

RESEARCH ARTICLE

Health-Related Quality of Life of Patients with Intermediate Hepatocellular Carcinoma after Liver Resection or Transcatheter Arterial Chemoembolization

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Abstract

Background: The aim of our present study was to compare quality of life (QoL) between intermediate-stage (BCLC-B) HCC patients who had undergone either liver resection or transcatheter arterial chemoembolization (TACE). **Materials and Methods:** A total of 102 intermediate-stage HCC patients participated in our study, including 58 who had undergone liver resection and 44 who had undergone TACE. Baseline demographic characteristics, tumor characteristics, and long-term outcomes, such as tumor recurrence, were compared and analyzed. QoL was assessed using the Short Form (SF)-36 health survey questionnaire with the mental and physical component scales (SF-36 MCS and PCS). This questionnaire was filled out at HCC diagnosis and 1, 3, 6, 12, 24 months after surgery. **Results:** For the preoperative QoL evaluation, the 8 domains related to QoL were comparable between the two groups. The PCS and MCS scores were significantly decreased in both the TACE and resection groups at 1 month after surgery, and this decrease was greater in the resection group. These scores were significantly lower in the resection group compared with the TACE group ($P < 0.05$). However, these differences disappeared at 3 and 6 months following surgery. One year after surgery, the resection group showed much higher PCS scores than the TACE patients ($P = 0.018$), and at 2 years after surgery, the PCS and MCS scores for the resection group were significantly higher than those for the TACE group ($P < 0.05$). Eleven patients (19.0%) in the resection group and 17 (38.6%) in the TACE group suffered HCC recurrence ($P < 0.05$). Univariate and multivariate analyses indicated that tumor recurrence (HR=1.211, 95% CI: 1.086-1.415, $P = 0.012$) was a significant risk factor for poor postoperative QoL in the HCC patients. **Conclusions:** Due to its effects on reducing HCC recurrence and improving long-term QoL, liver resection should be the first choice for the treatment of patients with intermediate-stage HCC.

Keywords: Hepatocellular carcinoma - quality of life - liver resection - transcatheter arterial chemoembolization

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most frequent cause of mortality in cancer patients (Jemal et al., 2011). Moreover, the burden of HCC is greater in China due to the high prevalence of hepatitis B virus (HBV) infection in this country (Maluccio et al., 2012). Radiofrequency ablation (RFA), liver resection, and liver transplantation represent the mainstay of radical therapy for early stage HCCs, and transcatheter arterial chemoembolization (TACE) is considered an alternative treatment for unresectable HCC (Bruix et al., 2014; Zuo et al., 2015). According to the Barcelona Clinic Liver Cancer (BCLC) HCC staging system, TACE should be considered for patients with BCLC-B (intermediate-stage) HCC, and hepatic resection is only recommended for patients with early-stage HCC and satisfactory liver function (BCLC-A) (Bruix et al., 2011; Xu et al., 2014). BCLC-B stage includes Child A and B patients with multifocal HCC, which is defined

as >3 tumors of any size or 2-3 tumors with a maximal diameter of >3 cm and the absence of vascular invasion or extrahepatic spread (Marrero et al., 2005). However, many studies have indicated that patients with intermediate-stage HCC may also benefit from radical hepatic resection with comparable long-term outcomes (Jiayong et al., 2014; Zhong et al., 2014). Therefore, controversy still exists regarding the choice of treatment for intermediate-stage HCC. However, although there have been many reports on long-term survival and tumor recurrence for patients receiving these therapies, no comparisons of their quality of life (QoL) have been performed.

In recent years, QoL has been proven to be a valuable parameter and is considered to be as important as overall survival and tumor-free survival for cancer patients (Slevin et al., 1992; Han et al., 2014). In fact, the multimodal concept of QoL has been used in many medical practices (Langenhoff et al., 2001; Scurtu et al., 2005). Moreover, QoL has become an important consideration when selecting an optimal treatment. Some studies have

evaluated the effects of treatment modalities on health-related QoL in HCC patients (Yeo et al., 2006; Fan et al., 2010; Diouf et al., 2013; Gandhi et al., 2014; Diouf et al., 2015). In addition, some researchers have discussed the impact of liver resection on postoperative QoL (Bruns et al., 2010; Mise et al., 2014), and others have studied QoL after TACE (Wang et al., 2007; Xing et al., 2015). Moreover, another report has compared the QoL outcomes for RFA, liver resection and TACE (Toro et al., 2012) and has found that hepatic resection provides the best QoL at 24 months compared with TACE or RFA. However, in this previous study, HCC was not graded according to tumor characteristics, such as tumor number, size, and liver function.

Therefore, in our present study, a retrospective QoL assessment was conducted to evaluate intermediate-stage HCC patients who had undergone liver resection or TACE as an initial treatment. The aim of this study was to assess the impacts of surgical protocols on postoperative QoL in patients with BCLC stage B HCC.

Materials and Methods

Patients who were diagnosed with HCC from Jan 2009 to Feb 2013 at the department of liver surgery, West China Hospital of Sichuan University were included in our present study. All of these patients had undergone liver resection or TACE as an initial therapy for HCC. The inclusion criteria were as follows: between 18 and 60 years of age at the time of HCC diagnosis; BCLC stage B HCC; Child A or B liver function; multifocal HCC, defined as >3 tumors of any size or 2-3 tumors with a maximal diameter of >3 cm; the absence of vascular invasion or extrahepatic spread; having undergone liver resection or TACE as an initial therapy; and no contraindication for surgery. The exclusion criteria were as follows: Child C liver function; BCLC stage A or C HCC; having undergone other procedures, such as liver transplantation or RFA; loss to follow-up; and inability to complete the questionnaire due to illiteracy. The present study conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committee of our hospital. All of the patients provided informed consent.

Based on the inclusion and exclusion criteria, 102 HCC patients were included in this study. Moreover, we divided the patients into two groups based on the initial therapy, the liver resection group (58 patients) and the TACE group (44 patients). All of these patients completed the Medical Outcomes Study Short Form-36 (SF-36) questionnaire pre-operatively and at 1, 3, 6, 12, and 24 months after surgery. We then compared the baseline demographics of these patients, such as age, gender, body mass index (BMI), underlying disease, liver function (Child score), liver cirrhosis, and tumor characteristics (i.e., tumor diameter, tumor number, alpha-fetoprotein (AFP) level, and tumor differentiation). We also compared the mental and physical component scores of the questionnaires completed at the above time points.

Health-related QoL was assessed using the validated Chinese version (2002) of the SF-36 (Li et al., 2002; Jin et al., 2010). The SF-36 is a validated, self-administered

questionnaire that is used internationally to measure the following 8 domains of health: general health, bodily pain, social functioning, role-physical, physical functioning, vitality, role-emotional, and mental health. The raw scores of each questionnaire were converted to scores ranging from 0 to 100, with higher scores indicating higher levels of functioning or well-being (Jin et al., 2010). QoL was compared between the two groups at the different time points. Scores representing overall physical and mental functioning were presented as physical component summary scale (PCS) and mental component summary scale (MCS) scores (Jin et al., 2010). The PCS, which is primarily based on the physical functioning, role-physical, bodily pain, and general health components, reflects a patient's overall physical health status. The MCS is based primarily on the vitality, social functioning, role-emotional, and mental health components and reflects a patient's overall mental health status.

All of the hepatic resection and TACE procedures have been described in our previous studies (Jiang et al., 2014; Zhang et al., 2014). All of these procedures were conducted by surgeons with over 20 years of hepatic resection and TACE experience. The efficacy of surgery was evaluated at 1 month by contrast-enhanced CT or MRI and according to the levels of tumor markers (AFP). Thereafter, efficacy was measured every 2 to 3 months over the following year and every 5-6 months from that point forward to check for recurrence. Chest radiography and bone scintigraphy were performed when extrahepatic HCC recurrence was suspected. Liver function was another key post-operative factor that was assessed.

Statistical analysis

Data were obtained by surgeons and nurses and analyzed by a biostatistics expert. All of the data were collected and analyzed using the SPSS statistical software package (SPSS Inc., Chicago, USA; version 17.0). Descriptive statistics were calculated to provide information regarding demographic and disease-specific characteristics. Comparisons between the two groups with respect to QoL were performed using independent-sample Student's t-test, analysis of variance, or a non-parametric test, if necessary. A *P* value of <0.05 was considered significant and that of <0.001 was considered highly significant.

Results

Patients' baseline and tumor characteristics

As shown in Table 1, the baseline demographic characteristics were compared between the two groups. No significant differences were observed between the resection and TACE groups in terms of age, gender, or BMI. HCC was caused by HBV infection in most patients (89.7% in the resection group and 90.9% in the TACE group, *P*=0.582). We also compared the patients' marital statuses, educational backgrounds, occupations and incomes because these factors may affect QoL after surgery and found no significant differences in these factors between the two groups. Although the liver resection group was found to have a lower monthly

Table 1. Baseline Characteristics of the Patients, Tumors and Recovery for the Two Groups

Patients' Baseline Characteristics	Resection group n=58	TACE group n=44	P value
Age	46.9±8.3	44.0±10.6	0.123
Gender (M:F)	48/10	38/6	0.622
BMI (kg/m ²)	23.0±2.2	23.1±2.2	0.766
Liver cirrhosis (HBV/HCV/no)	52/2/4	40/2/2	0.582
Marital status (yes/no/divorced)	53/2/3	41/2/1	0.975
Education (elementary/middle/university)	15/29/14	10/21/13	0.55
Occupation (Farmer/worker/servant/other)	14/21/13/10	9/21/9/5	0.67
Income (low/median/high)	21/28/9	7/29/8	0.069
Tumor characteristics			
Tumor target number	2.3±1.4	2.1±1.2	0.506
Tumor diameter per patient	7.6±1.8	7.7±2.3	0.665
AFP level	730.4±512.9	1688.3±5216.5	0.167
Postoperative recovery			
Complications (0/I/II/III/IV)	36/11/9/2/0	27/6/11/0/0	0.843
Hospital stay days	8.2±2.3	5.1±1.0	<0.001
New targets (recurrence or metastasis, yes/no)	11/47	17/27	0.028

*Income (dollars/month), low: ≤500; median: 500-800; high: ≥800

Table 2. Tumor Recurrence According To follow-Up Time

Groups	0-1 months	1-3 months	3-6 months	6-12 months	12-24 months
Liver resection (n=58)	0	1 (1.7%)	1 (1.7%)	4 (6.9%)	5 (8.6%)
TACE (n=44)	0	1 (2.3%)	3 (6.8%)	6 (13.6%)	7 (15.9%)
Overall	0	2 (2.0%)	4 (3.9%)	10 (9.8%)	12 (11.8%)

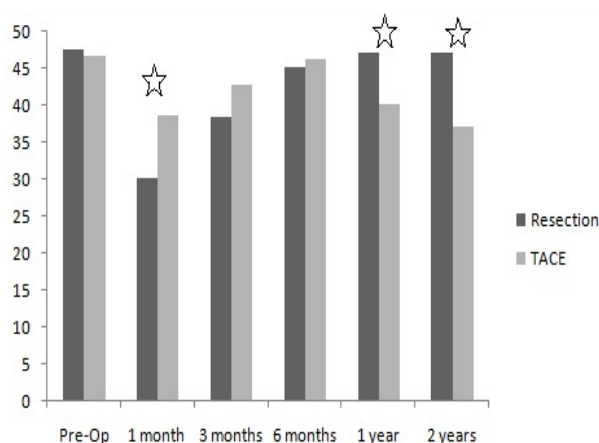


Figure 1. The PCS Scores were Comparable between the two Groups at Baseline. These scores were significantly decreased in both the TACE and resection groups at 1 month after surgery and were significantly lower in the resection group compared with the TACE group ($P<0.05$). However, opposite results were observed between the two groups at 1 and 2 years after surgery (indicated by the stars, $P<0.05$)

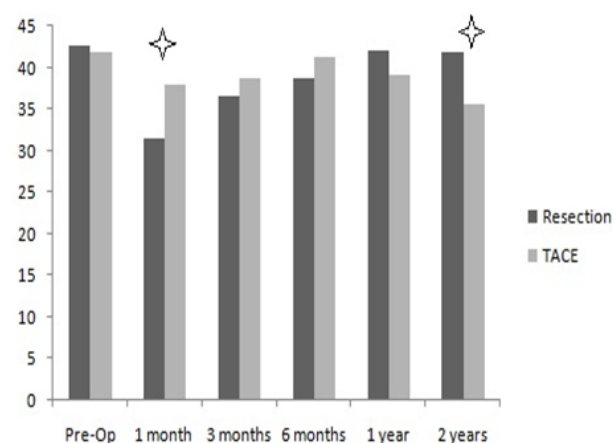


Figure 2. The MCS Score for the Resection Group was Also Significantly Lower than that for the TACE Group ($P<0.05$), but the Resection Group Showed a Much Higher Score Compared with the TACE Group at 2 Years after Surgery (Indicated by the Stars, $P<0.05$)

income, this difference was not significant ($P=0.069$).

Tumor characteristics, such as tumor number and diameter and the AFP level, between the two groups were also comparable. Moreover, when we compared postoperative recovery, we found most of the patients suffered no postoperative complications (62.1% in the resection group and 61.4% in the TACE group). Due to the more rapid recovery in TACE group, the duration of hospital stay (in days) for the TACE group was significantly shorter than that for the resection group (5.1 days vs. 8.2 days, $P<0.001$). However, more patients

suffered HCC recurrence or metastasis in the TACE group (38.6% in the TACE group vs. 19.0% in the resection group, $P=0.028$).

Health-related quality of life (HRQoL)

The results of the preoperative QoL evaluation showed that the 8 domains related to QoL were all comparable between the two groups, including physical functioning ($P=0.879$), role-physical ($P=0.632$), bodily pain ($P=0.651$), general health ($P=0.766$), vitality ($P=0.452$), social functioning ($P=0.238$), role-emotional

($P=0.108$), and mental health ($P=0.893$). In addition, the PCS and MCS scores were comparable between the two groups at baseline (as shown in Figures 1 and 2, $P>0.05$).

The PCS and MCS scores were significantly decreased in both the TACE and resection groups at 1 month after surgery. However, the decreases in both the PCS and MCS scores were greater in the resection group, and these scores were significantly lower than those in the TACE group ($P<0.05$). However, these significant differences were not present with the 3- and 6-month post-operative questionnaires.

For the 1-year survey, the resection group showed a much higher PCS score than the TACE group ($P=0.018$); however, the MCS scores of the two groups were not significantly different ($P=0.216$). Further, the PCS and MCS scores on the 2-year questionnaire for the resection group were all significantly higher than those for the TACE group (as shown in Figures 1 and 2, $P<0.05$).

Tumor recurrence

At the 2-year follow-up, 11 patients (19.0%) in the resection group and 17 (38.6%) in the TACE group suffered HCC recurrence in the liver or metastasis in non-liver organs. As shown in Table 2, the tumor recurrence rates were comparable between the resection and TACE groups at 0-1 month and 1-3 months post-operation. However, the recurrence rates were significantly higher in the TACE group than in the resection group at 3-6 months, 6-12 months, and 12-24 months after surgery.

Univariate and multivariate analyses

Additional analyses were performed to determine the risk factors for poor QoL. The analyzed factors, which included those that are linked to QoL, were as follows: patient age, gender, BMI, cause of liver disease, Child score, initial therapy (resection or TACE), marital status, education, occupation, income, tumor number, tumor diameter, AFP level, complications, hospital stay duration in days, and recurrence. Univariate analysis identified the following factors to be predictive of poor postoperative QoL: lower education, poor income, and tumor recurrence. Multivariate Cox regression analysis was performed to assess the significant factors identified in univariate analysis and showed that tumor recurrence ($HR=1.211$, 95%CI: 1.086-1.415, $P=0.012$) was a significant risk factor for poor postoperative QoL among the HCC patients.

Discussion

HCC is one of the most common cancers worldwide, especially in Asian countries, due to the high prevalence of HBV and hepatitis C virus (HCV) infection. Liver resection is the most common therapy for HCC because of the shortage of liver donors, especially for early stage tumors. TACE is the most common palliative treatment for HCC. However, the choice of treatment for this disease depends not only on tumor characteristics, such as the number of tumors and their diameters, but also on liver function, which is a very important consideration in this regard (Toro et al., 2012). However, with respect

to intermediate-stage HCC (BCLC-B), there is still controversy regarding which of these two methods provides better long-term overall survival, tumor-free survival, and tumor recurrence (Bruix et al., 2014; Zhong et al., 2014; Jianyong et al., 2015). With advances in therapies used to treat HCC, such as liver transplantation and sorafenib (Berk et al., 2013; Mancuso et al., 2015), QoL is considered to be as important as overall survival and tumor-free survival for these patients (Schipper et al., 1984); i.e., there is now a focus on not only achieving long-term survival but also patients' lives' in relation to their disease and treatment (Toro A et al., 2012). Moreover, a linear relationship was found between overall HRQoL and survival; specifically, patients reporting the highest level of overall HRQoL were found to have the longest survival time, followed by those reporting levels in the middle and lowest tertiles (Steel et al., 2014).

We found that both the PCS and MCS scores significantly decreased at 1 month after resection or TACE; however, this decrease was greater in the resection group. The TACE group may have experienced a higher QoL over the short term (less than 1 month) given that higher PCS and MCS scores were reported at the 1-month post-operative evaluation in this group compared with the liver resection group. The main reason for this finding was that trauma was caused by open-access liver resection, which led to a reduction in liver parenchyma and subsequently, to impaired liver function. Many of the resection patients' 1 month QoL scores may have been affected by pain, impaired wound healing and subjectively perceived deficiencies in their daily routines following liver resection (Bruns et al., 2010). Poon's study has revealed that the QoL after resection for HCC may increase more rapidly for patients who have undergone minor hepatic resection compared with routine-access resection (Martin et al., 2007). These results suggest that trauma from surgery may affect short- but not long-term QoL.

Surgical treatment for HCC temporarily decreased physical QoL component, and the PCS and MCS scores began to improve at 3 months after surgery. The two groups showed comparable PCS and MCS scores, which were even lower than those determined preoperatively. A similar outcome was observed at 6 months after surgery. Moreover, our results differ from those of Mise et al. Specifically, they found a decrease in QoL following surgical treatment, which returned to baseline within 6 months, and the MCS scores reached the national average at 12 months after surgery (Mise et al., 2014). Poon et al. (2001) even demonstrated significantly greater PCS and MCS scores at 3 months after surgery for HCC compared with pre-operative scores. The main reason for these differences may be that there is a higher frequency of families lying to patients about their HCC diagnosis in China. More patients' families are likely to lie to them about their diagnosis prior to surgery. However, patients may learn the truth from other patients in the ward or other individuals. Therefore, learning their actual diagnosis may have led to the lower post-operative PCS and MCS scores of the patients in this study compared with their preoperative scores.

With respect to long-term follow-up (6-24 months

after surgery), the resection group had the best post-operative QoL at 24 months after surgery, and that of the TACE group peaked at 6 months after surgery. The main reason for recovery in the resection group was hepatic regeneration (which was slow in the patients with cirrhosis), an increase in liver function and only a small number of HCC recurrences. Moreover, the primary reason for the better PCS and MCS scores in the resection group over the long term may have been the low frequency of HCC recurrence. Poon et al. (2001) have noted that the removal of tumors not only improves the physical well-being of patients but also enhances their social and emotional health statuses, and their improved relationships with physicians reflect their satisfaction with the surgical treatment. Long-term HCC recurrence was significantly higher in the TACE group. Univariate and multivariate analyses suggested that HCC recurrence was a strong risk factor for long-term poor postoperative QoL.

There are some limitations to our present study. First, this is a single-center study that evaluated a limited number of patients. Second, the longest follow-up time was only 2 years; a longer observation period would be more convincing. Third, a psychopathological profile should be generated for a more in-depth analysis and comparison of the use of resection versus TACE for the treatment of intermediate-stage HCC patients.

In conclusion, considering the low recurrence rate and higher long-term QoL in the resection group compared with the TACE group, liver resection should be the first choice for the treatment of intermediate-stage HCC patients.

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