

Living Donor Liver Transplantation Outcomes for Hepatocellular Carcinoma Beyond Milan or UCSF Criteria

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Abstract Liver transplantation (LT) is the most effective treatment for hepatocellular carcinoma (HCC) that arises from cirrhosis. The Milan and the University of California, San Francisco (UCSF) selection criteria have resulted in major improvements in patient survival. We assessed our outcomes for patients with HCC that were beyond the Milan and UCSF criteria after living donor liver transplantation. We reviewed the data for 109 patients with cirrhosis and HCC who underwent living donor right lobe liver transplantation (living donor liver transplantation; LDLT) during the period from July 2004 to July 2012. Sixteen (14.7 %) patients had HCC recurrences during a mean follow-up of 35.4 ± 26.2 months (range 4–100 months). The mean time to recurrence was 11 ± 9.4 months (range 4–26 months). Survival rates were not significantly different between patients with HCC that met and were beyond the Milan and UCSF criteria ($p=0.761$ and $p=0.861$, respectively). The Milan and UCSF criteria were not independent risk factors for HCC recurrence or patient survival. Only poorly differentiated tumors were associated with a lower survival rate (OR=8.656, 95 % confidence interval (CI) 2.01–37.16; $p=0.004$). Survival rates for patients with HCC that were beyond conventional selection criteria should encourage reconsidering the acceptable thresholds of these criteria so that more HCC patients may undergo LT without affecting outcomes.

Keywords Living donor liver transplantation · The Milan criteria · UCSF criteria · Hepatocellular carcinoma

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most common cause of cancer death worldwide [1]. Most HCC cases arise in the setting of cirrhosis due to multiple etiologies [2, 3]. Treatment options for patients with HCC include locoregional ablation, surgical resection, or liver transplantation (LT). LT is the most effective treatment for HCC that arises in cirrhotic liver [4] as it eliminates both the tumor and the underlying liver disease [5].

Living donor liver transplantation (LDLT) has become a significant option for treating HCC, especially in countries in which there are shortages of deceased donor organs. However, despite the advantages of LT, there are significant risks, such as complications related to lifelong immunosuppression, graft failure, and HCC recurrence rates of between 10 and 30 % [6]. It has been shown that HCC recurrence has a significant negative effect on patient survival after transplantation [7].

Although many criteria have been proposed for patient selection, the Milan criteria were the first to be implemented and are currently widely accepted. Implementing the Milan criteria has resulted in major improvements in patient survival [8]. In addition, patients who received transplants under expanded criteria, proposed as the University of California, San Francisco (UCSF) criteria, had outcomes comparable to those selected within the Milan criteria [9].

The success of LT for HCC and the increasing use of LDLT have raised questions regarding the outcomes of patients who underwent LDLT for HCC that exceeded these criteria. This study was undertaken to assess the outcomes of LDLT for patients with HCC that were beyond the Milan and UCSF selection criteria.

Patients and Methods

We reviewed the data for 109 patients with HCC due to liver cirrhosis who underwent living donor right lobe liver transplantation (living donor liver transplantation; LDLT) during the period from July 2004 to July 2012. Variables recorded included patient demographics, cancer treatments prior to transplant, pre-transplantation tumor numbers and sizes, recurrence dates, treatments used, Model for End-Stage Liver Disease (MELD) and Child-Pugh scores, and preoperative alpha-fetoprotein (AFP) levels. The indication for LDLT was HCC without extrahepatic metastasis or macroscopic vascular invasion on conventional imaging studies. Tumor size and number were not regarded as limitations.

Pathological staging of liver explants was done by reviewing pathology reports. Based on tumor sizes and numbers, each tumor in an explant liver was staged as either meeting or exceeding the Milan and UCSF criteria. When selecting patients for LDLT, the Milan criteria were observed: solitary tumor up to 5 cm in size or a maximum of three tumor nodules with each no larger than 3 cm [8]. The University of California, San Francisco (UCSF) criteria were as follows: one tumor of ≤ 6.5 cm or a maximum of three tumor nodules each of ≤ 4.5 cm and the sum of tumor diameters of ≤ 8 cm [9].

Statistical analysis

Results for continuous variables are given as means \pm standard deviations (SD), and results for categorical variables are given as numbers (percents). Comparisons of results for categorical variables were made by chi-square test or the Fisher's exact test. Results for non-normally distributed continuous variables were compared by Mann–Whitney *U* test. Logistic regression analysis was used for variables that were found to be statistically significant by univariate analyses. Survival was assessed using the Kaplan–Meier method, with comparisons made using a log-rank test. *p* values of <0.05 were considered significant. Risk prediction was reported as the odds ratio (OR), the corresponding 95 % confidence interval (95 % CI), and the *p* value. Statistical analysis was done using SPSS for Windows version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

This study included a total of 109 patients, 97 males and 12 females, whose mean age was 55.2 ± 7.8 years (range 26–72 years). The average pre-transplant MELD score was 13.1 (range 6–28), and 40.2 % of these patients had a Child-Pugh score of A. The etiologies of liver disease are shown in Table 1.

The mean preoperative AFP level was 137.9 ± 304.4 ng/mL (range 1–2,271 ng/mL). The mean number of tumors was 3.7

Table 1 Demographic and pathologic data of patients ($n=109$)

Age	55.2 \pm 7.8 (26–72)
Gender	
Female	12 (11 %)
Male	97 (89 %)
MELD score (mean)	13.1 (6–28)
Child-Pugh score (%)	
A	40.2 %
B	34.6 %
C	25.2 %
Etiology	
HBV	60 (55 %)
HCV	17 (15.5 %)
HBV+HDV	11 (10 %)
Alcohol	6 (5.5 %)
Criptogenic	13 (12 %)
Other	2 (2 %)
Preoperative AFP level (ng/mL)	137.9 \pm 304.4 (1–2271)
Number of tumor	3.7 \pm 4.7 (1–30)
Largest tumor size (mm)	36.4 \pm 22.6 (5–140)
Total tumor size (mm)	69.1 \pm 55 (5–300)
Multifocality	60 (55 %)
Vascular microinvasion	13 (11.9 %)
Differentiation	
Well	20 (18.9 %)
Moderate	72 (67.9 %)
Poor	14 (13.2 %)

± 4.7 (range 1–30), the mean largest tumor size was 36.4 ± 22.6 mm (range 5–140 mm), and the mean total tumor size was 69.1 ± 55 mm (range 5–300 mm). Of these 109 patients, 60 (55 %) had multifocal tumors and 13 (11.9 %) had microvascular invasion. Twenty (18.9 %) patients had well-differentiated, 72 (67.9 %) had moderately differentiated, and 14 (13.2 %) had poorly differentiated HCC identified in their explant livers (Table 1).

Prior to transplantation, eight patients received treatment for HCC, including left lateral segmentectomy for one, left hepatectomy for one, right hepatectomy for two, non-anatomical liver resection for two, chemoembolization for one, and radiofrequency ablation (RFA) for one. Sixteen patients (14.7 %) developed HCC recurrence at a mean follow-up of 35.4 ± 26.2 months (range 4–100 months). The mean time to recurrence was 11 ± 9.4 months (range 4–26 months). Tumor recurrence was observed in the liver graft ($n=4$), lungs ($n=3$), abdomen ($n=3$), adrenal gland ($n=3$), bone ($n=2$), and cranium ($n=1$).

There were 57 (52.3 %) patients with HCC that met the Milan criteria and 65 (59.6 %) patients with HCC that met the UCSF criteria. Of these patients, eight (7.3 %) had HCC that

Table 2 Tumor characteristics and outcomes of recipient within and beyond the Milan criteria ($n=109$)

Variables	Within ($n=57$)	Beyond ($n=52$)	<i>p</i> value
Preoperative AFP level (mean \pm SD)	83.8 \pm 168.9	194 \pm 393.4	0.028 ^a
Number of tumor (mean \pm SD)	1.4 \pm 0.7	6.2 \pm 5.9	<0.001 ^a
Total tumor size (mean \pm SD, mm)	30.3 \pm 13.2	110.2 \pm 52.6	<0.001 ^a
Multifocality, <i>n</i> , (%)	17 (29.8 %)	43 (82.7 %)	<0.001 ^b
Vascular invasion, <i>n</i> (%)	3 (5.4 %)	10 (18.9 %)	0.030 ^b
Poor differentiation	3 (5.4 %)	11 (20.8 %)	0.018 ^b
Recurrence rate, <i>n</i> (%)	3(5.4 %)	13(24.5 %)	0.005 ^b
Follow-up (mean \pm SD/median)	35.2 \pm 27.9/34.5	35.1 \pm 25.2/29.0	0.875 ^a

^a Mann–Whitney *U* test^b Chi-square test

exceeded the Milan criteria, but met the UCSF criteria. HCC that exceeded the Milan or UCSF criteria was associated with significantly higher preoperative AFP levels, the number of tumor for each patient, total tumor size, multifocality, and poorer differentiation as compared with HCC that met the Milan or UCSF criteria (Tables 2 and 3). The recurrence rate was significantly higher for patients with HCC that exceeded the Milan and the UCSF criteria as compared to those that met the criteria (5.4 versus 24.5 %; $p=0.005$ and 7.7 versus 22.7 %; $p=0.041$, Tables 2 and 3).

By univariate analyses, no statistically significant associations were found between recurrence and patient age, gender, pre-transplant MELD and Child-Pugh scores, pre-transplant AFP levels, pre-transplant waiting time, cirrhosis etiology, or the number of tumor (all $p>0.05$). Univariate analyses indicated associations between HCC recurrence and Milan criteria, UCSF criteria, largest and total tumor sizes, multifocality, and poorly differentiated tumors. Using risk factors that were identified as significant by univariate analyses, logistic regression analysis showed that there were no independent risk factors associated with tumor recurrence.

We assessed factors possibly associated with cancer-related death using univariate analysis. No significant associations

were found between survival and patient age, cirrhosis etiology, preoperative AFP levels, MELD and Child-Pugh scores, number of tumors, tumor multifocality, or tumors that exceeded the Milan and UCSF criteria (all $p>0.05$). Patients who died of cancer had significantly larger tumors (51.7 \pm 32.5 versus 34.6 \pm 20.6 mm; $p=0.022$) and higher rates of poorly differentiated tumors (5 (41.7 %) versus 9 (9.6 %); $p=0.004$). By multivariate analysis, only poorly differentiated tumors were associated with a lower survival rate (OR=8.7, 95 % CI 2.01–37.2; $p=0.004$).

Of 27 (24.8 %) patients who died after transplantation, 12 (44.4 %) died of HCC recurrence and the others died due to non-tumor-related causes such as biliary sepsis ($n=6$; 22.2 %), liver failure due to chronic rejection ($n=4$; 14.8 %), pneumonia and non-biliary sepsis ($n=4$; 14.8 %), and bleeding due to percutaneous transhepatic cholangiography. The overall patient survival rate was 75.2 %. The overall survival rates for those without recurrence and those with recurrence were 83 and 25 %, respectively. The survival rate was significantly lower for patients with recurrence ($p<0.001$).

There were no significant differences in the survival rates between patients with HCC that met and that exceeded the Milan criteria (1-, 3-, and 5-year survival rates 96, 85.7, and

Table 3 Tumor characteristics and outcomes of recipient within and beyond UCSF criteria ($n=109$)

Variables	Within ($n=65$)	Beyond ($n=44$)	<i>p</i> value
Preoperative AFP level (mean \pm SD)	80.7 \pm 161.9	221.1 \pm 424.5	0.015 ^a
Number of tumor (mean \pm SD)	1.5 \pm 1.0	6.9 \pm 6.1	<0.001 ^a
Total tumor size(mean \pm SD, mm)	34.4 \pm 16.7	120.4 \pm 51.9	<0.001 ^a
Multifocality, <i>n</i> (%)	23 (35.4 %)	37 (84.1 %)	<0.001 ^b
Vascular invasion <i>n</i> , (%)	6 (9.2 %)	7 (15.9 %)	0.291 ^b
Poor differentiation	4 (6.3 %)	10 (22.7 %)	0.012 ^b
Recurrence rate <i>n</i> (%)	5 (7.7 %)	10 (22.7 %)	0.041 ^b
Follow-up (median, months)	23	33.5	0.294 ^a

^a Mann–Whitney *U* test^b Chi-square test

76.6 % for those that met these criteria versus 91, 81.4, and 71.5 % for those that exceeded these criteria; $p=0.761$, log-rank test; Fig. 1). The survival rates for patients with HCC that met and exceeded the UCSF criteria were also similar (1-, 3-, and 5-year survival rates 94.8, 84, and 75 % for those that met these criteria versus 94.9, 78.3, and 70.1 % for those exceeded these criteria; $p=0.861$; Fig. 2). The 1-, 3-, and 5-year survival rates for patients with HCC that exceeded the Milan criteria but met the UCSF criteria were 75, 75, and 75 %, respectively. There were no significant differences in the survival rates between patients with HCC that met the Milan criteria, that exceeded the Milan criteria, but met the UCSF criteria, and those exceeded the UCSF criteria ($p=0.552$).

Discussion

Our results showed that there were no significant differences in the survival rates of patients with HCC that met the expanded selection criteria and those met conventional selection criteria. Moreover, the 5-year survival rate for patients with HCC that exceeded the Milan and UCSF criteria supported the proposition these two sets of criteria for transplantation may limit the transplant option for patients who might benefit from LT.

The first outcomes with LT for HCC showed low survival rates and high recurrence rates after transplantation [10, 11]. The early outcomes with LT for HCC with an extensive tumor burden had discouraging outcomes due to HCC recurrence

[12]. At that time, the recurrence rates at 3 years after LT were 43 and 54 %, respectively [13–15]. These disappointing outcomes ultimately resulted in refining patient selection criteria based on tumor sizes and numbers. These criteria, known as the Milan criteria, have significantly improved patient survival rates [8]. However, a subsequent report by Yao et al. indicated that the Milan criteria may be too restrictive [9], and they proposed the UCSF criteria. They found that patients who underwent LT for HCC under these more liberal criteria had outcomes that were comparable to those that met the Milan criteria. They suggested that expanding the conventional selection criteria would allow more patients with HCC to undergo LT without affecting the outcomes [9]. Moreover, several studies have shown that patients who did not meet these criteria survived longer than would be expected [16, 17].

The largest series from a multicenter study in Japan included a total of 316 patients; the 3-year patient survival rates were 79 % for patients with HCC that met the Milan criteria and 61 % for those did not [16]. The same study showed that among patients with HCC that met the Milan criteria, only 1.4 % had tumor recurrence, whereas 22.2 % of those who exceeded these criteria had recurrence. Another study done in the USA that included LDLT showed the 5-year survival rate was 87.1 % for patients with HCC that met the Milan criteria and was 80 % for those exceeded the Milan criteria. In that study, the HCC recurrence rate was 23 % for those with tumors met the Milan criteria and was 42.8 % for those with tumors exceeded the Milan criteria [18]. Our results in this study showed that the survival rates of patients with HCC that

Fig. 1 Survival in patients with HCC within and beyond the Milan criteria

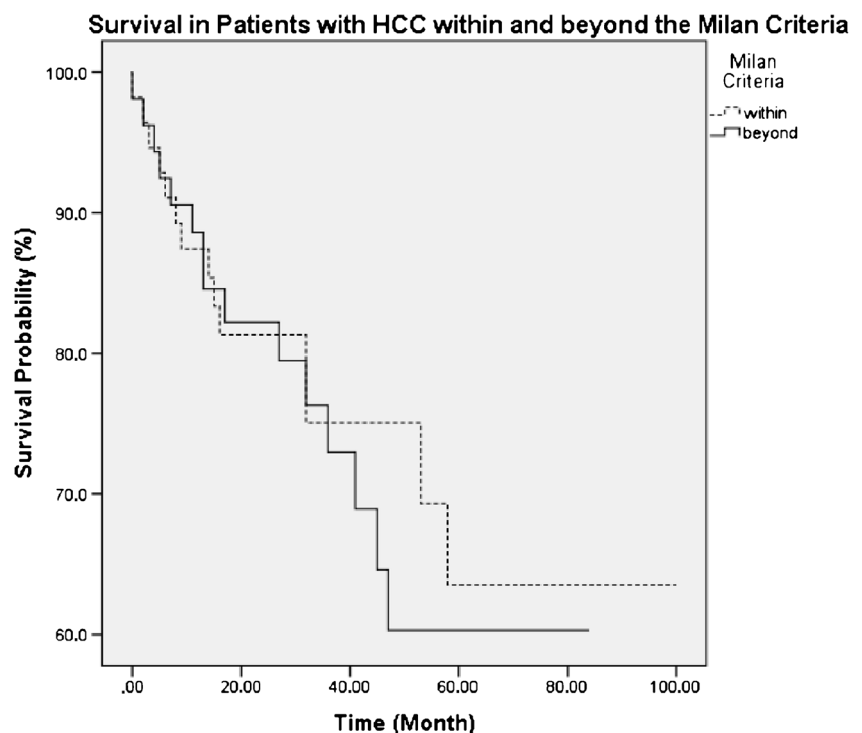
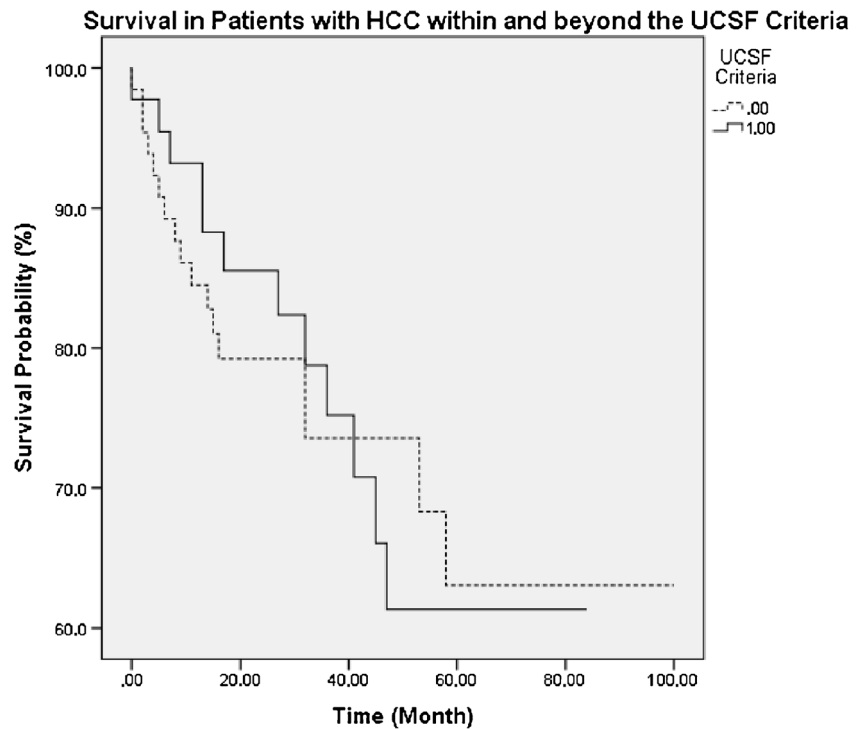


Fig. 2 Survival in patients with HCC within and beyond the UCSF criteria



met and those exceed the Milan criteria were comparable: 1-, 3-, and 5-year survival rates of 96, 85.7, and 76.6 %, respectively, when meeting these criteria versus 91, 81.4, and 71.5 %, respectively, when exceeding these criteria.

Using the UNOS database, Patel et al. showed that survivals between the Milan and UCSF criteria cohorts were similar (1-, 2-, 3-, and 4-year survival rates of 89, 81, 76, and 72 %, respectively, for the Milan criteria versus 91, 80, 68, and 51 %, respectively, for UCSF criteria. They concluded that both the Milan and UCSF criteria were not independent predictors of improved survival [19]. Our results were consistent with that study as our 1-, 3-, and 5-year survival rates were 96, 85.7, and 76.6 %, respectively, with the Milan criteria versus 94.8, 84, and 75 %, respectively, with the UCSF criteria. These results were supported by a large multicenter study that included LDLT for HCC that showed a 3-year survival rate of 91.4 % for those that met the Milan criteria and a 3-year survival rate of 90.6 % for those that met the UCSF criteria [17].

In another study that involved deceased donor liver transplantation (DDLT), Duffy et al. reported a 3-year survival of 89 % for patients with HCC that met the Milan criteria and 83 % for those that met the UCSF criteria [20]. Khashayar et al. found a 5-year survival rate of 87.1 % for patients with HCC that met the Milan criteria versus 80 % for patients with tumors exceeded the Milan criteria, but met the UCSF criteria [18].

There also remains controversy regarding the outcomes with LDLT versus DDLT for patients who receive LT for HCC. While some studies reported inferior results after LDLT

[21, 22], other studies reported similar outcomes. In a multi-center study done in Korea that included 237 LDLT and 75 DDLT recipients, when the UCSF criteria were met, there was no difference in the 3-year survival rate; 88 % with DDLT and 91 % with LDLT [17].

Given the similar survival rates of transplant patients who were selected using conventional and expanded criteria, questions arise regarding whether the current criteria are still too restrictive and, thus, exclude many candidates from LT who might otherwise do well with an acceptably low risk of post-transplant tumor recurrence. Therefore, appropriate selection of HCC patients is necessary to optimize the allocation of the limited organs available for DDLT and for justifying the risks to living donors for LDLT. In light of these concerns, extending the LT criteria for HCC needs to be carefully balanced with respect to the limited organs available and the outcomes of patients who undergo LT with HCC that exceeds the Milan and UCSF criteria. In the current study, 47.7 % of our patients had HCC that exceeded the Milan criteria and 40.4 % had HCC that exceeded the UCSF criteria, which allowed us to compare the outcomes of patients with HCC that both met and exceeded these two sets of criteria. Our study results were consistent with previous studies that showed no survival differences in patients with HCC for both those that met and those exceeded the Milan criteria [9, 16, 18] and for those that met both the Milan and UCSF criteria [17, 19]. Although the UCSF criteria have been shown to be associated with a long-term survival similar to the Milan criteria [23–25], little is known with regard to the outcomes of patients with HCC that exceed the UCSF criteria.

In one of the largest series, Duff et al. reported a 3-year survival of 83 % for those that met the UCSF criteria and 48 % for those exceeded the UCSF criteria [20]. A large series from an LDLT center showed that the overall 5-year survival rate, including perioperative mortalities, was 75.9 % for those that met the UCSF criteria and was 36.4 % for those exceeded the UCSF criteria. The same study reported 3-year HCC recurrence rates of 14.0 % for those that met the UCSF criteria and 51.6 % for those exceeded the UCSF criteria [26]. The reason why the latter group had a worse survival could be because this study included perioperative mortality. However, in both studies, the survival rates for those exceeded the UCSF criteria were disappointing. Our outcomes in this study were not consistent with these previous results, as we found that the 5-year survival rates for patients with HCC that met and exceeded the UCSF criteria were 75 and 70.1 %, respectively. In this study, the HCC recurrence rate was 9.1 % for those that met the UCSF criteria and was 22.7 % for those exceeded UCSF criteria.

Recent evaluations of the expanded selection criteria with a multicenter series suggested that the pathological characteristics of tumor grade and microvascular invasion may be more important determinants of survival than tumor size [24, 27]. In this study, although the rates of tumor multifocality and larger tumor size were higher for patients who had HCC recurrence, our multivariate analysis showed that only poor tumor differentiation was an independent risk factor for survival.

Although our results showed that liver transplantation (LT) provides excellent outcomes in patients with HCC within the Milan criteria, the appropriate treatment remains controversial in literature for patients with Child A and HCC within the Milan criteria. At our center, from the beginning, we have performed liver transplantation for patients with Child A and HCC within the Milan criteria as our center policy. Therefore, in this study, we had no data on outcomes of liver resection to compare with LT for these patients and to discuss in further for our outcomes. However, several studies compared the outcomes of LT and liver resection (LR) for these patients in literature. Some studies showed the superiority of LT over LR for patients with Child A and early HCC [28], while others recommend resection due to some reasons such as scarcity of organs and high cost despite they admit that the best option is still LT for these patients [29]. A meta-analysis showed that in patients with early HCC, LT is associated with a significant survival advantage over LR [30]. Overall, based on literature and our outcomes of LT for HCC within the Milan criteria, we recommend LT for these patients.

This study had several limitations. We recently began to routinely perform downstaging therapies at our center. All patients who had LDLT prior to this date were included in this study. Therefore, a few patients in this study had pre-transplant downstage therapy which was considered to be a limitation. Because there were some missing radiologic data,

another limitation was the selection criterion based solely on explant liver findings. Therefore, with the current data set, it was not possible to determine the correlation between prelisting imaging findings and explant pathology.

Conclusion

The survival rates of patients with HCC that exceed these expanded criteria may prompt the transplant community to reconsider an acceptable threshold of expanded criteria that may allow for more HCC patients to undergo LT without affecting their outcomes.

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