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The role of liver transplant for intrahepatic cholangiocarcinoma: the UK NHSBT liver advisory group pilot programme

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Abstract

Aim: Liver transplantation (LT) offers a potential curative treatment for non-metastatic intrahepatic cholangiocarcinoma (iCCA) in patients with chronic liver disease who are not amenable to liver resection (LR). Recent evidence suggests that cirrhotic patients with "very early" iCCA (single tumour, ≤ 2 cm) might benefit the most from LT, with a 5-year survival as high as 73%. In view of these developments, NHS Blood and Transplant's Liver Advisory Group (LAG) established a Fixed Term Working Group (FTWG) to determine whether iCCA in patients with background cirrhosis should be considered for LT in the United Kingdom.

Methods: The FTWG included cholangiocarcinoma/LT patient representatives, experts in cholangiocarcinoma surgery/oncology, LT surgery, hepatology, hepatobiliary radiology, hepatobiliary pathology, nuclear medicine, and representation from various national hepatobiliary/oncology and transplant professional bodies. The objective was to make recommendations on appropriate indications, patient selection criteria, referral criteria, radiological

assessment, transplant listing pathways, data management, and overall quality assurance.

Results: The FTWG recommended LT for very early iCCA in cirrhotics, who are otherwise not suitable for LR. In this paper, we summarise the selection criteria, patient pathways, referral framework, pre-transplant assessment criteria, outcome measures, and dissemination strategy for implementing this new indication for LT in the UK.

Conclusion: The introduction and evaluation of this pilot programme is an important breakthrough for iCCA patients in the UK, marking a significant stride in the field of transplant oncology. The results of this service evaluation will describe the role of LT in iCCA and guide future programmes to optimise patient selection, management, and outcomes.

Keywords: Intrahepatic cholangiocarcinoma, liver transplantation, working group, pilot programme, outcomes

INTRODUCTION

Intrahepatic cholangiocarcinoma (iCCA), although rare, constitutes the second most common primary liver cancer after hepatocellular carcinoma (HCC)[1]. In the United Kingdom (UK), the incidence rate of iCCA has nearly doubled from 1.8 to 3.3 per 100,000 from 1997 to 2017, which is an average annual percentage change of 3.8% and this continues to increase[2]. Despite significant advances in early diagnosis, surgical techniques, and chemotherapy regimens, the 5-year overall survival (OS) remains dismal between 15%-25%[3,4]. Liver cirrhosis significantly increases the risk of iCCA, with an odds ratio of 22.92 [95% confidence interval (CI), 18.24-28.79][5]. A National Cancer Database (NCDB) study from the United States (US) reported 28.9% of iCCA in patients with background cirrhotic liver (Ishak Fibrosis score 5-6)[6]. While liver resection (LR) is still considered the gold standard for curative treatment of iCCA, the outcomes are far from ideal. The 5-year recurrence-free survival (RFS) typically ranges between 9% and 31%, with 83% experiencing local recurrence within the first two years after surgery[7-11]. Although LT would appear an attractive option, associated chronic liver disease, tumour location, portal hypertension, and liver failure limit the applicability of LR even in patients with small iCCA[12,13].

Early experience in LT for iCCA, including both cirrhotic and non-cirrhotic patients, resulted in poor 1- and 3-year OS rates of 19.4%-38% and 4.9%-10%, respectively[14,15]. However, some encouraging results from multicentre studies have led to a re-evaluation of iCCA as a potential indication for LT in a select patient group[16-23]. A significant proportion of these LTs are actually incidental iCCAs on explants, either because of an unrecognized lesion not visible on pre-transplant radiology or a lesion wrongly diagnosed as HCC[19,24,25]. Explant data from the UK of 40 iCCAs showed a median survival of 68.5 months (25.3-109.7 months), with a reassuring 5-year OS of 57.1%[25].

According to a recent study from the US, out of 13 patients with iCCA, those with well-differentiated tumours had no recurrence, while those with moderately differentiated tumours had a recurrence rate of 78%. This highlights the significant role of tumour biology in post-transplant outcomes[22]. A multicentre study in Spain revealed that patients diagnosed with "very early" iCCA (defined by tumours that are solitary and ≤ 2 cm in size) had a 73% 5-year survival rate based on a small sample size of eight patients[16]. In an international multicentre study, the number and size of tumours were found to have a positive impact on long-term outcomes. Specifically, 15 patients with very early iCCA had a 5-year survival rate of 65%, with recurrence rates similar to those of HCC within Milan criteria[18]. Jung *et al.* compared 16 LT patients with incidental iCCA, with a propensity score matched 100 iCCA patients who underwent LR. At a mean follow-up of 39.1 months, three patients who had very early iCCA and underwent LT had no recurrence, while six out of 26 patients (24.2%) who had very early iCCA and underwent LR had

developed recurrence[24]. Half the recurrences in this study were intra-hepatic and the authors argued if the patients would have potentially benefited from LT rather than LR. However, these studies were heterogeneous and included both cirrhotics and non-cirrhotics[18]. Supportive of these data from incidentally diagnosed iCCA, data from the Barcelona clinic on an intention-to-treat curative LR on very early iCCA (n = 7) demonstrated a 68.6% 5-year OS with only one patient developing recurrence at 8.3 months, with a median follow-up of 23 months. Interestingly, five of these seven patients had background liver disease, and all were minor (< 3 segments) liver resections and six of them were well to moderately differentiated tumours[10].

According to a French multicentre study, cirrhotic patients with larger primary tumours may also benefit from LT. This retrospective study from three centres compared the outcomes of patients who underwent LT with incidental iCCA at explants (n = 49) with patients who underwent LR for iCCA (n = 26). At a median follow-up of 25 months, the LT patients had a better 3- and 5-year OS (76% and 67%, respectively) compared to 59% and 40% for patients who underwent LR. The LT patients enjoyed a significantly better RFS (recurrence-free survival) at 5 years (75% *vs.* 36% for LR patients). The size of the largest tumour and differentiation were identified as independent risk factors for recurrence. The study reported a similar 1-, 3- and 5-year OS for tumours ≤ 2 cm compared with tumours > 2-5 cm which had LT - 92%, 87% and 69% *vs.* 87%, 65% and 65%, respectively. These findings raise the possibility that the tumour size cut-off could be increased to 5 cm while remaining within the Milan criteria[19]. The role of neoadjuvant therapy before LT for large unresectable iCCA was assessed in few studies[20,21,26]. These studies, which employed systemic therapy and locoregional treatment with radioembolization, reported an excellent 5-year OS and RFS of 83% and 50%, respectively[20,21,26]. The studies indicate the potential benefit of neoadjuvant/adjuvant therapies for iCCA in LT settings and need further investigation through larger clinical trials.

CHOLANGIOCARCINOMA FIXED TERM WORKING GROUP

The International Liver Transplant Society (ILTS) Transplant Oncology Consensus Conference in 2019 reviewed the evidence for transplantation for iCCA and recommended two clear areas where this could be performed: (1) patients with very early disease (single tumour, ≤ 2 cm) with cirrhosis and who are not candidates for LR; (2) patients with advanced iCCA deemed unresectable in a noncirrhotic liver, if the disease remains stable for a period of 6 months after neoadjuvant chemotherapy[27,28].

As a result of these advancements, the Liver Advisory Group (LAG) of NHS Blood and Transplant (NHSBT), the regulatory body responsible for overseeing all donation and transplant-related operations in the UK, created a Fixed Term Working Group (FTWG) in June 2021, the cholangiocarcinoma-orthotopic liver transplantation (CCA-OLT) Implementation group. The objective of the group was to develop guidelines, protocols and processes that would enable the implementation of perihilar cholangiocarcinoma (pCCA) and iCCA as new indications for liver transplant in the UK. The FTWG recommendations for pCCA-OLT are not within the remits of this manuscript (this protocol is pending final approval and is not operational yet). Similar working group recommendations for unresectable colorectal liver metastases (CRLM) and grade 1 and 2 well-differentiated unresectable liver metastatic neuroendocrine tumours (NETs) have been accepted as newer indications for LT in the UK and have been active since December 2022[29,30].

The FTWG included cholangiocarcinoma and LT patient representatives, experts in cholangiocarcinoma surgery, LT surgery, hepatology, oncology, hepatobiliary radiology, hepatobiliary pathology, and nuclear medicine. The group has representation from various professional bodies including British Association of the Study of the Liver (BASL), British Liver Transplant Group (BLTG), British Transplant Society (BTS),

British Association of Surgical Oncology (BASO), Great Britain & Ireland Hepato Pancreato Biliary Association (GBIHPBA), British Society of Gastroenterology, and The British Society of Gastrointestinal and Abdominal Radiology (BSGAR). It also had representation from the LAG, NHSBT and NHS England (NHSE). AMMF, the largest cholangiocarcinoma charity in the UK and Europe and PSC Support (the UK PSC patient association) provided very valuable input from the patient and public perspective. The group also sought advice from the Medical Advisory Board of UK-PSC and the UK Digital Pathology Group.

SUMMARY OF GUIDELINES

The group met at four weekly intervals to address the objectives set out in the initial outline. The main objectives were to conduct a literature review and provide recommendations on appropriate indications, patient selection criteria, referral criteria, assessment prior to listing, transplant listing pathways, data management, and overall quality assurance for the service evaluation. The group put forth the following guidelines.

LT as an intervention in ≤ 2 cm iCCA with background chronic liver disease should be implemented as a pilot service evaluation in all seven adult LT units in the UK.

A National Expert Review Panel (NERP) will be formed to manage this emerging indication. The panel will help with trouble shooting any service evaluation pathway issues, provide quality assurance, overview data collection and management and will be an access for a "second opinion" if required. The panel will be a reassurance to patient groups and to individual centres.

Each transplant centre develops a core group of healthcare professionals interested in managing these patients and complex pathways. This is in keeping with the already established practices seen with HCC and LT. It is important to get support from Cancer Nurse Specialists along with the traditional support provided by transplant coordinator teams at each centre. It is acknowledged that surgical management could be challenging with a learning curve, and it is important that all transplant surgeons are supported to develop their operative experience.

It is expected that over the first year, 6-8 iCCA ≤ 2 cm will be transplanted within the UK, commencing December 2022. In order to maintain access to LT for existing indications, the UK iCCA LT protocol has been designed to be more conservative. However, the protocol will be regularly reviewed by the NERP, consisting of members from the FTWG, to ensure that it strikes a balance between being restrictive and allowing enough patients to be assessed for this intervention. At the conclusion of one year, the pilot programme will undergo a comprehensive national audit to assess safety, graft outcomes, and oncological results.

As per the ILTS consensus, the FTWG deliberated on the potential benefits of LT for patients with advanced iCCA undergoing downstaging using improved chemotherapeutic agents[27]. However, currently, favourable survival outcomes are lacking, making it an unacceptable indication[20,21,26]. As ongoing clinical trials are exploring this possibility, the working group decided not to include it in the pilot programme. Once the programme establishes safety and acceptable oncological outcomes, there is a definite prospect of expanding the eligibility criteria.

PATIENT SELECTION CRITERIA

To identify patients who would benefit the most from LT, the selection process would involve finding those with very early iCCA and cirrhosis. The group agreed with the following selection criteria:

Inclusion criteria

≤ 2 cm tumours with background chronic liver disease.

Resection is precluded because of underlying liver function or the location of the tumour.

Biopsy-proven and to exclude patients with mixed hepatocellular/cholangiocellular carcinoma (cHCC-CCA).

No signs of extrahepatic metastatic disease on imaging.

Good performance status; The Eastern Cooperative Oncology Group (ECOG) 0 or 1.

Signed, informed consent.

Exclusion criteria

Patients with extrahepatic disease or multiple tumours or satellite lesions.

Patients with previous liver resection for intrahepatic cholangiocarcinoma.

Patients not fit for LT due to other surgical or anaesthetic reasons.

Contraindications to liver resection

The FTWG recognised the importance of providing clear guidelines regarding the contraindications to liver resection, which include:

Patients with advanced liver cirrhosis.

Patient with inadequate functional liver remnant.

Inability to obtain a curative intent (R0) resection.

Presence of extrahepatic disease, lymph node metastases, or multicentric tumours.

The FTWG expressed concern that the number of patients diagnosed with biopsy-proven iCCA measuring ≤ 2 cm would be limited, owing to the difficulties in radiologically diagnosing nodules smaller than 2 cm in cirrhotic patients[31-34]. Solitary iCCA > 2-5 cm was discussed as a potential inclusion criterion. In fact, the French multicentre study showed that the outcomes in the > 2-5 cm group are comparable to the outcomes of tumours ≤ 2 cm very early iCCA, but this included patients with both iCCA (49%) and cHCC-CCA (51%), the latter has shown to have better overall survival outcomes[19,35,36]. According to the authors, the use of magnetic resonance imaging (MRI) and increased vigilance in cases where radiographic findings are atypical for HCC, combined with advancements in radiological techniques, could lead to a higher rate of preoperative diagnosis of iCCA and cHCC-CCA[37]. However, this remains easier for tumours up to 5 cm in size and very challenging for tumours smaller than 2 cm. The FTWG concluded that we

remain ≤ 2 cm as the current criterion and to consider expanding to > 2-5 cm after the first year of the pilot programme, considering the number of recruited patients with tumours ≤ 2 cm. It was acknowledged that a small proportion of patients with iCCA ≤ 2 cm may be offered resection in patients with chronic liver disease, good synthetic functions and no portal hypertension, and tumours in locations that would enable minor or segmental resections.

Few studies have included patients with cHCC-CCA in iCCA, leading to significant heterogeneity[16-18,38]. The rationale for the latter grouping is that distinguishing between iCCA and cHCC-CCA for a definite presurgical diagnosis is challenging and may not be feasible and thus more consistent with real-life clinical practice. It is worth noting that these mixed-type tumours typically have a prognosis between pure HCC and pure CCA, hence may not reliably indicate the oncological outcomes with LT for iCCA[39].

While the role of carbohydrate antigen 19-9 (CA 19-9) in liver resection for iCCA is well documented[40], there is currently no evidence suggesting a specific threshold of CA 19-9 that is associated with poor outcomes following LT. As a result, this criterion has not been included in the evaluation process for liver transplant candidates.

RADIOLOGICAL EVALUATION

The diagnosis of iCCA is made by a combination of radiological appearances and tissue diagnosis. Gadoxetic acid-enhanced MRI (Primovist® in Europe/Eovist® in the US) is recommended as the standard cross-sectional imaging, as it is the most accurate modality for identification of satellite lesions and intrahepatic metastases, and provides better diagnostic performance and may even give prognostic information[41-43]. The staging would include a dual-phase computed tomography (CT) of chest, abdomen and pelvis and a positron emission tomography (PET) CT. If a patient has once been listed for transplant and waits more than 3 months from previous cross-sectional imaging, we recommended further re-assessment at that time point with a contrast MRI, a dual-phase CT and a PET CT. The group felt the need for extensive evaluation to exclude patients with nascent extrahepatic disease and adverse biology to maximise the outcomes from service evaluation. Those with poor renal function will get a non-contrast CT of chest, abdomen and pelvis, with contrast MRI.

FITNESS ASSESSMENT & TIMING OF TRANSPLANTATION

Fitness evaluation will be as per local practice for LT assessment. Patients with iCCA with no extrahepatic disease and considered fit for transplantation will be discussed at the local LT MDT and the cancer MDT, and if both MDTs confirm that the patient is suitable for LT, oncologically and physiologically, the patient will be counselled and listed for this indication [Figure 1].

The implementation group recommended that patients are transplanted within three months of listing, as this is a life-threatening malignancy, with a risk of progression and drop out/death on the waiting list. Unlike the technical complexity of transplantation for pCCA after radiotherapy, there is no plan for iCCA to receive local therapy. Hence, the working group recommended all graft types be open for the iCCA patients, including marginal grafts such as donation after circulatory death (DCD) and machine-perfused grafts. The living donor liver transplantation (LDLT) was considered an ideal graft, as this would reduce the waiting time after completion of assessment and also avoid competing for precious resources with other patients on the waiting list.

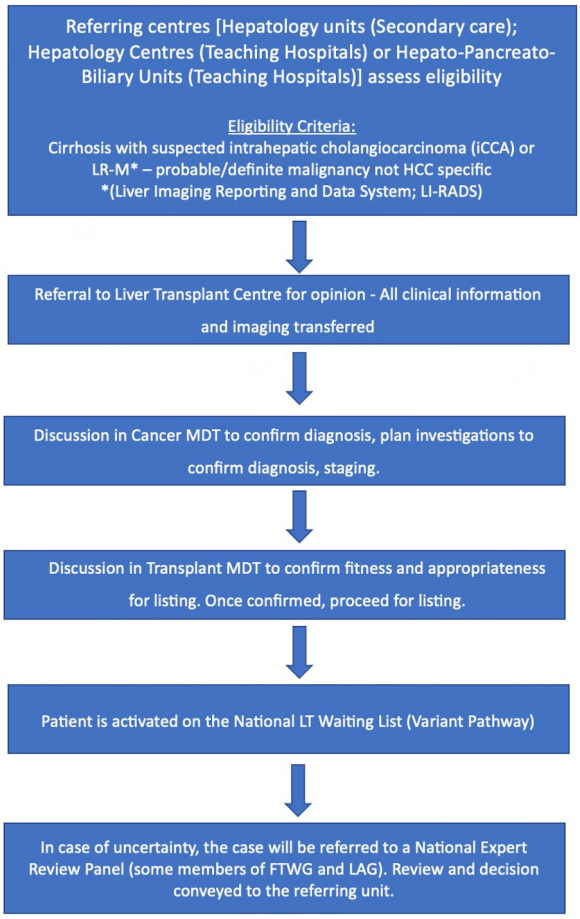

Figure 1. Flowchart depicting the patient pathway for the liver transplantation for ≤ 2 cm iCCA. iCCA: Intrahepatic cholangiocarcinoma.

ORGAN ALLOCATION AND PRIORITISATION

For elective adult LT in the UK, the patient selection criteria require a predicted 5-year survival rate of over 50% after transplantation, with an acceptable quality of life. Based on the published literature and a more conservative oncological approach, a similar survival rate cut-off would be reasonable for iCCA patients in this new service evaluation. An organ allocation system's main goal should be to distribute donor organs fairly to patients who are on the waitlist, in line with ethical principles such as equity, utility, benefit, urgency, and fairness. The NHSBT implemented the National Liver Offering Scheme (NLOS) in 2018. This revised method for matching livers from deceased donors to adult patients on the liver transplant matching list operates at a national level, as opposed to a regional one. The NLOS aims to allocate the liver to chronic liver disease and HCC patients who could benefit most from the transplant. The new scheme is comprehensive and considers 21 recipient factors and 7 donor factors. The patient with the best match will be shown at the top of the list and will have the highest Transplant Benefit Score (TBS), thereby giving them the maximum "net benefit" (difference in predicted survival with and without transplant). The FTWG plan is to provide a graft within the "variant group" of the UK NLOS to the patients who are listed for LT for iCCA. The variant list is specifically for patients with UKELD score < 49, such as those with diuretic-resistant ascites, hepatopulmonary syndrome, chronic hepatic encephalopathy, and other indications of quality of life. The algorithm will consider the three-month oncological window for iCCA patients, and they will be given priority on the variant list, both at the local center and at national levels. In view of this short window from assessment to transplant, the FTWG did not feel there was a need to bridge the tumour with

ablation or any other locoregional therapy on the waiting list. Any drop out/death on the waiting list will be notified to the NHSBT and appropriate root cause analysis will be performed.

SURGICAL PROTOCOL

Transplant surgery will be similar to transplantation for other indications. Unlike the pCCA patients, the FTWG did not recommend staging laparoscopy, as it is unlikely to add benefit in small iCCA tumours. The group discussed the pros and cons of routine lymphadenectomy. It was decided that formal lymphadenectomy is not recommended as a routine, as it is very unlikely that a ≤ 2 cm tumour will disseminate to the nodes. The lymph nodes that are part of the explant specimen will obviously be included for histological examination.

POST-TRANSPLANT IMMUNOSUPPRESSION AND FOLLOW-UP

The standard of care following LR for iCCA is adjuvant chemotherapy based on level 1 evidence[44,45]. For the service evaluation on LT for iCCA, patients will be managed with no adjuvant chemotherapy. The evidence for chemotherapy pre- and post-LT for iCCA is with tumours that were large and unresectable[20]. However, the published literature with good survival outcomes from very early tumours from the multicentre study and the UK data is without adjuvant therapy[17,18,25]. The current protocol on chemotherapy will be subject to review and these recommendations may evolve based on new evidence.

After LT for iCCA, the goal of immunosuppression is to maintain a balance between the risk of graft rejection and the risk of disease recurrence[3,46]. The FTWG recommends that for the first 6 weeks post-LT, the immunosuppressant protocol will be CNI-based, with either mycophenolate mofetil (MMF) or azathioprine (AZT) as the second agent and a period of steroids for about six weeks. Sirolimus, a mammalian target of rapamycin inhibitor (mTORi), has been found to have a positive impact on disease-free outcomes after LT in patients with HCC[47,48]. However, there are no such data available for CCA patients; hence, the FTWG did not feel any indication to convert CNI to mTORi. To facilitate renal sparing in the initial period, interleukin-2 (IL-2) inhibitors such as Basiliximab may be used at the discretion of individual units for induction and to maintain low CNI concentration. As no study has adequately evaluated either the role of post-LT immunosuppression in reducing the risk of recurrence or the effectiveness of adjuvant therapy in this setting, future studies should focus on identifying patients with high risk of recurrence who may benefit from adjuvant therapy[23].

Patients with hepatitis B virus (HBV) related cirrhosis who undergo LT will typically receive hepatitis B immunoglobulin (HBIG) in the peri-transplant period to prevent HBV reinfection of the transplanted liver. Additionally, they will be prescribed oral antiviral medications to suppress the replication of HBV and reduce the risk of post-transplant recurrence of the virus. Standard centre-based protocols will be followed for similar indications.

There are no clear guidelines regarding the duration and frequency of follow-up for surveillance after LT for iCCA[27]. The post-transplant surveillance recommended by the FTWG includes assessment of tumour marker (CA 19-9) at 3 monthly intervals for the first 3 years (to interpret the results using pre-LT values as the baseline) and cross-sectional imaging in the form of dual-phase CT of chest, abdomen and pelvis at 6 monthly intervals for the first 2 years. After 2 years, the cross-sectional imaging is recommended on an annual basis until the end of 5 years and the tumour markers are recommended at 6 monthly intervals, again until the end of 5 years [Figure 2]. The FTWG recommends that although the schedule may be too elaborate for a service evaluation, it must be adapted to have consistency in monitoring outcomes.

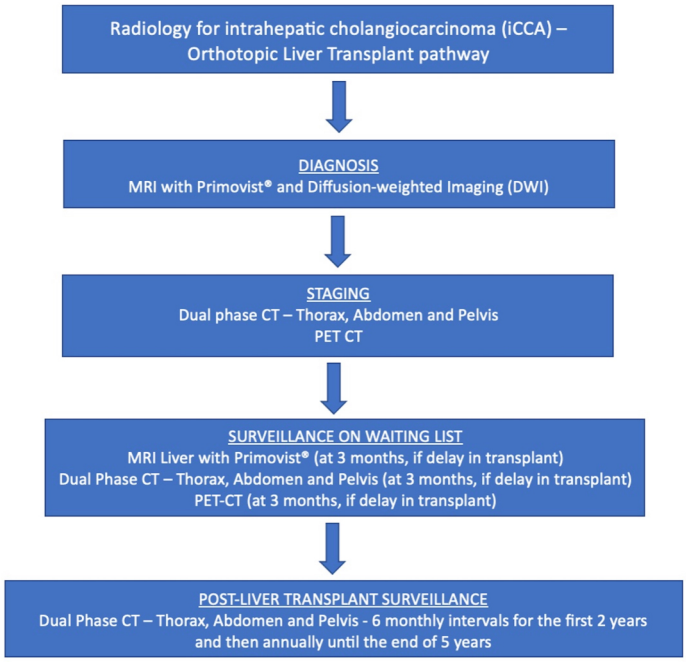

Figure 2. Radiology pathway for the patients in service evaluation protocol.

OUTCOME MEASURES AND DATA MANAGEMENT

The FTWG and LAG recognised the importance of having a set of triggers in the interim period till the service evaluation is completed. These triggers are to take stock of unexpected events and advise LAG and individual centres of necessary action points. These triggers may also mandate a re-evaluation of the protocol agreed upon by the FTWG.

The implementation group recommends analysis of the perioperative and cancer specific outcomes after recruitment and completion of treatment for 30 patients, including both iCCA and pCCA.

As the numbers are small, it was felt that trigger points should be based on events rather than percentage occurrence. The group agreed to label these as "adverse events of special interest", which will include vascular thrombosis within 3 months, recurrent cancer within 6 months, cancer-related mortality within 12 months, and re-transplantation for any reason.

The group recommended that such events should be discussed with the NERP to facilitate improvements in outcomes rather than imposing a moratorium.

A moratorium will only be advised if the events are felt to be repetitive with a clear pattern behind the failures.

In cases where the waiting list outcomes demonstrate a high rate of dropouts or significant delays in transplant patients, the process of offering donors may be reviewed and revised accordingly.

It was acknowledged by the group that accurate and relevant data collection is fundamental for delivering and improving services for these new indications. It was felt that the database should include patients considered but not assessed, assessed for malignancy but not assessed for transplant, and patients assessed for transplant but not listed due to frailty and fitness. For the data collection and service evaluation, funding and staffing arrangements will be sought through AMMF, PSC Support, NHSBT research grants and other external funding applications.

COMMUNICATION STRATEGY

A multi-pronged approach is proposed to provide appropriate information on this new indication to both patients, families and clinicians. The FTWG recommended the following programme of promotional events and arrangements for referrers and targeted relevant clinical bodies across the UK to highlight the endorsement of iCCA as a newly accepted indication for LT.

A series of road shows facilitated by LAG.

NHSBT website.

AMMF, PSC Support, British Liver Trust.

Engagement with BTS, GBIHPBA, BASL, BLTG, BSG, and BASO (*via* Special Interest Groups in Transplant Oncology).

ONGOING CLINICAL TRIALS

At present, there are three ongoing trials that seek to investigate the potential for LT for iCCA patients who are not eligible for LR. These trials separately focus on early iCCA, primary or recurrent iCCA, and locally advanced diseases necessitating downstaging therapy.

The clinical trial NCT02878473 "Liver Transplantation for the Treatment of Early Stages of Intrahepatic Cholangiocarcinoma in Cirrhotics" is being conducted in Toronto, Canada at the University Health Network and in Barcelona, Spain at the Hospital Clinic. The study started recruitment in April 2018, with the estimated primary completion date of January 2026. The study aims to recruit a total of 30 patients and the primary outcome measure is the 5-year OS. The eligibility criteria are similar to the UK pilot proposal - biopsy-confirmed single ≤ 2 cm iCCA, with background cirrhosis, not eligible for LR and CA-19-9 ≤ 100 ng/mL[49].

The clinical trial, NCT04195503 "Liver Transplant for Stable, Advanced Intrahepatic Cholangiocarcinoma". The study is being conducted at the University Health Network, Toronto and is designed as a single-group, open-label trial with an expected enrollment of 10 participants. The study started recruitment in December 2019, with the estimated primary completion date of December 2026. Primary endpoint is 5-year OS. To be eligible for this study, the patients must have > 6 months of disease stability or tumour regression on gemcitabine-based therapy and have at least one blood group compatible living donor who has stepped forward to donate[50].

The TESLA trial, NCT04556214 "Liver Transplantation in Locally-advanced, Unresectable, Non-metastatic Intrahepatic Cholangiocarcinoma treated with neoadjuvant systemic therapy: a Prospective Exploratory Trial". The study is being conducted at Oslo University in Norway and is designed as a single-group, open-

label trial with an expected enrollment of 15 participants. The study started recruitment in June 2020, with the estimated primary completion date of May 2035. Primary endpoint is to study the OS, and the main inclusion criteria are unsuitable for LR due to tumour location or underlying liver dysfunction (cirrhosis), 12 months or more time from the diagnosis of iCCA and date of listing for LT, and could have received at least 6 months of chemotherapy or locoregional therapy[51].

The outcomes from these small but prospective studies would help in proving the oncological benefit of LT in iCCA and the patient selection protocols for the future.

CONCLUSION

The NHSBT LAG pilot proposal for liver transplantation in cirrhotic patients with intrahepatic cholangiocarcinoma ≤ 2 cm, which has been operational since December 2022, signifies a significant advancement in the treatment of this cancer. The proposal suggests that patients with biopsy-proven very early iCCA who meet specific criteria may be suitable candidates for LT, which could ultimately offer a cure and improve overall outcomes for iCCA. In this paper, the indication for LT in this setting, referral framework, recipient selection criteria, peri-transplant management, and oncology-specific outcome measures are described. These elements will be used to evaluate the effectiveness of LT in this context and to determine its potential benefits or limitations. The results of the pilot programme will demonstrate the feasibility of LT in this setting. While this proposal may raise questions about equity of access to limited transplant resources in the UK, it is important to emphasise that the selection process for potential transplant recipients will be rigorous and the outcomes will be closely monitored. The national registry will collect the data from the service evaluation study, and the survival outcomes will be assessed and made public. Transplantation for iCCA should be encouraged but needs to be evaluated as a clinical trial, such as our pilot programme, in order to understand the tumour biology better and overall improve outcomes with iCCA.

DECLARATIONS

Authors' contributions

Participated in literature review, FTWG discussion and voting, article writing and editing, and critical review: Hakeem AR, Isaac J, Thorburn D, Heaton N, Prasad R, Walmsley M, Morement H, Watson S, Manas D, Bridgewater J, Hawkins M, Radhakrishna G, Dasari BVM, Attia M, Adair A, Gibbs P, Sharma D, Oppong K, Albazaz R, Malik H, Snowdon V, Aluvihare V, Crellin A, Valle J, Treanor D, Rushbrook S

The five authors were working group coordinators and contributed equally to the writing of the manuscript: Hakeem AR, Isaac J, Thorburn D, Heaton N, Prasad R

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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