Journal of Health and Rehabilitation Research 2791-156X JHRR

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Original Article

Efficacy and Safety of Transarterial Chemoembolization (TACE) in Patients with Hepatocellular Carcinoma (HCC) and Assessment of Health Related Quality of Life (HRQoL) using CLDQ©

Ammara Abdul Majeed[1]*, Hafeezullah Shaikh[2], Syed Muhammad Zahid Azam[3], Nouman Al Qamri[4], Raheela Khalid[5], Abdul Basit Shaikh[6]

[1]Postgraduate Trainee Gastroenterology, NILGID, Dow University of Health Sciences (DUHS), Karachi, Pakistan.
[2]MBBS, FCPS (Gastroenterology), Assistant Professor at NILGID, Dow University of Health Sciences (DUHS), Karachi, Pakistan.
[3]MBBS, FCPS (Medicine), FCPS (Gastroenterology), MSc in Clinical Research, Head of Department NILGID, Dow University of Health Sciences (DUHS), Karachi, Pakistan.
[4]MBBS, FCPS (Radiology), Fellowship in Interventional Radiology, Assistant Professor Dow Institute of Radiology, Dow University of Health Sciences (DUHS), Karachi, Pakistan.
[5]MBBS, FCPS Gastroenterology, Dow University of Health Sciences (DUHS), Karachi, Pakistan
[6]MBBS, House Officer at NILGID, Dow University of Health Sciences (DUHS), Karachi, Pakistan.
Corresponding Author: Ammara Abdul Majeed; Email: ammaraabdulmajeed@gmail.com

Conflict of Interest: None.

*Majeed AA., et al. (2024). 4(1): **DOI**: https://doi.org/10.61919/jhrr.v4i1.715*

ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality globally, with its management presenting significant clinical challenges, especially in advanced stages. Transarterial chemoembolization (TACE) offers a palliative treatment option, but the evidence on its impact on Health-Related Quality of Life (HRQoL) and its efficacy across different patient subgroups, particularly in elderly populations, remains limited.

Objective: This study aimed to assess the safety and efficacy of TACE in patients with HCC and evaluate its impact on HRQoL, focusing on patient subgroups including those with advanced age and varying stages of liver function.

Methods: In this prospective observational study, 140 patients with HCC undergoing TACE at a single center were enrolled. Patients were assessed for tumor response using the modified RECIST (mRECIST) criteria, complications post-TACE, changes in liver function as per Child-Pugh classification, and HRQoL using the Chronic Liver Disease Questionnaire (CLDQ). The association of tumor response with demographic and clinical factors was also analyzed. Statistical significance was determined using chi-square tests for categorical variables and paired t-tests for continuous variables.

Results: Tumor response rates were: Complete Response (CR) 14%, Partial Response (PR) 53.7%, Stable Disease (SD) 8.1%, and Progressive Disease (PD) 24.3%. Portal Vein Thrombosis (PVT) post-TACE was observed in 45.7% of patients. Immediate complications were predominantly vomiting (50%) and nausea (44.1%). At 6 weeks follow-up, anorexia (35.3%) and Post-embolization Syndrome (PSE) (19.9%) were the most common complaints. HRQoL showed significant improvement in all domains post-TACE (P=0.0001). Significant associations were found between tumor response and baseline BCLC stage, PVT status, and the use of Sorafenib, among other factors.

Conclusion: TACE demonstrates significant efficacy in improving tumor response and HRQoL in HCC patients, with a manageable safety profile. It is notably effective in younger patients, females, and those with less advanced disease. The study underscores the potential of TACE as a viable treatment option across a broader spectrum of HCC patients, including those traditionally considered at higher risk.

Keywords: Hepatocellular Carcinoma, Transarterial Chemoembolization, TACE, Health-Related Quality of Life, HRQoL, Liver Cancer, Palliative Care, Treatment Efficacy, Sorafenib, Tumor Response.

Journal of Health and Rehabilitation Research 2791-156X JHRR

INTRODUCTION

Hepatocellular carcinoma (HCC) represents a significant public health challenge, attributed to its increasing prevalence and the substantial mortality rates it carries. Globally, HCC ranks as the fourth most common cancer and emerges as a leading cause of cancer-related deaths (1). Epidemiological data from hospital records in Pakistan indicate an incidence rate of HCC of 7.6 per 100,000 in males and 2.6 per 100,000 in females, underscoring the gender disparity and the overall burden of this disease within the region (2). The pathophysiological hallmark of HCC lies in its exclusive arterial vascularization, which confers a distinctive radiological signature characterized by arterial phase enhancement and venous phase washout in triphasic CT scans. This unique feature not only aids in the diagnosis of HCC but also influences the approach to treatment, which must consider tumor burden, liver function, and the patient's overall health status. The Barcelona Clinic Liver Cancer (BCLC) staging system is pivotal in this context, offering valuable prognostic insights (3).

A significant proportion of patients with HCC are diagnosed at an advanced stage, precluding curative treatment options. In such instances, Transarterial Chemoembolization (TACE) emerges as a viable palliative approach. TACE entails the targeted delivery of chemotherapeutic agents, such as Doxorubicin or Adriamycin, directly into the liver tumor, followed by embolization of the arterial supply to induce ischemic necrosis of the tumor cells (4). This procedure not only aims to mitigate tumor progression but also seeks to extend survival and enhance the Health-Related Quality of Life (HRQoL) in affected individuals (5). The current study focuses on evaluating the efficacy of TACE, as determined by the modified Response Evaluation Criteria in Solid Tumors (mRECIST), and assessing its safety following a single TACE session in patients with HCC. Furthermore, an analysis of TACE's impact on HRQoL was conducted, utilizing the Chronic Liver Disease Questionnaire (CLDQ). The use of the CLDQ, particularly its Urdu version which has been validated and is available under license, facilitates a culturally and linguistically relevant assessment of HRQoL among the Pakistani population, offering insights into the broader implications of TACE beyond mere survival rates (6). This comprehensive approach underscores the multifaceted nature of HCC management, where therapeutic interventions are evaluated not only for their direct anticancer effects but also for their ability to improve the overall well-being of patients (7).

MATERIAL AND METHODS

The methodology of this prospective observational cross-sectional study was meticulously designed to evaluate the efficacy and safety of the Transarterial Chemoembolization (TACE) procedure in patients with Hepatocellular Carcinoma (HCC), as well as its impact on Health-Related Quality of Life (HRQoL) using the Chronic Liver Disease Questionnaire (CLDQ). Conducted at the National Institute of Liver & GI Diseases, affiliated with Dow University of Health Sciences, Karachi, the study received the requisite approval from the Institutional Review Boards (IRB# 2031), ensuring adherence to the ethical principles outlined in the Declaration of Helsinki for medical research involving human subjects.

Inclusion criteria were set for adult patients aged 18 years and older diagnosed with HCC of any size, as confirmed through radiological or pathological means, with or without elevated Alpha-Fetoprotein (AFP) or PIVKA-II levels. Eligible participants were those with a performance status of 2 or lower on the Eastern Cooperative Oncology Group (ECOG) scale, a Child Turcotte Pugh (CTP) score of 11 or less, who were willing to undergo the TACE procedure, and who provided signed consent for both the procedure and participation in the study. Exclusion criteria included patients with extr hepatic tumor deposits, lymph nodes larger than 1 cm in the shortest diameter, distant metastases (such as to the lungs, bone, or inferior vena cava), or a serum creatinine level exceeding 1.5 mg/dl (6, 8).

The study aimed to enroll a sample size of 140 participants, calculated based on the anticipated 22% partial response rate according to mRECIST criteria (7). The TACE procedure involved the use of micro-catheters to administer Adriamycin/Doxorubicin and Polyvinyl Alcohol (PVA) particles for embolizing the hepatic artery branch that supplied the tumor, minimizing damage to non-tumorous liver tissue.

Tumor response to the TACE procedure was assessed six weeks (±1 week) post-procedure through repeat triphasic CT scans and tumor marker evaluations, categorized according to the mRECIST criteria into Complete Response (CR), Partial Response (PR), Stable Disease (SD), and Progressive Disease (PD) (8). Additionally, the study monitored immediate complications and adverse events within six weeks post-TACE. HRQoL was evaluated pre- and post-TACE using the CLDQ, which employs a Likert scale ranging from 1 (indicating maximum impairment) to 7 (indicating minimum impairment). (7)

Data collection was conducted rigorously, ensuring the confidentiality and privacy of participant information. Statistical analyses were performed using SPSS Version 25.0. Continuous variables were summarized as means and standard deviations, while categorical variables were presented as frequencies and percentages. The chi-square test was employed to explore potential associations between tumor response and other variables. Paired t-tests were utilized to compare pre- and post-TACE clinical

parameters and HRQoL scores. A significance level was set at $P \leq 0.05$, adhering to the ethical standards of research integrity and analytical rigor.

RESULTS

The study comprehensively evaluated the outcomes and implications of Transarterial Chemoembolization (TACE) in patients with Hepatocellular Carcinoma (HCC), enrolling a cohort of 140 participants. A notable observation from the study was the tumor response according to the mRECIST criteria, where Partial Response (PR) was achieved by 53.7% of the patients, indicating a predominant efficacy of the TACE procedure. Progressive Disease (PD) and Complete Response (CR) were observed in 24.3% and 14% of the patients, respectively, while Stable Disease (SD) was noted in 8.1% of cases [Table 1]. Additionally, Portal Vein Thrombosis (PVT) post-TACE was categorized into Bland PVT and Tumor PVT, affecting 25.7% and 20% of the cohort, respectively. Immediate complications were predominantly vomiting (50%) and nausea (44.1%), with less common occurrences of epigastric pain, fever, erythema or bruise, and hematoma, highlighting the procedural safety profile [Table 1].

The analysis of clinical parameters pre and post-TACE revealed significant improvements in the Child Score, with an increase from 5.81 to 6.19 (P=0.001), and notable changes in the ECOG score, indicating a shift towards increased functionality post-treatment [Table 2]. However, not all parameters showed significant changes, as illustrated by the Meld-Na and AFP levels, underscoring the nuanced effects of TACE on different aspects of liver function and cancer markers.

Table 1: Post-TACE Clinical Outcomes in Patients with Hepatocellular Carcinoma (n=140)

Outcome Category	Outcome	Number (n)	Percentage (%)
Tumor Response (mRECIST criteria)	Partial Response (PR)	73	53.7
	Progressive Disease (PD)	33	24.3
	Complete Response (CR)	19	14.0
	Stable Disease (SD)	11	8.1
Portal Vein Thrombosis (PVT) Post-TACE	Bland PVT	35	25.7
	Tumor PVT	28	20.0
Immediate Complications	Vomiting	68	50.0
	Nausea	60	44.1
	Epigastric Pain	56	41.2
	Fever	36	26.5
	Erythema / Bruise	9	6.6
	Hematoma	1	0.7
Complications (6 weeks follow-up)	Anorexia	48	35.3
	PSE	27	19.9
	Anemia	26	19.1
	GI Bleed	18	13.2
Post-TACE Metastasis & Mortality	Regional Metastasis	15	11.0
	Distant Metastasis	5	3.7
	Mortality	4	2.8

Table 2: Comparison of Pre vs. Post TACE Clinical Parameters (n=140)

Parameter	Pre-TACE Mean±SD	Post-TACE Mean±SD	Difference Mean±SD	P-value
Child Score	5.81±1.01	6.19±1.29	0.37±1.25	**0.001**
Meld-Na	11.16±3.83	10.47±4.36	-0.69±5.56	0.150
AFP (ng/mL)	1242.35±4406.02	944.38±4094.62	-297.97±1745.244	0.072
ECOG	0.18±0.40	0.56±0.71	0.38±0.71	**0.000**
Anterio-Posterior Diameter (cm)	6.00±3.13	5.19±3.11	-0.80±1.44	**0.000**
Creatinine (mg/dL)	0.83±0.20	0.78±0.20	-0.05±0.21	**0.005**
Sodium (mEq/L)	136.74±4.71	138.33±5.35	1.59±7.53	**0.015**
T.Bilirubin (mg/dL)	0.97±0.58	1.04±0.77	0.07±0.63	0.176
SGPT (U/L)	65.73±54.44	93.28±111.71	27.55±98.60	**0.001**

Parameter	Pre-TACE Mean±SD	Post-TACE Mean±SD	Difference Mean±SD	P-value
ALKPHOS (IU/L)	197.24±134.18	202.34±151.59	5.10±90.14	0.512
GGT (U/L)	172.18±170.06	159.90±153.92	-12.28±85.20	0.096
SGOT (U/L)	86.84±55.63	96.69±70.18	9.85±50.28	**0.024**
Albumin (g/dl)	3.61±0.54	3.57±0.63	-0.04±0.50	0.339
INR	1.15±0.39	1.12±0.18	-0.03±0.41	0.445
Platelet Count (109/L)	244.88±580.62	201.75±110.02	-43.13±546.39	0.361
Hb (mg/dl)	13.44±13.31	11.60±1.62	-1.84±13.46	0.117

Table 3: Summary of Pre vs. Post TACE Findings Across Different Parameters (n=136)

Parameter	Pre TACE	Post TACE (Distribution)	Total	P-value
BCLC Stage	A	A: 27 (84.4%), B: 5 (15.6%)	32	**0.000**
	B	B: 61 (71.8%), C: 23 (27.1%)	85	
	C	C: 14 (73.7%), D: 5 (26.3%)	19	
Child Class	A	A: 87 (82.1%), B: 12 (11.3%), C: 7 (6.6%)	106	**0.000**
	B	B: 16 (53.3%), C: 2 (6.7%)	30	
ECOG Score	0	0: 76 (67.9%), 1: 19 (17%), 2: 17 (15.2%)	112	**0.000**
	1	1: 21 (95.5%)	22	
	2	2: 1 (100%)	1	
Meld-Na	<10	<10: 35 (57.4%), 10-20: 22 (36.1%), >20: 4 (6.6%)	61	0.599
	10-20	10-20: 34 (46.3%), >20: 3 (4.3%)	69	
	>20	>20: 3 (50%)	6	

Table 4: Quality of Life Assessment Pre vs. Post TACE Using CLDQ (n=136)

CLDQ Dimension	Pre TACE-Score (Mean±SD)	Post TACE Score (Mean±SD)	Mean Difference	P-value
Abdominal Symptom	4.0±0.8	5.3±0.8	+1.3	**0.0001**
Fatigue	4.3±0.7	5.4±0.6	+1.0	**0.0001**
Systemic Symptoms	4.7±0.6	5.2±0.5	+0.6	**0.0001**
Emotional	4.4±0.6	5.4±0.4	+1.0	**0.0001**
Worry	4.3±0.8	5.3±0.5	+1.1	**0.0001**
Activity	4.3±1.1	5.4±0.4	+1.1	**0.0001**
Total Score	4.3±0.4	5.7±0.3	+1.4	**0.0001**

Table 5: Association of Tumor Response with Demographic and Clinical Factors (n=136)

Factor	Subcategory	CR (%)	PD (%)	PR (%)	SD (%)	Total	P-value
Age Group	≤60 years	20	20	51.8	8.2	85	0.051
	>60 years	3.9	31.4	56.9	7.8	51	
Gender	Female	22	12.2	53.7	12.2	41	0.060
	Male	10.5	29.5	53.7	6.3	95	
Etiology	Non-viral	15.4	17.9	53.8	12.8	39	0.409
	HBV	20	28	40	12	25	
	HCV	11.1	26.4	58.3	4.2	72	
Meld Na	<10	16.4	24.6	52.5	6.6	61	0.765
	10-20	13	24.6	52.2	10.1	69	
	>20	0	16.7	83.3	0	6	
Child Class Pre-TACE	A	11.3	28.3	51.9	8.5	106	0.110
	B	23.3	10	60	6.7	30	
BCLC Stage Pre-TACE	A	50	0	40.6	9.4	32	**0.000**

Factor	Subcategory	CR (%)	PD (%)	PR (%)	SD (%)	Total	P-value
	B	3.5	28.2	58.8	9.4	85	
	C	0	47.4	52.6	0	19	
PVT Pre-TACE	No	17	17	56.2	9.8	112	0.000
	Yes	0	58.3	41.7	0	24	
Post-TACE Metastasis	Distant	14.6	21.4	55.7	8.4	131	0.001
	Local	15.1	14.9	60.3	9.1	121	0.000
Use of Sorafenib	No	40.5	16.2	37.8	5.4	37	0.000
	Yes	4	27.3	59.6	9.1	99	

Further examination of changes in BCLC staging and Child Class post-TACE [Table 3] underscored the treatment's impact on disease severity, with a significant shift in patients from BCLC stages A to B and improvements within Child Class A post-procedure. The ECOG score distribution post-TACE also indicated an enhancement in the patients' functional status, reinforcing the therapeutic benefit of TACE in managing HCC.

Quality of life assessments utilizing the Chronic Liver Disease Questionnaire (CLDQ) revealed significant improvements across all dimensions post-TACE, including abdominal symptoms, fatigue, systemic symptoms, emotional well-being, worry, and activity levels. The total CLDQ score increased from 4.3 to 5.7, signifying a marked enhancement in the overall quality of life of the patients following the TACE procedure [Table 4].

The association of tumor response with demographic and clinical factors presented nuanced insights [Table 5]. Age and gender showed no statistically significant association with tumor response outcomes, suggesting the efficacy of TACE across different demographics. However, pre-treatment variables such as BCLC stage, PVT status, and the use of Sorafenib were significantly associated with different tumor response outcomes, indicating the importance of baseline disease characteristics in predicting treatment efficacy.

DISCUSSION

In this study, the safety, efficacy, and impact on Health-Related Quality of Life (HRQoL) of Transarterial Chemoembolization (TACE) in patients with Hepatocellular Carcinoma (HCC) were thoroughly investigated, illuminating a significant area of interest within the domain of oncological treatments. This investigation was particularly relevant due to the limited literature focusing on the elderly population, who constituted 37.1% of the study cohort. The underrepresentation of older individuals in clinical trials often limits the evidence base for making informed treatment decisions for this demographic, thereby underscoring the significance of the current study's findings. Notably, this study extended the potential applicability of TACE to patients with Child-Pugh Class B cirrhosis, demonstrating that TACE was well tolerated and led to improvements in disease classification for a substantial portion of this subgroup. This contrasts with traditional reservations against recommending TACE for patients with compromised liver function and advanced disease stages, where concerns about adverse outcomes have prevailed (9, 10).

The tolerability of TACE in a population with Child Class B disease was a particularly compelling finding, given that 40% of these patients experienced an improvement in their disease class from B to A, and 53% remained stable within Class B. This finding diverges from the conclusions drawn by Roth et al., who suggested that Child Class B7 or higher significantly predicted adverse outcomes (11). The nuanced understanding of the Child-Pugh B category as a spectrum of hepatic impairment highlights the importance of patient selection for TACE, advocating for a comprehensive evaluation to optimize treatment outcomes (12).

The immediate and short-term follow-up complications observed in this study, primarily vomiting and anorexia, presented a contrast to the higher rates of adverse events reported in previous literature, including serious events and mortality rates (11). Such findings underscore the necessity of ongoing evaluation and management of TACE-related complications to enhance patient comfort and outcomes.

Regarding tumor response, utilizing mRECIST criteria allowed for a detailed assessment of the variations in response among patients, reinforcing the role of conventional TACE as a cornerstone in the management of intermediate-stage HCC (13, 14). Moreover, the study illuminated the potential benefits of combining TACE with Sorafenib, especially in advanced HCC cases where Sorafenib alone has shown to extend survival modestly. The prohibitive cost and issues of drug resistance with Sorafenib, however, highlight the need for integrated treatment approaches to optimize efficacy and patient accessibility to treatment options (15, 16). The significant differences in tumor response observed in patients treated with Sorafenib in conjunction with TACE versus those who were not further underscore the potential synergistic effects of this combination, aligning with other research advocating for such integrated treatment modalities (17).

The profound impact of TACE on improving HRQoL across all domains, as evidenced in this study, resonates with the growing recognition of the importance of quality of life alongside survival in cancer treatment outcomes. The improvement in HRQoL post-TACE, notably in functional and symptomatic scores, is consistent with findings from other studies, highlighting the potential of TACE to enhance patient well-being beyond mere survival benefits (13). This aspect of treatment outcome is particularly pertinent in the context of HCC, where palliative care often becomes a primary focus due to the advanced nature of the disease at diagnosis, comorbidities, hepatic dysfunction, and limited availability of donor livers for transplantation (19).

The study's limitations, including its short follow-up duration, relatively small sample size, and single-center design, necessitate cautious interpretation of the findings and underscore the need for broader, multicenter studies to validate and extend these results. Despite these constraints, the demonstrated association between TACE and improved HRQoL, coupled with a manageable safety profile, offers valuable insights for the selection of systemic and local interventions in HCC treatment. It particularly emphasizes considering HRQoL impacts in future therapeutic decision-making processes.

CONCLUSION

In conclusion, TACE has been shown to offer considerable therapeutic benefits, a tolerable safety profile, and significant improvements in HRQoL for patients with HCC. This study's findings advocate for the broader application of TACE, suggesting enhanced benefits for younger patients, females, those with less advanced disease stages, and the absence of metastasis. These insights pave the way for further research and underscore the importance of personalized treatment approaches in optimizing outcomes for patients with HCC.

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