Editorial

# Efficacy of radiofrequency ablation of hepatocellular carcinoma prior to liver transplantation and the need for competing-risk analysis

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Radiofrequency ablation (RFA) currently represents a potentially curative treatment for hepatocellular carcinoma (HCC) in its early stages (1,2). Providing higher rates of complete necrosis of target tumor than other loco-regional therapies (LRTs), RFA plays an important role as bridge therapy to liver transplantation (LT) (3). In the study from Lee and colleagues of the UCLA medical center, published in issue of June 2017 of Hepatology, Authors analyzed the outcome of 121 patients with 156 de-novo HCC treated with RFA as initial stand-alone therapy (4). The study is a fair attempt to analyze the efficacy of RFA as bridge therapy to LT, considering all potential outcome measures. Nevertheless, some results passed unnoticed, while instead deserve further discussion.

The therapeutic efficacy of RFA was assessed on a per-patient basis using the last imaging prior to LT or delisting or death (4). On this ground, 73.6% of patients had complete radiological response. This end-result comes from a study population with 80.9% of patients classified as UNOS-T2 and 10.7% classified as T1. Considering together these two aspects raises the following question: "did these patients actually need a liver transplant?". The answer is probably "yes", since to provide a cure for both HCC and cirrhosis, LT represents the only reliable chance (5). Therefore, the question should be modified as follows: "did these patients urgently need a liver transplant?". The answer is probably "no". That is because response to bridge therapy was not used as a priory criterion in this study population, dated 2004–2014, and this aspect is gaining importance in establishing the priority criteria for LT in recent years. In the US Organ Procurement and Transplantation Network (OPTN) revision of allocation rules of 2014, candidates with class 5T lesions (describing any residual lesion or perfusion defect at site of prior UNOS class 5 lesion) will receive priority extra-points (6,7). As outlined, most of candidates of the Lee's study probably did not need an immediate LT, an observation which contrasts with the mean time in waiting-list of 10.2 months (4). However, as stated, the study derived from a population dated before new OPTN policy and Authors cannot be blamed for having transplanted patients who could probably wait, disadvantaging other candidates on the waiting list.

In regards to dropout rates, Authors reported that 9 out of 121 patients dropped because of tumor progression (7.4%) whereas 89 underwent LT (73.6%). The cumulative tumor-specific dropout rates were estimated as 7.8%, 27.5%, and 27.5% at 1, 2, and 3 years, respectively (4). In the setting of transplantation, the presence of competing-risk is a major issue (8,9). During the waiting list for LT, candidates may experience an event other than that of interest (a competing event as LT), and this can alter the probability of experiencing the event of interest (tumor-specific dropout). In this setting, the calculation of the cumulative incidence of the specific event of interest is

more informative (10). Instead, Lee and colleagues applied the Kaplan-Meier (KM) method which do not account for competing events. Analyzing our previous published data on 315 adult patients with HCC who were listed for LT at our department (10), we verified differences existing between KM estimations and competing-risk results. In our published study, the drop-out probabilities assessed through competing-risk analysis at 3, 6 and 12 months were 3.5%, 6.5% and 19.9%, respectively (10). Censoring for LTs and applying the KM method resulted in an increase of the dropout rates at 5.1%, 10.3% and 22.7%, respectively. That is, the failure to account for such competing event inevitably results in an overestimate of the cumulative incidences of the event of interest (9,11). This bias in the Lee's study should be acknowledged.

Another interesting finding of Lee' study regards concordance between the last radiological assessment prior to LT and the pathologic findings on explanted livers. Pathology revealed complete pathological response (CPR) in 81 out of 113 available nodules (71.7%). The overall accuracy of common CT and routine magnetic resonance (MR) was about 70.8% with a positive predictive value of 71.8% in the prediction of CPR. Authors also showed that the rate of CPR of HCC was lower in patients with post-LT HCC recurrence (20.0%) than those without recurrence (67.9%; P=0.048). This is a very important finding which confirmed previous published data reporting that the achievement of CPR is determinant for the reduction of post-LT recurrence (12). Lee's data indirectly highlights that routine radiological assessment is still far from being accurate, suggesting the adoption of more refined techniques such as functional imaging like diffusion-weighted (DWI) and apparent diffusion coefficient (ADC) MRs, as potential adjunct tools in the radiological assessment of response after LRTs (13,14).

Overall, Lee's work reported a comprehensive analysis of outcomes after RFA prior to LT, but unfortunately suffers from a major analytical bias when analyzing dropout rates from the waiting-list due to tumor progression. Despite this aspect, the final analysis conducted from an intention-to-treat point of view, thus since inception, mitigates this inaccuracy providing a reliable evidence in supporting the role of RFA as chief in the neo-adjuvant setting prior to LT.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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