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TOPIC HIGHLIGHT

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Hepatocellular carcinoma: Surgical perspectives beyond the barcelona clinic liver cancer recommendations

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Abstract

The barcelona clinic liver cancer (BCLC) staging system has been approved as guidance for hepatocellular carcinoma (HCC) treatment guidelines by the main Western clinical liver associations. According to the BCLC classification, only patients with a small single HCC nodule without signs of portal hypertension or hyperbilirubinemia should undergo liver resection. In contrast, patients with intermediate-advanced HCC should be scheduled for palliative therapies, even if the lesion is resectable. Recent studies report good short-term and long-term outcomes in patients with intermediate-advanced HCC treated by liver resection. Therefore, this classification has been criticised because it excludes many patients who could benefit from curative resection. The aim of this review was to evaluate the role of surgery beyond the BCLC recommendations. Safe liver resection can be performed in patients with portal hypertension and well-compensated liver function with a 5-year survival rate of 50%. Surgery also offers good long-term result in selected patients with multiple or large HCCs with a reported 5-year survival rate of over 50% and 40%, respectively. Although macrovascular invasion is associated with a poor prognosis, liver resection provides better long-term results than palliative therapies or best supportive care. Recently, researchers have identified several genes whose altered expression influences the prognosis of patients with HCC. These genes may be useful for classifying the biological behaviour of different tumours. A revision of the BCLC classification should be introduced to provide the best treatment strategy and to ensure the best prognosis in patients with HCC.

Key words: Hepatocellular carcinoma; Liver resection; Hepatectomy; Barcelona clinic liver cancer; Surgical therapy

Core tip: The present review reports the results of surgery beyond the barcelona clinic liver cancer recommendations. Recent studies have reported that surgical resection can result in good short- and long-term survival in patients with early hepatocellular carcinoma (HCC) with portal hypertension and in patients with intermediate-advanced HCC. A careful preoperative evaluation, including liver function and remnant volume assessment, is mandatory before liver resection in HCC patients. An understanding of the biological behaviour of these tumours through molecular biology studies may be useful in choosing the optimal treatment strategy.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is ranked as the sixth most common cancer and the third leading cause of cancer-related deaths worldwide[1]. The incidence of HCC is rising in Western countries, likely as a result of the epidemic incidence of chronic liver disease and, more recently, as a result of hepatopathy related to metabolic syndrome[2-5]. Curative treatments, including liver transplantation, surgical resection or percutaneous ablation, are able to achieve a long-term survival of more than 50% at 5 years; however, only a small group of patients with early-stage HCC are eligible for these therapies[6-11]. Despite the increased frequency of surveillance programs, in Western countries, the majority of patients have an advanced HCC at diagnosis.

Thus, in the past decades, several HCC staging systems based on tumour burden and liver function have been proposed to guide therapeutic decisions[12-17]. The barcelona clinic liver cancer (BCLC) staging system has been validated by Western and Eastern groups[18-20] and has been approved as guidance for HCC treatment algorithms by the European Association for the Study of Liver (EASL), the European Organization of Research and Treatment of Cancer (EORTC) and the American Association for the Study of Liver Disease (AASLD), but not by the main Asian associations for the study of liver diseases[21-23]. This staging system currently recommends curative treatments for very early- or early-stage HCC (BCLC stage 0-A), palliative therapies such as transarterial chemoembolisation (TACE) for intermediate-stage HCC (BCLC stage B), sorafenib administration for advanced-stage HCC (BCLC stage C), and supportive care for end-stage HCC (BCLC stage D)[24]. According to the BCLC classification, liver resection should be performed only in patients with a small single HCC nodule without signs of portal hypertension or hyperbilirubinemia.

According to recent surgical series, the 5-year overall survival rate after liver resection ranges from 61% to 91% with postoperative mortality approaching 0%[25,26]. Based on the BCLC classification, patients with multiple, large and macrovascular invasive HCC should undergo palliative treatments with unsatisfactory long terms results even if the lesion is resectable[27-29]. However, recent studies have reported that surgical resection can lead to good short- and long-term survival in these patients[30-33]. Therefore, this classification has been criticised because it excludes many patients who could benefit from curative resection[34-37]. The aim of this review is to evaluate the role of surgery beyond the BCLC recommendations.

BCLC 0-A HCC WITH PORTAL HYPERTENSION (RECOMMENDED LIVER TRANSPLANTATION OR PERCUTANEOUS ABLATION)

According to the BCLC classification, the best treatment for BCLC 0-A HCC patients with portal hypertension (PH) is liver transplantation[24,38-40], which involves the resection of the entire potentially tumour-bearing liver and the removal of underlying liver disease. However, the limited availability of donors, high costs, and long wait period increases the demand for alternative treatment strategies for early HCC with portal hypertension.

The surgical indications for HCC patients with PH remain a matter of debate. Portal hypertension is associated with a high risk of postoperative liver failure[41]. Thus, it is consider a contraindication to surgery in the EASL/EORTC/AALSD guidelines[21,22,24]. In Eastern countries, however, PH is not considered a contraindication to liver resection due to the low rates of postoperative mortality and morbidity that can be achieved if a careful preoperative liver function evaluation is performed[12,42]. Nevertheless, several Western authors have also advocated for liver resection in cases of HCC with PH[43-45]. In recent years, authors have reported mortality and morbidity rates from 0.5% to 4.5% and 38% to 43%, respectively, in patients with PH and from 0.0% to 6.1% and 34.8% to 38.5%, respectively, in patients without PH. Considering long-term outcomes, the 5-year overall survival rates after liver resection varies from 48% to 51.5% in patients with PH and from 61.5% to 65% in patients without PH[44,45].

Similar results were reported in 2011 by Ruzzenente *et al*[46]. In fact, in a surgical series of 44 HCC patients with PH, the postoperative mortality and morbidity were of 4.6% and 37%, respectively, and the 3- and 5-year overall survival rates were 48.7% and 44.9%, respectively. Furthermore, the authors evaluated the prognostic value of the relationship between the extent of liver resection and PH in Child-Pugh A patients. In patients who underwent limited liver resection (wedge or one segment), no significant differences were found between patients with or without PH, and the 5-year survival rates were 72.4% and 61.4%, respectively ($P = 0.458$)[46] (Table 1).

Many studies have compared the survival rates between percutaneous ablation and liver resection for BCLC A HCC patients[47]. In patients with early HCC (single nodule larger than 2 cm), the survival rates are higher after surgery than after percutaneous ablation[11,48,49]. In patients with very early HCC (single nodule $\leqslant$ 2 cm), the long-term results of percutaneous ablation are comparable to liver resection, but percutaneous ablation is less invasive[49,50]. Therefore, portal hypertension should not be considered an absolute contraindication to limited liver resection in BCLC 0-A HCC patients with well-compensated liver function.

Table 1 Results of liver resection in a recently published surgical series (after 2005) in which surgery was performed beyond the beyond barcelona clinic liver cancer recommendations

Ref.	Year	Patients (*n*)	Mortality/morbidity	5-yr survival
BCLC 0-A HCC with portal hypertension				
Capussotti *et al*[43]	2006	66	6.1%/34.8%	40.80%
Ishizawa *et al*[51]	2008	136	-/10%	56.00%
Cucchetti *et al*[44]	2009	79	4.5%/38.5%	56.50%
Ruzzenente *et al*[46]	2011	29	2.2%/33.7%	57.3%(72.4%)[1]
Santambrogio *et al*[45]	2013	63	0.5%/28.6%	48.00%
BCLC A-B multiple HCCs				
Ishizawa *et al*[51]	2008	126	-/15%	58.00%
Ruzzenente *et al*[33]	2009	30 (≤ 3 nodules)	-/-	46.00%
Ho *et al*[59]	2009	97 (≤ 3 nodules)	-/-	40.00%
Huang *et al*[57]	2010	26 (≤ 3 nodules)	0%/27.8%	69.20%
Torzilli *et al*[25]	2013	54 (> 3 nodules)	-/-	12.00%
Zhong *et al*[29]	2013	58 (> 3 nodules)	3.1%[2]/28.0%[2]	24.00%
BCLC B large HCC				
Pawlik *et al*[64]	2005	300 (≥ 10 cm)	5.0%/-	27.00%
Pandey *et al*[62]	2007	166 (≥ 10 cm)	3.0%/30.0%	28.60%
Cho *et al*[63]	2007	61 (> 5 cm)	1.6%/-	52.90%
Ruzzenente *et al*[33]	2009	46 (> 5 cm)	-/-	29.00%
Yamashita *et al*[65]	2011	53 (≥ 10 cm)	3.8%/24.5%	35.00%
Zhong *et al*[29]	2013	199 (> 5 cm)	3.1%[2]/28.0%[2]	41.00%
BCLC C HCC with macrovascular invasion				
Pawlik *et al*[32]	2005	102 (PVTT and HVI)	5.9%/-	10.00%
Le Treut *et al*[84]	2006	26 (PVTT and HVI)	11.5%/38.5%	13.00%
Ruzzenente *et al*[33]	2009	17 (PVTT and HVI)	-/-	20.00%
Inoue *et al*[81]	2009	49 (PVTT)	0%/-	39%-41%
Ban *et al*[82]	2009	45 (PVTT)	0.0%/21.1%-23.1%	22.40%
Chok *et al*[79]	2013	88 (PVTT)	3.4%/37.1%	11.2%-14.3%
Wang *et al*[76]	2013	25 (HVI)	0.0%/40.0%	13.50%

[1]5-year survival rate after limited liver resection in Child-Pugh A patients; [2]Mortality and morbidity rates in BCLC B patients with both multinodular and large HCCs. PVTT: Portal vein tumour thrombosis; HVI: Hepatic veins invasion; BCLC: Barcelona clinic liver cancer; HCC: Hepatocellular carcinoma.

BCLC A-B MULTIPLE HCCS NOT SUITABLE FOR LIVER TRANSPLANTATION (RECOMMENDED PERCUTANEOUS ABLATION OR TACE)

Liver resection in the presence of multiple HCCs is still controversial[51,52]. According to BCLC, all patients with multiple HCCs should be scheduled for percutaneous ablation or TACE if liver transplantation is contraindicated[24].

Despite the guidelines, in the literature there are several surgical series that include patients with multiple HCCs with 5-year survival rates varying from 25% to 58%[51,53,54].

Some authors have reported that the presence of multiple nodules is an independent risk factor of recurrence after liver resection[37,55].

Poon *et al*[56] reported a 5-year survival rate of 60% after liver resection in patients with less than 3 HCC nodules ≤ 3 cm. Ruzzenente *et al*[33] conducted a study on 464 HCC patients from a multi-institutional database and found that patients with less than 3 nodules who underwent liver resection had a higher survival rate than those who were treated with local ablative therapies (including percutaneous ablation and TACE) with a median survival of 58 and 20 mo ($P < 0.01$), respectively. These data were confirmed by a subsequent randomised control trial. In patients with multifocal HCC meeting Milan Criteria, the authors reported a 5-year survival rate after liver resection and radiofrequency ablation of 69% and 45% ($P = 0.042$), respectively[57].

Furthermore, a Japanese nationwide survey reported that liver resection has an advantage over local ablative therapies because it can prevent recurrence in individuals with less than 3 HCC nodules that are ≤ 3 cm[58]. Liver resection also appears to provide better long-term survival than percutaneous ablation in patients with less than 3 HCC nodules that are > 3 cm[11].

In selected patients with multinodular BCLC B (more than 3 nodules) HCC and preserved liver function, liver resection yielded better long-term results than TACE with 5-year survival rates of 36%-37% and 11%-14%, respectively[29,59]. The results of liver resection in patients with multiple HCCs are shown in Table 1.

Although further studies are needed to confirm these results, liver resection seems to offer satisfactory long-term result in patients with multiple HCCs, especially for patients with small oligonodular HCCs.

BCLC B LARGE HCC (RECOMMENDED TACE)

There is no a univocal definition of "large" HCC in the

BCLC classification. In the first algorithm proposed in 1999, a single nodule greater than 5 cm was considered BCLC B, but this in subsequent updates[12,21,24]. Tumour size is not a clear limiting factor for liver resection, but it remains an important prognostic factor likely because the incidence of macrovascular invasion and distant metastases is related to size[60]. Furthermore many patients with large HCC should undergo major hepatectomy, which is considered a high-risk procedure especially in cirrhotic patients[21,22]. Nevertheless, recent surgical series indicate that over 20% of patient with large HCCs (> 5 cm) are treated with surgical resection[33,25].

In the last decades, with improvements in surgical techniques and careful preoperative evaluation, the short-term results for patients with large HCCs have been similar to patients with smaller tumours, with mortality rates from 3% to 5% and morbidity from 30%-35%[61,62] (Table 1).

In the literature, the 5-year survival rates after liver resection ranges from 29% to 53%[33,63] for HCC nodules > 5 cm and 27% to 35% for nodules ⩾ 10 cm[64,65]. A recent paper comparing liver resection to TACE in over 350 HCC BCLB B patients demonstrated that surgery is as safe as TACE and results in better overall survival. In particular, the 5-year overall survival rates for patients with a single large HCC nodule (mean size 8.8 cm) was 41% and 18%, in the liver resection and TACE groups, respectively ($P < 0.01$)[29] (Table 1).

In patients with large HCC, in which the presence of negative prognostic factors is frequent, the indication for preoperative TACE should be to improve the results of surgical resection. However, recent data did not show a survival benefit in the use of the combined approach preoperative TACE + surgery compared to surgery alone in patients with resectable large HCC[66,67].

Recently, metabolic syndrome related liver disease has been increasingly identified as a risk factor for HCC[4,5,68]. HCCs associated with metabolic syndrome are larger, frequently more well differentiated and arise in a less fibrotic liver than HCCs associated with cirrhosis[69].

Therefore, liver resection in patients with large HCCs and preserved liver function is likely to increase in patients with metabolic syndrome.

BCLC C HCC WITH MACROVASCULAR INVASION (RECOMMENDED SORAFENIB)

Macrovascular invasion (MVI) is one of the strongest predictors of survival in patients with HCC because it is related to an increased risk of intrahepatic or extrahepatic metastases[70,71]. The incidence of portal vein tumour thrombosis (PVTT) and hepatic veins invasion (HVI) reached 62% and 26%, respectively, in an autopsy series, and 5%-15% and 3%-4%, respectively in surgical series[32,72-74]. The resection of HCCs with macrovascular invasion is technically challenging with limited survival benefit. However, surgical resection has a higher survival rate than nonsurgical strategies or best supportive care[32,33]. The median survival of untreated HCC with PVTT and HVI are 2.7 and 5 mo, respectively[75,76]. The reported survival of these patients after Sorafenib treatment is 6 mo[77].

In recent surgical series including HCC patients with MVI, the postoperative mortality and morbidity ranges from 3.4% to 7.7% and from 30.8% to 37.1%, respectively[32,78,79]. In a multicentric study on 102 HCC patients with MVI treated by surgical resection, Pawlik et al. reported a 5-year survival rate of 10%[3]. In our surgical series published by Ruzzenente *et al*[33], the median survival after liver resection for patients with HCC and MVI was 10 mo with a 5-year survival rate of 20% (Table 1).

In the literature, better survival rates are reported for selected patients with PVTT, with a 5-year survival rate ranging from 11% to 42%[79-82]. In PVTT cases, two different surgical techniques have been reported with similar short- and long-term outcomes[79]. One is the anatomical en-block resection of the liver segment involved and portal vein bifurcation with or without the main trunk[80]. The other is thrombectomy using the peeling-off technique[83].

Recently, Chok *et al*[79] described the following three approaches for patients with PVTT based on the extension of the tumour thrombosis: group 1, HCC with ipsilateral PVTT resected in a hepatectomy; group 2, HCC with PVTT extending to or beyond the portal vein bifurcation, treated by en bloc resection followed by portal vein reconstruction; group 3, PVTT extending to or beyond the portal vein bifurcation, treated by thrombectomy.

The short and long-term results were similar among the three groups with a 5-year overall survival rate of 11.2%, 12.5% and 14.3%, respectively[79].

The reported survival after surgery for HCC patients with HVI or with caval invasion is approximately 13% at 5 years with a median survival of 9-19 mo[76,84].

PREOPERATIVE EVALUATION

The expansion of the indications for liver resection in HCC patients increases the risk of post-hepatectomy liver failure (PHLF) with a subsequent increase in postoperative morbidity and mortality[85]. PHLF is closely related to the volume and function of the remnant liver, and these two variables are the major determinants of the adequacy of the future remnant liver (FRL) after resection[86]. Thus, a meticulous preoperative assessment that includes an evaluation of liver volume and the function of the remnant liver is crucial before liver resection, especially in cirrhotic patients beyond the BCLC recommendations[87].

Liver function assessment includes conventional liver function tests (laboratory parameters), scoring systems (Child-Pugh and MELD) and qualitative tests (99-TC-GSA scintigraphy, indocyanine green test, MEGX and LiMAX). Of the proposed qualitative tests, the indocyanine green (ICG) test is considered the most powerful predictive test of operative mortality after a liver resection[88,89]. The 15 min ICG retention rate (ICGR15) is also

the most frequently used parameter in the decision-making protocol before hepatectomy in Western countries. There is no clear consensus on the cut-off value of ICG retention with a predictive value of postoperative hepatic insufficiency, but an ICGR15 equal or greater than 14% is indicative of inadequate clearance with limited hepatic reserve[90,91].

Different methods of estimating liver volume have been introduced, and the two most frequently utilised in the literature are the 3-D volume computed tomography calculation and the calculation of standardised liver volume using body surface area or body weight[92,93]. According to the date in the literature, the FRL volume limit for safe liver resection in cirrhotic patients is 30%-40%[87].

FUTURE PERSPECTIVES

Despite the technical improvements in diagnosis and treatment, the prognosis of HCC patients may differ widely among those with the same clinical and pathological features[26,94]. The survival of these patients is likely affected by the heterogeneity of the biological behaviour of tumour cells[95]. Many authors have studied the biological processes that leads to the development of HCC and have discovered that the main signal transduction pathways include PI3K/Akt/mTOR[96], Wnt/b-catenin[97], HGF/c-MET[98], and MAP/ERK/c-myc[99]. Researchers have identified several genes, including those involved in the pathways mentioned, whose altered expression has an influence on the prognosis of patients with HCC[100-103].

Pedica *et al*[104] reported that aberrant expression of c-myc affects the prognosis of HCC patients after liver resection; in particular, patients with amplified c-myc have a poorer prognosis than patients with normal c-myc levels (polysomic or disomic expression) with a 3-year survival rate of 35.7% and 65.2%, respectively.

Currently, a widely accepted molecular classification system for HCC is still not available. Future perspectives should include the identification of molecular panel able to classify different patients according to their expected survival. This molecular classification could suggest the tailored type of treatment including new target therapies.

CONCLUSION

Recent improvements in surgical techniques and perioperative care have enhanced the feasibility and safety of liver resection with satisfactory long-term results in selected patients with early HCC with PH and with intermediate-advanced HCC. Currently, based on the BCLC algorithm, the EASL/AASLD guidelines exclude many patients from curative treatment, although they may benefit from liver resection. Nowadays, no other HCC classification proposed has been approved worldwide and the treatment strategy should be tailored on the single patient, based on literature data. Thus, a revision of the BCLC algorithm and clinical guidelines should be introduced possibly including new molecular classifications.

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