NHS BLOOD AND TRANSPLANT

LIVER ADVISORY GROUP

Liver transplantation for hepatocellular carcinoma in the UK – report from a national consensus meeting (Birmingham January 2014)

Preamble

Liver transplantation is considered an excellent treatment for early stage hepatocellular carcinoma. It affords the opportunity to cure both the cancer and the underlying liver disease. Progress over the last two decades has established criteria, based on tumour size and number, by which patients may be selected for transplantation with acceptable five year outcomes.

This success has led centres around the world to consider expansion of these criteria to allow individuals to benefit from transplantation whilst still maintaining good outcomes. With this expansion has followed recognition that understanding tumour biology, measured by a number of surrogates that include tumour size and number, level of alpha-fetoprotein, and response to adjuvant treatment before transplantation, is paramount to maintaining outcomes.

In the United Kingdom there was a modest expansion of selection criteria in 2008 that aimed to increase the applicability of transplantation for patients with HCC. This change however had little impact on patients selected for transplantation with expanded indications accounting for fewer than 10% of all patients with HCC. Furthermore outcomes remain inferior to patients transplanted for non-HCC indications.

The aims of this consensus meeting were to review current selection criteria in light of new data supporting the use of additional predictors of outcome. Issues discussed included standardisation of radiology reporting and definitions for staging; defining minimum listing criteria for patients with HCC; parameters predictive of low recurrence post-transplant; appropriateness of treatment on the waiting list; the acceptability and role of down-staging; role of live related donation; and other areas for possible exploration through pilot studies.

Summary of Recommendations

1. Definition of acceptable outcomes after transplantation

Outcomes for patients with HCC selected for transplantation should be comparable to those for patients transplanted for non-HCC indications.

2. Tumour size and number

There is insufficient evidence available at present to support the use of expanded criteria based on size and number alone (i.e. up-to-seven) that would provide outcomes that are equivalent to the Milan criteria.

3. Prognostic significance of alphafetoprotein (AFP) alone

AFP concentration should be measured during assessment for liver transplantation.

AFP concentration should be measured every 6 weeks (or 3 months) whilst the patient is waiting for transplantation.

Liver transplantation should be restricted to patients with AFP<1000iu/mL at the current time.

4. Combining tumour size, number and AFP

Patients should be selected for liver transplantation based on the French model with a score of ≤2 (see appendix 1).

Whilst on the waiting list the score should be recalculated each time new information is available from either biochemical or radiological sources.

5. Neo-adjuvant treatment (bridging) and down-staging

5.1 Neo-adjuvant treatment

Neo-adjuvant treatment should be considered in all patients with UNOS T2 HCC.

Those patients without contra-indications to treatment and who are predicted to wait >6 months should receive neo-adjuvant treatment.

5.2 Down-staging

Patients with HCC who are outside currently accepted transplant criteria with the following tumour characteristics should be considered for down-staging: 1 lesion up to 8cm in diameter; 2 or 3 lesions, each less than 5cm in diameter, and total tumour diameter <8cm; 4 or 5 lesions all <3cm, and total tumour diameter <8cm.

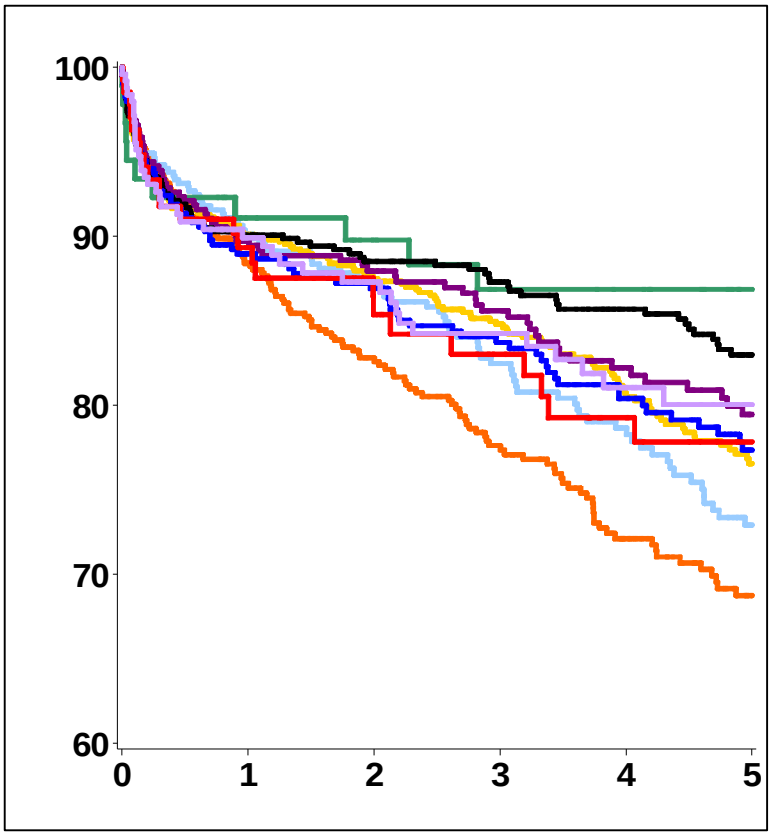
Down-staging should be assessed using the mRECIST criteria.

Successful down-staging is defined as radiological disease and AFP values acceptable within the AFP-model.

Following successful down-staging there is a mandatory three month observation period where disease must remain within acceptable AFP score criteria before the patient is listed for transplantation.

1. Definition of acceptable outcomes after liver transplantation

The role of liver transplantation in patients with HCC was recently reviewed by an international consensus panel (Clavien et al., 2012). The recommendation from this group was that “liver transplantation should be reserved for HCC patients who have a 5-year survival comparable to non-HCC patients”. This was debated in the light of data presented from UKT highlighting the current disparity between survival estimates for patients transplanted for HCC and those transplanted for non-HCC indications (Fig. 1).



	% survival
Cancer	68.7
HCV	72.9
ALD	76.6
HBV	86.9
PSC	79.5
PBC	83.0
AID	77.4
Metabolic	77.8
Other	80.0

Log-rank p-value=0.001

Figure 1 Five year overall survival after liver transplantation, stratified by primary disease indication.

This suggests that current selection criteria do not accurately select patients with favourable outcomes and that selection methods might be improved. As outlined above tumour biology is of critical importance, and without routine histological assessment of HCC there is necessary reliance on surrogate markers of biology. This report will summarise the presented evidence on three of these surrogates, namely tumour size and number, level of alpha-fetoprotein, and response to adjuvant treatment.

Recommendation

Outcomes for patients with HCC selected for transplantation should be comparable to those for patients transplanted for non-HCC indications.

2. Tumour size and number

The role of tumour size and number as surrogates of tumour biology and outcome was established in the seminal work from Mazzaferro and colleagues, the so called Milan criteria (Mazzaferro et al., 1996). Since that time a number of modifications or expanded criteria have been suggested, most notable from the group at UCSF (Yao et al., 2001), and also by Mazzaferro himself (Mazzaferro et al., 2009).

Perhaps the most attractive system based on size only is the up-to-seven criteria. The development of this system highlighted tumour characteristics that are associated with equivalent outcomes after transplantation in the so-called Metroticket approach (Mazzaferro et al., 2009). Here, up-to seven refers to the sum of the maximum tumour

diameter and the number of tumours. The method derived takes advantage of the relationships between those tumour characteristics and the risk of recurrence after transplantation. Tumour diameter shows a linear association with hazard whilst tumour number shows an inflection point at n=3 tumours and thereafter tumour number has a lesser impact on outcome. These criteria were described using an exploratory analysis of retrospective data and most importantly are based on explant pathology rather than pre-operative imaging. This approach has not been prospectively validated, indeed the only published "validation" study was a retrospective study including 82 patients where only 9 patients were beyond Milan criteria and within up-to-seven, and 15 patients were beyond both sets of criteria (Raj et al., 2011).

Recommendation

There is insufficient evidence available at present to support the use of expanded criteria based on size and number alone (i.e. up-to-seven) that would provide outcomes that are equivalent to the Milan criteria.

Prognostic significance of alpha-fetoprotein (AFP) alone

The addition of a plasma biomarker that is already in use in routine clinical practice is an attractive additional tool in the selection of patients with HCC for liver transplantation. AFP is recognised as a biomarker that has both diagnostic and prognostic significance in the management of HCC. A recent systematic review identified studies in which AFP had been studied in the context of recipient selection for liver transplantation (Hakeem et al., 2012). The review identified 12 relevant papers for inclusion and these are shown in Table 1. Whilst these studies were heterogeneous in terms of study design, data source and outcome measures. The results were consistent in so much as AFP was consistently associated with negative outcomes including vascular invasion, recurrence free survival and overall survival.

Author	Size criteria	Data source	AFP cut-off	Outcome
Merani	"Most within Milan"	SRTR	>400	OS
Mailey	Not stated	UNOS	>400	OS
Wang	33% within Milan	Single centre, China	>700	RFS
Xiao	30% within Milan	Single centre, China	>800	RR VI
Fujiki	60% within Milan	Single centre, Japan	>800	RFS, RR VI
Lao	Not stated	Single centre, US	>1000	RR RFS
Zou	Not stated	Single centre, China	>1000	RR OS
Adler	66% within Milan	Belgian registry	>100	RR RFS
Onaca	Not stated	Int'l registry	>200	RR RFS, OS
Perez-Salorido	75% within Milan	Single centre, Spain	>200	RR RFS
Yang	59% within Milan	Single centre, Korea	>200	RR RFS
Todo	Not stated	Japanese registry	>1000	OS, RFS

Table 1. Studies selected for analysis of the impact of AFP in patients undergoing liver transplantation. Adapted from (Hakeem et al., 2012).

The current UK selection criteria include AFP at a level of 10,000 iu/mL as an absolute contra-indication to liver transplantation to prevent futile transplantation. The data presented above suggest that this threshold is too high. To investigate this further data from Birmingham were analysed (Fig. 2). Patients were segregated by AFP concentrations recorded before transplantation at a level of </>1000 iu/mL. These studies showed that outcomes for individuals with AFP values >1000 iu/mL outcomes are clearly unacceptable with >50% of those individuals dying from recurrent HCC within five years of transplant.

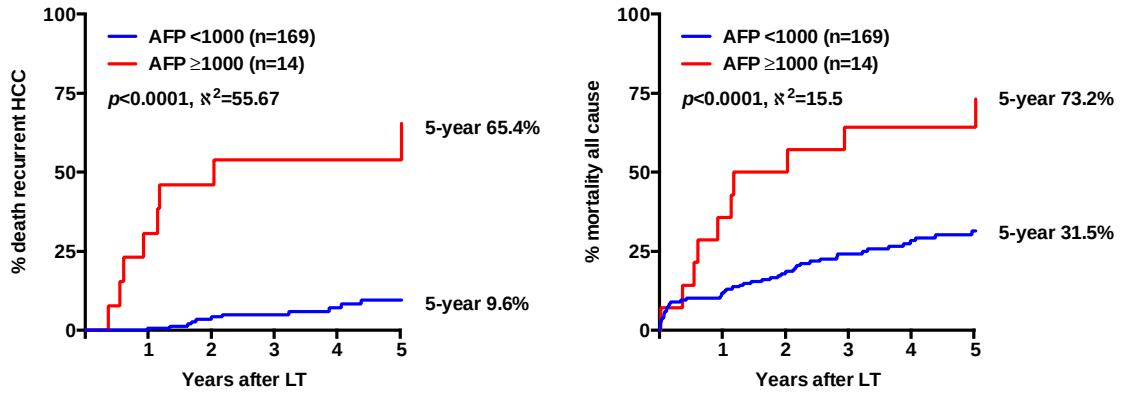


Figure 2. Outcomes of transplantation in patients transplanted at QEHB stratified by AFP at the time of transplantation.

Further analysis of these data indicated that a cut-off of 481 would maximise the number of patients selected for transplantation whilst maintaining current size and number selection criteria and favourable transplant outcomes (**Fig.3**) although these results require external validation.

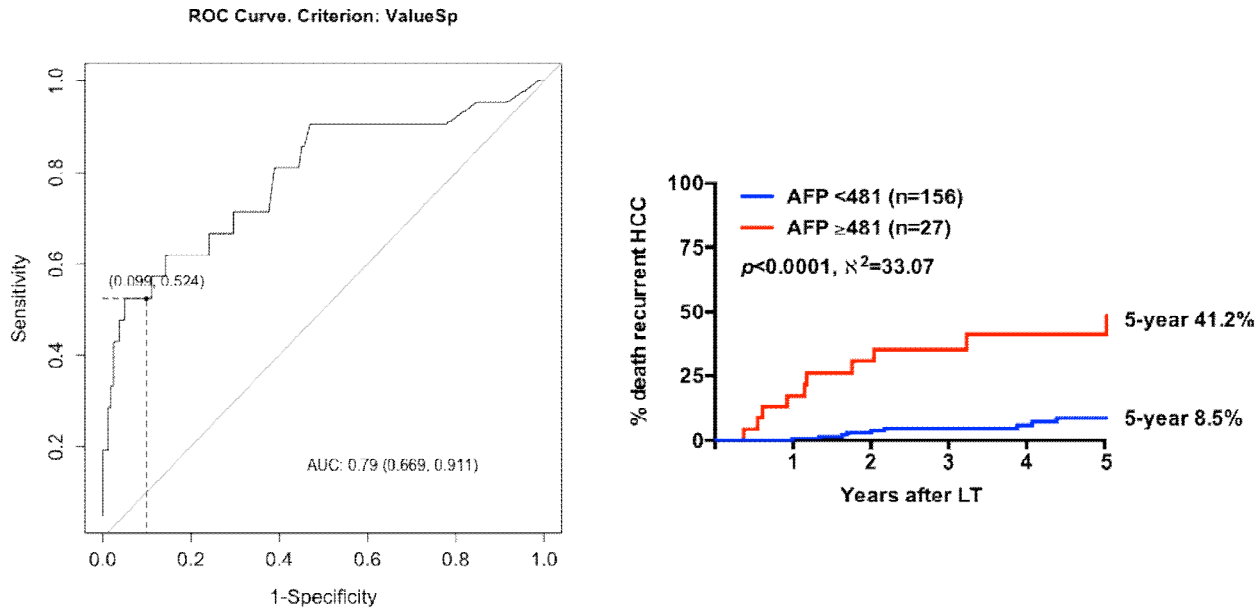


Figure 3 Receiver operator curve analysis allows selection of AFP cut-off that maximises specificity thus limiting the number of patients excluded from transplantation. Application of this cut-off to patients undergoing transplantation at QEHB identifies patients with acceptable, and unacceptable outcomes.

Recommendations

AFP concentration should be measured during assessment for liver transplantation.

AFP concentration should be measured every 6 weeks (or 3 months) whilst the patient is waiting for transplantation.

Liver transplantation should be restricted to patients with AFP<1000iu/mL at the current time.

4. Combining tumour size and number, and AFP

The recognition of AFP as a tool to improve the accuracy of recipient selection for transplantation has stimulated the rational combination of size and number characteristics, and AFP. Initial data came from retrospective analyses of single centre and registries including SRTR and UNOS. The best of these include analysis from the UNOS database (Berry and Ioannou, 2013, Mailey et al., 2011). Although the periods of study overlap these studies provide data to draw several conclusions. First, Mailey and colleagues confirm that even within the Milan criteria increasing levels of AFP increase the hazard ratio of death from any cause (AFP <20, HR 1.0; AFP 20-399, HR 1.6; AFP>400, HR2.12). Second, Berry and Ioannou extended these observations by examining the role of AFP both in patients within Milan criteria, and in patients outside Milan criteria. Overall outcomes were compared with non-HCC recipients and adjusted hazard ratios calculated. Again, patients within Milan criteria displayed adverse prognostic features with high AFP values whilst in contrast patients outside Milan criteria and low AFP values had 5-year outcomes comparable to non-HCC recipients (HR 0.97).

The interpretation of these studies is complex, particularly as a result of the heterogeneity of those studies and absence of detailed follow-up data in the registries. The data do however suggest that AFP at relatively low levels has prognostic significance, even amongst patients within Milan criteria and there are signals that AFP might be useful in expanding size and number criteria.

The recent publication of the French AFP model has provided additional data to support this approach (Duvoux et al., 2012). Here the authors studied a training cohort to identify independent predictors of HCC recurrence after liver transplantation. Taking this approach they defined a score that incorporates the maximum tumour diameter, the number of tumours, and AFP (**Table 2**) and identified a cut-off of ≤2 to predict favourable outcomes in liver transplantation.

Characteristic	Points
Diameter (cm)	
≤3	0
3-6	1
>6	4
Number of nodules	
1-3	0
≥4	2
AFP (iu/mL)	
≤100	0
100-1000	2
>1000	3

Table 2 The AFP model.

This score was validated in a cohort that was prospectively recruited for a study of waiting list mortality. Importantly the score was not prospectively applied but further retrospective

validation has been shown in studies of patients in Italian centres and at RFH (Duvoux, et al, unpublished observations).

Recommendation

Patients should be selected for liver transplantation based on the French model with a score of ≤2.

Whilst on the waiting list the score should be recalculated each time new information is available from either biochemical or radiological sources.

5. Neo-adjuvant treatment (bridging) and down-staging

These are two separate entities that should not be confused. Neo-adjuvant treatment, or bridging, refers to patients who are suitable for selection for transplantation who are given locoregional treatment in the form of RFA or TACE whilst waiting for transplantation. Down-staging refers to the treatment of patients with tumours outside accepted criteria for selection such that they may then be suitable candidates for transplantation.

5.1 Neo-adjuvant treatment

The purpose of neo-adjuvant treatment is to maximise the opportunity for the patient to receive a liver transplant. The risk of waiting list dropout is reduced in patients with UNOS T2 tumours who receive neo-adjuvant treatment with either TACE or RFA (Cescon et al., 2013, Cucchetti et al., 2011). There is no evidence that one or other treatment modality is superior and selection is dependent on local practice (Clavien et al., 2012). A failure to respond to neo-adjuvant treatment (i.e. progressive disease as defined by rapidly rising AFP, or by mRECIST criteria (Lencioni and Llovet, 2010)) may be associated with an adverse prognosis probably as a consequence of adverse tumour biology (Lai et al., 2013, Cucchetti et al., 2011). Consideration should be given to removing such patients from the waiting list.

The timing of neo-adjuvant treatment is challenging when the median waiting time for transplantation is short. Whilst in the UK there is no priority consistently awarded to individuals with HCC these potential recipients are *de facto* prioritised due to their eligibility for DCD liver transplantation. In patients who are predicted to wait less than 6 months for transplantation there is little evidence of benefit from neo-adjuvant treatment since the absolute risk of dropout is small.

Recommendation

Neo-adjuvant treatment should be considered in all patients with UNOS T2 HCC.

Those patients without contra-indications to treatment and who are predicted to wait >6 months should receive neo-adjuvant treatment.

(It is interesting that the NNT to prevent a single dropout is in the region of 20 before 6 months but in 6-12 months it is reduced to 10 as the absolute risk of dropout increases. It would be interesting to review the AEs of treatment to determine the balancing NNH, including possible arterial injury from TACE…)

5.2 Down-staging

The purpose of down-staging is to select for transplantation individuals with HCC, and with favourable tumour biology, who are outside of established criteria. A number of investigators have reported outcomes for this approach. By and large these studies have included patients with HCC just outside of the Milan criteria and with projected outcomes similar to the Metroticket approach (Cescon et al., 2013, Mazzaferro et al., 2009). In these studies successful down-staging is defined as imaging showing tumour characteristics within the Milan criteria. These studies highlight a significant risk of non-response to down-staging treatment (10-40%) and consequently between 50 and 80% of patients are eventually transplanted. Post-transplant outcomes are heterogeneous and are probably modestly inferior to patients transplanted within the Milan criteria (Silva and Sherman, 2011). These outcomes may be improved if a mandatory period of observation (e.g. three months) is included following the down-staging procedure to identify patients with adverse prognostic features (Yao et al., 2008). This is typically associated with a further 10% dropout rate, perhaps preventing early transplantation of these patients.

There are some limited data regarding down-staging to the AFP score criteria (Duvoux et al., 2012). These data suggest that reversion from outside criteria to within criteria is associated with a favourable prognosis. However these observations were based on a limited number of patients (7/17 who were initially outside AFP score criteria and were successfully down-staged).

At the current time down-staging *per se* is not permitted within UK guidelines and the quality of the evidence supporting this practice is weak and would be informed with a high quality prospective trial. Outcomes are likely inferior to those with T1/T2 HCC and the overall aim of the program to have outcomes that are comparable to those patients with non-malignant indications may preclude the introduction of downs-taging. Furthermore we have observed that the relaxation in UK selection criteria had (very) little impact on patients listed for LT suggesting that this possible group of patients is small. If down-staging were to be included these are the possible recommendations.

Recommendations

Patients with HCC who are outside currently accepted transplant criteria with the following tumour characteristics should be considered for down-staging: 1 lesion up to 8cm in diameter; 2 or 3 lesions, each less than 5cm, and total tumour diameter <8cm; 4 or 5 lesions all <3cm, and total tumour diameter <8cm.

Down-staging should be assessed using the mRECIST criteria.

Successful down-staging is defined as radiological disease and AFP values acceptable within the AFP model.

Following successful down-staging there is a mandatory three month observation period where disease must remain with acceptable AFP score criteria before the patient may be listed for transplantation.

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