Surgical Resection is An Effective Therapy for Single Large Hepatocellular Carcinom

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Research Article

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Abstract

Background

Identifying prognostic factors and therapeutic strategies for single large hepatocellular carcinoma (HCC) is crucial. This retrospective study investigated prognostic factors in patients with single large HCC (≥ 5 cm) and Child–Pugh (CP) class A liver disease and recommended therapeutic strategies.

Methods

In total, 305 patients with single large HCC and CP class A liver disease but without distant metastasis or macrovascular invasion were included. Their clinicopathological data, overall survival (OS), and progression-free survival (PFS) were recorded. OS and PFS rates were analyzed using the Kaplan–Meier method and Cox regression analysis.

Results

In this study, 77.8% of the patients were men; the median age was 63 years. Approximately 34.1% of the patients had cirrhosis and 89.6% had CP class A5 disease. The most common initial treatment was resection (49.5%), followed by transarterial chemoembolization (TACE; 48.2%). OS and PFS rates 1, 5, and 10 years after initial treatment were 88.6%, 58.0%, and 46.8% and 73.6%, 48.2%, and 31.3%, respectively. OS and PRS rates were significantly higher in patients receiving surgical resection than in those receiving TACE. The 1-, 5-, and 10-year OS rates were 94.6%, 76.7%, and 66.7% after resection and 83.1%, 39.0%, and 26.6% after TACE. The 1-, 5-, and 10-year PRS rates were 82.5%, 55.7%, and 51.0% after resection and 64.3%, 40.5%, and 22.7% after TACE. In multivariate analysis, CP class A5/6 (A5 vs. A6; hazard ratio [HR]: 0.23; 95% confidence interval [CI]: 0.15–0.38, P < 0.001) and initial treatment (resection vs. TACE; HR: 0.22; 95% CI: 0.15–0.36, P < 0.001; resection vs. other treatments; HR: 0.37; 95% CI: 0.17–0.65, P = 0.016) were significantly associated with OS. In addition, CP class A5/6 (A5 vs. A6; HR: 0.32; 95% CI: 0.18–0.56, P < 0.001) and initial treatment (resection vs. TACE; HR: 0.30; 95% CI: 0.16–0.51, P < 0.001; resection vs. other treatments; HR: 0.51; 95% CI: 0.26–0.81, P = 0.042) were significantly associated with PFS.

Conclusion

Surgical resection achieved significantly higher OS and PRS rates than TACE. Surgical resection is an effective and safe therapy for single large HCC.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second most common cause of cancer-related death worldwide [1–5]. Although HCC surveillance with alpha-fetoprotein (AFP) and
ultrasound is recommended in patients at risk of HCC [3–5], the proportion of HCC that is large at diagnosis is still high [6]. Liver resection has been reported to promote overall survival (OS) in patients with HCC across various Barcelona Clinic Liver Cancer (BCLC) stages [7, 8]. In 2012, the BCLC system designated a single large HCC (>5 cm) as BCLC stage A rather than stage B [9]. The revised BCLC classification schema has been endorsed by the American Association for the Study of Liver Diseases (AASLD) [3] and the European Association for the Study of the Liver [4]. Furthermore, the most recent version of the 2017 combined American Joint Committee on Cancer/Union for International Cancer Control tumor-node-metastasis staging system states that patients with multiple tumors, any of which are >5 cm, can be classified as T3 [10]. Recent studies have reported that approximately two-thirds of patients with tumor size >10 cm present microvascular invasion; more favorable outcomes have been reported after resection in these patients; thus, surgical resection should be considered for single large HCC [6, 11]. Several studies have also demonstrated that liver resection is a safe and effective treatment for single large HCC [12–17]. However, these studies had limitations, such as limited data availability, lack of comparison with different treatments, and/or selection bias. The treatment for single large HCC (≥5 cm) still remains largely unknown and needs to be studied further. This study investigated prognostic factors and effective therapies for single large HCC.

**Materials And Methods**

**Patients and follow-up**

We retrospectively enrolled 4092 HCC patients from 2007 to 2018 at E-Da Hospital, I-Shou University, Kaohsiung, Taiwan. In total, we excluded 3787 patients due to multiple tumors, tumor size <5 cm, presence of macrovascular invasion and/or distal metastasis, or Child–Pugh (CP) classes B and C. Ultimately, 305 patients with HCC and CP class A liver disease, a single tumor ≥5 cm, and no macrovascular invasion and/or distal metastasis were included in this retrospective study (Fig. 1). This study was approved by the Institutional Review Board at E-Da Hospital.

HCC was diagnosed based on histology or typical imaging methods on the basis of the guideline of the AASLD [18]. Demographic characteristics, etiology, blood tests, CP class, cirrhotic of liver, tumor size, AFP, mortality, disease progression, and follow-up time, were recorded. Tumor size and number were determined according to pathological confirmation and radiologic findings. Patients were treated with surgical resection, transarterial chemoembolization (TACE), hepatic artery infusion chemotherapy (HAIC), or liver transplantation. Our multidisciplinary team chose suitable therapies for each patient. Patients were followed up every 3 to 6 months by abdominal ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI), and AFP. OS and PFS was defined as the time from the date of diagnosis to the date of death and disease progression or the last visit; the last follow-up date was December 2020.

**Data analysis and statistics**

Numerical data are shown using medians and ranges. Categorical data are shown as numbers and percentages. OS and PFS rates were used by the Kaplan–Meier method. OS and PFS rates was analyzed
by Cox proportional hazards regression. A $P$ value of $<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 23.0 (SPSS, Chicago, IL, USA).

Results

Baseline characteristics

The demographic and clinical features of 305 patients with HCC and CP class A disease (77.8% male, median age 63 years) with single large tumors ($\geq 5$ cm) but without distant metastasis and/or macrovascular invasion are listed in Table 1. Regarding the etiology of HCC, 44.1% of the patients had hepatitis B virus (HBV) infection, 23.0% had hepatitis C virus (HCV) infection, and 30.9% had neither HBV nor HCV. Approximately 34.1% of patients had liver cirrhosis, and 89.6% had CP class A5 disease. The most common initial treatment modality was resection (49.5%), followed by TACE (48.2%), HAIC (1.3%), and liver transplantation (1%). The median follow-up time was 33 months.

OS and PFS rates in all patients

Kaplan–Meier analysis demonstrated that the 1-, 3-, 5-, and 10-year OS rates after initial treatment were 88.6%, 66.7%, 58.0%, and 46.8%, respectively (Fig. 2A), and the 1-, 3-, 5-, and 10-year PFS rates were 73.6%, 56.9%, 48.2%, and 31.3%, respectively (Fig. 2B). OS and PRS rates were significantly higher in patients receiving surgical resection than those receiving TACE, HAIC, or liver transplantation. The 1-, 3-, 5-, and 10-year OS rates were 94.6%, 82.4%, 76.7%, and 66.7% after resection and 83.1%, 50.1%, 39.0%, and 26.6% after TACE, respectively ($P < 0.001$, Fig. 3A). The 1-, 3-, 5-, and 10-year PRS rates were 82.5%, 66.8%, 55.7%, and 51.0% after resection and 64.3%, 47.2%, 40.5%, and 22.7% after TACE, respectively ($P < 0.001$, Fig. 3B).

Factors affecting OS and PFS

Sex, hypertension, CP class A5/6, ALT, AFP, tumor size $\geq 10$ cm, and initial treatment were significantly associated with OS in univariate analysis (Table 2). Furthermore, in multivariate analysis, CP class A5/6 (A5 vs. A6; hazard ratio [HR]: 0.23; 95% confidence interval [CI]: 0.15–0.38, $P < 0.001$) and initial treatment (resection vs. TACE; HR: 0.22; 95% CI: 0.15–0.36, $P < 0.001$; resection vs. other treatments; HR: 0.37; 95% CI: 0.17–0.65, $P = 0.016$) remained significantly associated with OS (Table 2). Furthermore, CP class A5/6, total bilirubin, INR, AFP, and initial treatment were significantly associated with PFS in univariate analysis (Table 2). Moreover, in multivariate analysis, CP class A5/6 (A5 vs. A6; HR: 0.32; 95% CI: 0.18–0.56, $P < 0.001$) and initial treatment (resection vs. TACE; HR: 0.30; 95% CI: 0.16–0.51, $P < 0.001$; resection vs. other treatments; HR: 0.51; 95% CI: 0.26–0.81, $P = 0.042$) remained significantly associated with PFS (Table 2).

OS in subgroup analysis

OS and PRS rates were significantly higher in patients with CP class A5 than in those with CP class A6 ($P < 0.001$, Figs. 4A-B). Of the 147 patients who underwent TACE as the initial treatment, 13 underwent
resection as the secondary treatment. Their OS rates was similar to that of patients who underwent resection as the initial treatment ($P = 0.241$; Fig. 4C). In subgroup analysis in patients with CP class A5/6, no significant difference was observed in OS rates between resection and TACE as the initial treatment in patients with CP class A5 or A6 (all $P > 0.05$; Fig. 4D).

**Discussion**

Our study demonstrated that OS and PRS rates were significantly higher in patients receiving surgical resection than in those receiving TACE. The 10-year OS rates after surgical resection and TACE were 66.7% and 26.6%, respectively. The 10-year PFS rates after surgical resection and TACE were 51.0% and 22.7%, respectively. CP class A5/6 and initial treatment were significantly associated with OS and PFS in multivariate analysis. Surgical resection is a safe and effective treatment for single large HCC.

Surgical resection is widely used as the first-line therapy in patients with HCC with favorable liver function and tumor factors [19, 20]. Previous studies have reported that hepatic resection in patients with CP class A resulted in favorable outcomes, with a 5-year OS rate of over 60% and a 5-year PFS rate of over 40% [12, 21, 22]. Our study demonstrated that 151 patients (49.5%) underwent surgical resection and showed higher 5-year OS rates (76.7%) and PFS (55.7%) rates. This is consistent with previous findings of a comparable prognosis in patients with large HCC, and hepatectomy can be considered regardless of tumor size [6, 11]. Previous studies have reported that patients receiving surgical resection had higher OS rates than those receiving TACE among patients with BCLC stage B HCC [8, 23]. Recently, several studies have reported a survival benefit for liver resection in patients with BCLC stage B HCC [16, 17, 24–27]. Our study finding is also consistent with that of a previous study demonstrating that surgical resection is significantly associated with higher OS and PFS than TACE [12].

Thirteen patients received resection as secondary treatment after TACE. Their OS rates were similar to that of patients who underwent resection as the initial treatment, suggesting that hepatectomy after TACE may be another choice for patients with single large HCC. This finding is similar to that of studies reporting that resection after TACE may be considered an effective treatment in patients with BCLC stage B HCC [28, 29].

CP class was significantly associated with OS in patients with different BCLC stages of HCC [3–5]. Our study demonstrated that CP class A5 was significantly associated with higher OS and PFS rates in patients with single large HCC in multivariate analysis. Our results differed from those of previous studies reporting no significant difference in OS or PFS between CP class A5 and A6 patients with single large HCC in multivariate analysis [12]. To the best of our knowledge, our study is the first to reveal that CP class A5 is significantly associated with OS and PFS in patients with single large HCC.

Limitations of the study include the following: First, the retrospective nature of the study might have resulted in unintended bias. Second, PFS may be biased, especially in patients receiving noncurative therapies.
Conclusions

Surgical resection was associated with significantly higher OS and PRS rates than TACE. CP class A5/6 and initial treatment were significantly associated with OS and PFS. Surgical resection is an effective and safe therapy for single large HCC.

Abbreviations

HCC
Hepatocellular carcinoma
BCLC
Barcelona Clinic Liver Cancer
AASLD
American Association for the Study of Liver Disease
TACE
Transarterial chemoembolization
HAIC
Hepatic artery infusion chemotherapy
OS
Overall survival
PFS
Progression-free survival
C-P class
Child–Pugh class
HR
Hazard ratio
CI
Confidence interval

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the guidelines of the International Conference on Harmonization for Good Clinical Practice and was approved by the Ethics Committee of E-Da Hospital, I-Shou University (EMRP-107-130). The consent for study participation is informed and signed.

Consent for Publication

Not applicable.

Availability of data and material
Data is available from the corresponding author upon reasonable request.

**Competing interests**

None declared.

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**Authors’ contributions**

PH, JHY and CMH: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; HYL, TQT, PNC, KCH, PMH, and YSC: study concept and design; critical revision of the manuscript for important intellectual content; administrative, technical, or material support; CWL: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content administrative, technical, or material support; study supervision. All authors approved the final version of the manuscript.

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References

1. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021; 7(1):6.

2. McGlynn KA, Petrick JL, El-Serag HB Epidemiology of Hepatocellular Carcinoma. Hepatology. 2021; 73 Suppl 1:4–13.

3. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018; 68(2):723–50.

4. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018; 69(1):182–236.

5. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017; 11(4):317–70.

6. Hwang S, Lee YJ, Kim KH, Ahn CS, Moon DB, Ha TY et al. Long-Term Outcome After Resection of Huge Hepatocellular Carcinoma >/= 10 cm: Single-Institution Experience with 471 Patients. World J Surg. 2015; 39(10):2519–28.

7. Vitale A, Burra P, Frigo AC, Trevisani F, Farinati F, Spolverato G et al. Survival benefit of liver resection for patients with hepatocellular carcinoma across different Barcelona Clinic Liver Cancer stages: a multicentre study. J Hepatol. 2015; 62(3):617–24.
8. Lin CW, Chen YS, Lo GH, Hsu YC, Hsu CC, Wu TC et al. Comparison of overall survival on surgical resection versus transarterial chemoembolization with or without radiofrequency ablation in intermediate stage hepatocellular carcinoma: a propensity score matching analysis. BMC Gastroenterol. 2020; 20(1):99.

9. European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012; 56(4):908–43.

10. Eighth Edition Updates and Corrections. AJCC Cancer Staging Manual. 2017.

11. Zhou YM, Li B, Xu DH, Yang JM. Safety and efficacy of partial heptectomy for huge (>10 cm) hepatocellular carcinoma: a systematic review. Med Sci Monit. 2011; 17(3):RA76-83.

12. Hong SK, Lee KW, Hong SY, Suh S, Hong K, Han ES et al. Efficacy of Liver Resection for Single Large Hepatocellular Carcinoma in Child-Pugh A Cirrhosis: Analysis of a Nationwide Cancer Registry Database. Front Oncol. 2021; 11:674603.

13. Fang KC, Kao WY, Su CW, Chen PC, Lee PC, Huang YH et al. The Prognosis of Single Large Hepatocellular Carcinoma Was Distinct from Barcelona Clinic Liver Cancer Stage A or B: The Role of Albumin-Bilirubin Grade. Liver Cancer. 2018; 7(4):335–58.

14. Zhong JH, Rodriguez AC, Ke Y, Wang YY, Wang L, Li LQ. Hepatic resection as a safe and effective treatment for hepatocellular carcinoma involving a single large tumor, multiple tumors, or macrovascular invasion. Medicine (Baltimore). 2015; 94(3):e396.

15. Noh JH, Kim TS, Ahn KS, Kim YH, Kang KJ. Prognostic factors after hepatic resection for the single hepatocellular carcinoma larger than 5 cm. Ann Surg Treat Res. 2016; 91(3):104–11.

16. Yang XD, Pan LH, Wang L, Ke Y, Cao J, Yang C et al. Systematic Review of Single Large and/or Multinodular Hepatocellular Carcinoma: Surgical Resection Improves Survival. Asian Pac J Cancer Prev. 2015; 16(13):5541–7.

17. LiuYW, Lin CC, Yong CC, Wang CC, Chen CL, Wang JH et al. Prognosis after resection of single large hepatocellular carcinoma: Results from an Asian high-volume liver surgery center. PLoS One. 2020; 15(3):e0230897.

18. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018; 67(1):358–80.

19. Poon RT, Fan ST, Lo CM, Ng IO, Liu CL, Lam CM et al. Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. Ann Surg. 2001; 234(1):63–70.

20. Lang H, Sotiropoulos GC, Domland M, Fruhauf NR, Paul A, Husing J et al. Liver resection for hepatocellular carcinoma in non-cirrhotic liver without underlying viral hepatitis. Br J Surg. 2005; 92(2):198–202.

21. Chen HY, Juan CC, Ker CG. Laparoscopic liver surgery for patients with hepatocellular carcinoma. Ann Surg Oncol. 2008; 15(3):800–6.
22. Yin Z, Fan X, Ye H, Yin D, Wang J Short- and long-term outcomes after laparoscopic and open hepatectomy for hepatocellular carcinoma: a global systematic review and meta-analysis. Ann Surg Oncol. 2013; 20(4):1203–15.

23. Lin CT, Hsu KF, Chen TW, Yu JC, Chan DC, Yu CY 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(9):2155–61.

24. Zhong JH, Ke Y, Wang YY, Li LQ Liver resection for patients with hepatocellular carcinoma and macrovascular invasion, multiple tumours, or portal hypertension. Gut. 2015; 64(3):520–1.

25. Zhong JH, Ke Y, Gong WF, Xiang BD, Ma L, Ye XP et al. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. Ann Surg. 2014; 260(2):329–40.

26. Kim H, Ahn SW, Hong SK, Yoon KC, Kim HS, Choi YR et al. Survival benefit of liver resection for Barcelona Clinic Liver Cancer stage B hepatocellular carcinoma. Br J Surg. 2017; 104(8):1045–52.

27. Chen YS, Hsieh PM, Lin HY, Hung CM, Lo GH, Hsu YC et al. Surgical resection significantly promotes the overall survival of patients with hepatocellular carcinoma: a propensity score matching analysis. BMC Gastroenterol. 2021; 21(1):220.

28. Lee HS, Kim KM, Yoon JH, Lee TR, Suh KS, Lee KU et al. Therapeutic efficacy of transcatheter arterial chemoembolization as compared with hepatic resection in hepatocellular carcinoma patients with compensated liver function in a hepatitis B virus-endemic area: a prospective cohort study. J Clin Oncol. 2002; 20(22):4459–65.

29. Chen J, Lai L, Lin Q, Huang W, Cai M, Zhu K et al. Hepatic resection after transarterial chemoembolization increases overall survival in large/multifocal hepatocellular carcinoma: a retrospective cohort study. Oncotarget. 2017; 8(1):408–17.

Tables
| Variables                        | Total patients         |
|---------------------------------|------------------------|
| **Demographic variables**       |                        |
| Age (years)                     | 63 (23-92)             |
| Sex: Male                       | 240 (78.70)            |
| BMI (kg/m$^2$)                  | 25.1 (15.9-38.9)       |
| Diabetes                        | 60 (19.7)              |
| Hypertension                    | 51 (16.7)              |
| Smoking                         | 84 (27.5)              |
| Alcohol use                     | 56 (18.4)              |
| **Etiology**                    |                        |
| Non-B Non-C                     | 94 (30.9)              |
| HBV positive                    | 134 (44.1)             |
| HCV positive                    | 70 (23.0)              |
| HBV+HCV                         | 6 (2.0)                |
| Cirrhosis                       | 104 (34.1)             |
| Child-Pugh class A5/A6          | 272/33 (89.2/10.8)     |
| **Antiviral therapy**           | 98 (32.1)              |
| **Laboratory variable**         |                        |
| Platelet count (10$^9$/L)       | 173 (62-401)           |
| Total Bilirubin (mg/dL)         | 0.9 (0.1-2.9)          |
| Serum albumin (g/dL)            | 4.1 (3.1-4.8)          |
| AST (IU/L)                      | 53 (16-259)            |
| ALT (IU/L)                      | 54 (13-403)            |
| INR                             | 1.1 (0.9-2.8)          |
| Creatinine (mg/dL)              | 1.2 (0.5-8.2)          |

Data are shown as number (%) or median (range). BMI: Body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; AST: Aspartate Transaminase; ALT: Alanine aminotransferase; INR: International Normalized Ratio; TACE: Transarterial chemoembolization; HAIC: Hepatic artery infusion chemotherapy;
| Variables                      | Total patients             |
|--------------------------------|----------------------------|
| Alpha-fetoprotein (ng/mL)      | 1138 (2-101685)            |
| **Tumor variable**             |                            |
| Maximum tumor size (cm)        | 7.6 (5.0-18.4)             |
| **Treatment variable**         |                            |
| Initial treatment              | 21 (7.0)                   |
| Resection                      | 151 (49.5)                 |
| TACE                           | 147 (48.2)                 |
| HAIC                           | 4 (1.3)                    |
| Liver transplantation          | 3 (1.0)                    |

Data are shown as number (%) or median (range). BMI: Body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; AST: Aspartate Transaminase; ALT: Alanine aminotransferase; INR: International Normalized Ratio; TACE: Transarterial chemoembolization; HAIC: Hepatic artery infusion chemotherapy.
Table 2
Univariate and multivariate analyses of factors associated with overall survival and progression-free survival.

| Demographic variables | N=305 | Overall survival | Progression-free survival |
|-----------------------|-------|------------------|--------------------------|
|                       |       | Univariate       | Multivariate             | Univariate       | Multivariate |
|                       |       | P-value          | HR (95% CI)              | P-value          | HR (95% CI)  |
| Age (years)           |       |                  |                          |                  |
| < 60                  | 99    | 1                | 1                        |                  |
| ≥ 60                  | 206   | 0.977            | 0.381                    |                  |
| Gender                |       |                  |                          |                  |
| Female                | 65    | 1                | 1                        | 1                |
| Male                  | 240   | 0.030            | 0.91 (0.57-1.45)         | 0.672            | 0.682        |
| BMI (kg/m²)           |       |                  |                          |                  |
| < 25                  | 172   | 1                | 1                        |                  |
| ≥ 25                  | 133   | 0.400            | 0.522                    |                  |
| Diabetes              |       |                  |                          |                  |
| Absent                | 254   | 1                | 1                        |                  |
| Present               | 51    | 0.091            | 0.690                    |                  |
| Hypertension          |       |                  |                          |                  |
| Absent                | 245   | 1                | 1                        |                  |
| Present               | 60    | 0.032            | 1.38 (0.78-2.38)         | 0.256            | 0.437        |
| Smoking               |       |                  |                          |                  |
| Absent                | 221   | 1                | 1                        |                  |
| Present               | 84    | 0.996            | 0.299                    |                  |
| Alcohol use           |       |                  |                          |                  |

HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; AST: Aspartate Transaminase; ALT: Alanine aminotransferase; INR: International Normalized Ratio; TACE: Transarterial chemoembolization; HAIC: Hepatic artery infusion chemotherapy;
| Demographic variables | N=305 | Overall survival | Progression-free survival |
|-----------------------|-------|------------------|----------------------------|
| Absent                | 249   | 1                | 1                          |
| Present               | 56    | 0.375            | 0.574                      |
| Etiology              |       |                  |                            |
| Non-B Non-C           | 94    | 1                | 1                          |
| HBV positive          | 134   | 0.133            | 0.243                      |
| HCV positive          | 70    | 0.952            | 0.786                      |
| HBV+HCV               | 6     | 0.787            | 0.167                      |
| Cirrhosis             |       |                  |                            |
| Absent                | 201   | 1                | 1                          |
| Present               | 104   | 0.192            | 0.668                      |
| Child-Pugh class      |       |                  |                            |
| A5                    | 272   | 1                | 1                          |
| A6                    | 33    | <0.001           | 0.32 (0.18-0.56)           |
| Antiviral therapy     |       |                  |                            |
| Absent                | 207   | 1                | 1                          |
| Present               | 98    | 0.656            | 0.360                      |
| Laboratory variable   |       |                  |                            |
| Platelet count (10^9/L) |    |                  |                            |
| < 150                 | 131   | 1                | 1                          |
| ≥ 150                 | 174   | 0.837            | 0.655                      |
| Total Bilirubin (mg/dL) |    |                  |                            |
| < 1.2                 | 238   | 1                | 1                          |

HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; AST: Aspartate Transaminase; ALT: Alanine aminotransferase; INR: International Normalized Ratio; TACE: Transarterial chemoembolization; HAIC: Hepatic artery infusion chemotherapy;
### Demographic variables

| Variable                        | N=305 | Overall survival | Progression-free survival |
|---------------------------------|-------|------------------|---------------------------|
| **Overall survival**            |       |                  |                           |
| ≥ 1.2                           | 67    | 0.276            | 0.005                     |
|                                 |       |                  | 0.62 (0.31-1.25)          |
|                                 |       |                  | 0.095                     |
| Serum albumin (g/dL)            |       |                  |                           |
| < 3.5                           | 14    | 1                | 1                         |
| ≥ 3.5                           | 291   | 0.329            | 0.971                     |
| AST (IU/L)                      |       |                  |                           |
| < 50                            | 179   | 1                | 1                         |
| ≥ 50                            | 172   | 0.041            | 0.105                     |
|                                 |       |                  | 0.347                     |
| ALT (IU/L)                      |       |                  |                           |
| < 50                            | 198   | 1                | 1                         |
| ≥ 50                            | 107   | 0.102            | 0.846                     |
| INR                             |       |                  |                           |
| < 1.2                           | 282   | 1                | 1                         |
| ≥ 1.2                           | 23    | 0.057            | <0.001                    |
|                                 |       |                  | 1.78 (0.33-1.22)          |
|                                 |       |                  | 0.177                     |
| Creatine (mg/dL)                |       |                  |                           |
| < 1.1                           | 105   | 1                | 1                         |
| ≥ 1.1                           | 200   | 0.971            | 0.617                     |
| Alpha-fetoprotein (ng/mL)       |       |                  |                           |
| < 200                           | 256   | 1                | 1                         |
| ≥ 200                           | 49    | 0.015            | 0.068                     |
|                                 |       |                  | 0.72 (0.43-1.16)          |
|                                 |       |                  | 0.181                     |

**Tumor variable**

HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; AST: Aspartate Transaminase; ALT: Alanine aminotransferase; INR: International Normalized Ratio; TACE: Transarterial chemoembolization; HAIC: Hepatic artery infusion chemotherapy;
| Demographic variables | N=305 | Overall survival | Progression-free survival |
|-----------------------|-------|------------------|--------------------------|
| Maximum tumor size (cm) |       |                  |                          |
| < 10                  | 256   | 1                | 1                        |
| ≥ 10                  | 49    | 0.038            | 1.28 (0.68-2.32)         |
|                       |       |                  | 0.440 0.645              |
| Treatment variable    |       |                  |                          |
| Initial treatment     |       |                  |                          |
| Resection             | 151   | 1                | 1                        |
| TACE                  | 147   | <0.001           | 0.22 (0.15-0.36)         |
|                       |       |                  | <0.001 <0.001 0.30 (0.16-0.51) |
| Others                | 7     | 0.011            | 0.37 (0.17-0.65)         |
|                       |       |                  | 0.016 0.033 0.51 (0.26-0.81) |
|                       |       |                  | 0.042                     |

HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; AST: Aspartate Transaminase; ALT: Alanine aminotransferase; INR: International Normalized Ratio; TACE: Transarterial chemoembolization; HAIC: Hepatic artery infusion chemotherapy;
Figure 1

Study flowchart and participant inclusion criteria.
Figure 2

Overall survival and progression-free survival of the total cohort.

Figure 3

(A) Overall survival (OS) and (B) progression-free survival (PFS) according to different treatment methods. Surgical resection resulted in significantly higher OS and PFS rates than transarterial chemoembolization or other treatments.
Figure 4

Overall survival (OS) and progression-free survival (PFS) in subgroup analysis. (A) OS and (B) PFS rates in patients with Child–Pugh (CP) class A5/6. The OS and PFS rates were significantly higher in patients with CP class A5 than those with CP class A6. (C) OS rates in patients with surgical resection vs. surgical resection after transarterial chemoembolization. The OS rates of patients who underwent resection after transarterial chemoembolization (TACE) was similar to that of patients who underwent resection as initial treatment. (D) OS rates in patients with treatment modality and CP class A. No significant differences were observed in OS rates between patients with resection or TACE as the initial treatment with CP class A5 or A6.
