ORIGINAL ARTICLE

Effect of Transarterial Chemoembolization on the Immediate Health-related Quality of Life of Patients with Hepatocellular Carcinoma in the Philippine Setting

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ABSTRACT

Background and Objective. Transarterial chemoembolization (TACE) is a locoregional therapy used in patients with unresectable intermediate-stage hepatocellular carcinoma (HCC). It has proven benefit on overall survival, but considerable side effects and potential complications may occur. Preservation of quality of life is a concern in many cancer-related therapies, and the same goal should apply in TACE. This study aimed to determine the effect of TACE on the immediate health-related quality of life (HRQoL) of Filipino patients with unresectable HCC.

Methods. A prospective observational survey study of 18 HCC patients who underwent TACE was conducted. HRQoL scores were measured using the validated EORTC QLQ-C30 and QLQ-HCC18 questionnaires, 1-2 days before and two weeks after TACE. Baseline clinical data, which included tumor characteristics, Child-Pugh score, and performance status score, were also obtained. Changes in HRQoL scores before and after TACE, and any association of demographic and clinical variables with HRQoL outcomes were assessed.

Results. Patients experienced overall decline in their global health status and functional scores with increase in their symptom scores after undergoing TACE. Statistically significant deterioration was observed in global health status (-13.9%), physical functioning (-23.0%), and role functioning (-31.4%). Alcohol users had lower global health status scores at baseline and follow-up, although there was no significant difference in the degree of decline in their post-TACE scores compared with non-alcohol users. Patients with BCLC stage C disease also had lower global health status scores at baseline, although scores were no longer significantly different from patients of other stages on post-TACE follow-up. Patients with BCLC stage B tumor experienced significant decline in their global health status scores. The presence of minimal ascites at baseline was associated with less deterioration in physical function scores after TACE. Largest and significant increases in symptomatology were seen for appetite loss (+41.1%), fever (+30.3%), fatigue (+28.5%), and general pain (+25.1%).

Conclusion. TACE can negatively affect the HRQoL of Filipino patients in the early phase after treatment, with significant deteriorations in global health status, physical, and role functioning, and increased severity in symptoms, especially appetite loss, fever, fatigue and pain. Knowledge of these changes should be used to improve patient care, compliance, and expectations.

Keywords: transarterial chemoembolization, hepatocellular carcinoma, health-related quality of life.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and the third most common cause of cancer-related death worldwide, just behind lung and colorectal cancers.[1] While the disease burden of many other major cancers has been decreasing, the overall burden of liver cancer remains increasing. It is just second to lung cancer as the leading cause for years of life lost from cancer between 2005 and 2015.[2] Its incidence and mortality are predicted to increase by 55.0% and 56.4%, respectively, between 2020 and 2040 as populations continue to grow and age worldwide.[3]

The incidence of HCC varies in different regions of the globe, with approximately 85% of cases occurring in low- to middle-resource countries, particularly highest in East Asia and sub-Saharan Africa.[2] Variations also exist in its age of onset, with median of above 60 years in Japan, North America, and Europe, and a younger age group (30-60 years) in the rest of Asia, including the Philippines, and most of Africa.[2,4] Majority are diagnosed at the intermediate to advanced stages of the disease due to poor surveillance and late clinical presentation. Fewer than 20% are eligible for curative resection at the time of diagnosis.[5] In patients with advanced disease, prognosis is poor and treatment is typically palliative.

Common symptoms of HCC include abdominal pain, jaundice, anorexia, fatigue, and weight loss. With progression of disease, these can be debilitating and can have a negative influence on health-related quality of life (HRQoL). Palliative management should thus include measures to maintain or improve HRQoL endpoints. While certain treatments may control tumor volume and improve survival, they may also produce side effects or complications that are significant enough to negatively affect HRQoL and eventually patient compliance.

Transarterial chemoembolization (TACE) is a loco-regional therapy with proven benefit on overall survival. It is the recommended first-line therapy for patients with unresectable intermediate-stage tumor based on the Barcelona Clinic Liver Cancer (BCLC) criteria.[6] It is also used as neoadjuvant therapy for candidate HCC patients awaiting liver transplantation.[7] It involves targeted delivery of antineoplastic drugs and embolic particles to the feeding arteries of the tumor to elicit both cytotoxic and ischemic effects. However, post-chemoembolization syndrome, composed of a triad of abdominal pain, nausea, and fever, is a common side effect and can be debilitating to some patients. Other complications may also occur, and include acute liver failure, hepatic abscess, and non-target embolization.[8]

Studies have been done to investigate the effect of TACE on the HRQoL of HCC patients, with variable results.[5,9-12] Furthermore, these were all conducted in high-resource Western settings, where socioeconomic factors affecting health-related behavior and access to medical care may be different from our local setting. Our study thus aimed to determine the early effects of TACE on the HRQoL of Filipino HCC patients. Specifically, we aimed to measure HRQoL endpoints of patients before and after TACE using standardized survey questionnaires, and to detect any statistically significant changes between them. We also aimed to identify any possible effect of demographic and clinical variables on HRQoL outcomes.

METHODS

Study Design and Population

A prospective observational study was conducted involving HCC patients who underwent TACE in a tertiary hospital with an interventional radiology team capable of performing the said procedure and managing its possible complications. This protocol was adapted from the studies of Hinrichs et al. and Hartrumpf et al.[9,10]

To be eligible, patients should be diagnosed with HCC based on either radiologic criteria or histopathological examination. They should undergo TACE as primary treatment for unresectable intermediate HCC (BCLC stage B), as bridge therapy for liver transplantation, or as neoadjuvant treatment for tumor downstaging. They should be free from any of the absolute contraindications to TACE, which include advanced decompensated liver disease (Child-Pugh class C), poor performance status (ECOG [Eastern Cooperative Oncology Group Score] 3-4), uncorrectable bleeding diathesis, extrahepatic metastasis, active infection, and encephalopathy. They should be older than 18 years of age and should participate in the study voluntarily. Patients who had previously underwent another cancer-related therapy and those who refused to participate in the study were excluded.

Due to the limited number of HCC patients undergoing TACE, all eligible patients were recruited during a 12-month period from October 2020 to September 2021.

Recruitment and Study Procedures

All eligible patients who were referred to our institution were invited to participate. The study investigators personally informed them about the nature, objectives, and process of the study. Those who expressed willingness to participate underwent the informed consent process upon admission to the hospital in preparation for TACE.

Upon inclusion in the study, demographic and baseline clinical data of patients were obtained by the study investigators through interview and review of health records. The validated European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3) and QLQ-HCC18 questionnaires were used to measure their HRQoL scores. The EORTC QLQ-C30 is a validated HRQoL instrument that was designed to be cancer-specific, multidimensional in structure, appropriate for self-administration, and applicable across a range of cultural settings. The QLQ-HCC18 is a supplementary module developed particularly for HCC

patients and consists of additional questions on HCC-related symptoms.[13,14] The questionnaires were made available in either English or Filipino language. The participants answered the self-administered questionnaires 1-2 days before TACE during their hospital stay, and then two weeks after TACE. This time interval was used to avoid bias by post-chemoembolization syndrome, which was expected to resolve by then.[9,10]

TACE was performed by trained interventional radiologist/s using standard protocol.[8,9] Percutaneous trans-arterial access was established using the common femoral artery, and a diagnostic catheter was used to perform initial angiograms of the celiac and superior mesenteric arterial systems. The angiograms were used to locate the vascular supply of the tumors and to plan the subsequent chemo-embolization technique. A coaxial microcatheter was then advanced to the target feeding arteries, and an emulsion of chemotherapeutic agents (doxorubicin 50 mg and mitomycin C 20 mg) in 10 mL ethiodized oil (Lipiodol) was injected. This was followed by embolization with gelatin sponge until sub-stasis or stasis of blood flow was achieved, unless otherwise inhibited by patient-specific, anatomic, or technical factors.

Study Outcomes

The following demographic and baseline clinical data were obtained from each patient: age, sex, risk factors (e.g., history of hepatitis, alcohol use), tumor characteristics (size, number, and distribution based on contrast-enhanced CT), history of previous TACE, Child-Pugh score, and ECOG score.

HRQoL scores were obtained using the EORTC QLQ-C30 and QLQ-HCC18 questionnaires, following the guidelines provided by the EORTC Scoring Manual.[15] Questionnaire items are divided into a global health status scale, 5 functional scales (physical, role, emotional, cognitive, social), 9 multi-item symptoms scales (fatigue, nausea and vomiting, general pain, HCC-related fatigue, body image, jaundice, nutrition, site-specific pain, fever), and 8 single-item symptom scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties, abdominal swelling, sex life). Changes in HRQoL scores before and after TACE procedures were determined.

Statistical Analysis

Descriptive statistics were calculated for demographic and baseline clinical variables. Significant changes in HRQoL and predictors of change were determined using mixed effects models, with the level of statistical significance set at 0.05. If a significant difference over time for a HRQoL function score was detected, further analysis was done by running models that included one additional demographic or clinical variable to the model, including an interaction term with time, to assess if the different variables had different changes in the HRQoL domain over time.

Ethical Considerations

The protocol of this study was reviewed and approved by the University of the Philippines Manila Research Ethics Boards (UPMREB) and was conducted in compliance with the Data Privacy Act of 2012, National Ethical Guidelines for Privacy and Health Related Research (NEGHHR) of 2017, and Helsinki Declaration. Written informed consents for both the study and the TACE procedure were obtained from each participant. The participants were provided with a personal copy of the signed informed consent form. They were allowed to withdraw at any point without affecting the services and treatment that they would receive from our hospital. There were no incentives from participating in this study.

The participants' right to privacy was respected, and all patient-related data were kept confidential. Their identities were concealed during data recording using identification numbers. All study procedures and data collection were done personally by the study investigators. All data collected were encoded in a secured electronic spreadsheet file that was accessible only to the investigators. Data were used only for the analysis of this study.

RESULTS

Demographic and Clinical Data

A total of 19 patients was recruited for this study. All participated voluntarily and answered the pre-TACE survey. Among these, there was one dropout due to an intraprocedural complication wherein TACE had to be aborted. This patient no longer continued with the post-TACE survey and his data were excluded in the analysis of HRQoL scores.

Table 1 shows the demographic and baseline clinical data of the sample population. The ages of our participants ranged from 43 to 75 years, with a mean of 63 years (SD 8 years). Majority (57.9%) belonged to the age group of 60-69 years. There were more males (68.4%) than females. The most common risk factors were history of hepatitis B infection (47.4%), alcohol use (42.1%), and diabetes (42.1%).

Most of the study participants had BCLC stage B of HCC (63.2%) and Child-Pugh score of A (89.5%). Two participants were classified as BCLC stage C due to the presence of portal vein invasion, but they were still deemed candidates for TACE as a means of downstaging the tumor. All participants had an ECOG score of 0. Most had multinodular tumor (52.6%), largest tumor size of >5 cm (84.2%), and unilobar-multisegmental (47.4%) or bilobar/multifocal tumor distribution (42.1%), reflecting unresectable disease. A minority (21.1%) had minimal ascites detected on pre-TACE imaging.

The complete survey was conducted in twelve patients who underwent TACE for the first time, five patients who underwent TACE for the second time, and one who underwent TACE for the third time. The sole dropout in the study had multinodular multifocal BCLC stage B tumor,

Table 1. Demographic and Baseline Clinical Data of the Sample Population

Parameter	Frequency (n)	Percentage (%)
Age (years)		
43-49	2	10.5
50-59	3	15.8
60-69	11	57.9
70-75	3	15.8
Sex		
Male	13	68.4
Female	6	31.6
Risk Factors		
Hepatitis B	9	47.4
Hepatitis C	2	10.5
Fatty liver	4	21.1
Diabetes	8	42.1
Obesity	4	21.1
Alcohol use	8	42.1
Smoking	4	21.1
BCLC stage		
A	5	26.3
B	12	63.2
C	2	10.5
Child-Pugh class		
A	17	89.5
B	2	10.5
Tumor number		
One	4	21.1
Two	5	26.3
Multiple (>3)	10	52.6
Size of largest tumor (cm)		
<3	1	5.3
3-5	2	10.5
>5	16	84.2
Tumor distribution		
One segment	2	10.5
One lobe	9	47.4
Bilateral / multifocal	8	42.1
Ascites		
Present (minimal)	4	21.1
Absent	15	78.9

with largest tumor size of >5 cm, Child-Pugh score of A, and minimal ascites.

HRQoL Data and Outcomes

Table 2 shows the mean scores and mean differences of the pre- and post-TACE surveys. A higher score for global health status and functional scales indicates higher QoL and healthier level of functioning, respectively.[15] Physical (83.3%) and cognitive (80.2%) functioning had the highest baseline scores, while global health status (67.2%) and social functioning (69.8%) were lowest. After TACE, cognitive functioning (70.4%) remained highest and had the least decrease in score, while role functioning (42.6%) now became lowest and showed the steepest decline. There was overall decrease in the scores post-procedure, but statistically significant changes were observed only for global health status (-13.9%), physical functioning (-23.0%), and role functioning (-31.4%).

Statistically significant changes were assessed for any association with the demographic and clinical variables of the sample population. Global health status (QL) was significantly associated with history of alcohol use and BCLC stage. Alcohol users had lower QL scores at baseline and follow-up, although there was no significant difference in the degree of decline in their scores compared with non-alcohol users on post-TACE follow-up. Patients with BCLC stage A and C tumors had higher and lower QL scores at baseline, respectively. However, QL scores were no longer significantly different across all groups on post-TACE follow-up. There was a significant decline in the QL scores of patients with BCLC stage B tumor on post-TACE survey.

Physical functioning (PF) was significantly associated with the presence of ascites. Although PF scores were statistically equal between patient with and without ascites at baseline and these exhibited decline in both groups on post-TACE follow-up, the decline was significantly smaller in patients with minimal ascites than those with no ascites. Role functioning (RF) was not significantly associated with any demographic or clinical variable.

Cancer-related symptoms and other problems were also assessed by the QLQ questionnaires. A higher score in the symptom scales represents higher level of symptomatology or problems.[15] Financial difficulties had the highest scores both at baseline (68.8%) and follow-up (68.5%), exhibiting no significant change with TACE. Similarly, insomnia (37.5%) and sex life problems (31.3%) were high at baseline and showed no statistically significant change on follow-up. Fever (10.4%), appetite loss (10.4%), diarrhea (10.4%), abdominal swelling (8.3%), and nausea and vomiting (4.2%) had the lowest baseline symptom scores. After TACE, there was an increase in majority of the symptom scores, exhibiting statistical significance for appetite loss (+41.1%), fever (+30.3%), fatigue (+28.5%), general pain (+25.1%), dyspnea (+22.5%), nutritional problems (+19.5%), nausea and vomiting (+18.1%), and site-specific pain (+17.4%).

DISCUSSION

The demographic and clinical profile of our sample population is consistent with published epidemiological data on HCC. In the Philippines, patients are mostly male and older than 50 years. Most reported risk factors are chronic or previous hepatitis B infection, alcohol drinking, and diabetes mellitus, similar to our data.[4,16,17] The tumor characteristics of our patients likewise reflect the population wherein TACE is most commonly indicated—patients with intermediate HCC (BCLC stage B), multinodular tumors without extrahepatic invasion, and good clinical status (ECOG 0; Child-Pugh class A or B).[7]

Table 2. Pre- and Post-TACE Mean Scores and Mean Difference for the QLQ-C30 and QLQ-HCC18 Questionnaires (*p<0.05)

	Pre-TACE scores (%)		Post-TACE scores (%)		Mean difference (%)
	Mean	SD	Mean	SD	
QLQ-C30					
Global health status	67.2	17.3	53.2	16.5	- 13.9 *
Functional scales					
Physical functioning	83.3	15.5	60.4	27.1	- 23.0 *
Role functioning	74.0	28.6	42.6	23.7	- 31.4 *
Emotional functioning	75.5	20.1	63.4	26.2	- 12.1
Cognitive functioning	80.2	14.6	70.4	24.0	- 9.8
Social functioning	69.8	32.3	54.6	27.3	-15.2
Symptom scales					
Fatigue	26.4	22.5	54.9	30.4	+ 28.5 *
Nausea and vomiting	4.2	15.7	22.2	29.1	+ 18.1 *
Pain	24.0	26.9	49.1	33.6	+ 25.1 *
Dyspnea	14.6	20.3	37.0	27.7	+ 22.5 *
Insomnia	37.5	32.1	48.1	38.3	+ 10.6
Appetite loss	10.4	22.9	51.9	32.8	+ 41.4 *
Constipation	14.6	16.7	13.0	20.3	- 1.6
Diarrhea	10.4	25.1	7.4	14.3	- 3.0
Financial difficulties	68.8	33.3	68.5	31.3	- 0.2
QLQ-HCC18					
Fatigue	38.9	23.9	50.0	20.3	+ 11.1
Body image	25.0	27.5	38.0	26.7	+ 13.0
Jaundice	15.6	22.1	16.7	16.2	+ 1.0
Nutrition	20.8	21.6	40.4	22.0	+ 19.5 *
Pain	27.1	21.6	44.4	24.3	+ 17.4 *
Fever	10.4	17.3	40.7	30.9	+ 30.3 *
Abdominal swelling	8.3	25.6	20.4	23.3	+ 12.0
Sex life	31.3	36.6	42.6	44.0	+ 11.3

Our study showed significant declines in global health, physical and role functioning, and increases in many symptoms after TACE. These results were similar to those of Hinrichs et al., whose study showed major decreases in global health (-12.1%), physical (-21.4%), role (-23.4%), and social (-21.5%) functioning, and increases in fatigue (+30.1%), loss of appetite (+25.3%), and pain (+19.4%) after initial TACE.[9] Similarly, Hartrumpf et al. reported significant decreases in global health score (-11.77%) and physical functioning (-17.25%), and increases in fever (+12.57%), pain (+9.21%), and nausea and vomiting (+10.09%) after first TACE, although these were no longer significantly changing on additional TACE sessions.[10] In our study, the number of TACE sessions received by patients did not show statistically significant association with HRQoL outcomes, although this may be a result of our small sample size and underrepresentation of patients with multiple TACE.

Statistically significant changes in global health status, physical and role functioning reflect the side effects of TACE and the resulting short-term limitations in one's physical and daily activities. Physical functioning measures one's ability to do strenuous tasks, short- and long-distance walks, and activities of daily living independently, while role functioning measures one's ability to do work- and leisure-related activities. Thus, the negative short-term effect of TACE on these appears to be an important issue that must be communicated well during pre-procedural appraisal and alignment of patient expectations.

The most commonly reported side effect of TACE is post-chemoembolization syndrome and is generally expected to resolve within one week post-procedure.[8] However, symptoms of fever, pain, nausea and vomiting, which characterize the syndrome, continued to be increased in our sample population post-TACE, suggesting that these side effects may last longer than reported in literature. Similarly, increased fatigue, appetite loss, and nutrition problems, which were notable in both our study and that of Hinrichs et al., were also likely related to the side effects of TACE.[9,18] Increased severity of these symptoms after TACE can be an important source of distress to patients and must be addressed accordingly by the medical team.

In our study, no statistically significant change was demonstrated in certain HRQoL scales, including emotional, cognitive, and social functioning, suggesting that these were not significantly affected by the conduct of TACE. Social functioning was notably lower than the other functional scales at baseline, signifying the impact of the disease on this aspect of our patients' lives. Similarly, financial difficulties, insomnia,

and sex life problems had high baseline scores and were not significantly changed post-TACE, suggesting that these were problems associated with the incidence and course of HCC rather than TACE itself.

Although chronic hepatitis B infection is the most cited risk factor for HCC in the Philippines,[4] it showed no significant association with HRQoL changes after TACE. On the other hand, alcohol use, the second most common risk factor in the local setting, was associated with lower global health status (QL) scores both at baseline and after TACE. This finding may suggest that HCC patients with alcoholic cirrhosis have worse HRQoL than those with virus-related cirrhosis, although no other literature reports have been found to support this hypothesis and confounding factors may be present in our sample population.

BCLC stage was expectedly associated with baseline QL scores, as patients with advanced disease (stage C) had lower baseline scores. However, it no longer appeared to be a reliable predictor of HRQoL outcome after TACE, as scores were no longer significantly different across different BCLC stages on follow-up. Thus, regardless of initial BCLC stage, HRQoL changes can occur following TACE. Patients with BCLC stage B tumor suffered from significant decline in QL score after TACE, corroborating its significant short-term negative effect on this aspect of HRQoL.

The impact of TACE on physical functioning (PF) was shown to have an interesting association with the presence of ascites at baseline. Patients with minimal ascites before TACE experienced significantly less decline in their PF scores after TACE. In the study by Hinrichs et al., a similar trend was observed wherein patients with moderate pain at baseline were less affected by new-onset pain following TACE as they were probably already used to a certain level of existing pain compared with baseline asymptomatic patients.[9] Similarly, Hartrumpf et al. demonstrated that patients with higher baseline QL and PF scores experienced greater deterioration after TACE, while those with higher baseline symptom scores had lesser increase in symptom severity post-TACE.[10]

In a descriptive review by Ahmed et al. of HRQoL studies on TACE involving heterogeneous methods and questionnaire tools, study outcomes appeared to depend on the time of questionnaire administration after intervention, which was divided into early (≤1 month), intermediate (1-3 months), and late (≥3 months).[5] Early administration tended to have negative effect on HRQoL scores in symptomatology, physical, and psychological domains due to post-procedural side effects and complications, as likely was the case in our study. Questionnaire administration during the intermediate phase was largely influenced by treatment response and patients' knowledge of treatment effectiveness, and studies performed during this phase generally showed improvement in HRQoL. On the other hand, late-phase studies had varying results, with some reporting stable HRQoL and others reporting significantly worse outcomes. Long-term disease activity appeared to be an important factor in late-phase HRQoL, as patients with decreased HRQoL mostly suffered from tumor progression.

Chie et al. compared the changes in HRQoL in HCC patients across different treatment strategies.[19] Surgery and TACE were shown to have similar intermediate-phase HRQoL outcomes, while local ablation had significantly poorer outcomes than either surgery or TACE. Thus, surgery remains as the first-line treatment for patients with resectable tumor due to its established and superior survival benefits. However, TACE might be the better option for unresectable cases over ablation considering their effects on HRQoL when other survival-related factors are equal. Klein et al. evaluated HRQoL of liver cancer patients who underwent stereotactic body radiation therapy and reported worsening of appetite loss and fatigue in the intermediate phase but stable overall HRQoL.[20] However, it is noteworthy that their sample included patients with worse ECOG scores (>2), which is a contraindication to TACE and an exclusion criterion in our study.

Preservation of HRQoL may be as important as survival benefits for patients undergoing TACE. Whether the intent of treatment is curative or palliative, the willingness of patients to continue with future sessions may be deterred if HRQoL outcomes become significantly worse. Availability and knowledge of HRQoL data can allow appropriate stratification of patients and influence decision-making in tumor boards.[9] Additionally, these can improve patient awareness on what to expect during and after treatment, and enable physicians to provide better supportive care.

Our study has few important limitations. First is our small sample size, owing to the limited number of patients undergoing TACE in our institution. Thus, statistical inferences from our data must made with caution. Second, total chemotherapeutic dose given to our patients may have slight variations depending on tumor load, patient-specific, or technical factors, and this may be a confounding factor on the effect of TACE on HRQoL outcomes. Lastly, we assessed HRQoL changes during the early phase after TACE, and our results are thus reflective of short-term HRQoL changes only. Further studies with larger sample size and longitudinal HRQoL assessment are suggested. Measurement of HRQoL scores at baseline, early, intermediate, and late post-treatment phases may provide better understanding on the impact of TACE on both short- and long-term HRQoL.

CONCLUSION

TACE can negatively affect the HRQoL of patients in the early phase after treatment, with significant deteriorations in global health status, physical, and role functioning, and increased severity in symptoms, especially appetite loss, fever, fatigue, and pain. Alcohol use and advanced BCLC stage are associated with lower global health status at baseline, although these do not appear to be reliable predictors of post-TACE HRQoL. Knowledge of HRQoL changes in TACE

can enable the medical team to provide better holistic care for their patients. It can also be used to improve patients' awareness on the effects of their treatment and alignment of expectations.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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