A Service Development Evaluation of Orthotopic Liver Transplantation For Patients Undergoing "Down-Staging" of Hepatocellular Carcinoma

Background

Current UK selection criteria[1] for patients with hepatocellular carcinoma (HCC) are a modification of the Milan Criteria[2]. Using size and number of HCC on pre-transplant imaging, these criteria aim to select at time of presentation patientsthat have HCC with favourable tumour biology and hence good outcome following liver transplantation. However, it is recognised that some patients outwith standard selection criteria based on size and number of HCC at the time of initial presentation have good biology disease and would benefit from liver transplantation. This recognition has led to the development of expanded criteria for listing of patients at presentation and the listing of patients who have undergone specific anti-cancer therapies resulting in apparent good response. This latter approach has been called "down-staging". At present down-staging of HCC allowing listing for liver transplantation is not permitted under UK liver transplant selection criteria. However a reassessment has been determined to be necessary given the growing body of evidence to support down-staging as an appropriate strategy[3].Consequently this Service Development Evaluation aims to evaluate and validate down-staging of HCC utilising the selection criteria as developed by Duvoux and colleagues[4]. Amongst all potential criteria for down staging the Duvoux criteria, which were developed and have been introduced for use in France,have been deemed appropriate for use within the UK at a recently convened consensus conference[3].

Aims of Evaluation

To assess and validate the Duvoux criteria for down-staging of HCC for use within the UK.

Inclusion criteria

- Not eligible for elective listing for under standard UK listing criteria for HCC[1]
- Within Duvoux criteria for down-staged HCC[4]

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[1]http://www.odt.nhs.uk/pdf/liver_selection_policy.pdf
[2]Mazzaferroet al. Liver transplantation for thetreatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl JMed. 1996 Mar 14;334(11):693-9.
[3]NHSBT/LAG/BTS Developing new guidelines for the use of liver transplantation in the treatment of HCC in the United Kingdom. January 17th 2014. Birmingham
[4]Duvoux et al. Liver transplantation for hepatocellular carcinoma: a model includingα-fetoprotein improves the performance of Milan criteria. Gastroenterology. 2012 Oct;143(4):986-94

- Interval of ≥6 months from down-staging treatment to imaging upon which registration based
- Interval of ≥3 months from imaging demonstrating patient within criteria to registration

Duvoux Criteria For Listing For HCC

Criteria for listing following "down-staging" treatment will be consistent with that detailed in Duvoux et al[4].

Variable	Points
Largest diameter (cm)	
≤3	0
3-6	1
>6	4
Number of nodules	
1-3	0
≤4	2
AFP (ng/mL)	
≤100	0
100-1000	2
>1000	3

Patients with a score ≤2 points following down-staging treatment will be eligible for registration for liver transplantation.

Either local or systemic anti-cancer therapies may be undertaken in order to achieve down-staging of HCC, but that for patients who have undergone either surgical resection or ablative therapies within 1 year of registration the resected or ablated lesions will continue to be counted with diameter of lesions as determined by the resection pathology or the pre-intervention imaging with the greatest diameter being used.

Exclusion Criteria

- Macrovascular invasion – identified at any time on radiological imaging or liver resection pathology
- Nodal metastases at any time
- Extrahepatic metastases at any time
- Ruptured HCC at any time
- Presence of an absolute contra-indication to liver transplantation as defined in the current UK selection assessment and selection criteria for liver transplantation[1].

Radiological Imaging

Patients with presumed HCC should undergo the following imaging modalities during assessment for liver transplantation

1. Contrast-enhanced CT of chest, abdomen and pelvis.
2. Contrast-enhanced MRI liver

Imaging for the purpose of diagnosis and assessment must be undertaken within 4 weeks of listing.

Two independent radiologists will review all imaging undertaken prior to listing in order to confirm that imaging demonstrates HCC within the Duvoux criteria with regard to size and number.

For any given lesion the longest axis will be determined and used for assessment purposes. Measurements will be determined from the imaging modality that provides the best definition of the lesions under investigation

Waiting List Management Of Patients

Local or systemic therapy for HCC is allowed whilst the patient is on the waiting list.

The maximum interval between repeat radiological imaging/AFP estimations will be 3 months.

Repeat imaging for estimation of HCC size and number will be with the modality (CT or MRI) that provides the best definition of identified liver lesions. The independent radiologists reviewing the initial imaging will determine the imaging modality to be used during follow up imaging.

CT chest, abdomen and pelvis will be required at 3 monthly intervals to assess the presence or absence of extra-hepatic disease.

Date of repeat imaging and lesion measurements will be provided to NHSBT along with other required variables as part of the Sequential Data Collection.

Removal from waiting list

Patients will be removed from the waiting list if they progress beyond the Duvoux criteria or develop an exclusion criteria as listed above.

Cohort Size

A maximum of 40 patients will be recruited.

Major Outcome Measures

- 2 year disease-free survival
- 5 year disease-free survival
- 2 year patient survival
- 5 year patient survival

Evaluation Monitoring

An independent Oversight Committee will be responsible for the running of the evaluation. This committee will consist of both clinicians and lay members.

The Oversight Committee will provide reports to the Liver Advisory Core Working Group.

The Core Working Group will report and be responsible to the Liver Advisory Wider Group at the 6 monthly meetings.

Termination Of Service Development Evaluation

The evaluation will be terminated if there is

1. Evidence of poor outcome following liver transplantation
2. Evidence of poor recruitment to the service development evaluation.

Dissemination Of Details of Planned Service Development Evaluation

Patients eligible for inclusion in the present evaluation may not have traditionally been managed within a liver transplant centre raising the possibility of inequity of access to a potentially curative treatment if referring centres are unaware of the proposed evaluation. Consequently details of the evaluation will be circulated to all cancer networks, gastroenterologists and hepatobiliary surgeons. Where possible information will be circulated through relevant professional bodies e.g. British Association for the Study of the Liver (BASL), GB and Ireland HepatoPancreaticoBiliary Association (GBIHPBA).