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Original Article

Oncology Section

Assessment of Quality of Life, Tumour Control and Adverse Effects Observed in Patients Treated with Palliative Radiotherapy for Unresectable Gallbladder Cancer: A Prospective Interventional Study

UTKARSHA SINGH[1], ARADHANA SINGH[2], ARUN KUMAR YADAV[3], TABASSUM SAMANI[4], HARI SINGH[5], ANUJ KUMAR[6]

ABSTRACT

Introduction: Treating advanced Gallbladder Cancer (GBC) poses a substantial therapeutic challenge. Palliative chemotherapy is the primary treatment for patients with unresectable tumours. The effectiveness of this treatment in extending lifespan is limited, usually quantified in a few months, and its accompanying harmful effects can significantly impair overall well-being. As a viable alternative, palliative radiation offers the benefits of shorter treatment duration and a potentially lower risk of harmful side-effects. Its potential in the treatment of advanced GBC has not been fully explored, and the existing medical literature on this topic is scarce. However, the promising aspects of palliative Radiotherapy (RT) suggest a hopeful future for its application in treating unresectable GBC.

Aim: To evaluate the Quality of Life (QoL), treatment-related toxicities and tumour response to palliative RT in unresectable GBC.

Materials and Methods: A single-arm prospective interventional study was conducted in the Department of Radiation Oncology Outpatient Department (OPD), Sarojini Naidu Medical College, Agra, Uttar Pradesh, India, from September 2022 to May 2024. The present study included all patients with unresectable advanced GBC reported to OPD. Patients who had been previously treated or had ascites or duodenal infiltration were excluded. Twenty-four patients were recruited to receive RT alone (30 Gy in 10 fractions, D1-D10 over two weeks, five fractions per week). Treatment planning was Computed Tomography (CT) scan-guided. Quality of life assessment was based on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and BIL-21 questionnaires, and the Analysis of Variance (ANOVA) test was applied to compare variables. Tumour response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, and a paired t-test was applied to compare pre and post-treatment values. Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5) was used to monitor toxicity. Descriptive statistics were used to examine patient demographics, baseline characteristics, treatment details and toxicity profiles.

Results: Initially, 24 patients were enrolled in the present study, out of which four defaulted before treatment began. The mean age was 49.48±5.2 years. There was a female predominance, with 17 (70.8%) female patients and 7 (29.2%) male patients. The most common stage of the disease was stage IV A, affecting 16 (66.6%) of the patients. The overall QoL score pretreatment was 37.50±21.54, the mid-treatment score was 45.85±11.18, and the post-treatment score was 54.65±16.11. The scores showed improvement but were not statistically significant. A combined tumour response (complete+partial) was achieved in 10 (50%) patients. Treatment-related toxicities were within tolerable limits, with two patients developing cholangitis grade 2.

Conclusion: Improvement was observed in the QoL score. Adverse effects were minimal, with a tumour response observed in 50% of patients. Hence, palliative RT showed promising results with the advantage of a short treatment time. However, a study with a larger sample size in different institutes is needed for a clearer picture.

Keywords: Palliative treatment, Radiation therapy, Tumour response, Treatment-related toxicities

INTRODUCTION

The GBC is a malignant neoplasm originating from the gallbladder, a pear-shaped organ situated beneath the liver. The gallbladder's primary function is to store and release bile into the digestive tract. According to the GLOBOCAN 2022, GBC is the 22nd most common occurring cancer worldwide, there were 1,22,491 new cases of GBC and 89,055 fatalities [1]. In India, particularly in the Gangetic Plain, the incidence of GBC is notably high. The ASR for GBC is significantly higher in northern and eastern India (7-14 per 100,000 population) compared to southern and western India (less than 1 per 100,000 population). In India, the highest ASR is observed among women from the Northeastern region, at 17.1 per 100,000 [2].

Female gender, ethnicity and cholelithiasis are the most common risk factors associated with GBC. Gallstones are present in 95% of cases of GBC, but only 1-2% of patients with gallstones develop GBC [3]. The majority of cases are sporadic, with only a few being hereditary. Common mutations include Kirsten Rat Sarcoma (KRAS) gene and tumour Protein 53 (p53) gene mutations. Overexpression of the Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2) {Human Epidermal growth factor Receptor 2 (HER2/neu)} oncoprotein is observed in one-third to two-thirds of cases. Epigenetic inactivation affects the Fragile Histidine Triad (FHIT) gene and Semaphorin-3B (SemaA3B) in certain instances. Chromatin remodelling genes like PBRM1 and MLL3 contribute to up to a quarter of cases. Other less common mutations include Breast Cancer 2 (BRCA2), followed by BRCA1, MLH1, MSH2, PALB2, RAD51D, BAP1, and ATM mutations [4].

The GBC has a poor prognosis due to its aggressive tumour biology, late presentation, complex anatomic site and advanced stage at

diagnosis. According to a distribution analysis, 60% of gallbladder tumours occur in the fundus, 30% in the body and 10% in the neck of the gallbladder [5]. The 5-year survival rate for GBC {Surveillance, Epidemiology and End Results (SEER) stage} is 69% for localised disease, 28% for regional disease, 3% for distant metastasis and a combined rate of 26% for all SEER stages [6]. Clinical features associated with GBC include pain, anorexia, nausea/vomiting, weight loss, jaundice and cholangitis [7]. A significant number of GBC patients present with jaundice at the time of diagnosis (33-56%), which is a poor prognostic factor [8].

Currently, palliative treatment options for unresectable GBC include endoscopy (endoscopic biliary drainage and percutaneous transhepatic biliary drainage) for obstructive jaundice, chemotherapy, and Radiation Therapy (RT) to control the progression of cancer. Chemotherapy for palliative care typically takes six months to complete. Additionally, clinical features such as pain and obstructive jaundice (not related to interventional biliary drainage due to anatomical constraints, like a broad range of strictures in the intrahepatic bile duct with severe stenosis in the portal vein near the narrow site [9], or economic affordability issues) necessitate a localised and shorter regimen that can provide symptomatic relief in a shorter duration. Therefore, the present study was conducted to evaluate the effectiveness of a shorter localised regimen, specifically palliative RT at 30 Gy in 10 fractions [10], in improving QoL, tumour response and symptom alleviation with fewer side-effects.

MATERIALS AND METHODS

The present single-arm prospective interventional study was conducted in the Radiation Oncology OPD, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India, from September 2022 to May 2024. Approval was taken from the Institutional Ethics Committee (IEC) (approval number is SNMC/IEC/2024/197). Study was conducted on patients with gallbladder carcinoma after obtaining informed consent from all patients and their attendants after explaining the disease stage, prognosis and palliative treatment options.

Patients were staged according to the American Joint Committee on Cancer (AJCC) edition 8 GBC staging guidelines, utilising clinical examination and imaging via Contrast-enhanced Computed Tomography (CECT) of the abdomen [11]. All eligible patients with stage IIIB, IVa, and IVb GBC who met the inclusion criteria were enrolled in the study.

Inclusion criteria:

- Biopsy/Fine Needle Aspiration Cytology (FNAC) proven adenocarcinoma of the gallbladder.
- Inoperable advanced-stage disease requiring palliative treatment.
- Karnofsky Performance Status (KPS) of 60 or greater.
- Serum direct bilirubin ≤7mg/dL
- Adequate blood counts (haemoglobin >10 gm/dL, white blood cell count >4000/cumm, platelet count >100,000/cumm).
- Normal renal function tests (blood urea nitrogen <10 mg/dL, serum creatinine <1.5 mg/dL).
- Signed informed consent and willingness to adhere to follow-up requirements.

Exclusion criteria:

- Prior surgery for gallbladder carcinoma.
- Prior radiation or chemotherapy for gallbladder carcinoma.
- Pregnancy or lactation.
- Presence of ascites or duodenal obstruction.

Study Procedure

Before starting treatment, performance status was assessed based on the KPS. All patients were evaluated according to their activity levels and medical assistance requirements [12], and QoL assessments were conducted based on the EORTC QLQ-C30 and BIL-21 [13-15].

Patients received a total radiation dose of 30 Gray (Gy) delivered in 10 fractions over two weeks (five fractions per week) using two Dimensional (2D) conventional planning, delivered by a Cobalt-60 Theratron® Phoenix teletherapy machine. This dose was planned for palliative treatment {Equivalent Dose in 2 Gy fractions (EQD2)=32.5 Gray, Biological Effective Dose (BED)=39 Gray}. Based on the diagnostic CECT, a 2 cm margin was added to the tumour volume and marked on the skin of the anterior right abdomen according to the right subcostal margin. The medial field was extended 2 cm to the left of the midline of the patient's body to include the coeliac lymph node, provided the lymph node size was >1 cm and its appearance was heterogeneous. Two treatment fields, an anterior and a right lateral field, were defined based on the simulation scan. A 15-degree wedge filter was applied after drawing beam profiles using an isodose chart on the patient's contour for homogeneous dose distribution.

Toxicity and QoL evaluation: The National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, was utilised to evaluate nausea, vomiting, anaemia, neutropenia, thrombocytopenia, diarrhoea and cholangitis during treatment [16].

The QLQ was evaluated mid-treatment, specifically after five fractions. The EORTC QLQ-C30 is a widely used tool that includes five functional scales assessing physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning; as well as, nine multi and single-item scales assessing fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties, and a global health status/QoL scale [13]. Additionally, the BIL-21 questionnaire focuses specifically on 21 questions: three single-item assessments relating to treatment side-effects, difficulties with drainage bags/tubes, and concerns regarding weight loss, along with 18 items grouped into five proposed scales: eating symptoms (four items), jaundice symptoms (three items), tiredness (three items), pain symptoms (four items), and anxiety symptoms (four items) [15]. A high score on a functional scale represents a high/healthy level of functioning; similarly, a high score on the global health status/QoL represents a high QoL, but a high score on a symptom scale/item indicates a high level of symptomatology/problems [14].

Tumour response was evaluated using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria 1.1 after four weeks of treatment completion [17].

Post-treatment follow-up: Following treatment completion, all patients were followed-up at two-week intervals in the OPD until disease progression. A comprehensive assessment of quality of life and performance status was conducted post-treatment (four weeks after completion). A CT scan was performed four weeks post-treatment to assess tumour response and identify any potential indicators of disease progression. Patients whose tumours exhibited Stable Disease (SD) or Partial Response (PR), along with effectively managed symptoms (e.g., pain, jaundice), were assigned a two-week follow-up schedule. Conversely, patients presenting with Progressive Disease (PD) or a recurrence of symptoms were placed on an alternative treatment regimen.

STATISTICAL ANALYSIS

Statistical data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 28.0.1 software. Descriptive statistics were used to examine patient demographics, baseline characteristics, treatment details and toxicity profiles. A paired t-test was used to assess tumour response, while an ANOVA test was employed to evaluate quality of life. A p-value of <0.05 was considered statistically significant.

RESULTS

Total 24 patients were included in the present study, out of which four defaulted before treatment. Twenty patients completed the treatment. All patients had unresectable GBC. Cholelithiasis was present in 9 (45%) patients. The most common symptom was loss of appetite, reported by 17 patients. Sixteen patients complained of pain, 15 patients experienced weight loss and 18 patients reported fatigue. Twelve patients complained of nausea and vomiting. Fifteen patients had obstructive jaundice. Among these fifteen patients, interventional biliary drainage was impossible in nine patients due to anatomical constraints. The other six patients declined referral to higher centres for interventional biliary drainage, as this facility was unavailable at the study Institute. All patients completed two weeks of radiation treatment. One patient expired one week post-RT due to persistent hyperbilirubinemia, and another patient defaulted after the first follow-up (one month post-RT). Thus, 18 patients survived at the one-month follow-up.

The majority of patients were in the 30-60 years age group, with a mean age of 49.48±5.2 years. Among 24 patients, 7 (29.2%) were males and 17 (70.8%) were females. The majority of patients were classified as stage IV A, i.e., 16 (66.6%) [Table/Fig-1].

Parameters	Patients	
	Number (n)	Percentage (%)
Age group (years)		
<30	0	0
30-60	18	75.0
>60	6	25.0
Gender		
Male	7	29.2
Female	17	70.8
Residence		
Rural	8	33.3
Urban	16	66.6
Stage AJCC edition 8		
III B	3	12.5
IV A	16	66.6
IV B	5	20.8

[Table/Fig-1]: Patients demographics.

Distribution of patients according to Karnofsky Performance Score (KPS): KPS improved from 62.5±4.44 to 74.0±5.03, with a p-value of <0.001 [Table/Fig-2].

KPS score	Pretreatment	Post-treatment (after 4 weeks)
Mean±SD	62.5±4.44	74.0±5.03
p-value	<0.001*	

[Table/Fig-2]: KPS change with treatment.
Paired t-test was used; *The p-value <0.05 was considered statistically significant

Toxicity assessment during treatment: Only two patients with cholangitis were admitted for conservative treatment, while the rest were treated on an outpatient basis [Table/Fig-3].

Grade	Patients (n=20)	
	Number (n)	Percentage (%)
Nausea		
I	7	34.00
II	2	10.00
III	2	10.00
Vomiting		
I	2	10.00
II	9	45.00
III	1	5.00
Anaemia		
I	7	35.00
II	4	20.00
III	0	0
Leukocytopenia		
I	4	20.00
II	1	5.00
III	0	0
Thrombocytopenia		
I	2	10.00
II	0	0
III	0	0
Diarrhoea		
I	4	20.00
II	3	15.00
III	1	5.00
Cholangitis		
I	0	0
II	2	10.00

[Table/Fig-3]: Toxicity assessment.

Assessment of quality of life and subjective response: There was an improvement in overall QoL and overall health, but the results were statistically insignificant. There was a substantial improvement in pain, jaundice and nausea/vomiting. Most patients, 18 (90%), needed assistance to answer both questionnaires [Table/Fig-4,5].

Particulars	Pretreatment (A day before treatment)	Mid-treatment (after 5 fraction)	Post-treatment (after 4 weeks)	p-value
EORTC QLQ-C30				
Physical function	44.2±6.4	45.9±7.1	53.2±10.6	0.2
Role function	33.2±20	47.2±1.9	55.3±22.2	0.14
Pain	80.2±7.1	60±9	43±8.6	<0.001*
Fatigue	80±9	77±8.2	74±30	0.30
Dyspnoea	0	0	0	-
Insomnia	87±18	72.6±15	68±18	0.4
Appetite loss	88.67±20	90.2±15	77±24	0.56
Nausea vomiting	52.22±20	54.4±18	37±9	<0.001*
Constipation	89±30	76±18	73±15	0.90
Diarrhoea	4.9±12.19	30.3±28	28±18	0.04*
Cognitive	70±14	67±12	77±9	0.40
Emotion	43±7	50±11	73±6	0.21
Social life	40±18	43±20	60±19	<0.01*
Financial difficulties	84±18	72.5±15	67±1.8	0.33
Overall health	29.17±17.83	41.67±21.29	49.67±14.43	0.08
Overall QoL	37.50±21.54	45.85±11.18	54.65±16.11	0.09

[Table/Fig-4]: Quality of life assessment QLQ-C30.
Results are presented as mean±SD; ANOVA was used; *The p-value <0.05 was considered statistically significant

Particulars	Pretreatment (A day before treatment)	Mid-treatment (after 5 fraction)	Post-treatment (after 4 weeks)	p-value
EORTC BIL-21				
Eating	33.4±8.3	31.2±13.94	48.6±13.6	0.06
Jaundice	67.8±29.4	50±16.8	46±16.85	0.01*
Tiredness	93.0±14.3	82.6±10	80.6±15.3	0.70
Pain	87±5	78±4.381	62.4±6.7	<0.05*
Anxiety	20±4.6	23±9.5	33±8	0.04*

Worried about weight loss	80±18	78.6±14.47	70.2±15.2	0.17
Side-effects	0	68.4±18.2	53.4±19.44	0.02*
Drain	-	-	-	-

[Table/Fig-5]: Quality of life assessment QLQ-C30 BIL-21. ANOVA was used

The drain score was not evaluated, as only those patients were included for whom interventional biliary drainage was not feasible or who could not afford it. In the present study, tumour response was observed in 10 (55.5%) patients, with PR in 4 (22.2%) patients, and SD in 6 (33.3%) patients. Progressive disease was observed in 8 (44.4%) patients [Table/Fig-6].

Tumour response	Patients (n=18), n (%)
Partial Response (PR)	4 (22.2)
Stable Disease (SD)	6 (33.3)
Progressive Disease (PD)	8 (44.4)

[Table/Fig-6]: Tumour response was assessed as per RECIST criteria 1.1, one month after treatment completion.

DISCUSSION

In the present study, most patients were aged 30-60 years, with a mean age of 49.48±5.2 years. This age data can be supported by an epidemiological study by Dutta U et al., in which the average age at diagnosis of GBC was 51±11 years in India [2]. The gender proportion of patients mirrored the established epidemiological pattern of GBC in India, with a higher prevalence observed in females (17, 70.8%) compared to males (7, 29.2%). This finding aligns with the data presented by Phadke PR et al., who documented a female-to-male incidence ratio of 6.04:3.17 in the Gangetic plains region of India [18].

Improvement in Karnofsky Performance Status (KPS) post-treatment was statistically significant, with a p-value of <0.001 in the current study. This result can be supported by a case study by Eleftheriadis N and Pistevou-Gompaki K, who documented the palliative management of unresectable gallbladder carcinoma. The RT dose was followed, and the patient's performance status remained favourable and alive for one year post-diagnosis [19].

Strikingly minimal treatment-related toxicities were observed in the present study. Ranjan A et al., also observed a lower incidence of vomiting compared to the chemotherapy arm [10]. In their research, grade 3 vomiting was experienced by 22.2% of patients in the RT arm. In the same study, grade 1 anaemia was found in 33.33% of patients in the RT arm, and 5.5% had grade 2 anaemia. Grade 1 leukocytopenia was reported in 5.5% of patients in the RT arm, with no cases of thrombocytopenia reported.

Palliative care options for unresectable GBC remain limited. Current approaches primarily focus on managing symptoms like obstructive jaundice through endoscopic or percutaneous biliary drainage. Chemotherapy and Concurrent Chemoradiotherapy (CTRT) are used to address disease progression and symptom palliation; however, these treatments often require extended durations and are associated with adverse effects. Dierks J et al., studied chemotherapy in patients with unresectable GBC, noting that grade 3 and 4 neutropenia was observed in 32.8% of patients, and thrombocytopenia was observed in 13.1% of patients [20]. In a study by Sinha S et al., CTRT was compared with chemotherapy in treating patients with unresectable GBC. Although tumour control was better with CTRT, it was associated with grade 3 neutropenia in 16% of patients [21].

Therefore, while radical approaches can offer significant benefits, they can also be associated with potential risks and challenges. The present study was designed to address the need for a palliative approach that can fulfill the requirement for a short and localised treatment option, aiming for better quality of life while addressing the need for tumour control and symptom management.

The financial difficulty score was important as all patients came from low-income groups. Upon analysing the financial difficulty score using the EORTC QLQ-C30, the results were as follows: the pretreatment score was 84±18, the mid-treatment score was 72.5±15, and the post-treatment score was 67±1.8, indicating a decreasing trend in financial difficulty. In the present study Institute, patients were offered 2D radiotherapy using the Theratron® Phoenix Co 60 for INR 350 for 10 fractions. However, some supportive medications that were unavailable in our institute still cost less than INR 500, despite requiring minimal supportive care. As evidenced by the scores for some patients, even spending this small amount was a difficult task for them to manage.

The present study showed improving trends in the overall quality of life score. This result can be supported by a study by Ranjan A et al., where quality of life was evaluated between the RT and chemotherapy groups using the University of Washington criteria. In the RT arm, with 30 Gray in 10 fractions, the majority of patients, 38.88%, had a fair quality of life, followed by 77.77% with a good quality of life [10]. Adding to the evidence, a study by Sekar V et al., found that symptomatic responses in the RT arm after one month of treatment were 61.4%, indicating a positive treatment response [22].

Tumour response was assessed four weeks after treatment completion. A total of 4 (20%) patients achieved a PR, 6 (30%) had SD, and 8 (40%) had progressive disease (PD). Similar results were reported in a study by Sekar V et al., [22]. A complete response was seen in 1 (3.8%) patient each in the RT and chemotherapy arms, and a PR was seen in 6 (23%) patients in the RT arm and 9 (34.6%) patients in the chemotherapy arm. SD was reported in 9 (34%) patients in the RT arm and 11 (42.3%) patients in the chemotherapy arm; PD was seen in 10 (38.4%) patients in the RT arm and 5 (19.2%) patients in the chemotherapy arm [22]. The study by Ranjan A et al., found a higher PR rate in the RT arm at two months (94.44%) compared to chemotherapy (82.35%), but again, this difference lacked statistical significance (p-value=0.52) [10].

Therefore, RT can be considered a palliative treatment option for patients with unresectable GBC. It was observed that there was an improvement in overall quality of life, performance status and tumour control. Adverse effects related to RT rarely tempered quality of life. Only two patients required hospitalisation to manage adverse effects.

Limitation(s)

The small sample size, the absence of a control group for comparison with standard treatment modalities, and the fact that it is a single-institution study are prominent limitations of the present study.

CONCLUSION(S)

For patients with advanced unresectable gallbladder cancer who are not candidates for surgery or biliary stenting, palliative radiation therapy may be considered. However, a detailed comparative study with a large sample size should be performed for a better understanding of palliative RT in unresectable GBC. By implementing a thorough research plan, a personalised treatment strategy can be selected that optimises patient outcomes. Therefore, improving quality of life, tumour response, and minimising adverse effects is the important goal for palliation.

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PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Radiation Oncology, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India.
2. Associate Professor, Department of General Surgery, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India.
3. Assistant Professor, Department of Radiation Oncology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.
4. Associate Professor, Department of Radiation Oncology, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India.
5. Professor, Department of Radiodiagnosis, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India.
6. Professor, Department of Radiation Oncology, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Tabassum Samani,
Associate Professor Department of Radiation Oncology, Sarojini Naidu Medical College, Agra-282002, Uttar Pradesh, India.
E-mail: tabassumsamani@yahoo.co.in

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