Nature Reviews Clinical Oncology published online 7 April 2015; doi:10.1038/nrclinonc.2014.122-c3

Intermediate-stage HCC—upfront resection can be feasible

Jian-Hong Zhong, Shi-Dong Lu, Yan-Yan Wang, Liang Ma and Le-Qun Li

We read with great interest the Review by Forner *et al.* (Treatment of intermediate-stage hepatocellular carcinoma. *Nat. Rev. Clin. Oncol.* **11**, 525–535; 2014),[1] which focused on the definition of and treatment options for intermediate-stage hepatocellular carcinoma (HCC). Their definition appropriately accounts for the clinical heterogeneity of intermediate-stage HCC, and we applaud their recommendation that disease involving a single large tumour (>5 cm) without vascular invasion should be classified as early-stage disease,[1] which contrasts with previous articles from the Barcelona Clinic Liver Cancer (BCLC) group.[2] We also applaud their suggestion that patients with a single large tumour (>5 cm) and no vascular invasion can benefit from hepatic resection, when technically feasible.[1] This article, written by members of the highly influential BCLC group, might help advance HCC treatment by updating diagnostic guidelines and providing tentative support for less restrictive use of hepatic resection. At the same time, the Review contains some statements regarding the treatment of intermediate-stage HCC that might not adequately reflect the available clinical evidence; these statements, in our opinion, overemphasize the appropriateness of transarterial chemoembolization (TACE) and sorafenib therapy, and severely underestimate the usefulness of hepatic resection.

Forner *et al.*[1] indicate that TACE should be considered as the first-line treatment option for patients with intermediate-stage HCC, and that patients for whom TACE is contraindicated or proves unsuccessful can be considered for sorafenib therapy or radioembolization. Although the authors are correct that TACE is widely accepted in clinical guidelines as the first-line therapy for patients with intermediate-stage HCC, this treatment has not been consistently associated with a survival benefit across a wide range of studies conducted in several countries. Studies demonstrating a survival benefit have compared TACE with best supportive care;[3] however, no benefit has been observed in studies comparing TACE with hepatic resection.[4] In addition, TACE outcomes depend strongly on the specific techniques and chemoembolization agents used. Indeed, in a Cochrane systematic review article published in 2011,[5] it was concluded that the available evidence does not clearly argue for or against the use of TACE for the treatment of patients with unresectable HCC. Moreover, some absolute and relative contraindications for TACE exist; as guidelines from Japan, Europe and the BCLC group itself indicate, not all patients with intermediate-stage HCC are eligible for TACE, nor do they all benefit from this treatment.[1,6,7] Moreover, the optimal criteria for selecting patients for TACE, for scheduling of repeat treatments, and for the termination of treatment remain unknown. Furthermore, TACE is associated with a wide range of adverse events.[5]

For patients with intermediate-stage HCC, treatments that are more aggressive than TACE might need to be considered for first-line therapy. For example, TACE with drug-eluting beads (DEB-TACE) might provide a more-reliable survival benefit with a reduced frequency of chemotherapy-related adverse events. Two case series, one comprising 173 patients and the other 104 patients with early-stage or intermediate-stage HCC who were not candidates for curative treatment, reported respective median overall survival durations of 43.8 months and 48.6 months after DEB-TACE;[8,9] median overall survival was 47.7 months specifically among patients with intermediate-stage disease in one of these studies.[9] Additional larger studies, preferably with parallel comparison groups, are needed to verify this clinical benefit. Another more-aggressive technique than TACE is transarterial radioembolization (TARE), which has been proposed for patients with unresectable HCC who are not suited for ablation therapy.[10] Nonrandomized prospective studies have suggested that TARE is associated with a median overall survival of around 17 months in patients with intermediate-stage HCC.[10] However, larger studies, preferably comparing TARE with TACE and/or sorafenib treatment, are needed.

Forner *et al.*[1] also indicate that sorafenib is considered the standard treatment for advanced-stage HCC. However, this statement requires strong qualification in light of the clinical evidence. In the SHARP trial,[11] sorafenib was associated with a median overall survival of 14.5 months among 54 patients with intermediate-stage HCC—only 3.1 months longer than the median survival of 11.4 months reported for the 51 patients in the placebo group. In addition, the GIDEON study[12] observed that sorafenib therapy was associated with adverse events in 69% and 66% of patients with intermediate-stage and advanced-stage disease, respectively; the corresponding rates of serious adverse events were 32% and 38%.[12] The BCLC group has reported a median survival of 16 months for previously untreated patients with intermediate-stage HCC,[13] which is longer than the 14.5 months survival duration reported for similar patients treated with sorafenib in the SHARP trial.[11] Thus, the limited efficacy and high risk of adverse events associated with sorafenib therapy, coupled with the drug's high cost, suggest that it should not be considered the standard treatment for advanced-stage HCC, let alone intermediate-stage disease.

The tentative recognition by Forner *et al.*[1] that hepatic resection might be useful for certain patients with intermediate-stage HCC does not do justice to the rapidly growing literature demonstrating a good survival benefit and the safety of hepatic resection in many patients with intermediate-stage and even advanced-stage disease—no evidence of which is cited in the Review by Forner and colleagues. For example, numerous large studies have demonstrated the benefit of hepatic resection for patients with multinodual tumours and Child-Pugh A–B liver function. We performed a systematic review of 21 studies involving a total of 4,945 patients, and found that resection in carefully

selected patients with multinodular HCC (≥2 tumours) was associated with a median overall survival of 41 months.[14] This outcome is similar to the survival reported for patients with multinodular HCC exceeding the Milan criteria (that is, BCLC immediate-stage HCC) in a randomized controlled trial;[15] the corresponding survival for patients treated with TACE was 14 months. More recently, we systematically reviewed 50 studies that investigated the use of hepatic resection to treat large (≥5 cm) or multinodular HCC, and 24 studies that investigated resection to treat HCC with macrovascular invasion (comprising 14,808 patients and 4,389 patients, respectively).[16] The median 5-year overall survival after resection of large or multinodular HCC was 42% for Asians patients and 32% for other ethnic groups.[16] In the patients with HCC and macrovascular involvement, median 5-year overall survival was as high as 14–18%.[16] This trend in overall survival improvement has been increasing over the past several decades among patients with either of these forms of HCC,[16] suggesting that survival might continue to increase as surgical techniques and perioperative care improve.

To assess the efficacy of hepatic resection in patients with intermediate-stage HCC in more detail, we retrospectively reanalysed patients who underwent initial potentially curative resection at our two hospitals between January 2000 to December 2010.[4,17] Subgroup analysis of data from 1,182 patients revealed that those with a single tumour >5 cm had a longer median survival duration and a higher rate of overall survival than patients with 2–3 tumours with a maximal diameter >3 cm or patients with >3 tumours of any size (Table 1). Although patients with >3 tumours had the worst overall survival after resection, median overall survival among this group (42 months) remained better than that reported for patients with intermediate-stage HCC who underwent TACE (14 months),[15] TARE (17 months),[10] or sorafenib (14.5 months)[11] therapy in previous studies.

In summary, we recommend strongly qualifying the suggestion by Forner and co-workers that TACE and sorafenib therapy should be the first-line treatments for patients with intermediate-stage and advanced-stage HCC, respectively. We suggest that for a substantial proportion of patients with intermediate-stage disease, more-aggressive treatments might need to be considered first. We also highlight the extensive literature documenting good clinical efficacy and safety of resection in certain patients with intermediate-stage and even advanced-stage disease. Importantly, if HCC recurs after initial resection, many patients could be eligible for a range of retreatments, including further resection, TACE, and radiofrequency ablation. Thus, it could be desirable to consider hepatic resection for the first-line treatment of many patients with intermediate-stage HCC.

*Hepatobiliary Surgery Department, Affiliated Tumour Hospital of Guangxi Medical University, 71 He Di Road, Nanning 530021, People's Republic of China (**J.-H.Z., S.-D.L., Y.-Y.W., L.M., L.-Q.L.**).*
Correspondence to: J.-H.Z.
zhongjianhong66@163.com
L-Q.L.
xitongpingjia@163.com

Acknowledgements
The authors thank Armando Chapin Rodríguez, PhD, for his language editing. The authors' research is supported by the Self-Raised Scientific Research Fund of the Ministry of Health of Guangxi Province (Z2014241), the Youth Science Foundation of Guangxi Medical University (GXMUYSF201302), the National Science and Technology Major Special Project (2012ZX10002010001009), and the National Natural Science Foundation of China (81160262/H1602).

Competing interests
The authors declare no competing interests.

1. Forner, A., Gilabert, M., Bruix, J. & Raoul, J. L. Treatment of intermediate-stage hepatocellular carcinoma. *Nat. Rev. Clin. Oncol.* **11**, 525–535 (2014).
2. Llovet, J. M., Brú, C. & Bruix, J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin. Liver. Dis.* **19**, 329–338 (1999).

Table 1 | Overall survival of patients with intermediate-stage HCC after hepatic resection*

Disease characteristics	Number of patients	Median overall survival (months)	Overall survival (%)		
			1 year	3 year	5 year
Single tumour >5 cm	700	54	94	74	56
2–3 tumours with maximum diameter >3 cm	308	47	91	67	45
>3 tumours, regardless of size	174	42	77	56	36
Total	1,182	51	92	71	47

*Data from patients who underwent initial resection at the Affiliated Tumour Hospital and the First Affiliated Hospital of Guangxi Medical University, People's Republic of China.[4,17] Abbreviation: HCC, hepatocellular carcinoma.

3. Llovet, J. M. & Bruix, J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology* **37**, 429–442 (2003).
4. Zhong, J. H. *et al.* Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. *Ann. Surg.* **260**, 329–340 (2014).
5. Oliveri, R. S., Wetterslev, J. & Gluud, C. Transarterial (chemo)embolisation for unresectable hepatocellular carcinoma. *Cochrane Database of Systematic Reviews*, Issue 3. Art. No.: CD004787. http://dx.doi.org/10.1002/14651858.CD004787.pub2 (2011).
6. Kudo, M. *et al.* Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. *Dig. Dis.* **29**, 339–364 (2011).
7. European Association for The Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL–EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J. Hepatol.* **56**, 908–943 (2012).
8. Malagari, K. *et al.* Chemoembolization with doxorubicin-eluting beads for unresectable hepatocellular carcinoma: five-year survival analysis. *Cardiovasc. Intervent. Radiol.* **35**, 1119–1128 (2012).
9. Burrel, M. *et al.* Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using drug eluting beads. Implications for clinical practice and trial design. *J. Hepatol.* **56**, 1330–1335 (2012).
10. Salem, R. *et al.* Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* **138**, 52–64 (2010).
11. Bruix, J. *et al.* Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J. Hepatol.* **57**, 821–829 (2012).
12. Lencioni, R. *et al.* GIDEON (global investigation of therapeutic decisions in hepatocellular carcinoma and of its treatment with sorafenib): second interim analysis. *Int. J. Clin. Pract.* **68**, 609–617 (2014).
13. Beaugrand, M. *et al.* Treatment of advanced hepatocellular carcinoma by seocalcitol (a vit D analogue): an international randomized double-blind placebo-controlled study in 747 patients [abstract 37]. *J. Hepatol.* **42** (Suppl. 2), 17 (2005).
14. Zhong, J. H., Wu, F.X & Li, H. Hepatic resection associated with good survival for selected patients with multinodular hepatocellular carcinoma. *Tumour Biol.* **35**, 8355–8358 (2014).
15. Yin, L. *et al.* Partial hepatectomy vs. transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan Criteria: a RCT. *J. Hepatol.* **61**, 82–88 (2014).
16. Zhong, J. H. *et al.* Hepatic resection as a safe and effective treatment for hepatocellular carcinoma involving a single large tumor, multiple tumors, or macrovascular invasion. *Medicine (Baltimore)* **94**, e396 (2015).
17. Zhong, J. H. *et al.* Hepatic resection is safe and effective for patients with hepatocellular carcinoma and portal hypertension. *PLoS ONE* **9**, e108755 (2014).