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Research Article

Impact of Gender on the Prognosis of Patients with Hepatocellular Carcinoma After Palliative Therapy

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Abstract

Objectives: Sex differences are ascribed to the risk of hepatocellular carcinoma (HCC); however, whether gender disparity also exists in the prognosis of palliative therapy is yet unclear. A retrospective cohort study was performed to assess the prognostic predictors after palliative therapy of HCC, focusing on sex differences.

Methods: This retrospective cohort study consisted of 2356 patients (270 women and 2086 men) with a diagnosis of HCC between 2006 and 2011. The patients received palliative care. Clinical and laboratory data were evaluated and compared.

Results: Overall, the two groups did not have significant sex-related differences in prognosis for overall survival (OS) of palliative care, including transarterial chemoembolization (TACE), chemotherapy, and best supportive care (BSC). Using multivariate analysis, the following were identified as independent risk factors of survival ($P<0.05$): smoking, liver cirrhosis, vascular invasions, tumor size, absolute value of neutrophils, and glutamyltransferase. Transarterial chemoembolization was regarded as protective factor of OS.

Conclusion: No significant differences were observed in the prognosis of male or female HCC patients after palliative care. The gender factor was not an independent predictor for OS.

Keywords: Gender, hepatocellular carcinoma, palliative care, prognosis, overall survival

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Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the fourth most common cause of cancer-related deaths.[1] Various predisposing risk factors, such as hepatitis B virus (HBV) or hepatitis C virus (HCV), alcohol abuse, aflatoxin-contaminated foodstuffs, non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, and long-term use of oral contraceptives and high-dose anabolic steroids can lead to the development of HCC.[2-4]

Gender disparity in HCC risk is well-known; male gender has a greater risk of developing HCC than females in all geographical regions.[1, 5] There are several reasons for male predominance in HCC. In estimation, hepatitis carrier states (hepatitis B virus or HCV infection in men), alcohol abuse, and smoking in men are suggested to be the causative factors[6, 7] of HCC. Additionally, some studies have suggested that a stimulatory effect of androgen and a protective ef-

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fect of estrogen for HCC might cause the sex disparity in HCC.[8-11]

Although sex differences in HCC risk are well-known, it is unclear whether sex differences exist in the prognosis of palliative care, such as TACE, chemotherapy, targeted drug therapy, and best supportive care (BSC). Therefore, we performed a retrospective cohort study to assess the prognostic predictors of HCC undergoing palliative treatment focusing on sex-based differences.

Methods

Patients

Patients who had received palliative care at Guangxi Medical University Cancer Hospital between 2006 and 2011 were considered for enrollment in this retrospective study. HCC diagnosis was confirmed by two types of clinical imaging (computed tomography (CT), or magnetic resonance imaging (MRI)), with or without a serum level of alpha-fetoprotein (AFP) >400 ng/mL. If diagnosis based on imaging and AFP level was uncertain, needle biopsy was performed. This study was approved by the Ethics Committee of Guangxi Medical University Cancer Hospital. It conformed to the ethical guidelines of the Declaration of Helsinki. Informed written consent was exempt because this was a retrospective study.

Data Collection

The following data were extracted from medical records: age, sex, HCC family history, HBsAg, anti-HCV antibody, treatment modality, AFP, hypertension, tumor number and size, liver cirrhosis, macrovascular invasion, and diabetes mellitus. The tumor stage was determined according to the Barcelona Clinic Liver Cancer (BCLC) system. The following indicators were also collected and used to assess liver function: platelet (PLT), white blood cell count, absolute value of neutrophils, lymphocyte, and monocytes, prothrombin time (PT), levels of albumin, prealbumin, alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin, and direct bilirubin (Dbil). The endpoint of the study was overall survival (OS), which was defined as the duration from the date of palliative therapy until death.

Treatment and Follow-up

The follow-up data for all patients were obtained from the hospital database. The follow-up time was calculated as the time from the start of palliative therapy to January 2019 or death. Because targeted drug therapy was available untill 2010 in our hosptial, few patients in our hospital received such therapy before 2011. The palliative treatment for HCC was divided into three categories in this study: (i) TACE; (ii) chemotherapy; (iii) BSC.

Statistical Analysis

Continuous data were expressed as median and interquartile range and categorical data as frequency or percentage. Differences between continuous data were analyzed using the Mann–Whitney U test. The categorical variables were compared using the $\chi 2$ test. OS curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate logistic regression analyses were used to determine independent risk factors for OS. Statistical analyses were performed using SPSS software version 23.0 (IBM, Chicago, IL, USA). $P<0.05$ was considered statistically significant.

Results

Baseline Clinicopathological Features

A total of 2356 patients with HCC who underwent palliative therapy were enrolled in this study. Among these patients, 270 were female and 2086 were male. Baseline demographic and clinical laboratory data were listed in Table 1. The female were older than male ($p<0.001$). The alcohol consumption ($p<0.001$) and cigarette consumption ($p<0.001$) were higher frequency in male than female patients. Compared to the female HCC patients, male patients showed significantly higher rates of hepatitis B infection ($p<0.001$), as well as an elevated macrovascular invasion ($p=0.02$). The liver function indices, such as total bilirubin, albumin, prealbumin, ALT, platelet, AST, alkaline phosphatase, and glutamyltransferase were significantly better in female than male patients ($p<0.05$), while albumin and prealbumin showed an opposite effect ($p<0.05$). In addition, male patients were more likely to have larger tumor size ($p=0.036$), longer PT (13.5s vs. 13.1s, $p<0.001$), higher absolute value of monocytes, lymphocyte, and neutrophils ($p<0.05$), higher count of white blood cell ($p<0.001$), urea ($p<0.001$), and creatinine ($p<0.001$) than the female patients. No significant differences were observed between the two groups in terms of other clinical and laboratory data.

Gender Differences in OS After Palliative Therapy

Based on total population, we observed no significant differences in OS between male and female HCC patients ($p=0.982$, Fig. 1a). The survival analysis between male and female patients who accepted only treatment modality of TACE did not detect any significant differences between the two groups ($p=0.197$, Fig. 1b). Similar results were obtained

Table 1. Sex differences in demographic and clinical parameters in HCC patients undergoing palliative therapy

Variables	Male (n=2086)	Female (n=270)	P
Age (years)	48 (40–57)	51 (41–60)	0.001
HCC family history	204 (9.8)	28 (10.4)	0.828
Smoking	638 (30.6)	0 (0)	<0.001
Drinking	595 (28.5)	0 (0)	<0.001
Liver cirrhosis	63 (3.0)	7 (2.6)	0.715
Macrovascular invasion	1094 (52.4)	121 (44.8)	0.020
Tumor number ≥3	859 (41.2)	100 (37.0)	0.211
Tumor size (cm)	10 (6–13)	9.5 (5.2–12.5)	0.036
Absolute value of monocytes	0.52 (0.39–0.73)	0.42 (0.30–0.59)	<0.001
Absolute value of lymphocyte	1.48 (1.12–1.90)	1.40 (1.02–1.86)	0.035
Absolute value of neutrophils	4.50 (3.30–6.24)	4.16 (2.93–5.54)	0.002
White blood cell	6.97 (5.43–8.90)	6.25 (4.87–7.90)	<0.001
PLT	188.34 (135.0–259.00)	213.50 (131.50–282.75)	0.050
PT	13.5 (12.4–14.9)	13.10 (12.08–14.20)	<0.001
Total bilirubin	17.8 (12.0–29.1)	13.90 (9.23–22.60)	<0.001
Albumin	37.8 (33.7–42.0)	36.80 (32.82–40.80)	0.034
Prealbumin	129.0 (86.0–177.25)	111.00 (72.00–166.25)	0.001
ALT (U/L)	50 (34–77)	37 (24–56)	<0.001
AST (U/L)	79 (51–135)	68 (40–127.5)	0.003
Alkaline phosphatase	131 (91–196)	116 (78–169.75)	<0.001
Glutamyltransferase	186 (106–322)	104 (49–222)	<0.001
Cholinesterase	5140 (3600–6588)	5421 (3646–7239)	0.087
Urea	4.81 (4.00–5.90)	3.9 (3.18–4.9)	<0.001
Creatinine	78 (68–89)	61 (51–70)	<0.001
Ascites	566 (27.1)	66 (24.4)	0.381
Portal hypertension	292 (14.0)	29 (10.7)	0.157
AFP (≥200 ng/mL)	1268 (60.8)	158 (58.5)	0.508
HBsAg (+)	1813 (86.9)	207 (76.7)	<0.001
Treatment modality			0.807
TACE	1326 (63.6)	168 (62.2)	
Chemotherapy	355 (17.0)	45 (16.7)	
Best supportive care	405 (19.4)	57 (21.1)	
BCLC stage			0.782
A	461 (22.1)	61 (22.6)	
B	279 (13.4)	37 (13.7)	
C	1320 (63.3)	167 (61.9)	
D	26 (1.2)	5 (1.9)	

TACE: transarterial chemoembolization; HCC: hepatocellular carcinoma; HBsAg: hepatitis B antigen; PLT: platelet; PT: prothrombin time; ALT: glutamic-pyruvic transaminase; AST: glutamic oxaloacetic transaminase; AFP: alpha-fetoprotein; BCLC: Barcelona clinic liver cancer.

for the treatment modality of chemotherapy (p=0.281, Fig. 1c) and BSC (p=0.205, Fig. 1d).

Predictors of OS

Univariate analysis showed that the following potential risk factors were associated with poor prognosis or death: treatment modality of TACE, HCC family history, smoking, liver cirrhosis, vascular invasion, tumor size, absolute value of neutrophils, glutamyltransferase, ascites, and AFP≥200 ng/mL (Table 2).

Multivariate analysis identified the following independent risk factors that were associated with OS: smoking, liver cirrhosis, vascular invasion, tumor size, absolute value of neutrophils, and glutamyltransferase. Transarterial chemoembolization was regarded as protective factor of OS.

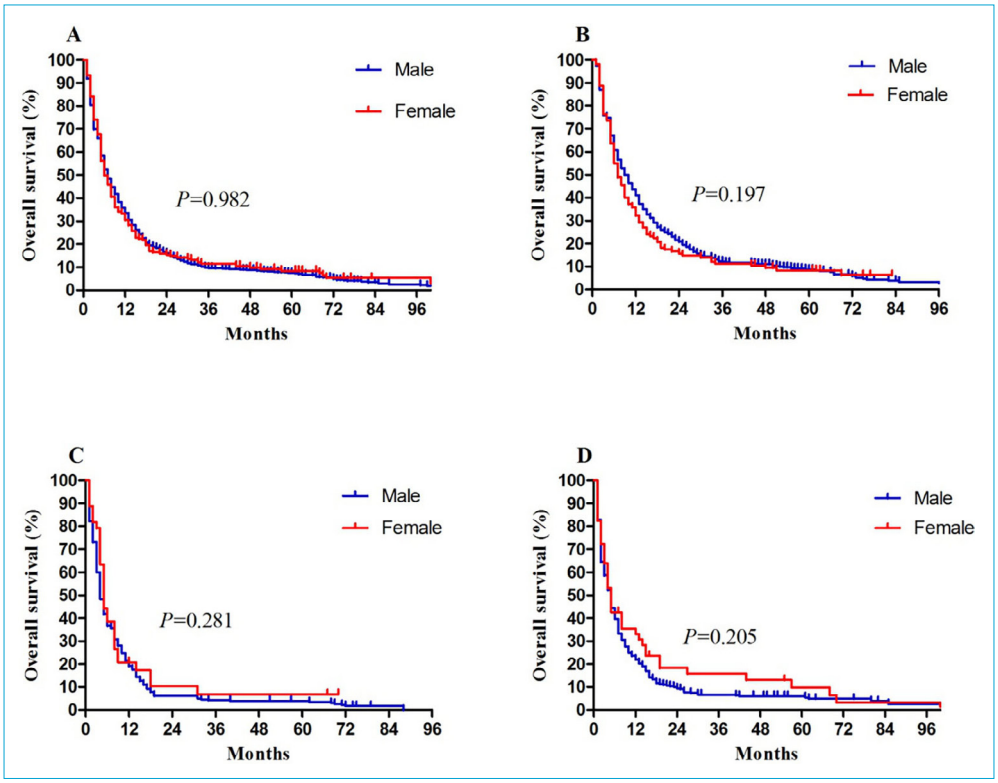

Figure 1. The OS rates of HCC patients after palliative therapy. **(a)** The treatment modality including all the three palliative therapies (TACE, chemotherapy, and BSC); **(b)** The treatment modality of TACE; **(c)** The treatment modality of chemotherapy; **(d)** The treatment modality of BSC.

Discussion

Sex disparity is a risk factor for HCC, and males pose a greater risk than females.[18] However, whether there are sex differences in the prognosis after treatments are yet to be elucidated. Herein, we conducted a retrospective study to analyze the effect of gender factor on the prognosis after palliative therapy. The current results showed that there was no significant difference in the OS between male and female HCC patients. Although previous studies have proposed that male gender shows poor OS, some reported a different conclusion.[19-21] In this study, gender was not analyzed to be an independent prognostic factor of OS in either univariate or multivariate analysis. However, there are some significant differences in the research between men and women patients.

According to the baseline clinicopathological features, male patients had more severe liver damage such as larger tumors, more macrovascular invasion, and worse liver function indices than females. The etiologic spectrum was the same as reported previously.[2, 9] Large tumors, more macrovascular invasion, and worse liver function are the clinicopathological features that indicate aggressive tumor behavior and poor liver reserves; these would affect the prognosis of patients with HCC after palliative therapy.

More than 80% male patients and 70% female patients in this study were chronically infected with HBV. This reflected the high incidence among HCC patients in Asia; however, it is not true in Western countries.[22, 23] The infection has been shown to be a risk factor for recurrence and death in HCC patients.[24] However, it has not been indicated as the potential risk factor with poor prognosis or death in both univariate and multivariate analyses in the current study. Some studies reflected that estrogen and its receptors exert protective effects and disrupt the androgen receptors.[25] These findings have not been substantiated in the current study.

Nevertheless, the present study has some limitations. First, this was a retrospective cohort study, and hence, we considered that sex hormones might be crucial for the outcome of HCC patients.[9] However, because of the retrospective design, we could not collect blood samples to analyze sex hormones. Second, the data was from a single center. Third, the number of female patients included in this study was small. Female patients accounted for only 1/9th of the cohort population, and therefore, we could not perform a propensity score matching analysis. Fourth, some patients received other treatments such as resection or radiofrequency ablation after diagnosis, leading to the speculation that other treatments would impact the results.

Table 2. Univariate and multivariate analysis of overall survival rates in HCC patients after palliative therapy

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Male sex	1.002 (0.868–1.156)	0.982	0.880 (0.755–1.025)	0.1
Treatment modality				
TACE	0.641 (0.571–0.721)	<0.001	0.645 (0.570–0.730)	<0.001
Chemotherapy	1.095 (0.947–1.267)	0.222	1.153 (0.990–1.342)	0.066
Best supportive care	-	-		
Age (years)	0.999 (0.995–1.003)	0.526		
HCC family history	1.171 (1.008–1.361)	0.039	1.123 (0.961–1.311)	0.144
BCLC stage	0.974 (0.922–1.028)	0.335		
Smoking	0.882 (0.796–0.978)	0.017	0.855 (0.767–0.954)	0.005
Drinking	0.944 (0.851–1.048)	0.280		
Liver cirrhosis	2.589 (1.950–3.436)	<0.001	2.519 (1.859–3.413)	<0.001
Vascular invasion	1.172 (1.070–1.285)	0.001	1.124 (1.015–1.246)	0.025
Tumor number >3	1.039 (0.946–1.140)	0.425		
Tumor size (cm)	1.017 (1.006–1.027)	0.002	1.014 (1.003–1.026)	0.013
Absolute value of monocytes	1.004 (0.966–1.044)	0.834		
Absolute value of lymphocyte	1.000 (0.998–1.002)	0.956		
Absolute value of neutrophils	1.006 (1.000–1.011)	0.032	1.005 (1.000-1.010)	0.039
HBsAg-positive	1.049 (0.922–1.194)	0.467		
Platelets ($\times 10^9$)	1.000 (1.000–1.000)	0.817		
PT (s)	1.000 (0.997–1.003)	0.992		
Albumin (g/L)	1.001 (1.000–1.002)	0.203		
Prealbumin (mg/L)	1.000 (0.999-1.000)	0.168		
ALT (U/L)	1.000 (1.000-1.001)	0.457		
AST (U/L)	1.000 (1.000-1.001)	0.184		
Alkaline phosphatase	1.000 (1.000-1.001)	0.082		
Glutamyltransferase	1.000 (1.000-1.000)	0.044	1.000 (0.999-1.000)	0.001
Cholinesterase	1.000 (1.000-1.000)	0.124		
Urea	1.001 (0.999–1.003)	0.283		
Creatinine	1.000 (0.999–1.002)	0.6087		
Ascites	1.155 (1.043–1.279)	0.006	1.064 (0.953–1.188)	0.271
AFP≥200 ng/mL	1.120 (1.020–1.230)	0.018	1.090 (0.986–1.205)	0.093
TB (μmol/L)	1.001 (1.000-1.001)	0.201		
Portal hypertension	1.128 (0.989–1.285)	0.072		

HR, baihazard ratio ; CI, confidence interval ; TACE, transarterial chemoembolization; HCC, hepatocellular carcinoma; PT, prothrombin time; ALT, glutamic-pyruvic transaminase; AST, glutamic oxaloacetic transaminase; AFP, alpha-fetoprotein; TB, total bilirubin; BCLC, Barcelona clinic liver cancer.

Conclusion

In the current study, the gender factor was not an independent predictor for OS. However, the treatment modality of TACE, smoking, liver cirrhosis, vascular invasion, tumor size, the absolute value of neutrophils, and glutamyltransferase were significant independent predictors of survival. Furthermore, multi-center studies should be performed to confirm the factors contributing to such disparities.

Disclosures

Ethics Committee Approval: the institutional review board of Guangxi Medical University Cancer Hospital (number LW2020085) (23 December, 2020).

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