

Hepatocellular carcinoma surgical therapy: perspectives on the current limits to resection

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Abstract: Hepatocellular carcinoma (HCC) patients often present with late stage disease, which removes surgical resection from the therapeutic treatment options. Only patients with very early disease are recommended for a potentially curative surgical resection. These guidelines have been broadly challenged due to the lack of evidence supporting the use of local therapies over surgery for resectable disease. This review highlights the role of surgical resection for HCC by disease stage, and reports data that supports treatment outside of the accepted Barcelona Clinic Liver Cancer (BCLC) treatment algorithm. As such, the role for surgery in advanced disease is also reviewed. We also highlight the limitations of surgical resection for HCC. With the available data, it is crucial that an update of the current clinical guidelines be introduced, as the current guidelines prohibit the benefit of surgical resection to patients who may be able to achieve a survival benefit.

Keywords: Liver cancer; liver resection; cancer treatment

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Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death world-wide (1). The prognosis of HCC depends on tumor stage at the time of diagnosis. Various staging criteria for HCC have been proposed. The Barcelona Clinic Liver Cancer (BCLC) staging system has emerged as a primary system for staging, as well as a clinical guideline, in an effort to standardize the care of HCC (2). The staging system incorporates the patient's performance status, the size and number of tumor nodules present, the presence of liver impairment, including portal hypertension, as well as degree of cirrhosis as measured by the Child-Pugh classification.

The BCLC system has been validated with regards to prognosis. Median survival ranges from 33 months in BCLC A patients as compared to 1.8 months in BCLC D

patients (3). The BCLC staging system stratifies treatment algorithms based on the above prognostic criteria and has been heavily criticized for its recommendations against potentially curative operations for "advanced" but technically resectable HCC. According to the algorithm, only patients with very early stage disease, with a single lesion less than 2 cm in size and no evidence of portal hypertension with a normal bilirubin are recommended to undergo liver resection. This extremely limited criteria for resection has been challenged by many. Despite this, the European Association for the Surgery of Liver/American Association for the Study of Liver Disease (EASL-AASLD) clinical practice guidelines are based off of the recommendations of the BCLC. In lieu of an operation, the BCLC recommends that more advanced patients be treated with less invasive local treatment modalities including ablative therapies and chemoembolization, despite lack of

level one evidence to support these treatment strategies over surgical resection. Furthermore, currently available systemic therapy for HCC has failed to demonstrate encouraging outcomes in the adjuvant setting following resection or ablative therapies (4). Currently, The EASL-AASLD guidelines state that surgery should be reserved for patients who have a single HCC lesion with completely preserved liver function, and no portal hypertension (5). The Asian Pacific Association for the Study of the Liver guidelines are broader and allow for surgical resection of solitary or multifocal HCC when anatomically feasible, as long as there is a satisfactory liver reserve (6).

Since the introduction of the BCLC treatment guidelines, there has been continuous and ongoing development of new surgical techniques allowing for safer and more aggressive resections to be performed with lower morbidity and mortality than in the past. In addition, surgeons have developed a deeper understanding of the physiologic reserve of patients with liver disease, in addition to techniques that reduce blood loss without performing complete occlusion of portal flow, and mechanisms that allow for increased hepatocellular tolerance to flow occlusion with ischemic preconditioning (7). Given the significant advancements in the field, the poor outcomes generally seen with available systemic treatments, and broad criticism of the BCLC guidelines for recommending conservative use of hepatectomy, expansion of surgical resection for the treatment of intermediate and advanced HCC should be explored.

This review focuses on the current data supporting the use of surgical resection for HCC. We identify areas in which surgery may be used as a treatment modality to improve survival outcomes as well as to achieve potential cure for intermediate and advanced disease.

Early stage disease

In the current BCLC guidelines, patients with early stage disease are not recommended to have surgical resection. Early stage disease in the BCLC staging system is defined as 3 nodules less than 3 cm or less, which mirrors the Milan criteria, first published more than two decades ago (8). These patients are recommended to undergo liver transplantation unless other comorbidities are present. Expanded criteria for liver transplantation, including UCSF criteria, are left out of the BCLC, despite numerous validation studies (9-11). While there is strong debate regarding transplantation *vs.* surgical resection for early

stage HCC, the downsides of lifelong immunosuppression, significantly larger healthcare costs, as well as availability of organs must be weighed against the possibility of leaving behind clinically occult disease with surgical resection. However, in patients with low-level cirrhosis and preserved liver function, liver resection has similar survival outcomes to transplantation (12). In these patients, therefore, resection is preferable to transplantation. Liver transplantation should be employed for early stage patients with more severe cirrhosis, as these patients benefit oncologically as well as from their life-limiting liver disease. As liver transplantation is also an important treatment modality for HCC, an in-depth discussion regarding advantages of resection *vs.* transplantation is outside the scope of this report, which focuses on the benefits of liver resection.

Beyond transplantation, only radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI) are recommended by the BCLC clinical treatment algorithm for early stage disease. Currently many institutions perform microwave ablation (MWA) rather than RFA due to the faster ablation time and the minimal heat sink effect of larger vessels. However, surgical resection has been shown to demonstrate superior survival outcomes in comparison to both RFA and PEI. A meta-analysis including over 21,000 patients from six randomized trials, demonstrated superiority of surgical resection over RFA and/or PEI in terms of overall survival (OS) and recurrence free survival (RFS) (13). Xu *et al.* also demonstrated superiority of surgical resection over RFA in their meta-analysis of over 2,500 patients (14). OS at 1, 3, and 5-year all favored surgical resection with odds ratios of 0.60, 0.49, and 0.60, respectively.

In a prospective trial comparing resection to RFA, 235 patients who met Milan criteria were randomized to receive resection or ablation (15). These patients were subsequently imaged every three months for 60 months after treatment. There were no differences in terms of clinical characteristics between these two groups, including tumor number or size, baseline level of liver disease, or alpha-feto protein (AFP). With a median follow up time of 3.1 years in the RFA group, and 3.8 years in the surgery group, 5-year OS was 76.65% in the surgery group *vs.* 54.78% in the RFA group ($P=0.001$). The 5-year RFS was 51.30% in the surgery group *vs.* 28.69% in the RFA group ($P=0.017$). These results underscore the significant advantages to liver resection in terms of survival when patients with HCC are optimized for an operation.

MWA has theoretical advantages over RFA and has recently been evaluated in a randomized controlled fashion for stage A patients, who were not considered for surgery. Results from this trial demonstrated no difference in local tumor progression and survival after a median OS period of 20 months (16). MWA is not part of the current BCLC guidelines. Regardless of ablative therapy, patients with early stage HCC by BCLC criteria, should undergo surgical resection if they can tolerate a hepatectomy based on underlying liver disease and general comorbidities. In patients who are not fit for a major operation, local ablative therapies may be considered. Transplantation should be considered for those with underlying life-limiting cirrhosis. In these patients, extended criteria for liver transplantation should be implemented into treatment algorithms.

Large solitary HCC falls outside of transplantation criteria based on size secondary to increased rates of recurrence (17). In addition, the utility of ablation in lesions greater than 5 cm is limited, as ablative zones with this technique are no larger than 3 to 4 cm with increased tumor size predicting high rates of recurrence (18-20). In addition, surgery has demonstrated increased survival over TACE in this subset of patients (21). Therefore, patients who can tolerate an operation should be offered surgery. TACE should be reserved as an option for patients who are not fit for surgery.

Intermediate stage disease

Intermediate stage HCC is defined by the BCLC staging system as patients with multinodular HCC with a good performance status. The guidelines do not delineate if patients with multifocal disease have unilobar confined disease, which may be more amenable to resection compared to those with bilobar disease. All patients are grouped within this broad category, as long as there is no clinical evidence of portal vein invasion, nodal disease, or distant metastases. BCLC stage B patients are recommended for transarterial chemoembolization (TACE).

Numerous studies support the use of surgical resection in intermediate stage HCC (22-25). Zhong *et al.* performed a retrospective analysis of 393 patients with BCLC stage B HCC who underwent either surgical resection or TACE (24). Patients who underwent resection were found to have improved OS compared to those who underwent TACE alone. Median OS was 59% *vs.* 29% at 3 years and 37% *vs.* 14% at 5 years which is a statistically significant improvement at both time points. In their

study, on multivariable analysis, only an elevated AFP level greater than 400, an elevated ALT level, and TACE were independently associated with a worse OS. Although surgery was associated with a greater complication rate than TACE (28% *vs.* 18.5%), mortality was similarly low. These findings were validated in a retrospective analysis including over a thousand patients comparing resection, TACE, systemic chemotherapy or supportive care in patients with multiple HCCs (25). This population included patients who had portal vein involvement. All patients were considered for surgical resection, and if not possible, patients then underwent TACE, which was only performed for patients without main portal vein trunk involvement. After a median follow up of 20.2 months, the median OS for patients was 37.9 months in patients who underwent surgical resection *vs.* only 17.4 months in those who underwent TACE. The 5-year survival rate was 36.6% in the surgery group *vs.* 11% in the TACE group ($P=0.05$). TACE was also an independent predictor of poor survival in this study with a hazard ratio of 1.614 when compared with resection; however, the patients receiving TACE were not considered surgical candidates. In a sub-analysis of these patients, those who received surgical resection had better survival outcomes than those who had TACE regardless of BCLC stage. In patients with specifically BCLC stage B disease, median OS was 41.8 *vs.* 16.8 months, further supporting the use of surgical resection within this group of patients.

In a prospective analysis of patients with resectable HCC with multiple large lesions greater than 5 cm, 85 patients were assigned to surgical resection and 83 patients to TACE. In 28 patients who had a response to neoadjuvant TACE, a subsequently operation was performed (22). Five-year survival in the surgery group was found to be 23.9% *vs.* 18.9% ($P>0.05$). However, in the group that responded to TACE and subsequently underwent a surgical resection, the 5-year survival was 50.5% ($P=0.04$). These results highlight the benefit of TACE as a strategy to downstage patients with large and multifocal, but resectable, tumors in order to enhance survival outcomes.

Similar results were seen in a retrospective study involving 110 patients with large multifocal HCC. A strategy involving TACE followed by surgical resection was found to be safe, with a low rate of serious complications (19). The median survival of patients who received TACE followed by surgical resection was 47 months compared to 20 months, which was statistically significant. In the subgroup analysis of patients who had a good tumor response to TACE prior to surgical resection, survival was

as high as 48 months in comparison to 35 months in those that had poor response to TACE followed by surgical resection. Response in this study was standardized by Response Evaluation Criteria In Solid Tumors (RECIST). These results further underscore that a strategy involving TACE followed by resection is beneficial for patients with large multifocal HCC who fall within BCLC stage B HCC.

Advanced stage disease

Treatment of advanced HCC has traditionally been managed with systemic therapy. Unfortunately, systemic therapy in HCC has not been promising in terms of survival benefit. Sorafenib is the only systemic agent approved for advanced HCC. Sorafenib has shown some benefit in unresectable HCC (26). However, the landmark randomized controlled phase III STORM clinical trial demonstrated no benefit of sorafenib in the adjuvant setting. In over 1,100 patients, this trial demonstrated no benefit of sorafenib over placebo in HCC following resection or ablation (4). Although new drugs are being investigated, currently none are approved for the adjuvant setting (27). The BCLC defines advanced stage disease (stage C) as HCC with portal vein involvement, nodal involvement, distant disease, or patients with poor performance status. The only clinical practice guideline in the BCLC algorithm for this situation calls for sorafenib therapy. However, in surgically fit patients with advanced stage disease, the question of whether patients with anatomically resectable disease may benefit from surgical resection must be explored.

Although clinically significant portal hypertension generally signifies the more advanced sequelae of hepatic cirrhosis, it has not been shown to effect survival in patients who are able to undergo resection for HCC (28). MELD score and extent of hepatectomy, not portal hypertension, have been shown to be predictors of postoperative liver failure after resection in cirrhotic patients (29). Therefore, the presence of portal hypertension, in and of itself, should not be a contraindication for liver resection in patients with advanced HCC. These patients, however, do require meticulous preoperative optimization for any consideration for surgical resection.

Pawlik and colleagues demonstrated favorable results in patients who underwent resection for HCC with major portal or hepatic vein invasion. In their retrospective review of over 100 patients from the MD Anderson Cancer Center, the perioperative mortality was found to be 5.9% (30). Over 90% of these patients had Child's A

cirrhosis, representing a carefully selected population of patients. Most patients either underwent hemi-hepatectomy or extended hepatectomy. In this selective cohort of patients with vascular involvement, there was no difference in survival seen in patients with single lesions *vs.* multiple lesions (7.8 *vs.* 11.1 months, $P=0.96$), although these results may be due to the study being underpowered. Similarly, size of the tumors was also not found to be prognostic. Only the presence of moderate to severe cirrhosis was able to independently predict survival in a multivariable analysis.

As systemic therapy options in HCC remain dismal, numerous studies have demonstrated the benefit of surgical resection or liver transplantation in appropriately selected patients over systemic therapy alone. Ruzzenente *et al.* demonstrated those who had vascular involvement with surgical resection and transplantation had median survival times of 27 and 30 months respectively, compared to a mere 12 months with systemic therapy only (31).

Lymph node metastases, not commonly seen in patients with HCC, are also listed within the BCLC staging criteria for advanced stage C disease. Portal lymphadenectomy is not mandatory for staging, and may be performed selectively for HCC (32). However, one study in which 523 patients underwent routine nodal dissection for HCC, only 7.45% were found to have nodal metastases (33). In these patients, the median survival time was 28 months as compared to 53 months in patients without nodal disease ($P<0.05$). Furthermore, with a median follow-up of 43 months, 82% of patients who had nodal metastases had recurrence of their disease, demonstrating the poor prognostic impact when nodal disease is involved.

In patients with advanced HCC with bilobar metastases, which have been traditionally deemed unresectable, there may be a role for surgical resection in combination with ablation in patients with an excellent performance status (34). Liu and colleagues demonstrated a survival benefit in surgical resection of bilobar metastases compared to non-resectional therapies (35). Contralateral metastases were treated with a combination of wedge resection, ablation, techniques, or TACE. The combination group performed better than those who did not have surgical resection of the dominant lobe. This study included 78 patients who were identified on laparoscopy or laparotomy to have contralateral lobe disease selecting for those patients who were fit for a major operation. Although these studies are retrospective in nature, the results of these investigations highlight the value of a combined strategy involving surgical resection with ablative modality treatments in a selected population of advanced

HCC patients with appropriate surgical risk, particularly when liver function is preserved. In Asia, where the incidence of HCC is over four times that in North America, surgical resection is commonly offered to such patients with advanced HCC (36,37).

Prospective studies are needed to obtain higher quality data in this subset of patients with advanced disease. Unfortunately, prospective randomized controlled trials in this setting are difficult to conduct due to not only the extent of tumor, but also the underlying liver dysfunction. However, the retrospective literature certainly points to a survival benefit in carefully selected patients. As survival is still poor in patients with advanced disease, regardless of treatment, further investigation involving multimodality treatment is needed.

Recurrence after resection

Recurrence of HCC generally occurs in two phases and as either local (intra hepatic) or distant metastases. Early intrahepatic recurrence, within two years of resection, is often due to aggressive tumor biology. Predictors of early recurrence after surgical resection in HCC include size greater than 5 cm, high histological grade, and the presence of microvascular invasion. In contrast, late recurrence within the liver, 2 years after resection, is generally related to *de novo* tumor formation (38). New tumor formation years after curative resection likely represents a field defect phenomenon, as these patients may have longstanding or advanced cirrhosis, increasing their carcinogenic capability. Late recurrence is often seen in patients with advanced cirrhosis, multinodularity, increasing age, male gender, as well as increased AST levels (39). Unfortunately, recurrence after resection or liver transplantation is as high as 70% at 5-year, with the presence of microscopic or macroscopic vascular invasion being the strongest predictor of both recurrence and poor survival (40).

Less than a quarter of all recurrences after curative resection are extra-hepatic. When present, they portend a worse prognosis than those patients with intrahepatic recurrence, with maximal observed 5-year survival of 24.0% *vs.* 57.7% after intrahepatic recurrence (41,42). Extreme blood loss during surgery and microscopic hepatic vein invasion are recognized independent predictors of extra-hepatic recurrence (42).

There are currently no standardized recommendations regarding resection for intrahepatic recurrence. Although safe, resection should be considered for patients with

single lesions with good liver function and sufficient FLR (43). Transplantation after recurrence may be also an option for patients who fall within criteria. In the seminal description by Majno *et al.*, salvage transplantation demonstrated OS and disease-free survival similar to that of primary liver transplantation for recurrence of HCC after curative-intent resection (44).

Limitations of surgery

Surgical resection for HCC should not be performed in patients with disease that is not amenable to a negative resection margin (R0). The size of an adequate margin continues to be a topic of debate. In addition, an operation should not be offered to patients with poor functional status who are not expected to have optimal outcomes regardless of treatment. Finally, surgical resection is limited by the need to maintain an adequate future liver remnant (FLR). A commonly quoted 20% future remnant is required to decrease the chance of postop-hepatectomy hepatic failure in patients with no pre-existing liver dysfunction. However, values are more conservative depending on the functional status of the liver (45). Generally accepted FLR values of 30% after chemotherapy treatment and 40% in patients with evidence of cirrhosis, derived from the colorectal literature, are used as a guide for resection in these patients (46). Numerous groups have developed models for prediction of post-hepatectomy liver failure (47-49). Patients with cirrhosis or those who have received cytotoxic chemotherapy have lower functional reserve and require a more conservative approach to large resections. More important than the volumetric prediction is the percentage of healthy functional remnant expected to remain after resection. Therefore, patients with advanced cirrhosis and sequelae of portal hypertension with insufficient remnant may be better managed by transplant or other local therapies. Although vascular invasion and infiltration of adjunct organs are poor prognostic indicators, they are not absolute contraindications for surgery (50,51). As such, the risk of resections must be balanced by the patient's potential benefit from aggressive surgery, taking into account tumor biology as well as the likelihood of early HCC recurrence.

Conclusions

Understanding tumor biology is of primary importance when offering surgical resections to patients with HCC. The risk of a significant operation in those with pre-

existing liver disease, which is present in greater than 90% of patients with HCC, must be balanced by the probability of recurrence (52). Meticulous preoperative evaluation and careful patient selection are the cornerstones to enhancing survival or potentially curing patients with surgical resection. As molecular mechanisms behind HCC oncogenesis continue to be clarified, progress with developing systemic therapies will greatly enhance outcomes in patients with advanced disease. A future prospective study is required to identify the optimal combinatorial strategies for patients with HCC who are amenable to resection.

The conservative limits of the BCLC guidelines must be expanded to include surgical resection in appropriately selected patients. The current guidelines fail to acknowledge surgical resection as the primary strategy for the control of early stage disease with a potentially curative role. In selected patients with intermediate or advanced stage disease, surgical resection should be advanced as a primary option for control of disease either as an individual strategy or in combination with other local therapies. It is imperative that an update of these guidelines or a new clinical treatment algorithm altogether be adopted so as to allow patients with resectable HCC a chance at potentially curative resection.

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Footnote

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