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# Biomarkers for living donor liver transplants in hepatocellular carcinoma

**Edward Butt[1], Rupak Kulkarni[2], Moghe Akshata[3]**

[1]Department of Internal Medicine, The University of Texas Medical Branch at Galveston, Galveston 77550, TX, USA.
[2]Department of Surgery, Division of Transplantation, The University of Texas Medical Branch at Galveston, Galveston 77550, TX, USA.
[3]Department of Internal Medicine, Division of Gastroenterology and Hepatology, The University of Texas Medical Branch at Galveston, Galveston 77550, TX, USA.

**Correspondence to:** Dr. Edward Butt, Department of Internal Medicine, University of Texas Medical Branch at Galveston, 301 University Blvd, Galveston 77555, Texas, USA. E-mail: edbutt@utmb.edu

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## Abstract

Liver transplantation is one of the more definitive treatments for hepatocellular carcinoma (HCC). In the United States, liver transplantation has historically been focused on deceased donor organs, and tumor burden is used for risk-stratifying patients on the transplant waitlist. Living donor liver transplantation (LDLT) is gaining popularity in the United States and has long been practiced in Asian countries. To improve outcomes of overall survival and disease-free survival post-living donor liver transplantation, surrogates of tumor biology are now being regarded to be as important as tumor burden. This article reviews the different surrogates of tumor biology and discusses their role in the application of LDLT for advanced HCC.

**Keywords:** LDLT, HCC, tumor biology

## INTRODUCTION

Liver transplantation is a potential treatment for those with hepatocellular carcinoma (HCC). The Milan Criteria and University of California San Francisco (UCSF) criteria allow patients to be appropriately selected for liver transplantation and remain the benchmark in many institutions. These criteria used solely

tumor burden (size and number) and were developed specifically in the deceased donor liver transplantation (DDLT) setting to help prioritize patients on the transplant waiting list and allow for fair allocation of the limited organs in the organ pool[1,2]. As many cases which exceed the Milan criteria have good prognoses, multiple attempts have been made to expand criteria, initially through the expansion of tumor burden. These criteria for living donor liver transplantation (LDLT) were not reported until 2007 and 2008, as the Tokyo and Asan criteria, respectively[3,4]. In recent years, partly due to very long waitlist times, LDLT has become a popular option to bypass the long waiting process in anticipation of liver transplantation.

### Living donor liver transplantation

In LDLT, a specific donor liver is dedicated to one specific recipient. This arrangement is made through a more personal process than DDLT. In LDLT, as the donor is still living, there are additional risks of donor-related complications, even mortality. LDLT donor death is approximated to be around 0.20%[5], while donor complication rates can be as high as 80%[6-10]. Keeping in mind the living donor's risks, a recent International Liver Transplantation Society (ILTS) statement declared that the accepted ethical justification for LDLT is a 5-year survival probability of at least 60%[11].

Further results comparing LDLT to DDLT in terms of overall survival (OS) and disease-free survival (DFS) are not in agreement, as some studies show worse outcomes with LDLT while others show no difference[12,13]. Regardless, many large LDLT institutions have attempted to expand their LDLT criteria to increase the number of eligible recipients with the aid of tumor biology[3,4,14-16]. For example, the initial Kyoto criteria included recipients with fewer than 10 tumors, with the largest tumor being smaller than 5 cm and a protein induced by vitamin K absence-II (PIVKA-II) or des-gamma carboxyprothrombin (DCP) level less than 400 mAU/ml[17]. These criteria provided an 82% 5-year post-LDLT survival rate. The National Cancer Center - Korea criteria included negative positron emission tomography (PET) scan and tumor diameter smaller than 10 cm for LDLT recipients, which allows for an 84% 5-year post LDLT survival rate compared to 60% for those outside these criteria[18].

## ROLE OF TUMOR BIOLOGY AND THE USE OF BIOMARKERS

Frequently, small HCC tumors may have more aggressive features leading to worse outcomes after liver transplantation, while larger tumors may have less aggressive features resulting in better post-transplant outcomes. Hence, tumor biology rather than tumor number or size is thought to better risk-stratify those undergoing liver transplantation. One method to examine the tumor biology of HCC in a patient is obtaining tissue via a liver biopsy. Although liver biopsy is the gold standard used to investigate the biological behavior of HCC, there are downsides to biopsy, and hence, HCCs are rarely biopsied. Besides the obvious risk of tumor seeding/spread, a pre-transplant tumor biopsy may underestimate tumor differentiation as HCC is highly heterogeneous[19]. In addition, it is difficult to assess microvascular invasion in a single biopsy due to sampling bias[20]. Therefore, surrogate markers of tumor biology such as PET, PIVKA-II, neutrophil to lymphocyte ratio (NLR), and alpha-fetoprotein (AFP) are very useful. We will review these in more detail in this manuscript.

### Positron-emission tomography

Positron-emission tomography (PET) avidity is one of the methods used to assess tumor biology. The more poorly differentiated HCC cells are, the higher their uptake of 18F-fluorodeoxyglucose [(18F)FDG][21,22]. Therefore, PET avidity is typically associated with high levels of AFP and microvascular invasion. Because normal liver physiology is associated with some uptake of 18F-FDG, the definition of PET positivity is not universally established. Objective markers to attempt to define positivity have been used, which include the

tumor-to-normal liver ratio maximum standardized uptake value (SUV), the maximum SUV of the tumor, and the ratio of the tumor SUV max to the normal liver mean SUV max. Optimal cut-offs for these values are still being debated[23,24].

Despite this lack of uniformity, PET avidity is used by many institutions as a surrogate of tumor biology as it has a high accuracy for detecting tumor differentiation (54 to 71%) and microvascular invasion (68 to 88%)[25-30]. In addition, PET avidity has allowed providers to predict HCC recurrence in advanced HCC. HCC with tumor burden beyond Milan/UCFS criteria but those which display non-avid [18F]FDG PET activity are shown to have a lower recurrence of HCC compared to patients with high avidity but within the conventional criteria[31,32]. Specifically, for those with high avidity, the recurrence-free survival rate 3 years after undergoing liver transplantation has been shown to be 35 to 57% versus 84 to 94% in those with non-avid PET scans[26-29,33]. The use of PET in selection criteria for LDLT was strongly recommended per the ILTS consensus in 2020[11]. However, cost-effectiveness, low sensitivity, and variable SUV cut-offs are barriers to incorporating the widespread use of PET avidity in transplant criteria[34].

### Protein induced by vitamin K absence-II / Des-gamma carboxyprothrombin

PIVKA-II or DCP is a form of prothrombin created in the absence of vitamin K. It is produced in large quantities in the setting of malignant hepatocytes. The abnormal prothrombin upregulates angiogenic factors which in turn increase the risk of metastasis and microvascular invasion[35-38]. Consequently, it has been shown to correlate with the degree of HCC malignancy, like PET avidity.

DCP is useful for predicting the risk of HCC recurrence after liver transplantation. Although there is no consensus cut-off value, it has been successfully incorporated into many criteria in combination with AFP. For example, the Kyushu and Kyoto criteria combine different levels of DCP and AFP to provide patients beyond the Milan criteria with survival rates over 80% who otherwise would not be able to undergo liver transplantation[37,39,40]. DCP's integration with AFP has been shown to be more effective than using one or the other alone. For instance, the Mayo Clinic reported a hazard ratio of HCC recurrence after liver transplantation of 2.8 and 3.5 when using AFP and DCP alone, respectively. With the combination of the two values, the hazard ratio increased to 5.2[41]. The integration of PIVKA-II into LDLT selection criteria was strongly recommended by the ILTS in 2020[11].

### Neutrophil-lymphocyte ratio

Neutrophil-lymphocyte ratio (NLR) is the ratio of neutrophils to lymphocytes in the blood. The rationale behind using NLR to measure tumor aggressiveness is thought to be explained by neutrophils upregulating angiogenic factors[42]. NLR is a widely used marker of tumor biology and is accepted by many as an independent risk factor for the recurrence of HCC post-transplant[43]. As a surrogate of tumor biology, it has shown its greatest efficacy in combination with other tumor markers[43-48].

The association between NLR and HCC recurrence was first shown in 2009 by Halazun *et al.*[49]. A meta-analysis by Xu *et al.* 9 years later showed that an elevated NLR correlated with higher odds of vascular invasion (Odds ratio 2.39) and lower recurrence-free survival after liver transplantation with a hazard ratio of 3.77[50]. This analysis also found that those with HCC outside the Milan criteria more frequently had an elevated NLR compared to those within the Milan criteria. The study suggested a cut-off value of 4 when incorporating NLR into liver transplantation criteria. While some have shown that NLR is a more reliable predictor of HCC recurrence than AFP or DCP[51], others have shown that DCP and AFP have larger predictive power than NLR[43]. As a result, there is not a universal consensus in terms of its consistency in predicting HCC recurrence or how it compares in relation to AFP or DCP[43,51-53].

### Alpha-fetoprotein and downstaging

AFP is thought to upregulate tumor proliferation by activating cell adhesion molecules and signaling tyrosine protein kinases which accelerate cellular growth[54,55]. AFP has been almost universally integrated into LDLT criteria and is commonly used to assess tumor biology. It can help predict post-transplant HCC recurrence and survival times in patients with advanced HCC, specifically in patients who undergo downstaging, which involves locoregional therapy (LRT) such as radiofrequency ablation or trans-arterial chemoembolization, to shrink the tumor dimensions to meet acceptable transplantation criteria[56,57]. For example, in those with AFP larger than 1,000 ng/ml, studies have shown that reducing this level to less than 100 ng/ml with DS allows a 5-year survival rate of 88% versus 67% in those whose AFP level only fell to 101-499 ng/ml with downstaging[58]. Halazun et al provided similar results showing that those with initial AFP 200-1000 which dropped to below 200 with LRT had better post-liver transplantation results[59]. Other studies have shown that AFP greater than 1,000 ng/ml prior to liver transplantation showed higher rates of HCC recurrence after liver transplantation even when HCC met UCSF criteria[56,60,61].

The roles of downstaging (DS) in LDLT are controversial. Historically, macrovascular invasion was an absolute contraindication to LDLT. However, the use of tumor biology and its surrogates have allowed those with macrovascular invasion to undergo LDLT if they have good tumor biology. For example, even in patients with advanced HCC and a tumor thrombus in segmental branches, an AFP 10-100 ng/ml and a great response to DS have been shown to be effective predictors of longer survival times for recipients of LDLT compared to those without sufficient DS response and AFP levels[56,62-64].

Although some pre-liver transplantation criteria have been proposed across the world for LDLT, the absence of widely accepted criteria for DS in LDLT in those with advanced HCC remains an issue. Many patients with advanced HCC are reasonable candidates for LDLT, while up to 1/5 of those within traditional Milan criteria are poor candidates for LDLT[65]. AFP is a useful tool that can be used to better identify those in either group. Although there is no consensus on the AFP cut-off value, the integration of AFP into LDLT and DDLT selection criteria has been strongly recommended by ILTS[11].

### Gene signature

Gene signature is another surrogate of tumor biology. Using silico gene expression analysis, scientists are able to observe which genes occur more frequently in HCC[66]. Genes that occur most frequently in HCC are grouped together to allow for the creation of multigene signature models to better inform clinicians of HCC management[67]. Patients with certain gene signatures are then stratified into different tiers based on their outcomes regarding HCC.

A study by Wang *et al.* investigated candidate genes selected from Gene Expression Profiling Interactive Analysis (GEPIA)[68]. These genes and their association with survivability and HCC were examined through reverse transcription PCR with cDNA microarrays. Seven genes of interest were compared with two reference genes to create a low, intermediate, and high-risk group of patients with HCC. The 3-year overall survival rate was 20.6% in the high risk, 74.5% in the intermediate risk, and 88.9% in the low-risk group. Another study by Son *et al.* identified the expression of five different genes with the use of quantitative reverse transcription PCR and found that certain combinations of genes (HMGA1 and MPZL1) better predicted HCC recurrence versus other combinations with an AUC (0.807, 95% confidence interval = 0.681-0.899)[66]. They also found certain combinations of genes to be upregulated in patients with microvascular invasion, while other genes, such as MPZL1 and SNRPB, were correlated to the degree of tumor differentiation. Overexpression of genes such as RAGCAP1 significantly affected overall survivability, while HMGA1 significantly affected DFS. Lastly, a review by Pinto-Marques *et al.* investigated a 4-gene signature in combination with different clinical variables to create an algorithm to identify which patients had over

99% DFR at 5 years, with 16-24% of these patients being outside clinical criteria[69]. Although gene signature is promising, many of the prior studies lack prospective validation, thus limiting its widespread use in clinical practice and LDLT.

## CRITERIA INCORPORATING TUMOR BIOLOGY

Different criteria incorporating various markers of tumor biology to predict HCC survival and recurrence after liver transplantation have been created. Specifically, for LDLT, many Asian institutions have created criteria incorporating tumor biology to predict outcomes and recurrence in those beyond the Milan criteria. Samsung Medical Center uses criteria incorporating tumor size less than 5 centimeters and an AFP less than 400 ng/ml with no limitation on the tumor number[15]. One- and five-year survival rates were 92.2% and 79.9%, respectively[15]. Seoul National University uses criteria incorporating a preoperative AFP of less than 400 ng/ml with no vascular invasion with a 3-year survival rate of 86.2%[70]. Asan Medical Center's LDLT criteria incorporate no more than 6 tumors, each no larger than 5 centimeters, with no gross vascular invasion, producing a five-year survival rate of 81.6%[3]. The University of Tokyo uses criteria that allow the number of tumors to be no more than 5, no larger than 5 cm, with a 94% recurrence-free survival rate after LDLT[4]. Kyoto University uses similar criteria, except they allow the number of tumors to reach 10 if PIVKA-II levels are less than 400 mAU/ml[17]. This criterion results in a 5-year survival rate of 86.7%. Lastly, a study in Japan regarding 653 patients found that patients with HCC extending past the Milan criteria had an 84.3% 5-year disease-free survival as long as AFP levels were no larger than 200 ng/ml and PIVKA-II levels were no larger than 100 mAU/ml[40].

## RECENT STUDIES INVESTIGATING THE IMPACT OF TUMOR BIOLOGY IN LDLT FOR ADVANCED HCC

A study by Suh *et al.* investigated the post-transplant recurrence rates for HCC in patients undergoing LDLT for HCC with portal vein tumor thrombus (PVTT)[71]. The type of PVTT (I, II, III, IV) did not significantly affect HCC recurrence rates. However, AFP level > 200 ng/ml was a significant risk factor for HCC recurrence. All patients with AFP > 200 ng/ml and PVTT had recurrence in 2 years post-LDLT, while those with PVTT but AFP level less than or equal to 200 ng/ml had a 3-year overall survival rate of 87.5% and disease-free survival rate of 65.6% 3 years after LDLT.

Regarding DDLT, transplant eligibility for T3–T4 HCC requires successful downstaging (DS). LDLT can be considered selectively in these patients without DS, but its role is not clearly defined. A more recent by Bhatti *et al.* looked carefully at the role of tumor biology in patients with advanced HCC based on UNOS staging who received LDLT without prior DS[72]. 5-year recurrence-free survival was compared in patients with advanced HCC. The recurrence rate of HCC in T3, T4a, and T4b HCC was 16.1, 5.9, and 37.5%, respectively. It was shown that T4b HCC (macrovascular invasion) and AFP > 600 ng/mL were significant predictors of recurrence. When excluding patients with AFP > 600 ng/mL, the 5-year recurrence-free survival for T3, and T4a HCC was 86% and 92%, respectively. The study found that in patients with UNOS T3 and T4a HCC who received LDLT without prior DS, comparable survival rates were found for UNOS T3, and T4a HCC if AFP was < 600 ng/mL.

Lastly, Bhatti *et al.* investigated the role of tumor biology in LDLT patients with advanced HCC and macrovascular invasion[73]. Patients that met A-VENA criteria[74] for macrovascular invasion were included in the study. A-VENA criteria were proposed by Sherman *et al.*, which accurately differentiates bland portal veisn thrombosis from tumor portal vein thrombosis in patients who meet at least three of the following: venous expansion, thrombus enhancement, an AFP > 1,000 ng/dl, adjacency to HCC, and neovascularity. Regarding PVTT, LDLT was considered in patients with tumor thrombosis in segmental branches (Vp1-2)

or lobar branches (Vp3)[74]. The role of AFP was studied in patients who met UCSF criteria, their center-specific USCF+ criteria (largest tumor diameter ≤ 10 cm, any tumor number, AFP ≤ 1,000 ng/ml), and those with macrovascular invasion. The recurrence rate of HCC was 13% for those within UCSF criteria versus 36% for those within UCSF+ criteria. In the UCSF+ group, the recurrence rate decreased from 36% to 27% when patients with AFP greater than 600 ng/ml were excluded.

Patients who underwent DS were characterized as being low risk (AFP less than or equal to 100 ng/ml and good response to DS) or high risk (AFP greater than 100 ng/ml or poor response to DS). In LDLT patients with macrovascular invasion who underwent DS, 80% of those in the low-risk group and 20% in the high-risk group remained alive at the end of a 5-year period after transplant. Patients who were not eligible to undergo DS were also divided into high-risk (AFP > 100 or Vp3 macrovascular invasion) or low-risk (AFP less than equal to 100 ng/ml and Vp1-2 macrovascular invasion) groups. All patients in the low-risk group were alive at the end of the 5-year period after transplant, while only 1/9 of patients in the high-risk group were alive at the time.

The study supported the idea that incorporating AFP into criteria can allow for acceptable survival in patients with advanced HCC who undergo LDLT. Specifically, those with Vp1-2 macrovascular invasion can undergo LDLT with good outcomes if AFP pre-liver transplantation is less than 100 ng/ml.

These results have changed Shifa International Hospital's protocol to incorporate the following: 1. All patients without evidence of extrahepatic disease and main portal vein tumor thrombosis but with AFP > 1000 ng/ml undergo DS; 2. All patients with macrovascular invasion have a staging PET scan, and in those who undergo DS, only those whose AFP drops below 100 ng/ml after DS undergo LDLT; 3. After PET, in those not eligible for DS, those with a low AFP and Vp1-2 macrovascular invasion can still be considered for LDLT.

## CONCLUSION

In patients with advanced HCC, LDLT can be a potential treatment option. The use of biomarkers for tumor biology is helping to expand the patient selection in those undergoing LDLT. As major advancements continue to be made in the detection of effective biomarkers for tumor biology, progress towards expanded criteria for LDLT in patients with advanced HCC will continue to be made. This progress will hopefully propel the Western world towards increasing the number of living donor liver transplants for HCC, following suit with their counterparts in the East[75].

## DECLARATIONS

### Authors' Contributions

Made substantial contributions to the gathering of information, analyzing of information, authorship, and editing of this article: Butt E, Kulkarni R, Akshata M

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Not applicable.

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### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Copyright



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