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REVIEW

Liver transplantation for hepatocellular carcinoma: Historical evolution of transplantation criteria

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Abstract

Liver transplantation (LT) for hepatocellular carcinoma is still a hot topic, and the main factor that is associated with the success of treatment is to determine the patients who will benefit from LT. Milan criteria have been defined 25 years ago and still is being used for patient selection for LT. However, in living donor LT, the Milan criteria is being extended. Current criteria for patient selection do not only consider morphologic characteristics such as tumor size and number of tumor nodules but also biologic markers that show tumor aggressiveness is also being considered. In the present review article, we have summarized all the criteria and scoring systems regarding LT for hepatocellular carcinoma. All criteria have 5-year overall survival rates that were comparable to the Milan Criteria and ranged between 60%-85%. On the other hand, it was seen that the recurrence rates had increased as the Milan criteria were exceeded; the 5-year recurrence rates ranged between 4.9% to 39.9%. Treatment of hepatocellular carcinoma needs a multidisciplinary approach. Ideal selection criteria are yet to be discovered. The same is true for treatment modalities. The goal will be achieved by a harmonic interplay between basic science researchers and clinicians.

Key Words: Liver transplantation; Hepatocellular carcinoma; Milan criteria; Expanded Malatya criteria

Core Tip: Hepatocellular carcinoma is the third most common cause of cancer-related deaths. Liver transplantation has an important place in the treatment of hepatocellular carcinoma. However, there is no consensus on which patients should receive a liver transplantation. For this reason, various criteria have been defined. In this study, we will discuss the criteria defined by our liver transplant institute in light of a literature analysis.

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INTRODUCTION

Currently, hepatocellular carcinoma (HCC) is the sixth most common cancer with 905677 new cases diagnosed annually. On the other hand, HCC is the third most common cause of cancer-related deaths causing 830180 deaths annually[1]. The main goal of treatment of patients with HCC is to provide prolonged and disease-free survival (DFS). Treatment options that will achieve this goal include many options, from minimally invasive interventional methods such as local regional treatments to highly complex treatment methods such as liver transplantation (LT). The success of treatment depends on the selection of patients that will benefit from the aggressive multimodality therapy. LT treats the underlying cirrhosis, and it is the gold standard treatment of the cancer. For LT, optimal patient selection criteria is the key to a successful outcome. Furthermore, living donor LT (LDLT) has revolutionized the treatment of HCC. LT from a living liver donor has a significant impact on patients with HCC. In patients with tumors within the Milan criteria, bridging procedures can be eliminated because patients do not have to wait on the deceased donor organ waiting list. On the other hand, in patients beyond the Milan criteria, the extended criteria can be chosen to optimally select the patient that will benefit most from the LT without risking the living donor. Since these patients do not have an impact on the waiting list, they can be rapidly transplanted. So far, this patient group has contributed to the accumulation of the data regarding the existing extended criteria that are available.

However, the demand for organs is overwhelmingly higher than the deceased donor organ supply. Therefore, using a valuable resource for patients with malignancy should be performed in accord with very strict criteria to choose the patient that will benefit the most from transplantation. In general, LT for any disease is considered acceptable if the 5-year survival rate is ≥ 50%[2,3]. Volk *et al*[4] stated that for HCC exceeding Milan criteria but within the University of California San Francisco (UCSF) criteria, the minimum overall 5-year survival rate requirement should be 61% so that it will not have a negative impact on other patients on the waiting list for non-malignant diseases. In 2020, the International Liver Transplantation Society Transplant Oncology consensus report stated that the minimum overall 5-year survival rate should be 60% for an acceptable result in LDLT for HCC[5].

However, the path from LT to definition of the current criteria has not been easy, and a lot of obstacles have been encountered and solutions have been developed. This resulted in development of diverse patient selection criteria and management protocols for approaching patients with HCC. Therefore, management of the patients with HCC up to the final point of LT forms the basis of all the auxiliary treatment methods including transarterial therapies, local ablative procedures and liver resections. The aim of the present review is to give a broad perspective regarding management of HCC prioritizing LT as the main treatment modality. Furthermore, we aimed to give a historical perspective regarding development of LT as a valid alternative for treatment of patients with HCC. Our main perspective is to convey our idea, which is that selection criteria that are and will be developed will never be ideal so they will be universally accepted. Therefore, our future perspectives are given at the end of our review to provide the future goals for the treatment of the disease in conjunction with LT.

HISTORICAL PERSPECTIVE: DEVELOPMENT OF THE PATIENT SELECTION CRITERIA BY PAUL-BROUSSE HOSPITAL AND THE EVOLUTION OF MILAN CRITERIA

The first LT was performed 58 years ago. This was a revolutionary therapeutic modality bringing hope to the treatment of patients with end-stage liver disease[6]. Initial LTs were performed in patients with advanced stage liver tumors. Only 1 patient amongst the first 7 LTs performed was due to liver disease without any malignancy. The remaining patients were diagnosed with HCC (3 patients), unresectable colorectal cancer metastasis (1 patient) and cholangiocarcinoma (1 patient)[7]. However, the results of the transplant technique were initially very poor, and physicians in the field had to go back to basic

science research to improve the transplant technique[7].

In 3 years, stable technique was established and longer survival rates exceeding 1 year were achieved. The results of these initial transplantations for HCC were not favorable. The longest survival was 400 d, and the patient died due to tumor recurrence. Initial dismal outcome after LT in patients with HCC resulted in the surgical community to declare that HCC was a contraindication for performing a LT[8]. However, studies on LT for HCC continued, and results showed that there was a correlation between the hepatic tumor burden and recurrence rates[9]. There were cornerstone studies showing efficacy and safety of LT in early-stage HCC[10]. LT provided a median overall survival of 16 mo (3-87 mo) in stage II HCC and 7.5 mo (2-20 mo) in stage III HCC[10]. First, definitive criteria were defined from Bismuth *et al*[11,12], and they have shown that less than 2 tumor nodules and a maximum tumor diameter less than 3 cm had lower recurrence when transplanted when compared to the resected patients. Criteria were named as the Paul-Brousse Hospital Criteria. LT using Paul-Brousse Hospital Criteria provided a 3-year DFS rate of 83%[12]. In the following years, Mazzaferro *et al*[13] defined the Milan criteria for selecting patients with HCC for LT. The Milan criteria includes tumors with no extrahepatic tumor involvement, without macroscopic portal vein invasion, solitary tumor ≤ 5 cm in diameter or a maximum of 3 tumors with each tumor diameter ≤ 3 cm. The patients with tumors that are within the Milan criteria had a 4-year overall survival rate of 85% following LT[13]. Currently, Milan criteria are used around the world to select patients with HCC for deceased donor LT (DDLT).

EXTENDING BEYOND THE MILAN CRITERIA: EXPAND OR NOT TO EXPAND?

Milan criteria depend on morphologic parameters, and it only provides a chance for LT to 30% of the patients with HCC[14]. However, various observations have shown that there are patients with tumors that are beyond Milan criteria, who have favorable outcomes after LT[15]. The idea of expanding beyond the Milan criteria spread rapidly among the transplant community.

In 2001, Yao *et al*[16] developed the UCSF criteria to extend the Milan criteria for patients with HCC. These criteria also depended on the morphologic criteria such as maximal tumor diameter and number tumor nodules. The UCSF criteria included solitary tumors ≤ 6.5 cm or a maximum of 3 tumor nodules with each nodule ≤ 4.5 cm or sum of diameter of all tumors ≤ 8 cm. The 5-year overall survival rate was 75.2% in patients within UCSF criteria after LT. The UCSF criteria extended the Milan criteria by 10% without causing a significant decrease in the long-term survival rates. In 2007, internal validation of the UCSF criteria came from Yao *et al*[17] on 168 patients. The evaluation was preoperatively done by radiologic evaluation. Thirty-eight patients exceeded the Milan criteria but were within the UCSF criteria and 1- and 5-year recurrence free survival rates were 92.1% and 80.7%, respectively. External validation was performed by Duffy *et al*[18] in 2007 on a cohort of 467 patients. Preoperative imaging showed that 173 tumors (37%) were within the Milan criteria, 185 (40%) were beyond Milan criteria but within UCSF criteria and the remaining 109 (23%) were beyond the UCSF criteria. The results of the study showed that patients with tumors within the UCSF criteria and Milan criteria had comparable 5-year survival of 79% and 64%; while the patients with tumors exceeding the UCSF criteria had a 5-year survival less than 50%[18].

In 2002, Barcelona Clinic Liver Cancer criteria were defined, and these criteria included tumors with a solitary nodule ≤ 7 cm or 3 tumor nodules each ≤ 5 cm or 5 tumor nodules each ≤ 3 cm[19]. There were two novel recommendations in Barcelona Clinic Liver Cancer criteria: First was the emphasis of the feasibility of LDLT in HCC and the second was the importance of response to downstaging by locoregional therapy. Therefore, the Barcelona Clinic Liver Cancer criteria was the first to combine the morphometric measurements with the biologic behavior of the tumors. The reported 5-year overall survival rates were above 50%[19,20]. In their study, the results of LDLT for HCC were better than DDLT for patients receiving planned liver grafts after combined multimodality treatment, which is especially important for patients with tumor beyond the Milan criteria.

In fact, the majority of the extended criteria that have been discussed in the following section were defined by centers that perform LDLT at a high volume (Table 1)[21-45]. As the new biomarkers have been incorporated to use during the evaluation of the patients with HCC, it was realized that tumor biology was more important in determining the prognosis of patients with HCC following LT. Kyoto criteria was one of the first to incorporate morphologic characteristics of the tumor with laboratory parameters such as Des-carboxyprothrombin. Des-carboxyprothrombin is also named protein induced vitamin K absence or antagonist II (PIVKA-II) and is a marker predicting the biologic behavior of HCC [23]. In 2011, Toronto criteria were developed. According to these criteria, a pretransplant tumor biopsy is performed and regardless of the size and the number of the tumors, LT could be performed for patients with tumors that do not have poor differentiation, no microvascular invasion, and no extrahepatic extension of the disease[34]. In 2016 the same group defined the extended Toronto criteria, which included absence of cancer related symptoms to the criteria[35]. In 2019 and 2020, Shimamura *et al*[38] and Ichida *et al*[45] defined the 5-5-500 criteria, which included tumors with a diameter ≤ 5 cm, number of tumor nodules ≤ 5 and alpha fetoprotein (AFP) ≤ 500 ng/mL.

Table 1 Features of liver transplant criteria for hepatocellular carcinoma and survival rates

Criteria	Single Tm LTD in cm	Multiple Tm as NN	Multiple Tm LTD in cm	TTD in cm	AFP in ng/mL	PIVKA II	Differ.	MiVi	LTD + NN	TTV in cm^3	GGT in IU/L	5-yr DFS criteria in, %	5-yr OS criteria, %	5-yr recurrence criteria, %
Paul-Brousse	3	1-2	3	-	-	-	-	-	-	-	-	83	83	-
Milan	≤ 5	2-3	≤ 3	-	-	-	-	-	-	-	-	82 (4 yr)	85 (4 yr)	8
UCSF	≤ 6.5	2-3	≤ 4.5	≤ 8	-	-	-	-	-	-	-	-	75.2	
BCLC	≤ 7	2-34-5	≤ 5≤ 7	-	-	-	-	-	-	-	-	-	80.2	23.8
Extended criteria	≤ 7.5	2-3	≤ 5	-	-	-	(> 5 cm with poor diff also excluded)	-	-	-		76.8 (4 yr)	82.9 (4 yr)	-
Berlin	≤ 6	No limit	≤ 6	≤ 15	-	-	-	-	-	-	-	64 (3 yr)	68 (3 yr)	-
Kyoto	≤ 5	2-10	≤ 5	-	-	≤ 400	-	-	-	-	-	-	86.7	4.9
Tokyo	≤ 5	2-5	≤ 5	-	-	-	-	-	-	-	-	94 (3 yr)	75	-
Onaca	≤ 6	2-4	≤ 5	-	-	-	-	-	-	-	-	64.6	-	-
Hangzhou	≤ 8	-	-	≤ 8	-	-	-	-	-	-	-	70.7	62.4	-
	> 8			> 8	≤ 400		Well/Moder							
Asan	≤ 5	2-6	≤ 5	-	-	-	-	-	-	-	-	-	76.3	13.6 (3 yr)
CUN	≤ 6	2-3	≤ 5	-	-	-	-	-	-	-	-	-	73	-
Valencia	≤ 5	2-3	≤ 5	≤ 10	-	-	-	-	-	-	-	-	67	9
Shangai	≤ 9	2-3	≤ 5	≤ 9	-	-	-	-	-	-	-	52.6	78.1	10.7
Kyushu	≤ 5	No limit	≤ 5	-	-	≤ 300	-	-	-	-	-	87	82.7	-
UpToSeven	≤ 6	-	-	-	-	-	-	Neg.	≤ 7	-	-	-	71.2	39.9
TTV/AFP[28]	-	-	-	-	≤ 400	-	-	-	-	≤ 115	-	-	Approximately 60 (4 yr)	-
Ext Toronto	No limit	No limit	No limit	-	-	-	Well/Moder	-	-	-	-	-	68	25.6
AFP-TTD	≤ 8	-	-	≤ 8	≤ 400	-	-	-	-	-	-	74.4	-	4.9
Samsung	≤ 6	2-7	≤ 6	-	≤ 1000	-	-	-	-	-	-	89.6	-	-
5-5-500	≤ 5	2-5	≤ 5	-	≤ 500	-	-	-	-	-	-	73.2	75.8	7.3
Malatya	≤ 6	No limit	≤ 6	-	≤ 200	-	Well/Moder	-	-	-	≤ 104	-	79.7	-
Exp Malatya	≤ 10	No limit	≤ 10	-	≤ 200	-	-	-	-	-	≤ 104	-	77.6	-

AFP: Alpha fetoprotein; BCLC: Barcelona Clinic Liver Cancer; CUN: Clinica Universitaria de Navarra criteria; DFS: Disease-free survival; Differ: Differentiation; GGT: Gamma glutamyl transferase; LTD: Largest tumor diameter; MiVi: Microvascular invasion; Moder: Moderate; NN: Number of nodules; OS: Overall survival; PIVKA II: Protein induced vitamin K antagonist II; Tm: Tumor; TTD: Total tumor diameter; TTV: Total tumor volume; UCSF: University of California San Francisco criteria.

Inonu University in Malatya has the highest volume of LDLT in Europe, and we are working extensively in the multimodality treatment of HCC[39,40,46-49]. Our recent studies concentrated on development criteria expanding the Milan criteria. Our criteria were called Malatya and expanded Malatya criteria[39,40]. The Malatya criteria included tumor with a maximum diameter ≤ 6 cm, AFP ≤ 200 ng/mL, gamma-glutamyl transpeptidase (GGT) ≤ 104 U/L and well/moderate tumor differentiation. We defined GGT as a biomarker to predict the tumor biology for the first time in the literature, which was a novel approach[39,40]. Expansion of the Milan criteria was 42.7% in expanded Malatya criteria[40], 19.0% in 5-5-500 criteria[29], 10.0% in UCSF criteria and 27.0% in Malatya criteria[39]. Isoenzyme type II of GGT has previously been suggested to be a surrogate for differentiation in HCC; for the first time we have shown GGT to have prognostic significance for patients with HCC that have undergone LT[50-54]. In Malatya criteria, tumor differentiation is another component that determines the prognosis of the patients. However, the differentiation status of the tumors is very hard to predict in the preoperative period. As an alternative we are currently studying the response rate of the tumors to downstaging procedures, and we are investigating the role of positron emission tomography computed tomography (PET-CT) in predicting the level of tumor differentiation[39]. The response to downstaging locoregional therapies and its implications will be discussed in the following sections.

During the analysis phase of the Malatya criteria, we observed that there were patients beyond the Malatya criteria, yet they had good prognosis following LT. In subgroup analysis we grouped patients according to the tumor diameters. Patients with a tumor diameter greater than 6 cm were analyzed. We defined expanded Malatya criteria as tumors that have a maximum tumor diameter ≤ 10 cm, AFP ≤ 200 ng/mL and GGT ≤ 104 IU/mL (normal range, 12–64 IU/mL)[40]. In summary, by using the expanded Malatya criteria we have increased the maximum tumor diameter to 10 cm. The tumor differentiation was not significant in our univariate analysis during the definition of the expanded Malatya criteria.

All the criteria that are defined above have an acceptable level of long-term overall survival rates well above 50%. However, the survival of the patients differs in accordance with different selection criteria depending on the inclusion of patients with advanced tumors. Furthermore, we still do not have an ideal selection criterion that has universal validity. In addition, a biomarker that predicts the biologic behavior of the tumors such as microvascular invasion or differentiation is needed for thorough clinical evaluation of patients with HCC. Survival data of different criteria and scoring systems are summarized in Table 2.

SCORING SYSTEMS

Accumulating research has shown that many parameters have an impact on the prognosis of the patients. Among these parameters are morphologic parameters such as the number and size of the tumors, serum biomarkers such as AFP, Des-carboxyprothrombin (PIVKA II), GGT, inflammatory

Table 2 Comparison of some improved criteria with Milan and expanded Malatya criteria on the basis of overall survival

Within criteria	Overall survival, %			
	1-yr	3-yr	5-yr	10-yr
Milan	88.8	86.2	81.9	72.5
UCSF	89	83	75	67
Up to Seven	90	86	78	69
BCLC	89	83	76	68
ETC	88	78	70	61
Hangzhou	88	79	70	61
Malatya	90.1	85.2	79.7	72.8

BCLC: Barcelona Clinic Liver Cancer; ETC: Extended Toronto criteria; UCSF: University of California San Francisco.

markers such as neutrophil to lymphocyte ratio and response to locoregional therapy. The selection criteria and scoring systems for HCC are similar in principle; they all predict the recurrence and survival of the patients following various treatment modalities[55-59]. The selection criteria are semi-quantitative determining high and low risk groups in terms of recurrence rates to determine whether the patient will benefit from a specific treatment modality, mainly LT[60]. However, scoring systems are more systematic and comprehensive. They define different stages of the disease that have different prognosis[60].

New scoring systems are being developed, combining all the above morphologic, biologic and inflammatory markers to optimize the selection of the patients with HCC for LT (Table 3). In 2012, Duvoux *et al*[55] from France defined a scoring system that they called the AFP model in which they incorporated AFP values to the morphologic characteristics such as tumor size and number. A score ≤ 2 was considered as low risk, and this scoring system is currently used for selecting patients with HCC for LT. Notarpaolo *et al*[60] validated the AFP model on a cohort of 574 patients. They showed that AFP score ≤ 2 *vs* > 2 was associated with 5-year recurrence rates of 13% *vs* 50%, respectively. Therefore, they showed that the AFP score well above 2 was 5 times more likely to develop recurrence in 5 years. The AFP model was validated by other researchers[60-64] and all reported similar results as Notarpaolo *et al*[60].

In 2017, the Risk Estimation of Tumor Recurrence After Liver Transplant (RETREAT) scoring system was defined, which included tumor burden, microvascular invasion and AFP values in the evaluation process. A score of 0 was associated with a 5-year recurrence rate < 3%, while a score > 5 was associated with a recurrence rate more than 75%[65]. This score has been validated by Abdelfattah *et al*[66] on a cohort of 73 patients who had tumors within Milan criteria. The results of the study showed that the Risk Estimation of Tumor Recurrence After Liver Transplant score> 5 was associated with a 67% recurrence rate and predicted the recurrence accurately.

Halazun *et al*[57] emphasized the importance of inflammatory markers in the prognosis of HCC. In 2017, they developed the MORAL scoring system, which included neutrophil to lymphocyte ratio as one of the prognostic factors. The objective of this scoring system was to determine the recurrence risk of the patients, and it had two components. The pre-MORAL component evaluated the largest tumor diameter (> 3 cm), neutrophil to lymphocyte ratio (> 5) and AFP (> 200 ng/dL). The post-MORAL component was dependent on the pathologic analysis such as largest tumor diameter (> 3 cm), number of tumor nodules (> 3), the tumor grade and presence of microvascular invasion. A score ≤ 2 was considered as low risk and the 5-year DFS rate was reported to be 97.4%. A score between 3 and 6 was considered as moderate risk and with a 5-year DFS rate of 75.1%. A score between 7 and 10 was considered as high risk and was associated with a 5-year DFS of 49.9%. A score above 10 had a very high risk of recurrence, and 5-year DFS was 22.1%.

In 2018, Halazun *et al*[58] defined the New York/California scoring system for selection of the patients with HCC for LT. They included the AFP response to locoregional therapy to the standard morphological criteria such as tumor size and number. A score between 0 and 2 was considered as low risk, and 5-year DFS was 90%. A score between 3 and 6 was considered as moderate risk, and the 5-year DFS was 70%. However, a score ≥ 7 was associated with a high risk of recurrence, and the 5-year DFS was 42%

Mazzaferro *et al*[59] developed the Metroticket 2.0 (AFP-adjusted-to-HCC size criteria) model in which they combined the serum AFP levels and Up-to-Seven scoring system. The low-risk group had an overall survival rate of 79.7% and a DFS of 89.6%. The most recent scoring system is from South Korea called SNAPP, which is an acronym for the tumor size, number, AFP, PIVKA II and PET-CT. This scoring system combined morphologic criteria, biologic markers and PET-CT findings. A score of 0-2

Table 3 Scoring systems for liver transplantation in hepatocellular carcinoma and survival rates stratified according to the recurrence rates

Scoring system	Scores of the parameters				Post-transplant recurrence risk	5-yr DFS in low risk	5-yr OS in low risk	Recurrence in low risk at 5-yr
AFP Model [44], 2012	LTD: ≤ 3 cm; 3-6 cm; > 6 cm. Point: = 0; = 1; = 4	NN: 1-3 nodule; > 4 nodule. Point: = 0; = 2	AFP: ≤ 100; 100-1000; > 1000. Point: = 0; = 2; = 3		Total point = score (0-9): Score ≤ 2, low risk; Score > 2, high risk		67.8; 47.5	8.8; 50.6
RETREAT [45], 2017	LTD + NVT: 0; 1.1-4.9; 5.0-9.9; ≥ 10. Point: = 0; = 1; = 2; = 3	MiVi: Positive. Point: = 2	AFP at LT: 21-99; 21-99; 100-999; ≥ 1000. Point: = 0; = 1; = 2; = 3		Total point = score (0-8): Score = 0; Score < 5, low risk; Score ≥ 5, high risk (RR)			2.9; 75.2
MORAL[46], 2017	Pre-LT-MORAL: LTD > 3 cm; NLR > 5; AFP > 200. Point: = 3; = 6; = 4		Post-LT-MORAL: LTD > 3 cm; NN > 3 nodules; Grade 4 tumor; MiVi positive. Point: = 3; = 2; = 6; = 2		Total point = score (0-13): Score 0-2, low risk; Score 3-6, medium risk; Score 7-10, high risk; Score > 10, very high risk	97.4; 75.1; 49.9; 22.1		
NYCA[47] 2018	LTD at diagnosis: 0-3 cm; > 3-6 cm; > 6 cm. Point: = 0; = 2; = 4	NN at diagnosis: 1 nodule; 2-3; ≥ 4. Point: = 0; = 2; = 4	AFP response: AFP always < 200; Point: = 0. Responders: Max > 200-1000 to final < 200; Point: = 2. Max > 1000 to final < 1000 (must be 50% drop); Point: = 2. Nonresponders: Max > 200-400 to final > 200; Point: = 3. Max > 400-1000 to final > 200; Point: = 4. Max > 1000 to final > 1000; Point: = 6		Total point = score (0-14): Score 0-2, low risk; Score 3-6, acceptable risk; Score ≥ 7, high risk	90; 70; 42		Cumulative: 7; 27.5; 62.5
Metroticket 2.0[48], 2018	LTD + NN ≤ 7 and AFP ≤ 200 or LTD + NN ≤ 5 and AFP 200-400 or LTD + NN ≤ 4 and AFP 400-1000				Low risk	87.4	78	
SNAPP[49], 2020	LTD: ≤ 3 cm; 3-6 cm; > 6 cm. Point: = 0; = 1; = 2	NN: 1 nodule; 2-3 nodule; ≥ 4 nodule. Point: = 0; = 1; = 2	AFP and PIVKA II: AFP ≤ 150 + PIVKA II ≤ 100; AFP ≤ 150 + PIVKA II > 100; AFP > 150 + PIVKA II ≤ 100; AFP > 150 + PIVKA II > 100. Point: = 0; = 1; = 2; = 3	PET-CT: Isometabolic; Hypermetabolic. Point: = 0; = 1	Total point = score (0-8): Score ≤ 2, low risk; Score 3-4, medium risk; Score > 5, high risk	97; 71; 31		3; 29; 69

AFP: Alpha fetoprotein; DFS: Disease-free survival; LT: Liver transplantation; LTD: Largest tumor diameter; MiVi: Microvascular invasion; NLR: Neutrophile to lymphocyte ratio; NN: Number of nodules; NVT: Number of viable tumors; NYCA: New York/California; OS: Overall survival; PET-CT: Positron emission tomography computed tomography; PIVKA II: Protein induced vitamin K antagonist II; RETREAT: Risk Estimation of Tumor Recurrence After Liver Transplant.

was defined as low risk, and 5-year DFS was 97%. A score of 3-4 was associated with a moderate risk of recurrence, and 5-year DFS was 71%. A score ≥ 5 was associated with a high risk of recurrence, and 5-year DFS was 31%[59].

The results of the scoring systems have shown that the efficacy depends on the advances in imaging systems and discovery of new biomarkers. Therefore, the transplant community needs basic science research in the field to meet these needs. Currently, there is no ideal scoring system/model that is universally validated for risk stratification of HCC.

LDLT FOR HCC

LDLT is an accepted treatment modality for end-stage liver disease. Furthermore, it is a very good alternative to DDLT[67]. LDLT has certain technical advantages over DDLT such as: (1) It provides an unlimited source of liver grafts; (2) Shorter cold/warm ischemia times providing better graft function and outcome; and (3) Since the source of the organ is a relative and they share similar genetic background, immunologically, LDLT is more favorable than DDLT[68].

In Turkey and many other Asian countries, deceased donor organ supply is limited, and LDLT is the only therapeutic option for many end-stage liver disease and liver cancer patients. There are two advantages of using living donor liver grafts: (1) It enables planning the timing of the transplant procedure; and (2) It is a "gift" from the relative that is exclusive for the patient. Therefore, the LDLT strategy enables planning of the sequential therapeutic modalities up to the point of LT. Furthermore, since the grafts are exclusive and readily available for the patients, Milan criteria can be expanded. Ideal selection criteria expanding the Milan criteria is especially important in the LDLT setting balancing the risks *vs* survival benefits in the recipient and the living donors. On the other hand, LDLT for patients with HCC is still controversial on many aspects. One aspect is the ethical dilemma to risk a healthy person for a recipient that has a fatal disease with a high risk of recurrence. Currently, the reported morbidity and mortality of living donor hepatectomy is 16% and 0.2%, respectively[69]. The second aspect of controversy is the high recurrence rates that are reported for LDLT[70,71]. These were attributed to rapid transplantation of patients receiving LDLT, which prevents selection process that is usually present during the listing period in DDLT. Therefore, biologically aggressive tumors are being transplanted rapidly in cases of LDLT. Furthermore, the regeneration process after the transplantation of the partial liver graft is thought to induce angiogenesis and tumor growth[70-74]. In addition, the LDLT is occasionally performed as a salvage procedure when other treatment modalities have failed, which means that more aggressive tumors are being transplanted[75]. Technically during LDLT, the long bile duct and hepatic artery are preserved for versatility of vasculobiliary complications, which may lead to higher tumor remnants that increase the risk of recurrence[71].

Despite these concerns that have been hypothesized, a meta-analysis published by Liang *et al*[76] in 2012 showed that in data of over 700 patients, the results of LDLT for HCC were comparable to that of DDLT in terms of recurrence rates and DFS. Furthermore, when considering the time spent on the waiting list and the risk of disease progression and drop-out, LDLT seems to be a feasible option for HCC provided that patient selection is performed accurately[24]. The results of LDLT and DDLT seems to be similar for tumors within Milan criteria, although Liang *et al*[76] reported that the 1-year recurrence rate was higher. The main issue is the feasibility of LDLT for tumors exceeding Milan criteria. A study by Hong *et al*[77] in 2016 reported that the annual rate of LDLT for extra-Milan or even very advanced stage HCC was increasing in Korea, and they showed that the low and intermediate risk group according to the Seoul National University criteria (low risk: AFP < 200 ng/mL and PET negative; intermediate risk: Either one is positive) for HCC within or beyond Milan criteria showed comparable 5-year DFS rates. Therefore, in countries where DDLT is limited due to limited organ supply, LDLT provides the means of transplantation of a higher number of patients with HCC; nevertheless, the biologic behavior of the tumors should be thoroughly evaluated[78]. As it can be seen from the data presented above, expansion of the Milan criteria and development of markers for tumor biology is especially important for LDLT for HCC. These controversies and discussions will continue until this goal is achieved.

THE BRIDGING AND DOWNSTAGING PROCEDURES

The demand for organs exceeds the deceased organ supply, and therefore the number of patients on the waiting list is increasing. This causes an increased wait time on the list before a suitable organ is available[65,79]. Bridging procedures are neoadjuvant therapeutic options that will prevent disease progression during the waiting time on the list and will prevent drop out of the patients with HCC[8]. Downstaging procedures are performed to the tumors that are beyond Milan criteria to downstage them to the limits of the Milan criteria or to United Organ Sharing (UNOS) T2 stage[48,80]. The studies have shown that LT for tumors already within Milan criteria and tumors downstaged to Milan criteria show similar results[81,82]. There are many options for locoregional therapies (either bridging or downstaging) including radiofrequency ablation, microwave ablation, trans (hepatic) arterial embolization, transarterial chemoembolization and transarterial radioembolization with yttrium-90 microspheres[83].

UNOS uses a specific classification for HCC[17]. Downstaging is performed for tumors that exceed the UNOS T2 criteria (solitary 2 to 5 cm or 2 or 3 nodules, each nodule diameter < 3 cm) and must be in accord with one of the following: (1) Single lesion < 8 cm; (2) 2 to 3 lesions each < 5 cm and total tumor diameter < 8 cm; or (3) 4 to 5 lesions each < 3 cm and total tumor diameter < 8 cm. Cross-sectional imaging studies must confirm the absence of extrahepatic disease and macrovascular invasion[79]. One important issue to be discussed is the treatment options if decompensation of the patient occurs while the downstaging protocol is continuing. The UNOS protocol is very strict regarding this scenario, and it states that if the patient decompensates after or during locoregional therapy and if the follow-up period is not completed or if the tumor does not respond to the downstaging procedure, then the patients should be considered ineligible for LT[79].

FUTURE DIRECTIONS

The most effective treatment of HCC is LT. Furthermore, there is no ideal criterion that can be universally used. Since there is a shortage of the deceased donor organ pool, selection of the patients with HCC for DDLT should be performed in accord with strict criteria to provide maximum benefit from the transplanted organ. Milan criteria is the ideal selection criteria for centers performing DDLT [65]. This requires thorough evaluation of the biologic behavior of the tumor using various biologic markers such as AFP, AFPL3 and PIVKA II, imaging studies such as positron emission tomography and response to various locoregional downstaging procedures[65]. None of the criteria using these parameters are proven to effective[84,85]. Therefore, the future lies in development of effective systemic therapies and strategies for evaluation of the tumor biology[85]. In particular, research in the genomic analysis of different phenotypes that increases the understanding of hepatic carcinogenesis should be pursued. This will allow researchers to develop targeted therapies that will be used in the neoadjuvant or adjuvant setting. Advancements in the software, imaging and advanced technologies such as radiomics provide accurate diagnosis and staging of the disease in the pretransplant period. This will increase the accuracy of patient selection. Perhaps newer selection criteria will be defined[86]. Genomics will also aid advancements in liquid biopsy, which will be effective for staging of the tumors[87-89]. Genomics can also provide information regarding biologic behavior of the tumors and will introduce a whole new era of patient evaluation and personalized medicine.

The future of cancer treatment depends on the advancements in basic science research. HCC is a typical example of the bench to clinical applications[90]. It has been shown that epidermal growth factor pathway is activated in HCC, and this results in activation of the tyrosine kinase system, which is a transcriptional hub for activation of the multiple growth factor pathways[90]. Furthermore, mitogen activated protein kinase has been shown to activate the vascular endothelial growth factor-dependent angiogenic switch in HCC[91,92]. All these give the physicians possibilities of small molecule targets for molecularly targeted new therapies. Sorafenib was one of the effective targeted therapies developed for HCC. It is a multikinase inhibitor targeting the vascular endothelial growth factor and platelet-derived growth factor pathways[93,94].

Epigenetic changes control the invasion and metastasis in HCC. This implies that the microvascular invasion capabilities are controlled by epigenetic mechanisms. These mechanisms include hyper-/hypomethylation of the DNA, histone associated mechanisms and non-coding RNA. These can be used as diagnostic tools or can give an idea regarding the prognosis of the patients[95,96]. For example, it has been shown that hypermethylation of RASSF1A has been associated with tumor growth and progression that is independent from AFP levels and has been proposed as a diagnostic marker in high risk groups[97]. On the other hand, many epigenetic markers, such as miR-122, EZH2, SUV39HZ, ARK-1 and ARK-2, have been studied showing strong correlation with poor prognosis[98-100]. These may provide the future of selection criteria for determining ideal patients for liver transplant.

One of the novel developments in the treatment of cancer is development of oncolytic viral therapy. Oncolytic viral therapies use genetically engineered or naturally occurring deficient viruses that can only replicate and kill cells with active mitosis. They cause viral oncolysis through the replication cycle and induce potent anti-tumor immunity. Some of them have been approved for the treatment of HCC. Among them is vaccinia virus JX-594 (Pexastimogene Devacirepvec) for HCC[101].

The cytotoxic T-lymphocyte-associated protein 4 and programmed cell death protein-1 pathway is activated in HCC[102,103]. Therefore, the microenvironment of HCC favors immune evasion. All these have prognostic significance for patients with HCC. The clinical trials using anti-cytotoxic T-lymphocyte-associated protein 4 and programmed cell death protein-1 antagonists have started; initial reports show a high rate of adverse effects with marginal improvement in patient survival[104]. However, continuing research will lead to development of more effective and specific therapeutic strategies.

Irreversible electroporation has been a new development for locoregional therapy of solid organ tumors. It is performed percutaneously, and electrical pulses are sent to the tissues generating pores in the cancer cell membrane, which leads to apoptosis[105,106]. It has minimal damage to the surrounding tissue. For this reason, it can be considered in tumors that are in close proximity to vascular structures [106]. It has been shown that irreversible electroporation provides complete response in 97% of the patients with tumors less than 3 cm[107,108]. Nevertheless, efficacy is reduced in tumors greater than 4 cm. There have been reports confirming the efficacy and safety of the procedure by leading to faster recovery and less liver damage[109].

There is still much to achieve in the treatment of HCC. LT is just one end of the spectrum. The main benefit will be obtained from therapies in the neoadjuvant and adjuvant setting to provide a better survival and reduced recurrence for patients transplanted for HCC curative treatment. Therefore, development of new therapeutics and new criteria/markers for thorough evaluation of the patients with HCC should be evaluated in the same context, and equivocal advancements should be performed in both areas to provide a favorable outcome in this aggressive tumor.

CONCLUSION

LT in HCC is still a hot topic with many controversies. We still need ideal selection criteria and prognostic scores to evaluate patients for LT and other adjuvant therapies. However, we may not achieve this goal for this is a very heterogenous tumor and none of the developed criteria will be ideal. It shows geographic diversities according to race and the established strategy of organ transplantation (LDLT *vs* DDLT). Achievements in therapeutic modalities are needed to develop effective treatment of the patients to achieve acceptable overall survival and DFS rates. Hence, a multidisciplinary approach is required for management of HCC. The basic science research seems to be the backbone of all the expectations in the field.

FOOTNOTES

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