The Role of Adjuvant Chemotherapy in Stage I Hepatocellular Carcinoma Patients

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Research Article

Keywords: adjuvant chemotherapy (CT), Surveillance, Epidemiology and End Results (SEER) database, High quality prospective trials

Posted Date: June 22nd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-635207/v1>

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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. 52.4 percent were diagnosed with a poorly differentiated or undifferentiated 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 at 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 bulid 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 high 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.

Acknowledgements

The authors thank Dr. Shaoxin Shen , and Dr. Xijing Ma for their technical support.

Conflicts of interest

All authors declare that they have no conflicts of interest.

Funding/Support:

This work was supported by the Department of hepatobiliary surgery, The First Affiliated Longyan Hospital of Fujian Medical University.

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.

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Tables

Table 1 The clinicopathological characteristics of stage II hepatocellular carcinoma patients according to the condition of adjuvant chemotherapy				
Variable	All patients	Initial cohort		P value
	Number (%)	Surgery alone	Surgery+Chemotherapy	
		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				0.858
Negative	65(13.3%)	43(13.4%)	22(13%)	
Positive	281(57.3%)	187(58.1%)	94(56.0%)	
Borderline + Unkonwn	144(29.4%)	92(28.5%)	52(31%)	
Fibrosis Score				0.511
F0	17(3.5%)	12(3.7%)	5(3.0%)	
F1	59(12.0%)	35(10.9%)	24(14.3%)	
Unknown	414(84.5%)	275(85.4%)	139(82.7%)	
Grade I well diferentiated; II moderately diferentiated; III poorly diferentiated; IV undiferentiated.				

Table 2 Prognostic factors for CSS and OS in stage I hepatocellular carcinoma patients using univariate COX analysis model and multivariate COX analysis model

Variable	OS						CSS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age (years)			0.816						0.941			
< 60	Reference						Reference					
≥ 60	0.978	0.814-1.176					1.007	0.831-1.221				
Race			0.019			0.609			0.102			
Black	Reference			Reference			Reference					
Other+Unknown	1.067	1.067-2.420	0.023	0.833	0.543-1.298	0.419	1.485	0.968-2.279	0.07			
White	1.146	0.806-1.630	0.447	0.985	0.671-1.446	0.939	1.137	0.791-1.634	0.489			
Sex			0.772						0.509			
Female	Reference						Reference					
male	0.97	0.787-1.195					0.93	0.750-1.154				
Year at diagnosis			< 0.001			0.005			< 0.001			0.004
2004-2006	Reference			Reference			Reference			Reference		
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	0.4	0.242-0.663	< 0.001	0.249	0.162-0.383	< 0.001	0.396	0.240-0.653	< 0.001
Marital status			0.533						0.364			
Married	Reference						Reference					
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			0.009			< 0.001			0.011			< 0.001
I + II	Reference			Reference			Reference			Reference		
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
Local destruction	Reference			Reference			Reference			Reference		
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						
≥ 3 cm	0.99	0.734-1.334					0.996	0.729-1.361				
AFP			0.188						0.226			
Negative	Reference					Reference						
Positive	1.297	0.974-1.727	0.075				1.282	0.952-1.726	0.101			
Borderline + Unkonwn	1.296	0.951-1.765	0.101				1.301	0.944-1.793	0.108			
Fibrosis Score			0.009			0.051			0.005	0.039		
F0	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			< 0.001			< 0.001	< 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 diferentiated; II moderately diferentiated; III poorly diferentiated; IV undiferentiated.

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.

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 $\geq$ hepatocellular carcinoma patients.