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LETTER TO THE EDITORS

Fifty-six-month survival after liver transplantation in a patient with more than one-hundred hepatocellular carcinoma nodules

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Dear Sirs,

Hepatocellular carcinoma (HCC) is the most frequent primary malignancy in the adult population, and responsible for about 600 000 deaths annually worldwide [1]. Most patients affected with HCC are diagnosed when curative treatments are not feasible. Liver transplantation (LT) has been defined as the ideal therapy in cases of HCC that fulfill the Milan criteria [2]. However, there is an increasing uncertainty regarding the possibility of restricting transplantation to these patients only, and a number of proposals to expand the Milan criteria have been made [3–5].

Two of the principal aspects of this debate regard the potential use of extended criteria donors (ECD) for recipients exceeding the Milan criteria [6], and the role of the molecular signature for HCC as both a predictive parameter of HCC recurrence after LT and a marker of selection before LT [7]. We report a case of 56-month survival after LT in a patient with more than 100 HCC nodules.

A particular type of ECD graft was used, and fractional allelic imbalance analysis confirmed a favorable prognosis for LT. In 2004, a 57-year-old man was diagnosed with a 14×12 cm HCC of the right lobe. His liver was non cirrhotic, and his viral serologies negative. He underwent embolization of the right portal vein, and, after unsatisfactory hypertrophy of the left lobe, embolization of the right branch of the hepatic artery. Two months later, he underwent explorative laparotomy, during which process spread of the HCC into the left lobe was discovered.

This patient, with a giant, multifocal HCC, was obviously an exception to the Milan criteria for LT in HCC patients. With consent from our Internal Review Board, which is composed entirely of clinicians, the patient was placed on a special list of potential recipients of ''livers that nobody wants'' [6]. A detailed informed consent was obtained. Over the following 3 years, the patient was followed-up with periodic CT and MRI scans, which showed progression of the neoplastic disease only within the liver, reaching up to 17×13 cm for the large lesion of the right lobe, and more than 100 HCC nodules between 1 and 4 cm (Fig. 1). His extra-hepatic portal vein remained patent. No additional therapy was undertaken.

Although otherwise stable, with preserved hepatic and renal function, the patient complained of discomfort, attributable to his hepatomegaly. His alfa-fetoprotein was 2.6 ng/ml. Liver biopsy confirmed a well differentiated HCC, and the remnant liver showed moderate portal fibrosis with focal portal bridging. There was no evidence of steatosis or parenchymal necrosis.

In June, 2007, a liver become available at a local hospital. The donor had died of a cerebral-vascular accident, and was judged at high risk of virally transmitted disease, particularly HIV, because of his social behavior. The donor's standard serology was negative, including antibody for HIV, but because he became hemodynamically unstable there was no time for the PCR test for HIV RNA. For this reason, the liver was rejected by all centers in Italy, and offered for our patient.

Liver transplantation was performed with venous-venous bypass during hepatectomy. No systemic anticoagulation was given. A standard technique was used to engraft the liver [8]; the weight of the explanted liver was 7 kg. The explanted liver histology reported ''multifocal well-to-moderately differentiated HCC; largest nodule 23.5 cm; multiple smaller nodules ranging from 0.5 to 2.5 cm, focal vascular invasion present, no perineural invasion identified. Non neoplastic liver parenchyma shows nodular regenerative changes and mild to moderate portal fibrosis; portal vein branches with minimal to mild fibrointimal hyperplasia; gallbladder with diffuse autolysis; adrenal gland negative for malignancy. TNM stage T3, NX, MX.'' The postoperative course was uncomplicated, and the patient was discharged home on postoperative day 14 on an immunosuppression regimen of tacrolimus and a low dose of steroids. The steroids were discontinued at 90 days.

The patient did very well for the first 2 years, but then developed a single-bone osteolitic lesion, which was treated with selective radiotherapy. Currently, the patient is doing very well 56 months after LT.

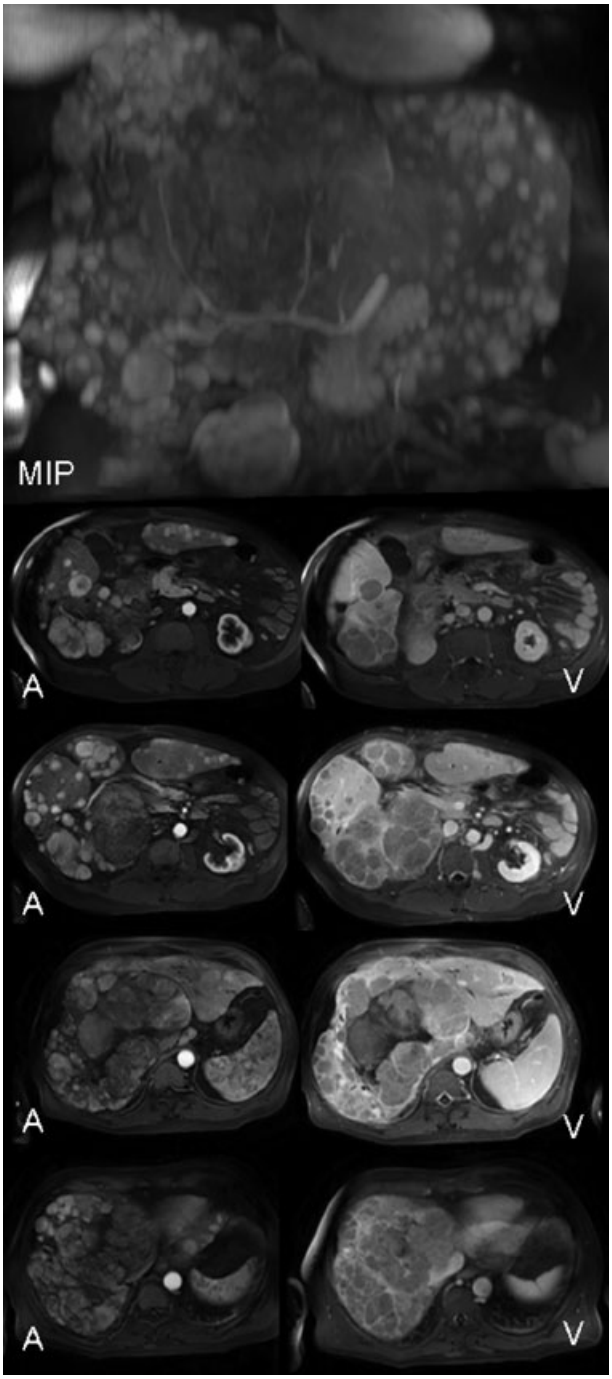

Figure 1 Magnetic resonance image with intravenous contrast media injection: oblique multi intensity projection (MIP) image acquired during the arterial phase shows multiple bilobar hypervascular lesions. The axial images show the hypervascular lesion visualized in the arterial phase (A), with corresponding washout in the venous phase (V.)

Based on newer methods of molecular classification of HCC [7], which provide better risk stratification and, in particular, define risk of recurrence after transplant, we retrospectively analyzed the genotype of the HCC. We performed an loss of heterozygosity (LOH) analysis, calculating the allelic imbalance in microsatellite regions of the tumor DNA compared with the same regions of DNA from the normal liver tissue. Of eight loci, only one showed LOH, with a calculated fractional allelic imbalance (FAI) equal to 16.6%, which is low, and associated with a low risk of recurrence.

In our case, it was the biology of the tumor rather than the radiologic characteristics that ultimately determined the clinical outcome. A member of our group (JWM) has described the correlation between loss of heterozygosisty (LOH) at different DNA loci and patterns of HCC recurrence after LT [9]. Those data were combined with an artificial neural network analysis, which provides high accuracy in terms of predictability of HCC recurrence after LT [10]. The finding of low FAI in our case, examined from the explanted liver, was associated with late recurrence, confirming the value of this molecular testing and its potential for clinical application.

In highly select patients, the possibility of using ''livers that nobody wants'' could be explored in the setting of a selection process based on the use of per-protocol liver biopsy, radiologic evidence of vascular infiltration, and molecular signature for HCC. This case stresses once again the notion that certain patients defined as outside the Milan criteria could benefit from LT.

Our case is not paradigmatic of any suggested algorithm or of a practice for listing patients with HCC outside the Milan criteria. Moreover this patient had neither cirrhosis nor viral hepatitis and by definition could not fit in the setting of the Milan criteria, but into a high selected subgroup. However, its uniqueness lies in the combination of extreme conditions, such as the number of HCC nodules, and long survival, confirmed by post transplant genetic analysis.

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