Editorial

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Ablation for hepatocellular carcinoma: Is there need to have a winning technique?

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Screening for hepatocellular carcinoma (HCC) in the population at risk (namely patients with liver cirrhosis) is now an established practice [1]. It aims to detect tumors at an early stage so that treatments that may provide a cure for the cancer can be implemented. Years ago, this was seen as an impossible goal and the efforts of those working in the field of clinical liver cancer were seen as unfruitful. However at present, liver resection, transplantation, and ablation are conventional treatments in clinical practice and the current debate centers around which treatments should be given as a priority to patients diagnosed with early HCC. The controversy affects only those individuals who stand to benefit from all treatments. It is clear that patients with early HCC in decompensated cirrhosis will be better served by transplantation if there are no contraindications for it because of age and/or co-morbidities. A commonly held belief is that the depicted uncertainty is easily solved by developing a large, prospective, randomized clinical trial comparing the three options or at least two of them. There are a small number of trials with limited sample sizes and heterogeneous patient populations which have not solved the debate in a robust manner. For a trial to be fully informative it needs to recruit patients whose profile makes them suitable candidates for all three options, as it would not be appropriate to compare suboptimal candidates for surgery with the best candidates for ablation. Since the outcome of liver transplantation is not affected by liver function or by tumor burden if it is still within the Milan criteria [2,3], the key would be to define the optimal candidates for resection and ablation, and then select as the target population for the trial the profile that is shared as optimal for both options and stratify them according to the most relevant. Several studies have shown that nodule size is the major parameter that predicts the success of ablation (the cut-off is around 3 cm in size) [4–7], while presence of more than one nodule also affects efficacy, recurrence, and ultimately, survival [8,9]. Hence, a valid trial should be restricted to this size and if aiming for optimal candidates, should only include solitary HCC. Data for selection of the best candidates for resection are also known: absence of clinically significant portal hypertension reflected by a hepatic vein pressure gradient <10 mm Hg and solitary HCC define the optimal population both in the West [10] and the East [11]. Following these comments, a trial comparing resection vs. ablation should optimally include patients without clinically significant portal hypertension diagnosed with solitary HCC <3 cm. The end-point of the trial should be survival, and available data in cohort studies indicate that we could have a 70% survival at five years in both arms. Accordingly, the trial could be designed as a non-inferiority trial, with the expectation of providing a basis for suggesting that ablation should be the first choice and leave resection for failures. Since the results for ablation are significantly better in HCC $\leqslant$2 cm [4,12] it would be advisable to stratify patients according to this size limit. Now that the trial design is defined, should we ask if such a trial feasible? The answer is clearly negative. The sample size for such a trial would exceed 1000 patients and the study duration would surely last at least 5 years. Liver cancer is not as prevalent as colorectal, breast, or lung cancer and the stratum of patients targeted is very narrow. In the BCLC group, this type of patient profile involves less than 1% of the global HCC population [13] and the proportion should be almost the same in most western referral centers where state of the art surgical and ablative skills are available. Hence, the study should be multi-centric and international and thus requires that a vast monitoring effort be in place for several years. As a whole, the budget projection for such a study would be extremely expensive and any assessment would classify the study as unfeasible and/or not robust enough to reach an unequivocal answer to the hypothesis posed.

In addition to the challenges highlighted above, the investigators would also have to use the optimal ablation technique and maintain it in place, even if new technologies are developed while the trial is running. This has been a very active research front, and as it frequently occurs with device development, the request for robust assessment is less intense than for pharmaceutical agents. The first technique that opened ablation activity for HCC patients consisted in the repeated injection of ethanol through a fine needle inserted into the HCC under US guidance. After initial proof of concept and wide application in several Units, it was clear that tumor size was the main determinant of success. Ethanol infiltration rarely affected all the mass beyond

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3 cm in size and the presence of intratumoral septa prevented diffusion of the ethanol within the HCC [14]. Acetic acid injection was suggested to be an alternative with better diffusion capacity [15], but the real breakthrough came with the development of radiofrequency (RF) [6]. Tumor necrosis was achieved by delivery of heat and all the issues related to diffusion of liquid were gone. In addition, RF has a more predictable necrotic capacity and with less treatment sessions achieves the same therapeutic action [7,16–19]. Hence, RF has become the preferred mode of ablation and ethanol has lost its primacy [20]. Other techniques with promising activity such as microwave, cryotherapy, high intensity focused ultrasound (HIFU) are far behind in the competition.

Is the primacy of RF justified with the available data and for all HCC amenable to be ablated? This is the question posed by Germani et al. in the meta-analysis published in this issue of the *Journal of Hepatology* [21]. Some randomized trials have suggested that this is indeed the case [7,18], but as usual, it might be argued that design details and sample size limitation may allow for some suboptimal evidence. It is in this type of setting that a meta-analytical approach helps to frame the evidence and critically exposes the limitations of the available data. The results confirm that the evaluation of different techniques is not fully robust since the nature of the studies to evaluate them is not homogeneous. Nevertheless, with all the concerns, it appears that the assumption of RF as the first line technique is not incorrect, but this does not mean that ethanol or acetic acid injection is to be dismissed. The data with acetic acid are limited, but the results of ethanol injection in HCC $\leqslant$2 cm in size are not different from those obtained by RF. Hence, the advantage of RF emerges when the success of ethanol is limited by septa and it fails to affect the entire mass. A second reason for better local control of the disease beyond this size is that RF may induce a safety ablation margin that would cause necrosis of already existing satellites and/or microscopic vascular invasions. Distant recurrence would appear whatever technique is in place, but in terms of primary tumor removal, RF would compete better with resection. Does this have an impact on survival or is it just a futile effort to enhance therapeutic response without long term consequences? Several investigations indicate that initial response to ablative treatment is related to improved survival [4] and the intensity of tumor necrosis also correlates with improved survival after TACE [22,23]. Accordingly, for ablation therapy to influence survival it is key to secure complete tumor necrosis as early as possible.

Does this mean that ethanol injection is not useful? Not at all! As said previously, in HCC $\leqslant$2 cm both ethanol and RFA are highly effective and beyond this size limit ethanol and RF will work simultaneously for a short period. Some tumors are located at risky sites and RFA treatment can incur severe complications [24]. In addition, in tumors larger than 2 cm in size, initial RF may leave a tiny nest of viable tissue that will easily be ablated by ethanol with a relevant saving of resources [20].

In summary, ablation is a powerful therapeutic tool for HCC patients and the available techniques have reached maturity with defined capacities and limitations. The current controversy is not about the effectiveness of ablation, but rather about how to prevent disease recurrence, a challenge that also affects surgical resection and limits long term survival. Hope is placed in the future use and efficacy of molecular therapies; however, such a breakthrough will take years to become a reality. In the meantime, data collected in studies like the one by Germani et al. serve to structure conventional clinical decision making. Such studies provide the necessary scientific background to establish the assumptions needed for the design of clinical trials that assess new agents for the prevention of recurrence.

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