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REPLY

Heterogeneity of intermediate-stage HCC necessitates personalized management including surgery

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We would like to thank Gao *et al.* for their correspondence (Heterogeneity of intermediate-stage HCC necessitates personalized management including surgery. *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2014.122-c1)[1] on our recent Review (Treatment of intermediate-stage hepatocellular carcinoma *Nat. Rev. Clin. Oncol.* **11**, 525–535; 2014).[2] In our Review, we outlined the current approaches to stratifying patients with intermediate-stage hepatocellular carcinoma (HCC), and discussed the potential heterogeneity that remains among this population. We stated that transarterial chemoembolization (TACE) is considered the standard treatment for intermediate-stage HCC, but emphasized that not all patients with intermediate-stage HCC are good candidates for TACE; those patients who are not candidates for TACE or patients in whom TACE has failed should be considered for other treatments, including sorafenib and radioembolization. In their correspondence, Gao *et al.*[1] criticized our Review for stating that TACE and sorafenib should be the only standard treatments for intermediate-stage HCC (a paradigm that they disagree with), whereas this statement is in fact far removed from the message delivered in our Review. Furthermore, Gao *et al.*[1] claim that the Barcelona Clinic Liver Cancer (BCLC) treatment recommendations[3] are based on findings in populations of patients with intermediate-stage HCC as a whole and, therefore, do not provide guidance as to which modality will yield the best result in individual patients. As a result, they state that deviations from the guidelines are highly frequent in clinical practice.[1] Guidelines are developed to help patients, health practitioners, healthcare providers and governments decide which treatment option is most appropriate for specific conditions and/or under particular circumstances.[4] Such recommendations should be based on the strongest scientific evidence, but of course their application to the treatment of individual patients should take into account several clinical factors that, for sure, are not detailed in guidelines.

Gao *et al.*[1] go on to highlight the important role of hepatic resection in the recently published Hong Kong Liver Cancer (HKLC) classification.[5] This proposed stratification system accepts that hepatic resection can be pursued in subgroups of patients with intermediate-stage or advanced-stage HCC.[5] Regrettably, the HKLC classification has several limitations, as summarized in an editorial that accompanied its publication.[6] The most-relevant concern is that the study on which the HKLC classification is based was retrospective and, therefore, was probably subject to an unintentional selection bias; patients who were selected for hepatic resection rather than TACE must have had features that gave the surgeon confidence that a good outcome would be achieved, whereas those selected for TACE probably lacked such characteristics, immediately introducing a bias against TACE.[7]

Gao *et al.*[1] also comment on a recent randomized controlled trial conducted by Yin *et al.*[8] in Shanghai, China, which compared hepatic resection and TACE. Although the results were clearly in favour of surgical treatment rather than TACE (median overall survival of 41 months versus 14 months; P <0.001), and the multivariate analysis demonstrated that type of treatment was an independent risk factor associated with overall survival,[8] this trial has some issues that deserve consideration. The major concern is the very poor outcome observed for the patients treated with TACE (that is, a median overall survival duration of only 14 months). The poor survival outcome did not seem to be related to treatment-related toxicity, as no grade 5 adverse events were reported.[8] However, this outcome could reflect the inexplicable mediocre response rate (objective response rate of 23%, comprising 10 complete responses and only 11 partial responses or stable disease), despite the fact that the modified Response Evaluation Criteria In Solid Tumors (mRECIST) response criteria were used.[8] Contemporary conventional TACE procedures, using a super-selective approach for patient stratification, are associated with objective response rates >50%.[9] Moreover, in Japan[10] and Europe,[11,12] TACE is associated with median survival durations of 40–48 months in patients with intermediate-stage HCC with preserved liver function—who according to Yin *et al.*[8] would be potential candidates for hepatic resection. Another issue with the trial by Yin and colleagues[8] is the ill-defined inclusion criteria, expressed simply as 'good surgical risk patient' and 'resectable HCC', which prevents any attempt to reproduce and validate the results. In addition, although not reaching statistical significance, patients in the TACE group had slightly larger tumours and slightly poorer liver function than those in the surgical cohort, and the authors did not report on performance status.[8] More interestingly, only 7% of the patients screened (180 out of 2,502 patients) met the inclusion criteria for being randomized,[8] confirming that just a minor proportion of patients with intermediate-stage HCC might be considered for hepatic resection.

Finally, regarding the suggested treatment allocation for patients with BCLC B (intermediate-stage) HCC summarized in Figure 1 of the correspondence by Gao and co-workers,[1] the BCLC proposals have always stated that patients with a solitary HCC larger than >5 cm that has expansive growth, and who remain free of symptoms, vascular invasion and tumour dissemination after proper imaging evaluation might benefit from surgical resection; disease in such patients should be classified as BCLC stage A.[3,13–15]

Additional trials comparing hepatic resection with state-of-the-art TACE are needed in order to evaluate the potential benefit of hepatic resection in patients with intermediate-stage HCC. The current evidence, however, does not support the recommendation of this treatment approach in patients with BCLC B disease.

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Competing interests
A.F. has acted as a consultant for Bayer HealthCare. J.B. has acted as a consultant or in an advisory role for ArQule, Bayer, Biocompatibles, Bristol–Myers Squibb, Celgene, Daiichi-Sankyo, Kowa, Lilly, Novartis, Roche, and Terumo. J.-L.R. has acted as a consultant or in an advisory role for Arqule, Bayer HealthCare, Biocompatibles, Bristol–Myers Squibb, and Merck Serono. M.G. declares no competing interests.

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