Liver resection for intermediate hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in China. The Barcelona Clinic Liver Cancer (BCLC) staging system is regarded as the gold standard staging system for HCC, classifying HCC as early, intermediate, or advanced. For intermediate HCC, trans-catheter arterial chemoembolization (TACE) is recommended as the optimal strategy by the BCLC guideline. This review investigates whether liver resection is better than TACE for intermediate HCC. Based on published studies, we compare the survival benefits and complications of liver resection and TACE for intermediate HCC. We also compare the survival benefits of liver resection in early and intermediate HCC. We find that liver resection can achieve better or at least comparable survival outcomes compared with TACE for intermediate HCC; however, we do not observe a significant difference between liver resection and TACE in terms of safety and morbidity. We conclude that liver resection may improve the short- and long-term survival of carefully selected intermediate HCC patients, and the procedure may be safely performed in the management of intermediate HCC.

Key words: Trans-catheter arterial chemoembolization; Intermediate hepatocellular carcinoma; Liver resection; Prognostic factor

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Core tip: Trans-catheter arterial chemoembolization (TACE) is recommended as the standard treatment of intermediate hepatocellular carcinoma (HCC) by the Barcelona Clinic Liver Cancer guideline, and this review investigates whether liver resection is better than TACE for intermediate HCC. Based on published studies, we compare the survival benefits and complications of liver resection and TACE for intermediate HCC. We also compare the survival benefits of liver resection in early and intermediate HCC. We find that liver resection could achieve better or at least comparable survival outcomes compared with TACE for intermediate HCC; however, we do not observe a significant difference between liver resection and TACE in terms of safety and morbidity.
INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer related death in the world\(^1\). In China, where about 120 million people are positive for hepatitis B surface antigen, HCC accounts for 300,000 deaths every year\(^2\). It is a great challenge for clinicians to cure HCC. In order to provide standardized treatment for HCC, numerous HCC staging systems have been proposed in recent decades, including the tumor-node-metastasis (TNM) system, the Okuda system, the Barcelona Clinic Liver Cancer (BCLC) system, the Cancer of the Liver Italian Program (CLIP), the Vienna classification, the Chinese University Prognostic Index, the Japan Integrated Staging score, and the Tokyo staging system\(^3\). All of these staging systems rely mainly on three variables: tumor characteristics, liver function, and general status. The TNM system is one of the oldest; however, the complexity of its variables has limited its application. The most widely adopted systems for staging HCC are the CLIP and the BCLC system (endorsed by European Association for the Study of the Liver and the American Association For the Study of the Liver)\(^4\). At present, the BCLC system is regarded as the optimal staging system to predict prognosis and guide treatment of HCC\(^5\).

The BCLC system was proposed by Llovet et al\(^6\) in 1999, and validated extensively in 2002, 2005, and 2010\(^7,8\). Based on the BCLC grading system, the corresponding recommended treatment for each stage is stratified. Curative treatment is advocated for early HCC (defined as a single tumor less than 5 cm in diameter, or up to three tumors less than 3 cm in diameter), such as surgery, radiofrequency ablation, and liver transplantation. For intermediate HCC (a single tumor more than 5 cm in diameter; two to three tumors of which at least one is more than 3 cm in diameter; or more than 3 tumors of any diameter), trans-catheter arterial chemoembolization (TACE) is recommended as the standardized treatment\(^9\). A large proportion of patients in China are classified at diagnosis with intermediate or advanced HCC (any tumor with radiologically evident and histologically proven macro-vascular invasion, spread to lymph nodes and/or distant metastases). Therefore, only a minority of Chinese patients are eligible for radical resection or other curative treatments.

Controversy over the optimal treatment for intermediate HCC has emerged in recent years, as some evidence has suggested that due to the heterogeneity of individuals in liver function and tumor size, patients with intermediate HCC may not all derive the same benefit from TACE. TACE cannot induce complete tumor necrosis, especially when large nodules are encountered. As the mortality and morbidity of liver resection are decreasing worldwide, surgery has been considered in some treatment models\(^12-14\). One study at Fudan University Hospital endorsed surgical resection for intermediate HCC\(^15\).

This review summarizes research on the role of liver resection in the management of intermediate HCC. Through comparison of liver resection and TACE, we seek to determine an optimal treatment for intermediate HCC.

LIVER RESECTION VS TACE FOR INTERMEDIATE HCC

The current treatment algorithm recommends TACE as the standard treatment for intermediate HCC based on two randomized controlled trials\(^16,17\). However, patients with intermediate HCC vary widely in tumor size, tumor volume, overall health, and other factors, and so derive different benefit from TACE. In recent years, many studies have validated the BCLC treatment recommendation\(^7,16-23\). Liver resection has been widely performed in patients with intermediate HCC, and many investigators have argued that liver resection is as safe as TACE for intermediate HCC and provides better survival outcomes in selected patients\(^12,24-31\). Several centers have proposed their own criteria for judging which intermediate HCC patients are most likely to benefit from liver resection; Zhang et al\(^22\) proposed that intermediate HCC cases with the following features should be considered for radical resection: Large or very large solitary tumor with swelling outward, clear border or pseudo-capsule, and less than 30% of the liver destroyed or more than 50% of hepatic hypertrophy; or multiple tumors limited to one segment or lobe. The authors also pointed out that confinement of tumors to one segment or lobe is not an absolute indication, considering that surgical outcomes could be affected by multi-center distribution and the relationship between lesions and major vessels.

Wang et al\(^25\) reported that the median overall survival of patients with intermediate HCC after liver resection was significantly higher than that after TACE. Additionally, the 1-, 3- and 5-year survival rates in the liver resection group were also significantly higher than those in the TACE group. The study found that liver resection provided the best survival outcomes for patients with early and intermediate HCC. In accordance with these findings, several studies found similar survival benefits of liver resection in the management of intermediate HCC\(^20,21\). Another group of investigators performed a propensity score study which enrolled patients with intermediate and advanced HCC, and observed survival benefits of liver resection by total analysis and propensity-matched analysis\(^25\). In addition,
they conducted a subgroup analysis to detect whether patients with liver resection had better survival rates than those with TACE, and survival benefits were observed in subgroup analysis by tumor size, tumor number, macrovascular invasion, and portal hypertension. Given that the heterogeneity of survival rates among different study cohorts, the highest and lowest 5-year survival rates were 63% and 37%, respectively. Due to the variation in regions and characteristics of enrolled patients and surveillance techniques in different centers, the survival rate might differ for these two procedures in different populations, and we cannot recommend that liver resection be the preferred treatment for intermediate HCC in all cases. However, we observed a similar linear trend of survival benefits of liver resection in the studies we examined (Table 1).

Several studies examined the complications and mortality rates of each treatment modality. Two groups of investigators observed that the incidence of complications in patients with liver resection was significantly higher than that in patients with TACE. Hsu et al. observed a higher mortality rate in the resection group than in the TACE group, which was contradicted by several other studies. This could perhaps be explained by the fact that the proportion of patients aged < 65 years differed between the liver resection group and the TACE group, which likely biased the analysis of mortality. As we know, elements associated with the mortality of patients with HCC include liver function, surgical procedures, and age. If the demographic characteristics of patients in different groups are not comparable, we cannot perform a reliable analysis of mortality and complications. Studies providing data related to complications of liver resection and TACE are summarized in Table 1.

Table 1 Studies related to complications of liver resection and transhepatic arterial chemotherapy and embolization for intermediate hepatocellular carcinoma

| Ref. | Patient | Median OS | Survival rate | DFS | Hospital mortality | Complications |
|------|---------|-----------|---------------|-----|--------------------|---------------|
| Wang et al. | LR: 243 | TACE: 741 | LR: 60.4 | 1-, 3- and 5-yr | LR: 81.5%, 64.4%, 50.5% | NR | NR | NR |
| Ho et al. | LR: 122 | TACE: 163 | LR: 41.8 | 1-, 3- and 5-yr | LR: 77.4%, 51.9%, 36.6% | NR | NR | NR |
| Lin et al. | LR: 93 | TACE: 73 | LR: 27.6 | 1-, 2- and 3-yr | LR: 83%, 62%, 49% | NR | LR: 3/78 (3.8%) | NR |
| Hsu et al. | LR: 268 | TACE: 455 | NR | 1-, 3- and 5-yr | LR: 81%, 68%, 63% | NR | LR: 4/146 (2.7%) | NR |
| Zhong et al. | LR: 660 | TACE: 319 | NR | 1-, 3- and 5-yr | LR: 91%, 67%, 44% | NR | LR vs TACE: 3.1% vs 3.7% | NR |
| Zhong et al. | LR: 257 | TACE: 135 | NR | 1-, 3- and 5-yr | LR: 84%, 59%, 37% | NR | LR vs TACE: 28% vs 18.5% | NR |
| Yin et al. | LR: 88 | TACE: 85 | NR | 1-, 2- and 3-yr | LR: 76.1%, 63.5%, 51.5% | NR | LR vs TACE: 3.1% vs 28% | NR |

NR: Not reported; OS: Overall survival; DFS: Disease-free survival; Sig: Significant difference; LR: Patients with liver resection; TACE: Patients with transcatheter arterial chemoembolization.

LIVER RESECTION IN PATIENTS WITH EARLY AND INTERMEDIATE HCC

The corresponding treatment recommendation for early HCC is a curative strategy such as liver resection, liver
transplantation, or radiofrequency ablation. Many multicenter studies with large sample sizes have validated liver resection for early HCC. Generally, patients with intermediate HCC are not candidates for radical resection based on the BCLC treatment algorithm. However, in recent decades, the question of whether liver resection is indicated for intermediate HCC has been debated worldwide. Ng et al. [38] found the 5-year survival rate to be 39% for intermediate HCC treated by liver resection, which was fairly acceptable. They advocated to perform liver resection in patients with intermediate HCC, and they also demonstrated that liver resection in carefully selected intermediate HCC patients could be as safe as in early HCC patients. Recently, numerous studies have demonstrated that liver resection for intermediate HCC can achieve comparable survival outcomes as in early HCC [18, 24, 39, 40]. Nevertheless, a group of investigators reported survival benefits of liver resection for early HCC [41]. This 10-center study found that disease-free survival and overall survival after liver resection were significantly higher for early HCC than for intermediate HCC, but the survival outcomes of liver resection for intermediate HCC were still acceptable, with 5-year survival rate estimated at 57%. They classified the patients receiving liver resection into three groups: BCLC A, BCLC B and BCLC C. The demographic characteristics of the BCLC A and BCLC B groups were not comparable, as both tumor number and average tumor size were lower in the BCLC A group, which may have biased the analysis of survival outcomes. Furthermore, surgical procedures differed significantly between these two groups, with a higher proportion of patients with minor resection in the BCLC A group than in the BCLC B group. Despite the survival advantages in the BCLC A group, the BCLC B group also achieved favorable short- and long-term survival outcomes, in accordance with other findings [35, 42, 43].

Regarding complications and mortality of liver resection for early and intermediate HCC, two groups of investigators did not observe differences in mortality and morbidity between patients with early and intermediate HCC after liver resection [38, 44]. Yamashita et al. [42] reported that the mortality and morbidity of patients with intermediate HCC receiving liver resection were 3.8% and 24.5%, respectively, which were higher than those in other investigations. The very large tumors (>10 cm in diameter) of patients in the Yamashita et al. study may explain the higher mortality and morbidity of this study compared with others. Recent studies comparing liver resection in early and intermediate HCC are presented in Table 2.

A high incidence of recurrence affects the survival rate of patients with HCC after liver resection, and recurrence rate has been identified as an independent prognostic factor for long-term survival [45]. Ng et al. [38] reported a higher incidence of intrahepatic recurrence after liver resection in intermediate HCC, but found no difference in the extra-hepatic recurrence of patients with early and intermediate HCC after liver resection.

Torzilli et al. [44] conducted a prospective cohort study in 2008, which did not find significant differences in either intrahepatic or extra-hepatic recurrence between patients with early and intermediate HCC receiving liver resection. Another study reported that the estimated 1-, 2-, 3- and 5-year recurrence rates of patients with intermediate HCC after liver resection were 44.2%, 54.5%, 60.6% and 68.1%, respectively [43]. Variables that help predict the risk of HCC recurrence are serum albumin level, microscopic vascular invasion, multinodularity, and advanced Edmondson stage [46]. Multinodularity and serum albumin level were identified as independent factors of recurrence by Chang et al. [43]. Given that the incidence of HCC recurrence is fairly high, routine surveillance by computed tomography scan or magnetic resonance imaging is strongly recommended for patients with intermediate HCC after resection [47, 48].

### PROGNOSTIC FACTORS OF SURVIVAL

Benefits of liver resection are tightly associated with numerous variables, such as liver function, tumor size, and tumor number. Investigators have identified several important variables correlated with survival outcomes of patients with intermediate HCC after liver resection (Table 3). Overall survival is one critical endpoint for the prognosis of patients. One group of investigators found that 8 of 16 variables analyzed had a significant prognostic influence on overall survival by univariate analysis, of which, only 5 variables showed significant prognostic influence by multivariate analysis [38], and they determined that patients without any prognostic risk factors had a higher 5-year survival rate than those with one or more prognostic risk factors. Another group of investigators identified serum albumin level, ICG-15R, tumor capsule, portal hypertension, and other measures as risk markers (variables in different studies related to overall survival are presented in Table 3). Many studies have found that tumor number is a key factor in predicting overall survival [41, 49-51], and it is a critical variable in different HCC staging systems. Incomplete radical resection and postoperative recurrence are closely associated with tumor number.

The Child-Pugh grade is another prognostic factor for overall survival that has been clarified by several studies [26, 35]. To our knowledge, the Child-Pugh grading is the most widely used system for evaluating liver function. Since liver resection, particularly extensive liver resection, can lead to liver failure in patients with insufficient liver volume, preoperative assessment of liver function will undoubtedly improve the intra-operative safety and postoperative survival rate. Specifically, T4 status of HCC stage was reported to be a prognostic factor of overall survival with a hazard ratio of 5.12 by a liver cancer study group in Japan [43]. However, as this variable is based on tumor size, tumor number, and macro-vascular invasion, we do not classify it as an independent variable for overall survival.

Disease-free survival was another key endpoint in
prognosis analysis of patients with malignant neoplasms. Microvascular invasion and Child-Pugh class B were two independent factors for disease-free survival in patients with single large or huge HCC. It is known that HCC patients with major vascular invasion have a poor survival rate and high incidence of recurrence. Single large or huge HCC is normally located adjacent to biliary ducts or vessels, making vascular invasion more probable. Alpha-fetoprotein level greater than 400 ng/mL is a significant

| Ref.         | Group            | Median OS (mo) | Median DFS (mo) | Accumulative DFS | Intrahepatic recurrence | Extra-hepatic recurrence | Survival rate | Mortality | Morbidity |
|--------------|------------------|----------------|-----------------|------------------|-------------------------|--------------------------|---------------|-----------|-----------|
| Ng et al[38] | BCLC A: 404      | A: 83.5 (67.9-99.1) | B: 36.9 (28.9-44.8) | A: 80, 64, 40% | A: 139/404 (34.4%) | A: 95/404 (23.5%) | 1-, 3- and 5-yr | A: 88%, 76%, 58% | B: 9/380 (24.4%) |
|              | BCLC B: 380      |                |                 | Sig              | B: 199/380 (52.4%) | B: 110/380 (29.0%) | No sig        | No sig    | No sig    |
| Cho et al[38]| BCLC A: 169      | NR             | NR              | NR               | NR                      | NR                       | No sig        | No sig    | No sig    |
|              | BCLC B: 61       |                |                 | NR               |                         |                          | No sig        | No sig    | No sig    |
| Torzilli et al[38] | BCLC A: 61    | NR             | NR              | NR               | A: 19/61 (31.14%) | B: 6/24 (25%)               | No sig        | No sig    | No sig    |
|              | BCLC B: 24       |                |                 | NR               | A: 2/61 (0.3%)        | B: 3/24 (12.5%)              | No sig        | No sig    | No sig    |
| Wang et al[38] | BCLC A: 202     | A: Can’t estimate | B: 60.4        | NR               | A: NR                   | B: NR                     | A: Cannot be estimated | B: 1-, 3- and 5-yr | A: 1/169 (0.6%) |
|              | BCLC B: 243      |                |                 | NR               |                         |                          | B: 1/61 (1.6%) | NR        | NR        |
| Wei et al[38] | BCLC A: 52      | NR             | NR              | NR               | NR                      | NR                       | NR            | NR        | NR        |
|              | BCLC B: 51       |                |                 | NR               | The 1-, 2-, 3- and 5-yr recurrence rates were 44.2%, 54.5%, 60.6%, and 68.1%, respectively, in BCLC stage B patients | No sig | NR        | NR        |
| Chang et al[38] | BCLC A: NR   | NR             | NR              | NR               | 5 yr                    | B: 28.6%                  | NR            | NR        | NR        |
|              | BCLC B: 318      |                |                 | NR               |                         |                          | NR            | NR        | NR        |
| Ma et al[38] | BCLC A: 92      | A: Cannot be estimated | B: 27.9 ± 3.1 (21.8-33.9) | NR               | NR                      | NR                       | NR            | NR        | NR        |
|              | BCLC B: 178      |                |                 | NR               |                         |                          | NR            | NR        | NR        |
| Torzilli et al[38] | BCLC A: 777 | 1-, 3- and 5-yr | A: 77%, 61.4%, 48% | B: 70.2%, 55.8%, 45.4% | NR                      | NR                       | NR            | NR        | NR        |
|              | BCLC B: 633      |                |                 | NR               |                         |                          | NR            | NR        | NR        |
| Cucchetti et al[38] | BCLC A: NR | NR             | NR              | NR               | NR                      | NR                       | NR            | NR        | NR        |
|              | BCLC B: 247      |                |                 | NR               |                         |                          | NR            | NR        | NR        |
| Yamashita et al[38] | BCLC A: NR   | NR             | NR              | NR               | Recurrence rate         | B: 2/53 (3.8%)             | NR            | NR        | NR        |
|              | BCLC B: 247      |                |                 | NR               | 5-yr                    | B: 32/53 (62%)             | NR            | NR        | NR        |

OS: Overall survival; DFS: Disease-free survival; A: Patients with HCC of BCLC A; B: Patients with HCC of BCLC B; NR: Not reported; HCC: Hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer; Sig: Significant difference.
prognostic risk factor for disease-free survival by multivariate analysis. However, previous studies have demonstrated that minor proportions of patients with HCC do not present with up-regulation of alpha-feto-protein, which makes the surveillance of onset and recurrence of HCC challenging\textsuperscript{(53-55)}. Variables in different studies related to overall survival are presented in Table 3.

**CONCLUSION**

According to the current BCLC treatment guideline, TACE is recommended as the optimal treatment strategy for intermediate HCC. However, the patients with HCC in Asia distribute among BCLC A, BCLC B, and BCLC C, despite advances in surveillance of HCC in recent years, and a large proportion of patients in Asia present as BCLC B or C when diagnosed. According to the recommendations by the BCLC guideline, these patients cannot benefit from surgical resection. Our review investigated whether liver resection is in fact a viable treatment for intermediate HCC patients.

We found that liver resection could achieve better or at least comparable survival outcomes compared with TACE for intermediate HCC. As for the safety and morbidity, controversy remains. Nevertheless, with advances in surgical equipment and perioperative management, we expect that survival benefits for intermediate HCC after liver resection will improve in the future.
In addition, we examined the outcomes of liver resection in patients with BCLC A and BCLC B. With two exceptions, most studies demonstrated that liver resection offers comparable survival benefits in intermediate HCC and early HCC.\(^{[38,41]}\) We conclude that liver resection may improve the short- and long-term survival of intermediate HCC when patients are carefully selected and it may be safely performed in the management of intermediate HCC. However, multi-center randomized controlled trials are needed to clarify which patients are most likely to benefit from liver resection. We identified several key prognostic risk factors for overall survival and disease-free survival. We noted that patients without any prognostic risk factors achieved better short- and long-term survival than those with one or more prognostic risk factors, which indicates that careful selection of patients is critical for satisfactory outcomes in intermediate HCC patients undergoing liver resection.

Controversy remains surrounding liver resection for the management of intermediate HCC. Surgical procedures have been proposed by some treatment algorithms, and even patients beyond the Milan criteria have been selected for liver transplantation\(^{[56-58]}\). However, more evidence is needed about whether the indications should be expanded for liver resection for intermediate HCC.

**REFERENCES**

1. Wörns MA, Klöckner R, Weinmann A, Galle PR. [Therapy of hepatocellular carcinoma. Internist (Berl) 2014; 55: 23-24, 26-30 [PMID: 24240604 DOI: 10.1007/s00108-013-3318-4]
2. Yau T, Tang YV, Yao TJ, Fan ST, Lo CM, Poon RT. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. Gastroenterology 2014; 146: 1691-700.e3 [PMID: 24583061 DOI: 10.1053/j.gastro.2014.02.032]
3. Maida M, Orlando E, Cannà M, Cabibbo G. Staging systems of hepatocellular carcinoma: a review of literature. World J Gastroenterol 2014; 20: 4141-4150 [PMID: 24764652 DOI: 10.3748/wjg.v20.i15.4141]
4. Gomaa AI, Hashim MS, Waked I. Comparing staging systems for predicting prognosis and survival in patients with hepatocellular carcinoma in Egypt. PLoS One 2014; 9: e90929 [PMID: 24603710 DOI: 10.1371/journal.pone.0090929]
5. Fong ZY, Tanabe KK. The clinical management of hepatocellular carcinoma in the United States, Europe, and Asia: a comprehensive and evidence-based comparison and review. Cancer 2014; 120: 2824-2838 [PMID: 24897995 DOI: 10.1002/cncr.28730]
6. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999; 19: 329-338 [PMID: 10518312 DOI: 10.1055/s-2007-1007122]
7. Cillo U, Vitale A, Grigoletto F, Farinati F, Broli A, Zanus G, Neri D, Boccagni P, Srsen N, D’Amico F, Carleoglio FA, Bridda A, D’Amico DF. Prospective validation of the Barcelona Clinic Liver Cancer staging system. J Hepatol 2006; 44: 723-731 [PMID: 16488851 DOI: 10.1016/j.jhep.2005.12.015]
8. Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 2010; 30: 61-74 [PMID: 20175034 DOI: 10.1055/s-0030-1247133]

**Ho EY**, Cozen ML, Shen H, Lerrigo R, Trimble E, Ryan JC, Corvera CU, Monto A. Expanded use of aggressive therapies improves survival in early and intermediate hepatocellular carcinoma. HPB (Oxford) 2014; 16: 758-767 [PMID: 24467780 DOI: 10.1111/hpb.12214]

10. Han KH, Kudo M, Ye SL, Choi JY, Poon RT, Seong J, Park JW, Ichida T, Chung JW, Chow P, Cheng AL. Asian consensus workshop report: expert consensus guideline for the management of intermediate and advanced hepatocellular carcinoma in Asia. Oncology 2011; 81 Suppl 1: 158-164 [PMID: 22212951 DOI: 10.1159/000333280]

11. Forner A, Gilabert M, Bruix J, Raoul JL. Treatment of intermediate-stage hepatocellular carcinoma. Nat Rev Clin Oncol 2014; 11: 525-535 [PMID: 25091611 DOI: 10.1038/nrclinonc.2014.122]

12. Kokudo N, Makuchii M. Evidence-based clinical practice guidelines for hepatocellular carcinoma in Japan: the JHCC guidelines. J Gastroenterol 2009; 44 Suppl 19: 119-121 [PMID: 19148805 DOI: 10.1002/jgs.2244-z]

13. Choi JY. Treatment algorithm for intermediate and advanced stage hepatocellular carcinoma: Korea. Oncology 2011; 81 Suppl 1: 141-147 [PMID: 22212948 DOI: 10.1159/000333277]

14. Takayasu K, Arii S, Kudo M, Ichida T, Matsui O, Izumi N, Matsuyama Y, Sakamoto M, Nakashima O, Ku Y, Kokudo N, Makuchii M. Superselective transarterial chemoembolization for hepatocellular carcinoma. Validation of treatment algorithm proposed by Japanese guidelines. J Hepatol 2012; 56: 886-892 [PMID: 22173160 DOI: 10.1016/j.jhep.2011.10.021]

15. Gao X, Wang XY, Zhou J, Fan J. Heterogeneity of intermediate-stage HCC necessitates personalized management including surgery. Nat Rev Clin Oncol 2015; 12: 10 [PMID: 25421283 DOI: 10.1038/nrclinonc.2014.122-c1]

16. Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, Rodés J, Bruix J. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002; 359: 1734-1739 [PMID: 12049862 DOI: 10.1016/s0140-6736(02)08649-x]

17. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Fan ST, Wong J. Randomized controlled trial of transarterial lipidol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002; 35: 1164-1171 [PMID: 11981766 DOI: 10.1053/jhep.2002.33156]

18. Vitale A, Saracino E, Boccagni P, Broli A, D’Amico F, Gringeri E, Neri D, Srsen N, Valmassoni M, Zanus G, Carraro A, Violi P, Paulotto A, Bassi D, Polacco M, Burra P, Farinati F, Feltracco P, Romano A, D’Amico DF, Cillo U. Validation of the BCLC prognostic system in surgical hepatocellular cancer patients. Transplant Proc 2009; 41: 1260-1263 [PMID: 19460533 DOI: 10.1016/j.transproceed.2009.03.054]

19. Huiztil-Melendez FD, Capanà M, O’Reilly EM, Duffy A, Gansukh B, Saltz L, Abou-Alfa GK. Advanced hepatocellular carcinoma: which staging systems best predict prognosis? J Clin Oncol 2010; 28: 2889-2895 [PMID: 20458042 DOI: 10.1200/jco.2009.25.9895]

20. Santambrogio R, Salceda J, Costa M, Kluger MD, Barabino M, Laurent A, Opocher E, Azoulay D, Cherqui D. External validation of a simplified BCLC staging system for early hepatocellular carcinoma. Eur J Surg Oncol 2013; 39: 827-834 [PMID: 22401647 DOI: 10.1016/j.ejso.2013.05.001]

21. Kitai S, Kudo M, Izumi N, Kaneko S, Ku Y, Kokudo N, Sakamoto M, Takayama T, Nakashima O, Kadoya M, Matsuyama Y, Matsuanga T. Validation of three staging systems for hepatocellular carcinoma: which staging systems best predict prognosis? J Clin Oncol 2010; 28: 777-785 [PMID: 19759679 DOI: 10.1200/jco.2008.21.0921]

22. Radu P, Groza I, Iancu C, Alecsandri N, Andreica V, Sparchez Z. Treatment of hepatocellular carcinoma in a tertiary Romanian center. Deviations from BCLC recommendations and influence on survival rate. J Gastrointest Liver Dis 2013; 22: 291-297 [PMID: 24078986]

23. Vitale A, Burra P, Frigo AC, Trevisani F, Farinati F, Spolverato G, Volk M, Giannini EG, Ciccarese F, Piscaglia F, Rapaccini GL, Di Marco M, Caturelli E, Zoli M, Borzio F, Cabibbo G, Felder M.
Cai ZQ, Si SB, Chen C, Zhao Y, Ma YY, Wang L, Geng ZM. Analysis of prognostic factors for survival after hepatectomy for hepatocellular carcinoma based on a bayesian network. *PLoS One* 2015; 10: e0120805 [PMID: 25826337 DOI: 10.1371/journal.pone.0120805]

Hsu CY, Liu PH, Lee YH, Hsia CY, Huang YH, Lin HC, Chiou YY, Lee FY, Hsu TI. Using serum α-fetoprotein for prognostic prediction in patients with hepatocellular carcinoma: what is the most optimal cutoff? *PLoS One* 2015; 10: e0118825 [PMID: 25738614 DOI: 10.1371/journal.pone.0118825]

Okuyama H, Ikeda M, Kuwahara A, Takahashi H, Ohno I, Shimizu S, Misunaga S, Senda S, Okusaka T. Prognostic factors in patients with hepatocellular carcinoma refractory or intolerant to sorafenib. *Oncology* 2015; 88: 241-246 [PMID: 25503567 DOI: 10.1159/000369351]

Zhao YJ, Ju Q, Li GC. Tumor markers for hepatocellular carcinoma. *Mol Clin Oncol* 2013; 1: 593-598 [PMID: 24649215 DOI: 10.3892/mco.2013.119]

Jia X, Liu J, Gao Y, Huang Y, Du Z. Diagnosis accuracy of serum glypican-3 in patients with hepatocellular carcinoma: a systematic review with meta-analysis. *Arch Med Res* 2014; 45: 580-588 [PMID: 25446613 DOI: 10.1016/j.arcmed.2014.11.002]

Rich N, Singal AG. Hepatocellular carcinoma tumour markers: current role and expectations. *Best Pract Res Clin Gastroenterol* 2014; 28: 843-853 [PMID: 25260312 DOI: 10.1016/j.bpg.2014.07.018]

Andreou A, Gül S, Pascher A, Schönig W, Al-Abadi H, Bahra M, Klein F, Denecke T, Strücker B, Puhl G, Pratschke J, Seehofer D. Patient and tumour biology predict survival beyond the Milan criteria in liver transplantation for hepatocellular carcinoma. *HPB* (Oxford) 2015; 17: 168-175 [PMID: 25263399 DOI: 10.1111/hpb.12345]

Shirabe K, Yoshiya S, Yoshizumi T, Uchiyama H, Soejima Y, Kawanaka H, Ikegami T, Yamashita Y, Ikeda T, Machara Y. Liver transplantation in the patients with hepatocellular carcinoma beyond Milan criteria—with special reference to extended criteria. *Nihon Shokakibyo Gakkai Zasshi* 2014; 111: 885-891 [PMID: 24806231]

Tuci F, Vitale A, D’Amico F, Gringeri E, Neri D, Zanus G, Bassi D, Polacco M, Boetto R, Lodo E, Germani G, Burra P, Angelì P, Cillo U. Survival benefit of transplantation for recurrence of hepatocellular carcinoma after liver resection. *Transplant Proc* 2014; 46: 2287-2289 [PMID: 25242770 DOI: 10.1016/j.transproceed.2014.07.031]
