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MINIREVIEWS

Liver resection for intermediate hepatocellular carcinoma

Peng-Sheng Yi, Ming Zhang, Ji-Tong Zhao, Ming-Qing Xu

Peng-Sheng Yi, Ming Zhang, Ming-Qing Xu, Department of Liver Surgery, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Ji-Tong Zhao, Department of Gynecology and Obstetrics, West China Second Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

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Correspondence to: Ming-Qing Xu, MD, Department of Liver Surgery, West China Hospital, Sichuan University, Guoxue Road, Chengdu 610041, Sichuan Province, China. xumingqing0018@163.com
Telephone: +86-28-85422870
Fax: +86-28-85422870

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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

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.

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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 300000 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[9-11]. 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[7,18-23]. 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[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*[32] 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*[24] 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[24-31]. 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[29]. In addition,

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*[24]	LR: 243 TACE: 741	LR: 60.4 TACE: 18.2 Sig	1-, 3- and 5-yr LR: 81.5%, 64.4%, 50.5% TACE: 61.9%, 29.1%, 16.4% Sig	NR	NR	NR
Ho *et al*[25]	LR: 122 TACE: 163	LR: 41.8 TACE: 16.8 Sig	1-, 3- and 5-yr LR: 77.4%, 51.9%, 36.6% TACE: 62.6%, 25.2%, 11% Sig	1-, 3- and 5-yr LR: 60.5%, 32.3%, 24.8%	NR	NR
Lin *et al*[26]	LR: 93 TACE: 73	LR: 27.6 TACE: 18.5	1-, 2- and 3-yr LR: 83%, 62%, 49% TACE: 39%, 5%, 2% Sig	NR	LR: 3/78 (3.8%) TACE: 5/93 (5.4%) No sig	NR
Hsu *et al*[27]	LR: 268 TACE: 455	NR	1-, 3- and 5-yr LR: 81%, 68%, 63% TACE: 30%, 43%, 15% Sig	NR	90 d LR: 4/146 (2.7%) TACE: 12/146 (8.2%) Sig	LR *vs* TACE: Acute liver failure (20% *vs* 11%) Sig Biliary tract injury (6.8% *vs* 0%) Sig
Zhong *et al*[28]	LR: 660 TACE: 319	NR	1-, 3- and 5-yr LR: 91%, 67%, 44% TACE: 83%, 35%, 17% Sig	NR	NR	NR
Zhong *et al*[29]	LR: 257 TACE: 135	LR: 42.9 TACE: 21 Sig	1-, 3- and 5-yr LR: 84%, 59%, 37% TACE: 69%, 29%, 14% Sig After propensity score analysis LR: 87%, 62%, 35% TACE: 77%, 44%, 20% Sig	NR	LR *vs* TACE: 3.1% *vs* 3.7% No sig	LR *vs* TACE: 28% *vs* 18.5% Sig
Yin *et al*[31]	LR: 88 TACE: 85	LR: 41 TACE: 14 Sig	1-, 2- and 3-yr LR: 76.1%, 63.5%, 51.5% TACE: 51.8%, 34.8%, 18.1% Sig	NR	LR: 1/88 (1.1%)	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.

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[27,29]. Hsu *et al*[27] noted that the liver resection group had a higher incidence of acute liver failure and biliary duct injury than did the TACE group. However, the incidence of fever was lower in the resection group. Studies reached inconsistent findings about the mortality rates associated with each treatment strategy. Hsu *et al*[27] observed a higher mortality rate in the resection group than in the TACE group, which was contradicted by several other studies[26,29]. 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[33,34]. 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.

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 multi-center studies with large sample sizes have validated liver resection for early HCC[35-37]. 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*[42] 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, multi-nodularity, and advanced Edmondson stage[46]. Multi-nodularity 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[42]. 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

Table 2 Studies comparing liver resection for Barcelona Clinic Liver Cancer A and B

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 BCLC B: 380	A: 83.5 (67.9-99.1) B: 36.9 (28.9-44.8) Sig	A: 77 (66, 87.9) B: 15.6 (10.8-20.4) Sig	A: 80%, 64%, 40% B: 54%, 38%, 26% Sig	A: 139/404 (34.4%) B: 199/380 (52.4%) Sig	A: 95/404 (23.5%) B: 110/380 (29.0%) No sig	1-, 3- and 5- yr A: 88%, 76%, 58% B: 74%, 50%, 39% Sig	A: 11/404 (2.7%) B: 9/380 (2.4%) No sig	93/404 (23.0%) 104/380 (27.4%) No sig
Cho *et al*[39]	BCLC A: 169 BCLC B: 61	NR	NR	1-, 3- and 5- yr A: 71.4%, 51.8%, 44.1% B: 58.3%, 40.0%, 31.7% No sig	NR	NR	1-, 3- and 5- yr A: 87.5%, 69.5%, 59.0% B: 85.0%, 59.3%, 52.9% No sig	A: 1/169 (0.6%) B: 1/61 (1.6%) No sig	NR
Torzilli *et al*[44]	BCLC A: 61 BCLC B: 24	NR	NR	A: 77%, 30% B: 75%, 35% No sig	A: 19/61 (31.14%) B: 6/24 (25%) No sig	A: 2/61 (3.3%) B: 3/24 (12.5%) No sig	1- and 3-yr A: 91.6%, 81% B: 85%, 67% No sig	A: 0 B: 0 No sig	A: 13/61 (21.3%) B: 7/24 (29.2%) No sig
Wang *et al*[24]	BCLC A: 202 BCLC B: 243	A: Can't estimate B: 60.4	A: NR B: NR	A: NR B: NR	A: NR B: NR	A: NR B: NR	A: Cannot be estimated B: 1-, 3- and 5- yr (81.5%, 64.4%, 50.5%)	NR	NR
Wei *et al*[40]	BCLC A: 52 BCLC: 51	NR	NR	1-, 2- and 3-yr A: 77.8%, 61.4%, 48.9% B: 70.2%, 55.8%, 45.4%; No sig	NR	NR	1-, 2- and 3-yr A: 86.5%, 75.0%, 69.2% B: 84.3%, 68.6%, 54.9% No sig	NR	NR
Chang *et al*[43]	BCLC A: NR BCLC B: 318	NR	NR	5 yr B: 28.6%	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		1-, 2-, 3- and 5-yr B: 81.2%, 68.1%, 59.4%, 46.5%	NR	NR
Ma *et al*[49]	BCLC A: 92 BCLC B: 178	A: Cannot be estimated B: 27.9 ± 3.1 (21.8-33.9)	A: Cannot be estimated B: 16.8 ± 1.65 (13.6-20.0)	NR	NR	NR	NR	NR	NR
Torzilli *et al*[41]	BCLC A: 777 BCLC B: 633	NR	NR	1-, 3- and 5-yr A: 77%, 41%, 21% B: 63%, 38%, 27% Sig	NR	NR	1-, 3- and 5-yr A: 9 5%, 80%, 61% B: 88%, 71%, 57% Sig	30 d A: 1.6% *vs* B: 3.1% No sig	Not significant in major complications
Cucchetti *et al*[35]	BCLC A: NR BCLC B: 247	B: 35 (26-42)	NR	NR	NR	NR	1-, 3- and 5-yr B: 77.8%, 48.7% 33.8%	NR	NR
Yamashita *et al*[42]	BCLC A: Cannot be estimated BCLC B: 53	NR	NR	5-yr B: 24%	Recurrence rate B: 32/53 (62%)		5 yr B: 35%	B: 2/53 (3.8%)	B: 13/53 (24.5%)

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.

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[39]. It is known that HCC patients with major vascular invasion have a poor survival rate and high incidence of recurrence[52]. 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

Table 3 Prognostic risk factors of overall survival and disease-free survival

Ref.	Prognostic factors of overall survival		Prognostic factors of disease-free survival	
	By univariate analysis	By multivariate analysis	By univariate analysis	By multivariate analysis
Ng *et al*[38]	Hepatitis B surface antigen carrier, serum AFP, symptomatic disease, presence of cirrhosis, number of tumor nodule, microvascular tumor invasion, tumor invasion of adjacent organs, histological margin involvement by tumor	Symptomatic disease, presence of cirrhosis, multi-nodular tumor, microvascular tumor invasion, positive histological margin	Serum AFP level, symptomatic disease, presence of cirrhosis, multi-nodular tumor, microvascular tumor invasion, tumor invasion of adjacent organ, positive histological margins, the presence of microsatellite nodules	Symptomatic disease, presence of cirrhosis, multi-nodular tumor, positive histological margins
Torzilli *et al*[44]	Tumor size, tumor grade	Tumor size, tumor grade	NR	NR
Chang *et al*[43]	NR	Serum albumin level, ICG-15R, serum creatinine, multi-nodularity, Edmondson stage, macro-vascular invasion	NR	NR
Ma *et al*[49]	Histopathological grade, tumor capsule, tumor number, cirrhosis, BCLC classification	Tumor capsule, BCLC classification	NR	Tumor capsule, BCLC classification
Torzilli *et al*[41]	Tumor number, tumor size, macro-vascular invasion, presence of cirrhosis, esophageal varices, major resection, BCLC classification, preoperative bilirubin values	NR	NR	NR
Cucchetti *et al*[35]	NR	Tumor number, presence of esophageal varices, Child-Pugh score	NR	NR
Cho *et al*[39]	Child-Pugh class B, AFP level > 400 ng/mL, histologically poor differentiation	Child-Pugh class B	Positivity of hepatitis B surface antigen, Child-Pugh class B, AFP level > 400 ng/mL, microvascular invasion, histologically poor differentiation	Child-Pugh class B, microvascular invasion
Yamashita *et al*[42]	NR	T4 status of HCC stage by liver cancer study group of Japan, thrombus in portal vein	NR	T4 status of HCC stage by liver cancer study group of Japan, intra-operative transfusion
Lin *et al*[26]	NR	Low albumin level, treatment modality (liver resection *vs* TACE)	NR	NR
Hsu *et al*[27]	NR	Serum AFP level, Child-Pugh class B, performance status ⩾ 2, TACE, tumor size, vascular invasion	NR	NR
Zhong *et al*[28]	NR	Serum AFP ⩾ 400 ng/mL, diabetes mellitus, macro-vascular invasion, portal hypertension, TACE treatment	NR	NR
Yin *et al*[31]	Treatment modality, serum AFP level, total tumor size, tumor number, gender	Tumor number, treatment modality, gender	NR	NR

TACE: Transhepatic arterial chemotherapy and embolization; NR: Not reported; HCC: Hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer; AFP: Alpha fetoprotein.

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[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.

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