Is There a Role for Surgery in BCLC B Hepatocellular Carcinoma?

Călin Popa¹,², Diana Schlanger¹,², Alina Buliarca³, Tudor Mocan³, Bogdan Procopet³, Zeno Spârchez³, Nadim Al Hajjar¹,²

¹Surgery Department, Regional Institute of Gastroenterology and Hepatology “Prof. Dr. O. Fodor”, Cluj-Napoca, Romania
²“Iuliu Hațieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania
³Gastroenterology Department, Regional Institute of Gastroenterology and Hepatology “Prof. Dr. O. Fodor”, Cluj-Napoca, Romania

Abstract
Intermediate stage hepatocarcinoma, classified b Barcelona Clinic Liver Cancer (BCLC) staging system.
Liver Cancer (BCLC) comprises a large number of patients, with diverse characteristics, being defined by multiple tumours, preserved liver function and good performance status. The recommended treatment for this stage is transarterial chemoembolization (TACE), but there are a few studies that discuss the role of surgery in this stage. We report a case of a 59-year-old woman diagnosed with BCLC B hepatocarcinoma (two tumours of 34 and 25 mm, in liver segments 5 and 6) who was successfully treated with surgical resection. This patient had additional risk factors like morbid obesity, clinically significant portal hypertension, and thrombocytopenia. Despite these characteristics, the evolution was favourable. In conclusion, we believe that surgery has an important role in the treatment of well-selected BCLC B patients and a good preoperative assessment of the patient can minimize the perioperative risk.

Key words: hepatocellular carcinoma, BCLC criteria, liver surgery

Introduction

An adequate staging of hepatocellular carcinoma (HCC) is necessary in order to guide the management and treatment of these tumours, as well as for defining the prognosis in each particular case (1).

Despite having its limitations, the Barcelona Clinic Liver Cancer (BCLC) staging system is one of the most widely used and accepted classifications (1). It uses data regarding the number of tumours, tumour size, functional liver status and the patient’s physical status to define five different stages (2).

According to the BCLC system, surgery is the treatment of choice in early stages (stage 0 and stage A), while other treatment options (transarterial chemoembolization = TACE or sorafenib) are recommended in intermediate and advanced stages (3). Lately, there have been discussions regarding expanding the indications for surgical resection to patients included in BCLC B stage (intermediate stage) (4,5); there has been proof that surgical resection may achieve a better overall survival (3,4).

Intermediate stage hepatocarcinoma is defined by multinodular disease, preserved liver function and good performance status. Therefore, patients included in BCLC B stage are part of a heterogenous population (5), with diverse characteristics, that might benefit from a more personalized approach in their treatment.

Indications for surgical resection in non-early HCC remain controversial. We present the management of an intermediate stage HCC, with multiple associated risk factors that supports the hypothesis that surgical resection can be a treatment option in well-selected patients.

Case Report

We present the case of a 59-year-old female patient with a 10-year history of viral C hepatitis; she followed an interferon-free treatment with a sustained virological response. In March 2019, she was diagnosed with liver cirrhosis: Fibroscan indicated F4 Metavir stage. The patient had a BMI of 46.8 kg/m² and no other associated conditions.

In July 2019, she had a follow-up appointment with the gastroenterologist. Routine imagistic evaluation by abdominal ultrasound revealed a suspicious nodule in the liver. Contrast-enhanced ultrasound described a hypoechoic subcapsular lesion of about 2 cm, between segment 5 and 6 of the liver; after the administration of the contrast agent, the lesion showed intense enhancement in the arterial phase with inhomogeneous wash-out in the portal phase. Another nodule of less than 1 cm, with the same characteristics was identified just under the hepatic capsule, in
hepatic segment 6. A CT scan was performed, and the two lesions were described. A 25 mm tumour was identified at the limit between liver segments 5 and 6, with a subcapsular situation, with inhomogeneous arterial enhancement and inhomogeneous wash-out; the imagistic suspicion was of hepatocellular carcinoma (Fig. 1). Another subcapsular tumour of 13 mm was described in liver segment 6; it had arterial enhancement but no wash-out, being considered a dysplastic lesion (Fig. 2). Blood tests showed moderate thrombocytopenia, normal bilirubin and albumin levels. At this time, the patient was staged as BCLC A (two nodules up to three centimeters, good performance status, preserved liver function). The patient did not undergo any treatment and there was no follow-up for about one year, the patient avoiding to make an appointment in the current pandemic context.

In September 2020, the patient presents to the gastroenterology department for reevaluation. After more than one year from the initial diagnosis, a CT scan was effectuated: the first tumour, described at the border between segments 5 and 6 has now approximately 34 mm (Figs. 3, 4), while the second tumour, localized in segment 6 has 24 mm and imagistic characteristics of a hepato-
Carcinoma as well (heterogenous arterial hyperenhancement and heterogenous wash-out) \( \text{Fig. 5, 6} \). The tumours were evaluated by contrast-enhanced ultrasound, which confirmed their position and typical characteristics for a hepatocellular carcinoma. Blood tests showed thrombocytopenia (63000/\,\mu L), mildly elevated bilirubin level (1.4 mg/dl), the albumin level was in normal ranges (3.7 g/dl), the INR was 1.27, and no other significant pathological alterations were identified. Given all these data, we could calculate a Child-Pugh score of 5 points, the diagnosis being Child A liver cirrhosis. The evolution of the tumours during the past year, one of them being larger than 3 cm included the patient in BCLC stage B. BMI was 52.5 kg/m\(^2\), the patient being morbidly obese.

Considering the characteristics of the two tumours, a multidisciplinary team considered...
that this patient might benefit from surgery. A cardiac and respiratory evaluation was indicated: a normal cardiac function and a mild ventilatory obstruction on spirometry permitted a safe surgical intervention. The hepatic venous pressure gradient was also measured, a value of 12 mmHG indicating clinically significant venous hypertension. We also performed a thromboelastography (TEG) in order to test the efficiency of hemostasis considering that thrombocytopenia was present. A TEG 5000 Hemostasis Analyzer was used. The result showed a hypercoagulation state with secondary fibrinolysis. Despite thrombocytopenia, the test showed a normal MA (maximum amplitude).

After the preoperative evaluation, we decided to proceed with the surgical intervention. A marginal resection of liver segments 5 and 6 was performed (Fig. 9). The postoperative evolution was favourable, the patient being discharged on postoperative day 5. The final histopathological report described two tumours of 35 and 24 mm, with hepatocellular carcinoma histology, and clear resection margins.

**Discussion**

The presented case illustrates the use of surgical resection as the treatment of choice for a patient beyond BCLC criteria for surgery. Although the patient had no indication for surgery based on BCLC criteria and had additional risk factors (thrombocytopenia, clinically significant HVPG, obesity), a multidisciplinary team decided that surgical intervention could be the best option for this patient.
patient, given the subcapsular localization of
the two tumours and the possibility of including
them in the same marginal resection. We
intend to integrate the particularities of our
case in the context of the published literature,
in order to discuss the controversial subject of
surgical resection in non-early HCC.

Hepatocellular carcinoma (HCC) is a
heterogenous disease, from its etiology to its
clinical-biological behaviour (6). Different
staging systems have been proposed in order
to standardize the management of this disease
and offer the best prognosis for each patient;
the Barcelona Clinical Liver Cancer (BCLC)
classification is used in most centers. Even
with the current classifications, the best
treatment for each stage is still poorly under-
stood and controversies exist especially
regarding non-early stages, for which non-
curative treatment options are recommended.
Intermediate stage disease (BCLC B)
comprises a very heterogenous group of
patients on its own, therefore posing unique
challenges for its therapeutic management (5).
Due to this reason, there have been attempts
to develop and validate subclassifications (7,8)
for a better stratification of the patients
included in this stage.

Several studies have discussed the role of
surgery in intermediate-stage patients, with
promising results. Ciria et al. (9) concluded
that surgical resection can offer survival
benefit with acceptable safety in BCLC B
patient: the major advantage of resection is
the fact that it offers a curative option of
treatment for these patients. Other studies
(3,10,11) report good results, while recom-
mending the careful selection of patients
for surgery. Wada et al. (11) proposed the
following indications for surgical intervention
in BCLC B patients: platelet count > 80000
/mm^3, total bilirubin in normal range, appro-
perate residual liver volume and no ascites.
Judging by these criteria, our patient had a
mildly elevated bilirubin level and thrombo-
cytopenia: we consider that even with these
issues, if a thorough preoperative evaluation
is performed, surgery can be a viable option.

From its introduction in 1985, TEG (a
viscoelastic test for the global evaluation of
hemostasis) has been used in liver transplan-
tation centers for the evaluation of hemostasis
in patients undergoing liver transplantation
and for the management of blood transfusions
(12,13). Despite the old belief that cirrhotic
patients are naturally anticoagulated, the
studies from the last decades have shown that
they express a normal balance of hemostasis
(14-17). Despite thrombocytopenia and
decreased levels of coagulation factors (pro-
and anti-coagulant), these patients are more
prone to hypercoagulability than bleeding
due to a normal or even increased level of
thrombin generation. (18,19). Our patient,
despite having a low platelet count, expressed
a hypercoagulative state associated with
secondary fibrinolysis as shown by TEG.
Contrary to what conventional management
would recommend – platelet transfusion,
she had to be anticoagulated. More factors –
obesity, cirrhosis, and hepatocarcinoma – could
have contributed to her hypercoagulative state.
With the use of TEG, we avoided an
unnecessary platelet transfusion, and the
patient could be operated in safe condition.

The recommended treatment by BCLC
criteria for intermediate stage patients is
TACE, according to clinical practice guide-
lines. In the medical literature, a few studies
compared TACE and surgical resection (20).
A meta-analysis (21) demonstrated that surgical
intervention has a statistically significant
survival benefit compared with TACE in
BCLC B patients. Another study (22) com-
pared the quality of life (QoL) between two
groups of patients who underwent surgery or
TACE: long-term QoL was better in the
resection group. The same study reported that
surgical treatment temporarily decreased QoL
on the short term: in our presented case, the
patient recovered quickly after the interven-
tion (even with morbid obesity being an
important risk factor), being discharged on
postoperative day 5.

Although, the advantages of surgical treat-
ment in BCLC B patients are significant, the
risk of recurrence exists and a close follow-up
is important. A recent study shows that early
recurrence rate is higher for patients beyond BCLC criteria, but after 2 years it is similar between BCLC 0/A and BCLC B/C after the second postoperative year (23). It is important to keep in mind this fact in order to ensure a close surveillance of the patient in early postoperative period.

Different treatment methods are used today as a bridging therapy to liver transplantation. Surgical resection may be a good choice of bridging therapy since it provides a better control of tumor growth, as well as an evaluation of tumor biology by pathological analysis (24).

While promising results regarding the role of surgery in intermediate stage HCC exist, a comprehensive stratification of the patient who would benefit the most from this course of treatment is very difficult to accomplish, especially due to the heterogeneity of the BCLC B stage. For this reason, we consider that an attentive evaluation of each case, and a discussion within a multidisciplinary team is the best way of making the best treatment choice for each patient. In our particular case, risk factors (liver cirrhosis, morbid obesity, thrombocytopenia, increased HVPG) had to be put in balance with the favourable factors that permitted the resection (the tumours localized in the anterior segments of the liver, superficial situation of tumours, the proximity of the two tumours, the cardiorespiratory assessment results, and the TEG results).

We believe that every classification has its limits, which can be overcome by clinical judgement in complex cases. The general status of the patient as well as the technical difficulty of the resection should be taken into consideration, thus we can evaluate the possibility of offering a treatment with curative intent to as many patients as possible.

Conclusions

Surgical resection is not recommended as a treatment for intermediate stage hepatocellular carcinoma by the BCLC staging system. However, our presented case supports the fact that well-selected patients, with a proper preoperative evaluation, can benefit from surgery. The current tendency is to perform surgical resection whenever possible, even beyond general recommendation, this type of approach being supported by our presented case as well.

Conflict of Interest

The authors declare no conflicts of interests.

References

1. Tellapuri S, Sutphin PD, Beg MS, Singh A, Kave SP. Staging systems of hepatocellular carcinoma: A review. Indian J. Gastroenterol. 2018; 37(6):481-491.
2. Pons F, Varela M, Llovet JM. Staging systems in hepatocellular carcinoma. HPB (Oxford). 2005;7(1):35-41.
3. Guo H, Wu T, Lu Q. Surgical resection improves long-term survival of patients with hepatocellular carcinoma across different Barcelona Clinic Liver Cancer stages. Cancer Manag. Res. 2018;10:361-369.
4. Chang WT, Kao YW, Chau GY, Su CW, Lei HJ, Wu JC, et al. Hepatic resection can provide long-term survival of patients with non-early-stage hepatocellular carcinoma: extending the indication for resection? Surgery. 2012;152(5):809-20.
5. Bolondi L, Burroughs A, Dufour JF, Galle PR, Mazzaletti V, Piscaglia F, et al. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin. Liver Dis. 2012;32(4):348-59.
6. Zhong YF, Zhou J, Wei W, Zou RH, Chen MS, Lau WY, et al. Intermediate-stage hepatocellular carcinoma treated with hepatic resection: the NSP score as an aid to decision-making. Br. J. Cancer. 2016;115(9):1039-1047.
7. Hiraoka A, Kumada T, Nouso K, Tsuchiya K, Kobayashi H, Hrioka M, et al. Proposed New Sub-Grouping for Intermediate-Stage Hepatocellular Carcinoma Using Albumin-Bilirubin Grade. Oncology. 2016;91(3):153-61.
8. Ciria R, Lopez-Ciller P, Gallardo AB, Cabrera J, Pleguezuelo M, Ayllon MD, et al. Optimizing the management of patients with BCLC stage-B hepatocellular carcinoma: Modern surgical resection as a feasible alternative to transarterial chemoembolization. Eur. J. Surg. Oncol. 2015;41(9):1153-61.
9. Bell R, Pandianaboyya S, Lodge JPA, Prasad KR, Jones R, Hidalgo E. Primary liver resection for patients with cirrhosis and hepatocellular carcinoma: the role of surgery in BCLC early (A) and intermediate stages (B). Langenbecks Arch. Surg. 2017;402(4):575-583.
10. Wada H, Eguchi H, Noda T, Ogawa H, Yamada D, Tomimaru Y, et al. Selection criteria for hepatic resection in intermediate-stage (BCLC stage B) multiple hepatocellular carcinoma. Surgery. 2016;160(5):1227-1235.
11. Wang SC, Sheih JF, Chang KY, Chu YC, Liu CS, Loong CC, et al. Thromboelastography-guided transfusion decreases intraoperative blood transfusion during orthotopic liver transplantation: Randomized clinical trial. Transplant. Proc. 2010;42:2590-2593.
12. Kang YG, Martin DJ, Marquez J, Lewis JH, Bontempo FA, Shaw BW Jr, et al. Intraoperative changes in blood coagulation and thromboelastographic monitoring in liver transplantation. Anesth. Analg. 1985;64:888-896.
13. Tripodi A. Hemostasis abnormalities in cirrhosis. Curr. Opin. Hematol. 2015;22(5):406-12.
14. Tripodi A, Primignani M, Mannucci PM, Caldwell SH. Changing Concepts of Cirrhotic Coagulopathy. Am. J. Gastroenterol. 2017;112(2):274-281.
15. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N. Engl.
Reviewer Comments

The article is well structured, featuring an well investigated clinical case. The role of surgery in stage BCLB B is an interesting topic introduced in debate more than a decade ago (1), and more and more clinical evidence sustain its effectiveness (2, 3). However, it cannot be analyzed / supported through the prism of a singular case, but on large study groups. Also, we have to admit that in this case the first-line surgical treatment (small subcapsular nodules on the edge lower part of the liver) is the laparoscopic approach. Nevertheless, even though just a clinical case, this is part of the concept of pushing the boundaries of the BCLC classification and it is welcomed as such.

1. Torzilli G, Donadon M, Marconi M, Palmisano A, Del Fabbro D, Spinelli A, Botta F, Montorsi M. Hepatectomy for stage B and stage C hepatocellular carcinoma in the Barcelona Clinic Liver Cancer classification: results of a prospective analysis. Arch Surg. 2008;143(11):1082-90.
2. Kaniyama T, Orito T, Wakayama K, Shimada S, Nagatsu A, Yokoo H, Kamachi H, Yamashita K, Shimamura T, Taketomi A. Survival outcomes of hepatectomy for stage B Hepatocellular carcinoma in the BCLC classification. World J Surg Oncol. 2017;15(1):156.
3. Tsilimigras DI, Bagante F, Sahara K, Moris D, Hyer JM, Wu L, Ratti F, Marques HP, Soubrane O, Paredes AZ, Lam V, Poultsides GA, Popescu I, Alexandrescu S, Martel G, Workneh A, Guglielmi A, Hugh T, Aldrichetti L, Endo I, Pawlik TM. Prognosis After Resection of Barcelona Clinic Liver Cancer (BCLC) Stage 0, A, and B Hepatocellular Carcinoma: A Comprehensive Assessment of the Current BCLC Classification. Ann Surg Oncol. 2019;26(11):3693-3700.