Prediction of Microvascular Tumor Invasion in Liver Transplant Candidates With Hepatocellular Carcinoma: A Feasible Concept or a Misleading Illusion?

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ABSTRACT

Introduction. Hepatocellular carcinoma (HCC) in cirrhosis is a widely accepted indication for liver transplantation (LT). Many scoring systems have been proposed intending to an extension of the established Milan criteria. Bridging treatments are systematically applied in order to maintain or to downstage such patients to the listing criteria. The objective of our study was to estimate the feasibility of the prediction of microvascular tumor invasion in transplant candidates.

Patients and methods. Data corresponding to transplanted HCC patients were reviewed for the purposes of this study. All tumor slices were blindly re-evaluated by a single pathologist in order to score for tumor necrosis and microvascular invasion. Recipients of pediatric or split LT were excluded.

Results. Eighty patients (30 women and 50 men) were included in the study. Tumor necrosis was absent in 29 of 80 liver explants (36.25%). In the majority of instances (63.75%) tumor necrosis was evident in proportions between 5% and 100%. In 58 liver explants showing 0%-60% tumor necrosis and 22 liver explants showing $>60\%$ tumor necrosis, microvascular tumor invasion was detectable in 11 and 0 cases, respectively ($P = .0385$).

Conclusion. In about one-fourth of the cases (27.5%) microvascular tumor invasion could not be detected due to extended areas of tumor necrosis. Preoperative detection of microvascular invasion is misleading.

SINCE the proposal of the Milan criteria by Mazzaferro in 1996 [1], hepatocellular carcinoma (HCC) in cirrhosis has become one of the leading indications for liver transplantation (LT). However, the current endemic of HCC and its increasing incidence, together with the encouraging oncologic long-term results after LT for HCC, is driving many transplant groups in remarkable efforts to expand these transplant criteria [2]. This has resulted in some 20 different transplant criteria for HCC coming from all over the world [3]. The strong will to open the transplant option to more HCC patients is also inspiring transplant surgeons to optimize and evolve transplant techniques, using split grafts and live donor grafts for this purpose [4–7].

A notable scoring system, proposed by the instructor of the Milan criteria through a multi-institutional study, was the "up-to-seven" criteria [8]. These incorporated HCCs "with seven as the sum of the size of the largest tumor (in cm) and the number of tumors" in the absence of microvascular invasion. Nonetheless, the feasibility of the pre-transplant detection of microvascular invasion in liver cirrhosis, in patients undergoing bridging treatments during the waiting time to LT may be questionable. The aim of this study was to assess the feasibility of the prediction of microvascular tumor invasion in transplant candidates.

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PATIENTS AND METHODS

Data corresponding to transplanted HCC patients in our institution during a 7-year period were reviewed for the purposes of this study. All tumor slices were blindly re-evaluated by a single pathologist (W.S.) in order to score for tumor necrosis and microvascular invasion. Recipients of pediatric, split, or live donor LT were excluded. Significance of differences was assessed by χ^2 test.

RESULTS

Eighty patients (30 women and 50 men) were included in the study. Liver cirrhosis was the result of viral infection (hepatitis B, hepatitis C) in the majority of instances (75%). More than half of the patients (n = 48) received tumor-specific bridging treatment (radiofrequency ablation, transarterial chemoembolization) prior to LT. Tumor differentiation/grade was well/low grade, moderate/intermediate grade, poor/high grade, or not possible/undetermined grade (due to extended areas of tumor necrosis) in 22, 38, 10, and 10 cases, respectively. Tumor necrosis was absent in 29 of 80 liver explants (36.25%). In the majority of instances (63.75%) tumor necrosis was evident in proportions between 5% and 100% (Table 1). In 58 liver explants showing 0%-60% tumor necrosis and 22 liver explants showing > 60% tumor necrosis, microvascular tumor invasion was detectable in 11 and 0 cases, respectively ($P = .0385$) (Table 2).

DISCUSSION

The achievement of extended tumor necrosis represents a cardinal goal of the applying tumor-specific bridging treatments during the waiting time to LT [9,10]. In the case of explanted livers, the success of these invasive radiological methods can be estimated not only in the post-interventional cross-sectional imaging, but it can also be particularly checked in the histological work-up of the specimen. Extended tumor necrosis obtained through these locoregional treatments can minimize the risk of tumor recurrence post-LT, especially if the gained necrosis is > 60% [11].

In 15% of our cases tumor grade was undetermined because of extended areas of tumor necrosis. Using the achievement of 60% tumor necrosis in our series of liver explants, we were surprised to realize that no microvascular invasion could be detected in HCCs with tumor necrosis more than this threshold. This observation is based on a small patients' cohort. Given that the bridging treatment policy is applied in most transplant centers and that such extended areas of tumor necrosis are to be expected, we believe that the preoperative detection of microvascular invasion is illusive and that this is one of the reasons that the "up-to-seven" criteria did not find broad acceptance [12].

Table 1. Patient Characteristics

Sex	
Male	50
Female	30
Median age (range)	59 (18–66)
Type of OLT	
DDLT	42
LDLT	33
SLT	5
Median number of tumors (range)	2 (1–4)
Median tumor size (cm) (range)	3 (1.1–3.6)
Bridging treatment	
TACE	36
RFA	9
TACE and RFA	3
Tumor grade	
G x	10
G I	22
G II	38
G III	10

Abbreviations: DDLT, deceased donor liver transplantation; G x, undetermined tumor grade; LDLT, live donor liver transplantation; OLT, orthotopic liver transplantation; RFA, radiofrequency ablation; SLT, split liver transplantation; TACE, transarterial chemoembolization.

Table 2. Correlation Between Percentage of Tumor Necrosis in Liver Explants and Detection of Microvascular Invasion

Tumor Necrosis (%)	Vascular Invasion microV1/total cases
0%	2/29
5%	1/2
10%	1/6
20%	1/4
30%	2/7
40%	1/4
50%	1/1
60%	2/5
70%	0/5
80%	0/2
90%	0/5
95%	0/1
100%	0/9
	11/80

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