

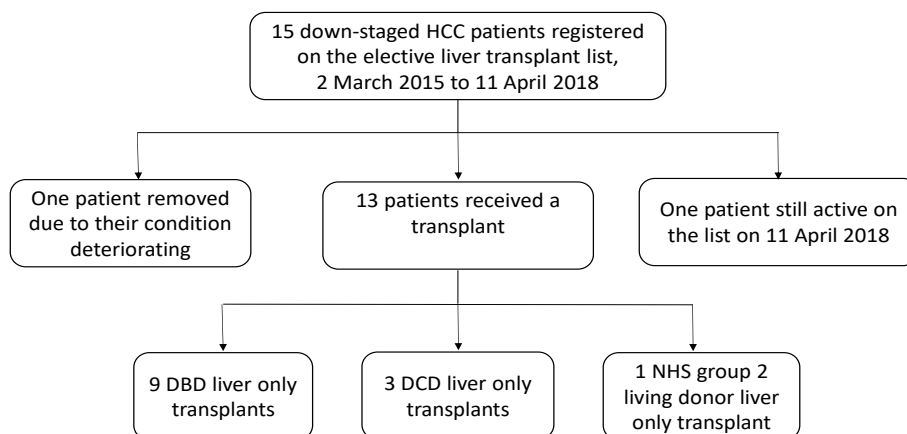
**NHS BLOOD AND TRANSPLANT  
ORGAN DONATION AND TRANSPLANTATION DIRECTORATE**

**LIVER ADVISORY GROUP**

**UPDATE ON THE HCC DOWN-STAGING SERVICE EVALUATION**

1. A service development evaluation to transplant down-staged HCC patients was successfully introduced on 2 March 2015. The inclusion and exclusion criteria for the service evaluation are shown in **Appendix A** and are also in the Liver Selection policy on the ODT website (<https://nhsbtdeb.blob.core.windows.net/umbraco-assets-corp/9861/pol195-liver-selection-policy.pdf>). Transplant centres are responsible for ensuring patients meet the eligibility criteria and deciding whether the patient should be removed from the waiting list.
2. As at 11 April 2018, there have been 15 down-staged HCC patients registered on the UK liver transplant list and all were registered electively. **Figure 1** shows the registration outcome as at 11 April 2018 and shows that 13 (87%) of the 15 patients received a liver only transplant. Of the 13 transplanted patients, 11 were known to be alive at their last follow-up. For the two patients, transplanted in January 2018 and April 2018, there was no follow-up information as at 11 April 2018.
3. The patient active on the transplant list was registered in November 2017 with autoimmune and cryptogenic liver disease and has been on the transplant list for 140 days.

**Figure 1 Registration outcome for 15 down-staged HCC patients registered on the UK elective liver transplant list, 2 March 2015 to 11 April 2018**



4. Two of the 15 patients have been included in the new National Liver Offering Scheme matching runs and one patient, registered in March 2018, declined four liver offers due to recipient reasons prior to receiving a liver transplant in April 2018. The second patient has not received any offers under the new scheme due to a low transplant benefit score.
5. Nine of the 15 patients registered for HCC down-staging were reported to have HCC in association with chronic liver disease on the Elective Liver Registration form. Of these nine patients, six had information reported under the HCC criteria on the Elective Liver Registration form and **Table 1** summarises this information. Pre downstaging information was only reported for one patient and this is footnoted in **Table 1**.

**Table 1** Summary of cancer information recorded on the Liver Elective Registration form for the six patients reported to have HCC, who were registered for HCC down-staging, 2 March 2015 – 10 April 2018

| Patient number | No. of tumours | All tumours ≤5cm | Tumour size (cm) if all tumours ≤5cm |          | Tumours >5cm and ≤7cm | Maximum dimensions (cm), if tumours >5cm and ≤7cm |                    | Maximum AFP level |
|----------------|----------------|------------------|--------------------------------------|----------|-----------------------|---|--------------------|-------------------|
|                |                |                  | Tumour 1                             | Tumour 2 |                       | Initial   | 6 month assessment |                   |
| 1              | 1              | Yes              | 2.3                                  | -        | No                    | -   | -                  | 175 <sup>1</sup>  |
| 2              | 2              | Yes              | 4.5                                  | 1.5      | No                    | -   | -                  | 3                 |
| 3              | 1              | Yes              | 4.1                                  | -        | No                    | -   | -                  | 1                 |
| 4              | 1              | No               | -                                    | -        | Yes                   | 6.7   | 5.3                | 1                 |
| 5              | 6              | Yes <sup>2</sup> | -                                    | -        | No                    | -   | -                  | 4                 |
| 6              | 1              | Yes              | 1.5                                  | -        | No                    | -   | -                  | 3                 |

<sup>1</sup> Notes on registration form: HCC tumour diameter 3.5 cm reduced to 2.3 cm and AFP Peak 1489 to 175 iu

<sup>2</sup> Tumour sizes were 0.8, 1.2, 1.6, 1.8, 2.1 and 2.8cm

6. **Table 2** provides a summary of primary, secondary and tertiary liver disease at the registration as well as Roberts disease group for the 15 patients who were registered for HCC down-staging between 2 March 2015 and 11 April 2018. Nine (60%) of the 15 patients had a UKELD value of 49 or greater at registration and, of the nine patients, two patients had cancer as their aetiology at registration (based on Roberts disease group) and would have been offered in the new National Liver Offering Scheme using the cancer model.
7. Thirteen patients included in the service evaluation received a liver transplant and 11 of the 13 had hepatocellular carcinoma reported as either primary, secondary or tertiary disease at transplant.

**Table 2 Primary, secondary and tertiary liver disease at registration as well as Roberts disease group for the 15 down-staged HCC patients who were registered on the elective liver transplant list, by UKELD at registration, 2 March 2015 - 10 April 2018**

| Roberts disease group<br>(used in TBS score) | Indication at registration        |                          |              | N (%)          |
|--|-----------------------------------|--------------------------|--------------|----------------|
|  | Primary                           | Secondary                | Tertiary     |                |
| <b>UKELD at registration ≥49</b>             |                                   |                          |              |                |
| Cancer                                       | Non-alcoholic fatty liver disease | Hepatocellular carcinoma | Other        | 1 (7)          |
| Cancer <sup>1</sup>                          | Hepatitis C cirrhosis             | Hepatocellular carcinoma | Other        | 1 (7)          |
| Alcoholic liver disease                      | Alcoholic liver disease           | Other                    | Not reported | 1 (7)          |
| Alcoholic liver disease                      | Other                             | Alcoholic liver disease  | Not reported | 1 (7)          |
| Hepatitis B cirrhosis                        | Hepatitis B cirrhosis             | Other                    | Not reported | 1 (7)          |
| Hepatitis C cirrhosis                        | Other                             | Hepatitis C cirrhosis    | Not reported | 1 (7)          |
| Hepatitis C cirrhosis                        | Hepatitis C cirrhosis             | Other                    | Not reported | 1 (7)          |
| Hepatitis C cirrhosis                        | Hepatitis C cirrhosis             | Not reported             | Not reported | 1 (7)          |
| Other  | Other                             | Not reported             | Not reported | 1 (7)          |
| <b>Total</b>                                 |                                   |                          |              | <b>9 (60%)</b> |
| <b>UKELD at registration &lt;49</b>          |                                   |                          |              |                |
| Cancer                                       | Hepatitis C cirrhosis             | Hepatocellular carcinoma | Other        | 1 (7)          |
| Cancer                                       | Alcoholic liver disease           | Hepatocellular carcinoma | Other        | 1 (7)          |
| Cancer                                       | Other                             | Hepatocellular carcinoma | Not reported | 1 (7)          |
| Other  | Other                             | Not reported             | Not reported | 1 (7)          |
| Alcoholic liver disease                      | Alcoholic liver disease           | Other                    | Not reported | 1 (7)          |
| Autoimmune and cryptogenic <sup>2</sup>      | Cryptogenic cirrhosis             | Other                    | Not reported | 1 (7)          |
| <b>Total</b>                                 |                                   |                          |              | <b>6 (40%)</b> |

<sup>1</sup> UKELD at registration was 49, UKELD on sequential update was 48

<sup>2</sup> UKELD at registration was 47, UKELD on sequential updates was 52 and 49

## RECOMMENDATIONS AND ADVICE REQUIRED

8. Transplant centres are reminded that down-staged HCC patients should be registered with other liver disease on the elective liver registration form and that the text "HCC down-staging cohort" should be included in the free text box under indication.
9. Members are asked to advise whether the TBS score calculated for down-staged HCC patients should utilise the cancer or non-cancer model.

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**APPENDIX A from the Liver Selection Policy****A SERVICE DEVELOPMENT EVALUATION OF ORTHOTOPIC LIVER TRANSPLANTATION FOR PATIENTS UNDERGOING “DOWN-STAGING” OF HEPATOCELLULAR CARCINOMA****Background**

Current UK selection criteria for patients with hepatocellular carcinoma (HCC) are a modification of the Milan Criteria<sup>1</sup>. Using size and number of HCC on pre-transplant imaging, these criteria aim to select at time of presentation patients that 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<sup>2</sup>. Consequently, this Service Development Evaluation aims to evaluate and validate down-staging of HCC utilising the selection criteria as developed by Duvoux and colleagues<sup>3</sup>. 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<sup>2</sup>.

**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
- Within Duvoux criteria for down-staged HCC<sup>3</sup>
- Interval of  $\geq 6$  months from down-staging treatment to imaging upon which registration based
- Interval of  $\geq 3$  months from first 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<sup>3</sup>.

| <b>Variable</b>              | <b>Points</b> |
|------------------------------|---------------|
| <b>Largest diameter (cm)</b> |               |
| ≤3                           | 0             |
| 3-6                          | 1             |
| >6                           | 4             |
| <b>Number of nodules</b>     |               |
| 1-3                          | 0             |
| ≥4                           | 2             |
| <b>AFP (ng/mL)</b>           |               |
| ≤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 •
- Absence of an absolute contra-indication to liver transplantation as defined in the current UK selection assessment and selection criteria for liver transplantation.

**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.

**Removal from waiting list**

Patients will be removed from the waiting list if they progress beyond the Duvoux criteria or develop an exclusion criterion 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).

**References**

<sup>1</sup> Mazzaferro et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med.* 1996 Mar 14;334(11):693-9.

<sup>2</sup> [http://www.odt.nhs.uk/pdf/advisory\\_group\\_papers/LAG/HCC\\_recommendations\\_IR\\_TS\\_b\\_NAS\\_Work\\_in\\_Progress.pdf](http://www.odt.nhs.uk/pdf/advisory_group_papers/LAG/HCC_recommendations_IR_TS_b_NAS_Work_in_Progress.pdf)

<sup>3</sup> Duvoux et al. Liver transplantation for hepatocellular carcinoma: a model including  $\alpha$ -fetoprotein improves the performance of Milan criteria. *Gastroenterology.* 2012 Oct;143(4):986-94