The Role of Adjuvant Chemotherapy in Stage 2 Hepatocellular Carcinoma Patients

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Research Article

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Abstract

Background and objectives The purpose of the present study was to comprehensively analyze the prognostic value of adjuvant chemotherapy (CT) in stage IV HCC patients.

Methods HCC patients were recognized in the Surveillance, Epidemiology and End Results (SEER) database. The effects of adjuvant CT on HCC patients were evaluated by Kaplan–Meier curves and multivariable Cox proportional hazards analyses.

Results A total of 490 HCC patients were enrolled in this study and the median follow-up time was 2.69 months (range: 0–102 months). 34.3% (168) HCC patients received adjuvant CT, of which 58.6% (287) received local destruction, 25.5% (125) were partial resection and 15.9% (78) underwent liver transplantation. Multivariate analysis showed that chemotherapy (P <0.001), surgery (P <0.001), year at diagnosis (P = 0.004), grade (P <0.001) and fibrosis score (P = 0.039) were independent factor of cancer specific survival (CSS), and that chemotherapy (P <0.001), surgery (P <0.001), year at diagnosis (P = 0.005), grade (P <0.001) were independent factor of overall survival (OS). Survival curves confirmed that patients achieved an increased OS or CSS from adjuvant CT (P <0.05).

Conclusions Our results concluded that compared to surgery alone, stage IV HCC patients could profit from adjuvant chemotherapy. High quality prospective trials are necessary to further confirm our results.

Introduction

Hepatocellular carcinoma (HCC) with extrahepatic metastasis is the advanced stage of the disease. According to the 7th American Joint Committee on Cancer (AJCC), HCCs with regional lymph node metastasis and distant metastasis are in a stage of IV. The prognosis is poor except for the rare cases of resectable primary tumors with single extrahepatic metastasis[1]. Currently, sorafenib is confirmed as one of standard treatments[2, 3]. Most patients (80%-95.7%) died of hepatic failure caused by progressive intrahepatic tumor without extrahepatic metastases[4–7]. In previous researches, transarterial chemoembolization (TACE), radiofrequency ablation (RFA) or primary tumor resection were applied to HCC patients with extrahepatic metastasis, which effectively controlled the primary tumors and received survival benefit[6–8]. As far as we know, no data on the effects of adjuvant chemotherapy for Stage IV HCC patients have been reported before[9].

According to the National Comprehensive Cancer Network (NCCN) guidelines, for patients with adequate liver function (Child-Pugh class A and some Child-Pugh class B patients without portal hypertension), adequate liver remnant volumes, and a solitary HCC without major vascular invasion, hepatic resection is a therapeutic option [10, 11]. The contraindication for hepatic resection is the existence of extrahepatic metastasis. And for advanced HCC, chemotherapy is one of the most important treatments. Patients who are evaluated as unsuitable candidates for surgical resection, local ablative therapy or transarterial chemoembolization (TACE), which is, patients who have extrahepatic metastasis, show evidence of vascular invasion or are refractory to TACE, are treated with chemotherapy [2, 12–16] (3–8).

The present study aims to explore whether Stage IV HCC patients benefit from adjuvant CT by analyzing a cohort of well-characterized patients, enrolled from the SEER database.

Materials And Methods

Patients

Data was obtained from the National Cancer Institute’s SEER program, which was composed of 18 population-based cancer registries, between 1988 and 2015. SEER is an open access resource for cancer-based demographic and clinical information, treatment and patient survival. SEER*Stat Version 8.3.5 (http://www.seer.cancer.gov/seerstat) was employed to screen eligible patients.

Patient selection criteria were as follows: (a) confirmation of HCC diagnosis histologically or imaging examinations; (b) exclusion of patients with multiple primary tumor sites; (c) exclusion of patients with unknown survival months; (d) exclusion of patients with radiotherapy; (e) exclusion of patients with unknown or absent metastatic status; (f) exclusion of patients who had unknown surgeries. As a result, 490 patients were assessed for eligibility. Clinical variables of enrolled patients included gender, year of diagnosis, age at diagnosis, race, marital status, tumor size, tumor grade, AFP and therapies employed (surgery, chemotherapy)
**Statistical analysis**

Patient and tumor characteristics, and surgery procedure were compared between those who received adjuvant CT and those who did not using the Chi square test. Overall survival (OS), defined as the time from tumor diagnosis to death from any cause, was used as the study outcome. Cancer-specific survival (CSS), defined as the time from tumor diagnosis to death due to HCC, was also compared. Kaplan–Meier method was used to draw survival curves and multivariate Cox proportional hazard models to determine the prognostic factors associated with CSS and OS. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were both reported. All analyses were performed with R version 3.5.0 (http://www.R-project.org/). p values < 0.05 was considered as statistical significance.

**Results**

Our study included 490 patients with Stage IV HCC and the median follow-up time was 2.69 months (range 0–102 months). 168 (34.3%) received adjuvant CT, while 322(65.7%) patients did not. The age at diagnosis of 59.4% (291) patients were older than 60 years. 52.4 percent of the HCC patients with known grade information was diagnosed with a undifferentiated or poorly differentiated tumor. 90.2% HCC patients were diagnosed with tumor larger than 30 mm. 287 (58.6%) received local destruction, 125 (25.5%) were partial resection and 78(15.9) underwent liver transplantation. Demographics, tumor characteristics, and therapy information of Stage IV HCC patients were presented in Table 1.

Univariate analysis found race(p=0.019), year at diagnosis(p<0.001), grade(p=0.009), surgery type (p<0.001), fibrosis score (p=0.009), chemotherapy(p=0.001) were significantly associated with overall survival. The results of cancer-specific survival were similar to those of overall survival with respect to direction and magnitude of the associations (Table 2).

In Multivariate Cox analysis, the result showed that Year at diagnosis (p=0.005), grade(p=0.009), surgery type (p<0.001), chemotherapy(p<0.001) were independent risk factors for OS, and the independent risk factors for CSS were Year at diagnosis (p=0.004), grade(p<0.001), surgery type (p<0.001), fibrosis score (p=0.039), chemotherapy(p<0.001) (Table 2).

There was a significant difference in OS and CSS between the surgery alone cohort and the surgery plus adjuvant CT cohort showed by Kaplan–Meier (p<0.001 and p<0.001, respectively) (Fig. 1 and Fig.2).

We found that the surgery plus adjuvant CT could prolong survival of the patients compared to the surgery alone in Stage IV HCC. Furthermore, we analyzed the prognostic consistency between these two treatment strategies. Stage IV HCC patients were divided into subgroups on basis of the clinicopathological characteristics showed in Table 2. HR and 95% CI in each subgroup were estimated using Cox’s regression model, respectively. In survival analysis, the Fig.3 and Fig.4 suggested that generally stage IV HCC patients who accepted surgery + CT could gain much more survival benefits than patients who received surgery alone for OS or CSS (P < 0.05 arrived in 17 subgroups in OS or CSS, respectively). In OS analysis (Fig.3), especially, stage IV HCC patients received local tumor destruction or partial resection benefited much from combining CT compared to no CT (HR = 0.43, 95% CI: 0.33-0.56, P < 0.001; HR = 0.56, 95% CI: 0.38-0.82, P = 0.003) while the survival benefit of liver transplantation combining CT was not statistically significant (P = 0.727). Similar results are also presented in CSS analysis (Fig.4). Therefore, it could be more meaningful to implement adjuvant CT in stage IV HCC patients underwent local tumor destruction or partial resection.

Collectively, the results of subgroup analysis demonstrated that there existed as least a selective subgroup of patients for stage IV HCC, who could receive survival benefit from surgery plus adjuvant CT.

**Discussion**

In present research, we analyzed a cohort of 126 025 HCC cancer patients, including 490 stage IV HCC patients who meet the criteria in our research, from the SEER database. As far as we know, this is the first large-scale population-based study to investigate the prognostic value of surgery plus adjuvant CT among stage IV HCC patients. Our major results were that there existed at least a selective group of patients who could have prolonged overall survival with surgery plus adjuvant chemotherapy compared to surgery alone for stage IV HCC.

As a common malignant neoplasm and a cause of cancer-related death in Asia and Africa, HCC is associated with a high rate of mortality due to lack of effective treatments against HCC invasion and metastasis. [17, 18] Metastasis has become the major obstacle to survival and quality of life in HCC patients. [18] As to metastasis, the mechanism behind the formation of HCC may contribute to
This features. It has been shown that encapsulated tumor clusters (VETC) pattern provides an important pathway for HCC metastasis, by which the whole tumor cluster may be released into the bloodstream in an Epithelial–mesenchymal transition (EMT)-independent manner.[19] Additionally, study have demonstrated the clinical significance of actopaxin in HCC, and that actopaxin was involved in the regulation of cell invasion, migration, and metastasis of HCC. Further, various microRNAs (miRNAs) have been implicated in regulation of pathogenesis of HCC, and could be potential biomarkers for diagnosis and prognosis[20]. Although these findings could explain the high incidence of HCC metastasis and reoccurrence, further clinical and genetic analyses are still needed to build improved therapeutic management of these stage IV patients.

Although there is a wide range of therapeutic options for HCC, chemotherapy is one of the most important treatment modalities for advanced HCC. Nevertheless, the effect of chemotherapy is still unsatisfactory and the prognosis of patients with advanced HCC remains poor[12–14]. The role of surgery for metastatic HCC cancer had been investigated in several studies and remained controversial until now. Aggressive surgical therapy was proved to elevate long-term survival in the selected patients with advanced HCC in many retrospective studies[21–25]. But, Chok et al explored the outcomes of three different surgical approaches in patients with advanced HCC[26]. They found that the three approaches had similar outcomes in terms of complication, survival and recurrence. The main arguments against resectional surgery for these patients are early recurrence and metastases. Effective adjuvant treatments are required to be developed to lower the incidence of recurrence. To effectively inhibit the high local recurrence, the role of adjuvant therapy has been demonstrated in some studies and main focus is put on postoperative chemotherapy. Recently, there is a published meta-analysis verified that the combination therapy of transarterial chemoembolization plus sorafenib in patients with intermediate or advanced stage HCC can improve OS, objective response rate and time to progression[27]. And Xia et al confirmed that the safety and potential benefits of sorafenib in reducing the incidence of HCC recurrence and prolonging the CSSS and OS rates for patients with advanced HCC after curative resection[28]. On the contrary, a phase III randomized controlled trial to access whether sorafenib could be used as an effective adjuvant therapy after resection or ablation (STORM trial, NCT00692770) was reported by Bruix et al recently[29]. The study showed the trial did not meet its main endpoint of improving recurrence-free survival.

In our analysis, Table 1 revealed that there existed no significant differences between the surgery plus adjuvant CT cohort and the surgery alone cohort. And multivariate Cox analysis showed that partial resection did improve survival compared to local destruction. Therefore, surgeons should give priority to partial resection for advanced HCC patients. Survival curves exhibited CSS or OS benefit from adjuvant CT among stage IV HCC patients. Moreover, in subgroup analysis, 17 of 27 subgroups of metastatic HCC obtained survival benefit from surgery plus adjuvant CT compared to the surgery alone, especially for those underwent local tumor destruction or partial resection.

There are several limitations of our study. Due to the nature of retrospective analysis, we cannot avoid selection bias. We used multivariate analysis to reduce potential confounders. Besides, it is worth noting that the variables that play an important prognostic role in HCC patients were not recorded in the SEER database, including tumor margin status, chemotherapy dose and other histological factors. Finally, because of the lack of information in the SEER database, we failed to demonstrate local recurrence data in our study. Taken together, these results demonstrated that adjuvant CT improved CSS or OS in stage IV HCC patients, confirmed by one of the largest population-based analysis to date.

Declarations

Conflicts of interest

All authors declare that they have no conflicts of interest.

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Conflicts of interest

All authors declare that they have no conflicts of interest.

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**Author contributions**

Quanhui Liao, Shaoxin Shen and Xijing Ma designed the research; Quanhui Liao, and Shaoxin Shen collected data; Guisen Dai, Lu Geng, and Chen Canmin performed the analysis; and Quanhui Liao, Shaoxin Shen and Xijing Ma wrote the manuscript.

1 Quanhui Liao, Shaoxin Shen and Xijing Ma contributed equally to this work.

**References**

[1] Lee HS. Management of patients with hepatocellular carcinoma and extrahepatic metastasis. Dig Dis 29: 333-8, 2011.

[2] Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 53: 1020-2, 2011.

[3] Kudo M, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, Kojiro M, Makuuchi M. Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. Dig Dis 29: 339-64, 2011.

[4] Uka K, Aikata H, Takaki S, Shirakawa H, Jeong SC, Yamashina K, Hiramatsu A, Kodama H, Takahashi S, Chayama K. Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma. World J Gastroenterol 13: 414-20, 2007.

[5] Uchino K, Tateishi R, Shiina S, Kanda M, Masuzaki R, Kondo Y, Goto T, Omata M, Yoshida H, Koike K. Hepatocellular carcinoma with extrahepatic metastasis: clinical features and prognostic factors. Cancer 117: 4475-83, 2011.

[6] Lee JI, Kim JK, Kim DY, Ahn SH, Park JY, Kim SU, Kim BK, Han KH, Lee KS. Prognosis of hepatocellular carcinoma patients with extrahepatic metastasis and the controllability of intrahepatic lesions. Clin Exp Metastasis 31: 475-82, 2014.

[7] Yoo DJ, Kim KM, Jin YJ, Shim JH, Ko GY, Yoon HK, Sung KB, Lee JL, Kang YK, Lim YS, et al.: Clinical outcome of 251 patients with extrahepatic metastasis at initial diagnosis of hepatocellular carcinoma: does transarterial chemoembolization improve survival in these patients? J Gastroenterol Hepatol 26: 145-54, 2011.

[8] Jung SM, Jang JW, You CR, Yoo SH, Kwon JH, Bae SH, Choi JY, Yoon SK, Chung KW, Kay CS, et al.: Role of intrahepatic tumor control in the prognosis of patients with hepatocellular carcinoma and extrahepatic metastases. J Gastroenterol Hepatol 27: 684-9, 2012.

[9] Mao K, Yan Y, Zhang J, Wang J, Wang R, Ling X, Liu Y, Lau WY, Jiang S, Liu J, et al.: The impact of liver resection on survival outcomes of hepatocellular carcinoma patients with extrahepatic metastases: A propensity score matching study. Cancer Med 7: 4475-4484, 2018.

[10] Benson AB, 3rd, D'Angelica MI, Abbott DE, Abrams TA, Alberts SR, Saenz DA, Are C, Brown DB, Chang DT, Covey AM, et al.: NCCN Guidelines Insights: Hepatobiliary Cancers, Version 1.2017. J Natl Compr Canc Netw 15: 563-573, 2017.

[11] Utsunomiya T, Shimada M, Kudo M, Ichida T, Matsui O, Izumi N, Matsuyama Y, Sakamoto M, Nakashima O, Ku Y, et al.: Nationwide study of 4741 patients with non-B non-C hepatocellular carcinoma with special reference to the therapeutic impact. Ann Surg 259: 336-45, 2014.

[12] Ikeda M, Mitsunaga S, Ohno I, Hashimoto Y, Takahashi H, Watanabe K, Umemoto K, Okusaka T. Systemic Chemotherapy for Advanced Hepatocellular Carcinoma: Past, Present, and Future. Diseases 3: 360-381, 2015.

[13] Kudo M, Trevisani F, Abou-Alfa GK, Rimassa L. Hepatocellular Carcinoma: Therapeutic Guidelines and Medical Treatment. Liver Cancer 6: 16-26, 2016.

[14] Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, Okusaka T, Miyayama S, Tsuchiya K, Ueshima K, et al.: JSH Consensus-Based Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma: 2014 Update by the Liver Cancer Study Group of
Japan. Liver Cancer 3: 458-68, 2014.

[15] EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 56: 908-43, 2012.

[16] Chow PK, Choo SP, Ng DC, Lo RH, Wang ML, Toh HC, Tai DW, Goh BK, Wong JS, Tay KH, et al.: National Cancer Centre Singapore Consensus Guidelines for Hepatocellular Carcinoma. Liver Cancer 5: 97-106, 2016.

[17] Tang ZY. Hepatocellular carcinoma surgery--review of the past and prospects for the 21st century. J Surg Oncol 91: 95-6, 2005.

[18] Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, Sherman M, Schwartz M, Lotze M, Talwalkar J, et al.: Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 100: 698-711, 2008.

[19] Fang JH, Zhou HC, Zhang C, Shang LR, Zhang L, Xu J, Zheng L, Yuan Y, Guo RP, Jia WH, et al.: A novel vascular pattern promotes metastasis of hepatocellular carcinoma in an epithelial-mesenchymal transition-independent manner. Hepatology 62: 452-65, 2015.

[20] Mao B, Wang G. MicroRNAs involved with hepatocellular carcinoma (Review). Oncol Rep 34: 2811-20, 2015.

[21] Bruix J, Fuster J. A Snapshot of the Effective Indications and Results of Surgery for Hepatocellular Carcinoma in Tertiary Referral Centers: Is It Adherent to the EASL/AASLD Recommendations? An Observational Study of the HCC East-West Study Group. Ann Surg 262: e30, 2015.

[22] Zhong JH, Ke Y, Gong WF, Xiang BD, Ma L, Ye XP, Peng T, Xie GS, Li LQ. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. Ann Surg 260: 329-40, 2014.

[23] Liang L, Chen TH, Li C, Xing H, Han J, Wang MD, Zhang H, Lau WY, Wu MC, Shen F, et al.: A systematic review comparing outcomes of surgical resection and non-surgical treatments for patients with hepatocellular carcinoma and portal vein tumor thrombus. HPB (Oxford) 20: 1119-1129, 2018.

[24] Kishi Y, Saiura A, Yamamoto J, Koga R, Seki M, Morimura R, Yoshioka R, Kokudo N, Yamaguchi T. Significance of anatomic resection for early and advanced hepatocellular carcinoma. Langenbecks Arch Surg 397: 85-92, 2012.

[25] Glantzounis GK, Paliouras A, Stylianidi MC, Milionis H, Tzimas P, Roukos D, Pentheroudakis G, Felekouras E. The role of liver resection in the management of intermediate and advanced stage hepatocellular carcinoma. A systematic review. Eur J Surg Oncol 44: 195-208, 2018.

[26] Chok KS, Cheung TT, Chan SC, Poon RT, Fan ST, Lo CM. Surgical outcomes in hepatocellular carcinoma patients with portal vein tumor thrombosis. World J Surg 38: 490-6, 2014.

[27] Wu FX, Chen J, Bai T, Zhu SL, Yang TB, Qi LN, Zou L, Li ZH, Ye JZ, Li LQ. The safety and efficacy of transarterial chemoembolization combined with sorafenib and sorafenib mono-therapy in patients with BCLC stage B/C hepatocellular carcinoma. BMC Cancer 17: 645, 2017.

[28] Xia F, Wu LL, Lau WY, Huan HB, Wen XD, Ma KS, Li XW, Bie P. Adjuvant sorafenib after hepatectomy for Barcelona Clinic Liver Cancer-stage C hepatocellular carcinoma patients. World J Gastroenterol 22: 5384-92, 2016.

[29] Bruix J, Takayama T, Mazzaferro V, Chau GY, Yang J, Kudo M, Cai J, Poon RT, Han KH, Tak WY, et al.: Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol 16: 1344-54, 2015.

Tables
| Variable                  | All patients | Initial cohort | P value |
|---------------------------|--------------|----------------|---------|
|                           | Number (%)   | Surgery alone  | Surgery+Chemotherapy |
|                           | Number (%)   | Number (%)     | Number (%)     |
| Age (years)               |              |                | 0.311               |
| < 60                      | 199(40.6%)   | 136(42.2%)     | 63(37.5%)         |
| ≥ 60                      | 291(59.4%)   | 186(57.8%)     | 105(62.5%)        |
| Race                      |              |                | 0.717               |
| Black                     | 35(7.1%)     | 23(7.2%)       | 12(7.1%)          |
| Other+Unknown             | 73(14.9%)    | 51(15.8%)      | 22(13.1%)         |
| White                     | 382(78.0%)   | 248(77.0%)     | 134(79.8%)        |
| Sex                       |              |                | 0.226               |
| Female                    | 121(24.7%)   | 85(26.4%)      | 36(21.4%)         |
| male                      | 369(75.3%)   | 237(73.6%)     | 132(78.6%)        |
| Year at diagnosis         |              |                | 0.143               |
| 2004-2006                 | 151(30.8%)   | 106(32.9%)     | 45(26.8%)         |
| 2007-2009                 | 253(51.6%)   | 168(52.2%)     | 85(50.6%)         |
| 2010-2011                 | 54(11.0%)    | 29(9.0%)       | 25(14.9%)         |
| 2012-2015                 | 32(6.5%)     | 19(5.9%)       | 13(7.7%)          |
| Marital status            |              |                | 0.68               |
| Married                   | 237(48.4%)   | 160(49.7%)     | 77(45.8%)         |
| Unknown                   | 15(3.1%)     | 9(2.8%)        | 5(3.6%)           |
| Unmarried                 | 238(48.5%)   | 153(47.5%)     | 85(50.6%)         |
| Grade                     |              |                | 0.553               |
| I + II                    | 233(47.6%)   | 150(46.6%)     | 83(49.4%)         |
| III + IV                  | 257(52.4%)   | 172(53.4%)     | 85(50.6%)         |
| Surgery                   |              |                | 0.275               |
| Local destruction         | 287(58.6%)   | 196(60.9%)     | 91(54.2%)         |
| Partial resection         | 125(25.5%)   | 80(24.8%)      | 45(26.8%)         |
| Liver transplantation     | 78(15.9%)    | 46(14.3%)      | 32(19.0%)         |
| Size                      |              |                | 0.431               |
| < 3 cm                    | 48(9.8%)     | 34(10.6%)      | 14(8.3%)          |
| ≥ 3 cm                    | 442(90.2%)   | 288(89.4%)     | 154(91.7%)        |
|          | AFP     | F0      | F1      | Unknown |
|----------|---------|---------|---------|---------|
| Negative | 65(13.3%) | 17(3.5%) | 59(12.0%) | 414(84.5%) |
| Positive | 281(57.3%) | 12(3.7%) | 35(10.9%) | 275(58.1%) |
| Borderline + Unknown | 144(29.4%) | 53.0% | 24(14.3%) | 139(82.7%) |

Grade I well differentiated; II moderately differentiated; III poorly differentiated; IV undifferentiated.

**Table 2** Prognostic factors for CSS and OS in stage Ⅱ hepatocellular carcinoma patients using univariate COX analysis model and multivariate COX analysis model
| Variable               | OS Univariate analysis | OS Multivariate analysis | CSS Univariate analysis | CSS Multivariate analysis |
|------------------------|------------------------|--------------------------|-------------------------|----------------------------|
|                        | HR 95% CI | P value | HR 95% CI | P value | HR 95% CI | P value | HR 95% CI | P value |
| Age (years)            |           |         |           |         |           |         |           |         |
| < 60                   | Reference |         | Reference |         | 0.978     | 0.814-1.176 | 0.941     |         |
| ≥ 60                   | 0.978     | 0.814-1.176 | 1.007 | 0.831-1.221 |         |         |           |         |
| Race                   |           |         |           |         |           |         |           |         |
| Black                  | Reference |         | Reference |         | 1.067     | 1.067-2.420 | 0.07      |         |
| Other+Unknown          | 1.067     | 1.067-2.420 | 0.023 | 1.485 | 0.968-2.279 | 0.019     | 0.609     | 0.102   |
| White                  | 1.146     | 0.806-1.630 | 0.447 | 0.985 | 0.671-1.446 | 0.019 | 0.609 | 0.102 |
| Sex                    |           |         |           |         |           |         |           |         |
| Female                 | Reference |         | Reference |         | 0.97      | 0.787-1.195 | 0.772     |         |
| male                   | 0.97      | 0.787-1.195 |         |         | 0.93 | 0.750-1.154 |         |         |
| Year at diagnosis      |           |         |           |         |           |         |           |         |
| < 0.001                | 0.005     | 0.004   |           |         |           |         |           |         |
| 2004-2006              | Reference |         | Reference |         | 0.906 | 0.737-1.114 | 0.35      |         |
| 2007-2009              | 0.906 | 0.737-1.114 | 0.35 | 0.813 | 0.606-1.089 | 0.164 | 0.923 | 0.743-1.145 | 0.465 | 0.927 | 0.735-1.168 | 0.52 |         |
| 2010-2011              | 0.889 | 0.646-1.224 | 0.471 | 0.817 | 0.531-1.255 | 0.356 | 0.919 | 0.660-1.279 | 0.616 | 0.955 | 0.633-1.441 | 0.827 |         |
| 2012-2015              | 0.248 | 0.164-0.376 | < 0.001 | 0.242 | 0.162-0.663 | < 0.001 | 0.249 | 0.162-0.383 | < 0.001 | 0.396 | 0.240-0.653 | < 0.001 |         |
| Marital status         |           |         |           |         |           |         |           |         |
| Married                | Reference |         | Reference |         | 0.533 |               | 0.364 |         |         |
| Unknown                | 1.291 | 0.762-2.186 | 0.342 |         |         | 1.42 | 0.837-2.409 | 0.194 |         |         |
| Unmarried              | 0.962 | 0.800-1.156 | 0.679 |         |         | 0.969 | 0.800-1.174 | 0.748 |         |         |
| Grade                  |           |         |           |         |           |         |           |         |
| < 0.001                | < 0.001 | 0.011   | < 0.001 | 0.11   | < 0.001 |         |         |         |
| I + II                 | Reference |         | Reference |         | 0.009 |             | < 0.001 |         |         |
| III + IV               | 1.274 | 1.062-1.527 | 1.556 | 1.290-1.878 | 1.276 | 1.056-1.541 | 1.549 | 1.273-1.884 |         |         |
| Surgery                |           |         |           |         |           |         |           |         |
| < 0.001                | < 0.001 | < 0.001 | < 0.001 | < 0.001 |         |         |         |         |
| Local destruction      | Reference |         | Reference |         | 0.35 | 0.269-0.455 | < 0.001 |         |         |
| Partial resection      | 0.35 | 0.269-0.455 | < 0.001 | 0.385 | 0.276-0.536 | < 0.001 | 0.375 | 0.287-0.490 | < 0.001 | 0.449 | 0.327-0.617 | < 0.001 |         |
| Liver transplantation | 0.958 | 0.773-1.187 | 0.696 | 0.987 | 0.754-1.291 | 0.922 | 0.945 | 0.754-1.185 | 0.624 | 0.955 | 0.721-1.263 | 0.745 |
|----------------------|-------|-------------|-------|-------|-------------|-------|-------|-------------|-------|-------|-------------|-------|
| **Size**             | 0.945 |             |       |       |             |       |       |             |       |       |             | 0.981 |
| < 3 cm               |       | Reference   |       |       | Reference   |       |       | Reference   |       |       | Reference   |       |
| ≥ 3 cm               | 0.99  | 0.734-1.334 | 0.996 | 0.729-1.361 |             |       |       |             |       |       |             |       |
| **AFP**              | 0.188 |             |       |       |             |       |       |             |       |       |             | 0.226 |
| Negative             |       | Reference   |       |       | Reference   |       |       | Reference   |       |       | Reference   |       |
| Positive             | 1.297 | 0.974-1.727 | 0.075 |       | 1.282       | 0.952-1.726 | 0.101 |       | 1.301       | 0.944-1.793 | 0.108 |       |
| Borderline + Unknown | 1.296 | 0.951-1.765 | 0.101 |       | 1.301       | 0.944-1.793 | 0.108 |       | 1.301       | 0.944-1.793 | 0.108 |       |
| **Fibrosis Score**   | 0.009 | 0.051       | 0.005 |       | 0.039       |       |       |             |       |       |             |       |
| F0                   |       | Reference   |       |       | Reference   |       |       | Reference   |       |       | Reference   |       |
| F1                   | 1.262 | 0.723-2.204 | 0.413 | 1.325 | 0.752-2.335 | 0.329 | 1.079 | 0.611-1.904 | 0.793 | 1.132 | 0.636-2.013 | 0.674 |
| Unknown              | 1.763 | 1.068-2.910 | 0.027 | 1.672 | 1.006-2.779 | 0.047 | 1.65  | 0.999-2.726 | 0.051 | 1.559 | 0.938-2.591 | 0.087 |
| **Chemotherapy**     |       |             |       |       |             |       |       |             |       |       |             | 0.001 |
| No                   |       | Reference   |       |       | Reference   |       |       | Reference   |       |       | Reference   |       |
| Yes                  | 0.608 | 0.501-0.737 | 0.535 | 0.438-0.653 | 0.617 | 0.505-0.755 | 0.545 | 0.444-0.670 |       |       |             |       |

CSS cancer-specific survival, OS overall survival, HR hazard ratio, CI confidence interval,

Grade I well differentiated; II moderately differentiated; III poorly differentiated; IV undifferentiated.

Figures
Figure 1

The effect of adjuvant chemotherapy in stage II hepatocellular carcinoma patients for overall survival time.

Figure 2

The effect of adjuvant chemotherapy in stage II hepatocellular carcinoma patients for cancer specific survival time.
| Subgroup | No. of patients | Surgery alone(%) | Surgery+Chemotherapy(%) | HR(95%CI) | P value |
|----------|----------------|-----------------|------------------------|-----------|---------|
| Overall  | 490            | 322(65.7)       | 168(34.3)              | +         | 0.56(0.46-0.68) | <0.001 |
| Age (years) |                |                 |                        |           |         |
| < 60     | 199            | 139(42.2)       | 63(37.5)               | +         | 0.41(0.34-0.49) | <0.001 |
| ≥ 60     | 291            | 106(37.8)       | 100(62.2)              | +         | 0.64(0.54-0.75) | <0.001 |
| Race     |                |                 |                        |           |         |
| Black    | 35             | 23(71.4)        | 12(71.4)               | +         | 0.86(0.32-1.36) | 0.264  |
| Other+Unknown | 70       | 51(73.1)        | 23(32.1)               | +         | 0.48(0.29-0.81) | 0.066  |
| White    | 382            | 248(77.0)       | 134(79.8)              | +         | 0.56(0.45-0.72) | <0.001 |
| Sex      |                |                 |                        |           |         |
| Female   | 121            | 85(68.4)        | 36(29.4)               | +         | 0.59(0.39-0.89) | 0.011  |
| Male     | 369            | 23(73.6)        | 132(78.6)              | +         | 0.54(0.43-0.67) | <0.001 |
| Year at diagnosis |      |                 |                        |           |         |
| 2004-2006| 151            | 106(32.9)       | 46(26.8)               | +         | 0.56(0.39-0.81) | 0.002  |
| 2007-2009| 253            | 166(65.2)       | 85(50.6)               | +         | 0.50(0.38-0.65) | <0.001 |
| 2010-2011| 54             | 29(9.0)         | 25(49.0)               | +         | 0.61(0.36-1.06) | 0.081  |
| 2012-2015| 32             | 19(5.9)         | 13(7.7)                | +         | 0.73(0.34-1.60) | 0.405  |
| Marital status |      |                 |                        |           |         |
| Married  | 237            | 160(68.0)       | 77(32.0)               | +         | 0.43(0.32-0.57) | <0.001 |
| Unknown  | 15             | 9(60.0)         | 6(40.0)                | +         | 0.82(0.27-2.48) | 0.731  |
| Unmarried| 238            | 153(64.0)       | 85(50.6)               | +         | 0.77(0.59-1.01) | 0.062  |
| Grade    |                |                 |                        |           |         |
| I + II   | 233            | 159(67.6)       | 83(49.4)               | +         | 0.63(0.48-0.83) | 0.001  |
| III + IV | 257            | 172(67.1)       | 85(50.6)               | +         | 0.51(0.39-0.69) | <0.001 |
| Surgery  |                |                 |                        |           |         |
| Local destruction | 287 | 196(68.0)       | 91(32.0)               | +         | 0.43(0.33-0.56) | <0.001 |
| Partial resection | 125 | 80(64.0)        | 46(36.0)               | +         | 0.56(0.38-0.82) | 0.003  |
| Liver transplantation | 76  | 46(42.1)        | 30(29.4)               | +         | 0.52(0.30-0.88) | 0.001  |
| Size     |                |                 |                        |           |         |
| < 3 cm   | 48             | 34(71.7)        | 14(28.3)               | +         | 0.75(0.44-1.26) | 0.371  |
| ≥ 3cm    | 442            | 288(64.8)       | 154(35.2)              | +         | 0.55(0.45-0.67) | <0.001 |
| AFP      |                |                 |                        |           |         |
| Negative | 65             | 43(66.2)        | 22(33.8)               | +         | 0.59(0.34-1.03) | 0.061  |
| Positive | 281            | 187(66.1)       | 94(33.9)               | +         | 0.53(0.31-0.89) | 0.001  |
| Borderline + Unknown | 144 | 92(63.4)        | 52(36.6)               | +         | 0.64(0.45-0.91) | 0.011  |
| Fibrosis Score |     |                 |                        |           |         |
| F0       | 17             | 12(70.6)        | 5(30.4)                | +         | 0.40(0.11-1.48) | 0.166  |
| F1       | 59             | 35(59.1)        | 24(40.9)               | +         | 0.61(0.35-1.04) | 0.077  |
| Unknown  | 414            | 275(66.5)       | 139(33.5)              | +         | 0.55(0.45-0.68) | <0.001 |

**Figure 3**

Subgroup analysis to identify the effect of adjuvant chemotherapy on overall survival time of stage Ⅱ hepatocellular carcinoma patients.
Figure 4

Subgroup analysis to identify the effect of adjuvant chemotherapy on cancer specific survival time of stage II hepatocellular carcinoma patients.