



Treatment of Barcelona Clinic Liver Cancer Stage C hepatocellular carcinoma: liver resection versus TACE and beyond

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This issue of *Annals of Translational Medicine* provides a thought-provoking study by Zhao and colleagues “Identifying optimal candidates for liver resection or TACE in patients with unresectable hepatocellular carcinoma” (1). This retrospective study adds to the current literature in treating hepatocellular carcinoma (HCC) in Barcelona Clinic Liver Cancer (BCLC) stage C patients.

According to the European Association of Study of Liver recommendations, systemic therapy such as sorafenib is first-line therapy for BCLC stage C patients, whilst surgical resection is recommended for BCLC Stage 0 HCC and TACE for BCLC Stage B (2). Since the introduction of sorafenib, BCLC Stage B patients who received TACE were also commenced on sorafenib if patients agreed. In BCLC Stage C patients, TACE was offered in addition to sorafenib in those who did not have contraindications (3). It is important to highlight that the BCLC staging was developed in Western countries where non-alcoholic fatty liver disease, alcohol-related cirrhosis and hepatitis C virus (HCV) infection were the main attributable factors for HCC (4).

In comparison, the study by Zhao *et al.* was performed in China where endemic hepatitis B virus (HBV) infection is the main attributable factor for HCC (1). Many physicians in Asia take a more aggressive treatment approach than the BCLC staging classification such as the Hong Kong Liver Cancer (HKLC) classification, particularly with a broader use of surgical resection in identified subsets of BCLC Stage B and C patients (5). The Asian Pacific

Association for the Study of Liver recommends that surgical resection is the best treatment for long-term survival in selected patients with multinodular, large solitary, or macrovascular invasion HCC (6). Due to these different treatment recommendations across countries, there is an increasing interest identifying which subgroup of BCLC Stage C patients would benefit from resection, TACE and/or sorafenib. BCLC Stage C includes a large heterogeneous group of patients, ranging from patients who have a performance status (PS) 1–2, to those with extrahepatic spread and/or macrovascular invasion. Consequently, a wide range of survival outcomes has been observed in BCLC Stage C patients treated with sorafenib alone, for whom overall survival is still poor (7,8).

Zhao and colleagues (2020) have compared survival outcomes following TACE or liver resection in retrospectively selected BCLC Stage C patients who have a PS of 1, a single tumour, Child-Pugh A and no vascular invasion or extrahepatic spread. The mean tumour size was 7.9 and 8.0 cm in the surgery and TACE group respectively. It is likely that Zhao *et al.* followed the HKLC classification treatment recommendations, in which this subset of BCLC Stage C patients were either HKLC Stage I or IIb (ECOG 0–1, Child-Pugh A, no extra or intra-hepatic vascular invasion, single nodule) and resection is first-line treatment (5). Zhao and colleagues [2020] demonstrated that in these selected BCLC Stage C patients, there was significantly better overall survival with liver resection than TACE with 1-, 3- and 5-year survival of 83.2%, 60.8%, 33.3% *vs.* 66%, 25.2%

and 13.4%, respectively. These findings are in keeping with multiple other studies which have demonstrated significantly better survival outcomes with liver resection compared to TACE in selected BCLC Stage C patients (9,10). Moreover, the benefit of resection over TACE has been demonstrated in other studies to be independent of tumour size, tumour number, presence of macrovascular invasion or presence of portal hypertension (9,10).

Surgical resection has traditionally been limited due to high perioperative morbidity and mortality. However advances in optimisation of anaesthetic management, improvement in surgical techniques and creation of specialised high-volume centres have considerably reduced perioperative morbidity and mortality in HCC patients undergoing resection (11,12). Nevertheless, the likelihood of serious complications are still greater in higher BCLC Stages, where a study in 2015 demonstrated at least one Stage 3–5 Clavien-Dindo complication occurred in 30.2% for BCLC Stage A, 43.5% for BCLC Stage B and 64.3% for BCLC Stage C patients (13). Important factors for a patient to be a suitable “surgical candidate” is at least Child-Pugh Class A preoperative liver function, a low MELD score (9 or lower) and adequate future liver remnant function (14,15). Therefore, surgery can be a safe treatment in carefully selected patients.

Despite hepatic resection remaining the most important curative treatment for HCC, the long-term survival of these patients remains poor due to post-operative recurrence, which occurs in up to 60% of patients and most within 2 years after surgery (16). Multiple Asian hospitals are administering TACE post-resection (adjuvant TACE). A recent meta-analysis of 26 studies, demonstrated resection followed by adjuvant TACE significantly improved 1- to 5-year survival (OR: 2.53, 2.39, 1.83, 2.12, 1.87, respectively) and 1- to 4-year DFS (OR: 1.91, 1.85, 1.24, 1.67, respectively) compared to resection alone (17). Unlike pre-operative TACE which selectively targets a lesion, adjuvant TACE is administered more proximally into the hepatic artery with the aim to destroy residual micro-metastases and cancer cells within the remaining entire liver whilst minimising systemic side effects (17). Subgroup analysis showed resection plus aTACE had the strongest survival benefit in microvascular invasion (MVI)-positive HCC. MVI occurs in up to 57% of HCC cases and is linked to intrahepatic metastasis and a strong risk factor for postoperative occurrence (18). Previous authors hypothesized that patients with MVI-positive

HCC have residual cancer cells within the remaining liver which would be in the process of developing or already have formed arterial hypervascularization, whilst MVI-negative HCCs do not have residual tumour cells (17). This would explain why adjuvant TACE was associated with an improved OS and DFS in MVI-positive patients only and not MVI-negative patients. As MVI is only diagnosed microscopically on resected HCC specimens, this adds an additional benefit for treatment of HCC with resection. Future studies assessing the benefit of resection plus aTACE compared to resection alone in BCLC Stage C would be useful.

An alternative treatment which has demonstrated outcomes similar to resection is ablative TARE (A-TARE) in HCC. In BCLC Stage A or B patients, previous studies have reported that A-TARE has delivered radiographic outcomes similar to resection (segmentectomy) and as bridge-to-resection for unresectable HCC (lobectomy) (19,20). A recent study compared survival outcomes between A-TARE and conventional TARE (cTARE) in advanced HCC with PVTT (21). In A-TARE, a high dose of radioactivity is delivered to the hepatic segment or lobe where the HCC is located to destroy both the tumour as well as surrounding normal parenchyma (19). In cTARE, radioactive microspheres are delivered via the hepatic artery to destroy HCC, but not the surrounding segment or lobe. In advanced HCC with PVTT and a mean tumour size of 7cm, A-TARE had a significantly longer survival than cTARE (45.3 vs. 18.2 months, $P=0.003$) (21). These are impressive results considering the patients in Zhao *et al.* treated with surgical resection had a median survival of 19.5 months with tumours 5cm or greater (1). Similar to the criteria for surgery, in A-TARE, a majority of the liver can be ablated as long as the future liver remaining is >40% in Child Pugh A5, A6 or B7 patients (21). Future studies comparing survival outcomes between resection and A-TARE would be useful.

The limitations in the study by Zhao *et al.* should be kept in mind when interpreting their findings. Firstly, TACE was administered every 6 weeks during the first year and every 6 to 8 weeks thereafter, depending on their liver function. The study did not quantify the average number of TACE per patient or whether they continued to administer TACE even with non-viable or TACE-resistant HCC (1). At our institution, we perform multiphase imaging approximately 4 weeks after TACE to assess for residual viable tumour using the LI-RADS criteria. If there is residual viable

tumour, repetition of TACE at 4–6 weeks post initial TACE (sometimes up to 8 weeks to allow the liver to heal) may be considered after discussion at a multidisciplinary meeting. However, if there was persistent residual tumour after 2–3 TACEs, alternatives such as ablation, resection or TARE would be considered as the residual tumour is likely TACE-resistant. We do not advise administering TACE every 6 weeks without evidence of residual tumour or poor response to TACE. Secondly, a majority of the patients had HBV-related HCC. This limits the external validity of such findings where HCV infection, alcohol-related cirrhosis, and non-alcoholic fatty liver disease are the main attributable factors for HCC in Western populations. Thirdly, the authors did not disclose complication or mortality rates in the TACE or surgery group.

It is also important to highlight that Zhao *et al.* did not describe whether patients were treated with systemic anti-angiogenic therapy such as sorafenib. This is important as previous studies have demonstrated sorafenib after resection improved outcomes compared to patients who received sorafenib alone in BCLC Stage C patients (22). Similarly, studies have demonstrated the synergy of TACE and sorafenib improves disease free and overall survival outcomes compared to TACE or sorafenib alone in BCLC Stage B/C (3). Sorafenib is an oral multikinase inhibitor which exerts an anti-angiogenic effect by blocking the vascular endothelial growth factor (VEGF) receptor-2 and -3 and platelet derived growth factor receptor tyrosine kinase. VEGF is known to be the strongest angiogenic factor in HCC patients (23). Therefore, future studies need to control for the potential confounding effect of systemic therapy on outcomes.

It is important to highlight that there are novel systemic antiangiogenic therapies being investigated for the treatment of advanced HCC. The first being lenvatinib, which has been demonstrated in the Phase 3 REFLECT trial to have significantly better progression free survival and objective response rate whilst having equivalent survival outcomes compared to sorafenib in unresectable HCC (24). Compared to sorafenib, lenvatinib is a more potent anti-VEGF agent which also targets the fibroblast growth factor axis, which plays an important role in HCC and resistance to anti-VEGF therapy (24). The second novel treatment is the combination of atezolizumab and bevacizumab which has been demonstrated in the Phase 3 randomised IMbrave150 trial to have better progression-free survival and response rate compared to sorafenib alone (25). However, we hypothesise these novel treatments are

unlikely to be superior to the survival benefit gained with surgical resection for advanced HCC. Future studies assessing the combination of surgery and a novel systemic therapy for BCLC Stage C HCC would be useful.

In summary, the findings by Zhao *et al.* adds to the current literature which suggest that resection provides a survival benefit over TACE for selected BCLC Stage C patients. This study challenges some guidelines concerning the role of surgery for patients who are not considered “ideal” candidates. However, just as guidelines were developed from previously published research, guidelines are evolving and will be continually updated based on further data from high-quality trials. Although more evidence is required, novel treatments which have also demonstrated promising results in advanced HCC include lenvatinib, combination of atezolizumab and bevacizumab, A-TARE and adjuvant TACE following resection, particularly in MVI-positive HCC.

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