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 death. 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. Gender disparity in HCC risk is well-known; male gender has a greater risk of developing HCC than females in all geographical regions. 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 of HCC. Additionally, some studies have suggested that a stimulatory effect of androgen and a protective ef-
Effect 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, ALT, 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...
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.
Sex disparity is a risk factor for HCC, and males pose a greater risk than females. 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. 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. 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. The infection has been shown to be a risk factor for recurrence and death in HCC patients. 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. 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. 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.

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.
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.

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 (x10^9)         | 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, hazard 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.

Disclosures

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

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