e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(7); 477-487

Original Research Article

A Retrospective Study on Comparison of Weekly versus Three Weekly Cisplatin Based Chemotherapy with Concurrent Radiotherapy in Treatment of Oropharyngeal Cancer

Santosh Shubham[1], Tanmoy Roy[2], Maria Rose Joseph[3], Nisha Jha[4]

[1]Senior Resident, Department of Radiation Oncology, Mahavir Cancer Sansthan, Patna
[2]Junior resident, Mahavir Cancer Sansthan, Patna.
[3]Junior resident, Mahavir Cancer Sansthan, Patna.
[4] Senior Resident, IGIMS, Patna

Received: 20-03-2023 / Revised: 21-04-2023 / Accepted: 25-05-2023
Corresponding author: Dr Nisha Jha
Conflict of interest: Nil

Abstract:

This retrospective study evaluated the toxicity and loco regional response of cisplatin-based chemotherapy administered in conjunction with radiation therapy for oropharyngeal carcinoma. Group A received 30mg/m2 intravenously every week, while Group B received 100mg/m2 every three weeks for 120 patients with histopathology-confirmed oropharyngeal cancer. Both groups were treated with 66–70 Gy of 2D radiation. Chemotherapy and radiation weekly evaluated acute toxicity. The study found that weekly and triweekly cisplatin-based chemotherapy could be used to treat oropharyngeal cancer. Both groups had comparable rates of acute toxicity. Nevertheless, Group B (tri weekly regimen) demonstrated a higher loco regional response rate than Group A (weekly regimen), indicating treatment efficacy. This study demonstrates that concurrent chemoradiation with weekly or tri weekly cisplatin-based chemotherapy is feasible and well-tolerated for oropharyngeal carcinoma. Greater loco regional response rates and comparable toxicity were observed with the tri weekly regimen. These discoveries facilitate research on the treatment of oropharyngeal cancer.

Keywords: Cisplatin-based chemotherapy, Concurrent chemoradiation, Loco-regional response, Oropharyngeal carcinoma, Toxicity.

Introduction

Head and Neck Cancers (HNC) is a common cancer, 50%–2/3 of HNC patients present with the locally advanced disease. Concurrent chemoradiation is best for these patients. Chemoradiation (CRT) surpasses radiation therapy alone in Loco-Regional Control (LRC) and overall survival (OS) in locally advanced Head and Neck Squamous Cell Cancer (HNSCC). HNSCC ranks sixth worldwide, 350,000 die worldwide, and 650,000 are diagnosed [1]. HNSCC primarily affects the upper aerodigestive tract (nose, sinuses, middle ear fissure, mouth, pharynx, oropharynx, hypopharynx, and larynx). Upper aerodigestive tract squamous cell cancer is risky, alcohol, HPV, and cigarettes are the most common. Oral cancer is the most common HNSCC in India, Pakistan, and Southeast Asia andover 500,000 new cases are predicted annually. In nations like India, almost 60% of head and neck squamous cell tumours are advanced, and their prognosis has not changed in 30 years. > 60% of these tumours are locoregionally advanced stage III or IV, with 30% cure rates and significant morbidity from surgery and non-surgical treatment. India has oropharyngeal cancer. According to national registries, Trivandrum (South) has the highest rate of oropharyngeal cancers other than tonsils. Human papillomavirus may increase oropharyngeal cancer in young Westerners [2]. MRI and PET scans help diagnose rare oropharyngeal Squamous Cell Carcinoma (SCC). Serial computed tomography scanning dominates imaging in the US. Surgeons and radiation oncologists can treat T1-2 oropharyngeal SCCs with a neck strategy. T3-T4 nodally aggressive oropharyngeal SCC require surgery, adjuvant irradiation, or concurrent chemoradiation and salvage surgery. Combination ChemoRadiation (CCRT) outperformed Radiation Therapy (RT) alone in two large randomised controlled studies [3,] for locally advanced head and neck cancer patients with high-risk features such as T3 or T4 and positive lymph nodes. Cisplatin-based regimens work best because of single-agent activity, synergistic interaction, and nonoverlapping toxicity. Cisplatin doses range from 100 mg/m every three weeks for three cycles

to 6 mg/day [4]. Daily or weekly low-dose CT radio sensitises, while high-dose CT removes occult micro metastasis to avoid distant metastasis. In this study, two locally advanced oropharyngeal carcinoma CCRT regimens gave cisplatinum weekly and every three weeks and Comparing response rate, loco-regional control, disease stage, and acute and late toxicity of the two CCRT regimens.

Aim

This study compares weekly versus tri weekly cisplatin-based chemotherapy with concurrent radiation therapy to treat oropharyngeal carcinoma.

Objectives

1. To compare the toxicity of weekly and three-weekly cisplatin-based chemotherapy concurrent with radiotherapy in oropharyngeal carcinoma in a definitive setting.
2. To assess and compare loco-regional response by both modalities.

Literature Review

Anatomy

The proximal boundary is the hard palate and distally bounded by valleculae and hyoid bone. Palatoglossal muscle & circumvallate papillae form anterior boundary and muscular pharyngeal wall forms posterior wall of the oropharynx. For treating oropharyngeal cancers requires distinguishing between the tonsil, tonsillar fossa, tonsil pillars, soft palate, posterior pharyngeal wall, and tongue base [5].

Histopathology

Most oropharyngeal lesions are SCC and minor salivary tumours (adenomas/adenocarcinomas) & other histology are less common. This article covers invasive oropharyngeal squamous cell neoplasm diagnosis and therapy unless otherwise stated.

Malignant epithelial tumours	
Squamous cell carcinoma	8070/3
Verrucous carcinoma	8051/3
Basaloid squamous cell carcinoma	8083/3
Papillary squamous cell carcinoma	8052/3
Spindle cell carcinoma	8074/3
Acantholytic squamous cell carcinoma	8075/3
Adenosquamous carcinoma	8560/3
Carcinoma cuniculatum	8051/3
Lymphoepithelial carcinoma	8082/3
Epithelial precursor lesions	
Benign epithelial tumours	
Papillomas	8050/0
Squamous cell papilloma and verruca vulgaris	
Condyloma acuminatum	
Focal epithelial hyperplasia	
Granular cell tumour	9580/0
Keratoacanthoma	8071/1
Salivary gland tumours	
Salivary gland carcinomas	
Acinic cell carcinoma	8550/3
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Polymorphous low-grade adenocarcinoma	8525/3
Basal cell adenocarcinoma	8147/3
Epithelial-myoepithelial carcinoma	8562/3
Clear cell carcinoma, not otherwise specified	8310/3
Cystadenocarcinoma	8450/3
Mucinous adenocarcinoma	8480/3
Oncocytic carcinoma	8290/3
Salivary duct carcinoma	8500/3
Myoepithelial carcinoma	8982/3
Carcinoma ex pleomorphic adenoma	8941/3
Salivary gland adenomas	
Pleomorphic adenoma	8940/0
Myoepithelioma	8982/0
Basal cell adenoma	8147/0
Canalicular adenoma	8149/0
Duct papilloma	8503/0
Cystadenoma	8440/0
Soft tissue tumours	
Kaposi sarcoma	9140/3
Lymphangioma	9170/0
Ectomesenchymal chondromyxoid tumour	
Focal oral mucinosis	
Congenital granular cell epulis	
Haematolymphoid tumours	
Diffuse large B-cell lymphoma (DLBCL)	9680/3
Mantle cell lymphoma	9673/3
Follicular lymphoma	9690/3
Extranodal marginal zone B-cell lymphoma of MALT type	9699/3
Burkitt lymphoma	9687/3
T-cell lymphoma (including anaplastic large cell lymphoma	9714/3
Extramedullary plasmacytoma	9734/3
Langerhans cell histiocytosis	9751/1
Extramedullary myeloid sarcoma	9930/3
Follicular dendritic cell sarcoma / tumour	9758/3
Mucosal malignant melanoma	8720/3
Secondary tumours	

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {821} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

Figure 1: **Classification of Oral Cavity and Oropharyngeal Tumors by Histologic Type**

Indian Scenario

3.8% of Indians will develop pharyngeal (non-nasopharynx) cancer, 4.8% will die, and 6.4% will survive 5 years later. It is the fifth most common male malignancy and the ninth most common worldwide [6].

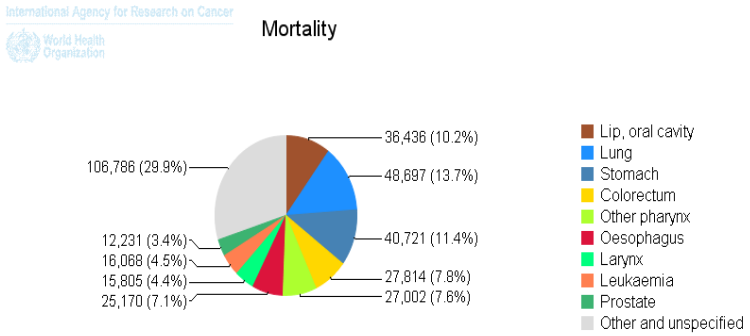


Figure 2: **Morality**

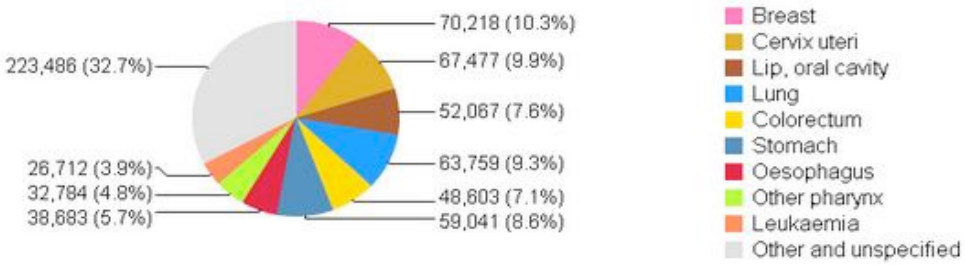


Figure 3: **Different Cancers in India**

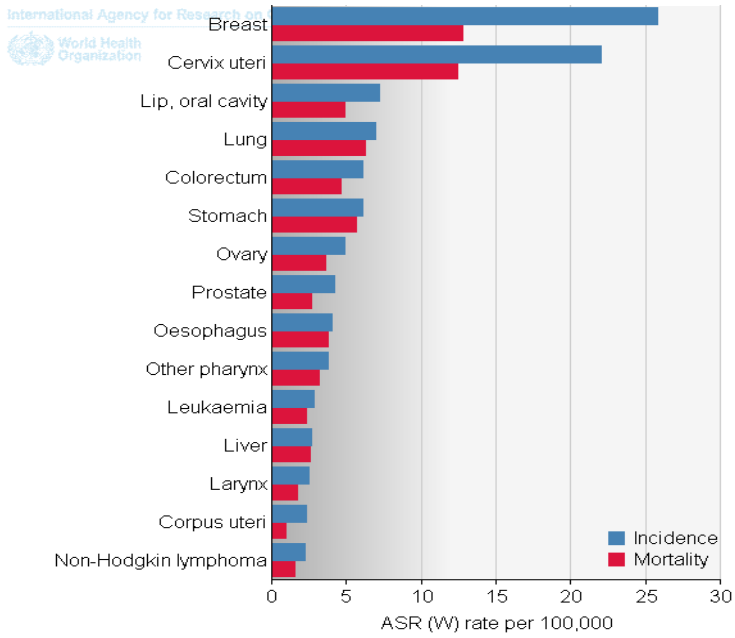


Figure 4: **Estimated age-standardized incidence and mortality rates: both sexes**

Etiology

Smoking causes pharyngeal cancer; tobacco is more causative than chewing. Smoking a pack and a half a day for ten years triples oropharyngeal cancer risk and its abstinence for 16 years lowered risk from 14.3 to 2.5. Alcohol causes oropharyngeal cancer, alcoholics (non-smokers) have 5.6 times the laryngeal cancer risk.

HPV is regularly researched in oropharyngeal SCC oncogenesis. Several studies have linked OSCC to oral HPV infection, seropositivity, or both and despite sexual behaviour patterns, younger groups

seem to be more affected. Scientists believe HPV-associated oropharyngeal cancers are less aggressive than those caused by other viruses and enhance survival rates. HPV causes most Fanconianaemia head and neck SCC, the risk of head and neck SCC at any site, including the oropharynx, doubles or quadruples with a family history and family alcohol and cigarette usage increased Relative Risk (RR) [7].

Relative Distribution

Local Spread

Multiple studies suggest that 66–76% of tonsillar SCC patients have clinically positive nodal metastases upon diagnosis. Palatal and posterior pharyngeal wall tumours only spread to ipsilateral jugulodigastric lymph nodes.

Local, regional, or systemic tongue-base SCC aggressiveness. One study found 60% of tongue-root tumours were poorly differentiated, 20% of T1/T2 individuals had bilateral lymph node illness. Untreated loco-regional tongue SCC patients had 30%–50% more distant metastases [8].

Lymphatic Spread

Anatomic barriers and location affect sub-anatomic cancers' metastasis. Soft-palate tumour patients often develop a second oral tumour on the floor. T3 and T4 tumours have 50% bilateral nodal metastases despite ipsilateral spread being more common. Posterior pharyngeal wall tumours commonly metastasise to bilateral lymph nodes. Levels I–III often have oral cavity SCC metastases. Level II, III, and IV tumours are common.

Diagnostic Workup for Oropharyngeal Carcinoma

The patient's medical history should include dysphagia, odynophagia, discomfort, trismus, speech difficulties, hoarseness, unstable teeth, ill-fitting dentures, hypoesthesia in the lips or mandible, weight loss, and malnutrition.

Otalgia signals ninth or tenth cranial nerve issues, Mandible-to-inferior alveolar nerve perineural invasion can cause hypoesthesia. Trismus, pterygoid muscle extension, indicates localised disease. Chronic ulcers, haemorrhages, drooling, and respiratory difficulties may ensue. Oral cavity palpation can assess bone involvement, tongue fixation, and involvement depth. RI is better than CT for contrast allergies and poorly visible lesions and MRI measures perineural dissemination [9]. Stage III and IV distant metastases detection, in radiation therapy patients, PET may detect persistent or recurrent sickness better than CT and MRI.

Concomitant Chemoradiotherapy in Locally Advanced Head and Neck Squamous Cell Cancer

LASCCHN treatment has evolved over decades, although the medical community still debates interdisciplinary approaches. HNSCC was only treated non-surgically with radiation until 2000, CRT was utilised after phase III trials [10] revealed that chemotherapy plus radiation in locally advanced HNSCC enhanced survival. Systemic CCRT improves locoregional control, not micrometastases. Remote disease control is improving with Induction Chemotherapy (IC) followed by radiation (CCRT), this helps LASCCHN. LASCCHN patients do not benefit from CCRT and was typically treated with CCRT. IC with CCRT may improve clinical results, definitive chemoradiotherapy has treated LAHNC for a decade. In a meta-analysis of randomised trials, concomitant chemoradiotherapy improved 5-year OS by 6.5% compared to radiation alone. These findings suggest cisplatin (CDDP) is the best radiation treatment. Concurrent CDDP chemoradiotherapy enhances short-term morbidity and long-term side effects. Safer is cetuximab (C225). Pignonet al. [11] meta-analysed 87 trials with 16485 patients between 1965 and 2000 and found that chemotherapy increased 5-year survival by 4.5% and concomitant CRT by 6.5%. Mortality was 0.81 (0.78-0.86, $P < 0.0001$). After 5 years of induction chemotherapy, the mortality hazard ratio was 0.96 (0.9-1.02, $P = 0.18$), while the absolute benefit was 2.4%. This meta-analysis indicated that chemotherapy and radiation did not benefit certain patient groupings, which smaller trials could not show.

ECOG performance levels 2 and 3, stage I and II malignancies, and "orphan cancers"—HNSCC outside the oral cavity, oropharynx, larynx, hypopharynx, and nasopharynx—were investigated independently. Over-70s did not benefit from radiation or platinum-based chemotherapy. Radiation enhances chemotherapy toxicity but improves locally advanced HNSCC survival.

Evolution in Radiotherapy Treatment Technique

Breast cancer X-rays originated in January 1896; Early 1900s X-rays treated cancer. The new beams ' unknown biological effects and action mechanisms generated different illnesses and poor cancer care.[12] These findings spurred radiotherapy delivery, cell effects, and radiation properties study. Since external beams were unavailable, intracavitary and interstitial radium irradiation treated deep cancers. Coolidge's super voltage X-ray tube and post-WWII radiation physics used megavoltage, megavoltage linear electron accelerators and cobalt teletherapy treat deep cancers and cobalt teletherapy produced 1.3MVX-ray-like gammas. In the mid-1950s, electron linear accelerator therapy began [13]. 2D radiotherapy uses one beam, beam design used opposed lateral fields or four fields' 'boxes'. 3D conformal radiotherapy minimized tissue dam-

age, treating 3D anatomy, Axis and neck-shoulder hourglass. 3D conformal radiotherapy calculates radiation doses to irregular targets while protecting healthy tissue. Beam intensity adjustment within the treatment field was necessary despite these developments. Intensity-modulated radiotherapy solved this. IMRT target dosage is altered by beamlet intensity. The software reduced radiation, instead of doctors choosing beam angles and weights, computer optimisation calculated intensity distribution across a treatment volume.

Material and Methods

Oropharyngeal cancer patients undergoing pretreatment evaluation at MCS OPD were recruited for the study.

- History
- Physical examination
- Chest X-ray
- Complete blood count
- LFT
- KFT
- Direct & Indirect laryngoscopy.
- CECT scan of face and neck.
- Biopsy from the primary lesion.

Our Scientific and Ethical Committee approved all patients who gave informed consent for the study. June 2015 to December 2016 was the period of investigation.

Inclusion Criteria

1. A tissue biopsy confirmed oral and pharyngeal malignancies.
2. Patients aged 18 to 70 years old.
3. Persons with a Kornofsky Performance Status of at least 70.
4. Patients without severe coexisting conditions.
5. Those who are in stages III and IVA.
6. Patients with a normal white blood cell count, kidney, cardiac, and liver function.

a) Hemoglobin at least 10gm/dl
b) TLC>4000/mm3
c) Platelet count >1,00,000/mm3

Exclusion Criteria

1. Histology of non-squamous cell carcinomas
2. A synchronous double primary is present.
3. Oro-pharyngeal carcinoma has returned.
4. Patient has a history of head and neck cancer treatment.
5. In the wake of surgery.
6. Nursing and pregnancies.
7. distant metastasis.
8. Anterior to the Oral Cavity.
9. Patient refuses to fill out a consent form.

Included were 120 individuals with histopathology-confirmed oropharyngeal cancer. Consenting patients were randomly assigned to Group A or Group B.

Treatment Plan

The Theratron 780E Cobalt delivered 2D conventional radiation to Groups A and B. 66–70 Gy were delivered by 33–35 2Gy fractions. Cisplatin was used in concomitant chemotherapy.

Group A: 30mg/m^2 IV weekly.
Group B: 100mg/m^2 IV three weekly.

After hydration, cisplatin was administered intravenously with normal saline. Intravenous infusions of mannitol, potassium chloride, and magnesium sulphate were administered. During chemotherapy and radiotherapy, acute toxicities were assessed weekly.

Chemotherapy Protocol

During radiotherapy, patients were administered Cisplatin 30 mg/m2 intravenously weekly (on days 1,8,15,22,29, and 36) or 100 mg/m2 every three weeks (on days 1,22, and 43). In the 3 weekly arms, cisplatin was administered intravenously over 2 days, with the patient being admitted the day before ensure adequate hydration, anti-emetic prophylaxis, and mannitol infusions. In the weekly arm, the same doses were administered on an outpatient basis in a daycare ward. Hospitalisation, colony-stimulating factors, and Rye's tube nutrition saved lives. Before every chemotherapy treatment, blood and renal parameters were evaluated. Details regarding Cisplatin, chemotherapeutic cycles, and RT were recorded andtherapy was suspended due to delays.

Monitoring of the Patients on Radiotherapy

Acute toxicity

Radiation therapy started the 90-day acute toxicity evaluation and Radiation patients were monitored weekly. Acute toxicity monitoring required weekly Radiotherapy Out Patient Department (OPD) visits. Acute toxicities were assessed weekly for chemotherapy and radiation patients using CTCAE version 4.03. Age, sex, KPS, site, preR Thaemoglobin, TNM stage, HDR, GDR, and total treatment time were investigated as loco-regional control confounders. Morbidities were assessed and treated,acute toxicities stopped two groups of A patients after 54 Gy.

Evaluation of Response

- The major tumour location vanished and stayed gone.
- No neck lymph nodes form.
- Clinical and radiographic disease-free after treatment.

Assessment of Late Toxicities

Late radiation morbidity was scored and graded using the RTOG/EORTC Late Radiation Morbidity Scoring Schema (Appendix-3).

- Skin toxicity
- Subcutaneous Tissue toxicity
- Mucous membrane toxicity
- Salivary gland toxicity
- Laryngeal toxicity
- Dysphagia (Esophageal Toxicity)

Statistical Analyses

The trial included 120 people in two groups and Fisher's exact and Chi-square tests were used to compare patient characteristics between groups, prognostic variables, and toxicities. We used an unpaired T-test to evaluate the treatment time between the two groups and determine if it correlated with illness progression.

Observation and Results

The Mahavir Cancer Sansthan's Department of Radiation Oncology at Phulwarisharif, Patna, conducted the research from July 2015 to December 2016. Sixty received cisplatin every three weeks and sixty weeklies,patients were evaluated after the trial.

Patient Characteristics

We documented patient data to compare them to a control group and assess if there were statistically significant differences.

Table 1: Age distribution

Age	Weekly		3 Weekly	
	No. of Patient	%	No. of Patient	%
≤30	2	3.33%	1	1.67%
31-40	6	10.00%	13	21.67%
41-50	18	30.00%	21	35.00%
51-60	28	46.67%	22	36.67%
61-70	6	10.00%	3	5.00%
Total	60	100%	60	100%

The previous table showed the two groups' ages. Group A has a 52.5% average age, and Group B has 48.5%.

Table 2: **Sex Distribution**

Sex	Weekly		3 Weekly	
	No. of Patient	%	No. of Patient	%
Male	47	78.33%	40	66.67%
Female	13	21.67%	20	33.33%
Total	60	100%	60	100%

Treatment Outcome

Table 3: **Follow Up of Treatment**

Follow Up	Weekly		3 Weekly	
	No. of Patient	%	No. of Patient	%
3 month	6	10.00%	7	11.67%
6 month	36	60.00%	34	56.67%
9 month	9	15.00%	11	18.33%
12 month	8	13.33%	3	5.00%
Na	1	1.67%	5	8.33%
Total	60	100%	60	100%

Chi-square =5.273,4 ; P=0.2604 (P>0.05, Non-Significant)

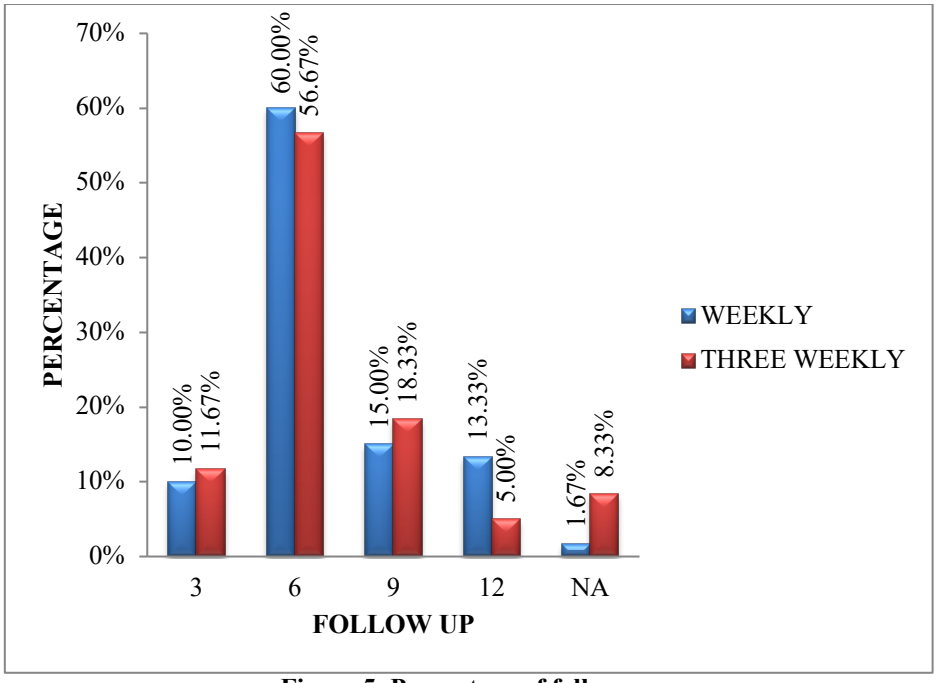


Figure 5: **Percentage of follow up**

Both groups had follow-up interviews at 3, 6, 9, and 12 months andboth groups were monitored for 6 months. One Group A and six Group B patients were unavailable for follow-up and excluded from the final tally. Chi-square analysis showed no significant group divide.

Table 4: **Disease Status**

Disease Status	Weekly		3 Weekly	
	No. of Patient	%	No. of Patient	%
Controlled	50	83.33%	48	80.00%
Dm	2	3.33%	1	1.67%
Lr	7	11.67%	6	10.00%
Na	1	1.67%	5	8.33%
Total	60	100%	60	100%

Chi-square =3.118, 3; P=0.3738(P>0.05, Non-Significant)

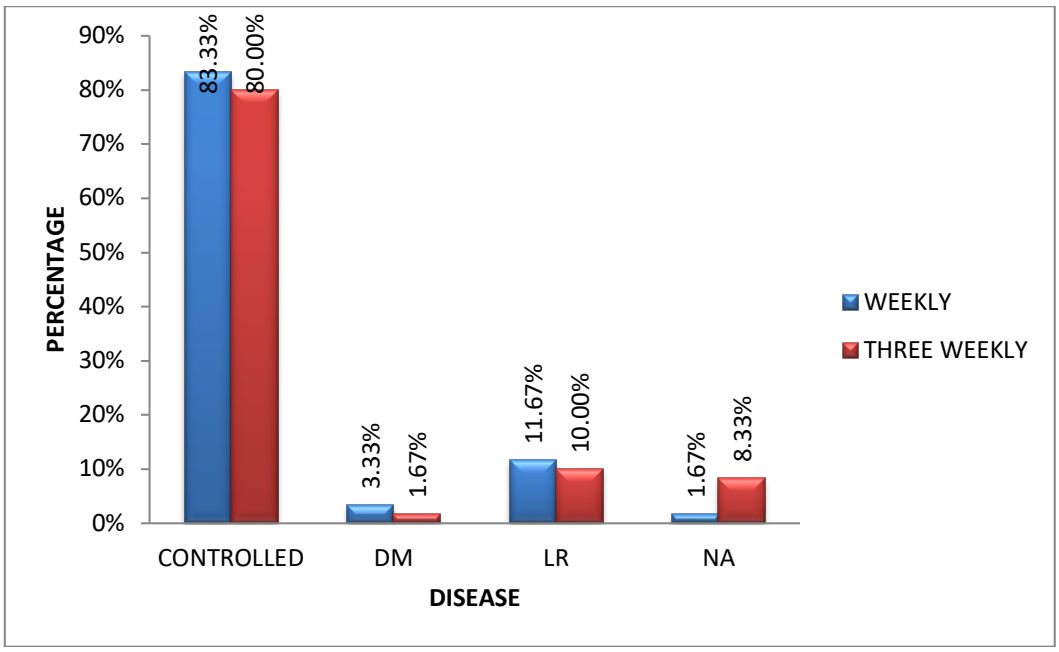


Figure 6: **Diseases status percentage**

Finally, the disease status of 2 groups was shown above,in Group A, 50 patients (83.3%) had a loco-regionally controlled disease, 7 patients had a loco-regional recurrence, and 2 had distant metastasis.
In Group B, 48 patients (80%) had a locoregionally controlled disease, 6 patients had local recurrence, and 1 had distant metastasis. Disease status in the 2 groups was found non-significant.

Toxicity – Maximum Late Toxicity

Table 5: **Maximum late toxicity**

Skin	Weekly		3 Weekly	
	No. of Patient	%	No. of Patient	%
0	30	50.85%	25	45.45%
1	29	49.15%	30	54.55%
Total	59	100%	55	100%

Chi-square = 0.3316, 1; P=0.5647 (P>0.05, Non-Significant)

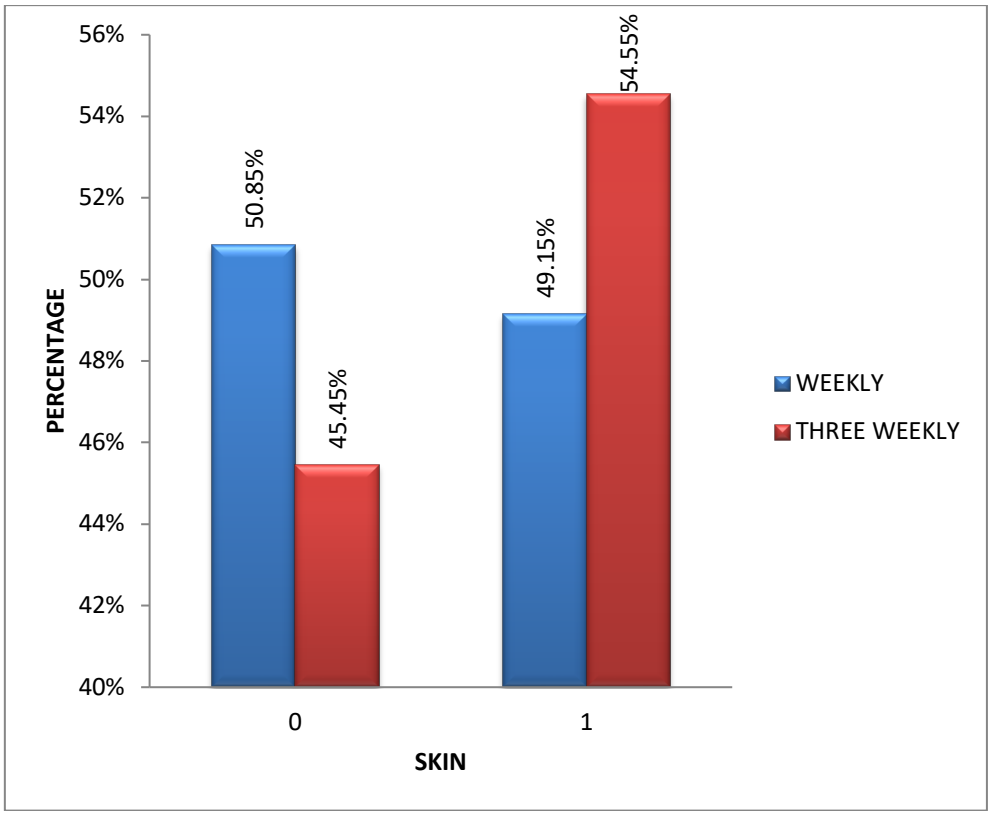


Figure 7: **Maximum late toxicity percentage**

Group A had 49.1% grade 1 late-onset cutaneous toxicity, Group B had 54.5% grade 1 toxicity. Group A had 50.8% and group B 45.4% without toxicity. Chi-square tests showed no significant differences between groups.

Discussion

Many head and neck malignancies in underdeveloped nations are diagnosed late and patients receive chemoradiotherapy. Combining treatments for locally advanced HNC can be effective yet hazardous, thus, RT regimens with cisplatin are being examined to reduce early toxicity. In a crucial condition for locally advanced HNC, we compared 30 mg/m2 cisplatin weekly to 3-weekly 100 mg/m2 with RT. 21.67% (13) and 33.3% (20) were female patients, low female-to-male ratio and groups were gender-neutral [14] found that 47% had pre-RT haemoglobin levels below 12 gm/dl, while 53% had 12 or higher and groups matches. Oropharyngeal cancer is mostly squamous cells, only SCC were investigated, SCC were both keratinising and non-keratinising. 93% had KSCC, 7% had NKSCC and mucositis dominated both groups. The 3-weekly arm had 31.6% grade 3 mucositis versus 21.6% in the weekly arm (p = 0.25), no significant mucositis. The 3-weekly arm had 40% grade I, 55% grade II, and 5% grade III mucositis. The daily arm had 60% grade I mucositis, 30% grade II, and 10% degree III. [15] discovered weekly patients had more grade 3 mucositis, Cisplatin every three weeks causes grade 3 and 4 mucositis. Arm A showed 20% grade 3 acute dermatitis, and arm B was 3.3%. The largest single-centre trial of weekly

cisplatin 30mg/m2 with radiation (n = 264) showed a median of six treatment cycles with 70 Gy administered in seven weeks. 65% of patients received 85% of their cisplatin. 29% and 35% had acute grade 3 mucositis and dermatitis. 43% survived 5 years disease-free, Arm B completed fewer weekly OPD visits and treatments. Three-week cisplatin produces more grade three vomiting than weekly (p = 0.0003), each 3-weekly treatment cycle's high cisplatin dose may have led to this discovery, showed 15% of 3-weekly patients had grade 3 vomiting compared to 5% of weekly patients (p = 0.23). [16] found that weekly cisplatin caused fewer renal difficulties than 3-weekly, 23.3% of group A patients suffered acute toxicity, with 50% experiencing nausea. 25–45% of group B had grade 1 and 2 toxicity, 14 and 15 patients received no negative effects. Chi-square indicated no significant group difference. Finally, two disease groupings were created: Group A had 50 locally treated patients (83.3%) and Group B had 7 local recurrences and 2 distant metastases. Eighty per cent of Group B patients achieved local control, six had recurrences, and one had distant metastases, they have similar diseases. Our trial compares 30 mg/m2 concurrent cisplatin weekly to 3-weekly as a definitive therapy for locally advanced oropharyngeal cancer. Weekly 30 mg/m2 cisplatin and RT can treat localised squamous cell HNC. 61% of RTOG 9501 patients had three cisplatin cycles, 23% received two, 13% received one, and 2% received no chemotherapy. 88%, 66%, and 49% received their first, second, and third chemotherapy regimens in EORTC 22931. Cisplatin at 40 mg/m2 weekly is easier to administer than 100 mg/m2 every 3 weeks. Cisplatin cumulative dosages cannot reach 200 mg/m2 or 5 weekly cycles, making weekly treatment inferior to every-3-week chemotherapy. [17] found that 71.4% had grade II xerostomia, dysphagia, and neck fibrosis,no patients experienced grade III dysphagia or neck fibrosis; however, 5.7% had xerostomia, all patients survived, and late toxicities were evenly distributed throughout the weekly and three-weekly arms. Three patients in Arm A needed supportive care and nasogastric tube feeding, while three in Arm B needed hospitalisation and five tube feeding. None had aspiration pneumonitis or febrile neutropenia,1 Arm A and 5 Arm B patients lost to follow-up after therapy survived. Because we could compare group toxicity, our study was successful. The 3-week regimen modestly increased toxicity, weekly compliance improved.

Summary

Oropharyngeal cancer patients at Mahavir Carcinoma Sansthan, Patna, were randomly assigned weekly or three-weekly cisplatin with radiation. July 2015–December 2016,60 eligible patients received weekly or three-weekly cisplatin. Group A median age is 52.5%, and Group B 48.5%. 21.6% (13) and 33.3% (20) of group A and B patients were female. Cigarettes, bidis, chains, and other addictions affected 85% of our sample. 78.33% had KPSs exceeding 70, group A had 68.3% and Group B 76.6% pre-RT haemoglobins of 12 or above. Both groups had KSCC and NKSCC equally, B has 83.3% KSCC, and A 93%. 33–35 2Gy fractions yielded 66–70 Gy. A and B received 30mg/m2 weekly and 100mg/m3 thrice weekly cisplatin, Group A completed the treatment cycle 78.3% (47/100), and Group B 43.3% (26/100). Both groups got 3-, 6-, 9-, and 12-month follow-ups, both groups were followed for 6 months. 1 Group A and 5 Group B patients missed late toxicity testing. 84% of Group A (n=50) and 80% of Group B (n=48) patients achieved loco-regional disease control, with 11.6% and 10% failing treatment and median therapy was 53 days.

Pre-radiation haemoglobin and pathological nodal status affected local disease control. The 3-weekly group had more mucositis, vomiting, thrombocytopenia, and renal toxicity. Grade 3 salivary gland & grade 1 skin were mostly among late toxicity. Between two groups there was non-significant difference in terms of loco-regional control.

Conclusion

The study showed its feasibility for both the arms & equally effective in terms of loco regional control for management of oropharyngeal carcinoma. Mucositis was the most common acute toxicity, somewhat more common in the 3-weekly cisplatin arm but otherwise comparable,31.6% of 3-weekly patients had grade 3 mucositis (P=0.3132).The 3-weekly group had more vomiting, rashes, and dysphagia, although not statistically significant and after 6 months, the 3 weekly arm followed up 91.6% (55/60) and the weekly arm 98% (59/60).Our weekly cisplatin group completed their treatment (77% versus 44%).Thus, weekly cisplatin had batter compliance & relatively easier to manage in treating oropharyngeal cancer than three-weekly.

Recommendation

More patients and longer-term studies are required to determine whether more conformal technique like IMRT with chemotherapy reduces acute and late toxicity and improves loco-regional control and survival rates.

Reference

1. Pignon JP, le Maitre A, Maillard E, Bourhis J, Group MNC.Metaanalysis of chemotherapy in head and neck cancer (MACHNC): an update on 93 randomised trials and 17,346 patients. RadiotherOncol. 2009;92(1):4–14.
2. Scully C, Bagan JV. Recent advances in oral oncology 2007: imaging, treatment and treatment outcomes. Oral Oncol 2008; 44:211–215.

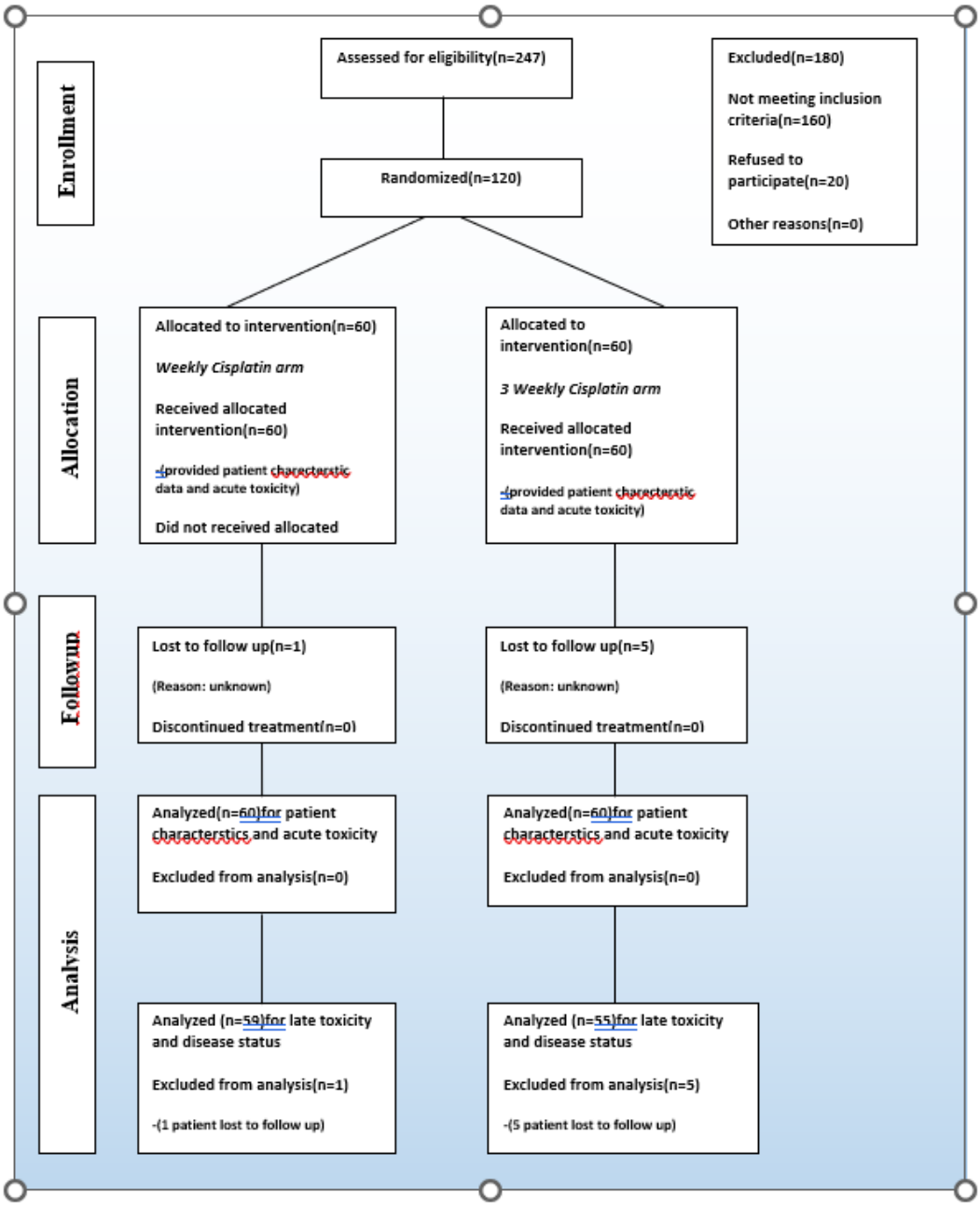
3. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004 May; 350(19): 1937–44.
4. Bernier J, Bentzen SM. Head and Neck cancer management: Which postoperative treatment best serves your patient? ASCO: Educational Book; 2003; 306–12.
5. Osborne RF, Brown JJ. Carcinoma of the oral pharynx: an analysis of subsite treatment heterogeneity. Surg Oncol Clin N Am 2004; 13: 71–80.
6. Gillison ML. Current topics in the epidemiology of oral cavity and oropharyngeal cancers. Head Neck. 2007; 29:779–792. This study provides a comprehensive review of epidemiological trends in oral cancer.
7. 2 Lin DT, Cohen SM, Coppit GL, Burkey BB. Squamous cell carcinoma of the oropharynx and hypopharynx. OtolaryngolClin North Am 2005; 38:59–74.
8. Perez and Brady's Principles and practice of Radiation Oncology.6th ed. Lippincott Williams & Wilkins: Philadelphia; 2013; 795-804.
9. Adelstein DJ, Li Y, Adams GL, Wagner H, Kish JA, Ensley JF, Schuller DE, Forastiere AA. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol. 2003; 21:92–98.
10. Fletcher GH, Evers W. Radiotherapeutic management of surgical recurrences and postoperative residuals in tumors of the head and neck. Radiology 1970; 95:185–188.
11. E.H. Grubb´e. Priority in the therapeutic use of X-rays. Radiology 1933; 21:156–62.
12. H.S. Kaplan. Basic principles in radiation oncology. Cancer 1977;39(Suppl 2):689–93.
13. C.J. Karzmark. N.C. Pering, Electron linear accelerators for radiation therapy: history, principles, and contemporary developments. Phys. Med. Biol. 1973; 18:321–54.
14. Ang KK. Concurrent radiation chemotherapy for locally advanced head and neck carcinoma: are we addressing burning subjects? J Clin Oncol. 2004; 22:4657–4659.
15. Osman N, Elamin YY, Rafee S, et al. Weekly cisplatin concurrently with radiotherapy in head and neck squamous cell cancer: a retrospective analysis of a tertiary institute experience. Eur Arch Otorhinolaryngol. 2014; 271(8):2253–9.
16. Ho KF, Swindell R, Brammer CV. Dose intensity comparison between weekly and 3-weekly Cisplatin delivered concurrently with radical radiotherapy for head and neck cancer: a retrospective comparison from New Cross Hospital, Wolverhampton, UK. Acta Oncol (Stockholm, Sweden). 2008;47(8):1513–8.
17. Mitra D, Choudhury K, Rashid MA. Concurrent chemotherapy in advanced head and neck carcinoma prospective randomized trial. Bangladesh J Otorhinolaryngol. 2011;17(2):88–95.

Appendix

Abbreviations

HNC - Head and Neck Cancers
CRT - Chemoradiation
LRC - Loco-Regional Control
OS - Overall Survival
HNSCC - Head and Neck Squamous Cell Cancer
HPV - Human Papillomavirus
SCC - Squamous Cell Carcinoma
CCRT - Combination Chemoradiation
RT - Radiation Therapy
CT - Computed Tomography
MRI - Magnetic Resonance Imaging
PET - Positron Emission Tomography
T1-2 - Tumor Stage 1-2
T3-T4 - Tumor Stage 3-4
ECOG - Eastern Cooperative Oncology Group
CDDP - Cisplatin
IC - Induction Chemotherapy
LAHNC - Locally Advanced Head and Neck Cancer
OSCC - Oropharyngeal Squamous Cell Carcinoma
RR - Relative Risk
IMRT - Intensity-Modulated Radiotherapy
MCS OPD - Multispecialty Clinic Outpatient Department
LFT - Liver Function Test
KFT - Kidney Function Test
TLC - Total Leukocyte Count IV - Intravenous
Gy - Gray (unit of radiation dose)
mm3 - Cubic Millimeter

Consort Diagram


Enrollment
Assessed for eligibility(n=247)
Excluded(n=180)
Not meeting inclusion criteria(n=160)
Refused to participate(n=20)
Other reasons(n=0)
Randomized(n=120)
Allocation
Allocated to intervention(n=60)
Weekly Cisplatin arm
Received allocated intervention(n=60)
-(provided patient charecteristic data and acute toxicity)
Did not received allocated
Allocated to intervention(n=60)
3 Weekly Cisplatin arm
Received allocated intervention(n=60)
-(provided patient charecteristic data and acute toxicity)
Followup
Lost to follow up(n=1)
(Reason: unknown)
Discontinued treatment(n=0)
Lost to follow up(n=5)
(Reason: unknown)
Discontinued treatment(n=0)
Analysis
Analyzed(n=60)for patient characterstics and acute toxicity
Excluded from analysis(n=0)
Analyzed(n=60)for patient characterstics and acute toxicity
Excluded from analysis(n=0)
Analyzed (n=59)for late toxicity and disease status
Excluded from analysis(n=1)
-(1 patient lost to follow up)
Analyzed (n=55)for late toxicity and disease status
Excluded from analysis(n=5)
-(5 patient lost to follow up)