Systematic review: the role of liver transplantation in the management of hepatocellular carcinoma

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SUMMARY

Background
Hepatocellular carcinoma (HCC) is a major cause of morbidity and mortality worldwide. Liver transplantation offers a potential cure for this otherwise devastating disease. The selection of the most appropriate candidates is paramount in an era of graft shortage.

Aim
To review systematically the role of liver transplantation in the management of HCC in current clinical practice.

Methods
An electronic literature search using PUBMED (1980–2010) was performed. Search terms included HCC, hepatoma, liver cancer, and liver transplantation.

Results
Liver transplantation is a highly successful treatment for HCC, in patients within Milan criteria (MC), defined as a solitary tumour ≤ 50 mm in diameter or ≤ 3 tumours ≤ 30 mm in diameter in the absence of extra-hepatic or vascular spread. Other eligibility criteria for liver transplantation are also used in clinical practice, such as the University of California, San Francisco criteria, with outcomes comparable to MC. Loco-regional therapies have a role in the bridging treatment of HCC by minimising wait-list drop-out secondary to tumour progression. Beyond MC, encouraging results have been demonstrated for patients with down-staged tumours. Post-liver transplantation, there is no evidence to support a specific immunosuppressive regimen. In the context of an insufficient cadaveric donor pool to meet demand, the role of adult living donation may be increasingly important.

Conclusions
Liver transplantation offers a curative therapy for selected patients with HCC. The optimisation of eligibility criteria is paramount to ensure that maximum benefit is accrued. Although wait-list therapies have been incorporated into clinical practice, additional high quality data are required to support this strategy.

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INTRODUCTION

The majority of cases of hepatocellular carcinoma (HCC) arise on a background of cirrhosis. This in itself complicates management as hepatocellular dysfunction and/or portal hypertension can limit the tolerability of ‘classical’ cancer treatments such as resection or systemic cytotoxic chemotherapy. However, in selected patients, liver transplantation (LT) enables resection of the tumour with the widest possible surgical margin as well as treating the underlying cirrhosis, the latter strategy reducing the risk of subsequent de novo HCC formation.

Early experiences of LT as a treatment for HCC were associated with poor outcomes, reflecting the fact that the selected patients had advanced disease.\(^1\)\(^-\)\(^5\) However, patients in whom HCC was diagnosed on the basis of explant pathology alone were demonstrated to have a survival rate comparable to patients without malignancy, thereby indicating that LT might still be an appropriate treatment for early HCC.\(^6\) This was supported by Mazzaferro in a seminal paper,\(^7\) whereby 4-year survival of 75% was demonstrated in 48 patients with either one tumour ≤ 50 mm in diameter or ≤ 3 tumours each with diameter ≤ 30 mm, and with no vascular invasion evident on imaging or extra-hepatic disease.\(^7\) Survival rates in those selected were similar to patients transplanted for non-malignant liver disease.\(^7\) These aforementioned criteria have since been referred to as the ‘Milan criteria’ (MC), and have been widely adopted into clinical practice, including integration into the Union for International Cancer Control (UICC) TMN and United Network for Organ Sharing (UNOS) staging systems for HCC (Table 1), as well as providing a benchmark for other eligibility criteria.

LT continues to be associated with significant morbidity and mortality despite improvements in surgical technique and immunosuppressive regimens. Furthermore, unlike other forms of oncological surgery, LT requires a donor organ. In view of this, utility and fairness need to be considered in relation to allocation for both donor and recipient. For this reason, the application of strict eligibility criteria, such as MC has evolved as an important aspect of current clinical practice. This theoretically ensures that LT is offered to patients with HCC who are most likely to gain the greatest benefit, whilst not disadvantaging patients requiring LT for non-oncological indications.

Whilst the importance of eligibility criteria for LT is clear cut, the optimisation of these criteria as well as the management of patients already listed for LT remains a source of debate. In this article, we systematically review the role of LT in the management of HCC arising in the cirrhotic liver including the expansion of eligibility criteria beyond MC, the role of neo-adjuvant or adjuvant therapies (such as bridging therapy and down-staging), and organ allocation strategies. HCC surveillance, diagnostic strategies, and the management of patients not eligible for LT will not be discussed, although these topics have recently reviewed in this journal.\(^8\)\(^-\)\(^13\) Furthermore, the potential role of LT in the management of other liver tumours, such as cholangiocarcinoma, haemangioendothelioma, and neuro-endocrine tumours is beyond the scope of this article and therefore not discussed.\(^14\)

METHODS

Source material for this systematic review was obtained by an electronic literature search using PUBMED, employing the terms ‘HCC’, ‘hepatoma’ and ‘liver cancer’ in combination with ‘liver transplant’ and ‘OLT’. English language abstracts published between January 1980 and December 2010 were reviewed to identify relevant articles, with a particular focus towards prospective and controlled studies, and material published after 1996 (i.e. following the definition of MC). In addition, review of the references of the important studies and relevant review articles was undertaken to ensure identification of all appropriate source material.

Definitions and metrics

Several points need to be considered when reviewing the literature on the role of LT in the management of HCC. Firstly, LT per se cannot be viewed in isolation since neo-adjuvant therapies are an integral component of patient management. Secondly, interpretation of the data is complicated by the inconsistent terminology in the literature used to refer to neo-adjuvant therapies, particularly interventions referred to as ‘bridging’ and ‘down-staging’. Henceforth, ‘bridging’ therapy is defined as treatment undertaken to maintain a tumour within pre-

| Table 1 | United network for organ sharing HCC staging system (Stages T1 and T2 equate to the Milan criteria) |
|---------|--------------------------------------------------------------------------------------------------|
| T0      | Tumour not found                                                                                 |
| T1      | 1 nodule: <20 mm                                                                                 |
| T2      | 1 nodule 20–50 mm                                                                                 |
|         | 2–3 nodules: each ≤ 30 mm                                                                        |
| T3      | 1 nodule: >50 mm                                                                                 |
|         | 2–3 nodules: at least one nodule >30 mm                                                           |
| T4a     | ≥ 4 nodules: any size                                                                             |
| T4b     | T2, T3 or T4a plus intra-hepatic portal or hepatic vein involvement                              |
defined eligibility criteria when a patient has been listed for LT, with the aim of preventing progression of the tumour beyond eligibility which would, thus, result in drop-out from the wait-list. In contrast ‘down-staging’ is defined as a therapeutic intervention to convert a tumour which is beyond eligibility criteria to be within criteria and therefore render the patient a candidate for LT.

In the absence of randomised trials, the majority of data relating to LT in the management of HCC has been obtained from retrospective review of clinical practice. Interpretation of outcomes defined in such studies requires consideration of the methods of analysis. In particular, the use of intention-to-treat (ITT) analysis when reporting survival data incorporates the effect of wait-list drop-out; thus providing an more accurate indication of benefit to an individual patient who is listed for LT. In addition, although tumour recurrence is a feared complication, since the use of immunosuppression may modify its natural history, disease-free survival (DFS) is not necessarily a surrogate marker of overall survival (OS). Indeed, it is conceivable that other non-cancer factors may influence outcome, such as recurrent liver disease within the graft, and therefore DFS may be less clinically relevant.

Indications for LT

Following the demonstration of comparable outcomes in patients with early stage HCC and non-malignant liver disease in 1996 and subsequent confirmation in other studies, LT has been widely adopted as a treatment for HCC, where the appropriate medical and technological infra-structure exists. However, only a minority of patients with HCC are potential candidates for LT, and of these patients, LT may not be the most appropriate intervention particularly in those with very-early stage tumours and well preserved liver function (as the risks of LT may outweigh both its potential benefits and the risks associated with alternative treatment modalities). Furthermore, by reducing demand on the donor pool, alternative therapies may advantage patients with a greater need for LT. An important exception to this rule is the patient with advanced liver disease and hepato-pathological indications for LT, in whom an early (and therefore potentially clinically irrelevant) tumour has been identified.

Eligibility criteria: Milan and beyond. Since the MC were defined by Mazzaferro in 1996, their utility, as a good discriminator of favourable post-LT outcomes, has been validated in numerous studies (summarised in Table 2). However, alternative eligibility criteria, that more accurately predict post-LT outcomes, have since been proposed and/or incorporated into clinical practice. The key aims in the selection of patients with HCC for LT, and therefore in defining eligibility criteria, is to minimise tumour recurrence rates, to enhance survival, and, ultimately, to permit the fair allocation of liver grafts between potential recipients.

Well recognised predictors of recurrence include tumour size and number, bi-lobar disease, tumour differentiation, the presence of macro- or micro-vascular invasion and the presence of tumour satellites. More recently, specific molecular signatures or markers in tumour or adjacent liver tissue have been demonstrated to correlate with outcome. These include: epithelial cell adhesion molecule (EpCAM), G3-proliferation subclass, expression status of the miR-26 miRNA precursor, a hepatic stem cell marker in tumour tissue, and two gene prognostic signature in non-tumour hepatic tissue, which have consistently been demonstrated to correlate with survival in HCC patients. Furthermore, such

### Table 2 | Reported 5-year overall survival rates in patients undergoing liver transplantation for hepatocellular carcinoma within Milan criteria (solitary tumour ≤ 50 mm in diameter or ≤ 3 tumours ≤ 30 mm in diameter)

| Reference (year) | Pre-operative imaging | Explant pathology |
|------------------|-----------------------|-------------------|
| Mazzaferro (1996) | 75*                   | 85*               |
| Yao (2001)       | 72.4                  |                   |
| Fernandez (2003) | 68                    |                   |
| Lohe (2005)      | 70                    |                   |
| Duffy (2007)     | 79                    | 86                |
| Ito (2007)       | 72                    |                   |
| Kwon (2007)      | >80                   |                   |
| Poon (2007)      | 81                    |                   |
| Takada (2007)    | 73                    |                   |
| Herrera (2008)   | 70                    |                   |
| Lee (2008)       | 76                    |                   |
| Silva (2008)     | 69                    |                   |
| Toso (2008)      | 82                    |                   |
| Zheng (2008)     | 78.3                  |                   |
| Chen (2009)      | 74.3                  | 77.1              |
| Mazzaferro (2009)| 73.3                  |                   |
| Muscari (2009)   | 77                    |                   |
| Santoyo (2009)   | 65                    |                   |
| Gabrielli (2010) | 94.7                  |                   |
| DuBay (2011)     | 72                    |                   |

* Results reported at 4 years.
Biomarkers have been demonstrated to predict the risk of tumour recurrence following treatment.\textsuperscript{30, 31} For example, allelic imbalance in 9 microsatellites has been associated with the risk of post-LT recurrence in tumours beyond MC (85% 5-year recurrence with fractional allelic imbalance $\geq 0.27\%$ vs. 10% when $<0.27$, $P = 0.0002$).\textsuperscript{31}

Although many of the aforementioned predictors of recurrence can be assessed prior to LT, histological examination of the tumour (particularly the liver explant) provides a more accurate assessment. Histology is essential in the assessment of some factors (e.g. microvascular invasion), thus ultimately limiting the accuracy of any 'non-invasive' system employed.

One common methodological flaw in studies identifying clinical predictors of favourable outcome is the use of explant pathology to provide information on tumour size and number, with the derived criteria being subsequently applied to radiological assessments of tumour burden. However, radiological staging can be limited in accuracy; indeed, review of the Eurotransplant Allocation System demonstrated a 34% accuracy of radiology in comparison to explant pathology, with tumour absent in 8.3% of patients, over-staging of the tumour in 36.2% and under-staging in 10.4%.\textsuperscript{32} This is clinically significant as radiological under-staging translates into inferior outcomes.\textsuperscript{19}

Proposed, and in some cases commonly used, eligibility criteria beyond MC are summarised in Table 3.

The University of California, San Francisco (UCSF) criteria constitutes a well recognised extension to MC which has been applied to clinical practice. Initially described by Yao et al. in 2001, it was demonstrated that patients with a solitary tumour $\leq 65$ mm in diameter, or 2–3 tumours each with diameter $\leq 45$ mm and total tumour diameter (TTD) $\leq 80$ mm had an OS of 90% and 72.5% at 1 and 5 years respectively.\textsuperscript{28} These results were comparable to those achieved with MC. Although the original study utilised pathological examination of the explant to determine tumour burden, subsequent studies using radiological staging have demonstrated the utility of these criteria in the selection of patients for LT.\textsuperscript{33–35} In a follow-up study, the application of the UCSF criteria to pre-LT radiological staging was validated by Yao et al. in a cohort of 168 patients. No difference in 5-year DFS between patients with tumours within MC or with UNOS Stage T3a tumours (i.e. within UCSF but beyond MC) was observed (90.1% vs. 93.6%, $P = 0.58$).\textsuperscript{33} In a larger cohort of patients from multiple French centres ($n = 479$), the 5-year OS was 60.1% and 45.6% for tumours within MC and tumours within UCSF but beyond MC, respectively ($P = 0.33$).\textsuperscript{35} These two studies are potentially limited by the relatively low number of patients with tumours fulfilling the extending criteria (18–22%); however, in a retrospective study from the University of California, Los Angeles (UCLA), in which 173 patients had tumours within MC and 185 patients had tumours outwith MC but within UCSF, no difference in 5-year OS was demonstrated (79% vs. 64%, $P = 0.061$).\textsuperscript{34} Although, the aforementioned studies report favourable results in patients with tumour beyond MC but within UCSF, these observations are likely to be attributable to the influence of tumour biology on which patients listed for LT eventually receive a liver graft. It is presumable that patients with tumours that exhibit unfavourable biology, and thus be more likely to develop recurrence following LT, would have a greater risk of waitlist drop-out as a result of tumour progression beyond criteria. Therefore, it is probable that within the ‘extended criteria’ cohort only those patients with tumours that exhibit favourable biology, and thus be expected to have good long-term survival, come to LT.

A recent study by Mazzaferro et al. has resulted in the introduction of the ‘up-to-seven’ criteria.\textsuperscript{23} A large multi-centred exploratory analysis was performed to investigate predictors of survival post-LT by collecting data via a web-based questionnaire. Data from 1556 patients were obtained. Cox-regression analysis was performed to determine risk factors of poor outcome and risk-tables to predict OS were derived (accessible at www.hcc-olt-metroticket.org/). The results propose that outcomes comparable to those achieved with MC were obtained with the ‘up-to-seven’ criteria, defined as the sum of the number of tumour nodules and the diameter of the largest nodule (in centimetres) being $\leq 7$. The utility of the ‘up-to-seven’ criteria has subsequently been validated in an independent Australasian cohort.\textsuperscript{36} The demonstration that outcomes progressively declined with increasing tumour size or number has lead to the ‘Metroticket’ concept of: ‘the further the distance, the higher the price’. In the context of these findings, a paradigm shift from a ‘yes/no’ approach to an individualised risk-based system has been proposed in determining candidacy for LT.\textsuperscript{23}

An alternative approach for the assessment of tumour burden is the estimation of total tumour volume (TTV) as opposed to nodule diameter or number. Following review of 52 patients undergoing LT for HCC in Alberta, Toso et al. report that a TTV $\leq 115$ cm$^3$ was an accurate predictor of recurrence post-LT and therefore a suit-
| Reference (year) | Eligibility criteria: name and definition | Study design and staging method | Waitlist treatment permitted | Tumour characteristics | OS (%) 1 year | OS (%) 3 years | OS (%) 5 years | DFS (%) 1 year | DFS (%) 3 years | DFS (%) 5 years |
|-----------------|-----------------------------------------|---------------------------------|-----------------------------|----------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Yao (2001)      | UCSF No extrahepatic spread or MaVI solitary tumour with diameter ≤ 65 mm, OR ≤ 3 nodules with maximum diameter ≤ 45 mm and TTD ≤ 80 mm | Retrospective analysis to determine extended criteria Staging: explant pathology | yes | EC+ MC+ | 60 | 90 | 75 | 51 | 91 | 72 |
| Ito (2007)      | 'Kyoto criteria' No extrahepatic disease or MaVI ≤ 10 nodules with maximum diameter ≤ 50 mm, AND PIVKA-II ≤ 400 mAU/mL | Retrospective analysis to determine extended criteria Staging: explant pathology | yes | yes | EC+ MC+ | 78 | 87 | 72 | 70 |
| Jonas (2007)    | No extra-hepatic spread or MaVI solitary nodule of any diameter, OR multiple nodules with individual diameter ≤ 60 mm & TTD 150 mm | Analysis against predetermined criteria (some exceptions included) Staging: pre-op radiology | yes | yes | EC+ MC+ | 13 | 68 | 62 | 8 | 75 |
| Kwon (2007)     | No extra-hepatic spread or MaVI unlimited number of nodules if maximum diameter ≤ 50 mm AND AFP <400 ng/mL | Retrospective analysis to determine extended criteria Staging: explant pathology | yes | yes | EC+ MC+ | 114 | 87 | 88 | 100 | 95 | >80 |
| Sugawara (2007) | 5–5’ No extrahepatic disease or MaVI nodules ≤ 5 with maximum diameter ≤ 50 mm | Analysis against predefined criteria Staging: pre-op radiology | yes | | EC+ MC+ | 68 | | | |
| Takada (2007)   | 'Kyoto criteria' No extrahepatic disease or MaVI ≤ 10 nodules with maximum diameter ≤ 50 mm PIVKA-II ≤ 400 mAU/mL | Retrospective analysis to determine extended criteria Staging: pre-op radiology | yes | yes | EC+ MC+ | 83 | 87 | 74 | 88 | 87 | 73 |
| Reference (year) | Eligibility criteria: name and definition | Study design and staging method | Waitlist treatment permitted | LDLT | Tumour characteristics | n | OS (%) 1 year | OS (%) 3 years | OS (%) 5 years | DFS (%) 1 year | DFS (%) 3 years | DFS (%) 5 years |
|-----------------|-------------------------------------------|--------------------------------|-----------------------------|------|------------------------|----|---------------|---------------|---------------|---------------|---------------|---------------|
| Herrero (2008)³⁹ | ‘CUN’ | Analysis against predefined criteria staging: pre-op radiology | yes | EC+,MC− | 26 | 88 | 72 | 68 | | | | |
| | | | | MC+ | 59 | 88 | 73 | 66 | | | | |
| Lee (2008)⁴³ | ‘Asan criteria’ | Retrospective analysis to determine extended criteria Staging: explant pathology | yes | yes | EC+ | 186 | 76 | | 76 | | |
| | | | | MC+ | 164 | 76 | | | | | |
| Silva (2008)⁴¹ | No extrahepatic disease or MaVI ≤ 3 nodules with maximum diameter ≤ 50 mm | Analysis against predefined criteria intention-to-treat analysis Staging: pre-op radiology & explant pathology | yes | EC+ | 26 | 92 | 79 | 69 | | |
| | | | | MC+ | 231 | 82 | 68 | 69 | | | |
| Toso (2008)³⁷ | No extrahepatic disease or MaVI TTV <115 cm³ | Retrospective analysis to determine extended criteria and validation of criteria staging in other centres Staging: pre-op radiology | yes | EC+ | 251 | 80 | | | 80 | | | |
| | | | | MC+ | 157 | 82 | | | | | | |
| Zheng (2008)⁴⁷ | ‘Hangzhou criteria’ | Retrospective analysis to determine extended criteria Staging: explant pathology | ND | EC+ | 99 | 93 | 71 | 71 | 84 | 66 | 62 | |
| | | | | MC+ | 72 | 94 | 78 | 78 | 87 | 74 | 70 | |
| Mazzoforo (2009)²³ | ‘Up-to-seven’ | Multi-centred retrospective analysis to determine extended criteria Staging: explant pathology | yes | EC+,MC− | 283 | 66 | | 71 | | | |
| | | | | MiVI− | 116 | 60 | | 47 | | | |
| | | | | EC+,MC− | 362 | 82 | | 76 | | | |
| | | | | MiVI+ | 44 | 77 | | 72 | | | |
able selection criterion for LT. This cut-off was subsequently validated in populations from Toronto and Colorado, wherein 28–53% more patients would be eligible for LT in comparison to MC, without demonstrable deterioration in outcome. In a subsequent study, TTV has been confirmed as a predictor of survival in a large patient cohort using the Scientific Registry of Transplant Recipients (SRTR) database. Furthermore, it was demonstrated that the combination of TTV <115 cm³ and AFP <400 ng/mL effectively predicted post-LT OS; indeed, patients not fulfilling these criteria had a predicted OS <50% at 3 years.

The Clinica Universitaria de Navarra (CUN) criteria are defined as a solitary nodule ≤60 mm in diameter or 2–3 nodules each with diameter ≤50 mm. There was no significant difference in outcome between patients fulfilling the aforementioned criteria and MC. However, it was observed that wait-list drop-out was 7% in MC group and 30% in the CUN group; a difference which is likely to reflect the selection of patients with tumours that exhibit favourable tumour biology within the CUN group.

Sugarwara et al. reported the experience from Tokyo where the ’5–5 rule’ is applied (defined as ≤5 nodules each with a ≤50 mm). In their cohort, OS and DFS at 5 years was 75% and 90%, respectively. Although all patients were staged within these criteria on pre-operative assessment, pathological examination demonstrated that in fact six of the patients exceeded criteria. Subgroup analysis of these six patients revealed that they had an inferior outcome with a 5-year DFS of 50% compared with 94% seen in those patients within criteria. A retrospective study with ITT survival analysis, by Silva et al., of patients listed or transplanted for HCC resulted in the proposal of the extended criteria of ≤3 nodules each with diameter ≤50 mm and TTD ≤100 mm. Using these criteria, an 8.5% wait-list drop-out rate was observed. All but one of these patients that did not come to LT had tumour within MC at listing. No significant difference in ITT OS at 5 years between patients with tumours within or beyond MC was observed \( (P = 0.487) \). In fact, the data suggests a trend towards improved outcomes with tumours beyond MC, however this is likely to represent selection bias.

Other published extended criteria include: all solitary tumours and multiple tumours each ≤60 mm in diameter and TTD ≤150 mm, and ≤6 tumour nodules with each nodule ≤50 mm in diameter, both of which are associated with favourable outcomes in comparison to MC.
In addition to modifications in eligibility criteria by altering the permissible number or maximum diameter of nodules, some groups have proposed the inclusion of biomarkers into their criteria. Blood parameters such as serum alpha-foetoprotein (AFP) have been shown to have clinical utility, with increasing levels associated with inferior outcomes.

Retrospective analysis of outcomes and factors predictive of outcome in 125 patients with HCC undergoing living donor LT (LDLT) was undertaken by Ito et al. Multivariate analysis resulted in proposed extend criteria of ≤ 10 tumours each ≤ 50 mm in conjunction with levels of vitamin K absence or antagonist-II (PIVKA-II) ≤ 400 mAU/mL. Patients within these criteria had a 5-year OS of 86.7% and 5-year recurrence rate 4.9%. The same criteria were proposed by Takada et al. following analysis of a cohort of 136 patients of which over 50% had tumours beyond MC. OS for the whole cohort was 70% at 5 years, with outcomes similar in those both within MC and in patients with ≤ 10 tumours each ≤ 50 mm in diameter (irrespective of PIVKA-II levels). Fulfilment of the combination of the aforementioned physical parameters and PIVKA-II level ≤ 400 mAU/mL was associated with a 5-year recurrence rate and OS of 5% and 87%, respectively, in comparison to 61% (P < 0.0001) and 37% (P < 0.0001), respectively in those who did not meet these criteria.

In a review of 60 patients undergoing LDLT for HCC, Soejima et al. demonstrated that a tumour diameter ≥ 50 mm was associated with worse prognosis and levels of des-gamma-carboxy-prothrombin > 300 mAU/mL was highly associated with recurrence. Tumour number was not predictive of outcome. Although extension of eligibility criteria to patients within the aforementioned limits was proposed, no survival data has been published to support this conclusion.

Retrospective analysis of LT experience in Hangzhou, China, by Zheng et al. proposed that patients with TTD ≤ 80 mm, or TTD >80 mm with AFP ≤ 400 ng/mL and histopathological tumour grade I or II, were suitable candidates for LT. No difference in 5-year OS was demonstrated between those fulfilling their proposed criteria compared with those within MC (72.3% vs. 78.3%, respectively). Kwon et al. proposed that an unrestricted number of tumours if each had a diameter ≤ 50 mm and AFP <400 ng/mL was a suitable discriminator between patients with HCC undergoing LT with favourable outcome. Indeed, 5-year OS and DFS of 87% and 88%, respectively, was reported. However, survival ≥ 3 months post-LDLT was an inclusion criterion for the analysis which would conceivably exclude patients with aggressive disease recurrence leading to rapid cancer-related mortality.

Current guidance would suggests that liver biopsy is not an absolute requirement for the diagnosis of HCC. However, as previously discussed, the additional information gained from histological examination of tumours can be helpful in assessing the risk of HCC recurrence post-LT. The use of liver biopsy has been incorporated into the 'Toronto criteria', in which patients with HCC beyond MC may still be eligible for LT if proven not to have a poorly differentiated tumour. Results comparable to MC have recently been reported with the application of these criteria, with 5-year OS and DFS of 72% and 70%, respectively, in those patients within MC, and 70% and 66% in those beyond. Although the aforementioned results demonstrate the benefit of histology in selecting patients for LT, the fear of needle-track seeding of tumour may limit wider adoption of this approach into clinical practice. However, no patient was excluded from LT due to tumour seeding in this cohort, and there was only one reported case of abdominal wall recurrence in the Toronto cohort, which was successfully treated with local resection. Meta-analysis of published data has concluded that the approximate incidence of needle track tumour seeding following biopsy is 2.7%, therefore the results reported from Toronto are favourable in comparison and suggest that this strategy does not disadvantage patients excessively.

In a shift from current practice, the inclusion of dynamic factors within eligibility criteria has been suggested as a means of providing a surrogate marker of tumour biology, thereby providing a method of excluding patients with aggressive disease, independent of absolute tumour burden. Proposed relevant indicators include responsiveness to loco-regional therapies. For example, a study of 33 patients from Pisa, Italy, has demonstrated that a complete response to TACE on the basis of amended Response Evaluation Criteria in Solid Tumours (RECIST) in patients with tumours beyond MC was associated with a post-LT 5-year DFS of 94.4%, in comparison to 46.7% in patients who only had a partial response (P = 0.008).

Adjuvant and neo-adjuvant therapy

As previously discussed, neo-adjuvant therapies employed in the context of LT for HCC typically take the form of bridging therapy or down-staging. In current clinical practice loco-regional treatment modalities are
most frequently used, however the role of liver resection (LR) must not be discounted as evidenced by its inclusion as an appropriate treatment for Barcelona Clinic Liver Cancer (BCLC) Stage 0 and Stage A1 disease.19

Liver resection: primary and salvage. In selected patients, LR may offer an alternative and less radical curative intervention which, unlike LT, does not require the availability of a donor organ, thereby permitting almost instant access to treatment and thus minimising tumour progression whilst awaiting surgery. Furthermore, peri-operative morbidity and mortality is lower, recovery is faster, and patients are not exposed to the potential complications of long-term immunosuppressive therapy.55-57 For this reason, LR needs to be given consideration in all patients with HCC who are potential candidates for LT.

As for LT, careful selection of candidates for LR is necessary. The option of LR may be precluded by anatomical factors such as the presence of bi-lobar disease, central positioning of the tumour, and the proximity of the tumour to major vessels. Furthermore the estimated volume of residual liver needs to be considered. Liver disease-related factors such as portal hypertension and impaired hepatocellular function may also be a contraindication. The most favourable outcomes have been observed in patients with small tumours, normal serum bilirubin, and portal pressure gradient of <10 mmHg.20

Early experience suggests that the outcome achievable with LR is more favourable than LT. However these observations appear to be a reflection of patient selection as bi-lobar disease and vascular invasion (denoting more advanced disease) were more frequent in the patients undergoing LT.58 Although the published data are not entirely consistent, and in contradiction of the results of early studies, it appears that LT is associated with superior outcomes to LR (Table 4). However, an important caveat to consider in making this conclusion is the presence of bias in patient selection, with assignment to treatment groups having been made on clinical assessment of suitability, i.e. patients with contra-indications to LT may still be offered LR. Furthermore, any assessment of treatment superiority requires consideration of the expected waiting time, as the risk of tumour progression and therefore wait-list drop-out increases in tandem with increasing waiting times. Therefore, it remains imperative that the individual characteristics of a patient and wait-list dynamics are included in any decision making process.

The BCLC group have previously compared outcomes of LR and LT with ITT analysis.20 The results from 77 patients assigned to LR as primary treatment and 87 patients listed for LT were reported. No drop-outs occurred in the LR group, with 1-, 3-, and 5-year OS and DFS of 85%, 62%, and 51%, and 73%, 39%, and 25%, respectively. In the LT cohort there was a 23% drop-out rate, associated with a mean waiting time of 105 days, resulting in a 1-, 3-, and 5-year OS of 82%, 63%, and 63%, respectively. OS results were not different between groups (log rank 0.3). In addition, multivariate analysis disclosed tumour differentiation (P = 0.013), multiple nodules (P = 0.045), and the presence of satellite lesions (P = 0.02) as predictors of recurrence.

In contrast to this, another study also utilising ITT analysis of outcomes, demonstrated less favourable results with LR.59 In this cohort, a median wait-list time for LT of 118 days, was associated with a drop-out rate of two of the 48 patients. Three- and 5-year OS was 79% and 74% respectively for LT patients, in comparison to 61% and 26% in those undergoing LR. Furthermore, in LT and LR patients the 3- and 5-year DFS was 74% and 74%, and 41% and 11%, respectively. The authors discuss the caveat that these results are only applicable in the context of a waiting time between 6 and 10 months, and extension beyond these times is likely to increase the LT wait-list drop-out rate with a resultant negative impact on outcome in patients assigned to LT.

Pooled data from centres in Tokyo and Pittsburgh compared outcomes in 294 and 270 cirrhotic patients undergoing curative LR and LT, respectively.55 Although early (30-day and 150-day) mortality was significantly reduced in the LR cohort in comparison to LT (P = 0.001 and P = 0.00007, respectively) and OS was similar between groups, DFS was significantly less in the LR group (5-year DFS: 14.3% vs. 53.9%, P < 0.0001). Other studies, mainly consisting of retrospective review of outcomes in clinical practice have supported these findings with fewer peri-operative complications56, 57 but inferior DFS with LR in comparison to LT57, 60-63, as well as similar56, 57 or superior OS60, 62, 63 with LT.

In a retrospective review, Poon et al. investigated the tumour characteristics and long-term outcome in 204 cirrhotics undergoing LR and 43 undergoing LT for HCC within MC.64 The LT group had a lower incidence of high-grade tumours, microscopic vascular invasion and satellite nodules and therefore, not unexpectedly, was observed to have a superior 5-year OS in comparison to LR. However, when the results were stratified according to the presence or absence of microvascular invasion there was no difference in OS between the two groups. Interestingly, multivariate analysis disclosed that Hepatitis C viral serology, tumour size, tumour number,
| Reference (year) | Study design | ITT | n | Child Pugh A (%) | Adjuvant therapy | Tumour characteristics | DFS (%) | OS (%) |
|-----------------|--------------|-----|---|------------------|------------------|-----------------------|---------|--------|
| Otto (1997)     | Retrospective No | LR | 52 | 96% | 0% | pT1/2: 40% pT1/2: 30% | 76 | 64 | 51 |
|                 |              | LT | 50 | 96% | 0% | Mean diameter: 33.4 mm | 64 | 51 | 51 |
| Llovet (1999)   | Retrospective Yes | LR | 87 | 43% | 0% | Mean diameter: 24.1 mm | 84 | 69 | 69 |
|                 |              | LT | 87 | 43% | 0% | Mean diameter: 24.1 mm | 84 | 69 | 69 |
| Yamamoto (1999) | Retrospective No | LR | 294 | 66% | 0% | Single: 56.1% <20 mm: 24.1% | 84 | 69 | 69 |
|                 |              | LT | 270 | 4% | 0% | Single: 53.3% <20 mm: 46.3% | 84 | 69 | 69 |
| Shabahang (2002) | Retrospective No | LR | 44 | 100% | 23% | T1/2: 43% T1/2: 75% | 36 | 57 | 57 |
|                 |              | LT | 65 (10 incidental) | 100% | 23% | T1/2: 43% T1/2: 75% | 36 | 57 | 57 |
| Bigourdan (2003) | Retrospective Yes | LR | 20 | 100% | 20% | Solitary: 70% T1/2: 86% Solitary: 80% T1/2: 76% | 52 | 40 | 67 | 87 |
|                 |              | LT | 17 | 100% | 24% | Solitary: 70% T1/2: 86% Solitary: 80% T1/2: 76% | 52 | 40 | 67 | 87 |
| Margarit (2005) | Retrospective No | LR | 37 | 100% | 22% | Mean diameter: 30 mm Mean diameter: 30 mm | 77 | 39 | 39 | 39 |
|                 |              | LT | 36 | 100% | 50% | Mean diameter: 30 mm Mean diameter: 30 mm | 84 | 64 | 64 | 64 |
| Moon (2007)     | Retrospective No | LR | 100 | 31% | 0% | Mean diameter: 24 mm Mean diameter: 19 mm | 78 | 65 | 55 | 93 | 79 | 67 |
|                 |              | LT | 17 | 71% | 0% | Mean diameter: 24 mm Mean diameter: 19 mm | 100 | 75 | 75 | 94 | 94 | 94 |
| Poon (2007)     | Retrospective No | LR | 204 | 95% | 0% | Solitary: 88.7% Diameter <30 mm: 57.8% Solitary: 72% Diameter <30 mm: 73.5% | 44 | 68 | 68 |
|                 |              | LT | 43 | 19% | 0% | Solitary: 88.7% Diameter <30 mm: 57.8% Solitary: 72% Diameter <30 mm: 73.5% | 84 | 81 | 81 |
| Baccarani (2008) | Retrospective Yes | LR | 38 | 74% | 0% | Mean nodule number: 1.2 Mean diameter: 35 mm Mean nodule number: 2.0 Mean diameter: 37 mm | 41 | 11 | 61 | 26 |
|                 |              | LT | 48 | 47% | 0% | Mean nodule number: 1.2 Mean diameter: 35 mm Mean nodule number: 2.0 Mean diameter: 37 mm | 74 | 74 | 74 | 74 | 74 | 74 |

DFS, disease free survival; ITT, intention to treat analysis; LR, liver resection; LT, liver transplant; OS, overall survival.
and microscopic vascular invasion influenced prognosis, but treatment with LT or LR did not.

LR should not only be viewed as a potential curative approach, as it may also provide either bridging therapy whilst awaiting a liver graft or an initial intervention which can be ‘salvaged’ with LT, if recurrence arises at a later date. However, LT obviously remains the treatment of choice for patients with multifocal disease and/or decompensated liver disease. In theory, the strategy of salvage LT to treat recurrent HCC following primary LR has several advantages in comparison to primary LT. Firstly, patients receive a potentially curative intervention more rapidly, as there is no initial wait for a liver graft. Secondly, the number of ‘unnecessary’ LTs may be reduced thereby reducing patient exposure to the morbidity and mortality associated with LT as well as improving access to LT for other patients on the wait-list. Multiple studies have reported similar outcomes in patients undergoing primary LT or primary LR ± salvage LT.57, 65–70 In fact, Scatton et al. advocate the use of primary LR to help guide future management, suggesting that patients with an adverse histological profile be listed immediately from LT whereas others be considered for salvage LT only in the event of HCC recurrence.71 However, as yet there is no comparative outcome data to support the routine application of this approach to clinical practice.

A potential drawback of the aforementioned strategy is that patients may present with recurrent HCC beyond eligibility criteria and therefore would not be a transplant candidate. In such circumstances, a patient would be seen to have been ‘denied’ potentially curative intervention. Reported rates of ‘transplantable recurrence’ vary from approximately 60–80%.72, 73 However, ITT analysis of data from Bologna demonstrated that only 26% of patients underwent LT.59

A recent Markov model has suggested that primary LT is superior to primary LR with salvage LT when the expected 5-year post-LT life expectancy is greater than 60%.74 This conclusion was dependent on the characteristics of the wait-list: LT is increasingly favoured as the number of patients with HCC on a wait-list declines, whereas primary LR with salvage LT offers the greatest benefit and least harm to the wait-list, as either or both the number of patients on the wait-list or waiting times increase.

Loco-regional treatment modalities. Various loco-regional treatment modalities have been employed in the treatment of HCC, the most common of which, particularly in the context of bridging and down-staging, are radio-frequency ablation (RFA) and trans-arterial chemo-embolisation (TACE). However, other interventions such as external beam radiotherapy (DXT), trans-arterial embolisation, trans-arterial chemotherapy without embolisation (TAC), and trans-arterial radioablation (also referred to as selective internal radiation therapy or SIRT) may have a role.

The efficacy of RFA to induce tumour necrosis in small HCCs has been established by pathological examination of liver explants from patients undergoing LT following RFA.75 Although an OS and DFS comparable to that of LR has been observed in patients with tumours of diameter ≤ 50 mm,76 this translates into a 5-year DFS of only 20% in some series.77 Furthermore, the results obtained with RFA vary in accordance with multiple factors related to either the tumour or procedure. These factors therefore need to be considered on an individual basis. For example, a multivariate meta-analysis of outcomes following hepatic RFA (including non-HCC malignancies) demonstrated lower recurrence rates with small tumours, and tumours with non-capsular location or location away from large blood vessels.78

At present, there are no prospective studies comparing RFA to LT with ITT analysis of results, and it is unlikely that such a study will ever be performed. However, as well as being employed within bridging or down-staging protocols, as with LR, it is conceivable that patients with small volume HCC may be treated with RFA as a primary therapy, with salvage LT in reserve for those who have sub-optimal response or develop recurrence or de novo disease.

Although, TACE has an established role in the management of unresectable HCC,79 it cannot be considered as a ‘curative’ treatment. This however does not preclude it from having a role in either bridging or down-staging, either alone or in combination with ablative therapies. In fact, the combination of TACE with ablative therapy may offer a superior outcome. This was demonstrated in a retrospective review of 268 patients with Child-Pugh Stage A/B cirrhosis complicated by previously untreated early stage HCC who received TACE alone or TACE in combination with ablation (percutaneous ethanol injection and/or RFA).80 Patients with ≤ 3 lesions each with diameter ≤ 30 mm had improved survival when they received combination ablation and TACE (n = 61) in comparison to ablation alone (n = 19); however, this did not reach statistical significance.

Bridging therapy. As previously discussed, the aim of bridging therapy is to halt tumour progression and

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minimising wait-list drop-out. Data from the Organ Procurement Transplant Network (OPTN) estimate that HCC patients have an 18% wait-list drop-out rate.81 The need for bridging therapy must be considered as a function of expected waiting times on the list which vary according to wait-list length, severity of liver disease of those listed, and organ availability. A summary of studies investigating the use of bridging therapies is presented in Table 5.

Markov modelling of the role of neo-adjuvant LR for HCC whilst awaiting LT, where wait-lists were a year or more in length, showed that it was both cost effective and associated with a moderate gain in life expectancy.82 Furthermore, for shorter wait-lists, ablative therapy provided a relative survival advantage.

A systematic review of bridging therapy by Lesurtel et al. in 2006 concluded that there was insufficient good quality evidence to demonstrate that TACE either improved post-LT survival, altered post-LT complication rates, or impacted on wait-list drop out.83 When considering bridging therapy with RFA alone, there is a paucity of good quality data. Both the safety and efficacy of RFA in the treatment of small HCC has been reported by Mazzaferrro et al.84 In a prospective study, it was demonstrated that waiting times >1 year and tumours >30 mm in diameter were associated with higher levels of tumour persistence.84 Unfortunately, the lack of any wait-list drop-out, and the absence of a comparison group do not allow conclusions relating to survival benefit to be drawn. Review of the individual studies using TACE as bridging therapy (Table 5) does not yield encouraging results with retrospective studies by both Perez Saborido et al.85 and DeCaens et al.86 failing to demonstrate either improvement in OS or DFS.

Retrospective data published recently by Frangakis et al. report the outcomes of 43 patients who underwent TACE and 22 who did not.87 All patients were listed for LT for HCC within MC. The risk of drop-out was 3% and 15% in the TACE and non-TACE groups respectively ($P = 0.04$). Patients in the TACE group had higher tumours (mean diameter: $3.0 \pm 1.1$ cm vs. $2.0 \pm 1.1$ cm, $P = 0.002$) and higher serum AFP ($2301 \pm 6340$ ng/mL vs. $350 \pm 1103$ ng/mL, $P = 0.002$), in comparison to the non-TACE patients. Despite these differences, survival appeared superior in the TACE patients although this did not reach statistical significance.

The use of multimodal loco-regional therapy in patients awaiting LT is more likely to reflect actual clinical practice as opposed to single modality treatment as described in the aforementioned studies. Interestingly, data derived for subgroup analysis of patients with HCC within UCSF criteria awaiting LT who received multimodal bridging treatment demonstrated improved outcomes.88 Specifically, 5-year DFS was 93.8% and 80.6% in patients receiving and not receiving wait-list therapy, respectively ($P = 0.045$), with the greatest difference observed in the patients with Stage T3 tumours.

The use of DXT has also been suggested as a potential bridging therapy to LT.89 Sandroussi et al. report have recently reported their experience of DXT in 10 patients with HCC. Encouraging results were observed, with no treated tumour nodule progressing. However, these patients were beyond MC, as this group used the more liberal ‘Toronto’ LT eligibility criteria. Therefore, caution is required when interpreting these results, particularly when considering the use of DXT in the setting of more restrictive criteria such as are applied in most transplant centres.

Sorafenib is an orally active multi-kinase inhibitor, which has been demonstrated to improve survival in advanced HCC and has an increasing role in the management of HCC.90 However, as yet no specific data have been published exploring its role in bridging therapy, although a prospective, double-blinded randomised study is underway exploring the effect of TACE alone or TACE plus sorafenib in patients with HCC awaiting LT.91 Whilst we await this data, a recent Markov model has concluded that the use of sorafenib (alone) as bridging therapy would be a cost effective intervention.92

**Downstaging.** As previously stated, the term ‘down-staging’ when used in the context of LT for HCC, refers specifically to treatment undertaken to convert a tumour with morphology beyond established LT criteria (and therefore not a candidate for LT), to a size that is within criteria and therefore enable a patient to become a LT candidate. Any assessment of the efficacy of a down-staging protocol needs not only a clear definition of which patients would be considered for down-staging, but also a clear definition of eligibility criteria that need to be met for the patient to qualify for LT. Furthermore, some protocols require a period of stability once LT criteria have been met prior to activation on the wait-list. Such a restriction should ensure that patients with tumours that exhibit unfavourable biology, which would be expected to translate into an increased risk of recurrence, are excluded.

There is a wide variation in the reported success rates for patients undergoing down-staging, which may be due, at least in part, to differences in the entry criteria for individual studies (presented in Table 6). It follows...
Table 5 | Published outcomes of studies investigating the efficacy of bridging therapies whilst awaiting liver transplantation for hepatocellular carcinoma

| Reference (year) | Study design | Tumour characteristics | Bridging treatment | n* | Mean time on wait-list | DO rate (%) | OS (%)† | 1 year | 2 years | 3 years | 5 years |
|------------------|--------------|------------------------|--------------------|----|------------------------|-------------|---------|--------|---------|---------|---------|        |
| Hayashi (2004)\(^{24}\) | Retrospective | Within MC: 100% | TACE (doxorubicin 50 mg, mitomycin-c 10 mg, cisplatin 40 mg) | 20 | 11 months | 35 | ~85 | ~70 | ~62 |
| Maddala (2004)\(^{25}\) | Retrospective | Within MC: 87% | TACE (doxorubicin 50 mg, mitomycin-c 10 mg) | 54 | 7 months | 15 @6 months | 61 |
| Decaens (2005)\(^{86}\) | Retrospective case-controlled study | within MC: 71% | TACE (doxorubicin 1 mg/kg) | 100 | 4.2 months | n/a | 59 |
| None | 4.3 months | n/a | 59 |
| Lu (2005)\(^{26}\) | Retrospective | Within MC: 81% | RFA | 52 | 12.7 months | 6 | (98) | (84) | (74) |
| Perez-Saborido (2005)\(^{85}\) | Retrospective | Within MC: 72% | TACE | 18 | n/a | n/a | (83.3) | (60.5) | (60.5) |
| None | 28 | n/a | n/a | (77.2) | (58.7) | (38.1) |
| Yao (2005)\(^{88}\) | Multi-centred retrospective | Within MC: 68.6%; within UCSF: 90.9% | Multi-modal | 103 | n/a | n/a | (96.4)‡ | (93.8) | (91.5)‡ | (80.6) |
| None | 65 | n/a | n/a | (91.5)‡ | (80.6) |
| Frangakis (2010)\(^{87}\) | Retrospective | Within MC: 100% | TACE (doxorubicin 50 mg, mitomycin-c 10 mg) | 22 | 17 weeks (132 weeks)§ | 3 | 76 |
| None | 43 | 20 weeks (28 weeks)§ | 15 | 57 |

DO, dropout; MC, Milan criteria; n/a, no data available; OS, overall survival; RFA, radio-frequency ablation; TACE, trans-arterial chemo-embolisation; UCSF, University of California, San Francisco criteria.

* Incidental tumours excluded.
† Bracketed numbers refers to data from only patients who underwent LT.
‡ Disease free survival in patients with T 2/3 tumours.
§ Waitlist times for patients undergoing liver transplantation with time from listing to dropout denoted in brackets.
Table 6 | Summary of reports of down-staging in patients with HCC beyond conventional eligibility criteria

| Reference (year) | Inclusion criteria | Transplant criteria | Downstaging treatment | Minimum period of stable disease (months) | Success-fully down-staged (%) | Survival (%) | Measure reported | 1 year | 2 years | 3 years | 4 years | 5 years |
|------------------|--------------------|---------------------|-----------------------|------------------------------------------|-------------------------------|----------------|----------------|------|-------|-------|-------|-------|
| Graziadei (2003)<sup>98</sup> | Beyond MC | >50% tumour reduction | TACE (70 mg epirubicin) | 15 | 41.6 | OS (successfully down-staged patients only) | 93 | 78 | | | 31 |
| Otto (2006)<sup>53</sup> | Beyond MC | Tumour regression | TACE (mitomycin 10 mg) | 62 | 54.8 | DFS (post LT) | 82 | 55 | 41 | | |
| Chapman (2008)<sup>93</sup> | Any size, excluding major vessel involvement or metastatic disease | MC | TACE (50 mg cisplatin, 50 mg doxorubicin, 10 mg mitomycin-c) | 4 | 76 | OS (LT patients) | 100 | 48 | 100 | 10 | 94 |
| Ravaioli (2008)<sup>94</sup> | Single nodule ≤ 80 mm, or two nodules ≤ 50 mm, or ≤ 6 mm & TTD ≤ 120 mm, no macrovascular, biliary invasion or metastases | MC; AFP < 400 | TACE, resection, PEI or RFA | 3 | 48 | OS (ITT) | 56<sup>1</sup> | | | | 62.8 |
| Yao (2008)<sup>95</sup> | Solitary nodule 50–80 mm, 2–3 nodules <50 mm and 1 x >3 cm & TTD <80 mm; 4–5 nodules, each <30 mm & TTD <80 mm | MC | TACE, RFA, PEI, resection | 3 | 61 | OS (ITT) | 88 | | | | 92 |
| De Luna (2009)<sup>96</sup> | Beyond MC | | TAC (cisplatin/doxorubicin) | 27 | 63 | OS (ITT) | 96 | 90 | 79 | 84 | |
| Jang (2010)<sup>97</sup> | Beyond MC, no MaVI or metastatic disease | MC | TACL (epirubicin 50 mg/m² or cisplatin 60 mg/m²) | 386 | 41.5 | OS (ITT) | 71 | 51 | 25 | | |

AFP, alpha-feto protein; DFS: disease free survival; ITT, intention-to-treat; LT, liver transplant; MaVI, macrovascular invasion; MC, Milan criteria; OS, overall survival; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TAC, transarterial chemotherapy; TACE, transarterial chemoembolisation; TACL, transarterial chemo-lipiodolisation; TARE, transarterial radio-embolisation; TTD, total tumour diameter.
that the rate of successful down-staging, leading eventually to LT, should be lower in studies with more liberal eligibility criteria. This is illustrated by data from studies by Chapman et al.\textsuperscript{93} and Ravaioli et al.\textsuperscript{94} In the former only 23.7\% of patients were successfully down-staged from Stage T3/T4 tumours to within MC with TACE, whereas a success rate of 90\% was described in the latter. This difference is likely to reflect the more specific entry criteria, in the study by Ravaioli et al., of solitary tumours with a diameter >50 mm but <80 mm, or two tumours with diameter ≤50 mm, or <6 tumours ≤40 mm in diameter with TTD ≤120 mm.\textsuperscript{94} However, both these studies demonstrated comparable post-LT outcomes between patients with tumours within MC from the outset and patients with successfully down-staged tumours.\textsuperscript{93, 94}

Data from UCSF, reported on the role of down-staging in a selected group of patients with a tumour burden beyond MC.\textsuperscript{95} Entry criteria for down-staging were: solitary lesions >50 mm but <80 mm, 2–3 lesions with at least one lesion >30 mm but <50 mm in association with TTD ≤80 mm, or 4–5 lesions with none >30 mm and TTD ≤80 mm. Down-staging was attempted using multi-modal loco-regional therapy and success was defined as achieving MC. In addition, a minimum observation period of 3 months was required prior to LT. Within a cohort of 61 patients, down-staging was achieved, on the basis of radiological assessment, in 43 patients. Thirty-five patients underwent LT, in which explant pathology demonstrated tumour beyond MC in five patients. Although 4-year OS was 69.3\% on ITT analysis and 92\% post-LT, median follow-up duration was only 25 months post-LT.\textsuperscript{95}

In a study exploring both down-staging and bridging therapy with TAC, DeLuna et al. observed a 63\% success rate with down-staging.\textsuperscript{96} Further data are provided by Jang et al. who reviewed the use of transarterial chemo-lipiodolisation (TACL) to down-stage 386 patients with HCC beyond MC.\textsuperscript{97} 41.5\% of patients were successfully down-staged to MC, with a subsequent 5-year OS of 54\%. Multivariate analysis identified elevated AFP, tumour diameter ≥70 mm and lack of complete tumour necrosis as predictors of recurrence, with patients who did not possess any of these risk factors having an 87.5\% 6-year DFS. However, these results were based on only 37 patients who had undergone LT (mainly LDLT) with 33 patients remaining on the wait-list at the time of publication.\textsuperscript{97}

The need for clear definitions of entry criteria and successful down-staging is illustrated by data from Grazi-adai et al.\textsuperscript{98} In their study, the entry criteria was described as ‘advanced HCC’ and a >50\% reduction in tumour size constituted successful down-staging with resultant eligibility for LT. Of the 15 patients reported who were eligible for LT, there was a 20\% wait-list drop-out rate and 30\% recurrence rate post-LT.

**Systemic therapy.** In addition to bridging and down-staging, neo-adjuvant and adjuvant therapies have been applied to patients undergoing LT for HCC in order to improve eventual outcomes as opposed to minimising drop-out or rendering a tumour transplantable. Almost universally, the results from both retrospective\textsuperscript{99} and prospective studies\textsuperscript{100–102} of systemic cytotoxic chemotherapy with doxorubicin, cisplatin, and gemcitabine (summarised in Table 7) demonstrate no survival advantage.

A novel approach to HCC treatment is the use of [131I]-metuximab (Licartin). [131I]-metuximab is a radio-labelled murine monoclonal antibody Fab’ fragment that targets HAb18/G/CD147 (an HCC associated antigen); in phase 1 and phase 2 trials it was found to be concentrated in the tumour region and be an effective treatment for HCC.\textsuperscript{103} In a study by Xu et al., 60 patients with Stage T3 and T4 HCC were randomised to receive either [131I]-metuximab, 3 weeks post-LT and then on a further three occasions at 4-week intervals, or placebo.\textsuperscript{104} The preliminary results are encouraging with a significant reduction in recurrence rates (30.4\%, \(P = 0.0174\)) and improvement in survival (20.6\%, \(P = 0.0289\)), however, further studies are required to confirm these results and determine its applicability to patients with early stage disease.

**Post-transplant immunosuppression**

The use of immunosuppressive therapy has the potential to alter the natural history of malignancy; this is particularly important following LT for HCC which is associated with the risk of recurrence. One potential approach to improve outcomes is the tailoring of immunosuppressive agents. The use of sirolimus, an mTOR inhibitor with anti-tumour activity, or sirolimus-based regimens may have an advantage over standard calcineurin inhibitor-based strategies. Several studies (summarised in Table 8) have investigated this, although the data quality at present remains sub-optimal. The safety of sirolimus and a reduced risk of HCC recurrence has been observed retrospectively,\textsuperscript{105–107} including data from a large LT registry.\textsuperscript{108} At present, no prospective trial data are available; however this subject is the focus of a clinical trial,\textsuperscript{109} the results of which are awaited.
Table 7 | Summary of reports of neo-adjuvant/adjuvant systemic chemotherapy in patients with HCC undergoing liver transplantation

| Reference (year) | Study design           | Protocol                                                                 | n   | Tumour characteristics | DFS 3 years | DFS 5 years | OS 2 years | OS 3 years | OS 5 years |
|------------------|------------------------|--------------------------------------------------------------------------|-----|------------------------|--------------|-------------|------------|------------|------------|
| Pokorny (2005)   | Prospective randomised trial | doxorubicin (15 mg/m² fortnightly from listing, intra-operatively and post-operatively, up to cumulative dose of 300 mg/m²) | Treatment 34 | Within MC: 18%          | 43           | 53          | 38         | 40         |
|                  |                        |                                                                          | Control 28 | Within MC: 18%          |              |             |            |            |
| Bharat (2006)    | Retrospective          | comparison between patients receiving loco-regional therapy whilst on wait-list | Treatment 46 | Within MC: 76.1%        | 84           | 76          | 82         | 52         |
|                  |                        |                                                                          | Control 51 | Within MC: 31.4%        |              |             |            |            |
| Soderdahl (2006) | Prospective, randomised, multi-centred trial | placebo vs. doxorubicin (10 mg/m² weekly from listing, 15 mg/m² intra-op & 10 mg/m² weekly post-LT up to cumulative dose of 400 mg/m²) | Treatment 19 | Within MC: 47.1%        | 63           | 50          | 63         | 58         |
|                  |                        |                                                                          | Control 27 | Within MC: 32%          |              |             |            |            |
| Hsieh (2008)     | Retrospective          | patients outside MC comparison of patients receiving gemcitabine (600–800 mg/m² on D1, 8, 15 and cisplatin 80 mg/m² on D15 | Treatment 17 | Mean number of nodules: 3.3 | 56           |             |            |            |
|                  |                        |                                                                          |             | Mean nodule diameter: 83 mm |              |             |            |            |
|                  |                        |                                                                          | Control 13 | Mean number of nodules: 3 | 38           |             |            |            |
|                  |                        |                                                                          |             | Mean nodule diameter: 63 mm |              |             |            |            |

DFS, disease free survival; MC, Milan criteria; OS, overall survival.
Irrespective of the specific eligibility criteria for LT in HCC, a system is required to allocate available donor organs to appropriate recipients. These systems should allocate organs according to need, minimise wait-list drop-out, and should also be designed to ensure that certain groups of patients are not unfairly advantaged or disadvantaged over others.

In the USA, a Model of End-Stage Liver Disease (MELD)-based system of allocation has been employed since 2002, which awards greater priority to patients with decompensated liver disease over patients with well compensated liver disease and HCC even though the risk of wait-list drop-out is potential greater in the HCC patients due to tumour progression. Therefore, to address this issue, additional ‘priority’ (or ‘exception’) points are awarded to patients with HCC awaiting LT to attempt to equalise this disparity. When initially instituted in February 2002, 24 and 29 points were awarded to Stage T1 and T2 tumours respectively. However, subsequent analysis of UNOS registry data concluded that this was too generous, thus excessively favouring HCC patients with well compensated liver disease and HCC, even though the risk of wait-list drop-out is obviously greater in the HCC patients due to tumour progression. Therefore, additional ‘priority’ points are awarded to patients with well compensated liver disease and HCC, a system is required to allocate available donor organs to appropriate recipients. These systems should allocate organs according to need, minimise wait-list drop-out and should also be designed to ensure that certain groups of patients are not unfairly advantaged or disadvantaged over others.

### Table 8 | Summary of studies comparing sirolimus and non-sirolimus based immunosuppression post-liver transplantation for HCC

| Reference (year) | Study design | Protocol | CP-A (%) | MELD (mean) | DFS (%) | OS (%) |
|------------------|--------------|----------|----------|-------------|---------|--------|
| Zimmerman (2008)<sup>107</sup> | Retrospective comparison of standard immunosuppression vs. SIR + CNIs | SIR | 45 | 22 | 93 | 79 | 96 | 79 | No difference in major complications |
| Chinnakotla (2009)<sup>106</sup> | Case-control review | SIR vs. MMF + tacrolimus; some patients also received adjuvant doxorubicin | SIR | 106 | 13.6 | 94 | 85 | 80 | Significantly reduced risk of recurrent with SIR |
| Toso (2010)<sup>108</sup> | Retrospective (registry data) | Comparison of patients on SIR and SIR-free, with sub-group analysis of HCC patients | SIR | 109 | 15 | | | | Improved survival |
| | | | SIR-free | 2382 | 14 | | | | |

CNI, calcineurin inhibitor; CP-A, Child-Pugh A; DFS, disease free survival; HCC, hepatocellular carcinoma; HR, hazard ratio; MELD, Model of End-Stage Liver Disease; MMF, mycophenolate mofetil; OS, overall survival; RR, relapse rate; SIR, sirolimus.

### Table 9 | The evolution of UNOS MELD priority points since 2002

| Reference (year) | Study design | Protocol | UNOS HCC Stage | T1 | T2 |
|------------------|--------------|----------|----------------|----|----|
| Zimmerman (2008)<sup>107</sup> | Retrospective comparison of standard immunosuppression vs. SIR + CNIs | SIR | 20 | 24 |
| Chinnakotla (2009)<sup>106</sup> | Case-control review | SIR vs. MMF + tacrolimus; some patients also received adjuvant doxorubicin | SIR | 29 |
| Toso (2010)<sup>108</sup> | Retrospective (registry data) | Comparison of patients on SIR and SIR-free, with sub-group analysis of HCC patients | SIR | 24 |

UNOS, United Network for Organ Sharing; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease.

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of other listed patients, wait-list length and organ availability need to be considered in any allocation system, with no single system being universally appropriate. Indeed, this has been demonstrated with the use of a Markov model using data from Padua and the USA. In Padua, there is a lower wait-list mortality rate and higher proportion of patients listed with HCC (25% vs. 10%) in comparison to the USA. It was therefore calculated that a minimum 5-year OS of 30% was needed in Padua post-LT for HCC vs. 61% in the US for the benefit to outweigh the harm to the wait-list.111

Refinement of the priority systems have been proposed in the form of a continuous scoring system to be used alongside the MELD score. A combination of MELD score with adjustments for tumour volume and time on the wait-list has been suggested by Piscaglia et al.112 Furthermore, data from the OPTN has demonstrated MELD, AFP and maximum tumour diameter as predictors of wait-list drop-out in patients listed for LT with HCC.81, 113, 114 Thus, incorporation of these factors into a continuous score may help equate drop-out rates between patients with or without HCC thereby equalising access to LT across indications.

Living donor liver transplantation
Separate consideration to LDLT for HCC is required, as the patient already has an 'allocated' liver graft and is therefore not dependent on the donor pool. It can therefore be argued that the application of strict eligibility criteria as required with cadaveric grafts for patients with HCC is not necessary. However, in these circumstances the risk to the donor must be incorporated into any decision, since it is clearly unethical to expose a donor to a significant risk of morbidity or mortality, if LT will not provide any tangible survival benefit to the recipient. Generally, similar criteria apply to patients undergoing deceased donor LT (DDLT) or LDLT. In fact, similar outcomes are observed in patients receiving DDLT or LDLT for HCC within MC.115, 116 However, in South East Asia East, where adult living donation is the most common source of grafts, expansion of eligibility criteria has been explored with satisfactory results, as discussed previously.

The shorter wait prior to LT seen with LDLT also requires consideration when interpreting results. It has been suggested that patients with unfavourable tumour biology are identified by wait-list drop-out if there is a delay between listing and DDLT. However, without a waiting period to select out those patients with more aggressive tumours, it would be expected that LDLT be associated with an increased rate of post-LT tumour recurrence. In support of this theory, Vakili et al. recently reported a greater recurrence rate with LDLT in comparison to deceased donor LT (28.6% vs. 12.1%, \( P < 0.05 \)), although no difference in OS was observed.117 Whereas, investigation of outcomes stratified against wait-list time by Chao et al. did not observe any difference in DFS between those waiting <3 months, 3–6 months and >6 months.118

CONCLUSIONS
LT is an established treatment for HCC in selected patients. MC are an accepted benchmark for eligibility for LT in patients with HCC; however, there is continued debate as to how improvements may be made. Increases in permissible nodule size, diameter or volume have been suggested as well as the inclusion of serum biomarkers or surrogate markers of tumour biology into selection criteria. Furthermore, the expansion of eligibility has a secondary effect on LT wait-lists with possible negative implications for other patients, which may be compounded by the expansion of eligibility to include patients who have undergone down-staging of tumours to within transplant criteria. With increasing duration on the wait-list and therefore a greater risk of drop-out in HCC patients, there is increasing demand for bridging therapy. At present, there is no data to recommend the use of SIR-based immunosuppression post-LT for HCC although a trial to address this is underway. The potential role of sorafenib either prior to or after LT in HCC patients is yet to be defined although may offer additional intervention in at-risk patients.

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