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An Experimental Study to Compare Treatment Response and Toxicities of Concurrent Chemoradiation With Weekly Cisplatin and Three Weekly Cisplatin in Locally Advanced Head and Neck Cancer. (NCT03998696)

Conducted by:

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Introduction

Cancer is a leading cause of disease worldwide. In 2020, there were an estimated 19.1 million new cases and 10.2 million cancer deaths occurred in world (GLOBOCAN, 2020). Bangladesh, at 142 million people, is the 9th most populous country in the world. There are 1.3 to 1.5 million cancer patients in Bangladesh, with about 0.2 million patients newly diagnosed with cancer each year (Uddin et al., 2013).

The annual incidence of head and neck cancers worldwide is more than 550,000 cases with around 300,000 deaths each year (Jemal et al., 2011). Male to female ratio ranges from 2:1 to 4:1. About 90% of all head and neck cancers are squamous cell carcinomas (HNSCC). HNSCC is the sixth leading cancer by incidence worldwide. Most HNSCCs arise in the epithelial lining of the oral cavity, oropharynx, larynx and hypopharynx (Boyle et al., 2008).

In Bangladesh, head and neck cancer holds the 4th position (1238, 11.1%), among all cancers after lung, GIT and breast in 2014 (Cancer Registry Report, 2014).

The epidemiology of head and neck cancer strongly reflects exposure to certain environmental agents, particularly tobacco and alcohol. There is a strong causal relationship between smoking and cancer of the oral cavity. Smoking is identified as an independent risk factor in 80% to 90% of patients (Kurumatani et al., 1999, Macfarlane et al., 1995). The combined use of alcohol and tobacco may have a synergistic effect on carcinogenesis (Lambert et al., 2011). Other important risk factors include betel-quid and areca-nut chewing, ultraviolet radiation. Herpes simplex virus (HSV) and human papilloma virus (HPV) have also been implicated in the etiology of head and neck cancer. Approximately 50% of patients with oropharyngeal cancer and 0% to 20% with oral

cavity cancers are positive for HPV-16 DNA. A meta-analysis of 17 studies demonstrated a weak association between HPV and oral cancer (Hobbs et al., 2006).

Management of carcinoma of head and neck represents a significant treatment challenge because the disease is within such an anatomic environment that contains several critical structures, such as the salivary glands, mandible, nerves, major blood vessels, spinal cord and the organs of taste & speech, swallowing organs, hearing organs as well as close proximity of different sub sites.

Unfortunately, in our country, most of the patients with HNC attend the oncology department in advanced stages, may be due to ignorance, poverty, lack of proper referral system, illiteracy and some traditional belief.

Advances in surgical techniques continue to improve operative outcome but the overall morbidity associated with resection remains substantial. Non operative treatment strategies involve Radiotherapy (RT) and Chemotherapy (CT). The basic principle of radiotherapy is to treat the patient with minimal functional and structural impairment. Small primary lesions (T1 and T2) with negative cervical lymph nodes are generally treated with one modality (radiotherapy or surgery). Small lesion with nodal involvement requires both surgery and irradiation for control of neck disease. Large primary lesions (T3 and T4) and /or extension to cervical nodes usually need both surgery and radiotherapy. Sometimes surgery is not possible due to involvement of certain anatomical sites, critical structures and associated medical co-morbidity.

Standard treatment for inoperable, locally advanced squamous cell carcinoma of the head and neck is chemo-radiotherapy. In unresectable disease, a phase-III trial showed significantly improved survival with addition of CT (Adelstein et al., 2003). Meta-analysis of CT-RT trials showed the benefit of adding CT to loco-regional therapy for non-metastatic disease (Pignon et

al., 2005). Cisplatin based regimens were established as the most effective regimens with single agent activity, synergistic interaction and non-overlapping toxicity. A 100 mg/m^2 dose of cisplatin administered once every 3 weeks concurrently with radiotherapy is a commonly recommended treatment regimen during concurrent chemoradiotherapy (CCRT) for squamous cell carcinomas of the head and neck. Several other chemotherapy regimens for CCRT use a different schedule of cisplatin to improve compliance and the toxicity profile. Among these regimens, weekly cisplatin doses ranging from 30 to 40 mg/m^2 are used most widely in the radical and adjuvant settings (Gupta et al., 2009).

Several studies have compared the weekly and 3-weekly cisplatin CCRT regimens in patients with HNSCC but the results have been inconclusive in terms of loco-regional control (LRC) and/or overall survival (OS). (Geeta et al., 2009, Ho, Swindell and Brammer., 2008). Recently, randomized trials have studied whether 3-weekly cisplatin CCRT regimen could be superior to weekly cisplatin. The multicenter, prospective, randomized trials have shown better response and lower acute toxicity of three-weekly high-dose cisplatin treatment compared to weekly low-dose cisplatin in patient with locally advanced HNSCC (Mitra et al., 2011, Tsan et al., 2012).

Rationale of the study:

The standard treatment of inoperable, locally advanced, non-metastatic, squamous cell carcinoma of head and neck is chemo-radiotherapy. Chemotherapy given during a course of conventionally fractionated radiation improves survival compared with radiation alone. The Pignon meta-analysis has suggested this approach may provide an improvement in overall survival by an absolute figure of 8% when compared to radiotherapy alone ($p < 0.0001$). Cisplatin is among the most common agents used in combination with radiotherapy as well as one of the most studied. It has radiosensitizing properties and its toxicity does not overlap radiotherapy. The MACH-NC update suggested that the magnitude of benefit was higher ($p < 0.01$) for platinum based chemoradiotherapy compared concomitant therapy with other cytotoxic agents (Adelstein et al., 2003).

Single agent Cisplatin has been used in various different schedules when given along with radiotherapy. Three recently published trials using high dose Cisplatin 100 mg/m2 given every 3-weekly concurrently with radiotherapy have shown better local control compared with radiotherapy alone, two of these have indicated an overall survival benefit (Adelstein et al., 2003, Cooper et al., 2004, Forastiere et al., 2003). In theory, high dose CT acts by eradicating occult micrometastases where as low dose daily or weekly CT has only pure radio sensitizing effect.

RTOG 0129 and other studies have suggested that there may be a minimum cumulative threshold dose of approximately 200 mg/m^2 of cisplatin that is required to achieve maximal benefit when used concomitantly with radiation.

There are excellent (50–70 per cent) response rates of head and neck cancers to cisplatin-based chemotherapy. Chemotherapy can be started quickly, can reduce the volume of disease and

theoretically make curative EBRT (External Beam Radiotherapy) more likely to succeed, and may reduce the rate of distant metastases (Dobbs et al., 2008).

Three weekly cisplatin has the advantage of providing higher peak concentration of cisplatin than weekly cisplatin. This higher concentration of cisplatin is more critical to enhance the synergistic effect of radiotherapy.

Bangladesh is a developing country with a dense population. A huge number of HNC cases present at an advanced stage with a high mortality rate may be due to poverty, lack of knowledge or proper referral system. We are facing difficulties in managing head-neck cancers due to limited resources, high cancer burden with problems in health care infrastructure and capacity; then strategies are needed that can be adopted to optimize the treatment of this significant public health problem.

So it will be more flexible and convenient for patients to receive three weekly intravenous cisplatin than weekly cisplatin and hence patients will be more compliant to three weekly cisplatin. In three weekly schedules patients will get more time to recover from acute toxicities of cisplatin. Debabrata Mitra showed that three weekly cisplatin is more effective and less toxic than weekly cisplatin (Mitra et al., 2011). Unfortunately, in Bangladesh there is no such study to see the outcome.

So my study is to observe and compare the clinical outcome and toxicity profile of concurrent chemoradiation with weekly cisplatin and three weekly cisplatin of locally advanced head and neck cancer.

Hypothesis:

Concurrent chemoradiation with three weekly cisplatin is more effective in loco-regional tumor control and minimizing toxicity than weekly cisplatin in management of locally advanced head and neck cancer.

Objective of the study:

General objective

- To compare loco-regional tumor control and toxicities of concurrent chemoradiation with weekly cisplatin and three weekly cisplatin in locally advanced head and neck cancers.

Specific objective

- To measure tumor size and toxicities at baseline in the two modalities of treatment.
- To measure loco-regional tumor control and toxicities of two modalities during regular follow up.
- To compare tumor control and toxicities between baseline and follow ups of two groups.
- To measure the compliances in the two modalities of treatment.
- To assess regression of signs and symptoms.

Materials and methods:

Study design:

Interventional

Duration of the study:

January 2024 to June 2025.

Place of the study:

This study will be conducted in following institutions of Bangladesh**.**

1. Department of Clinical Oncology

   Bangabandhu Sheikh Mujib Medical University

   Shahbagh, Dhaka.

2. Department of Clinical Oncology

   Square Hospitals Ltd

   Panthapath, Dhaka.

Permission for the study:

- Proper permission will be taken from the department concerning the study.
- Informed consent will be taken from each patient before enrolling in the study.

Study population:

Patients with locally advanced, inoperable, squamous cell carcinoma of the head and neck treated with weekly cisplatin and three weekly cisplatin concurrent with radiation from January 2024 to June 2025 will be enrolled in the study.

Missing data imputation:

In the analysis of clinical trial results, dropouts need to be addressed during the trial. In this trial, the Intention-to-treat analysis (ITT) method will be used. It is considered good practice not to ignore dropouts. ITT analysis includes every subject who is randomized according to randomized treatment assignment. It ignores noncompliance, protocol deviations, withdrawal, and anything that happens after randomization (Gupta, 2011). US Food and Drug Administration (FDA) guidelines for „The Format and Content of the Clinical and Statistical Sections of Applications" explains that the results of a clinical trial should be assessed not only for the subset of patients who completed the study, but also for the entire patient population randomized (FDA, 1988). ITT analysis reflects the practical clinical scenario because it admits noncompliance and protocol deviations. ITT analysis maintains prognostic balance generated from the original random treatment allocation. It gives an unbiased estimate of treatment effect (Montori and Guyatt, 2001).

ITT analysis preserves the sample size because if noncompliant subjects and dropouts are excluded from the final analysis, it might significantly reduce the sample size, leading to reduced statistical power (Wertz, 1995). Also, it minimizes type I error due to cautious approach and allows for the greatest generalizability (Fergusson et al., 2002).

Confounding variables analysis:

Confounding variables should be addressed after data gathering, using statistical models by Stratification and Multivariate methods.

Sample size:

For determination of sample size following formula has been applied: -

$$n = \frac{p1(1-p1) + p2\,(1-p2)}{(P1-P2)2}\, x\, (Z\alpha + Z\beta)2$$

P_1 = Proportion of patients developing outcome in one arm.

P_2 = Proportion of patients developing outcome in another arm.

Zα=Z-value (two tail) at a definite level of significance e.g 1.96 at 5% level of significance.

Zβ=Z-value (one tail) at a definite power e.g .85 at 80% power (Haque, 2009).

Sample size has to be calculated to examine which treatment is better at 5% level of significance with 95% confidence interval.

Here, P_1 = 75 % (0.75), P2 = 40 % (0.4) (Tsan et al., 2012).

Zα = 1.96, Zβ =.85,

n = Sample size

$$n = \frac{(0.75\ x\ 0.25) + (0.4x0.6)}{(0.75-0.40)2}\, x\, (1.96 + 0.85)2 = 27.30$$

With 10% allowance for loss to follow up, final sample size = 27+3=30.

A total of 60 patients with above mentioned criteria will be selected as sample 30 in each arm.

Selection of patients: Patients will be selected after fulfillment of inclusion and exclusion criteria.

A. Inclusion Criteria:

- Patients with locally advanced (stage III/IV without distant metastasis) head and neck cancer.
- Squamous cell carcinoma of the head and neck region.
- Patients who are inoperable
- Patients Eastern Co-operative Oncology Group (ECOG) performance status score up to grade 2.

Laboratory criteria required to include:

- Hemoglobin should be more than 10 gm/dl or more than 60%.
- An absolute WBC count more than or equal to 4000cell/cmm
- Platelet count more than or equal to100000cell/cmm.
- Bilirubin level should be equal to or less than 1.5mg/dl.
- SGPT level not more than 4 times of the upper limit
- Serum creatinine level should be equal to or less than 1.5 mg/dl
- Blood urea level less than 50 mg/dl

B. Exclusion Criteria:

- Age below 18 years**.**
- Patients with history of prior chemotherapy or radiotherapy to the head and neck region.
- Serious concomitant medical illness including severe heart disease, Uncontrolled diabetes mellitus or hypertension
- Life expectancy < 6 months.
- Patients with uncontrolled infection.
- Diagnosed cases of head and neck cancer other than squamous cell carcinoma.
- Patients with double primaries.
- Initial surgery (excluding diagnostic biopsy) of the primary site.
- Pregnant or lactating woman.
- Prisoners.

Sampling technique:

Randomized sampling by random number generator. A random number generator is a computational process that produces random numbers by using statistical algorithm.

Research instrument:

A structured data collection form will be the research instrument (attached here with).

Study method:

- After fulfillment of inclusion and exclusion criteria, patients with locally advanced head and neck cancer will be selected for the study.
- Objectives, nature, purpose and potential risks and benefits of all procedures of the study will be explained in detail to the patients.
- Informed written consent will be taken for agreement.
- A total number of 60 patients will be recruited and then randomized into two arms (30 patients in each arm).
- Randomization will be done by random number generators. A random number generator is a computational process that produces random numbers by using statistical algorithms.
- Detail history, clinical examination and pretreatment evaluation will be done accordingly.
- Patients will be registered after pretreatment evaluation is completed and eligibility criteria met.
- Treatment will be delivered to Arm A and Arm B alternatively. . Arm A will receive Inj. cisplatin 40 mg/m^2 weekly along with radiotherapy and Arm B will receive cisplatin 100 mg/m^2 on a three-weekly basis with radiotherapy.
- Chemotheapeutic agents with same company and batch number will be administered.
- Patients will be assessed three weekly for treatment response and weekly for side effects during treatment.

- Post treatment assessment will be done at a regular interval.
- Data will be compiled and analyzed.
- Results will be presented in tables, figures, diagrams.
- The final response will be assessed six months after completion of all therapy.

Case collection:

Patients will be selected from inpatient and outpatient department of different hospitals mentioned above. The researcher will interview each patient and history will be documented according to prescribed data-sheet. After selecting patients, a written informed consent will be taken from each patient before his / her participation in the study. Clinical examinations and necessary investigations will be done.

Pretreatment evaluation:

Following procedures will be followed to evaluate the patient's condition before treatment -

- Complete history, performance status and physical examination.
- Location and size of the tumor were recorded prior to treatment.
- Histopathology reports, which has already been done by taking biopsy from primary tumor site.

Laboratory studies:

- Complete blood count
- Kidney function test (serum creatinine, creatinine clearance rate if needed).

- Liver function test (serum bilirubin, SGPT, SGOT).
- ECG
- Echocardiogram

Radiological studies:

- X-ray chest P/A view.
- X-ray of the soft tissue of the neck lateral view.
- CT scan / MRI of the head and neck region.
- USG of whole abdomen.

Others:

- Fine needle aspiration cytology (FNAC) or biopsy.
- Pan Endoscopy.

Registration procedures:

Patients will be registered after pretreatment evaluation is completed and eligibility criteria met. Following information will be provided -

- Patient's name and registration.
- Eligibility criteria information.
- Treatment date.

Treatment plan:

Concurrent chemotherapy:

Treatment schedule for arm A is Inj. Cisplatin 40 mg / m^2 intravenously 2 hours infusion on day 1, weekly schedule. It starts on the first day of radiotherapy, continued weekly. Proper hydration should be maintained and pre-and-post chemotherapy medication with antiemetic, steroid, H_2 blocker will be given before and after chemotherapy.

Treatment schedule for arm B is Cisplatin at a dose of 100 mg/m^2, intravenously, on a three-weekly basis on days 1, 22 and 43. Any pre-existing dehydration should be corrected prior to chemotherapy with intravenous fluid. Antiemetic, steroid & H_2 blocker or proton pump inhibitor (PPI) will be given prior to chemotherapy. Appropriate post-chemotherapy hydration & electrolytes will also be maintained.

Radiotherapy:

Basic principle of radiotherapy is to cure the patient with minimal functional and structural impairment. Treatment planning involves accurate localization of the tumor and prescription of daily fractions of radiation for a specific period. Biological effect of radiation depends on the amount of energy absorbed per unit mass. For irradiation of oral cavity, all the patients will be treated by parallel opposed fields. Extension of the field depends on the site and size of primary lesions and involving neck nodes. Exclusion of the spinal cord after 40 Gy is necessary. Before irradiation dental examination must be done.

Dose and energy**:** All patients will receive 66-70 Gy in 33-35 daily fractions (02 Gy per fraction/day, five days per week) over 6.5-7 weeks.

After radiotherapy, all patients should undergo ENT evaluation by physical examination and CT imaging of primary tumor and neck. The response criteria are based on cross-sectional diameter and tumor response, nodal response, and overall response according to WHO response criteria (Appendix-I).

Patient assessment:

1. Assessment during treatment:

- Patient will be assessed three weekly for treatment response and weekly for side effects.

Response criteria:

- Tumor response will be evaluated according to the WHO guideline of responses (Appendix-I).

Relief of symptoms:

- Symptomatic responses will be assessed weekly during chemo-radiotherapy.

Quality of life:

- Improvement of quality of life will be assessed by ECOG performance scale (Appendix-II).

Toxicity reporting:

- To assess toxicity, the national cancer institute's "Common Terminology Criteria for Adverse Events, v.3.0" published on June 10, 2003, will be used (Appendix-III).

- If any toxicity develops during treatment, it will be managed appropriately.

2. Assessment after treatment:

- After completion of treatment patient will be carefully supervised to attain first follow-up in the 6th week.
- Subsequent follow-up will be done every six weeks interval.

- Follow up examination will be inspection and palpation and laboratory tests if needed.
- The final response will be assessed after clinical examination, CT scan / MRI of the head and neck, chest X-ray P/A view, USG of whole abdomen, will be done 6 months after completion of all therapy.
- Designation of complete response, partial response, stable disease, or progressive disease will be based on standard WHO criteria (Appendix-I).

Data collection:

- Findings of observation will be recorded in prescribed data collection from (attached here with).

Analysis and interpretation of data:

- The data will be tabulated in separate tables for both arm A and arm B. It will be checked, edited, coded manually and entered in computer. Data analysis will be done according to the objectives of the study by using the SPSS 17 (Statistical Package for Social Science) software program for windows.
- To prevent bias lost to follow up patients will be included.
- Smoking, tobacco, betel leaf chewing, age, gender, tumor location, TNM staging are the possible potential confounding variables. By randomizing groups, utilizing strict controls and sound operationalization practice confounding variables will be controlled.

Ethical considerations:

I must be duly careful about ethical issues related to the study and follow the Good Clinical Practice (GCP) rule. In this study the following criteria will be set to ensure maintaining ethical values.

- All patients will be explained the study including the aims, objectives, procedures, risks and benefits in easily understandable language.
- All patients will be included in this study after taking their informed consent supplied in Bengali and English version.
- I shall also explain that they have the right to refuse or accept to participate in the study at any time.
- The patient will not be gained financially from the study.
- All data obtained during the study period from the patient remain confidential.
- Permission for the study will be granted from the concern department and also will be approved by the ethical committee.

Dummy Tables

Table 1- Patient characteristics:

Characteristics	**Arm A**	**Arm B**
Number of patients eligible		
Age, years <60 >60		
Sex Male female		
ECOG <2 =2		
Weight loss <5% 5-10%		
AJCC stage III A III B		

Table -2 Grade 3 and 4 toxicities in both arms, toxicity criteria based on Common Terminology Criteria for Adverse Events, v.3.0" published on June 10, 2003 (Appendix-III).

	Arm A		**Arm B**	
Toxicity	**No. of pts.**	**%**	**No. of pts.**	**%**
Anemia				
Leukopenia				
Granulocytopenia				
Thrombocytopenia				
Mucositis				
Nausea/Vomiting				
Esophagitis				
Electrolyte Imbalance				
Nephrological				
Neurological				

Table 3– Clinical response base on RECIST criteria (Appendix-I)

Response	**Arm A (n=30)**	**Arm A (%)**	**Arm B (n=30)**	**Arm B (%)**	**P value**
Complete response(CR)					
Partial response(PR)					
Progressive disease(PD)					
Stable disease(SD)					

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Code No: ☐☐

Data collection sheet

Title of the study: Concurrent weekly versus three weekly cisplatin based chemotherapy with radiotherapy in locally advanced head and neck cancer.

Principal investigator: Dr. Ishtiaq-Ur-Rahim

1. Reg. No: ☐☐☐☐☐☐☐☐

2. Name of the hospital:

3. Sex: ☐ 1-Male, 2-Female

4. Age (in years): ☐☐

5. Religion: ☐ 1 = Muslim, 2 = Hinduism, 3 = Christian, 4 = Buddhism, 5 = Others

6. Marital status: ☐ 1 = married, 2 = unmarried, 3 = widow, 4 = separated

7. Socio-economic condition: ☐

1= Group I (Poor) monthly income TK < 10,000/=

2= Group II (Lower middle class) monthly income TK. 10,001 – 30,000/=

3= Group III (Middle class) monthly income TK. 30,001 – 40,000/=

4= Group IV (Rich) monthly income TK. > 40,000/=

8. Educational qualification: ☐ 1 = Illiterate, 2 = below primary,
3 = above primary up to SSC, 4 = HSC, 5 = Graduate, 6 = Postgraduate

9. Occupation: ☐ 1 = Student, 2 = Farmer, 3 = Service holder, 4 = Business, 5 = others

10. History of risk factors:

Item	Duration	Amount
Smoking		
Alcohol		
Betel Leaf		
Betel Nut Chewing		
Tobacco Leaf / Jarda		

11. Treatment history -

a) Previous Surgery: ☐ 1 = Yes, 2 = No

b) Previous Chemotherapy: ☐ 1 = Yes, 2 =

c) Previous Radiotherapy: ☐ 1 = Yes, 2 = No

12. Significant Family History -☐

1 = Present, 2= Absent

If present,.....

.....

13. General examination:

Performance status (ECOG) ☐ 0/ 1/ 2/ 3/ 4/ 5

Body weight (in Kg) ☐☐

Height (in cm) ☐☐☐

Body surface area (in square meter) ☐☐☐☐

Anemia: ☐ 1 = No 2 = Mild 3 = Moderate 4 = Severe

Jaundice: ☐ 1 = No 2 = Mild 3 = Moderate 4 = Severe

Edema: ☐ 1 = Yes 2 = No

Dehydration: ☐ 1 = Yes 2 = No

Palpable lymph node (with site): ☐ 1 = Yes 2 = No

……
……
…….....
.....
.....

Body temperature: ☐ 1 = Raised 2 = Normal

14. Local Examination:

Primary site:

Lymph Node examination:

15. Systemic Examination:

16. Investigations:

Laboratory investigations:

i) Routine Blood Examination:

Hemoglobin.....gm/dl.

Total count of WBC ..... /ul.

Differential count of WBC:

Neutrophil .....%

Lymphocyte.....%

Eosinophil .....%

Monocyte.....%

Basophil.....%

ESR .....mm in 1st hour.

Platelet count..... /ul.

ii) Serum bilirubin… ..... mg/dl.

iii) SGPT .....IU/L.

iv) SGOT ..... IU/L.

v) Serum creatinine .....mmol/l.

vi) ECG:

vii) ECHO:

Radiology and imaging:

1. X- ray chest P/A view. ☐
   Positive -1 Negative – 2

2. X-ray soft tissue of the neck lateral view. ☐
   Positive -1 Negative -2

3. X-ray PNS OM view. ☐
   Positive -1 Negative -2

4. CT scan of the neck. ☐
   Positive -1 Negative -2

17. Staging at Diagnosis: ☐ 1= Stage-III, 2= Stage -IV.

18. Treatment:

18.1 Concurrent chemo-radiotherapy

19. Assessment of Treatment Response:

20. Assessment of Toxicity:

21. Follow up:

Face sheet

Code No - ☐☐

Reg. No: ☐☐☐☐☐☐☐☐

Patients Name –

Fathers/ Husbands Name –

Mobile No - ☐☐☐☐☐☐☐☐☐☐

Address -

Appendix-i

WHO guideline of responses:

(RECIST criteria)

Responses	Description
Complete Response (CR)	Disappearance of all known diseases, confirmed at ≥ 4 weeks.
Partial Response (PR)	≥ 50 % decrease from baseline, confirmed at ≥ 4 weeks.
Progressive disease (PD)	≥ 25 % increase in one or more lesions or appearance of new lesions
Stable disease (SD)	Neither PR or PD criteria met

Appendix - ii

Eastern cooperative oncology group (ECOG) performance scale -

0 : Normal activity; asymptomatic

1 : Symptomatic; fully ambulatory

2 : Symptomatic; in bed < 50% of time

3 : Symptomatic; in bed > 50% of time; bedridden

4 : 100% bedridden

5 : Dead

Appendix - iii

Common toxicity criteria:

(The National Cancer Institute's "Common Terminology Criteria for Adverse Events, v.3.0" date published: June 10, 2003 will be used to score all acute toxicities)

A. Hematological:

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
a. Hb (gm/dl)	10.0 – LLN	8.0 - 10.0	6.5 – 7.9	< 6.5
b. Platelets (count/µl)	75,000 - LLN	50,000 - 74,000	25,000 - 49,000	< 25,000
c. WBC (count/µl)	3,000 - LLN	2,000 - 3,000	1,000 - 2,000	< 1,000
d.Neutrophil (count/µl)	1,500 - LLN	1,000 - 1,500	5,00 - 1,000	< 5,00
e.Lymphocyte(count/µl)	1,500 - 2,000	1,000 - 1,500	5,00 - 1,000	< 5,00
f.Haemorrhage(clinical)	Mild, no transfusion	Gross, 1-2 units transfusion per episode	Gross, 3-4 units transfusion per episode	Massive, > 4 units per episode
g.Infection	Mild	Moderate	Severe	Life threatening

B. Liver function:

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
a. S.Billirubin	--	< 1.5 X N	1.5 – 3.0 X N	> 3.O X N
b.SGPT / SGOT	< 2.5 X N	2.6 – 5.0 X N	5.1- 20.0 X N	> 20.0 X N
c.Alkaline phos. / 5- Nucleotide	< 2.5 X N	2.6 – 5.0 X N	5.1- 20.0 X N	> 20.0 X N
d.Liver (clinical)	--	--	Pre coma	Hepatic coma

C. Alimentary:

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
a. Nausea	Reduced but reasonable intake	Intake significantly decreased	IVF or Alimentation ≥ 24hour	Life threatening consequences
b.Vomiting	One episode in 24 hour	2-5 episode in 24 hour; IVF< 24hour	6 or more episode in 24 hour; IVF ≥ 24 hour	Life threatening consequences
c. Diarrhea	Increase of <4 stools/day over baseline	Increase of 4-6 stools/day, IVF < 24 hour: not IWADL.	Increase of ≥ 7 stools/day or incontinence; hospitalization; IWADL	Life threatening consequences
d.Stomatitis	Painless ulcers, erythema or mild soreness	Painful erythema, oedema or ulcers but can eat.	Painful erythema, oedema or ulcers but cannot eat	Requires parenteral support or enteral support
e.Mucositis	Erythema of mucosa	Patchy pseudomemb ramous reaction (patch < 1.5 cm in diameter and non contiguous)	Contiguous patchy generally > 1.5 cm in diameter	Necrosis or deep ulceration may include bleeding

D. Urinary function:

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
a. Creatinine	ULN-1.5×ULN	1.6 - 3.0×ULN	3.1 – 6.0 ×ULN	> 6.0 ×ULN
b. Protenuria	1+ or 0.15 - 1.0g/24 hour	2+ to 3+ or 1.1 - 3.5g/24hour	4+ or >3.5g / 24hour	Nephrotic syndrome
c.Heamaturia	Microscopic only	Gross but no clot	Gross with clot	Requires transfusion

E. Others:

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
a. Weight gain / loss	5.0% - 9.9%	10% - 19.9%	>20% of baseline	_
b. Allergic reaction	Transient rash or flushing; drug fever < 100.4^0 F	Urticaria, rash; drug fever ≥100.4^0F, dyspnoea	Serum sickness or bronco spasm, require parenteral medication	Anaphylaxis
c. Alopecia	Thinning or patchy	Complete	_	_
d.Febrile neutropenia	_	_	Present	Life threatening consequences
e.Local	Pain	Pain and swelling with inflammation or phlebitis	Ulceration	Plastic surgery indicated
f.Skin	Erythema	Early desquamation / pigmentation	Moderate dry desquamation	Blister foeming/Skin peeling/Bleeding ulcer

Appendix – iv

TNM Staging for Head and Neck Cancer (Excluding Nasopharynx)

Primary Tumor (T)

T staging for tumors of the lip and oral cavity is based on size alone as below.

T staging of the oropharynx, hypopharynx and major salivary gland has the same definitions for tumor size but also depends on local tumor extension.

T staging for the tumors of the larynx, nasal cavity and paranasal sinuses have specific definitions that do not depend on tumor size.

TX – Primary tumor cannot be assessed

T0 – No evidence of primary tumor

Tis – Carcinoma in situ

T1 – Tumor ≤ 2 cm in greater dimension

T2 – Tumor > 2 cm but ≤ 4 cm

T3 – Tumor > 4 cm

T4 – Tumor invades adjacent structures (defined under specific sites)

T4a – Moderately advanced local disease (potentially resectable)

T4b – Very advanced locally disease (unresectable)

Regional Lymph Nodes (N)

NX – Regional lymph nodes cannot be assessed

N0 – No regional node metastasis

N1 – Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension

N2a – Metastasis in a single ipsilateral lymp node, > 3 cm but ≤ 6 cm

N2b – Metastasis in multiple ipsilateral lymph nodes, none > 6 cm

N2c – Metastasis in bilateral or contralateral lymph nodes, none > 6 cm

N3 – Metastasis in a lymph node > 6 cm in greatest dimension

Distant Metastatic (M)

M0 – No distant metastasis

M1 – Distant metastasis

Staging Groupings

0 – Tis N0 M0

I – T1 N0 M0

II – T2 N0 M0

III – T1-3 N1 M0, T3 N0 M0

IVa – T4a N0-2 M0, T1-3 N2 M0

IVb – T4b Any N M0, Any T N3 M0

IVc – Any T Any N M1

(AJCC Cancer Staging Manual, 7th ed, 2010)

TNM Staging for Nasopharynx:

Primary Tumor (T)

T1 – Tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension.

T2 – Tumor with parapharyngeal extension (posterolateral infiltration of tumor)

T3 – Tumor invades bony structures of skull base and/or paranasal sinuses

T4 – Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit or with extension to the infratemporal fossa/masticator space

Regional Lymph Nodes (N) [note: midline nodes are considered ipsilateral nodes]

NX – Regional lymph nodes cannot be assessed

N0 – No regional node metastasis

N1 – Unilateral metastasis in cervical lymph nodes, ≤ 6 cm in greater dimension, above the supraclavicular fossa, and/or unilateral or bilateral retropharyngeal lymph nodes ≤ 6 cm in greatest dimension

N2 – Bilateral metastasis in cervical lymph nodes ≤ 6 cm in greatest dimension, above the supraclavicular fossa

N3a – Metastasis > 6 cm in greatest dimension

N3b – Extension to supraclavicular fossa

Distant Metastatic (M)

M0 – No distant metastasis

M1 – Distant metastasis

Staging Groupings

0 – Tis N0 M0

I – T1 N0 M0

II – T1,2 N0 M0, T2 N0 M0

III – T1-3 N2 M0, T3 N0-1 M0

IVa – T4 Any N M0

IVb – Any T N3 M0

IVc – Any T Any N M1

(AJCC Cancer Staging Manual, 7th ed, 2010)

Operational definition:

Head and neck cancer:

Head and neck cancers are defined as the cancers that arise from the lining epithelium of upper aero-digestive tract. Most of the head and cancers are squamous cell carcinoma. Further, cancer of the head and neck region are categorized by the area of the head and neck from which they arise.

Cancers of the CNS, the eye, the esophagus, and the thyroid gland, as well as those of the scalp, skin, muscles, and bones of the head and neck, are not classified as head and neck cancers. Sometimes, squamous cell cancer can be found in the lymph nodes of the upper neck when there is no evidence of cancer in the head and neck region; it is then called metastatic squamous cell carcinoma of the neck with unknown primary.

Locally advanced cancer:

Cancer that spread to nearby tissue or lymph nodes but not spread from the original (primary) tumor to distant organs or distant lymph nodes. (NCI Dictionary of cancer terms)

Locally advanced Head and Neck cancer (excluding Nasopharynx):

- Any tumor size with metastasis to cervical lymph node(s).
- Tumor size > 4 cm with or without metastasis to cervical lymph node(s).
- No distant metastasis.

Locally advanced Nasopharyngeal carcinoma:

- Tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension or tumor with parapharyngeal extension or tumor

invades bony structures of skull base and/or paranasal sinuses with bilateral metastasis in cervical lymph nodes ≤ 6 cm in greatest dimension, above the supraclavicular fossa. or,

- Tumor invades bony structures of skull base and/or paranasal sinuses or tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit or with extension to the infratemporal fossa/masticator space with or without regional lymph node(s) metastasis. or,
- Any size and extension of the tumor with metastatic lymph node > 6 cm in greatest dimension or Extension to supraclavicular fossa.
- And no distant metastasis.

(AJCC Cancer Staging Manual, 7th ed, 2010)

Concurrent Chemoradiation (CCRT):

The use of chemotherapy delivered concurrently with radiation. Either chemotherapy can act as a radiosensitizer, improving the probability of local control and potentially the survival, by aiding the destruction of radio-resistant clones, or it can be used with organ-preserving intent, resulting in improved function and/or cosmetic results compared with surgical resection with/without adjuvant treatment. In addition, chemotherapy given as part of concurrent chemoradiation may act systemically and potentially prevent distant metastases.

Appendix-v

Follow up

Code No: ☐☐ Follow up No: ☐ Date: ☐☐☐☐☐☐☐☐

Complaints:

General examination:

Weight (kg)	BP (mmHg)	Temperature (^{0}C)	Respiration (times/min)

Local examination:

Primary site:

	Before treatment	**1st wk**	**2nd wk**	**3rd wk**	**4th wk**	**5th wk**	**6th wk**	**7th wk**	**During F/U**
Direct inspection/Indirect laryngoscopy (T_0,T_1,T_2,T_3, T_4)									

Lymph Node examination:

		Before treatm-ent	1st wk of CCRT	2nd wk of CCRT	3rd wk of CCRT	4th wk of CCRT	5th wk of CCRT	6th wk of CCRT	7th wk of CCRT	During Follow UP
1	Neck node positive(N) N_0,N_1,N_2,N_3.									
2	Tenderness no-0, mild-1, moderate-2, severe-3.									
3	Temp. Normal- 1 Raised- 2									
4	consistency Soft-1 Hard- 2									
5	Mobility Mobile-1 Fixed-2									
6	Surface Regular-1 Irregular-2									

*CCRT= Concurrent Chemo-radiation

Systemic examination (important findings)-

Investigations findings:

Blood for routine examination	
Serum billirubin SGOT Serum creatinine	
Chest X-Ray P/A view	

CT scan of the neck	
Others	

Appendix-vi

Specific Treatment:

A) Concurrent chemotherapy:

- Inj. Cisplatin 40 mg/m^2 /day every weekly
- Inj. Cisplatin 100 mg/m^2/day, 03 weekly for 03 cycles

B) Radiotherapy /Concurrent radiotherapy**:**

Machine	**1st wk**	**2nd wk**	**3rd wk**	**4th wk**	**5th wk**	**6th wk**	**7th wk**
Tumor dose							
Field size							
Daily dose							
Fractionation							
No. of port							

Appendix-vii

Assessment of treatment response: Concurrent chemo-radiation (CCRT)

According to WHO response criteria (Appendix-I)

	1st wk of CCRT	2nd wk of CCRT	3rd wk of CCRT	4th wk of CCRT	5th wk of CCRT	6th wk of CCRT	7th wk of CCRT	During follow up
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Keys to table: 1= Complete response, 2= Partial response, 3=Stable disease, 4= Progressive disease

Appendix-viii

Assessment of toxicity:

A) Common Toxicities:

	After 1st wk	After 2ndwk	After 3rd wk	After 4th wk	After 5th wk	After 6th wk	After 7th wk
Nausea							
Vomiting							
Diarrhea							
Stomatitis							
Mucositis							
Alopecia							
Weight loss							
Anemia							
Febrile neutropenia							
Peripheral neuropathy							
Renal toxicity							

Keys to table: 0=no symptom, 1=mild symptom, 2=moderate symptom, 3=severe symptom

B) Skin Reaction:

Skin reaction	**1st wk**	**2nd wks**	**3rd wks**	**4th wks**	**5thwks**	**6th wks**	**7th wks**
Grade							

Grade 0- Nil,

Grade 1- Erythema

Grade 2- Early desquamation/ pigmentation

Grade 3- Moderate dry desquamation/ early moist desquamation

Grade 4- Blister formation/ skin peeling bleeding ulcers