Review Article

Patient selection in liver transplantation for hepatocellular carcinoma

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Abstract: Liver transplantation is the best therapy for selected patients with unresectable hepatocellular carcinoma (HCC). The worldwide incidence of the disease and the success of liver transplantation have produced a high demand, which has led different countries to adopt heterogeneous policies to allocate deceased donor livers for these patients. Even though tumor burden is the criteria with strongest evidence, there is continuous evolution of the interaction of factors that can improve the prediction of disease recurrence and long-term survival, such as tumor size, number of nodules, tumor volume, cancer-related symptoms, alpha fetoprotein serum level, imaging studies, pretransplant biopsy, response to liver-directed therapies and waiting time. In this manuscript, we summarize recent literature on the selection criteria of candidates with HCC undergoing liver transplant evaluation around the world. We review the evidence behind deceased donor liver allocation systems in different countries and the current role of living donor liver transplantation (LDLT). The largest studies come from United Network for Organ Sharing (UNOS) and European databases, however, there is high-impact data coming from Eastern countries with high HCC incidence and high-volume transplant centers, such as China, India, Japan, and South Korea. Soon, a slow shift towards transplant survival benefit in combination with overall survival may be observed in the allocation policies around the world.

Keywords: Hepatocellular carcinoma (HCC); liver cancer; liver transplantation; liver transplant

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Introduction

Liver transplantation is currently recommended for patients with unresectable very early (Barcelona Clinic Liver Cancer stage, BCLC 0), early (BCLC A) and highly-selected intermediate (BCLC B) and advanced (BCLC C/D) stages of hepatocellular carcinoma (HCC) (1). Liver transplantation on unselected patients with HCC led to disastrous results during the early days of transplantation. The University of Pittsburgh group reported encouraging results among patients undergoing deceased donor liver transplantation for nonmalignant liver diseases in the 1980's with incidental HCC findings in the explant (2,3). From this early experience, along with inferences from studies on HCC liver resection (4,5), the Milan group developed the first morphologic selection criteria for unresectable disease, demonstrating consisting 4-year survival after

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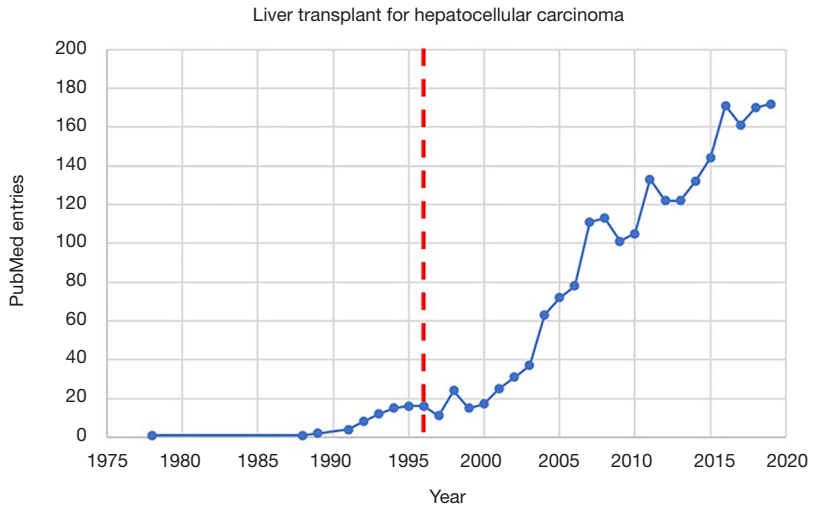

Figure 1 PubMed entries per year on liver transplantation for hepatocellular carcinoma. Note the increase since the publication of the Milan criteria by Mazzaferro *et al*. in 1996 (red dotted line) (6).

transplantation for patients with one lesion (≤5 cm) or up to three lesions (largest ≤3 cm) (6). The 'Milan criteria' led to dramatically reduced HCC recurrence rates after transplantation and the number of cases and publications on transplantation for HCC over the following decades exploded (*Figure 1*).

Yet, HCC still recurs in patients within Milan criteria at a low rate and transplantation provides the best therapy for selected patients beyond these criteria. These observations have led to an evolving refinement in transplant eligibility criteria, together with improvements in perioperative care, imaging studies, surgical technique, and long-term management. This review will briefly summarize the most important clinical developments over the last decade on patient selection in transplantation for HCC in adult patients.

Deceased donor liver transplantation

Transplantation requires the use of an allograft from a cadaveric or living donor. Living donor liver transplantation (LDLT) for HCC will be discussed in a different section. Deceased donor liver transplantation for HCC reduces the available pool of allografts for patients with endstage liver disease without cancer. Patients with HCC must have a risk of progression out of criteria equivalent to the risk of death of patients with endstage liver disease and a similar expected 5-year survival to access deceased donor livers. The patients with very early HCCs exhibit the highest 5-year survival after transplantation, however, they have the lowest risk of dropout and the lowest survival benefit from transplantation (7). For example, patients with single lesions ≤3 cm, complete response to liver-directed therapies and alpha-fetoprotein (AFP) level ≤ 20 ng/mL after liver-directed therapies, have a 1- and 2-year HCC progression risk beyond Milan criteria of 1.6% and 1.9%, respectively (8); therefore, even though 5-year survival would be excellent, HCC-specific access priority to deceased donor livers in this group of patients may not be justified (9). Multiple markers have been used as surrogates of tumor biology to predict HCC recurrence and survival after transplantation, which have led to different deceased donor allocation policies in several countries. Many of these risk factors are indirect makers of microvascular invasion and/or poorly differentiated tumors. The rationale for a country to use a given criteria is based on its allograft supply/demand relationship, with more stringent criteria being used in countries with deceased donor organ shortage, whereas countries with lower demand and/or higher availability of organs may decide to a less stringent criteria. For example, the United States of America (USA) adopted the Milan criteria in 2002 and continued to use only Milan criteria for 15 years, even though the Milan group stopped using such criteria several years before and there was growing evidence for potential expansion; however, the high demand of deceased donor livers did not justify modification of HCC

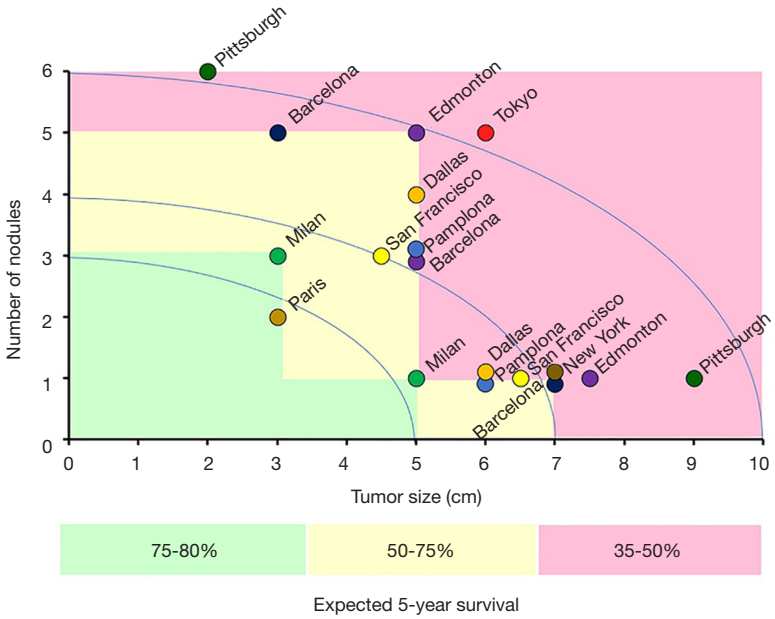

Figure 2 Center-based selection criteria for liver transplantation according to size and number of nodules of hepatocellular carcinoma. Modified and updated from original (11,12). Note the increase in the yellow area due to inclusion of two studies (13,14).

allocation criteria, until the evidence of excessive access of patients with HCC over patients with endstage liver disease without cancer led to significant changes in their allocation system.

Tumor burden

Tumor burden measured by the size and number of nodules alone were the basis of patient selection in the late 1990's and the 2000's, with multiple groups reporting different criteria, but the limit to which these criteria could and should be expanded was not clear. A Markov model suggested that the adverse effects of expanding deceased donor liver transplantation tumor burden criteria beyond Milan would outweigh its benefits if the expected 5-year overall survival of a patient transplanted outside Milan criteria was <61% (10).

The Metroticket international database (updated on *Figure 2*) was a milestone study that included 1,556 patients from 36 transplant centers in 9 countries and demonstrated that the recurrence rate of tumors within Milan with microvascular invasion and/or poorly differentiated pattern was similar to tumors within Milan without these features; however, tumors outside Milan with microvascular invasion or poorly differentiated pattern had a higher risk of recurrence (15), showing the need for other biological markers beyond tumor burden and the identification before transplantation of tumor differentiation and microvascular invasion as major HCC recurrence predictors and selection criteria. Patients fulfilling the "up-to-seven" criteria in this study (HCC with seven as the sum of the size of the largest tumor in centimeters and the number of tumors, ej. one 6 cm tumor, 1+6=7) had a 5-year survival of 71.2% (73.3% within Milan, P=NS) (15). An online calculator based on the study database is available (http://www.hcc-olt-metroticket.org/), which allows to calculate 5-year survival according to preoperative images or postoperative findings.

Serum AFP

Serum AFP has long been used as a tumor marker for HCC (16). Initially a diagnostic/screening tool, AFP has progressively evolved into a marker of tumor biology and is now included as a HCC selection criteria for transplantation in some regions and countries. An analysis of the French National Program demonstrated that the interaction of serum AFP levels and tumor burden is a better predictor of HCC recurrence than the Milan criteria. Patients within Milan criteria and AFP levels >1,000 ng/mL have a three-fold higher risk of HCC recurrence, while patients exceeding Milan criteria and serum AFP levels <100 ng/mL have similar risk of recurrence to patients within Milan

criteria (17). A serum AFP cutoff level >1,000 ng/mL excludes only 4.7% of HCC patients and reduces overall recurrence rate by 20% (18). Among patients within Milan criteria in a United Network for Organ Sharing (UNOS) region in the USA with long waiting time, a AFP slope ≥7.5 ng/mL per month was associated with microvascular invasion and HCC recurrence after transplantation (19).

A UNOS database analysis of 45,267 patients demonstrated that serum AFP levels above 15 ng/mL was positively associated with increased risk of death after transplantation for HCC in a dose-dependent effect for each group analyzed: serum AFP 16–65 ng/mL, adjusted hazard ratio =1.38; AFP 66–320 ng/mL, adjusted hazard ratio=1.65, and; AFP >320 ng/mL, adjusted hazard ratio =2.37 (20). Patients beyond Milan criteria and serum AFP 0–15 ng/mL had similar survival to patients without HCC, while patients within Milan criteria and serum AFP ≥66 ng/mL had an increased risk of death after transplantation compared to patients without HCC (adjusted hazard ratio =1.93). Furthermore, patients whose serum AFP level decreased after liver-directed therapies while on the waitlist (from >320 to ≤320 or 16–320 to 0–15 ng/mL) had no excess risk of death after transplantation. In contrast, patients with rising serum AFP level (from 0–15 to ≥16 ng/mL or from 16–320 to >320 ng/mL) had a very significantly elevated risk of death after transplantation compared to patients without HCC (20). Two separate analysis of the Scientific Registry of Transplant Recipients by the same corresponding author have identified a cutoff of serum AFP level of 400 ng/mL to have an area under the curve of 0.7 to discriminate the risk of HCC recurrence after transplantation (21-23). The same cutoff was used by a center in China (24). Patients with serum AFP levels >400 ng/mL that decrease to ≤400 ng/mL after liver-directed therapies have similar dropout rate and 3-year survival as patients with initial AFP ≤400 ng/mL, even if the initial level was ≥1,000 ng/mL (23).

Based on these data, UNOS modified their criteria for HCC exception points in relation to AFP. Candidates with lesions meeting Milan criteria, but with an AFP greater than 1,000, are not initially eligible for a MELD exception points. Candidates with AFP <500 after liver-directed therapy are eligible for MELD exception points. Candidates with an AFP ≥500 at any time following liver-directed therapy are referred to the National Review Board (25).

Another UNOS database analysis of 7,491 patients listed with HCC-specific priority analyzed the interaction of the MELD score, serum AFP level, number of lesions and maximum tumor size (26). This study showed that serum AFP was an independent predictor of survival after LT and its inclusion with the variables of liver function (MELD) and tumor burden could help to balance the priority of HCC and endstage liver disease in the waitlist (26). The authors named this "MELDEQ score", but like other modifications for MELD in the setting of HCC, it has not been incorporated into national allocation policies (27-31).

Mazzaferro led a binational study group that updated the Metroticket criteria in 2018 (version 2.0) (32). Through competing-risk regression of training set from 3 Italian centers, the sum of tumor number and size (in centimeters) and AFP serum level were significantly associated with HCC-specific death. For patients with HCC to have a 70% chance of HCC-specific survival 5 years after transplantation, their level of AFP should be <200 ng/mL and the sum of number and size of tumors should not exceed 7; if the level of AFP was 200–400 ng/mL, the sum of the number and size of tumors should be ≤5; if their level of AFP was 400–1,000 ng/mL, the sum of the number and size of tumors should be ≤4. This model was validated with cohort from China, showing an accuracy of 72% (32).

Additional serum markers associated with lower 5-year survival after transplantation for HCC include: neutrophil-to-lymphocyte ratio >5, AFP-L3 >35%, and des-γ carboxyprothrombin >7.5 ng/mL or ≤400 mAU/mL (33-35), however, none of these alternative serum markers have become widespread used.

Imaging findings

Imaging studies are readily available in patients with HCC evaluated for liver transplantation. Several studies have assessed the correlation of imaging findings with HCC recurrence rate and microvascular invasion.

The combination of three computed tomography findings has been described to be associated with microvascular invasion (36). The three findings are: persistence of discrete arterial enhancement within the tumor in the venous phase; a rim of hypoattenuation partially or completely circumscribing the tumor, and; focal or circumferential sharp transition in attenuation between the tumor and the adjacent liver parenchyma in the absence of a hypodense halo of internal arteries. These three findings have a diagnostic accuracy, sensitivity, and specificity in predicting microvascular invasion of 89%, 76%, and 94%, respectively (36).

Magnetic resonance imaging findings using gadoxetic

acid contrast enhancement have been associated with microvascular invasion and early HCC recurrence: arterial peritumoral enhancement, non-smooth tumor margin and peritumoral hypointensity on hepatobiliary phase. Early recurrence rates are higher in patients with two or three of these findings, compared to those with none (27.9% *vs.* 12.6%) (37).

Fluorodeoxyglucose (18FDG) positron-emitted tomography-computed tomography is not recommended for routine HCC staging, however, several studies have shown that hypermetabolic HCC are associated with microvascular invasion on the explant, as well as to higher risk of early HCC recurrence and extrahepatic metastases (38-43).

Pretransplant biopsy

Tumor differentiation has been used by centers in China, Italy and Canada as a selection criterion for HCC (24,44). The Toronto group developed a strategy selecting patients with HCC regardless of the size and number of lesions (45). Patients with cancer-related symptoms, and/or poorly differentiated or undifferentiated tumors on a preoperative percutaneous liver biopsy were excluded and aggressive liver-directed therapies was performed among patients with well- or moderately-differentiated tumors during the waiting period. Even though the initial reports were encouraging (46), the waitlist dropout rate was higher and intention-to-treat 5- and 10-year survival of patients was lower compared to patients within Milan criteria. Survival, however, was still acceptable as compared to patients with endstage liver disease without cancer, but the correlation of preoperative biopsies with explant studies is relatively poor (47), and there has been changes in the national/regional allocation policies in Canada, preventing from further development of this strategy (48).

Response to liver-directed therapies

Multiple options of loco-regional therapy are available and they are grouped as liver-directed therapies, including several forms of ablation (radiofrequency, microwave, cryoablation, irreversible electroporation), transarterial therapies (transarterial chemoembolization, transarterial radioembolization) and radiotherapy (stereotactic beam radiotherapy, proton beam therapy). The response to liver-directed therapies predicts outcome after transplantation (49-51). Patients with stable or progressive disease after liver-directed therapies have a three-fold higher risk of recurrence compared to those with partial or complete response (17.6% *vs.* 5.3%, P=0.014) (52). The effect of liver-directed therapies response on HCC recurrence after transplantation is related to the treatment response and not to the number of treatments (53). Even when evidence for the effect of liver-directed therapies as a bridge to liver transplantation on dropout rate is limited (54), most centers provide liver-directed therapies for patients on the deceased donor waiting list. There is significant heterogeneity in the election of liver-directed therapies among transplant centers. Some centers advocate for transarterial chemoembolization due to the risk of needle-track tumor seeding with ablation (55), others advocate for percutaneous ablation when possible due to the risk of arterial injury with chemoembolization (56,57), while some centers advocate for a specific form of radiation therapy due to its prolonged effect (58), and others advocate for an aggressive approach using multiple techniques (59). Liver-directed therapies should be fashioned to the patient's tumor burden and liver function, as most forms of liver-directed therapies are only recommended for Child A or B patients with bilirubin <3 mg/dL.

The heterogeneity of deceased donor allografts availability across the UNOS regions in the USA has led to the observation that patients with short waiting time between listing and liver transplantation exhibit a higher risk of HCC recurrence after transplantation (60). The opposite is observed in regions with high waiting time, where there is a higher dropout rate due to HCC progression, but patients undergoing transplantation have a lower HCC recurrence rate and higher survival (61). This phenomenon has been interpreted as a 'test of time', where patients with unfavorable biology progress during wait time while those with favorable biology reach liver transplantation despite waiting after liver-directed therapies; this measure has become a marker of tumor biology. An excessively long period of waiting time could lead to HCC progression beyond transplantation criteria. A multicenter analysis from 3 centers in the USA showed that waiting time less than 6 months and more than 18 months was associated with increased 1- and 5-year risk of HCC recurrence after transplantation compared to a waiting time between 6 and 18 months (6.4% and 15.5% *vs.* 4.5% and 9.8%, respectively; P=0.049) (62). These observations have led to changes in the USA national allocation system for HCC.

An UNOS database analysis reviewed the initial, maximum and last tumor burden of patients with HCC listed for liver transplantation (63). Tumor burden was classified as: A, single HCC <2 cm; B, HCC within Milan;

C, HCC outside Milan within UCSF, and; D, HCC outside Milan and UCSF. The response to liver-directed therapies was critical for the risk of recurrence of HCC after transplantation (63). Using their data, the authors developed an online calculator (https://clifeuw.org/rhiml/), which can be useful in daily decision-making.

'Downstaging'

The concept of 'down-staging' into Milan criteria has long been discussed in the literature, however, by inducing partial or complete response of HCC by liver-directed therapies the stage of the tumor is not modified, only tumor burden, therefore, the correct term is 'down-sizing' (64). Although some groups have proposed higher rates of success and lower recurrence rate with a given strategy (65), there seems to be no significant difference as far as a partial or complete response is achieved and tumor burden falls under Milan criteria after liver-directed therapies (64). UNOS has established selection criteria for these patients based on the experience of the group of the University of California in San Francisco (66): one lesion >5 and ≤8 cm, two to three lesions with at least one >3 cm and ≤5 cm with total tumor diameter ≤8 cm, or four to five lesions each ≤3 cm with total tumor diameter ≤8 cm. In an UNOS database analysis, including 3,819 patients, Mehta *et al*. found that 422 patients who underwent down-sizing were within UNOS criteria and 121 were outside UNOS criteria (67). Three-year survival was not different when patients within UNOS down-sizing criteria were compared with patients within Milan criteria (79.1% *vs*. 83.2%, P=NS), while patients outside UNOS criteria had statistically lower 3-year survival (71.4%, P=0.04). However, the risk of HCC recurrence was higher in patients undergoing downsizing before transplantation and further higher among patients outside criteria (Milan 6.9%, UNOS 12.8% and outside criteria 16.7%). Considering only patients within UNOS criteria, 3-year survival was higher among regions with a longer waiting time (92.3% for regions with median time >9 months *vs*. 78.7% for regions with median time <3 months) (67).

Instead of the number and size of nodules, the calculated total tumor volume has been proposed as a tumor burden selection criteria, considering ≤115 cm^3 as a cutoff, which is equivalent to a single lesion of 6 cm (68). Patients beyond Milan criteria had a higher waitlist dropout rate and lower intention-to-treat survival, but similar survival after LT (68). Three of five Canadian regions have adopted total liver volume/AFP criteria for the allocation of deceased donor livers for patients with HCC, and a forth region (Ontario) have modified such criteria (total liver volume <145 cm^3 and AFP <1,000 ng/mL) (48).

The future of patient selection for deceased donor liver transplantation

The application of the USA model for deceased donor liver allocation was applied in Argentina in the late 2000's. This experience represents a cautionary tale for the reproduction of liver allocation systems in countries (or regions) with different donation dynamics and resource availability. After MELD implementation, waitlist mortality increased (particularly among patients with chronic liver disease a low MELD score) while patients with HCC had the highest probability of being transplanted (up to 84% compared with 3% for patients with chronic liver disease and a low MELD score) (69). Even though the increase in waitlist mortality may be multifactorial, the same phenomenon among patients with HCC has been observed in the US, which has led changes in the allocation system through the use of median MELD score for the region for patients with HCC fulfilling exception criteria (25).

The risk of HCC progression beyond transplantation criteria and the 5-year survival of patients with HCC undergoing liver transplantation have been the variables used to determine deceased donor liver allocation. However, it is progressively clear that patients with smaller/earlier tumors have a very high 5-year survival but low to no survival benefit from transplantation. On the contrary, patients with larger, more advanced tumors have a lower 5-year survival after transplantation but a higher overall survival benefit. A very forward-thinking intention-to-treat analysis of 2,103 patients from 10 transplant centers in 5 European countries demonstrated the interaction of age, HCC-specific criteria (Milan criteria, serum AFP and response to liver-directed therapies), endstage liver disease severity (MELD score) and waiting time in the survival benefit of transplantation for HCC (70). The study found that patients with 3 or 4 factors (biological MELD ≤13, HCC within Milan criteria, complete response or disease progression after liver-directed therapies and AFP ≥1,000 ng/mL) showed no survival benefit, while patients with 2, 1 and no risk factors exhibited 20, 40 and 60 months of survival benefit, respectively, thereby proposing varying degrees of priority to access transplantation and even delisting for patients with HCC in the waiting list (70). For instance, patients within Milan criteria with complete response to liver-directed therapies

and biological MELD score ≤13 would be delisted, while patients outside Milan criteria with partial response to liver-directed therapies, biological MELD score >13 and AFP <1,000 ng/mL would access a deceased donor liver allograft with the highest priority. On the other hand, patients outside Milan with progressive disease after liver-directed therapies and AFP ≥1,000 ng/mL would be delisted, while patients within Milan with stable disease on liver-directed therapies, MELD score >13 and AFP <1,000 ng/mL would also access a deceased donor liver allograft with the highest priority (70).

Given the growing evidence, changes in the deceased donor liver allocation policies are likely to be observed worldwide during the following decade to favor a combination of survival benefit and 5-year survival instead of 5-year survival alone.

LDLT for HCC

The evidence supporting selection criteria based on tumor burden and markers of tumor biology for deceased donor live transplantation for HCC is robust. As explained before, this selection is mandatory to allocate deceased donor liver allografts, thereby obtaining the highest benefit from a scarce resource in the selected patients, while maintaining justice for the patients in the waiting list without cancer. However, these principles do not apply to LDLT, as the donor organ is readily available for a specific recipient. This situation has created controversy around LDLT for HCC and transplant centers have adopted different selection criteria; a full supplement of Liver Transplantation was dedicated to analyze this issue (71-73). Some authors have suggested tolerance to "slightly" lower benefit from LDLT (expected 40% 5-year survival) (74). A survey among transplant surgeons indicated that they would request a minimal projected 1-year survival of 79% (75), however, surveys amongst living donor candidates have reported a minimal acceptable survival after transplantation as low as 6 months (76). It is the opinion of the authors that transplant centers should use the same criteria for deceased donor and liver donor transplantation. Ethical principles of living donation in the setting of HCC are the same as for any other indication. In some instances, the transplant center selection criteria will be beyond those established by the national policies for deceased donor allocation, in which case the transplant center could congruently offer LDLT to the patient.

Living vs. deceased donor transplantation

The logistical differences and heterogeneous HCC selection criteria between deceased donor and LDLT have made it difficult to compare their outcome. Many authors have analyzed this issue (*Table 1*). Unfortunately, many studies have methodological issues. There is no prospective study evaluating the problem and most retrospective studies do not match patients based on either recipient or HCC-specific characteristics. Three meta-analyses have addressed the impact of each strategy on HCC recurrence (including between 7 and 29 retrospective studies) with diverging results (96-98). Properly matched studies report similar HCC recurrence after deceased and LDLT, while intention-to-treat studies show that LDLT offer similar or superior survival compared to deceased donor liver transplantation (85,86,93-95).

LDLT tumor burden selection criteria

Immediate allograft availability allows prompt transplantation after donor and recipient's work-up is completed. This has generated controversy regarding the benefit of an observation period as it has been described for deceased donor liver transplantation (99), while some LDLT groups have raised concerns regarding a higher risk of arterial complications after arterial-based liver-directed therapies (100). A retrospective analysis of patients with HCC undergoing LDLT after transarterial chemoembolization showed a survival benefit among patients with partial or complete response after an observation period of at least 2 months (101). However, there is no consensus as to whether or not LDLT should be delayed in order to assess liver-directed therapy response (102).

Liver transplantation for HCC in Japan is performed under selection criteria based on institutional and regional experience. The University of Tokyo reported 75% 5-year survival after LDLT among patients with ≤5 nodules, none >5 cm (5-5 rule) (103-105); while Kyoto University established a combination criteria of tumor number ≤10, maximal diameter of each tumor ≤5 cm, and serum des-gamma-carboxy prothrombin levels ≤400 mAU/mL, reporting 5-year HCC recurrence rate of 7% and 5-year of 82% (35).

LDLT is offered in Korea to any patient with HCC without distant metastasis. A single-center experience from Seoul, where >50% of LDLT are performed for HCC,

Table 1 Studies evaluating the outcome after deceased donor and living donor liver transplantation for hepatocellular carcinoma

Reference	Country	Year	Criteria	Patients DDLT/LDLT	Matching	Recurrence DDLT/LDLT	Survival DDLT/ LDLT	ITT survival DDLT/LDLT	Findings
(77)	USA	2004	NA	165/36	None	3-year 17%/26%	NA	NA	DDLT=LDLT
(78)	Korea	2005	NA	75/237	None	3-year 12%/18%	NA	NA	DDLT=LDLT
(79)	Hong Kong	2007	Milan/UCSF*	17/43	None	5-year 0%/29%	5-year 94%/58%	NA	DDLT>LDLT
(80)	USA	2007	Milan/UCSF*	34/58	None	4-year 0%/35%	4-year 64.7%/62%	NA	DDLT>LDLT
(81)	Germany	2007	UCSF	55/45	None	3-year 19%/25%	NA	NA	DDLT=LDLT
(82)	Italy	2009	Milan	154/25	None	5-year 10.6%/4.5%	5-year 76.7%/68.7%	NA	DDLT=LDLT
(83)	USA	2009	Milan	65/28	None	27%/44%	NA	NA	DDLT>LDLT
(84)	China	2010	NA	101/38	None	4-year 37%/38%	4-year 38%/45%	NA	DDLT=LDLT
(85)	France	2011	Milan/UCSF*	147/36	None	5-year 14%/12%	5-year 82%/73%	71%/73%	DDLT=LDLT
(86)	Canada	2012	Toronto	287/58	None	5-year 15.4%/17%	5-year 75.2%/74.6%	NA	DDLT=LDLT
				39/39	Sensitivity analysis	5-year 20.3%/12.5%	5-year 86.5%/79.3%	NA	DDLT=LDLT
(87)	USA	2012	Milan*	97/100	NA	5-year 11%/38%	5-year 66%/59%	NA	DDLT>LDLT
(88)	Korea	2014	UCSF	50/166	NA	5-year 6%/19.3%	NA	NA	DDLT>LDLT
(89)	China	2014	Milan*	80/40	Pair 2:1	5-year 29.1%/27.1%	5-year 66.6%/74.1%	NA	DDLT=LDLT
(90)	China	2014	Hangzhou	276/84	NA	5-year 54.7%/47.1%	5-year 38.3%/43%	NA	DDLT=LDLT
(91)	China	2014	Hangzhou	94/47	Pair 2:1	5-year 23.9%/19.7%	5-year 80.8%/87.7%	NA	DDLT<LDLT
(92)	Japan	2015	Milan*	50/133	NA	5-year /14.8%	5-year 63.5%/84.2%	NA	DDLT=LDLT
(93)	France	2017	NA	782/79	Cox model	5-year 11.2%/10.9%	5-year 73%/73.2%	5-year 66.7%/73.2%	DDLT<LDLT
(94)	Canada	2019	NA	632/219	NA	5-year 28%/72.2%	5-year 76%/79%	5-year 57%/68%	DDLT<LDLT
(95)	Hong Kong	2019	Milan/UCSF	187/188	Propensity score matched	19.5%/27.8%	5-year 84.4%/73.4%	5-year 40.8%/75.9%	DDLT<LDLT

*, study included patients outside criteria. NA, not available; DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation; UCSF, University of California, San Francisco.

reported expanding LDLT for "far advanced" HCC (106). The National Cancer Center in Korea has proposed specific criteria in LDLT for HCC through the combination of tumor burden (sum of diameter of lesions ≤10 cm) and a hypermetabolic tumor (107). Under this criteria, LDLT is performed ~15 days after staging with no bridging or downstaging therapy. An initial experience of 280 LDLT showed similar survival for patients fulfilling this criteria compared to patients within Milan criteria, while patients within Milan criteria and hypermetabolic tumors exhibited a trend towards lower survival (108).

Unique LDLT HCC experience

Macrovascular invasion is a contraindication in most Western centers, however, after initial experience in Eastern centers with LDLT, reports from Western countries are emerging. LDLT for HCC with macrovascular invasion was reported in three studies from different centers in Korea. Two of the three studies identified tumor thrombus in the major portal vein branches as a risk factor for HCC recurrence and survival, showing that macrovascular invasion of segmentary portal vein branches had limited impact on outcome (109,110). The three studies identified serum markers that may play a role in the selection of patients with macrovascular invasion for transplantation (109-111).

A multicenter international retrospective study evaluated the outcome of 30 patients after transplantation for HCC and macrovascular invasion after successful liver-directed therapies, reporting 5-year recurrence rate of 45.7% and 59.7% survival. Patients with response to liver-directed therapies and serum AFP ≤10 ng/mL after liver-directed therapy and before transplantation had a recurrence rate of 11.1% and 5-year survival of 83.3% (112).

Bile duct tumor thrombus is an infrequent finding associated with poorly differentiated tumors, microvascular and macrovascular invasion. Two meta-analyses of 11 studies identified similar short-term outcome after resection (1- and 3-year survival) to that of patients without bile duct tumor thrombus, but long-term survival is lower (mean difference –20 months) (113,114). A recent multicenter study from Korea and Japan demonstrated that the outcomes after liver resection for HCC with bile duct tumor thrombus were influenced by stage at presentation and underlying liver function, suggesting that the impact of biliary invasion on survival is less prominent than vascular invasion (115). Transplantation experience for HCC with bile duct tumor thrombus is very limited, mostly restricted to LDLT in Eastern centers. Two series of 8 and 14 patients (only 1 deceased donor liver transplant) were reported from Korea, observing a 5-year recurrence rate of 46.2–75% and 50% 5-year survival (116,117).

Similar to deceased donor liver transplantation, serum markers have been used to predict HCC recurrence after LDLT, without reaching widespread use (118-120). Other factors reportedly associated with HCC recurrence after LDLT include male donor sex, higher donor bilirubin and higher recipient platelet count, but the causal relationship of these statistical associations is unclear (121-123).

Conclusions

There is robust data to assess tumor burden, serum markers (AFP), imaging findings and response to liver-directed therapies as selection criteria to allocate deceased donor livers according to each country's donation rate. These criteria will likely continue to evolve in the following decade to include survival benefit as a variable along with 5-year survival. Downsizing HCC through liver-directed therapies into Milan criteria is growingly accepted worldwide. LDLT offers a viable option for patients with HCC in areas with a low donation rate and/or high HCC incidence, with similar recurrence rates and equivalent (possibly higher) intention-to-treat survival. The data from adult cirrhotic patients undergoing LT evaluation for HCC cannot be extrapolated to adult patients with normal livers and/or pediatric patients.

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Footnote

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