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Original article

Comparison of surgical resection and transarterial chemoembolization for patients with intermediate stage hepatocellular carcinoma

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ABSTRACT

Objective: Current guidelines recommend transarterial chemoembolization (TACE) as the standard treatment for patients with intermediate stage hepatocellular carcinoma (HCC). However, choosing the optimal treatments for patients with intermediate stage HCC still remains challenging for clinicians. The purpose of our study was to compare the long-term survival of intermediate stage HCC patients treated with surgical resection or TACE.

Methods: We obtained the baseline characteristics of 210 intermediate stage HCC patients that were recruited for this study. Survival analysis was performed by Kaplan–Meier method and a comparison was made by log-rank test. Factors associated with survival rate were analyzed by Cox's regression.

Results: There were 164 men and 46 women in the study group, with a mean age of 63 ± 11 years (range, 31–92 years). Among them, 67 patients (31.9%) received surgical resection and 143 patients (68.1%) received TACE. Patients receiving surgical resection had a significantly larger mean of maximum tumor size (6.8 ± 2.8 vs. 5.8 ± 3.2 cm, $P = 0.016$), higher ratio of solitary tumor (68.7% vs. 17.5%, $P < 0.001$), and Child-Pugh class A (97% vs. 85%, $P = 0.009$) than those with TACE. Patients receiving surgical resection had a significantly higher 1, 3, and 5 year survival rate compared with those treated with TACE (87.4%, 62.8% and 57.3% vs. 58.1%, 29.9% and 16.6%, $P < 0.001$). Multivariate analysis revealed that AFP level >400 ng/ml [hazard ratio (HR):2.141, 95% CI: 1.091–4.203, $P = 0.027$], Child B cirrhosis (HR: 4.726, 95% CI: 1.021–21.884, $P = 0.047$), and TACE (HR:3.391, 95% CI: 1.625–7.076, $P = 0.001$) were independent risk factors associated with poor prognosis.

Conclusions: Our results indicated that surgical resection provided superior survival benefit than TACE to patients with intermediate-stage HCC. This is in part attributable to advances in liver surgery which make the resection of intermediate-stage HCC possible. Surgical resection should be considered first for patients with preserved liver function.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world. More than 75% of HCC cases occur in the Far East and Southeast Asia.[1] Only a small proportion of patients have their HCC detected in an early curable stage, thus the worldwide 5-year survival rate of HCC only slightly increased from 5 to 15% over the past two decades.[2] The major causes of unsatisfactory prognosis of HCC include degree of liver function impairment and heterogeneous nature of HCC, which affect treatment outcome.[3] Cumulative evidence also suggests that accurate assessment and staging of HCC, and correct designation of optimal treatments may prolong survival rate of HCC.[4,5] Among current HCC staging systems, the Barcelona Clinic Liver Cancer (BCLC) classification is the one of most

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reliable for prognosis prediction at the time of HCC diagnosis.[6,7] To be categorized as BCLC intermediate-stage, patients are asymptomatic (performance status score, 0) with multinodular tumors but without vascular invasion or extrahepatic spread. The median survival time was 16 months for patients with BCLC intermediate-stage HCC.[6] Based on the AASLD guideline, a revised version of the Barcelona Clinic Liver Cancer (BCLC) staging system by the American Association for the Study of Liver Diseases (AASLD),[4,5] transarterial chemoembolization (TACE) has been recognized as an effective option for those with intermediate stage HCC.[4,5,8] Although TACE has been considered a palliative treatment for unresectable HCC, previous meta-analyses indicated that treatment with TACE is associated with a significantly higher 2-year survival rate than those patients receiving conservative management or suboptimal therapies.[9,10] Nonetheless, the improvement in long-term survival is not clear. In addition, TACE-associated adverse events include post-embolization syndrome, relevant liver function deterioration, ascites and gastrointestinal bleeding; such adverse events are not unusual.[11] Because intermediate stage HCC includes both Child-Turcotte-Pugh (CTP) class A and B patients, ascertaining the optimal treatments for these patients still remains a substantial challenge. Recent advances in liver surgery make the resection of intermediate stage HCC possible.[12–15] It is therefore important to clarify the optimal and effective therapy for intermediate stage HCC patients. The purpose of our study was to compare the long-term survival of intermediate stage HCC patients treated with surgical resection or TACE.

2. Materials and methods

2.1. Patients

A total of 210 newly diagnosed intermediate stage HCC patients, including 67 patients (31.9%) with surgical resection and 143 patients (68.1%) with TACE, were retrospectively enrolled from Ren-Ai Branch, Taipei City Hospital between January 1998 and May 2013. The liver function reserve was assessed by the Child-Turcotte-Pugh (CTP) score.[16] The diagnosis of HCC was histologically confirmed in all patients receiving surgical resection and 87 (60.8%) of patients with TACE treatment. The remaining 56 (39.2%) patients with TACE treatment were confirmed by typical imaging exhibited through arterial enhancement and portal venous washout on multiphasic computed tomography (CT) or magnetic resonance imaging (MRI).[4,5] According to the BCLC staging system, the intermediate stage HCC was defined as CTP class A and B cirrhotic patients with large or multifocal HCC who do not have cancer-related symptoms and do not have macrovascular invasion or extrahepatic spread.[8] Treatment for intermediate HCC was guided by a multidisciplinary model (Fig. 1). In the weekly multidisciplinary conference, all patients were discussed, and their eligibility for surgical resection or TACE was evaluated based on images, laboratory analyses and medical history. This study protocol was approved by the institutional review board of Taipei City Hospital.

2.2. Biochemical and serological testing

The biochemical tests were measured using routine automated methods. The HBsAg and anti-HCV were assayed using commercial kits (General Biological HBsAg RIA, General Biological Cooperation, Taiwan. HCV EIA II. Abbott Laboratories, North Chicago, IL, USA).

2.3. Procedure of surgical resection

Indications for surgery were: 1) CTP classification grade of A or B, 2) performance status test was grade 0 or 1, 3) solitary or multiple tumors which were clinically resectable, or 4) the presence of appropriate residual liver volume.[17] Intraoperative ultrasound was routinely performed to determine tumor location and precise definition of tumor–vessel relationship. Anatomic segmental resections were performed for potentially curative operation. Additionally, the resection margin was more than 1 cm.

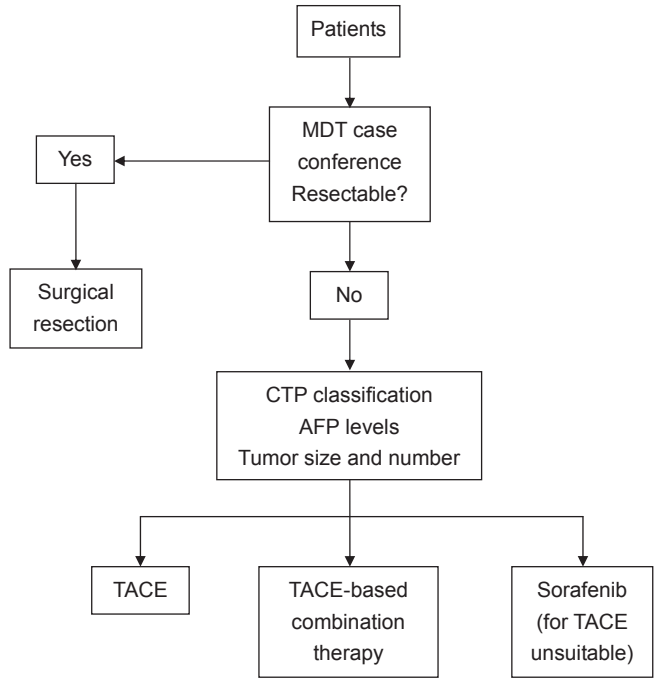

Fig. 1. Ren-Ai multidisciplinary model for treatment of intermediate stage HCC.

2.4. Procedure of TACE

The standardized procedure of TACE was described previously.[18] In brief, TACE procedures were performed in a dedicated angiography suite DFP8000D (Toshiba Medical Systems, Otawara, Japan) with 4Fr J-Curve catheters (Terumo Medical Corporation, Tokyo, Japan) inserted via the right external femoral artery puncture, guided by a matching mandrel (Terumo Medical Corporation, Tokyo). The J-Curve catheter tip was placed in the celiac axis orifice, and one set of digital subtraction angiography was performed. For patients with S5 or S6 tumors which might draw their tumor vessels from superior mesenteric branches, a set of digitally-subtracted superior mesenteric angiography was also performed. If the tumor stains and the supplying vessels were not well-demonstrated by the above angiograms, further superselective angiograms were performed including angiograms of the common hepatic artery, proper hepatic artery, right or left hepatic arteries, and sometimes even the smaller segmental branches. Embolization was performed from the appropriate site, which usually was the proper hepatic artery for multiple bilateral tumors, and the right or left hepatic arteries for unilateral tumors. The embolization agents were ethiodized oil Lipiodol® (Guerbet, Villepinte, France) and absorbable gelatin sponge Surgifoam® (Ethicon, Somerville, NJ, USA), and the chemotherapy agents were mitomycin and doxorubicin. The dosage of lipiodol and gelatin sponge was based on a

sufficient slowing of the arterial flow as demonstrated by fluoroscopy, with a typical dose ranging from 3 to 15 mL of Lipiodol®. The dosage of mitomycin and doxorubicin were determined by patient weight, and a typical dose of mitomycin was 4–8 mg and 20–30 mg for doxorubicin.

2.5. Patient follow-up

After surgical resection or TACE, all patients underwent regular follow-up, including a liver function test, measurement of serum alpha fetoprotein (AFP) levels and abdominal ultrasonography at an interval of 2–3 months. For patients with TACE treatment, the presence of viable tumor was confirmed on multiphasic CT or MRI one to two months after TACE. Thereafter, TACE was repeated in 2–3 month intervals until complete tumor necrosis. When intrahepatic recurrence was suspected, further investigation was carried out using CT or MRI. Patients with recurrence would receive the appropriate treatment options based on clinical decision making.

2.6. Statistical analysis

Data were analyzed by chi-square test, Fisher's exact test, Student's t-test and logistic regression where appropriate. Overall survival was measured from the day of HCC diagnosis and when patient survival was confirmed through June 2013. Cumulative survival was calculated according to the Kaplan–Meier method. The association of potential risk factors of mortality was determined by univariate and multivariate logistic regression. All tests were two-tailed and a P value of less than 0.05 was considered statistically significant.

3. Results

Baseline clinical characteristics of the 210 intermediate stage HCC patients are shown in Table 1. There were 164 men (78.1%) and 46 women (21.9%), with a mean age of 63 ± 11 years (range: 31–92 years). Among them, 67 patients (31.9%) received surgical resection and 143 patients (68.1%) received TACE. There were no significant differences in terms of sex, age, prevalence of HBV/HCV infection and ratio of AFP >400 ng/ml between patients treated with surgical resection and TACE. Compared to patients receiving TACE treatment, patients with surgical resection had a significantly larger mean of maximum tumor size (6.8 ± 2.8 vs. 5.8 ± 3.2 cm, P = 0.016), a higher ratio of tumor number <3 (89.6% vs. 40.6%, P < 0.001), CTP class A cirrhosis (97% vs. 85%, P = 0.009), higher serum albumin level (3.86 ± 0.48 vs. 3.44 ± 0.38 g/dL, P = 0.003), lower serum total bilirubin level (0.92 ± 0.51 vs. 1.25 ± 0.89 mg/dL, P = 0.003), and lower serum AST level (60 ± 53 vs. 93 ± 104 U/L, P = 0.015).

During a median (25–75 percentile) follow-up period of 17 (39–7) months, patients receiving surgical resection had a significantly higher 1, 3, and 5 year survival rate compared with those treated with TACE (87.4%, 62.8% and 57.3% vs. 58.1%, 29.9% and 16.6%, P < 0.001) (Fig. 2). The median survival time was 70 months in patients receiving surgical resection and 17 months in those with TACE (P < 0.001).

Cox regression analysis for risk factors associated with survival was shown in Table 2. Serum levels of total bilirubin [hazard ratio (HR):1.838, 95% CI:1.147–2.944, P = 0.011], AST (HR: 1.007, 95% CI:1.001–1.014, P = 0.025), prothrombin time (HR: 1.318, 95% CI:1.032–1.684, P = 0.027), AFP level > 400 ng/ml (HR:2.220, 95% CI: 1.192–4.135, P = 0.012), multiple tumor (HR:2.245, 95% CI: 1.245–4.049, P = 0.007), CTP class B cirrhosis (HR:7.268, 95% CI:1.659–31.832, P = 0.008) and TACE treatment (HR:3.99, 95% CI:2.162–7.366, P < 0.001) were significantly associated with mortality in univariate analysis. Since albumin, total bilirubin and prothrombin time are the components of Child classification, only Child classification was included in multivariate logistic analysis. Multivariate analysis revealed that AFP level >400 ng/ml (HR:2.141, 95% CI: 1.091–4.203, P = 0.027), CTP class B cirrhosis (HR: 4.726, 95% CI: 1.021–21.884, P = 0.047) and TACE (HR:3.391, 95% CI: 1.625–7.076, P = 0.001) were independent risk factors associated with poor prognosis.

Table 1
Demographic and clinical characteristics of 210 patients with intermediate stage hepatocellular carcinoma treated with surgical resection and transarterial chemoembolization.

Characteristics	TACE (n = 143)	Surgical resection (n = 67)	P value
Age	64 ± 11	62 ± 11	0.156
≤60 years (%)	53 (37.1)	31 (46.3)	0.228
>60 years (%)	90 (62.9)	36 (53.7)	
Male, n (%)	108 (76)	56 (84)	0.214
Positive for HBsAg, n (%)	75 (52)	40 (60)	0.338
Positive for anti-HCV, n (%)	56 (39)	16 (24)	0.056
Alcoholism, n (%)	27 (19)	12 (18)	1.0
CTP class, n (%)			0.009
A	121 (85)	65 (97)	
B	22 (15)	2 (3)	
Mean maximum tumor size	5.8 ± 3.2	6.8 ± 2.8	0.016
Tumor size > 3 cm, n (%)	119 (83.2%)	64 (96)	0.014
Tumor size > 5 cm, n (%)	75 (52.4%)	56 (83.6%)	<0.001
Tumor number (1/2/≧3)	25/33/85	46/14/7	<0.001
Biochemistries[a], mean ± SD			
Albumin (g/dL)	3.44 ± 0.38	3.86 ± 0.48	0.003
Bilirubin (mg/dL)	1.25 ± 0.89	0.92 ± 0.51	0.003
AST (U/L)	93 ± 104	60 ± 53	0.015
ALT (U/L)	83 ± 100	61 ± 49	0.095
PT (second)	12.2 ± 1.63	11.9 ± 1.45	0.337
AFP <400 (ng/ml), n, %	92 (64)	44 (66)	1.0
Diabetes mellitus, n (%)	46 (32)	16 (24)	0.257
Survival rate			<0.001
1 year	58.1%	87.4%	
3 years	29.9%	62.8%	
5 years	16.6%	57.3%	

AFP: alpha-fetoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTP: Child-Turcotte-Pugh; HBV: hepatitis B virus; HCV: hepatitis C virus; PT: prothrombin time.
[a] Missing data in one patient with TACE treatment.

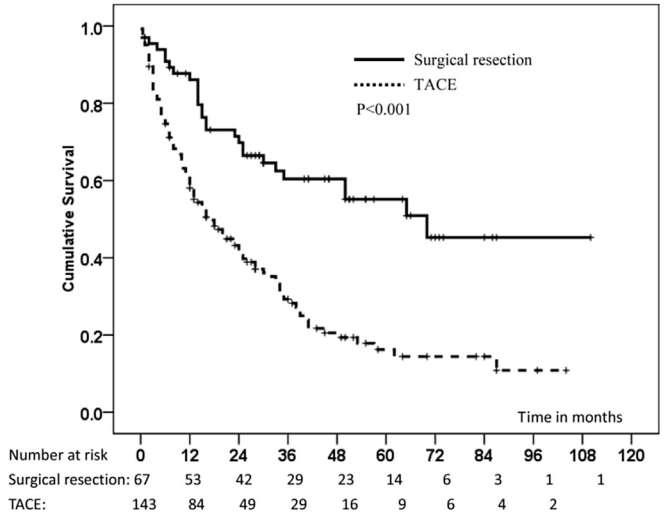

Fig. 2. The cumulative survival curve of 210 patients with intermediate stage hepatocellular carcinoma treated with surgical resection and transarterial chemoembolization (TACE).

Table 2
Univariate and multivariate Cox regression analysis of factors associated with survival in 210 patients with intermediate stage hepatocellular carcinoma treated with surgical resection and transarterial chemoembolization.

Factor	Univariate		Multivariate	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Gender		0.359		
female	1			
male	0.72 (0.356–1.454)			
Age		0.86		
≤60 years	1			
>60 years	1.053 (0.593–1.869)			
Creatinine	2.088 (0.486–8.974)	0.322		
Albumin	1.003 (0.998–1.007)	0.219		
Bilirubin	1.838 (1.147–2.944)	0.011		
AST	1.007 (1.001–1.014)	0.025	1.003 (0.997–1.009)	0.3
ALT	1.003 (0.998–1.007)	0.219		
Prothrombin time	1.318 (1.032–1.684)	0.027		
AFP		0.012		0.027
≤400	1		1	
>400	2.220 (1.192–4.135)		2.141 (1.091–4.203)	
Etiology		0.387		
HBV	1			
HCV	1.35 (0.684–2.664)			
Alcoholism		0.487		
No	1			
Yes	0.777 (0.382–1.582)			
Diabetes mellitus		0.420		
No	1			
Yes	0.778 (0.423–1.423)			
Tumor size		0.922		
≤3 cm	1			
>3 cm	1.043 (0.451–2.409)			
Tumor size		0.637		
≤5 cm	1			
>5 cm	0.869 (0.484–1.559)			
Tumor number		0.007		0.935
Single	1		1	
Multiple	2.245 (1.245–4.049)		1.031 (0.498–2.132)	
Child classification		0.008		0.047
A	1		1	
B	7.268 (1.659–31.832)		4.726 (1.021–21.884)	
Treatment		<0.0011		0.001
Resection	1		1	
TACE	3.99 (2.162–7.366)		3.391 (1.625–7.076)	

AFP: alpha-fetoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTP: Child-Turcotte-Pugh; HBV: hepatitis B virus; HCV: hepatitis C virus; TACE: transarterial chemoembolization.

Further subgroup survival analysis was performed for 108 intermediate stage hepatocellular carcinoma patients with CTP class A and a tumor number less than three. Similar to the entire cohort, patients receiving surgical resection had a significantly higher 1, 3, and 5 year survival rate compared with those treated with TACE (89.2%, 65.2% and 58.7% vs. 63%, 41.4% and 18.4%, $P < 0.001$) (Fig. 3). The median survival time was 70 months in patients receiving surgical resection and 32 months in those with TACE ($P < 0.001$).

4. Discussion

Our results indicated that surgical resection provided superior survival benefit than TACE to patients with intermediate stage HCC, irrespective of CTP class A or B cirrhosis. Surgical resection was identified as an independent factor associated with survival by Cox regression analysis.

According to the BCLC staging system and recommended treatment strategy (AASLD guideline), TACE has been recognized as an effective treatment option for those with intermediate stage HCC.[4,5] Cumulative meta-analysis of published randomized controlled trials further indicates that patient survival is significantly improved after TACE.[10] However, the 1-year mortality of intermediate stage HCC patients receiving TACE still remains

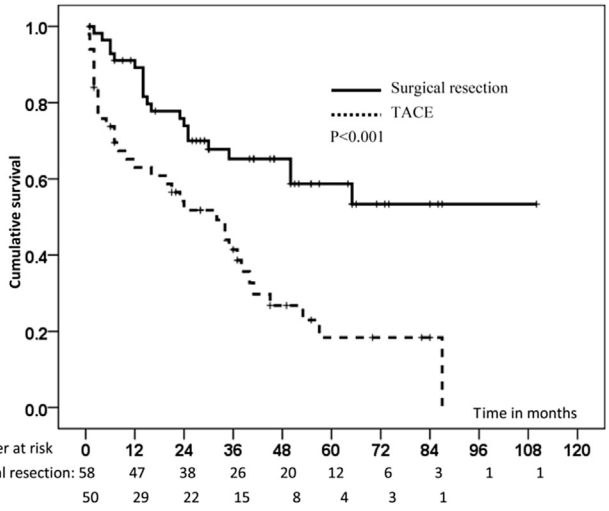

Fig. 3. The cumulative survival curve of 108 intermediate stage hepatocellular carcinoma patients with Child-Turcotte-Pugh class A and tumor number less than 3 treated with surgical resection and transarterial chemoembolization (TACE).

unsatisfactory.[18] It would appear that TACE may not be the optimal therapy for all intermediate stage HCC patients.

Curative treatments, which include surgical resection, percutaneous ablation and liver transplantation, were considered as the optimal treatment for patients with very early/early stage HCC by BCLC criteria.[4,5] Furthermore, advances in liver surgery make the resection of large and/or multifocal HCC possible.[19–22] Therefore, surgical resection may be a safe and effective therapy for a certain segment of intermediate stage HCC patients. A previous study of intermediate stage HCC, CTP class A cirrhotic patients reported that patients receiving surgical resection had better survival than those with TACE.[23,24] In our study, most patients (97%) who received surgical resection had CTP class A cirrhosis. Similar to previous studies, our results showed that patients with surgical resection had significantly higher long-term survival rates than patients with TACE. In addition, CTP class B cirrhosis was identified as independent risk factors associated with poor prognosis. Taken together, the selection of ideal candidates with preserved liver function for surgical resection should improve long-term survival of intermediate stage HCC.

In our study, AFP level >400 ng/ml was a risk factor associated with poor prognosis. Serum AFP level has been recognized as a poor prognostic factor through poor tumor biological behavior, such as tumor multiplicity, poor differentiation and carcinoma cell embolus, as well as moderate/severe cirrhosis.[18,25–27] Therefore, incorporation of AFP level to current HCC staging systems is recommended in evaluating prognosis and subclassification for intermediate stage HCC patients to tailor optimal therapeutic modality.[28]

There are several limitations of this study. First, as a retrospective study design, the existence of patient selection bias for surgical resection or TACE should be considered. Second, the standard selection criteria for surgical resection are not well established. In addition, the frequency of TACE administration for individual patients varies in our study, which was influenced by tumor progression and severity of cirrhosis during the follow-up period. Therefore, large cohort studies are required to further evaluate the optimum treatment strategy for intermediate stage HCC patients.

In conclusion, our results indicated that surgical resection provides superior survival benefit than TACE to patients with intermediate stage HCC. Advances in liver surgery make the resection of intermediate stage HCC possible. Surgical resection should be considered first for patients with preserved liver functions. However, standard selection criteria for surgical resection are needed. It is foreseen that surgical resection will play an important role in treatment for intermediate stage HCC, now and into the future.

Conflict of interest

All authors have no conflict of interest.

Acknowledgments

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References

1. Kao JH, Chen DS. Changing disease burden of hepatocellular carcinoma in the Far East and Southeast Asia. *Liver Int*. 2005;25:696–703.
2. American Cancer Society. *Cancer Facts & Figures 2012*. Atlanta: American Cancer Society; 2012.
3. Lin CL, Kao JH. Optimal management of hepatocellular carcinoma: challenges and opportunities. *J Gastroenterol Hepatol*. 2010;25:1336–1338.
4. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology*. 2005;42:1208–1236.
5. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53:1020–1022.
6. Llovet JM, Brù C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC-staging classification. *Semin Liver Dis*. 1999;19:329–338.
7. Cillo U, Vitale A, Grigoletto F, et al. Prospective validation of the Barcelona clinic liver cancer staging system. *J Hepatol*. 2006;44:723–731.
8. Forner A, Reig ME, de Lope CR, et al. Current strategy for staging and treatment: the BCLC update and future prospects. *Semin Liver Dis*. 2010;30:61–74.
9. Cammà C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. *Radiology*. 2002;224:47–54.
10. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology*. 2003;37:429–442.
11. Raoul JL, Sangro B, Forner A, et al. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. *Cancer Treat Rev*. 2011;37:212–220.
12. Chang WT, Kao WY, Chau GY, et al. Hepatic resection can provide long-term survival of patients with non-early-stage hepatocellular carcinoma: extending the indication for resection? *Surgery*. 2012;152:809–820.
13. Wang JH, Changchien CS, Hu TH, et al. The efficacy of treatment schedules according to Barcelona Clinic Liver Cancer staging for hepatocellular carcinoma – survival analysis of 3892 patients. *Eur J Cancer*. 2008;44:1000–1006.
14. Hsu CY, Hsia CY, Huang YH, et al. Comparison of surgical resection and transarterial chemoembolization for hepatocellular carcinoma beyond the Milan criteria: a propensity score analysis. *Ann Surg Oncol*. 2012;19:842–849.
15. Zhong JH, Ke Y, Gong WF, et al. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. *Ann Surg*. 2014;260:329–340.
16. Pugh RN, Muray-Lyon IM, Dawson JL, et al. Transection of the esophagus in the bleeding esophageal varices. *Br J Surg*. 1973;60:648–652.
17. Ting CT, Chen RC, Chen CC, et al. Diabetes worsens the surgical outcomes in cirrhotic patients with hepatocellular carcinoma. *Tohoku J Exp Med*. 2012;227:73–81.
18. Lin CL, Hsieh CF, Chen T, et al. Risk factors for one-year mortality in patients with intermediate stage hepatocellular carcinoma treated solely with transcatheter arterial chemoembolization. *Adv Dig Med*. 2014;1:126–131.
19. Shah SA, Wei AC, Cleary SP, et al. Prognosis and results after resection of very large (>or=10 cm) hepatocellular carcinoma. *J Gastrointest Surg*. 2007;11:589–595.
20. Ishizawa T, Hasegawa K, Aoki T, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology*. 2008;134:1908–1916.
21. Ruzzenente A, Capra F, Pachera S, et al. Is liver resection justified in advanced hepatocellular carcinoma? Results of an observational study in 464 patients. *J Gastrointest Surg*. 2009;13:1313–1320.
22. Ho MC, Huang GT, Tsang YM, et al. Liver resection improves the survival of patients with multiple hepatocellular carcinomas. *Ann Surg Oncol*. 2009;16:848–855.
23. Lin CT, Hsu KF, Chen TW, et al. Comparing hepatic resection and transarterial chemoembolization for Barcelona Clinic Liver Cancer (BCLC) stage B hepatocellular carcinoma: change for treatment of choice? *World J Surg*. 2010;34:2155–2161.
24. Zhong JH, Xiang BD, Gong WF, et al. Comparison of long-term survival of patients with BCLC stage B hepatocellular carcinoma after liver resection or transarterial chemoembolization. *PLos One*. 2007;8:e681932013.
25. Santambrogio R, Opocher E, Costa M, et al. Hepatic resection for "BCLC stage A" hepatocellular carcinoma. The prognostic role of alpha-fetoprotein. *Ann Surg Oncol*. 2012;19:426–434.
26. Zhong JH, Xiang BD, Gong WF, et al. Comparison of long-term survival of patients with BCLC stage B hepatocellular carcinoma after liver resection or transarterial chemoembolization. *PLoS One*. 2013;8:e68193.
27. Zhou J, Yan T, Bi X, et al. Evaluation of seven different staging systems for alpha-fetoprotein expression in hepatocellular carcinoma after hepatectomy. *Tumour Biol*. 2013;34:1061–1070.
28. Bolondi L, Burroughs A, Dufour JF, et al. Heterogeneity of patients with intermediate (BCLC B) hepatocellular carcinoma: proposal for a subclassification to facilitate treatment decisions. *Semin Liver Dis*. 2012;32:348–359.