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Selection of Hepatocellular Carcinoma Patients for Liver Transplantation: Should the Threshold for Expected Oncological Survival Be Lowered?

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Liver transplantations are performed on patients affected by a variety of pathologies. Observed survival rates are quite variable.

To set a standard for selecting recipients among Hepatocellular carcinoma (HCC) patients, the *Milano criteria*[1] were proposed in 1996. They require a recipient's tumor status allowing a 70% rate for oncological survival at 5 years to be expected.

Transplants are also performed in patients with other indications and smaller expected survival rates.

Because of organ shortage, strict rules might be recommended to ensure successful long-term transplantations in carefully selected recipients, and yet lower values of expected survival rates as well as shorter terms of survival seem to be tolerated for several categories of recipients. The single notable outliers are HCC patients for whom the general agreement is that the Milano criteria must be satisfied.

One might raise the question about transplantation in those HCC patients with a priori survival chances at 5 years smaller than 70%. Indeed, improved harvesting possibilities and reduced prevalence of Hepatitis C, as well as excess of donors in some specific geographical regions, make us feel that in this case too the expected rate of oncological survival can be lowered. In this way, a larger number of HCC patients with low laboratory Model for End-Stage Liver Disease (Lab-MELD) and excellent medical conditions could receive the graft and improve their life conditions.

This letter aims at pointing out the reasons that lead us to this conclusion.

The difficulty in setting the goal of liver transplantation (LT) for hepatobiliary malignancies has been mentioned in several publications.[2-5] According to a recent editorial published on *Annals of Surgery*, to make the best out of a donated liver, the acceptable survival rate is 50% at 5 years.[4]

The Euro-transplant Organ Sharing Organization reported that a group of transplanted patients with Lab-MELD score ≥40 had a 57% survival rate at 3 years, whereas high urgency status patients with Lab-MELD ≥45 and patients with high urgency status for acute retransplantations and Lab-MELD ≥35 had a 3-year survival rate of 46% and 42%, respectively.[6] The Mayo Clinic reports that transplants performed because of de novo hilar cholangiocarcinoma had a five-year survival rate of 56%.[4] The Norwegian SECA-I trial found a 56% overall survival rate at 5 years in 21 patients transplanted for locally advanced colorectal liver metastases, with 19 out of the 21 patients developing recurrent disease in the liver graft after a median time of 6 months.[7,8] The University of California, Los Angeles group reported an average survival rate at 5 years of 48% among 426 adult patients who underwent 466 retransplantations between 1984 and 2010, with survival rates at 5 years varying from 22% to 79%.[9] The European Transplant Registry reports that before the introduction of the Direct-Acting Antivirals, the rate of survival of patients transplanted because of HCV-related cirrhosis was 60% at 3 years after transplant.[10] Moreover, the number of patients with HCV-related cirrhosis in waiting list for transplantation has dropped by >30% in <4 years since the introduction of the Direct-Acting Antivirals.[11] Last but not least, an "excess donors" is being experienced in countries such as Norway, where livers are transplanted even in patients with hepatic metastases from colorectal carcinomas[7] with expected rates of oncological survival at 5 years smaller than 70%, and several countries are following the Norwegian lead.[5,12]

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Countries with excess donors, because of their culture or organization, will perhaps be able to extend the indications. It can be hoped that these countries will enter new experimental trials or even share the surplus with neighbors where grafts are scarce.

In countries of the so-called Far East, >1 in 3 transplantations in HCC recipients is performed neglecting the Milano criteria.[13] In these countries, the majority of grafts are from living donors that might be considered private acts warranting different indications for the recipient while in keeping with the double equipose. Because the need for an urgent retransplantation can never be excluded, when the recipient needs a new graft from a deceased donor, the principles of equity demand that the recipients of grafts from living donors fulfill the same criteria as the patients on the waiting list for grafts from deceased donors.

In 2017, an algorithm has been generated, the Metro Ticket 2.0,[14] able to predict with reasonable accuracy the rate of oncological survival at 5 years after transplantation in HCC patients. The access to the Web site is free and anybody can receive in real time the prognostic when the characteristics of the tumor (number and size of the nodules, serum level of alpha fetoprotein) are keyed in.

That the general conditions for LT have changed in recent years is indicated by the very existence of this algorithm and the general acceptance of transplant indications with low survival rate at 5 years for non-HCC patients, as well as the excess donors linked to the progressive reduction of HCV-related cirrhosis. And indeed, to give an example, even the group that proposed the Milano criteria would agree on extending *with a grain of salt* the oncologic indications in LT "Pro (with cautions)."[3]

Perhaps the time is appropriate to consider the possibility of extending the rules of 70% survival at 5 years for HCC-related liver transplants. For instance, selected HCC patients with chances of oncological survival at 5 years between 70% and 50% could be accepted on the waiting lists, with 50% being the commonly accepted reasonable chance for success.[4] When establishing a waiting list for HCC patients with expected shorter oncological survival, we would recommend following the same allocation algorithm that is in use for the other HCC patients in the organ-sharing region.

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