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Review article: liver transplantation for hepatocellular carcinoma – a critical appraisal of the current worldwide listing criteria

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SUMMARY

Background
Liver transplantation (LT) plays an important role in the management of patients with hepatocellular carcinoma (HCC). Although early results following LT for HCC were poor, since the introduction of the Milan criteria in 1996 morphological criteria have since been well established. Thereafter, various expansions of the Milan criteria were introduced worldwide. Listing criteria for LT for HCC in the United Kingdom (UK) initially conformed to the Milan criteria but were re-defined in 2009 by expansion of the Milan criteria.

Aims
To look at the evidence in literature on listing criteria and management of HCC worldwide in comparison with the UK. Secondly, we aim to review worldwide vs. UK literature on prioritisation models, loco-regional therapy protocols and role of alpha-fetoprotein (AFP) in LT for HCC.

Methods
An electronic literature search with Medline was carried out to identify articles related to LT for HCC.

Results
Although various expansions of the Milan criteria have been described, they remain the gold standard against which other criteria are measured. The UK criteria are an expansion of the Milan criteria that go beyond Milan and University of California, San Francisco (UCSF) criteria. The current UK listing criteria for LT for HCC when compared to the worldwide criteria have a worse survival benefit (projected 5-year survival between 35-50%) when plotted on the metroticket calculator.

Conclusions
In keeping with most transplant centres worldwide, the UK have adopted expansions to Milan to allow more patients to benefit from LT. However, currently, as it stands the UK criteria when plotted in the modification of the Metroticket model project worse survival that would seem unjustified.

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INTRODUCTION

Hepatocellular carcinoma (HCC) of the liver is the commonest primary liver malignancy in the world and the incidence is expected to increase with the observed and predicted rise in chronic liver disease including viral hepatitis B and C, alcohol and obesity related chronic liver disease.[1–4] Treatment of HCC has evolved over the years.[5–9] Liver resection is the most appropriate treatment for patients with solitary tumours <5 cm that occur in the background of chronic liver disease Child's A with preserved synthetic function and no evidence of portal hypertension (normal portal pressures: hepatic vein wedge pressure <10 mmHg).[10] Liver transplantation (LT) on the other hand, is offered to patients with unresectable HCC or tumours associated with more advanced chronic liver disease.

Early results following LT for HCC were associated with high recurrence rates and poor outcomes.[11, 12] However, as introduction of 'Milan criteria' in 1996 by Mazzaferro *et al.* showed an overall 4-year actuarial survival of 75% and recurrence free survival of 83%, most centres adopted these criteria as the basis to offer LT for HCC.[13] Nevertheless, over the recent years, there has been ongoing debate as regards modification of the criteria to allow more patients to benefit from LT.[14] The selection criteria have therefore become variable worldwide with centres adopting different strategies.[15, 16] In the United Kingdom (UK), Milan criteria were used for listing patients for HCC up to 2009 and following a consensus meeting the expansion of Milan criteria were introduced after 2009. The current UK LT listing criteria for HCC are therefore expansion of Milan criteria, although there are no specific allocation policies, particularly with regards to prioritisation.

The aims of this review were firstly, to review the listing criteria for HCC worldwide and the UK. Secondly, to review the management of HCC worldwide vs. UK – the prioritisation models for patients with HCC on the waiting list, the evidence for loco-regional therapy as a bridge to LT and the role of alpha-fetoprotein (AFP) as a tumour marker.

METHODS

An electronic literature search with Medline was carried out to identify articles related to LT for HCC using the terms 'listing criteria liver transplantation', 'liver transplantation' and 'hepatocellular carcinoma', 'recurrent hepatocellular carcinoma' and 'liver transplantation' and 'biomarkers' and 'hepatocellular carcinoma' limited to the English language. Secondary references were obtained from the key articles.

RESULTS

Listing criteria for LT for HCC – Milan and worldwide

The Milan criteria for LT for HCC include presence of a tumour 5 cm or less in diameter in patients with a single tumour nodule and no more than three tumour nodules, each 3 cm or less in diameter, in patients with multiple tumours. Patients with tumour invasion of blood vessels or lymph nodes that was evident or suspected pre-operatively were excluded.[13] The use of the Milan selection criteria worldwide resulted in improved outcomes for LT for HCC.[17–21] However, as a result of improved outcomes with LT for HCC worldwide it was felt that the Milan criteria were too restrictive possibly denying more patients a LT. There have been several proposed expansions to the Milan criteria that have been listed in Table 1.

The original University of California, San Francisco (UCSF) criteria were drawn up based on explant histology and thereafter were validated prospectively using radiology.[22, 23] The UCSF criteria for listing patients with HCC for LT include, 1 nodule ≤6.5 cm, or 2–3 nodules ≤4.5 cm and total tumour diameter ≤8 cm. The 5-year recurrence free probabilities for the tumour stage within Milan was 90% and 94% for those meeting UCSF but outside Milan criteria. The risk of tumour understaging was similar for both groups – 20% (Milan) vs. 29% (UCSF).[23] The Pamplona group reported their experience on outcomes for 47 patients meeting expanded criteria (1 nodule ≤6 cm, or 2–3 nodules each ≤5 cm), with recurrence free survival rates of 70%. However, the study did not separately analyse the outcomes for patients exceeding the Milan criteria.[24]

Roayaie *et al.* used a multimodality neoadjuvant treatment protocol (systemic chemotherapy with doxorubicin and chemoembolisation) in 80 patients meeting expanded criteria (1 or more nodules 5–7 cm). The survival for patients with tumours between 5 and 7 cm was significantly better than >7 cm in diameter [55% vs. 34%, $P = 0.024$].[25] Kneteman *et al.* compared 19 patients with HCC meeting the Milan criteria with 21 patients meeting the expanded criteria (1 nodule <7.5 cm or any number <5 cm), using a Sirolimus-based immunosuppressive protocol. The 4-year recurrence free survival rates were 81.1% and 76.8% in the Milan and extended criteria group respectively.[26]

Mazzaferro *et al.* performed a retrospective multicenter study that included 1156 patients who underwent

Table 1 | Beyond the Milan criteria and outcomes following liver transplantation

Study group/year	Total number of patients	Milan in (MI)/ Milan out (MO)	Milan out (MO) expanded criteria	Survival
Yao *et al.*, UCSF, 2001[22]	60	46/14	1 nodule ≤6.5 cm, or 2–3 nodules ≤4.5 cm and total tumour diameter ≤8 cm	5-year MI – 72% MO – 73%
Herrero *et al.*, Pamplona, 2001[24]	61	49/12	1 nodule ≤6 cm, or 2–3 nodules each ≤5 cm	5-year entire group – 79%
Roayaie *et al.*, Mt.Sinai, 2002[25]	31	0/31	1 or more nodules 5–7 cm	5-year MO – 55%
Kneteman *et al.*, Edmonton, 2004[26]	40	19/21	1 nodule <7.5 cm any number <5 cm	4-year MI – 87% MO – 83%
Yao *et al.*, UCSF, 2007[23]	168	130/38	1 nodule ≤6.5 cm, or 2-3 nodules ≤4.5 cm and total tumour diameter ≤8 cm	5-year MI – 80% MO – 82%
Onaca *et al.*, International Tumour Registry, 2007[88]	1152	1038/114	1 nodule ≤6 cm 2–4 nodules each ≤5 cm	5-year MI – 62% MO – 54.3%
Cillo *et al.*, Padova, 2007[92]	100	60/40	Number of tumours – 3 ± 1.2 Size of largest tumour – 4.0 ± 1.6	3-year MI – 69% MO – 85%
Mazzaferro *et al.*, Metroticket Investigator Group, 2009[27]	1556	444/1112	2 subgroups-'Up-to-seven' (7 cm sum of the size of largest tumour and number of tumours) and 'Exceeding up-to seven'	5-year MI – 73.3% MO – 53.6% (up-to + exceeding 7 group) 5-year MI – 73.3% MO – 71.2% (up-to- 7 subgroup)
Guiteau *et al.*, Houston, 2010[28]	445	363/82	1 lesion <6 cm ≤3 lesions none >5 cm total diameter 9 cm	5-year MI – 72.9% MO – 70.2%

UCSF, University of California, San Francisco.

LT for HCC in 36 centres, and compared the outcomes for patients who fulfilled the Milan criteria and those that exceeded the Milan criteria. Those patients exceeding the Milan criteria were analysed in two subgroups -'Up-to-seven' (7 cm sum of the size of largest tumour and number of tumours) and 'Exceeding up-to seven'. The 5-year overall survival was 53.6% for those transplanted outside the Milan criteria compared with 73.3% for those that met the criteria. However, in the subgroup of 283 patients without microvascular invasion but who fell within the up-to-seven criteria (HCC's with seven as the sum of the size of the largest tumour [in cm] and the number of tumours) achieved a 5-year overall survival of 71.2%. The study concluded, that more patients with HCC could be candidates for LT if the current dual (yes/no) approach to candidacy, based on strict Milan criteria, were replaced with a more precise estimation of survival contouring individual tumour characteristics and the use of the up-to-seven criteria.[27]

Guiteau *et al.*, reported their outcomes on 445 patients who underwent LT for HCC – 363 patients within Milan criteria and 82 meeting the expanded criteria (1 lesion <6 cm, ≤3 lesions none >5 cm, total diameter 9 cm). The recurrence free survival rates for the Milan group and the extended criteria groups were 71% vs. 86.9% respectively.[28] The only expanded criteria that have been validated independently are the UCSF criteria on either explant pathology or radiology.[29–33]

Current UK listing criteria for LT for HCC

All patients with HCC in the UK were listed for LT based on the 'Milan criteria' prior to 2009. The criteria for listing patients with HCC for LT in the UK were subsequently revised in 2009 allowing for some expansion

of the Milan criteria. The current 'UK criteria' for LT for HCC are:

- a single tumour ≤5 cm diameter
- up to 5 tumours all ≤3 cm
- single tumour >5 cm and ≤7 cm diameter where there has been no evidence of tumour progression (volume increase by <20%) and no extrahepatic spread and no new nodule formation over a 6 month period; LRT ± chemotherapy may be given during that time

Tumour rupture and an AFP >10 000 IU/mL are absolute contraindications to transplantation as are extra-hepatic spread and macroscopic vascular invasion.[34]

Listing criteria worldwide vs. UK – a comparison

The first criterion of a single tumour ≤5 cm is essentially within Milan criteria and patients within this group have been shown to have a 5-year disease free survival of 75%.[13] Studies that used tumour size of 5 cm as a cut-off reported a significantly decreased overall survival,[35–43] disease free survival[36, 41, 44–46] and increased recurrence rates[47–50] for tumour size >5 cm. Therefore, data on diameter of the largest nodule and outcomes would therefore suggest that a single tumour size of up to 5 cm as proposed in the Milan and the current UK criteria would be associated with the a disease free survival of >70%.

The second criterion that allows for 5 tumours up to 3 cm allows for a maximum tumour diameter of 15 cm. Studies that looked at number of nodules as a continuous variable reported an increased risk of death for number of nodules ≥3 but the impact on disease free survival or recurrence was not significant.[27, 36, 41, 45, 51–53] However, current evidence from the Metroticket Investigator Study Group would suggest that simply allowing for morphological expansion alone to a total tumour size >7 cm would result in increased recurrence rates.[27] Studies that used a cut-off of 10 cm[22, 54, 55] and 9 cm[52, 56] also reported an inferior disease free survival. Considering the above data and that the Milan criteria have a maximum tumour diameter cut-off of 9 cm and UCSF of 8 cm, a total tumour size based on morphology alone, should be no more than 10 cm.

The third criterion of single tumour >5 cm and ≤7 cm diameter where there has been no evidence of tumour progression (volume increase by <20%) and no extrahepatic spread and no new nodule formation over a 6-month period attempts to expand the Milan criteria by including a combination of the 'up-to-seven criteria' of the Metroticket Investigator Study Group[27] and the Mt. Sinai group criteria.[25]

Firstly, morphological extension of the diameter of a single tumour >5 cm is not supported by current data as this is associated with an inferior disease free survival.[35–37, 39, 41–48] Secondly, there has been only one study that analysed tumour volume using a cut-off of 115 cm^3 and reported a decreased overall survival in tumours with a volume >115 cm^3.[57] Therefore, a volume increase by <20% for tumours >5 cm and ≤7 cm diameter is ambiguous and also, there is no clear guidance on whether this increase is based on any specific radiological criteria. Thirdly, although no new nodule formation over a 6 month period is a good test of time, this would mean repeated imaging over a 3–4-month interval while patients are on the waiting list. However, radiology often under-reports the number of tumours and this was well described in the original study by Mazzaferro *et al.* when the Milan criteria were proposed.[13] Therefore, although in the UK criteria the intention is to select patients who will benefit from LT in terms of recurrence and survival, explant histology is likely to detect more tumours thus defying the objective. There is no doubt that outcomes of LT in the presence of extrahepatic tumour spread and macroscopic vascular invasion are dismal and this would be a contra-indication to LT.

The data on overall survival and recurrence free survival post-LT for HCC within UK is limited to few reports and all of them are before 2009, i.e. prior to acceptance of criteria's exceeding Milan. Marelli *et al.* from Royal Free Transplant unit reported 100 consecutive patients who were transplanted for HCC within Milan criteria and showed a 5-year recurrence free survival of 67 ± 7% and 5-year overall survival of 45 ± 6%.[58] There were three other reports from the same unit, with overlapping data and hence were excluded from this review.[59–61] There are other reports of LT for HCC from UK, but these were tumours noted on explants rather than prior to transplant and some with short-term (less than 5 years) post-LT follow-up and hence were excluded from this review.[50, 62, 63]

Worldwide vs. UK – Prioritisation on the waiting list

Traditionally, listing criteria have not awarded extra points for patients with HCC on the waiting list and thereby puts them at risk from dropout through tumour progression.[64] The counter-argument has been patients who are fast-tracked by prioritisation run the risk of a higher incidence of recurrence post-LT. In the United States (US) previously the allocation policy also did not

allow for prioritisation on the waiting list. The UCSF group published their results on LT for HCC looking at survival according to the intention-to-treat principle and dropout from the waiting list in the Model for End Stage Liver Disease (MELD) pre-prioritisation era (January 1998–January 2001). They concluded that the cumulative probability of dropout increased significantly with time on the waiting list and the predictors for dropout being two or three tumour nodules or a solitary lesion > 3 cm at presentation thus supporting changes in the scheme of organ allocation.[65]

However, since February 2002, in the US the new allocation policy of the United Network for Organ Sharing (UNOS) based on the MELD gave candidates with stage T1 or stage T2 hepatocellular HCC a priority MELD score (24 and 29 points respectively) beyond their degree of hepatic decompensation and this allowed for patients with HCC to be prioritised while on the waiting list.[66, 67] Following the introduction of new allocation policy, a study from the Mayo clinic compared the pre-MELD and post-MELD period showed a significant difference that favoured the new criteria looking at: time to LT – 2.28 vs. 0.69 years respectively ($P < 0.001$), number of patients transplanted 0.439 transplant/person-years vs. 1.454 transplant/person-years ($P < 0.001$), 5 month waiting list survival 90.3% vs. 95.7% ($P < 0.001$) and the 5 month dropout rate 16.5% vs. 8.5% ($P < 0.001$). They concluded the new allocation policy has led to an increased incidence rate of Deceased Donor Liver Transplant (DDLT) in HCC candidates. Furthermore, the 5 month dropout rate has decreased significantly with an increase in the 5 month survival while waiting in the post-MELD period. Thus, the new MELD-based allocation policy had benefited HCC candidates.[67]

The Miami group also published their results with LT for HCC under the new allocation system (March 2002–April 2009). The study reported 244 patients were transplanted with a median time from listing to transplantation of 48 days and excellent recurrence free 5 year survival of 83.6% over a median follow-up of 27.4 months. Also, the survival for T3 HCC was similar to those in patients with T2 HCC ($P > 0.05$).[68] Overall, following the changes to the allocation policy data reported that 87% of patients with HCC underwent a LT within 3 months.[67, 69] It was felt therefore that patients with HCC were being unduly prioritised, and since 2004 UNOS have introduced further changes to the allocation policy and only patients with T2 tumours currently get a score of 22 MELD points for prioritisation on the waiting list. This was based on dropout data that showed patients with T1 tumours do not have an increased risk of dropout from the waiting list when compared to patients with T2 lesions. This latest policy has been further evaluated by the Mayo clinic that concluded that the reduced MELD priority score for HCC does not adversely impact survival of patients awaiting LT.[70]

In contrast, patients with HCC in the UK do not have any extra points allocated to allow for prioritisation. In the UK, the MELD score is used without any extra points for patients with HCC, in conjunction with the UK End-stage Liver Disease (UKELD) score that does not allocate points for aetiology of liver disease.[71] This puts patients with HCC in the UK at an increased risk of dropout from the waiting list. The first study to report a dropout from the waiting list for patients with HCC was the original paper from the Barcelona Clinic Liver Cancer (BCLC) group that reported a total dropout rate of 23%.[72] The UCSF group also reported the dropout rate for HCC patients within Milan criteria was 0% at 3 months, 11.0% at 6 months, 57.4% at 12 months and 68.7% at 18 months. The overall total dropout rate was 22% with a median waiting time of 330 days.[73] Recent studies have reported that T2 patients are at an increased risk of dropout and the dropout rate depends markedly on AFP: dropout at 180 days – 7.4% for AFP <500–24.9% for AFP >1000 after listing.[74, 75]

To date, there is no published data from the UK transplant registry on dropout from the waiting list as a result of tumour progression in patients with HCC. The overall dropout rate from the waiting list for 2009–2010 was 19%, 10% being waiting list mortality and 9% were patients removed from the list [UK Transplant (UKT) report 2009–2010].[76] However, this does not specifically address the dropout rate for patients with HCC. Similarly, the current waiting times for patients awaiting LT in the UK are on an average 6 months for Blood Group A and 12–18 months for Blood Group O, but with a significant inter centre variation and there is no data specifically for HCC.[76]

Worldwide vs. UK – loco-regional therapy as a bridge to LT

The current UK criteria recommend that LRT ± chemotherapy may be given as a bridge to LT during the time the patient is on the waiting list. LRT can vary from radiofrequency ablation (RFA), transarterial chemoembolisation (TACE), percutaneous ethanol injection (PEI), selective internal radiation therapy (SIRT) with Yttrium-90 microspheres or resection. There have been few studies that have looked at LRT and the effect on

dropout from the waiting list. Bharat *et al.* investigated the efficacy of LRT as a strategy to improve long-term survival after LT. They reported their results on 100 patients who underwent LT for HCC of whom 46 underwent LRT prior to LT. The LRT group had significant tumour downstaging (1.50 ± 1.34 vs. 2.49 ± 1.17; $P < 0.01$) and better 5-year survival (82.4% vs. 51.8%; $P = 0.01$) with a reduction in the dropout rate from the waiting list.[77]

The Milan group looked at RFA as a bridge to LT and showed a 1 and 3 year overall survival of 95% and 83% respectively at 22 months.[78] A further study by Graziadei *et al.* evaluated the effect of pre-operative TACE on preventing tumour progression while on the waiting list in patients meeting the Milan selection criteria. Forty-eight patients met the selection criteria, none were removed from the list because of tumour progression after a mean waiting time of 178 days (23 patients ≥180 days). The 1-, 2-, and 5-year intention-to-treat survival was 98%, 98%, and 94%. The outcome after LT was also excellent with 1-, 2- and 5-year survival rates of 98%, 98%, and 93% respectively. Tumour recurrence occurred only in one patient (2.4%). This study suggested, that TACE followed by LT was associated with an excellent outcome in selected patients and was highly efficacious in preventing tumour progression while waiting for LT.[79]

The current UK criteria recommend that LRT ± chemotherapy may be given as a bridge to LT during the time the patient is on the waiting list and LRT should be considered for all transplant list patients who have HCC. Currently there is lack of uniformity on the type of LRT used within the transplant centres in the UK although TACE and RFA are the most widely used.[80]

Worldwide vs. UK – role of Alpha-fetoprotein

Alpha-fetoprotein (AFP) is produced by 60% of HCC's and has been widely used as a tumour marker for the diagnosis of HCC as it is a simple inexpensive test. However, the role of AFP as a prognostic marker during follow-up and as a listing criterion has been much debated.[81, 82] The Scientific Registry of Transplant Recipients (SRTR) database review by the Edmonton group on patients transplanted for HCC reported that only tumour volume (<115 cm^3) and AFP (<400 ng/mL) predicted post-transplantation survival [hazard ratio 2.95 (1.7–2.4): $P < 0.001$].[83] Measurement of serial AFP to follow-up patients on the waiting list to help predict tumour progression has been shown to be beneficial in some studies. On multivariate analysis pre-operative AFP slope and total tumour volume >7 cm by pathology were identified as predictors of tumour recurrence.[84]

Similarly, data from Vibert *et al.* have reported a 5-year recurrence free survival rates were 23% lower in the above 400 ng/mL and 28% lower at 1000 ng/mL although this was not statistically significant.[85] The current UK criteria recommend that tumour rupture and an AFP >10 000 IU/mL are absolute contraindications to transplantation and this would be justified based on the evidence that AFP levels of > 1000 ng/mL are associated with worse outcomes.[86]

Currently, tumour markers and biomarkers do not form part of the UK or other worldwide listing criteria but there is future potential for biomarkers to be used with tumour markers such as AFP to monitor patients with HCC awaiting LT on the waiting list.

The HCC Metro Ticket

The various expansions of 'Milan criteria' have been philosophically compared to the 'European Metroticket' system with the paradigm of 'the further the distance, the greater the price' (Figure 1).[29, 87] The modification of the HCC Metroticket calculator showed 5-year survival rates between 75% and 80% are the best outcomes reported for the Milan criteria while others have reported only 5-year survivals of between 50% and 70% using the Milan criteria that are similar to projected survival figures for modest expansion of the criteria[29, 31, 32, 88] (Figure 1). The Metroticket calculator has put the expanded criteria in perspective and showed that there would be a subgroup of patients outside Milan criteria who would benefit from LT.

The current UK criteria have been plotted as per the tumour number and size within the Metroticket calculator (Figure 1) and the 5- year survival rates are likely to be between 35% and 50% that are significantly lower than the 75–80% that are observed for patients within Milan or the 50–80% for those within the UCSF criteria. This questions the rationale for selection of the UK criteria that are an expansion of both the Milan and the UCSF criteria.

Summary

In summary, the UK listing criteria for LT for HCC have some morphological criteria that are well established and comparable to the rest to the transplant centres worldwide while there are others that are questionable and require more discussion based on the review of literature. LT for single tumours up to 5 cm (Milan and UK criteria) have 5-year overall and disease free survival of 75%

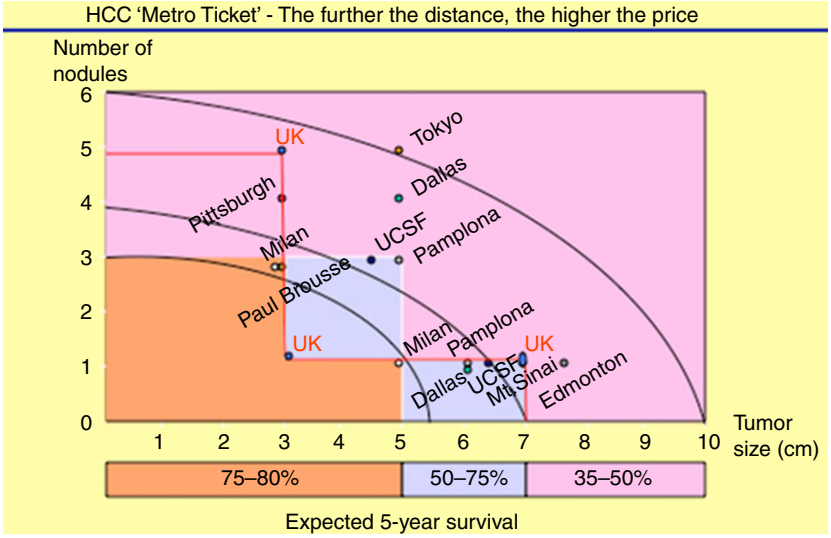

Figure 1 | The HCC Metro Ticket – modified from Yao *et al.*[22]

and 83% respectively and cannot be disputed. However, outcomes of LT for 5 tumours all ≤3 cm or single tumour >5 cm and ≤7 cm diameter where there has been no evidence of tumour progression (volume increase by <20%) and no extrahepatic spread and no new nodule formation over a 6 month period (UK criteria only) that are an expansion of both Milan and UCSF should be carefully evaluated. LT for 5 tumours up to 3 cm gives a maximum tumour diameter of 15 cm within the UK criteria (Milan criteria have a cut-off of 9 cm and UCSF of 8 cm) while evidence would suggest that simply allowing for morphological expansion alone to a total tumour size should be no more than 10 cm as this would be associated with increased recurrence rates. Morphological extension of the diameter of a single tumour >5 cm in the UK criteria is not supported by current data, as this is associated with an inferior disease free survival. Also, volume of tumour increase by <20% for tumours >5 cm and ≤7 cm diameter has been poorly defined with no clear guidance in the UK criteria on whether this increase is based on any specific radiological criteria. The UK criterion of no new nodule formation over a 6 month period is a good test of time although this would mean repeated imaging over a 3–4 month interval while patients are on the waiting list. There is little doubt that the presence of extrahepatic tumour spread and macroscopic vascular invasion are a contra-indication to LT (UK and other criteria) and this is accepted worldwide.

As regards prioritisation, MELD exception points as per the UNOS allocation policy to HCC patients on the basis of an estimated dropout rate due to tumour progression does balance allocation for HCC and non-HCC patients particularly for T2 stage patients.[89] Prioritisation on the waiting list has been much debated and currently, patients with HCC in the UK do not have any extra points allocated to allow for prioritisation. Currently, there little evidence worldwide to support prioritisation for the expanded Milan criteria (UK beyond Milan).

Worldwide evidence supports the use of LRT as a bridge to LT and although UK recommendation is LRT should be used, the type of LRT has not been standardised and as a result interpretation of long-term follow-up data would be difficult. UK criteria recommend that tumour rupture and an AFP >10 000 IU/mL are absolute contra-indications to LT and this is supported by a number of studies.

Recently a Markov model comparing the survival benefit of DDLT for patients with HCC beyond the Milan criteria vs. harm to other patients on the waiting list demonstrated that a higher threshold of 61% 5-year survival was needed to justify expansion of the criteria in the US.[90, 91]

In conclusion, although the Milan criteria remain the gold standard, most centres worldwide including the UK have adopted expansions to Milan to allow more patients to benefit from LT. However, currently, as it stands the UK criteria when plotted in the modification of the Metroticket model projects 5-year survival outcomes between 35% and 50% that would seem unjustified.

AUTHORSHIP

Guarantor of the article: K. V. Menon.

Author contributions: KVM and NDH conceptualised and designed the study. ARH and KVM performed the literature search and extracted data. KVM wrote the

initial draft. Tables and references were reviewed by ARH. NDH made the final corrections to the manuscript and will be the corresponding author. All authors approved the final version of the manuscript.

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