Editorial

The addition of radiofrequency ablation for patients receiving sorafenib: new evidence for a new standard?

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Despite ground-breaking drug advances and collaborative research, the outcome of unresec/advanced hepatocellular carcinoma (HCC) patients remains dismal. Sorafenib, a tyrosine kinase inhibitor (TKI), was the first treatment to demonstrate overall survival (OS) improvements in two level I randomized trials (1,2). In the last two years, positive data has come out for additional therapies in advanced HCC, including Lenvatinib, and Atezolizumab and Bevacizumab. However, the improved survival is measured in months and additional treatments are needed. In Annals of Translational Medicine, Liu and colleagues present results from a study suggesting that radiofrequency ablation (RFA) may be one such option to improve OS (3).

Given that surgery provides the best outcome results in this disease, the addition of other local treatments has long been postulated to improve survival (4,5). For unresectable, non-transplantable disease, local therapies vary based on local expertise. Definitive, randomized trials on the management by different stages, disease characteristics, and patient comorbidities are unlikely to accrue due to this heterogeneity (6). A review of clinicaltrials.org indicates no trials with RFA combined with sorafenib in HCC with the power to assess for a survival improvement (7). As such, lower level evidence may be required to guide optimal management in clinical scenarios. To date, studies have been non-randomized, highly selected and/or with small sample sizes of variably treated patients.

Biologically, combining RFA with sorafenib demonstrates suppression of epithelial-mesenchymal transition of HCC cells after insufficient RFA or through activation of signalling pathways, mTOR, AKT & PI3K expression, and vascular endothelial growth factor receptors (8,9). The concept of combining multiple approaches in HCC is appealing to lower the high risk of progression.

Liu *et al.* were able to demonstrate an OS benefit at 1, 3 and 5 years with the Kaplan Meier curves separating almost immediately. Importantly, the authors went on to analyze which patients should receive combination treatment; this provides a valuable addition to the literature that has so far found no clear benefit due to varied inclusion criteria and methodological problems in positive trials. Can we rely on this analysis for patient care?

Acknowledging the limitations of the retrospective analysis, a review of study quality is necessary to determine validity and if the conclusions can be applied broadly. A formal review using the Oxford developed Critical Appraisal Skills Program (CASP) (10) was undertaken. In this single institution retrospective study, Liu and colleagues followed 276 consecutive patients with HCC suitable for sorafenib. Importantly, a specific uniform high-risk subgroup [Barcelona Clinic Liver Clinic (BCLC) Stage C, no vascular invasion or extrahepatic spread, no previous liver directed therapy with a good Eastern Cooperative Oncology Group Performance Status (ECOG PS)] was selected to better select a subgroup that would demonstrate an OS benefit and avoid known confounding factors. One hundred and eighty-six patients received a combination of RFA and sorafenib, with the remaining 90 patients receiving sorafenib alone. Given the retrospective nature, there are a number of reasons patients may have received

Table 1 Clinical studies with RFA in combination with standard sorafenib

Study	Study category	Sample size	Endpoint (combination *vs*. sorafenib alone)	Comment (active/closed)
Liu *et al.* (3)	Retrospective cohorts of sorafenib +/-RFA	276	5-year OS 23% *vs*. 5% OS	Current study reviewed in this editorial (closed)
Briux *et al.* STORM (11)	Randomized controlled trial of ablation +/-sorafenib	1,114	No difference in recurrence and survival	Large multicentre trial, but only a subgroup had RFA (closed)
Feng *et al.* (12)	Multicentre retrospective case cohort of RFA +/-sorafenib	128	4-year OS 50.3% *vs*. 30.9%	Direct comparison to Liu study with focus on BCLC 0-B1, but with an RFA only arm (closed)
Bullock *et al.*, NCT 00813293	Randomized phase II of sorafenib 10 days before RFA	20	Coagulation zone	No publication found (closed)
de Stefano *et al.* (13)	Case series of sorafenib after RFA	44	Time to progression 10.3 *vs*. 7.2 months	No safety concerns (closed)
Giorgio *et al.* (14)	Randomized controlled trial of sorafenib +/-RFA	99	2-year OS 35% *vs*. 0	All patients had portal vein tumor thrombus. Direct comparison to Liu *et al.*
Fukuda *et al.* (15)	Case cohort of sorafenib +/-RFA	16	Coagulation area larger for combination treatment	propensity score matched (closed)
Kan *et al.* (16)	Case cohort of sorafenib +/-RFA	207	Median OS was 14 *vs*. 9 months	Consecutive patients (closed)

sorafenib alone: borderline liver function, functional status, more extensive disease volume and either poor tolerance to therapy or toxicity.

The study demonstrated generally strong compliance with the CASP checklist, though the number of patients lost to follow-up was not specifically noted. The characteristics of patient receiving and not receiving RFA were remarkably comparable for all variables (*Table 1* in Liu *et al.*). As expected, the majority of patients were Child-Pugh A with 8% in each arm having Child-Pugh B7. Propensity score matching remains the gold standard to address possible introduction of bias in retrospective analysis, but the highly consistent characteristics, particularly on known independent predictor variables, suggest that this would not change the conclusions of Liu and his colleagues. The treatments were described in good detail, but the number of RFA treatments was not noted. The number of RFA treatments may impact on toxicity, but as no significant toxicity was noted, this likely would have no impact on this particular trial. The statistical analysis plan was well stated and had a sufficient sample size to investigate the number of parameters entered into analysis. The generalizability of the trial may be specific to Asian patients given the Chinese study population where, unlike in Western patients, hepatitis B is a common cause of HCC and may have a higher risk of hepatic complications. The authors also note that data was collected from a single institution thereby possibly introducing an information bias; however, the advantage with a single team is a lower variation in technique and experience inherent in a multi-institutional trial. The consecutive patient data was collected between 2010 and 2017. It should be noted that the two phase III papers demonstrating the benefit of sorafenib were published in 2008 (1,2)—which was at the start of this study. Median follow-up was 24.9 months using the censoring method. In the sorafenib arm, the median follow-up was 39.7 months. Follow-up was every 2 weeks for the first 6 weeks and then every 6–8 weeks thereafter. OS at 1, 3 and 5 years was 84% *vs*. 55.6%, 43% *vs*. 29.6%, and 23% *vs*. 5% for the combination *vs*. the sorafenib alone arm; the response rate and progression-free survival was not presented, presumably better in the combination arm. The early split in the curves further suggests that immediate RFA as opposed to salvage RFA is warranted to obtain a better survival rate. In practice, many patients are treated with a single modality and 'salvaged' when there is evidence of progression. In future analyses, the number of distant metastases would be a valuable addition to the literature

to clarify if this local treatment impacts on non-local dissemination.

Two multivariate analyses were performed to avoid colinearity. Model 1 selected from the 16 variables, but excluded Child-Pugh score. Model 2 included Child-Pugh score, but not albumin and bilirubin. In model 1, tumour related factors (size and number of lesions), and liver function status (bilirubin and albumin) were found to be predictive of OS. Treatment with RFA was also important, but to a lesser degree. Number of lesions (HR 1.94) and albumin level (0.887) were most important. In model 2, size, number of lesions, Child-Pugh score and treatment were predictive. In this stepwise multivariate model, the combination treatment had a hazard ratio of 2.273; the addition of RFA was the most important factor predicting survival followed by number of lesions at 2.007 and Child-Pugh score at 1.367. A subgroup analysis was performed to better assess how the tumour related factors of size and number of lesions impacted on survival. The inclusion of RFA was beneficial for all sizes and number of lesions except for in patients with ≥4 lesions. There were a sufficient number of patients in the ≥4 subgroup for statistical determination of benefit.

There is level 1 evidence on this topic, albeit with more advanced disease and a small sample size. Giorgio *et al*. looked at the same treatment combination in 2016 multicentre Italian publication randomizing patients to sorafenib or sorafenib plus RFA. 99 patients with Child-Pugh A with presence of portal vein tumour thrombus were randomized (14). Combination therapy was shown to improve 3-year OS (26% *vs*. 0) with a significant statistical difference (HR =2.87; 95% CI, 1.61–5.39, P<0.001). These patients would have been excluded in Liu *et al.*, due to their extra-hepatic spread and main portal vein thrombus involvement. However, Giorgio *et al.* provide confidence that the results of Liu *et al.* are generalizable to Western and Asian patients.

A 2017 systematic review, by Chen *et al.*, compiled studies with at least one cohort that received RFA in combination with sorafenib (4). Seven studies involving 1,765 patients with HCC were analysed. Pooled analysis failed to show a difference in 2-, 3-, 4-, and 5-year OS, and 1-, 2-, 3-, and 5-year recurrence rates between those treated with a single modality versus combination of sorafenib and RFA. However, there was substantial heterogeneity in the studies as noted by the authors themselves. The clinicopathological features, such as size of lesions, number of lesions, age of patients and number of previous treatments, may not be comparable between the single modality alone versus the combination treatment arms. Importantly, the single modality arms differed with most having RFA alone. One study included in the analysis, by Yan *et al.*, compared surgery versus RFA plus sorafenib with no sorafenib alone arm. Only the Giorgio *et al.* study directly compares the current standard systemic treatment of sorafenib alone versus combination treatment. Furthermore, unlike Liu *et al.*, the studies did not control for important factors such as BCLC stage C inclusion, and vascular involvement.

Two studies with combination arms are worth noting as they support the conclusion of the Liu *et al.* that combination therapy provides additional benefit over single modality treatment. While Liu *et al.* used sorafenib in the control arm, the Kan *et al.* (16) and Feng *et al.* (12) study used RFA alone as the control arm. Kan *et al.* randomized 62 patients randomized to RFA or combination of RFA plus sorafenib (16). This study had possible methodological issues; notably randomization still resulted in important patient differences such as a varied BCLC stage C inclusion (56% *vs*. 73% for RFA alone *vs*. combination treatment) which Liu *et al.* suggests is an important factor in the survival benefit of RFA. Furthermore, follow-up was not clearly described with the median length of follow-up not specifically stated and likely in the range of one year. This is the possible reason OS could not be determined in the Kan *et al.* study as most of the patients were still alive at time of analysis. Overall recurrence rates were 87.5% *vs*. 56.7% in the RFA alone *vs*. combination arm. Time to progression was 17 *vs*. 6 months.

In a retrospective analysis Feng *et al.*, used case matching in 128 patients with BCLC stage 0 to B1 who underwent either RFA alone, or RFA combined with sorafenib, they found a decreased rate of recurrence as the primary endpoint (12). Importantly, Feng *et al.* found that there was a 4-year OS advantage of 50.3% *vs*. 30.9% in the combination arm compared to RFA alone. Similar to the Kan and Liu studies, adverse effects were primarily related to the targeted systemic management with minimal adverse effects related to the RFA.

However, the literature has data that contradicts the assertion that combination therapy, in studies such as Liu and Giorgio, provide a survival advantage. A landmark large multicentre randomized trial called STORM (Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma) assessing the additive benefit of sorafenib to local ablation including resection, PEI and RFA, found no impact on recurrence-free survival or OS (11). Briux and colleagues concluded

from this 1,602 patients' trial that adding sorafenib post a local treatment was not warranted. The patient characteristics were similar to Liu *et al.*, but had important differences. Specifically, only 19% received RFA and 32% had vascular invasion. Furthermore, the higher discontinuation rate in STORM because of adverse effects (24%) or withdrawal of consent (17%) are likely to have diminished the impact of combination treatment on the chance of progression and survival. This sorafenib discontinuation rate was not seen in either the Liu study. Though a stratification based on ablation technique was performed by Briux *et al.* in STORM, there has been a recommendation to provide a specific study addressing the value of combination versus sorafenib alone based on the STORM subgroup, but without the inclusion of PEI and hepatectomy (17,18). Liu and his colleagues have successfully performed this recommended study and appropriately focussed on BCLC stage C where STORM only included BCLC stage A patients.

An observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice. However, current standard of care provides a suboptimal clinical outcome, a large randomized study to answer this question is not likely to accrue sufficient patient numbers, and RFA is a standard treatment with a documented low toxicity profile; Liu *et al.* provides valuable data to allow health care providers the confidence to discuss this option with patients and, furthermore, better select patients that would likely benefit. This study must also be assessed in context of multiple trials demonstrating the value of other combinations of local and systemic treatments over single modality treatments. In the future, more recently released systemic agents may be more active with or without ablative approaches. The biggest uncertainty remains how to tailor this approach to individual patients.

Based on this analysis, and until larger case series or randomized evidence becomes available, RFA can considered in HCC patients started on sorafenib due to its possible survival advantage and demonstrated low toxicity profile. However, patients must be carefully selected as detailed in this study; specifically, those with less than 4 lesions, BCLC stage C, performance status 1, and without vascular invasion or extrahepatic spread.

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