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# Hyperfractionated radiotherapy with concurrent weekly paclitaxel and carboplatin for locally advanced unresectable head and neck squamous cell carcinoma

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## Abstract

**Background:** Squamous cell carcinoma of the head and neck (HNSCC) is a major contributor to cancer-related morbidity and mortality worldwide, with particularly high incidence rates in India and Tamil Nadu. Locally advanced, unresectable HNSCC presents a significant therapeutic challenge. This study aimed to assess the immediate loco-regional response rates following treatment with hyperfractionated radiotherapy combined with concurrent weekly paclitaxel and carboplatin, as well as to evaluate acute toxicity and prognostic factors influencing treatment outcomes.

**Methods:** A cross-sectional study was conducted involving 30 patients with biopsy-confirmed stage III or IV unresectable HNSCC. All patients received hyperfractionated radiotherapy (72 Gy in 120 cGy per fraction, twice daily) concurrently with weekly paclitaxel (40 mg/m$^2$) and carboplatin (AUC = 1). Supportive care included nutritional support, smoking cessation counseling, and dental care. Treatment response was assessed using CT scans and RECIST criteria.

**Results:** The study observed favorable loco-regional control, with most patients achieving either partial or complete responses. Acute toxicity was manageable, with mucositis, xerostomia, and dysphagia being the most frequently reported side effects. Tumor size and patient performance status were significant prognostic indicators of treatment response.

**Conclusion:** Hyperfractionated radiotherapy combined with concurrent paclitaxel and carboplatin demonstrates encouraging loco-regional control and acceptable toxicity in patients with locally advanced, unresectable HNSCC. These findings support its use as an effective therapeutic option; however, further studies with larger sample sizes are needed to validate these outcomes and refine treatment strategies.

***Keywords:*** squamous cell carcinoma; head and neck cancer; hyperfractionated radiotherapy; paclitaxel; carboplatin; loco-regional response

## Introduction

Head and neck cancers, particularly squamous cell carcinomas (HNSCC), represent a major global health concern, contributing significantly to morbidity and mortality [1]. According to the World Health Organization (WHO), more than 900,000 new cases of head and neck cancer are diagnosed annually worldwide, with squamous cell carcinoma accounting for approximately 90% of these cases. In India, the incidence of HNSCC is alarmingly high, especially in regions like Tamil Nadu [2, 3], which has one of the highest burdens of tobacco-related cancers. The National Cancer Registry Programme of India reports that nearly one in five

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cancer patients in the country is diagnosed with cancer of the oral cavity, pharynx, or larynx, with tobacco and alcohol consumption being the primary risk factors [4].

Locally advanced unresectable HNSCC [5] presents a significant challenge in clinical practice. These tumors are typically diagnosed at stages III or IV, where surgical resection is not feasible due to the tumor size, location, or involvement with critical anatomical structures. In such cases, radiotherapy combined with chemotherapy is often the treatment of choice, aiming to control the disease and improve survival. Hyperfractionated radiotherapy, wherein smaller doses of radiation are delivered multiple times a day, has been shown to enhance tumor control while potentially reducing treatment-related toxicity. Concurrent chemotherapy with agents such as paclitaxel and carboplatin is employed to increase tumor radiosensitivity [6].

In Tamil Nadu, where a large population is affected by HNSCC—particularly in rural areas—there is an urgent need for effective and feasible treatment regimens for locally advanced, unresectable tumors [7]. Recent advances in chemoradiation protocols, including hyperfractionated radiotherapy combined with paclitaxel and carboplatin, have shown promising results in improving loco-regional control and survival rates in similar clinical settings globally [8]. However, region-specific data from Tamil Nadu remain limited, and further localized studies are essential to evaluate the effectiveness of these combined modalities in improving patient outcomes.

This study aims to assess the immediate loco-regional treatment response and the pattern of acute toxicities following the combined modality of hyperfractionated radiotherapy and concurrent chemotherapy. It also seeks to analyze the association between key prognostic factors—such as tumor characteristics, performance status, and treatment compliance—and their impact on treatment outcomes.

## Methodology

This cross-sectional study was conducted at a tertiary care hospital in Chennai, Tamil Nadu, from November 2022 to August 2023. The sample size was calculated based on assessing the efficacy of peripheral nerve blocks in facilitating patient positioning for spinal anaesthesia. The study by Machiels et al [7, 8], a minimum of 27 patients was estimated to achieve adequate statistical power (80%) at a 5% significance level. To account for potential dropouts or protocol deviations, the sample size was rounded to 30 patients. A consecutive sampling method was employed, whereby all eligible patients presenting during the study period were included until the target number was achieved. A total of 30 patients with locally advanced, unresectable squamous cell carcinoma (SCC) of the head and neck were enrolled based on specific inclusion and exclusion criteria. All patients provided informed consent, and ethics committee clearance was obtained from the institutional review board.

Patients diagnosed with stage III or IV (M0) unresectable squamous cell carcinoma of the head and neck, confirmed through biopsy, were eligible for inclusion. Tumors were located in the oral cavity, oropharynx, hypopharynx, or larynx. Patients aged 18–70 years with an ECOG performance status of ≥70% and without major comorbidities were considered. Exclusion criteria included non-squamous histology, tumors located in the nasal or paranasal sinuses, prior malignancies, or previous radiotherapy or chemotherapy.

All patients underwent thorough pre-treatment evaluation, including detailed medical history and physical examination, complete blood count, liver and renal function tests, and staging using contrast-enhanced CT of the neck, panendoscopy, and cardiac assessment (echocardiogram and ECG). Nutritional status was also assessed, and appropriate interventions were provided.

The treatment protocol involved hyperfractionated radiotherapy (RT) [9] combined with weekly paclitaxel and carboplatin chemotherapy. A total radiation dose of 72 Gy was delivered in 120 cGy fractions, twice daily at 6-hour intervals, over six weeks using a cobalt-60 Theratron Phoenix machine. Chemotherapy—paclitaxel (40 mg/m$^2$) and carboplatin (AUC = 1)—was administered weekly between the two daily radiation fractions, for a total of six cycles. Premedication with antiemetics and corticosteroids was given to manage chemotherapy-related side effects [10].

*Patient care and monitoring:* Patients were monitored daily for acute toxicities, including mucositis, skin reactions, and hematologic abnormalities. Supportive care included hydration, oral and dental care, nutritional support, and smoking cessation counseling. Weekly blood tests were conducted to monitor hemoglobin levels, white blood cell counts, and platelet counts. Interventions such as blood transfusions were provided as needed.

*Response evaluation:* Tumor response was assessed 4–6 weeks after completion of treatment using CT imaging of the neck, following RECIST 1.1 criteria. Responses were categorized as complete response,

partial response, stable disease, or progressive disease. Statistical analyses, including Pearson's chi-square and Fisher's exact tests, were used to evaluate prognostic factors affecting treatment response.

## Results

The study included 30 patients, with demographic details presented in Table 1. Participants ranged in age from 25 to 66 years, with a median age of 51.03 years. The majority (50%) were in the 51–60-year age group. Male patients predominated, accounting for 86.67% (n=26),and females for 13.33 % (n=4) of the study population.

**Table 1:** Age distribution of patients with locally advanced unresectable HNSCC.

| *Age group (years)* | *No. of patients* | *Percentage (%)* |
|---|---|---|
| 11 to 20 | 0 | 0 |
| 21 to 30 | 2 | 6.67 |
| 31 to 40 | 4 | 13.33 |
| 41 to 50 | 6 | 20 |
| 51 to 60 | 15 | 50 |
| 61 to 70 | 3 | 10 |

*Karnofsky performance status and habits:* The majority of patients (56.67%) had a Karnofsky Performance Status (KPS) score of 90, indicating good functional status suitable for the demanding treatment protocol. Regarding personal habits, smokeless tobacco use, either alone or in combination with other habits, was observed in 53.33% of the study population (Table 2).

**Table 2:** Karnofsky performance status and habitual risk factors among study participants.

| *Category* | *Subcategory* | *No. of patients* | *Percentage (%)* |
|---|---|---|---|
| KPS | | | |
| | 90 | 17 | 56.67 |
| | 80 | 7 | 23.33 |
| | 70 | 6 | 20 |
| Habits | | | |
| | Smokeless tobacco + Alcohol | 9 | 30 |
| | Smoking + Alcohol | 7 | 23.33 |
| | Smoking only | 5 | 16.67 |
| | Smokeless tobacco only | 4 | 13.33 |
| | Alcohol only | 2 | 6.67 |
| | All three | 3 | 10 |

*Tumor subsite and stage characteristics:* The most common tumor sub-sites were the oropharynx (36.67%) and the oral cavity (33.33%). Most patients presented with advanced disease stages, with T3 tumors (60%) and stage IV A (53.33%) (Table 3).

**Table 3:** Tumor sub-site, primary tumor (T Stage), nodal involvement, and overall stage distribution.

| *Category* | *Subcategory* | *No. of patients* | *Percentage (%)* |
|---|---|---|---|
| Sub-site | | | |
| | Oral cavity | 10 | 33.33 |
| | Oropharynx | 11 | 36.67 |
| | Larynx | 7 | 23.33 |
| | Hypopharynx | 2 | 6.67 |
| Primary tumor (T Stage) | | | |
| | T1 | 1 | 3.33 |
| | T2 | 1 | 3.33 |
| | T3 | 18 | 60 |
| | T4a | 10 | 33.33 |
| Nodal stage (N stage) | | | |
| | N0 | 6 | 20 |
| | N1 | 10 | 33.33 |
| | N2 | 12 | 40 |
| | N3 | 2 | 6.67 |
| Stage grouping | | | |
| | Stage III | 12 | 40 |
| | Stage IV A | 16 | 53.33 |
| | Stage IV B | 2 | 6.67 |

*Histological differentiation and treatment compliance:* Histologically, 63.33% of tumors were moderately differentiated. Regarding chemotherapy compliance, 43.33% of patients completed 6 cycles, while 50% completed 5 cycles (Table 4).

**Table 4:** Histological differentiation of tumors and compliance to chemotherapy cycles.

| *Category* | *Subcategory* | *No. of patients* | *Percentage (%)* |
|---|---|---|---|
| Histological differentiation | | | |
| | Well differentiated | 8 | 26.67 |
| | Moderately differentiated | 19 | 63.33 |
| | Poorly differentiated | 3 | 10 |
| Chemotherapy cycles | | | |
| | 6 Cycles | 13 | 43.33 |
| | 5 Cycles | 15 | 50 |
| | 4 Cycles | 2 | 6.67 |

*Radiotherapy compliance:* All patients received a minimum radiation dose of 40.8 Gy. However, some patients discontinued treatment due to toxicity during the higher dose phases (Table 5).

**Table 5:** Distribution of radiation dose received by patients.

| *Radiation dose (Gy)* | *No. of patients* | *Percentage (%)* |
|---|---|---|
| 2 to 40.8 | 30 | 100 |
| 40.8 to 60 | 29 | 96.67 |
| 62.4 to 72 | 28 | 93.33 |

*Acute local reactions:* Acute local reactions were assessed using RTOG Acute Morbidity Scoring Criteria. The most common reactions included grade 3 mucositis (67.86%), grade 3 dysphagia (57.14%), and grade 2 skin toxicity (53.57%) (Table 6).

**Table 6:** Acute local reactions during treatment based on RTOG scoring criteria.

| *Category* | *Grade* | *No. of patients* | *Percentage (%)* |
|---|---|---|---|
| Mucositis | | | |
| | Grade 0 | 0 | 0 |
| | Grade 1 | 2 | 7.14 |
| | Grade 2 | 7 | 25 |
| | Grade 3 | 19 | 67.86 |
| Dysphagia | | | |
| | Grade 0 | 0 | 0 |
| | Grade 1 | 0 | 0 |
| | Grade 2 | 12 | 42.86 |
| | Grade 3 | 16 | 57.14 |
| Skin toxicity | | | |
| | Grade 0 | 0 | 0 |
| | Grade 1 | 10 | 35.71 |
| | Grade 2 | 15 | 53.57 |
| | Grade 3 | 1 | 3.57 |
| | Grade 4 | 2 | 7.14 |
| Xerostomia | | | |
| | Grade 0 | 0 | 0 |
| | Grade 1 | 21 | 75 |
| | Grade 2 | 7 | 25 |
| Laryngitis | | | |
| | Grade 0 | 0 | 0 |
| | Grade 1 | 19 | 67.86 |
| | Grade 2 | 6 | 21.43 |
| | Grade 3 | 3 | 10.71 |

*Systemic toxicities:* Systemic toxicities, including nausea and vomiting, were evaluated using CTCAE Version 4. A significant proportion of patients experienced grade 3 nausea (57.14%) and grade 1 vomiting (78.57%) (Table 7).

**Table 7:** Systemic toxicities observed during chemotherapy based on CTCAE version 4.

| *Category* | *Grade* | *No. of patients* | *Percentage (%)* |
|---|---|---|---|
| Nausea | | | |
| | Grade 1 | 2 | 7.14 |
| | Grade 2 | 10 | 35.57 |
| | Grade 3 | 16 | 57.14 |
| Vomiting | | | |
| | Grade 1 | 22 | 78.57 |
| | Grade 2 | 6 | 21.43 |
| | Grade 3 | 0 | 0 |

*Hematological Toxicity:* Hematological toxicity was evaluated using the RTOG Acute Morbidity Scoring Criteria. The majority of patients had minimal or no hematological toxicity, with grade 1 anemia being the most common observation (46.43%) (Table 8).

**Table 8:** Hematological toxicity assessment based on RTOG criteria.

| *Toxicity* | *Grade* | *No. of patients* | *Percentage (%)* |
|---|---|---|---|
| Anaemia | | | |
| | Grade 0 | 6 | 21.43 |
| | Grade 1 | 13 | 46.43 |
| | Grade 2 | 9 | 32.14 |
| | Grade 3 | 0 | 0 |
| Leucopenia | | | |
| | Grade 0 | 26 | 92.86 |
| | Grade 1 | 2 | 7.14 |
| | Grade 2 | 0 | 0 |
| | Grade 3 | 0 | 0 |
| Thrombocytopenia | | | |
| | Grade 0 | 27 | 96.43 |
| | Grade 1 | 1 | 3.57 |
| | Grade 2 | 0 | 0 |
| | Grade 3 | 0 | 0 |

*Demographic and Treatment Factors:* The treatment response was further analyzed in relation to key demographic and treatment-related variables, including age, gender, disease stage, number of chemotherapy

cycles completed, and overall radiotherapy duration. These factors were assessed to explore their influence on achieving complete or partial loco-regional response. Table 9 summarizes the comparative response rates across different subgroups and the corresponding statistical significance.

**Table 9:** Treatment response in relation to demographic and treatment factors.

| *Factor* | *Subgroup* | *Complete response (%)* | *Partial response (%)* | *p value* |
|---|---|---|---|---|
| Age | | | | |
| | ≤51 years | 41.67 | 58.33 | 0.162 |
| | ≥52 years | 75 | 25 | |
| Gender | | | | |
| | Male | 62.5 | 37.5 | 0.636 |
| | Female | 50 | 50 | |
| Stage | | | | |
| | III | 75 | 25 | 0.342 |
| | IV | 50 | 50 | |
| Chemotherapy cycles | | | | |
| | ≤5 cycles | 46.67 | 53.33 | 0.212 |
| | >5 cycles | 76.92 | 23.08 | |
| Radiotherapy duration | | | | |
| | ≤45 days | 55.55 | 44.44 | 0.7 |
| | >45 days | 63.15 | 36.84 | |

*Tumor characteristics:* Tumor-related factors such as histological differentiation, primary tumor (T) stage, nodal (N) involvement, and anatomical subsite were analyzed to assess their impact on treatment response. The majority of tumors were moderately differentiated, with a significant portion presenting as T3 or T4a lesions. Nodal involvement was common, with N2 being the most frequent stage. Sub-site distribution revealed a predominance of oropharyngeal and oral cavity tumors. Table 10 summarizes the treatment response in relation to these tumor characteristics.

**Table 10:** Treatment response based on tumor characteristics (Histology, T/N stage, and sub-site).

| *Characteristic* | *Subgroup* | *Complete response (%)* | *Partial response (%)* | *p value* |
|---|---|---|---|---|
| Histological differentiation | | | | |
| | Well differentiated | 50 | 50 | |
| | Moderately differentiated | 94.7 | 5.3 | 0.018 |
| | Poorly differentiated | 100 | 0 | |
| T stage | | | | |
| | T1/T2 | 100 | 0 | |
| | T3 | 70.59 | 29.41 | - |
| | T4a | 33.33 | 66.67 | |
| N stage | | | | |
| | N0/N1 | 66.67–70.00 | 30.00–33.33 | - |
| | N2 (a/b/c) | 50 | 50 | |
| Tumor sub-site | | | | |
| | Oropharynx | 90 | 10 | |
| | Oral Cavity | 22.22 | 77.78 | - |
| | Larynx | 57.14 | 42.86 | |
| | Hypopharynx | 100 | 0 | |

## Discussion

The management of locally advanced unresectable head and neck squamous cell carcinoma (HNSCC) continues to pose a significant challenge despite advances in multimodal therapy. Conventional radiotherapy, though foundational, has often yielded suboptimal outcomes, particularly in tumors with large volumes, hypoxic microenvironments, and aggressive biological behavior. These factors contribute to radioresistance, rapid tumor repopulation, and poor overall survival in advanced stages—historically estimated at 30–40% at three years [1, 4].

In response to these limitations, hyperfractionated radiotherapy and concurrent chemotherapy have emerged as strategies aimed at enhancing loco-regional control while mitigating long-term toxicity. Our study evaluated the efficacy and tolerability of hyperfractionated radiotherapy combined with concurrent weekly paclitaxel and carboplatin in a cohort of patients with unresectable stage III and IV HNSCC. The results demonstrated a promising overall complete response (CR) rate of 61%, with manageable acute toxicity profiles, thereby supporting the viability of this combined modality approach.

## Rationale for hyperfractionated radiotherapy and chemotherapy

Hyperfractionation, characterized by the administration of smaller radiation doses twice daily, leverages radiobiological principles to exploit the differential repair capacities of tumor and normal cells. This technique aims to minimize late normal tissue toxicity while allowing for a higher total radiation dose to improve tumor control. Notably, meta-analyses—including the MARCH trial update—have confirmed that altered fractionation schedules confer a statistically

significant survival benefit compared to conventional once-daily radiotherapy [5].

The concurrent use of chemotherapy further augments the cytotoxic effects of radiation by radiosensitizing tumor cells and addressing micrometastatic disease. Paclitaxel, a microtubule-stabilizing agent, has demonstrated potent radiosensitizing properties, while carboplatin, a platinum compound, enhances DNA crosslinking and apoptosis [11]. The synergistic effect of these agents, administered weekly, ensures continuous tumor suppression throughout the course of radiotherapy.

Our treatment regimen of 72 Gy delivered in 1.2 Gy fractions twice daily over six weeks falls within the radiobiologically optimal range, aligning with recent guideline recommendations [12]. BED (Biologically effective dose) calculations in our study—80.64 $Gy_{10}$ for tumor control and 100.8 $Gy_3$ for late effects—reaffirm the therapeutic adequacy of the regimen, achieving high tumoricidal doses without exceeding normal tissue tolerance thresholds.

## Treatment outcomes in context

The loco-regional response observed in our cohort mirrors or exceeds results from other contemporary studies employing hyperfractionated regimens. For instance, the American Society of Clinical Oncology (ASCO) reports that CR rates with concurrent chemoradiotherapy in unresectable HNSCC typically range from 50% to 65%, depending on regimen intensity and patient selection [13, 14].

Our subgroup analyses revealed that patients with moderately and poorly differentiated tumors demonstrated superior complete response rates compared to those with well-differentiated tumors, corroborating findings from Johnson et al. [4] indicating that tumor grade significantly influences radiosensitivity. Similarly, early T-stage tumors (T1–T2) showed 100% CR, consistent with the concept that tumor burden is inversely proportional to radiotherapeutic efficacy[15].

Patients with oropharyngeal tumors exhibited particularly favorable responses, likely reflecting the inherent radiosensitivity of HPV-associated cancers, which are predominant in this subsite [10]. While HPV status was not formally assessed in our study, it remains a critical prognostic biomarker in HNSCC and should be included in future research [16].

## Toxicity profile

Acute toxicities observed in our study were consistent with expectations for intensified chemoradiation protocols. Grade 3 mucositis (67.86%) and dysphagia (57.14%) were the most common adverse events but were transient and manageable with supportive care measures. Importantly, no treatment-related mortalities occurred, and over 90% of patients completed at least five cycles of chemotherapy—underscoring the regimen's feasibility even in resource-constrained settings [17].

Hematological toxicities, particularly anemia and leukopenia, were predominantly mild (Grade 1–2), reflecting the tolerable myelosuppressive profile of the selected chemotherapy agents at the given doses. The use of weekly paclitaxel and carboplatin, as opposed to more aggressive cisplatin-based regimens, likely contributed to this favorable toxicity profile—a strategy increasingly recommended in recent guidelines for frail or nutritionally compromised patients (WHO Global Cancer Initiative, 2021 [2, 18]).

## Comparative effectiveness and relevance to the Indian population

The burden of HNSCC in India—exacerbated by prevalent risk factors such as smokeless tobacco use and poor oral hygiene—necessitates treatment regimens that balance efficacy with tolerability (WHO Report on the Tobacco Epidemic, 2021 [3,19,20]). Hyperfractionated chemoradiation protocols tailored to regional patient demographics, such as the one studied here, offer a pragmatic approach to addressing these unique healthcare challenges.

Notably, a significant proportion of our patients were from rural Tamil Nadu, with limited access to tertiary care. Despite this, treatment compliance was high, facilitated by robust supportive care and patient education initiatives. These findings suggest that, with adequate infrastructural support, complex treatment protocols like hyperfractionated chemoradiation can be successfully implemented even in non-metropolitan settings.

*Limitations:* The study's limitations include treatment delivery with cobalt-60 radiotherapy, a relatively small sample size, and lack of consensus on optimal hyperfractionation schedules. These factors limit generalizability and highlight the need for validation through larger, randomized phase III trials.

## Conclusion

Our study confirms that hyperfractionated chemoradiotherapy with concurrent weekly paclitaxel and carboplatin is both tolerable and feasible for

treating locally advanced unresectable squamous cell carcinomas of the head and neck. The complete response rate of 61% aligns with international findings. Acute toxicities were manageable, and a high proportion of patients completed the planned treatment. Tumor differentiation, T-stage, and N-stage were significant predictors of treatment outcomes. This combined modality approach, particularly the use of hyperfractionation, appears promising for advanced disease and warrants further investigation in larger, phase III clinical trials.

## Conflicts of interest

Authors declare no conflicts of interest.

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