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# A study on patient compliance and acute toxicity in the management of head and neck cancers treated with concurrent weekly cisplatin and radiotherapy

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## ABSTRACT

Head and neck cancer is one of the ten most common cancers in the World constituting 15% of all malignancies. Head & Neck cancers rank 3rd in developing countries.In the prementioned context the current study is aimed at assessing patient compliance to concurrent chemo- radiation and also about the various factors influencing the outcome in the cases of head and neck cancers attending to Department of Radiotherapy, Government Medical College and General Hospital, Anantapuramu. Of a total number of 135 cases of head and neck tumours were treated with Radiation during the aforementioned period, 70 cases of locally advanced disease that are treated with Radical Radiation and concurrent chemotherapy were included in the study. In our study, we noticed complete response in 60 % of the patients. Response was significantly influenced by the site of the primary. Patients with primary in Nasopharynx and Larynx had better response, 80 % and 70 % respectively compared to. Tumor response was better in patients who completed treatment without breaks and with good performance status. Concurrent chemoradiation results in grade III reactions which have to be managed aggressively. Nutrition of the patient should be maintained with nasogastric or PEG tubes if needed along with parenteral nutrition. Weekly blood counts should be checked. Antifungals and antibiotics should be used whenever needed. Patients need counselling regarding diet and high protein diet should be advised.

**Keywords:** Head and neck cancer, Toxicity, Radiotherapy

## Introduction

Head and neck cancer is one of the ten most common cancers in the World constituting 15% of all malignancies. Head & Neck cancers rank 3rd in developing countries.The age-adjusted rates of head and neck cancers are highest in countries like France, India, Brazil, and USA (blacks). Among females the age-adjusted rates of India are the highest in the world [1-2]. Its incidence is high in Central & South East Asian Countries and is linked mainly to tobacco chewing and tobacco smoking.

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However, there is an overall reduction in the incidence of head and neck cancers in both urban and rural community. This is more pronounced in the urban community, probably due to the reduction in the use of tobacco in that population [11].

Radiotherapy is one of the lone long standing standard non-surgical therapy for locally advanced disease. Optimizing locoregional control disease-free and overall survival remains a challenging goal in management of Head & Neck Cancers. Reducing toxicity and organ preservation are laudable pursuits, but the prime concern will always remain optimizing the cure. Many fractionationed regimens conventional once daily treatments, hyper fractionation regimens, concomitant boost and accelerated fractionation have been used. These emerging newer strategies lead to a 10% to 15% improvement in locoregional control relative to once daily treatment scheme. Even the most effective RT regimens result in local control rates of

50% to 70% and disease-free survival rates of 30% to 40%. This led to management of cancers by the combination of chemotherapy with Radiotherapy [3]. Radiotherapy and concurrent chemotherapy is more attractive strategy because some chemotherapeutic agents may both radio sensitise cells and provide additive toxicity. This has been demonstrated to produce a small but significant survival advantage. However, concurrent use of chemotherapy and radiotherapy is known to increase toxicity which may compromise radiation dose or may prolong the treatment time that may ultimately affect the potential gains of combined modality. In the prementioned context the current study is aimed at assessing patient compliance to concurrent chemo- radiation and also about the various factors influencing the outcome in the cases of head and neck cancers attending to Department of Radiotherapy, Government Medical College and General Hospital, Anantapuramu.

**Materials and methods**

The current prospective study was carried out from January 2014 and May 2015 at Department of Radiotherapy and Department of Pathology, Government Medical College and General Hospital, Anantapuramu after obtaining clearance from Institutional Ethics Committee and consent from all the patients who are included in the study. Of a total number of 135 cases of head and neck tumours were treated with Radiation during the aforementioned period, 70 cases of locally advanced disease that are treated with Radical Radiation and concurrent chemotherapy were included in the study. All the subjects were histologically proven to have squamous cell carcinoma. AJCC cancer staging manual ($7^{th}$edition)[4] was used for staging. Complete haematological and biochemical profiles were done before starting the treatment. CT and MRI are done whenever necessary. Toxicity was documented using NCIC common toxicity criteria [5]. Radiotherapy was given with Cobalt 60 machine (Theratron 780C). Dose was 63 to 72 Gy in 35 to 40 fractions for definitive concurrent chemo radiotherapy with 180 cGy per fraction, five days per week. Patient is treated in supine position. Immobilization with thermoplastic mask was done. EBRT was performed through two lateral opposing portals or two lateral portals and an anterior neck field. Spinal cord was shielded after 40 Gy and posterior neck was treated with appropriate tangential fields sparing spinal cord. Check films are done to verify field borders. Chemotherapy consisted of Cisplatin, administered weekly at a dose of 40 mg/$m^2$ with a total single dose of up to 60 mg. Cisplatin dose was adjusted based on 24-hour creatinine clearance, body surface area and performance status. Cisplatin was administered with normal saline over two hours with appropriate pre-andpost-hydration. Antiemetic therapy with ondansetron and steroids were given routinely on the day of Chemotherapy.Complete haematological and biochemical profiles were done before starting chemotherapy. Urinary creatinine clearance of at least 50 ml/min was required; otherwise dose of Cisplatin was adjusted. Haemoglobin, white blood cell count and platelet counts were assayed before each Cisplatin administration. Chemotherapy was given only when counts were normal. Colony stimulating factors were not used. Patients were evaluated every week for toxicity during treatment period. Mucositis, skin reaction and haematological toxicity were assessed. If needed, ryles tube placement was done for nutrition. Routine mouth gargles and dental care was taken. Antibiotics and antifungals were used whenever needed. Anaesthetic gels and steroids were used. Packed cell transfusions were given whenever needed.

**Observations**

Of a total 135 cases of head and neck cancers treated during the study period, 82 cases were treated with radical radiotherapy and chemotherapy. Of these 75 cases 70 cases were treated with radiotherapy and concurrent weekly Cisplatin, two were treated with concurrent Taxol and ten were treated with concurrent Cisplatin and 5FU. The 70 cases treated with radical radiotherapy and concurrent weekly Cisplatin are taken into the study. In the remaining cases seven were treated with only radical radiotherapy, eight cases were treated with palliative radiotherapy, three cases did not receive any treatment, four cases discontinued treatment after one week and 29 cases were treated postoperatively. Of the seventy cases that are managed with radical radiotherapy and weekly dose of Cisplatin, the commonest site was oral cavity constituting nearly half of the total cases, tongue being commonest of all. The median age was 56 years. Around 90% of the cases had nodal disease and 35% of cases had $T_4$ disease. 10 patients had performance status below 70%. Cisplatin dose ranged from 30 to 60 mg. Dose was adjusted according to creatinine clearance body surface area and performance status. The General Features of observations are presented in Tale No.1 below and Cancer staging and particulars as to chemotherapy, radiotherapy, overall treatment times and treatment breaks are depicted in Table-2.

**Table 1: Statistics as to age, sex and site of cancer**

| Characteristic | Value |
|---|---|
| **Age:** | |
| **Range** | 18-78 |
| **Median** | 56 |
| **Sex:** | |
| **Male** | 48 |
| **Female** | 22 |
| **Site:** | |
| **Oral cavity** | 23 |
| **Oropharynx** | 11 |
| **Hypopharynx** | 20 |
| **Nasopharynx** | 5 |
| **Larynx** | 8 |
| **Unknown** | 3 |

**Table 2: Distribution of cases as to cancer staging and management strategies**

| Characteristic | value |
|---|---|
| **T stage:** | |
| **$T_x$** | 3 |
| **$T_2$** | 10 |
| **$T_3$** | 33 |
| **$T_4$** | 24 |
| **N stage:** | |
| **$N_0$** | 5 |
| **$N_1$** | 21 |
| **$N_2$** | 27 |
| **$N_3$** | 17 |
| **Chemotherapy:** | |
| **Six cycles** | 37 |
| **Five cycles** | 22 |
| **Four cycles** | 10 |
| **Three cycles** | 1 |
| **Radiotherapy:** | |
| **65 – 75 Gy** | 66 |
| **Discontinued** | 4 |
| **Overall treatment time:** | |
| **Range** | 42 – 70 days |
| **Median** | 56 days |
| **Treatment breaks:** | |
| **Without break** | 43 |
| **With break** | 23 |

**Toxicity**: Skin, mucous membrane, pharynx (dysphagia), salivary gland, gastrointestinal and hematological toxicity were graded according to NCIC Common Toxicity Criteria.

**Hematological Toxicity**:Hematological toxicity was mild. Grade I leucopenia was seen in 10 patients. Chemotherapy was skipped for that week though radiation was not stopped. No grade II or III leucopenia

were noted.Anemia of grade I was noted in 11 patients, though treatment was not interrupted. Grade II anemia was seen in 5 patients and grade III in three patients. Blood transfusions (packed cells) were given for all patients with anaemia. No grade IV anaemia was noted.No patient developed thrombocytopenia.

**GI Toxicity**:Gastrointestinal toxicity was mild. 35 patients had grade I nausea and no grade II or III nausea seen. Grade-I vomiting was noted in 51 patients and grade II vomiting in 12 patients. No grade III or IV vomiting noted. All the patients were treated with antiemetics and steroids prior to chemotherapy.

**Skin Toxicity**:Grade I dermatitis is noted in 15 patients. Grade II skin reaction is seen in 45 patients. Grade III reaction seen in 10 patients. No grade IV reaction is seen. Treatment was interrupted in patients with grade III dermatitis. Supportive care was given with Gentian violet paint and steroid ointments. Antibiotics were added whenever needed.

**Mucositis**: Grade I mucositis was seen in nine patients. Grade II Mucositis is noted in 46 patients and grade III Mucositis in 15 patients. Treatment was interrupted in patients with grade III mucositis. Supportive care is given with mouth gargles and anaesthetic gels. Antibiotics were given routinely in patients with grade III mucositis. 36 patients developed oral candidiasis and were treated with candid mouth paints and oral fluconazole. No grade IV Mucositis is noted.

**Dysphagia (pharynx )**:Grade I dysphagia was seen in 16 patients. Grade II dysphagia was noted in 31 patients and grade III in 23 patients. Ryles tube placement was done in these patients with grade III reaction to maintain nutrition. Ten patients had Ryles tube placed from the beginning of treatment.

**Salivary Gland Toxicity**: Grade I reaction (thickened sputum) was seen in 31 patients and grade II reaction in 39 patients. No grade IV reaction was noted

Treatment was interrupted in 23 patients (33 %). Treatment break was due to grade III mucositis or dysphagia or skin reaction. One week to ten days rest was given. In one patient the gap was for three weeks. One patient died on treatment due to aspiration pneumonitis and four patients discontinued treatment after 40 Gy. The overall treatment time ranged from seven weeks to ten weeks with a median of eight weeks. Patients with good performance status and good nutritional status tolerated the treatment well.

chemotherapy dose was reduced after three weeks in seven patients due to grade III reaction. Chemotherapy was discontinued in six patients after four cycles due to grade III reaction. No renal toxicity was found. One patient developed ototoxicity in the form of loss of hearing after one month of treatment completion.

Complete tumour response was seen in 42 patients clinically immediately after completion of treatment and 33 patients had partial response. At the end of the treatment, response was assessed only clinically. At the first follow-up, done after one month of completion of treatment, response and reactions were reassessed. Response was assessed clinically and with cytology in tumours of oral cavity and with endoscopies in cases of oropharynx,hypopharynx and larynx. CT scan and barium swallow were done whenever needed. At first follow up 60 % of the patients showed complete response and 22 % of the patients showed partial response. Four patients (5.7 %) discontinued treatment. One patient (1.4 %) expired during treatment. The remaining 11 % of the patients had progressive disease.

Response rates depended on site, stage (tumour burden) and performance status. Patients with primary in the tongue had poorer response rates and patients with primary in larynx had better response. Performance status at the beginning of treatment also mattered. Patients with good performance status were able to complete treatment without breaks and had good response. In our study, we had 23 cases of primary in oral cavity. Of these, 12 patients showed complete response (52%). Of 11 patients with carcinoma oropharynx, 5 patients had complete response (45.5%). 14 of 20 patients (70%) with primary in hypopharynx had complete response. We had 5 cases of Nasopharynx, of these 4 patients had complete response (80%) and 6 cases out of 8 with primary in larynx had complete response (75%).

## Discussion

The yield of radiotherapy alone in advanced squamous cell carcinoma of head and neck, decreases with increasing stage of the disease. For some advanced lesions, combination of surgery and radiation are feasible, but a significant percentage of these tumors are not surgically resect able and the alternative of using initial radical radiotherapy and chemotherapy, reserving surgery for salvage seems to show almost equal results as combined radiation and surgery.

The concomitant use of chemotherapy and radiotherapy has been most promising approach to combine radiation and chemotherapy, compared to neoadjuvant or adjuvant chemotherapy. A variety of chemotherapeutic drugs have been used concurrently with radiotherapy as monotherapy or combination therapy.

Several groups have evaluated Cisplatin and 5-FU in combination with radiation and shown improved control but at the cost of increased toxicity. More

recently, Paclitaxel has been investigated with radiation treatment, both as a single agent and in combination with Cisplatin. Results are promising, but need phase III trial evaluation and toxicity is the main concern. In the concurrent set up single agent chemotherapy based on platinum compound is the treatment of choice.

The dose and delivery schedules of Cisplatin have ranged from intermittent higher dose (100 mg/m$^2$) every three weeks to low dose (6 mg/m$^2$) daily administration. At our institute we use Cisplatin 40 mg/m$^2$ weekly concurrently with radiotherapy. Cisplatin dose is adjusted according to creatinine clearance, body surface area and performance status.

Serin et al[6] , used weekly Cisplatin 30 mg/m$^2$, reported better response rates and 14% of grade III toxicity.Porceddu et al [7], used weekly Cisplatin 35 mg/m$^2$ following surgery in 47 patients. They reported 40% grade III mucositis.Glaser et al [8], used weekly Cisplatin 35 mg/m$^2$ and 87% of patients could complete treatment without breaks and 13% had grade III mucositis.

Concurrent chemotherapy with three weekly Cisplatin 100mg/m$^2$ was used in a quite a number of trials. RTOG 9501and EORTC 22931 trials [9] showed 55% and 41% mucositis.In our study we have noticed 61 % grade II and 13 % grade III skin reaction. Grade II mucositis was seen in 58 % and grade III in 21 % of patients. Grade II dysphagia was seen in 44 % and grade III in 32 % of patients. Overall, we have noticed 22% of grade III reaction and 33% of treatment breaks. Response rates were 60%.A study conducted at Amritha Institute of Medical Sciences, Kochi [10], compared acute toxicities of two chemotherapy schedules – weekly Cisplatin (40 mg/m$^2$) and three weekly Cisplatin (100 mg/m$^2$) administered on week 1, 4 and 7. Results showed 8% grade III skin reaction and 4% grade III mucositis in three weekly regimens. 16% grade III skin reaction and 28% grade III mucositis in weekly regimen.

The results of our study were comparable to the other studies. We noticed 22 % grade III reaction. In RTOG 9501 trial, where three weekly Cisplatin (100 mg/ m$^2$) was given, 55 % grade III toxicity was reported. Trials using weekly Cisplatin showed less toxicity. Serin etal reported only 14 % grade III toxicity. In this study, dose of Cisplatin was 30 mg/ m$^2$. it appears that dose less than 40 mg/m$^2$ is better tolerated.

In our study, we noticed complete response in 60 % of the patients. Response was significantly influenced by the site of the primary. Patients with primary in Nasopharynx and Larynx had better response, 80 % and 70 % respectively compared to.Tumor response was better in patients who completed treatment without breaks and with good performance status.

Concurrent chemoradiation results in grade III reactions which have to be managed aggressively. Nutrition of the patient should be maintained with nasogastric or PEG tubes if needed along with parenteral nutrition. Weekly blood counts should be checked. Antifungals and antibiotics should be used whenever needed. Patients need counselling regarding diet and high protein diet should be advised.

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