

# Expanded Criteria for Resection: Are Current Guidelines Too Conservative?

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**Abstract** The surgical treatment of hepatocellular carcinoma (HCC) relies on the guidelines edited by the American (AASLD) and Europe (EASL) societies, according to the evidence-based Barcelona clinic liver cancer (BCLC) staging system. One drawback of the BCLC system is that it is not acknowledged by surgeons. For patients with locally advanced HCC (BCLC stage B and C) treatments such as transarterial chemoembolization (TACE) and Sorafenib are preferred over surgery as they have shown survival benefits in nonrandomized series. While the BCLC management schema has been adopted into hepatology-driven Western guidelines, algorithms from Asian countries are advocating to extend the criteria for surgery in HCC. In this chapter, we will assess if the guidelines for resection are too restrictive in the management of HCC.

**Keywords** Hepatocellular carcinoma · Guidelines · Resection · BCLC staging

## Introduction

Societies of physicians dedicated to the study and treatment of disease commonly take it upon themselves to periodically

develop and publish guidelines for the management of patients with diseases that they feel are within their area of interest and expertise. The idea of evidence-based medicine has gained a lot of attention over recent years and has evolved into a formalized system where various approaches to the treatment of disease are rated as to the level of evidence that supports their use, with the assumption that treatments backed by high levels of evidence are to be preferred; incorporation of an evidence-based approach is a key feature in the creation of guidelines. Apart from level of evidence, guidelines also consider the authority of the evidence source in their ultimate development of recommendations.

The process of creating guidelines has also been formalized. It begins with the appointment by the society of one or perhaps two individuals who are widely recognized authorities to lead the process; typically, together with a small committee of key society members, they identify experts in the field to contribute to the process. There are published guidelines for the creation of guidelines to which the reader may refer to gain further insight into the process [1]. The likelihood of adoption of guidelines by physicians in practice is proportional to the extent to which they acknowledge the authority of the creators of the guidelines and feel enfranchised in their creation through adequate representation by like-minded individuals in the process.

There are many areas in medicine where it is generally acknowledged that everyday practice in the community is at odds with the recommendations of published guidelines. The treatment of hepatocellular carcinoma (HCC) is a prime example. The care of patients with HCC has long been the domain of surgeons, and surgery is universally recognized to be the only potentially curative treatment, but creation of the guidelines most commonly cited in the USA (AASLD) and Europe (EASL) was led by hepatologists and relies heavily on the Barcelona clinic liver cancer (BCLC) staging and the

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treatment algorithm created by those same hepatologists [1–3]. The authority of the creators of the BCLC system to create guidelines for HCC treatment is not generally acknowledged by surgeons. While the BCLC system is clearly evidence-based, it starts off with an assumption that surgery should only be offered to the best candidates and is something to be avoided unless clearly proven to be superior to the alternatives, whereas surgeons have long taken the approach that resection is the preferred treatment for all HCC confined to the liver unless it cannot be safely carried out.

Whether due to the nature of surgical treatment or to the inadequacy of surgeons as clinical investigators, there are no randomized trials demonstrating its superiority over alternative treatments, or indeed over no treatment. As a result, when carefully performed randomized trials for nonsurgical treatments such as transarterial chemoembolization (TACE) or sorafenib have demonstrated survival benefit, these treatments have been incorporated into the BCLC system in preference to surgery for the populations that were the targets of the trials proving their efficacy, namely BCLC classes B and C, respectively [1, 2]. Surgeons, on the other hand, while acknowledging the trial results demonstrating benefit of these treatments, feel that they (1) do not offer sufficient prolongation of survival compared to published and personal results of surgery, despite the absence of randomized trials, to warrant their replacing surgery as the treatment of choice in suitable cases of BCLC B or C HCC and (2) essentially eliminate the possibility of cure, which surgeons in the field know from personal experience exists with surgery.

Relevant to this concern is the focus in clinical trials on median survival as the primary index by which treatments are compared, as opposed to focusing on the tail of the survival curves. Focus on median survival carries the implicit assumption that cure is not achievable, and the goal of treatment is thus to prolong survival with disease. It is entirely possible for two treatments to have similar median survivals, yet for long-term survival—i.e., rate of cure—to be dramatically different. A likely example is patients with preserved liver function and HCC with limited macroscopic vascular invasion (MVI) who are treated with resection vs. sorafenib, where multiple large cohort studies show 5-year survival rates with surgery that most physicians acknowledge are not achievable with systemic therapy [4, 5]. Surgeons tend to pay more attention to the tail of the curve since we see these patients returning to the clinic year after year; patients, not surprisingly, tend to share this view and readily opt for surgery over sorafenib.

### **The Evidence for Surgical Treatment of BCLC Intermediate and Advanced HCC**

As a result of advances in patient selection, surgical technique, and perioperative care, resection for HCC in experienced

centers is safe with perioperative mortality in the range of 0–2% in patients with compensated liver disease. While there is little (not nothing!) in the way of randomized trials, there are many cohort studies that provide a clear picture of what can be achieved with surgery [6]. While the issue of case selection bias looms over any attempt to compare results of different treatments, it should be remembered that the randomized trials of nonsurgical treatments on which Western guidelines are based have employed strict entry criteria including normal liver function and performance status. Moreover, surgeons would not contest claims of selection bias in choosing surgical candidates; case selection is in fact the key to successful surgery. The following are three examples of recent studies that present results of resection in patients with BCLC B or C HCC that compare favorably with those of the treatments espoused in Western guidelines.

In 2014, Yin et al. published a randomized trial of TACE vs. resection in 173 patients with BCLC B HCC [7]. All patients had multiple HCC nodules. TACE was carried out with selective infusion of chemotherapy mixed with lipiodol followed by gelatin-foam particles, similar to the randomized trial of Llovet et al. that provided evidence for the inclusion of TACE in BCLC guidelines. In the TACE group, crossover to resection was allowed in patients who achieved complete response. Overall survival was greater in the resection group ( $p < 0.001$ ) with 3-year and median survival of 51.5% and 41 months for resection vs. 18.1% and 14 months for TACE.

A group of surgeons from Europe, Japan, and America published an analysis of pooled data on 1870 patients from 10 centers who underwent resection of HCC, including 663 beyond Milan criteria without MVI and 274 with MVI (portal vein, hepatic vein, inferior vena cava) based on preoperative imaging [8]. The authors' aim in this analysis was to challenge the BCLC treatment allocation and advocate for surgery in selected cases of BCLC B and C. Unfortunately, as a result of misinterpretation of the BCLC classification, in reporting outcomes of resection, they considered the 663 patients with HCC beyond Milan criteria and without MVI to be BCLC B where, in fact, nearly 70% of these patients had single tumors >5 cm and were thus in fact BCLC A. Since the patients with single vs. multiple tumors were not analyzed separately, it is impossible to glean from the paper the results in patients with BCLC B HCC. For the 274 patients resected with preoperatively recognized MVI (BCLC C), however, overall survival at 1, 3, and 5 years was 76, 49, and 38%, respectively.

In 2016, the Liver Cancer Study Group of Japan published an analysis of 6474 patients from a Japanese national survey with HCC and MVI, of whom 2093 underwent resection [9]. The analysis classified the extent of portal invasion as Vp1 (segmental), Vp2 (sectoral), Vp3 (lobar), and Vp4 (main portal vein). Among 1877

patients with MVI and Child-Pugh A cirrhosis who underwent resection, survival at 1, 3, and 5 years was 74.8, 49.1, and 39.1%, respectively, with median survival of 2.87 years. Among 216 patients with MVI and Child-Pugh B cirrhosis, survival at 1, 3, and 5 years was 1.3, 35.2, and 25.6%, respectively, with median survival of 1.44 years. In an attempt to account for case selection bias, propensity scores were successfully matched for 1058 patients with Child-Pugh A cirrhosis who underwent resection and 1058 who were treated nonsurgically; median survival after surgery was 2.45 vs. 1.57 years with nonsurgical treatment ( $p = 0.0001$ ). Subgroup analysis showed that extent of portal invasion correlated with survival, but survival benefit of surgical vs. nonsurgical therapy was observed in all groups except Vp4.

### Recommendations in Other Guidelines

While the BCLC management schema has been adopted into hepatology-driven Western guidelines, the reader should bear in mind that 75–80% of the worldwide HCC burden lies in Asia. Management of HCC in Asia has traditionally been driven by surgeons, and Asian staging/treatment algorithms and guidelines thus reflect an opt-out attitude towards surgery, with resection being the preferred treatment for all patients with technically resectable HCC and sufficiently intact liver function to withstand surgery in the absence of evidence that nonsurgical treatment is superior. Below are a few examples of Asian algorithms/guidelines.

The Hong Kong liver cancer (HKLC) staging system with treatment stratification, published in 2014 [10], was developed based on a retrospective analysis of 3856 patients treated at St. Mary's Hospital over a 14-year period. Patients were randomly divided into a training set used to develop a prognostic staging system incorporating tumor factors, liver function, and functional status (similar to the BCLC scheme), and a validation set. Treatment recommendations were assigned based on classification and regression tree (CART) methodology. The resultant system assigns patients with early HCC (defined as within Milan criteria) to resection whether Child-Pugh A or B and assigns patients with Child-Pugh A cirrhosis and intermediate HCC (defined as  $\leq 3$  tumors  $> 5$  cm without MVI,  $> 3$  tumors  $\leq 5$  cm without MVI, or  $\leq 3$  tumors  $\leq 5$  cm with unilateral MVI) to resection rather than nonsurgical treatment. Comparison of projected outcomes with treatment according to HKLC vs. BCLC recommendations, while subject to possible methodological concerns, showed substantially better survival when the more surgically aggressive HKLC recommendations were followed [10].

The Asian Pacific Association for the Study of the Liver (APASL) brought together an interdisciplinary working group to develop consensus recommendations regarding management of HCC that were published in 2010 [11]. A formal

process was undertaken, analyzing and grading the strength of evidence and their recommendations according to the Oxford system. The recommendation concerning hepatic resection, with evidence grade 2b and strength of recommendation B, was that “Liver resection is a first-line curative treatment of solitary or multifocal HCC confined to the liver, anatomically resectable, and with satisfactory liver function reserve.”

From Japan where, similar to Western countries, hepatitis C is the predominant underlying liver disease, the Japanese Society of Hepatology produced the third version of its JSH-HCC guidelines in 2013 [12]. The methodology and references used in the creation of the guidelines are extensively documented on the JSH website. As concerns the extent of HCC suitable for resection, the guidelines state, “Liver resection is indicated for HCC if there are three or fewer tumors and all are limited to the liver. There is no restriction on tumor size. It is suggested that patients with tumor invasion to the portal vein be indicated for surgery if the tumor has not progressed beyond the first-order branches.”

### Conclusion

Western guidelines for the management of HCC and the BCLC staging and treatment algorithm on which they are grounded are the product of expert physicians applying the principles of evidence-based medicine. The guidelines are subject to continual revision based on new evidence; the latest adds regorafenib as a second-line treatment for patients with BCLC stage C HCC and Child-Pugh A cirrhosis who progress on sorafenib. Cohort studies can, in fact, provide sufficient evidence for surgical treatment to be included in the guidelines, as in the case of resection and transplantation for BCLC stage A HCC. However, with advancing tumor stage, as results of surgery decline and nonsurgical treatments with proven benefit are available, the threshold to include surgery for BCLC stage B and C HCC has not been reached. Mounting trials that randomize surgery against nonsurgical treatments poses major challenges. In the case of BCLC stage B, a randomized trial of TACE vs. resection has in fact been published, as noted above, with nearly three times the number of patients per arm as the Barcelona trial that initially established benefit of TACE, demonstrating results strongly favoring resection. Perhaps the tide will turn. Meanwhile, as the authors of the guidelines readily admit, guidelines are not a substitute for the judgment of physicians (including surgeons!) caring for individual patients; the many surgeons whose personal and collective experience leads them to recommend surgery to selected patients with BCLC stage B and C HCC, and the patients who readily agree, provide evidence for the limitations of current Western guidelines in defining patient care for HCC patients.

## Compliance with Ethical Standards

**Conflict of Interest** Dr. Tian Yang, Dr. Emmanuel Melloul, Dr. Parissa Tabrizian, and Dr. Myron Schwartz declare that they have no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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