

# Comment on staging hepatocellular carcinoma involving a single large tumor

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Many patients with primary hepatocellular carcinoma (HCC) have a single large tumor (>5 cm). Official guidelines (1,2) and large retrospective studies (3,4) assign these patients to different Barcelona Clinic Liver Cancer (BCLC) stages, leading to different treatment recommendations. Current BCLC guidelines recommend transarterial chemoembolization (TACE) for BCLC stage B patients (1,2). However, improvements in surgical technique and perioperative care at several large liver centers have made hepatic resection (HR) a first-line therapy for many patients in stage B as well as earlier and advanced stages (5-7).

In a recent issue of *J Gastroenterol Hepatol*, Jung and coworkers retrospectively analyzed 1,005 HCC patients to determine the optimal staging of patients with a single large HCC tumor, based on median survival time and overall survival. They found that patients with a single nodule >5 cm had worse prognosis than those in BCLC stage A, who had a single nodule >2 cm and ≤5 cm or 2-3 nodules ≤3 cm; and similar prognosis to those in BCLC stage B, who had 2 or 3 nodules >3 cm or >3 nodules (8). Those authors concluded that BCLC stage B is the best designation for patients with a single large tumor. We believe this conclusion should be treated with caution because it is inconsistent with the results of our study involving 927 patients without macrovascular invasion or tumor metastasis who underwent initial HR, in which we found patients with a single large tumor were with significantly better overall survival than those with two to three tumors with a maximum diameter >3 cm or those with more than three tumors of any diameter (all these patients were classified as BCLC stage B) (9).

In addition, potentially serious problems in how Jung *et al.* (8) designed and executed their study weaken its

conclusions. Each of the three patient groups underwent heterogeneous treatments involving HR alone (20%), radiofrequency ablation with or without TACE (31%), or TACE alone (49%). Main factors influence patients survival includes not only tumor stage, but also treatment modality. Large original study (3) and systematic reviews (6,7) have associated HR with significantly greater overall survival than TACE for patients with BCLC stage A, B, and C HCC. Indeed, the authors' own subgroup analyses based on treatment modality within each HCC group showed that HR was associated with significantly better overall survival than TACE alone in all three groups. Thus treatment modality is a known confounder in the authors' comparisons based on tumor stage, yet they did not control for this by grouping patients by treatment and subsequently stratifying by HCC type.

Among patients who underwent HR alone in the study by Jung *et al.* (8), median survival time in those with a single nodule >5 cm (84.2 months, n=41) was slightly shorter than survival in those with stage B disease (110.7 months, n=27). This conflicts with the authors' conclusion that stage B is the most accurate classification for patients with a single nodule >5 cm. In fact, median survival time among patients treated by HR did not differ significantly across all three HCC groups (8).

We congratulate Jung and coworkers for using evidence-based methods to resolve discrepancies among official treatment guidelines. Work from our own group suggests the need to revise recommended treatments for patients with stage B HCC by including HR as a potential treatment (3,6,9-11). Consistent with that work, and with numerous studies from other medical centers, Jung *et al.* (8) found that HR was associated with significantly better overall survival

than radiofrequency ablation with or without TACE, or TACE alone. It may be that expanding the indications for HR in the BCLC staging scheme may be therapeutically more useful than attempting to determine an “optimal” BCLC stage for patients with single large tumors >5 cm.

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### Footnote

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

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