



# The Chengdu system for recurrent hepatocellular carcinoma: A step in the right direction

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Liver cancer is the fourth leading cause of cancer-related death worldwide. Hepatocellular carcinoma (HCC), the most prevalent cause of primary liver cancer, is observed highest in the Far East, South-Eastern Asia and East Africa (1). In most endemic regions this is secondary to the prevalence of specific risk factors including chronic hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection and aflatoxin-exposure (1,2). The development of HBV vaccination and programmes to reduce HBV transmission has reduced the risk of HCC in high-risk Asian countries (1). Global incidence of HCC however continues to rise and major contributory factors to this are alcohol misuse and the obesity epidemic, resulting in non-alcoholic fatty liver disease, in Western nations (1,2).

The presentation of HCC is heterogeneous in nature, giving rise to the necessity of differing therapeutic approaches. For patients with 3 or fewer small ( $\leq 3$  cm) nodules with preserved liver function resection is the optimal treatment strategy according to both European and Asia-Pacific clinical guidelines (3,4). However, recurrence can occur in up to 70% of cases at 5 years. Most of these occur within the first 9 months to 2 years and may represent *de novo* tumours, rather than true recurrence (3). Whilst clear guidance exists on management of primary tumours, it is regretful that professional societies provide limited direction for management of HCC recurrence.

In the October 2018 issue of *Hepatobiliary Surgery and Nutrition*, Wen *et al.* published an international expert consensus for management of recurrent and metastatic HCC following resection (5). This consensus committee

consisted of members predominantly from Chinese institutions, but also Japan, Korea, Italy and the USA.

Four of the ten expert recommendations detail factors that are associated with increased risk of recurrence and suggested management for these patients. Postoperative adjuvant therapy was recommended by the authors for select use in patients at high risk of recurrence, as there is little evidence to support its use (5). This is supported by data from a Cochrane systematic review, which failed to show clinical benefit from adjuvant systemic and regional chemotherapy (6). The STORM trial also failed to provide evidence to support the adjuvant use of sorafenib, a tyrosine kinase inhibitor typically used as a treatment for advanced HCC (7). However, there is promising data to suggest that in the future the development of immunotherapy in cancer treatment may herald added benefit in the adjuvant setting for patients at high risk of recurrence (8).

The proposed Chengdu management for recurrent HCC management is heavily influenced by algorithms for primary HCC management, in particular the guidelines for treatment of primary liver cancer in China (9). Patients who present with late HCC recurrence of 1 year or greater are likely to have suffered from *de novo* mutations due to underlying liver pathology, such as cirrhosis or HBV. Late recurrence and so-called multicentric recurrent HCC are associated with improved prognosis. As such optimal management of recurrent HCC of multicentric origin is likely to benefit from a similar treatment approach to primary HCC (10). Patients with early recurrence however may benefit from more aggressive management approaches,

including trans-arterial chemoembolization (TACE), as their tumour factors are commonly associated with poor prognosis. The authors of the Chengdu management algorithm have incorporated this important distinction in tumour biology and suggest treatment with TACE, ablation or radiotherapy and monitoring for response before further consideration of locoregional approaches (5).

An important consideration of recurrent HCC management is whether ablation provides clinical benefit in comparison to resection in recurrent HCC. A recent meta-analysis from our group failed to find a difference in overall survival between ablation and resection for treatment of recurrent HCC following resection (11). This meta-analysis also identified negative prognostic factors (short disease-free interval, multiple hepatic metastases and large hepatic metastases), which should be taken into consideration when considering individual patient treatment options.

Patients who undergo repeat hepatectomy may be at high risk of hepatic dysfunction, especially in the setting of underlying chronic liver disease, due to low functional residual liver volumes as demonstrated in primary hepatectomy (12). The Chengdu guidelines reflect this by indicating that patients who meet criteria for either resection or ablation may benefit from each (9).

Innovation in ablation techniques will continue to advance the locoregional treatment of HCC. Significant differences have not been found in overall survival between radiofrequency ablation (RFA) or microwave ablation (MWA) presently (13). The development of MWA may allow for future treatment of HCCs up to 5cm via ablative techniques. The current limitation of RFA is that local vessels can reduce energy delivered to peripheries due to the 'heat-sink' effect, therefore only allowing treatment of tumours up to 3 cm in diameter. MWA is less averse to this as electromagnetic waves are not as affected by the 'heat-sink' effect as radio waves produced in RFA (3). Moreover, irreversible electroporation (IRE), a novel ablative technique that causes tumour necrosis through electrical waves, may herald further benefits for treatment of recurrent HCC in the future. It is thought to increase the treatment area as it is minimally affected by 'heat-sink', but also produces less damage to surrounding vessels and bile ducts (3). The technology will require further investigation before it becomes a widely recommended treatment modality.

The consensus statement present by Wen *et al.* is an exciting initial recommendation for the management of recurrent HCC that will help guide multidisciplinary

management for these patients. It represents the first attempt to synthesise the evidence available for recurrent HCC in the form of guidelines. The major limitation of this recommendation is the basis of the literature upon which it is based. Due to the heterogeneous nature of recurrent disease there is a paucity of high-level evidence provided globally. Additionally, HCC diagnoses are largely concentrated in East and South-East Asia as well as notable African nations (1,2). As such the majority of literature is adopted from institutions in these nations. Western nations, where the incidence of HCC is increasing, are subject to a differing aetiologies and underlying chronic liver disease (1,2). Future developments shall be needed to provide high quality studies from Western nations. This shall likely require a collaborative approach between institutions and nations to ensure large patient numbers can be incorporated. This may see a divergence of management of recurrent HCC according to geography and underlying factors. However, the Chengdu recommendation provides a well-founded basis from which institutions and nations can generate their own guidelines according to local disease factors.

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## Footnote

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

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