



# Combination surgery for hepatocellular carcinoma: slashing and burning to improved survival

John C. McVey<sup>1,2</sup>, Kazunari Sasaki<sup>3</sup>

<sup>1</sup>Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, USA; <sup>2</sup>Gastrointestinal and Thoracic Malignancy Section, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; <sup>3</sup>Department of General Surgery, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, OH, USA

Correspondence to: Kazunari Sasaki, MD. 9500 Euclid Ave., Cleveland, OH, USA. Email: sasakik@ccf.org.

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Due to its poor response to systemic therapy, hepatocellular carcinoma (HCC) is largely considered a surgically treated disease with the potential for a cure if qualified patients undergo liver resection or transplantation. Qualification for these lifesaving procedures has largely been guided by the Barcelona Clinic Liver Cancer (BCLC) staging system, with candidates for liver resection falling into the early stages of disease. The article written by Zhang *et al.* in this issue of *Annals of Translation Medicine*, demonstrated that the addition of microwave coagulation with liver resection margin can improve the recurrence-free survival (RFS) and overall survival (OS) for solitary HCC patients compared to resection alone (1). This finding suggests that HCC liver resection patients could experience greater survival benefit if the BCLC was modified to include a resection with adjuvant ablation treatment option.

In their article, Zhang *et al.* conducted a retrospective study on 236 consecutive HCC BCLC stage A patients with solitary tumor from a single institution. Analysis showed that patients who underwent resection with adjuvant ablation had longer RFS (3-year =36.2% *vs.* 13.5%,  $P<0.001$ ) and OS (3-year =33.2% *vs.* 15.5%,  $P<0.001$ ) compared to resection alone. This finding remained significant even after controlling for other important variables such as Child-Pugh score, tumor size, albumin, and bilirubin levels. Interestingly, while tumor size was an important predictor of OS, it did not decrease the benefit

conveyed by resection and ablation combination when stratified by tumors less than or greater than 5 cm. This is an especially significant finding since larger tumors are known to have microsatellite metastasis surrounding the tumor which may not be completely removed by resection alone (2). Not tested in this study was the effect of various resection margins on RFS and OS. Testing whether larger margins diminished the benefit provided by combination treatment could have helped explain if the addition of ablation provided a protective effect against local microsatellite metastasis or if the effect was through other mechanisms. Given this limitation, the study still puts forth interesting findings that fit into a broader argument towards combination therapy with ablation to improve HCC outcomes.

In other forms of treatment for HCC, the combination of ablation with systemic therapy are being tested and, in some instances, has demonstrated improved outcomes. Current first- and second-line FDA approved systemic therapy for HCC include the multi-kinase inhibitors (Sorafenib) and VEGF inhibitors (Bevacizumab, Ramucirumab, etc.). Many of these drugs have been tested in combination with locoregional therapy (LRT) and have shown survival benefit, but the results are not always straight forward (3). In a recent phase I prospective trial, 36 patients with advanced HCC were treated with the immune checkpoint inhibitor, tremelimumab, and subtotal LRT (4). Objective

response was then followed in the non-treated lesions to determine if the combination treatment could improve responses to untreated lesions. The group showed a median OS of 10.9 months (95% CI, 8.0–13.7 months) with one complete response, 7 partial responses, and 15 patients with stable disease. Of note, there was an influx of T-cells into the tumors of patients that responded to therapy. The results of this study have sparked the addition of numerous other proposed clinical trials investigating the combination of immunotherapy and LRT (5).

The mechanism by which combination resection and ablation improves survival has yet to be explained. One potential mechanism is the priming of the immune system through the release of tumor specific antigens post-ablation therapy. In mouse studies, experiments have revealed that apoptotic cells are capable of proteasome-dependent antigen production and thus cross-priming of CD8<sup>+</sup> T-cell (6). This suggests that ablation therapy could release an abundance of tumor antigens which are picked up by antigen presenting cells. These cells can then prime the immune system to remove residual cancer post-liver resection. It is important to note that the type of LRT can effect antigen processing and thus diminish the anti-tumor response generated by combination therapy (5). Only microwave ablation was used in the current study, so it is impossible to know if their results are generalizable to other forms of LRT. Another potential mechanism put forth by the authors is the reduction in operative time when adjuvant ablation is used. This could potentially reduce intraoperative bleeding and complication.

Further investigation into the findings put forth by Zhang *et al.* is warranted given that HCC is still largely a surgically treated disease with the potential for curable results. A recent report has shown that a subset of patients undergoing liver resection can achieve similar life expectancies to those with chronic liver disease without HCC (26.3%) and the general population (17.1%) (7). It is possible that the combination of resection with adjuvant ablation could increase the number of cured patients if the BCLC guidelines were modified to reflect Zhang *et al.*'s findings. Before this could happen, however, there would need to be a more detailed investigation into the type of patient and tumors that could benefit most from liver resection combined with microwave ablation therapy. There would also need to be a prospective trial to confirm that the findings shown in this study are generalizable to a wider population. Nevertheless, the results shown in this study are promising and open the door to future studies that hold the

potential to impact the treatment of HCC patients.

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## Footnote

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