Editorial

Resection *vs*. transplantation for hepatocellular carcinoma: a never ending challenge

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Liver transplantation (LT) is fully established in conventional clinical care for patients with hepatocellular carcinoma (HCC). The long-term survival of transplanted patients competes with the survival offered by surgical resection and this sets the scene for a debate for which a consensus answer based in evidence is not available. Resection outcomes have steadily improved due a refined selection of patients and the availability of other effective options such as ablation or locoregional approach (chemoembolization or radioembolization) has allowed to avoid its indication as a last effective resource for desperate cases. Same evolution has taken place for LT as it was early shown that if the tumor burden was reduced the survival results would be encouraging (1). Ultimately, Mazzaferro *et al.* established the so-called Milan criteria (single tumor <5 cm or up to three nodules <3 cm) that provided a median 5-year survival beyond 70% with a reduced recurrence rate (2). These criteria have been extensively validated and are applied worldwide, while at the same time being the benchmark against which any expansion needs to be compared. As exposed, the criteria define two distinct groups of patients with a completely different profile in terms of tumor burden leading to a different risk of recurrence after resection. Hence, the debate around resection *vs*. transplantation for HCC patients within the Milan criteria should analyze these two groups in a separate manner as has been done by Koh *et al.* (3). Further complexity has to be taken into account in the comparison. Impaired liver function prevents safe resection and, in such instance, there is no debate as transplant always offers a better outcome. However, transplantation indication may imply a waiting time during which the tumor may progress and prevent effective transplantation. This may be surpassed by live donation that is frequent in Asia, while in the West it still occupies a minority role as most transplants are based on cadaveric donation.

The metanalysis by Koh *et al.* (3) inspects all these aspects and offers a major set of data to inform physicians at the time of treatment recommendation. The authors analysis reports recurrence-free survival and overall survival in studies identified by an extensive search. They have included investigations from Europe, North America, and Asia with a total of 35 studies involving 18,421 patients. Among LT recipients, 78% underwent living donor

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liver transplantation (LDLT), the dominant mode of LT in Asia, while 19.89% underwent deceased donor liver transplantation (DDLT). In non-Asian transplant centers, there was a similar proportion of patients that underwent LDLT and DDLT. It has to be stressed that recurrence-free survival has to be seen as a vulnerable end-point as it is influenced by the heterogeneous follow-up strategy in separate centers, and affecting interval of assessment, imaging techniques used and criteria applied to register recurrence. By contrast, survival is a hard end-point and indeed, is the aspect most valued by patients. They always ask: "How much time I have? How long will I survive?".

First message from the metanalysis is that in patients with impaired liver function the survival outcome is always better for LT independently of the tumor profile. This is not a novel finding but serves to understand why resection provides competing outcomes if patients are properly selected according to state of the art knowledge. This has increased in the last decades and as a consequence, patients who could have been selected for surgery decades ago, are now discarded for it and either be derived to transplantation or to any locoregional approach (4). The recognition of the importance of portal hypertension to be associated to poorer outcomes has primed the exclusion of those with severe portal hypertension, even in the absence of decompensation, that would clearly suggest to avoid resection (5). Laparoscopic (6) and/or robotic resection (7) and better intra and postoperative management have sure had a favorable impact. These comments serve to understand why survival after resection in patients with single tumors is not different from transplantation, while this was not the case years ago. On the contrary, in patients with multifocal disease, even if defined as within Milan criteria, the survival is better after transplantation and this is associated to a clearly lower recurrence rate. This is not an unexpected result as multifocal disease is an established predictor of higher recurrence risk and as a consequence an impaired long-term outcome. Furthermore, imaging techniques have improved significantly along the years, but sure there are still unrecognized disseminated nests. These may be more frequent in multifocal tumors and emerge during follow-up. Obviously, liver resection may be safely performed if liver function is preserved (8), but recommending resection because of the aim to achieve "cure" may not be beneficial. Survival may be better with transplantation and locoregional approach may provide similar life expectancy (9,10). A prospective trial comparing resection *vs.* locoregional intervention seems to have the needed background. Survival figures described in resected candidates with preserved liver function and outcomes reported in cohort studies and trials testing ablation and chemoembolization or transarterial radioembolization, provide the needed assumptions to design and run such a needed investigation. It should be a multicenter international effort that would control the relevant heterogeneity of the target population. Thereby, while in the West most of the patients with HCC present underlying chronic liver disease due cirrhosis related to hepatitis C virus (HCV), alcohol or non-alcoholic steatohepatitis, patients in the East more frequently present hepatitis B virus (HBV) infection without advanced liver disease reaching cirrhosis. This sure introduces complexity in trial design but it can be solved by adequate stratification prior to randomization.

Having raised all these comments, do we think that the debate is over? Not the case at all. The access to LT is still very limited by the number of available organs. This is especially intense in Asia and has primed the development of very active and successful programs of live donation. Survival and recurrence are the same, if not better, as with cadaveric donation (11). As a consequence, this option should not be neglected in the West in areas with a relevant shortage of donors that is unable to solve the demand of organs for HCC and non-HCC patients. The effectiveness of surgery could be expanded by establishing strategies to improve liver function and prevent its deterioration associated to surgery. This could increase the proportion of patients who may benefit from safe resection and reduce the pressure in the transplant demand.

The fact that resection provides the same survival as transplantation in well selected patients with single HCC has allowed to give priority to resection and reserve transplantation for those at risk of recurrence as predicted by the pathology analysis of the resected tissue. No effective option to reduce recurrence risk was available until the recent announcement of the positive results of a trial testing the combination of atezolizumab and bevacizumab *vs.* placebo in patients with HCC treated by resection or ablation and classified as at high risk of recurrence (12). Availability of the data will allow to define if such treatment prevents recurrence or just delays its emergence and does not modify the final number of patients with recurrence in need of salvage transplantation or other treatment. Presence of microvascular invasion and/or satellites is associated to a high risk of recurrence and transplant could be proposed because of such risk. This is known as "ab initio"

strategy (13) that differs from the usual delay of transplant consideration until recurrence is in place. Unfortunately, there is no molecular profile that is able to surpass the eye of the pathologist and this is an area of active investigation.

However, while some strategies may expand the availability of organs, the current trend is to increase the number of enlisted patients through different proposals. In some settings, if the patients exceed Milan criteria while waiting for a donor, they are excluded from the waiting list. However, allowing some minor progression even beyond Milan criteria may still offer acceptable outcome but at the cost of a higher recurrence rate (14). This is also observed in any proposal to expand the criteria for enlistment or incorporate those patients with excessive tumor burden but in whom locoregional or systemic treatment reduces tumor extension and bring the patients into the Milan criteria. This downstaging strategy is usually based in the activity of locoregional therapies to induce tumor necrosis and hence, reduction in total tumor load. Several studies report encouraging data (15) but critical methodological aspects have to be taken into account to fully accept that the downstaging strategy has a robust scientific evidence (16). This comment also applies to the recent suggestions about the capacity of immune oncology agents (IOs) to convert patients with advanced HCC (even with vascular invasion) into resectable or transplantable candidates (17). Large studies are awaited in order to confirm the potential efficacy of such agents, as well as their safety both in the pretransplant setting as well after transplant.

In summary, the data offered by Koh *et al.* provide the information needed to develop a sound strategy in the area of surgical treatment for HCC. This will be a moving target since further developments in several fronts will sure modify treatment priorities and clinical decision making. Clinicians should be aware of all novelties that may occur and through a step by step incorporation of relevant advancements, we will see how the management and outcome of patients with HCC has been dramatically improved as compared to decades ago.

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