FDG PET-CT as a second-stage examination in all patients to identify extra-hepatic disease (28,34). Histological confirmation of liver lesions observed on cross sectional imaging will not be mandatory in our evaluation, as studies have suggested that percutaneous biopsy of liver tumours may be associated with extra-hepatic dissemination of tumour and result in a decreased prospect of long-term survival even when complete resection of hepatic metastases is performed (35,36).

Primary tumour burden and morphology prior to LT consideration

The removal of all macroscopic local disease is a pre-requisite to liver transplantation. There is evidence to suggest that patients with extensive lymph nodal disease around the primary, tumours of poor differentiation and signet-cell varieties have poor survival following resection or LT (2,37). However, in the absence of recurrence in the extended observation period of 2 years that will be maintained after induction CT, initial tumour differentiation and primary nodal staging may be of less prognostic significance. Therefore, the FTWG recommends that the service evaluation will include patients with tumours of any epithelial differentiation, mucinous, signet-cell type tumours and any nodal burden, including those with extramural vascular, peri-neural or lymphovascular invasion who maintain 30%

reduction in tumour burden on neoadjuvant therapy with disease stability through the observation phase. From a genotype perspective, patients will also not be excluded based on right or left sided tumours or the presence/absence of specific genetic mutations (Microsatellite Instability, BRAF V600E, KRAS) based on the 2-year 'time test' that would exclude poor biology tumours.

Metastatic tumour burden

Currently, there is no evidence to suggest a benefit of LT in resectible disease, although this may be refuted in future studies, particularly in a subgroup of these patients, as technical resectibility is not closely associated with tumour biology and varies between centres and surgeons. Therefore, all resectible CRCLM should undergo resection with curative intent such as staged hepatectomies, including associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), or other down-staging therapies such as hepatic arterial infusion (HAI) therapy and trans arterial chemoembolization with drug-eluting beads (DEBIRI-TACE), where appropriate (38–41). Patients who have been successfully down-staged with CT and resected have a 5-year OS of up to 50% in studies (42,43). Patients who have undergone previous metastatectomy of the liver at any time and currently harbour unresectable disease will not be considered in the initial phase of the service evaluation study. However, the national panel would monitor the study with regards to recruitment and review that decision if necessary. Moreover, size and number of metastatic lesions will not have an absolute cut off in the selection criteria.

The development of extra-hepatic metastases is indicative of disseminated disease and an adverse prognostic marker in metastatic CRC (44). Any current or previous extra-hepatic disease will preclude eligibility for LT. Patients with lung nodules will need to undergo percutaneous biopsy to histologically confirm the absence of metastatic colorectal

adenocarcinoma before being considered eligible for LT. In addition to cross-sectional imaging, eligible patients will undergo a colonoscopy in the last year prior to transplant to exclude local luminal recurrence or second primary tumours.

The FTWG agreed that in case of >/= T3 colon tumours or presence of other high risk pathological/radiological features, a diagnostic laparoscopy performed by the local colorectal team will be mandated prior to referral, or an MRI of the abdomen and pelvis with DWI in two planes where laparoscopy is not technically feasible, to exclude peritoneal disease. Referral to a National Peritoneal Disease Centre may be considered by the specialist team reviewing the case if there is any concern of peritoneal spread. There will be no absolute cut off value for CEA, but a rising CEA, particularly in secretors will be considered an exclusion criterion. Patients with complete clinical response of primary tumour will be excluded, including rectal cancer patients treated with chemoradiotherapy and without anterior resection, even in the absence of disease at the primary site. Finally, patients with all other malignancies would be excluded, apart from histologically confirmed basal cell or squamous cell skin cancers. The patient selection criteria for UKCoMET evaluation are summarised in **Table 1**. Prior to the commencement of the service evaluation, a national audit will be undertaken at every colorectal/HPB centre to identify eligible patients on systemic CT who meet the criteria.

Transplant evaluation and listing

All patients identified as being suitable for this evaluation by local colorectal MDTs will be referred to the local Hepatobiliary MDT. The Hepatobiliary MDT will further ascertain if the patient meets the inclusion criteria for transplantation and proceed with onward referral to the regional LT Centre. All pertinent disease-specific documentation of the patient including histopathology, imaging, surgical and medical treatment information with confirmation that

the isolated CRCLM are not technically resectable should be enclosed in the initial referral. In addition, any critical information including general investigations, and comorbidities, psychosocial factors and addiction data should be included. Formal transplant assessment will then be undertaken routinely by the LT Centre and may include an inpatient review and/or an outpatient review. In general, listing discussions for LT are three-tiered and involve the acceptance of indication and non-reversibility of condition, an evaluation of comorbidities and exclusion of contraindications by the experts in the meeting. If the patient is found suitable for LT by the LT Centre, the patient would proceed to being listed for a LT at the Centre after appropriate anaesthetic work up.

If there is any concern with regards to candidacy of the patient being listed the case will be reviewed by the National Expert Review Panel. Once on the waiting list, all systemic treatment will be stopped, and it is anticipated that transplantation will occur within a three-month period. Deterioration in performance status, disease progression either within the liver or extra-hepatically while on the waiting list and development of additional malignancies will lead to de-listing of the patient. Therefore, from the time of listing to transplantation, the FTWG recommends re-imaging (CT Chest, Abdomen and Pelvis, FDG PET-CT) every 6 weeks, or earlier if clinically indicated.

Organ allocation and prioritisation

At present, all patients selected for elective adult liver transplantation in the United Kingdom must have a predicted 5-year survival after transplantation of >50% with acceptable quality of life, and the same cut off survival rate will be a rather justifiable expectation in unresectable CRCLM if LT is accepted as a form of therapy (25). This translates into an approximate 1-year patient survival of >60% based on the anticipated rate of attrition from years 2 to 5 in current patients transplanted from the urgent waiting list. The main goal of any organ allocation

system is to guarantee an impartial distribution of donor organs to waitlisted patients, in keeping with the ethical principles of equity, utility, benefit, urgency, and fairness. With this in consideration, since 2018, NHS Blood and Transplant moved the offering process for donation after brain death (DBD) livers in the United Kingdom from unit- based organ offering and allocation to a centralised nationwide organ distribution scheme, called the National Liver Offering Scheme based on the Transplant Benefit Score (TBS) to maximise survival benefit for the whole waiting list population over a five year period (45). The TBS is derived from a computer-based algorithm which incorporates seven donor characteristics and 21 recipient characteristics. Once a donor is realised the TBS is used to identify the hierarchy of patients with the highest TBS to be offered that liver with the accepting team then deciding on the suitability of that donor organ for that patient. The TBS only applies to those patients with underlying chronic liver disease or HCC. While the TBS suffices for those patients, there are patients listed for LT where the TBS does not adequately estimate the need for liver transplantation such as cases where the indication is impaired quality of life in patients with normal liver function or without cirrhosis e.g., polycystic liver disease, recurrent cholangitis, pruritus, or genetic disorders. For these categories of variant indications, where TBS does not adequately assess need for transplantation offering of organs occurs proportional to the frequency of their registration (10% of registrations currently) and organs are offered based on blood group, size and time waiting on the list. In the United States, patients with HCC have received Model for end-stage liver disease (MELD) exception points to prioritize them on the waitlist and reflect mortality rates (46,47). However, the UK listing criteria for HCC does not include such special allocation policy and is matched through the allocation model. It is planned that the patient listed for LT for unresectable CRCLM will be offered a graft within 'variant group' of the UK National Organ Allocation Scheme. The same approach will be

undertaken for other new transplant oncology indications for metastatic neuroendocrine tumours and cholangiocarcinoma. The algorithm will factor in the timely oncological window of three months that has been set to be suitable for these patients. The FTWG recommends caution in the use of marginal/ extended criteria donor grafts, including DCD livers, for these patients. However, they may be utilised following assessment of organ viability such as through machine perfusion (48,49). Living donation and transplantation may be considered for these patients if they meet inclusion criteria, and the centre meets internationally accepted, standard peri- operative outcomes. The RAPID technique may be employed in highly selective patients as a bridge to total hepatectomy in the event of a long waiting period. The procedure involves partial liver resection and transplantation, with right portal vein ligation and delayed remnant hepatectomy after graft regeneration (50,51). Nevertheless, this technique comes with morbidity of a second surgery and the oncological effects of leaving behind malignant disease in an immunocompromised patient and therefore, warrants caution.

Post- transplant immunosuppression and follow up

Immunosuppression is a contentious theme in LT for malignant diseases in terms of achieving a balance between the risk of graft rejection and the risk of disease recurrence. Graft rejection requiring treatment with T-cell depleting antibodies is associated with an increased risk of cancer in solid organ transplantation (52). Calcineurin Inhibitor (CNI)-based immunosuppression is the current standard of care in all centres in the United Kingdom, and worldwide. The FTWG recommends that for the first 6 weeks post LT, the immunosuppressant protocol will be CNI- based. Studies have shown that the mTOR inhibitor Sirolimus is an effective immunosuppressant that contributes favourably to post transplant disease-free outcomes in the first 3-5 year period in patients with HCC (53,54). Moreover, Sirolimus was

the immunosuppressive agent used in the SECA studies (17,37). Therefore, the FTWG proposes conversion to an mTOR-based immunosuppressive regimen, including Mycophenolate and steroids after 6 weeks post-transplant in this service evaluation. Induction with an IL-2 inhibitor like Basiliximab may be used at the discretion of individual units to facilitate low Tacrolimus concentration in the initial period for renal sparing. Steroids will be weaned off gradually between 3 and 6 months, and Sirolimus trough levels will be maintained between 5 and 10 ng/ml. It is advisable to have a close follow up of these patients in a MDT team consisting of dedicated surgeons, hepatologists and oncologists to monitor for recurrence. As per the SECA I and II studies, the recommendation would be that patients are seen every month for the first year, thereafter every 3 months for the second year, and every 6 months from the third year. CT scan of the chest, abdomen and pelvis is recommended every 2 months in the first year, every 3 months in the second year and every six months thereafter. The FTWG recommends although the schedule may be too elaborate for a service evaluation, it must be adapted to have consistency in monitoring outcomes. From the SECA studies, we gather that most recurrences following LT are pulmonary and mostly amenable to resection. Therefore, the Thoracic Commissioning Group will be made aware of this service evaluation study for input and management of pulmonary recurrences.

Outcome measures of the service evaluation

Outcomes of patients referred into the pilot for consideration of LT and outcomes on the waiting list after registration will be monitored. After transplantation overall survival, progression- free survival, disease recurrence sites and volume, and the number and type of oncological interventions post-transplant will be recorded. Quality of life will be measured using validated questionnaires (QLQ-C30 and EuroQoL EQ- 5D) at specific time points throughout the evaluation. Recorded variables will be compared with patients considered for

listing but found unfit for surgery. A national registry will be maintained to record graft and oncological outcomes for the purpose of audit and research.

Futility will be estimated by a <60% 1- year overall survival and ultimately a <50% overall survival after transplantation. If accrual to the evaluation is slower than predicted the entry criteria will be reviewed and revised if necessary. If outcomes on the waiting list are unfavourable with significant rate of drop-outs on the list, or significant delays to patients being transplanted, the process of offering donors to such cases will be reviewed and potentially revised.

Conclusion

The addition of unresectable CRCLM as an indication for LT represents a significant development for UK patients with colorectal cancer and a meaningful step forward in the emerging field of transplant oncology. This paper details the proposed service evaluation protocol for referring and listing patients with unresectable CRCLM for LT in the United Kingdom, scheduled to begin in the fourth quarter of 2022.

It outlines selection criteria, the UK framework for referral for LT, criteria for delisting, peri-transplant management protocols and the oncology-specific outcome measures that will be utilised to determine the benefit or futility of LT in this setting. A programme of promotional events will be arranged by the FTWG throughout 2022 and 2023 for referrers and targeted relevant clinical bodies across the UK to highlight the endorsement of CRCLM as a newly accepted indication for liver transplantation. Prior to this clinical service evaluation, a national audit will be undertaken to identify patients on systemic CT who meet the criteria for the proposed intervention. Data from the service evaluation study will be collected in a national registry and the survival outcomes will be evaluated and published.

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Table 1 Patient selection criteria for UKCoMET Service Evaluation

Inclusion criteria

1. Histologically verified primary adenocarcinoma in colon or rectum that has been fully resected at least 3 months before listing, with microscopically negative resection margins (including CRM of ≥ 1mm).
2. Isolated synchronous/ metachronous CRCLM on CT and liver MR with no liver resection option, based on the outcome of local MDT and sanctioned by Independent National Panel.
3. At least 30% sustained response to induction CT over a 2-year period, based on RECIST criteria; Disease progression/ second line therapy will lead to 'reset' of clock.
4. No signs of extra hepatic metastatic disease or local recurrence on FDG PET-CT within 4 weeks of listing.
5. No signs of extra-hepatic metastatic disease or local recurrence according to CT and MR (thorax/abdomen/pelvis) scan within 4 weeks prior to listing.
6. No signs of local recurrence on colonoscopy / CT colonography within 12 months prior to listing.
7. No evidence of peritoneal recurrence on diagnostic laparoscopy and/ or MR abdomen and pelvis with DWI in two planes, in case of T3 or more tumours, within 4 weeks of listing.
8. Good performance status, ECOG 0 or 1.
9. Hb >10g/dl, Serum Bilirubin < 5 x upper normal level, Serum Creatinine < 1.25 times ULN, albumin above lower range of normal
10. Signed, informed consent as per GCP

Exclusion Criteria

1. Weight loss >10% the last 6 months
2. Patient BMI > 30
3. Any second primary malignancies, except non-melanoma skin cancers
4. Prior extra-hepatic metastatic disease or local relapse.
5. Sequentially increasing serum CEA assays
6. Patients who have not received standard operative treatment for the primary CRC.
7. Patients who have undergone palliative resection of primary CRC tumour
8. Patients with complete clinical response of primary tumours, without radical resection.

Special considerations

1. Following morpho- pathological factors will ***not*** be used as exclusion criteria
    - Mucinous differentiation
    - Signet-ring cell morphology
    - Tumour differentiation status
    - Nodal metastases, extramural/ lymphovascular/ perineural invasion
    - BRAF V600R, KRAS, mismatch repair protein status, or right sided tumours
2. Patients requiring salvage transplantation and previously resected liver metastases will be excluded for the evaluation, however the decision may be reviewed by the National Expert Panel following at commencement of the study and after assessing initial recruitment.

Figure 1 – Workflow for UKCoMeT