

EDITORIAL

Treatment allocation in patients with hepatocellular carcinoma: Need for a paradigm shift?

Treatment allocation of patients with hepatocellular carcinoma (HCC) is an extremely complex process as this tumour usually arises in patients with liver cirrhosis, that may be complicated by features of portal hypertension and liver failure, and patients often present additional comorbidities, thus making the therapeutic decision process even more challenging.¹ The complexity of this scenario has further increased in the last years due to a dramatic change in the treatment paradigm of HCC patients as well as in the landscape of patients developing this tumour.^{2,3} These changes mainly concerned systemic and surgical therapies of HCC but also the treatment of unresectable advanced tumours due to the current availability of three lines of systemic therapy with tyrosine kinase inhibitors and the recent advent of a front-line therapy more effective than sorafenib (ie, atezolizumab plus bevacizumab) that are the available novel standard of care as it is European Medicines Agency and Food and Drug Administration approved them for unresectable HCC.^{4,5} These advancements are expanding the reach of systemic therapy beyond the conventional limit of the advanced stage of the disease and, likely, such therapies will represent a valid therapeutic option together, or as an alternative, to loco-regional therapies in all patients with unresectable HCC independently of tumour stage.

On the contrary, the rising spread of mini-invasive approaches has radically improved the surgical treatment of HCC. The mini-invasive approach, in fact, has become a well-established positive prognostic factor in patients undergoing liver resection for HCC.⁶ The optimal candidacy to liver resection, in fact, now depends on a multi-parametric evaluation that includes residual liver function, grade of portal hypertension, the volume of the remaining liver parenchyma and the possibility to apply a mini-invasive approach.⁷ Based on this new concept of resectability,⁸ liver resection should not be confined to specific sub-populations (or sub-stages) based on the absence of a single adverse prognostic factor (ie, clinically relevant portal hypertension, increased serum bilirubin, multinodular pattern or vascular invasion). Lastly, the boundaries for the selection of patients for liver transplantation have widened due to the application of the transplant benefit concept and to the results of well-conducted, prospective studies that have demonstrated the effectiveness of down-staging strategies, thus increasing the candidacy to this curative procedure. Thus, on the basis of local organ resources, availability of alternative therapies, and waiting list

competition issues, the indication to liver transplantation for HCC can include patients in almost all stages of liver disease (from very early to terminal stage HCC).

These recent, relevant advances in the treatment, both systemic and surgical, of HCC patients, have made even more evident the limitations of a 'stage hierarchy approach' rigidly linking each stage (or sub-stage) to a specific treatment as recommended by the Barcelona Clinic Liver Cancer (BCLC) algorithm¹⁰. The limits of this conceptual approach to HCC management are witnessed by the recent introduction of the novel concepts of 'treatment stage migration' and 'treatment stage alternative' introduced by Western guidelines^{5,9} with the aim to increase the plasticity of the 'stage hierarchy' approach and its adaptability to the need of such an evolving clinical landscape. In practice, the 'treatment stage migration' strategy allows moving to another treatment (generally that of the subsequent more advanced stage) if the suggested stage-linked treatment is unfeasible, while the 'treatment stage alternative' approach proposes more than one therapeutic option for each BCLC stage. Both these strategies, however, maintain a 'stage hierarchy' in establishing the treatment modality, since they do not always support the choice of hierarchically superior therapies, thus causing and justifying also suboptimal therapeutic decisions responsible for a worsening of patient prognosis.

This awareness is the main cause of the poor adherence to a stage-dictated therapy reported by expert centres where 42%-45% of patients belonging to the advanced or intermediate BCLC stage undergo upward treatments with significantly better survival compared to that observed with the recommended one.¹⁰

A conceptually alternative approach to the HCC treatment aligned to the 'stage hierarchy' is the 'therapeutic hierarchy'¹ which is well represented by the ITA.LI.CA staging system for treatment allocation (Figure 1). This emerging concept relies on an evidence-based sequence of HCC treatments, hierarchically based on their proven effectiveness, and brings the clinician thought towards the most effective therapy feasible in the patient. If it is judged as unfeasible, a downward choice ordered according to the proven therapeutic efficacy is adopted. In other words, this strategy systematically forces clinicians to search for the best survival benefit for any patient and to taper the treatment selection process according to evidence provided by clinical practice.¹¹

All in all, we feel that this novel conceptual approach to the management of HCC patients has the inherent possibility of welcoming

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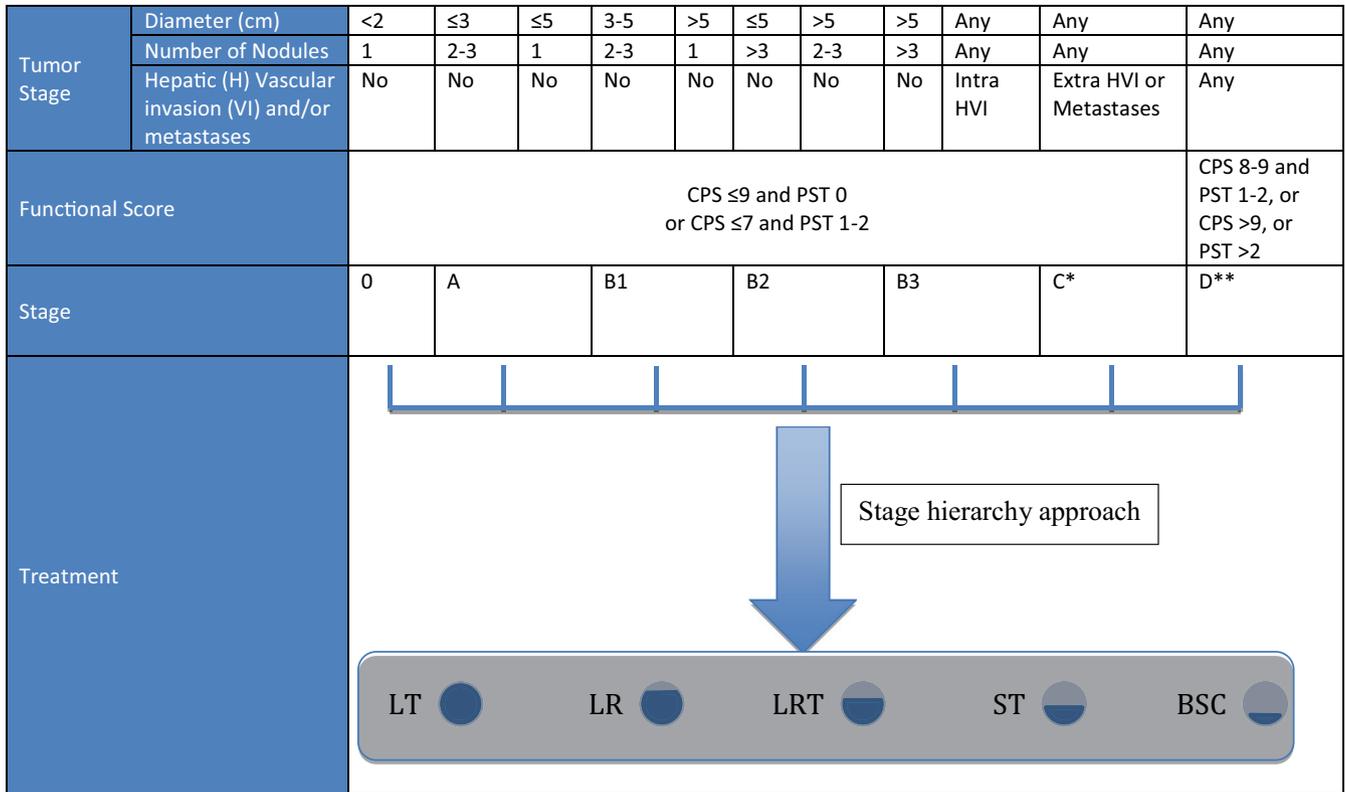


FIGURE 1 The concept of ‘therapeutic hierarchy’ represented in the ITA.LI.CA staging for treatment allocation. The degree of filling of the circles indicates the median survival that can be reached in each stage. CPS, Child Pugh score; PST, performance status; LT, liver transplantation; LR, liver resection; LRT, loco regional therapies (including ablation procedures or intra-arterial therapies); ST, systemic therapy; BSC, best supportive care. *With exception of anecdotal cases in stage C only ST or BSC can be used. **With exception of anecdotal cases in stage D only ST or BSC can be used

the recent improvements in HCC treatment and their most appropriate implementation. We are convinced that the current revolutionary changes in the HCC treatment strategy, mainly related to radical improvements in both surgical and systemic therapies, requires a paradigm shift also in the view of HCC management, moving from a rigid stage-based approach to a fluid treatment-hierarchy approach so as to optimize both the resource utilization and patient prognosis.

CONFLICT OF INTEREST

All authors have declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed to writing and revising the original draft.

DATA STATEMENT PERMISSION

The authors have permission to reproduce material from other sources.

DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated.

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