REVIEW

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Hepatic Oncology

Liver transplantation for hepatocellular carcinoma: how far have we come and what is the future?

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Practice points

- Liver resection continues to be the mainstay of treatment for hepatocellular carcinoma in the absence of cirrhosis, while liver transplant offers definitive cure of malignancy and underlying chronic liver disease in patients with baseline liver dysfunction.
- The Milan criteria remains the standard transplant selection criteria, with inclusion criteria of single tumors ≤ 5 cm, or up to three tumors not exceeding 3 cm, without vascular invasion.
- The restrictiveness of the Milan criteria is being challenged by various groups, to include patients with tumors that are larger in size and greater in number, with promising results.
- Pretransplant bridging or downstaging therapies using locoregional methods have been successful for selecting for less aggressive disease.
- Adjunct therapies have begun to show effectiveness as therapeutic modalities for effective oncologic treatment in addition to surgery.
- Controversy exists in the use of living donor transplantation for the treatment of hepatocellular carcinoma, with conflicting outcomes.

SUMMARY: Liver transplantation is the best treatment for hepatocellular carcinoma in the setting of chronic liver disease, completely removing malignancy and underlying diseased liver tissue. Technical aspects of liver transplantation have improved over the years, along with outcomes. But challenges continue in the areas of expanding existing indications for transplant with limited organ supply, calling for optimization of patient selection and the development of alternative or adjunctive treatment options. Expansion of existing transplant criteria will help identify patients most likely to have good outcomes. Locoregional and systemic treatments showing therapeutic promise are being investigated for use in achieving acceptable oncologic effect. Improvements in post-transplant treatment and continued attempts to enlarge the donor pool will continue to provide avenues for further improvements in outcomes.

KEYWORDS

- Child-Turcotte-Pugh
- hepatocellular carcinoma
- liver transplant
- locoregional therapy
- model for end-stage liver disease
- transarterial radioembolization with yttrium-90 microspheres
- tumor node metastasis
- United Network for Organ Sharing

Historical background

At the time of the first liver transplant (LT) performed in a human in 1963, unresectable primary malignancy of the liver was considered to be an ideal indication for liver transplantation, in addition to chronic hepatitis, alcoholic cirrhosis and biliary atresia [1]. High rates of recurrent cancer and unacceptably high mortality rates, however, dampened enthusiasm for liver replacement as a treatment for malignancy [1–3]. In these early series, outcomes of liver transplantation were markedly inferior to those of subtotal hepatectomy, with an observed 3-year survival of 29% in LT, compared with 52% in hepatectomy [2]. Currently, liver resection continues to be the mainstay of treatment for hepatocellular carcinoma (HCC) in the absence of cirrhosis, while LT offers definitive cure of malignancy and underlying chronic liver disease in patients with baseline liver dysfunction [4].

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The poor outcomes observed in early experiences with LT for HCC was likely due to poor patient selection, as LT was reserved for patients with very advanced unresectable tumors, selecting for aggressive biology and patients with poor long-term prognosis.

By the late 1980s and 1990s, with advances in surgical techniques of liver transplantation and medical management of postoperative patients, interest grew in revisiting LT as a viable treatment option for HCC [5]. During this period, long-term (3- to 5-year) post-transplant survival (35–49%) improved to become equivalent to that of hepatic resection (32–52%) [6,7]. These improvements came from technical advancements such as the use of caval sparing explant hepatectomy, which eliminated the need for extracorporeal circulation [8,9], and medical advancements in post-transplant immunosuppression. However, post-transplant recurrence of disease continued to be high at 65–75% [5,10]. This high recurrence rate was replicated in several centers [5,11,12] and given the prohibitively high recurrence rates after LT, its use as treatment for HCC waned.

Milan criteria

It was not until 1996 when Mazzaferro's group in Italy introduced selection criteria, now commonly known as the Milan criteria, that improved outcomes after LT for HCC were observed. The Milan group conducted a prospective cohort study of 48 patients receiving LT for HCC in the setting of cirrhosis, with inclusion criteria of single tumors ≤ 5 cm, or up to three tumors not exceeding 3 cm, without vascular invasion [13]. Prior observations had suggested a relationship between tumor stage and rate of recurrence [6,7,14,15] and the tumor node metastasis staging system was revised to reflect this. In Mazzaferro's work, 4-year survival for patients undergoing LT for HCC was 75%, equivalent to outcomes expected of patients undergoing LT for nonmalignant indications. Other studies validating these results reinforced a renewed optimism for LT as treatment for early-stage HCC [16,17].

With the introduction of the Milan criteria, concrete albeit somewhat arbitrary standards for patient selection for LT were established. Improvement in patient selection has significantly impacted outcomes for patients undergoing LT for HCC, as seen in an analysis of the United Network for Organ Sharing database of

transplanted patients between 1987 and 2001. This study showed that over the period observed, there was a steady and significant improvement in survival in patients undergoing LT for HCC, with the 5-year survival in HCC patients improving from 25.3% during the 1987–1991 period, to 61.1% between 1996 and 2001. A similar improvement in survival was not observed in LT patients with nonmalignant indications, suggesting that improved HCC patient selection was responsible for this difference, especially in the post-Milan era [18].

Subsequent validation of the Milan criteria by the same group in a prospective study including 161 LT candidates with HCC showed a 5-year survival of 87% and recurrence-free survival of 96% for those patients with tumors within criteria. For patients outside of criteria, however, 5-year survival and disease-free survival were significantly lower, at 62 and 64%, respectively [19].

Further validation has been provided by retrospective studies, including a large, single-center study at University of California, Los Angeles (CA, USA), in which 467 patients underwent LT for HCC. Overall 5-year survival was 52% and recurrence rate was 21.2%. Patients with tumors within the Milan criteria had a 5-year survival of 87% – significantly superior to the 62% for those outside criteria, as well as improved recurrence-free survival of 74 vs 27% [20]. This study showed that the model for end-stage liver disease (MELD)-based allocation system has improved survival from a pre-MELD 5-year survival of 47% to a MELD era survival rate of 74%.

These results were duplicated at Baylor University (TX, USA), where outcomes improved after the application of the Milan criteria. Overall 5-year survival improved from 28.6% during the time period of 1987–1992, to 42.3% during the period 1992–1997, to 76% after 1997, corresponding to the year that the Milan criteria went into effect. Up until 1997, the survival in LT patients with HCC was lower than survival achieved in LT patients with non-HCC indications. Tumor recurrence also showed a similar trend: 52.9% in the period of 1987–1992, to 48.2% during 1992–1997, and 11.4% in 1997–2002 [21].

The restrictions of the Milan criteria have since been challenged, with attempts to expand the criteria to include larger and more diffuse HCC for LT consideration. The restrictiveness of the Milan criteria can contribute to the

prolongation of wait time for HCC patients, by virtue of lengthening the process by which these patients become eligible to be listed for transplantation, and the 1-year drop-out rate can be as high as 20–50% [22]. In addition, while the current drop-out rate in the USA is closer to the 10–20% range [23–25], an evaluation of the current criteria is necessary to optimize outcomes for those on the waiting list.

Expanding the restrictions of the Milan criteria has been the subject of growing interest, with encouraging outcomes. The group in University of California, San Francisco (UCSF; CA, USA) has used the criteria of single tumors up to 6.5 cm and cumulative tumor burden ≤ 8 cm, and showed that 5-year survival rates are similar to those of Milan criteria [26]. The strength of these studies have, however, been called into question, given underpowering and limited data, in addition to the fact that the initial UCSF data was based on explanted pathology, rather than preoperative imaging criteria.

MELD-based allocation system

Organ allocation in the USA was initially based on the Child-Turcotte-Pugh score, which categorized patients according to disease severity [27]. Patients with HCC within Milan criteria were grouped into the largest subgroup under this system, thereby increasing the wait time for limited donor organs, and over 45% of HCC patients waited for up to 2 years before receiving an organ, resulting in a high mortality and drop-out rate due to progression of disease.

The promising outcomes of LT for early stage HCC, while offering an optimistic treatment option, emerged in the setting of this time-based Child-Turcotte-Pugh allocation system, which placed HCC patients at a disadvantage for receiving organs in a timely fashion before progression of disease. This, in conjunction with a Tufts study showing that wait list mortality was not clearly associated with waiting time [28], led to efforts to identify an accurate prediction score for waiting list drop out and mortality.

On 27 February 2002, the MELD was adopted as the system for determining the allocation of deceased donor livers in the USA. Initially developed to predict survival and identify patients with high mortality risk after elective transjugular intrahepatic portosystemic shunts procedure, the MELD incorporates international normalized ratio, bilirubin and creatinine levels to predict severity of liver disease [29].

The MELD shifted the focus from a time-based allocation system to one based on severity of disease. Since its introduction for the purposes of organ allocation, the MELD's accuracy to predict mortality in end-stage liver disease has been demonstrated [30,31]. The elimination of wait time from the allocation system effectively eradicated the practice of listing patients with relatively mild disease early in the course of their disease in order to gain wait time advantage [32].

While the MELD had a positive impact on the allocation of organs for patients with end-stage liver disease, it introduced the predicament of heightened demand for donor organs for HCC patients with low MELD scores due to early disease. Disease progression while waiting would contribute to wait list drop out or mortality. The challenge was to devise a system that would favor organ allocation to HCC patients within Milan criteria before disease progression without biasing the system to increase mortality for transplant candidates for non-HCC indications. To this end, HCC patients were assigned a MELD score to minimize wait time for an organ, and every 3 months, accrued additional MELD points as a surrogate for occult disease progression.

Implementation of this new allocation system saw an increase in the rate of transplantation for HCC from 7 to 22% [27]. In the CTP-based system, LT incidence rate was 0.439 transplant/person years. Post-MELD, this rate increased to 1.454 transplant/person years ($p < 0.001$). Time to transplant was 2.28 years pre-MELD and dropped to 0.69 years post-MELD ($p < 0.001$). The 5-month drop-out rate was 16.5% pre-MELD, and decreased to 8.6% post-MELD ($p < 0.001$) [33]. However, after these changes took place, it became evident that the mortality rate in HCC patients due to progression of disease was found to be lower than mortality rates for patients with similar MELD scores who had nonmalignant indications for transplant candidacy. This led to several subsequent adjustments in the priority point system, with follow-up studies showing an effective decrease in transplantation rate without adversely affecting wait list drop out [34].

These advances increased the number of transplant candidates for a limited number of donor organs available, leading to continued search to streamline the allocation process. Explant pathology report analysis of patients transplanted for stage I HCC showed that 31% of

livers of patients had no evidence of malignancy in the specimen, leading to the abandonment of granting priority points to HCC patients with stage I tumors [27]. Currently, patients meeting the Milan criteria either at diagnosis or after downstaging, receive 22 MELD priority points coinciding with a 15% waiting list mortality risk. Patients are then recertified every 3 months to receive an additional 10% mortality risk points if they continue to meet criteria [35].

Pretransplant treatment strategies

The effectiveness of the new allocation system has not changed the persistent problem of limited supply of deceased donor organs for steadily growing demand. An 8-year retrospective study of the United Network for Organ Sharing/Organ Procurement and Transplant Network registry data on outcomes of LT candidates with HCC showed that the post-transplant survival rate for those meeting Milan criteria was 61% at 5 years versus 32% for those exceeding criteria, confirming the previously established data. However, it also showed significant wait list drop-out rates of 12 and 20% at 1- and 3-years, respectively [36], and this has shown to lead to worse overall survival for HCC patients on the waiting list for LT [37]. The problem of increased wait time for organs is not limited to HCC patients, however, and is a universal phenomenon due to increasing indications for LT. Some argue that HCC patients may be at a slight advantage over those with nonmalignant indications in receiving timely LT.

Slowing disease progression to prevent wait list mortality and drop-out rates has been the driving force behind the development of loco-regional therapies (LRT), such as percutaneous ethanol injection (PEI), transarterial chemoembolization (TACE) and radiofrequency ablation (RFA). HCC has a median doubling time of 6 months [38], making disease progression a real possibility while on the waiting list, potentially compromising LT candidacy and disease-free survival post-transplant.

• Bridging therapy

Pretransplant therapies can be categorized into two groups: bridging and downstaging. Bridging therapy is used for tumors meeting criteria for LT and is administered while a patient is waiting for an available organ. The risk of drop out increases along with length of time on the waiting list, and it has been shown that at 3 months,

drop out begins to exceed that seen for non-malignant diagnoses for which patients are on the wait list [39]. There have been retrospective studies that show pretransplant LRT prevents wait list drop out [40–47] and that it is possible for patients with advanced HCC to be treated with TACE as a bridge to transplantation or to successfully downstage tumors to meet Milan criteria [48,49]. However, given the amount of variability between different regions and centers with regard to wait time and allocation policies, generating meaningful conclusions about the effectiveness of bridging therapies is difficult [50].

Results from a single-center and a Markov model analysis suggest that tumor progression at 3 months is estimated at 8% for T1 and 15% for T2 disease [51,52]. Tumor burden has been shown to be associated with drop out, with >50% risk of 1-year drop out for single lesions >3 cm, compared with a 10% risk for smaller tumors [47]. If risk of progression beyond criteria is equivalent to drop-out rates, using bridging therapy for T2 tumors is warranted.

A Markov analysis on the use of PEI was performed in Barcelona (Spain), concluding that PEI is cost effective in increasing survival if wait time is >6 months [53]. RFA has been shown as an effective bridging option in various studies [42,44,54,55]. TACE has been shown in a randomized controlled trial to cause measurable tumor response [56]. Its effect on drop-out rates, however, has not been elucidated. A meta-analysis showed insufficient evidence that TACE decreases wait list drop out [57].

Clinically, patients with HCC placed on the wait list for LT most often undergo neoadjuvant chemoembolization for bridging, with an observed cumulative drop out probability of 15 and 20% at 6 and 12 months, respectively [43]. A UCSF retrospective analysis validated the recurrence-free survival benefit of LRT in patients who underwent LT for T2 and T3 disease. The 5-year disease-free survival in patients receiving LRT was 93.8%, compared with 80.6% ($p = 0.049$) in those who did not undergo treatment. Benefit was most notable in T3 tumors, and results suggested that pretransplant LRT adds a survival benefit, potentially through the selection of less aggressive tumors that are more responsive to therapy [49].

• Downstaging therapy

Downstaging involves treatment of patients with tumor burdens outside of transplant criteria to

convert them to be suitable candidates for LT. Response to treatments is used as a marker of tumor aggressiveness, selecting out those patients who would have a better prognosis based on their response to pre-LT treatment. Additional benefit of prolonging survival by virtue of the oncologic treatment effect of LRT is less certain.

There are multiple downstaging protocols that have been proposed, with results suggesting that tumor bulk at time of treatment is the more important determinant of treatment efficacy than the treatment protocol itself. TACE has been the preferred mode of pretransplant LRT for downstaging purposes, especially in treating multifocal disease. Disease stability after LRT, usually 3–6 months after treatment, is required before transplant listing, in order to select for patients with less aggressive disease and therefore a lower likelihood of recurrence post-transplant [58,59]. Combining treatment modalities has also shown to be effective. The recent introduction of the use of transarterial radioembolization with yttrium-90 (TARE-Y90) as a downstaging modality will also open new avenues of treatment.

In 1997, Majno *et al.* performed the first downstaging therapy for tumors beyond the Milan criteria in order to facilitate LT. TACE was performed in patients undergoing hepatic resection versus LT. Total necrosis of tumor led to higher disease-free survival in both the resection and LT groups, and downstaging was more successful for tumors >5 cm [60].

A study of pretransplant RFA by Mazzaferro in 2004 showed a mean interval from RFA to LT to be 9.5 months, with a complete histologic response rate of 55%, and no incidence of tumor progression or metastases. Complete tumor response was related only to tumor size. At follow-up, the 1- and 3- year patient and graft survival were 95 and 83%, respectively [44].

In a retrospective study performed in 2006, Bharat studied 100 patients undergoing LT for HCC, of which approximately half received LRT in the form of TACE, RFA, PEI or combination therapy. The LRT group had a 5-year survival of 82.4 versus 51.8% in those who received no pre-transplant therapy. This effect was seen only in tumors staged T2–T4, while tumors staged T1 had good prognosis regardless of pretreatment status (Figure 1) [61].

Successful downstaging of advanced tumors for LT was demonstrated in a series of patients at Washington University (MO, USA) in 2008. A

total of 76 patients who presented with advanced (stage III or IV) underwent TACE therapy regardless of tumor size or lesion number, and 23.7% (n = 18) of patients underwent successful downstaging to meet criteria for LT by imaging. Of these 18 patients, 17 patients underwent LT, with a median time to transplant of 5.8 months from the time of first TACE session. The 5-year survival for these downstaged patients was 93.8% as compared with patients with stage II disease who underwent therapy and LT (66%; $p = 0.03$) [48]. This approach promotes the selection of patients with less aggressive tumors whose biology is likely to respond well to therapy, and therefore favorable prognosis. The Washington University downstaging model does not preselect patients for an upper limit on tumor size or number, and involves evaluation of patients for treatment effect during the pretransplant observation period (Figure 2).

A similar series was performed at UCSF in the same year, where TACE was used for tumors outside of Milan but meeting UCSF criteria, with upper limits in size and lesion number. Downstaging was successful in 70.5% of patients, treatment failure occurred in 29.5%

Figure 1. Washington University (MO, USA) outcomes data by Bharat *et al.* showing effects of pretransplant therapy on survival by tumor stage.

LRT: Locoregional therapy; OLT: Orthotopic liver transplant.

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Figure 2. Washington University (MO, USA) downstaging protocol. The protocol does not involve an upper size or nodule number limit, and consists of a pretransplantation observation period, during which response to therapy is followed.

HCC: Hepatocellular carcinoma; OLT: Orthotopic liver transplant; TACE: Transarterial chemoembolization.

due to disease progression, and of the 35 patients who received LT, 13 displayed complete treatment response as determined by tissue necrosis; 17 patients met pathologic criteria for stage II disease, and five were beyond stage II [59].

A recent advancement in LRT is TARE-Y90, which uses delivery of Y-90 impregnated glass microspheres via intra-arterial injection. Selective brachytherapy is thereby delivered to a selected area of liver with low toxicity to surrounding tissue. Various studies have demonstrated the safety and efficacy of Y-90 therapy [62,63]. A recent comparative analysis showed a 58% tumor response rate in T3 stage tumors [64]. Prospective analysis is needed, but TARE-Y90 use is likely to become an important pretransplant therapy, especially in providing a prolonged response in advanced tumors not meeting criteria.

Much of the literature evaluates tumor response and subsequent downstaging after treatment, and suggests that response to treatment can lead to good outcomes [59]. Future studies must, however, address the question of definite survival benefit of LRT in the setting of advanced disease. The effectiveness of LRT at various HCC stages needs quantitative measurement in order to develop treatment regimens for patients whose HCC exceeds criteria for LT.

In addition, further investigations into the role of systemic chemotherapeutic agents will impact future management of patients awaiting

LT. The multikinase inhibitor sorafenib has been shown in a multicenter trial to increase median survival and slow disease progression [65]. While its safety is under investigation, a Markov model quantifying the cost-to-benefit ratio of chemotherapeutic regimens concluded that the use of sorafenib offered a cost benefit, compared with no treatment for T2 stage disease, especially when median time to transplant is <6 months [66].

In 2003, a systematic review of randomized trials for unresectable HCC was published showing a survival advantage to TACE for unresectable HCC when used as a palliative therapy, which suggests its role in improving survival in advanced disease [67]. In a 1997, prospective study of the effect of TACE on preoperative downsizing for resection and transplant, there was an improvement in disease-free survival seen both after liver resection and transplantation. In particular, downstaging those tumors >3 cm was associated with survival similar to that of patients who presented with less extensive disease [60]. A randomized controlled trial, however, is needed to definitively address this question.

• Pretransplant hepatic resection

Tumor resection continues to be a first-line treatment option for HCC patients who have preserved liver function, and who do not

otherwise have contraindications. Worldwide, approximately 25% of HCC-diagnosed patients are eligible for both resection and LT and are evaluated first for resection. This proportion is much smaller in the Western population, where patients presenting with surgically curative disease are fewer. Especially for patients aged >65 years, liver resection offers a no-wait, low-mortality treatment option. For patients meeting the Milan criteria, the 5-year survival rates after resection are equivalent to that after LT, although disease recurrence is significantly higher after resection [41]. In those whose resection pathology is unfavorable due to high grade differentiation, microsatellitosis or microvascular invasion, pre-emptive salvage LT may be attempted [68], although this is not standard practice due to lack of a system of allocation of organs to these patients given the high risk of recurrence.

Regarding salvage LT, there have been two series to evaluate outcomes, with conflicting results: Belghiti's group studied 107 patients who underwent LT for HCC; 70 patients received primary LT, and 18 underwent liver resection followed by secondary LT, with the observation that there were no 3- or 5-year survival differences between primary and secondary liver transplantation [69]. A second, larger series by Adam *et al.* observed 358 patients, of which 98 underwent resection, and 195 primary LT. Operative mortality of LT following resection was significantly increased at 28.6 versus 2.1% after primary LT. Recurrence of disease was more frequent after secondary LT (54%) versus after primary LT (18%). The observed 5-year survival was slightly worse in the hepatectomy group, 50 versus 61%. Importantly, initial therapy with liver resection can significantly diminish the patient's qualification for salvage LT, with only 25% of the resection group having transplantable recurrence of disease [70].

A Markov model developed to evaluate the balance between harm to resection patients and benefit to waiting list patients of primary versus salvage LT concluded that primary LT has survival advantages, provided that post-transplant survival continues to be high. Consideration of LT early for HCC patients would improve survival in a population where the prevalence of HCC is low and hence the number of potential organs to be diverted to the non-HCC population is small. For instance, in the USA, where 10% of the waiting list population have HCC,

and median time to transplant is 90 days, the potential harm to HCC patients to undergo hepatic resection outweighs the benefit of diverting organs from HCC patients to non-HCC patients [71]. In some European countries where the proportion of HCC patients on the waiting list population is higher, the benefit of diverting HCC patients from primary LT to resection resulted in an increase in survival, as organs were directed to non-HCC patients, for an overall survival benefit for the population.

Although complication and survival rates appear to be worse in patients undergoing salvage transplantation, in a large series, the implementation of resection followed by salvage LT for recurrence has been shown to be effective [72]. Especially in the setting of continued shortage of available organs for LT, this regimen of therapy has become more widespread in use. The alternative, pre-emptive approach to LT in high-risk patients is limited by variable procurement rates and prioritization policies. Given these logistical limitations, salvage LT for recurrence after resection is to be preferred over a pre-emptive approach [73,74].

• Beyond the Milan criteria

In a recent international consensus report, the Milan criteria was recognized to remain the benchmark for patient selection and its application is strongly recommended, while there is some evidence to support a modest expansion of the criteria to achieve comparable survival rates [75]. The Milan criteria, therefore, continues to be the gold standard by which candidacy for LT for HCC is determined. Improvements in post-transplant survival can be attributed to the optimization of patient selection offered by the Milan criteria. Experiences suggesting that the restrictive criteria may exclude patients from LT who would otherwise benefit from complete liver replacement, and the advancement of LRT to effectively downstage advanced disease have called for an expansion of these criteria by various groups. It is notable that most of these criteria rely on radiographic staging and therefore are subject to limitations thereof, which has been the reason for slow progress in expanding the existing criteria.

• UCSF

The most widely adopted expansion of criteria of clinical significance has been from the group in UCSF, with the introduction of size criteria

of a single tumor ≤ 6.5 cm or up to three tumors with the largest not exceeding 4.5 cm, and a total tumor diameter ≤ 8 cm in the absence of visible invasion of vessels [26]. These criteria were also derived from observing the pathology of explanted livers, given the phenomenon of understaging based on imaging criteria. Of the 168 patients studied, 130 patients met the Milan criteria and had a 5-year recurrence-free survival of 90%, while the 30 exceeding Milan but meeting UCSF criteria had a survival of 94% ($p = 0.58$).

Duffy *et al.* at University of California, Los Angeles evaluated 467 patients, of which 173 patients met the Milan criteria, 185 patients were within UCSF criteria, and 109 patients exceeded both criteria. Of note, these patients were not evaluated for response to pretransplant therapy prior to transplantation. The 5-year survival for those within Milan criteria was 79 versus 64% for those within UCSF criteria ($p = 0.061$). Staging based on explant pathology showed 5-year survival rates of 86% for disease meeting Milan criteria versus 81% for those within UCSF criteria [20]. Overall, the UCSF criteria is a modest expansion of the existing Milan criteria, and significant overlap inevitably exists between the two criteria.

• Toronto

The University of Toronto group has also challenged the restrictiveness of the Milan criteria, using preoperative biopsy pathology to determine candidacy for transplant. Criteria included imaging studies ruling out vascular invasion, tumor confinement to the liver, and pathology showing HCC that was not poorly differentiated. Results revealed an overstaging phenomenon in 23% of patients who were deemed to be beyond Milan criteria, and understaging in 30% of patients within Milan criteria. They saw no survival difference between patients meeting criteria (5-year survival of 72%), and those exceeding criteria (5-year survival of 70%). Disease-free survival was also comparable: 70% in patients meeting, and 66% in those exceeding Milan criteria. The institution of a protocol for preoperative biopsy to exclude patients with poorly differentiated tumors and bridging therapy saw an improvement in survival: from a 5-year survival rate of 61 to 79%, and a similar increase in the 5-year disease-free survival: 58 to 76%. The introduced criteria had no survival effects on patients meeting Milan criteria [76].

• Up-to-seven

The authors of the original Milan criteria answered various groups' challenges to the restrictions of the selection criteria by introducing the up-to-seven criteria, in which a sum of the size (in centimeters) of the largest tumor and the total number of tumors was obtained, thereby attempting to expand on the existing Milan criteria. In a large retrospective cohort study of LT patients with HCC beyond Milan criteria, good outcome has been shown with a redefined limit as defined by the absence of vascular invasion and the 'up-to-seven' principle [77]. This new proposal calls for a sum of the combination of size and number covariates to be ≤ 7 . For instance, four nodules up to 3 cm ($4 + 3 = 7$) or a single nodule up to 6 cm ($1 + 6 = 7$) would be acceptable for LT. The limitation of this proposal is its basis on explant pathology, rather than preoperative imaging findings. A recent single study experience demonstrated a significantly lower survival rate in patients meeting the up-to-seven criteria group compared with those within Milan criteria, suggesting that more experience is necessary before wide application [78].

In patients who were outside of Milan but within the up-to-seven criteria, an overall 5-year survival of 71.2% was seen, comparable with the 76.1% seen in patients within Milan, and significantly higher than the 64% survival for patients exceeding up-to-seven criteria. The comparability of the 5-year survival rates was seen only in tumors that lacked microvascular invasion, making preoperative imaging assessment crucial [77].

• France

The French experience reported the value of incorporating serum alpha-fetoprotein (AFP) levels, along with size and number criteria in order to improve the existing predictive model. Results confirmed that AFP level was an independent predictor of recurrence, and also associated with vascular invasion and tumor differentiation. A model taking tumor size, number and a log of the serum AFP was proposed for adoption [79].

Future developments in this area of criteria expansion are likely to include calculation of total tumor volume, associated serum AFP levels and pathologic characteristics to generate a composite score to encompass as many features of the tumor as possible. Combined total tumor volume/AFP score was shown to have predictive

value in post-transplant survival, and may be a way to expand on the currently restrictive Milan criteria [80].

Living donor transplantation

In the pre-MELD era, when HCC patients were disadvantaged in organ allocation, living donor transplantation was explored as an option to minimize wait time and thereby the potential for disease progression while on the waiting list. Decision analyses showed a survival advantage in utilizing living donor LT (LDLT) in patients expected to be on the waiting list for 7 months with early stage HCC [37,81]. With the implementation of MELD and the awarding of priority points for patients with HCC, interest in live donor LT waned, given the high risks associated with the donor operation. However, the number of patients awaiting LT steadily grows, while organ shortage continues. Regional variation in drop-out rate and disease progression on the wait list has been demonstrated, with a range of 6.8% in Region 6 to 28.6% in Region 9 (Figure 3) [36]. Renewed interest in living organ donation is observed, especially in US centers where MELD scores at listing are high.

Recurrence of HCC after LDLT was found to be high in several studies. In a cohort study performed by Kulik *et al.*, tumor recurrence after adult-to-adult LDLT was found to be 27%. Of 63 patients, 56 met Milan criteria by imaging criteria, but by explant pathology, 88% had more advanced stage disease, reiterating the issue of the understaging phenomenon by pretransplant imaging [82].

An analysis of the A2ALL study by Berg *et al.* concluded that live donor transplant did not improve survival. Stratification and analysis by MELD yielded the conclusion that overall, LDLT recipients had a survival advantage, with 56% reduction in mortality as compared with those undergoing deceased donor LT. However, in the subgroup of patients with HCC and a MELD score <15, there was no survival benefit of LDLT. Post-transplant survival was not significantly different between the living versus deceased donor organ recipients [83]. However, an observed higher rate of recurrence was seen in those who received LDLT, with a likely explanation for such difference as being differences in tumor characteristics, pretransplant management and wait time [84].

A meta-analysis performed at the University of Toledo (OH, USA) studied the outcomes of

LDLT as compared with standard, deceased donor transplantation (DDLT). Comparable 5-year overall and disease-free survival rates, and defined time point recurrence rates were observed, supporting the use of LDLT for the treatment of HCC, especially those meeting Milan criteria [85].

Concerns over the reportedly higher recurrence rates after LDLT as compared with DDLT raised by the A2ALL study, and as evidenced in a systematic review and meta-analysis performed in Toronto [86] led to a study focusing on the outcome of recurrence and overall survival by Sandhu *et al.* of the same Toronto group, which showed no significant difference between the two groups [87]. The LDLT group was far smaller in size (17% of patients receiving LDLT), however, and a better powered study is needed that can definitively confirm or disprove the question of higher recurrence rate in either type of graft.

In the international consensus report from 2012, living donor transplantation was recommended to be performed in centers of excellence with experience in obtaining acceptable outcomes. Graft failure after LDLT may qualify patients for retransplantation only for HCCs within accepted criteria for DDLT [75].

Figure 3. Organ Procurement and Transplant Network regional map. The states comprising each region are as follows: region 1: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Eastern Vermont; region 2: Delaware, District of Columbia, Maryland, New Jersey, Pennsylvania, West Virginia, Northern Virginia; region 3: Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, Puerto Rico; region 4: Oklahoma, Texas; region 5: Arizona, California, Nevada, New Mexico, Utah; region 6: Alaska, Hawaii, Idaho, Montana, Oregon, Washington; region 7: Illinois, Minnesota, North Dakota, South Dakota, Wisconsin; region 8: Colorado, Iowa, Kansas, Missouri, Nebraska, Wyoming; region 9: New York, Western Vermont; region 10: Indiana, Michigan, Ohio; and region 11: Kentucky, North Carolina, South Carolina, Tennessee, Virginia.

Living donor transplants are much more prevalent in the Asian countries, where cultural and religious beliefs dampen enthusiasm for DDLT, and therefore, there is greater experience in the area of living donor programs. Given the technically challenging operation involved in LDLTs, and the significant risks to the donor, who is by definition otherwise healthy, the use of LDLT has not thrived in the USA as much as it has in other parts of the world.

Immunosuppression in HCC

Post-transplant immunosuppression has a deleterious effect on malignancy – both the risk of recurrence and the development of new tumors. The dose-dependent effect of calcineurin inhibitors on the post-transplant risk of recurrent HCC has been demonstrated [88]. Initial experiments with rapamycin (sirolimus) in animals were encouraging, as it was shown to be an effective immunosuppressive with antitumor properties via pathways that block angiogenesis. During Phase II trials of the drug, however, there were reports of hepatic artery thrombosis and infectious complications leading to death, and the US FDA placed a black box warning on sirolimus for use in transplant patients. There have since been further studies that refuted these findings, and verified the safety of the drug [89,90], rekindling interest in the use of sirolimus as a primary immunosuppressive drug.

Toso *et al.* performed a study based on the Scientific Registry of Transplant Recipients, and saw that sirolimus-based maintenance immunosuppression was associated with higher rates of survival after LT for HCC (hazard ratio: 0.53; 95% CI: 0.31–0.92; $p \leq 0.05$). Analysis performed on non-HCC LT patients showed worse survival, confirming the cancer patient-specific benefits of the drug [91]. A group in Germany is currently conducting a randomized control trial evaluating sirolimus use for immunosuppression in post-transplant HCC patients [92]. Everolimus is also emerging as the subject of active investigations in the field of chemotherapeutic approaches. Based on these findings, the standard postoperative immunosuppression regimen for patients undergoing LT for HCC may change.

Conclusion

The developments in the field of liver transplantation for the treatment of HCC parallel the history of liver transplantation itself. While the first

two decades saw advances in technique and the resultant improvements in survival, subsequent optimization of patient selection and nonsurgical treatment options have been the focus of recent studies and responsible for further improvements in outcome.

Liver transplantation continues to be the best treatment for HCC, for the removal of malignancy and of the diseased liver, which can continue to harbor malignant potential. However, due to limited supplies of adequate organs, it is necessary to identify those patients most likely to benefit from total liver replacement and have good long-term outcomes. Continuing to develop optimal modes to identify adequate candidates through expansion of the Milan criteria, and exploring additional parameters such as accurate measurement of tumor volume and biologic characteristics of the tumor will be important discoveries to make.

Neoadjuvant and adjuvant therapies to prevent progression and recurrence of disease are also under heavy investigation, but so far there is a lack of prospective studies in this area – specifically, in the evaluation of the long-term survival benefits of pretransplant LRT. Adjunct therapies should no longer be used merely for the purposes of selecting for tumors with favorable biology, but also as effective therapeutic modes to address all tumor stages for effective oncologic treatment in addition to surgery.

The ever-present need for more donor organs is an issue that is not specific to the treatment of HCC. Continued work is needed to expand the donor pool, including ways to salvage damaged organs, better preservation methods, use of living donors, and split liver transplantation.

Although many of the aspects of liver transplantation surgery have largely been solved over the years, many technical, pharmacological and policy challenges have yet to be resolved for the optimal treatment of patients with HCC. Especially in the setting of the realities of recent healthcare reforms in the USA, more efficacious use of resources while maximizing outcomes will be necessary.

Future perspective

With the recent changes in US healthcare policies, there is likely to be increasing pressure placed on researchers, clinicians and industries to optimize resource allocation to benefit patient care. The overwhelming cost associated with liver transplantation for HCC is a reality; and

further advancements in the areas of adjunct therapy, chemotherapeutic and immunosuppressive agents, and ways to expand the donor pool are needed in order to maximize the benefits to patients and society as a whole. With further elucidation in these areas, more comprehensive and concise indications for liver transplantation will emerge to replace the current size/number criteria. Protocolization of pretransplant and post-transplant therapies will also become necessary, as quantitative outcomes data is generated on these adjunctive therapies. In addition, advances in organ preservation and salvage will offer tremendous potential benefit. *Ex vivo* perfusion techniques have been the subject of intensified research in various centers, with the most

recent update from the Oxford group, where successful large animal studies have already been completed [93]. Furthering of such advances will be useful for not only HCC patients, but all LT candidates.

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