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A study on clinical response and toxicity in locally advanced head and neck cancers

[1]**Dr Dasari Praveena**, Assistant Professor, Radiotherapy, Government Medical College, Kadapa

[2]**Dr B Sweta,** Assistant Professor, Radiotherapy, Kurnool Medical College/ Government General Hospital, Kurnool

[3]**Dr G David Chakravarthi**, Assistant Professor, Radiology, Government Medical College, Kadapa

[4]**Dr P NagaJyothi**, Oral Medicine and Radiology, Government Medical College, Kadapa

[5]**Dr V Nagesh Kumar**, Assistant Professor, Government Medical College, Kadapa

CORRESPONDING AUTHOR:
[4]Dr P NagaJyothi,
Oral Medicine and Radiology,
Government Medical College,
Kadapa
E mail: aarushank@gmail.com
Contact: 9652125527

ABSTRACT:
Background: Treatment of locally advanced head and neck cancer is a clinical challenge and requires aggressive and concerted measures. Radiotherapy with concurrent chemotherapy is the standard curative treatment strategy for the locally advanced head and neck cancer. The ultimate aim of radiation therapy is the maximum local control of the tumour with minimal toxicity. **Objectives:** To assess the clinical response of treatment using RECIST (version1.1) criteria. To assess the toxicities among the study population during chemo-radiation. **Methodology:** Hospital based observational prospective study was conducted at Department of Radiation oncology, in a Tertiary cancer care centre among Head and neck Cancer patients. **Results:** Most common site of head and neck cancer in the study was oral cavity followed by oropharynx and hypo pharynx. At the end of 4^{th} week 58.33% had grade1 and 33.33% grade2 mucositis. Response to treatment was found to be statistically significant. **Conclusion:** Mucositis was significant toxicities during treatment followed by dysphagia and radiation dermatitis. Complete response is seen in 50% of the patients clinically and radiologically. No patient died during treatment or at follow up.

Key words: Toxicities, Head & Neck cancer, Radiotherapy

INTRODUCTION:

Head and neck cancer (HNC) was the seventh most common cancer worldwide in 2018 (890,000 new cases and 450,000 deaths). (1) 197649 new cases and117728 deaths reported in

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India according to GLOBOCAN 2018 report showing HNC statistics of India. In India, among patients diagnosed with HNC, 86.5% were reported as tobacco users and 23.2% were reported as alcohol users. Head and neck squamous cell carcinoma can arise from subsites within the oral cavity, oropharynx, hypopharynx, larynx, and nasopharynx. Around 30% of HNC patients in India and Southeast Asia present with genetic abnormalities like preponderance of Ha-ras mutations, loss of heterozygosity of Ha-ras, N-ras amplification, and N-myc amplification.Theserasoncogenesmutationsareuncommoninthewesternworld.(2)

Treatment of locally advanced head and neck cancer is a clinical challenge and requires aggressive and concerted measures. Radiotherapy with concurrent chemotherapy is the standard curative treatment strategy for the locally advanced head and neck cancer. The ultimate aim of radiation therapy is the maximum local control of the tumor with minimal toxicity. Introduction of three-dimensional conformal radiotherapy (3D-CRT) allowed irradiating the target volumes more precisely with better sparing of surrounding healthy tissues. Advent of intensity-modulated radiotherapy (IMRT) facilitated even more conformity in dose shaping, providing higher dose to target volumes, further limiting the dose to organs at risk thus leading to less toxicity [3,4]. The state of the art regarding radiation dose fractionation has evolved from once-daily treatment to hyper fractionation and accelerated fractionation. Several chemotherapy regimens using cisplatin, 5Fluorouracil, paclitaxel have been used with increased local control but higher toxicities. The most frequently utilized regimen for concurrent chemoradiotherapy remains single-agent cisplatin. Anti–EGFR-targeted therapy also enhances the effectiveness of RT in recurrent and advanced-stage disease.

OBJECTIVES:

To assess the clinical response of treatment using RECIST (version1.1) criteria and also assess the toxicities by CTCAEv5 among the study population both compared with baseline, during chemo-radiation of 1^{st} week,4^{th} week ,7^{th} week and after two months of treatment.

METHODOLOGY:

Study design and setting: Hospital based observational prospective study was conducted at Department of Radiation oncology, Tertiary cancer care centre.

Duration of study: January 2020-December 2021 (24months)

Sample Size: The following formula was used to calculate the required number of patients in the study: N=4PQ/L2; where P is the prevalence of head and neck cancers, which is 10% approximately at this Hospital; Q is 100-P and L=permissible error=10%. Hence, n=4x10x90/100=36.thus, 36 patients were enrolled who underwent treatment at Department of Radiation oncology, Tertiary cancer care centre.

Study subjects: Head and neck Cancer patients

Inclusion criteria:

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Age: 18-75years.

ECOG: Performance status 0-2 on a scale of 0-5.

Histopathologically confirmed squamous cell carcinoma in locally advanced head and neck cancers.

Normal hemogram, Renal function tests and Liver function tests within normal limits.

Patients who gave informed consent.

Exclusion criteria:

1. Any prior treatment received for tumour. 2. Patients with distant metastasis.

3. Patients with thyroid carcinoma, salivary gland tumours are excluded.

Ethical permissions and informed consent: This study was initiated after obtaining approval from the Institutional ethical committee. After taking informed consent from the patients, evaluation and enrolment started.

Initial evaluation: Complete medical history, physical examination and diagnostic workup were done. X ray chest PA view and radiological assessment with a contrast enhanced CT scan for site and extent of the disease. Assessment of ECOG performance score.

Treatment planning and delivery:

Dose prescription and Treatment delivery: patients received 66-70Gy/33-35 fractions over 7 weeks: Phase 1: 54 Gy/27 fractions, 5 fractions per week to volume comprising the gross

disease with extension and the nodal areas at risk.

Phase 2: 12-16 Gy/6-8 fractions, 5 fractions per week to the boost volume, which included the gross tumour volume with margin.

IMRT radiation therapy plans were generated for the patients. Radiotherapy was delivered by linear accelerator (LINAC) using 6MV X rays. Concurrent chemotherapy planned with weekly with cisplatin 40 mg/m2 iv in 90 minutes. Premedication with Inj.Palanosetron, Inj.Rantac, given. Patient is pre-hydrated with at least 500 ml of normal saline. Before administering Cisplatin, Mannitol (20%) 100 ml is given intravenously. Minimum of one litre normal saline post hydration fluid is given.

All patients were assessed at 1^{st} week,4^{th} week and 7^{th} week for treatment related acute toxicity. Acute treatment related toxicity was assessed and graded using Common terminology criteria for adverse events (CTCAEv5) and supportive treatment was given.

Follow up: After completion of treatment, patients were followed up as outlined below:

First follow up was done at 4 weeks from the completion of treatment. Second follow up at 8 weeks from the completion of treatment.

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Patients were assessed for acute toxicity and tumour response at 2nd month follow up based on: Symptom history and toxicity grading using CTCAEv5.

Local examination using inspection, palpation, and indirect laryngoscopy to assess mucosal integrity, skin integrity, tumour and nodal status including bi-dimensional measurement of the tumour and the nodal site. CT scan at second follow up visit to know tumour and nodal response.

Patients were also encouraged to visit earlier if new or progressive symptoms developed. All patients were encouraged to adhere to the prescribed regimen for good oral hygiene and abstain from any form of tobacco use.

Locoregional tumour response evaluation was done by clinically and radiologically at 8 weeks using the RECIST (1.1) criteria which has defined various outcomes as follows:

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Data collection and statistical analysis: The collected data was analysed using standard statistical software package (SSPS version 26.0).

Response to treatment was assessed; analysis was done using descriptive statistics and using Chi square test.

RESULTS & DISCUSSION:

Thirty six subjects were participated and all of them received radiotherapy by IMRT technique. Eighty percent were males and twenty percent were female subjects with an age range of 34-70 years.

TABLE: Baseline data of the study participants (n=36)

Variable		**Frequency (%)**
Presenting	Ulcer	18 (58.33)
	Dysphasia	10(19.44)
	Epistaxis	1 (2.78)

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symptoms	Shortness of breath	3 (8.33)
	Neck swelling	4 (11.11)
Histopathology	Well differentiated squamous cell carcinoma	20 (55.56)
	Moderately differentiated squamous cell carcinoma	12 (33.33)
	Poorly differentiated squamous cell carcinoma	4 (11.11)
Stage	Stage III	13 (36.11)
	Stage IV A	19 (52.78)
	Stage IV B	4 (11.11)
Over all treatment time	Less than 50days	9 (25)
	More than 50days	27 (75)
Tumour site	Oral cavity	18 (50)
	Oropharynx	9 (25)
	Hypo pharynx	7 (19.44)
	Nasopharynx	1 (2.78)
	Nasal cavity	1 (2.78)

The ulcer was most common symptom seen in 58.33% patients. Other symptoms were dysphagia, epistaxis, shortness of breath, neck swelling. Among 55.56% patients had well differentiated squamous cell carcinoma being the most common histology. Of which 36.11% patients of stage III, 52.78% of stage IV A and 11.11% patients of stage IV B. Average duration of treatment was 50 days. Most common site of head and neck cancer in the study was oral cavity (50%) followed by oropharynx and hypo pharynx. In a study by *N. Kucha et al.* Median age of the patients was 52 years of which 82% were male and 18% were female. Oropharynx, larynx and hypopharnx as primary tumor site was in 58.9%.

TABLE: Response at end of treatment and 2months follow-up (n=36)

Response	**At end of treatment**	**At 2months follow-up**	
Complete response	12 (33%)	18 (50%)	**X^2=7.8316**
Partial response	24 (67%)	14 (39%)	**P**
Progression of disease	0	4 (11%)	**value=0.0199**

Response to treatment was found to be statistically significant. Rate of response to treatment was good at 2months of follow-up as compared to at end of treatment. There was no progression of disease. No patient died during treatment.

Similar results were seen in a study conducted by Saptarshi Ghosh et al. single-institution retrospective study showed the most common site of involvement was the oral cavity Response to treatment was assessed till two months after the completion of treatment.

Singh NP, Khurana R, Complete response was seen in 42 (93.33%), partial response in 2 (4.44%) and progressive disease in 1 (2.22%) patient.

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TABLE: Toxicities at week 1, week 4 and week 7 (n=36)

TOXICITY		Week 1	Week 4	Week 7	P value
Dysphagia	Grade I	41.67	3 (8.33)	1 (2.78)	χ^2= 3.4706 p=0.176
	Grade II	0	19 (52.78)	15 (41.67)	
	Grade III	0	6 (16.67)	12 (33.33)	
Mucositis	Grade I	0	21 (58.33)	5 (13.80)	χ^2= 20.6942 **p=0.000032**
	Grade II	0	12 (33.33)	19 (52.78)	
	Grade III	0	1 (2.78)	12 (33.33)	
Skin Reaction	Grade I	0	28 (77.78)	9 (25)	χ^2=23.0899 **p=0.00001**
	Grade II	0	5 (13.89)	23 (63.89)	
	Grade III	0	1 (2.78)	4 (11.11)	
Xerostomia	Grade I	0	27 (75)	22 (61.11)	χ^2=8.8591 **p=0.0029**
	Grade II	0	2 (5.56)	14 (38.89)	
Nausea	Grade I	30.56	22 (61.11)	7 (19.44)	χ^2= 21.118 **p=0.0003**
	Grade II	0	11 (30.56)	23 (63.89)	
	Grade III	0	1 (2.78)	5 (13.89)	
	Grade IV	0	1 (2.78)	10 (27.78)	
	Grade V	0	1 (2.78)	1 (2.78)	
Anorexia	Grade I	88.89	12 (33.33)	5 (13.89)	χ^2= 13.770 **p=0.0010**
	Grade II	11.11	22 (61.11)	16 (44.44)	
	Grade III	0	2 (5.56)	15 (41.67)	
Weight loss	Grade I	0	7 (19.44)	22 (61.11)	χ^2= 0.0575 p=0.8105
	Grade II	0	2 (5.55)	5 (13.89)	
Pain	Score 2	38.89	4 (11.11)	1 (2.78)	χ^2= 16.384 p=**0.00094**
	Score 4	58.33	14 (38.89)	6 (16.67)	
	Score 6	2.78	18 (50)	16 (44.44)	
	Score 8	0	1 (2.78)	14 (38.89)	

*percentages were shown in the brackets

41.67%patients had grade 1 dysphagia, 19.44% grade 2 dysphagia at the end of 1st week. At the end of 4th week 8.33% patients had grade1, 52.78% had grade 2 ,16.67% patients had grade 3 dysphagia .2.78% had grade 1 ,41.67 % had grade 2,33.33% had grade 3 dysphagia at the end of treatment which was not stastically signifant.

At the end of 4th week 58.33% had grade1 and 33.33% grade2 mucositis. 13.89% had grade 1, 52.78% had grade2, 33.33% had grade3 mucositis at the end of treatment. At the end of 4th week 77.78% patients had grade1, 13.89% had grade2 skin reaction.25% patients had grade 1,63.89% had grade 2 ,11.11% had grade 3, no had grade4 skin reaction at the end of treatment.

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Similar results were seen in a study done by Bhide SA et al. The acute toxicities of RT include mucositis, dysphagia, xerostomia, dermatitis, and pain. Muhammad Shahid Iqbal et al., reported that 33% had mucositis, 41% dermatitis, 15% dysphagia and 17% mouth/neck pain. In a study by Mauro palazzi et al. dermatitis was the most frequent adverse event, sparing <1 % population, at treatment completion, skin toxicity was Grade 1 in 31%, Grade 2 in 56%, and Grade 3 in 12% patients, similar to this study. Contrast to this study Andy Trotti et al. reported mucositis in 90% of patients undergoing chemoradiotherapy, out of which grade 3-4 mucositis was seen in 43% patients.

25% patients needed NG tube feeds at the end of 4^{th} week, 58.33% by the end of treatment. 17(47.22%) patients continued NG tube feeding even at 2^{nd} month follow up, while 5 patients (13.88%) were able take oral feeds among who had NG tube at the end of treatment. Findings of Nguyen NP et al. regarding dysphagia, loss of weight, need for Ryles tube similar to present study.

At the end of 4^{th} week 75% patients had grade1, 5.56% had grade2 xerostomia.61.11% patients had grade 1, 38.89% had grade 2xerostomia at the end of treatment. Findings of Tejpal Gupta et al. were in line with this study.30.56%patients had grade 1 nausea at the end of 1^{st} week. At the end of 4^{th} week 61.11% patients had grade1, 30.56% had grade 2 .19.44 % patients had grade 1 nausea ,30.56% had grade 2 ,13.89 % had grade 3 nausea at the end of treatment. 5.56%patients had grade1 at the end of 1^{st} week. At the end of 4^{th} week 27.78% patients had grade1, 2.78% had grade2 and 2.78 % patients had grade3 vomiting.44.44 % patients had grade 1,27.78% had grade 2 vomiting at the end of treatment. 88.89%patients had grade 1, 11.11% patients had grade 2 anorexia at the end of 1^{st} week. At the end of 4^{th} week 33.33% patients had grade1, 61.11% had grade2 and 5.56 % patients had grade3 anorexia.13.89% patients had grade1,44.44 had grade 2,41.67 % had grade 3 anorexia at the end of treatment**.** At the end of 4^{th} week 19.44% patients had grade1, 5.56% had grade2 weight loss.61.11% patients had grade1, and 13.89% patients had grade 2weight loss at the end of treatment. grade 1 loss of weight was seen in more number patients, and grade 2 weight loss was seen less number of patients when compared to study done by Pirus Ghadjar et al.,.

On visual analogue scale pain score is measured .38.89%patients had score of 2, 58.33% patients had score of 4 and 2.78% had score of 6 at the end of 1^{st} week. At the end of 4^{th} week 11.11% patients had score 2, 38.89% had score of 4 and 50 % patients had score of 6.16.67 % patients had score of 4, 44.44 % had scoreof6,38.89%hadscore 8 at the end of treatment. Mauro palazzi et al. observed that the pain of any grade from RT was reported by 93% of patients (40% reported Grade 3 pain at the end of treatment).

There was a general trend toward decreasing the incidence of toxicities as the type of radiation therapy advanced from lateral opposing fields to IMRT.

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CONCLUSION:

Mucositis was significant toxicities during treatment followed by dysphagia and radiation dermatitis, but they were not severe due to the advanced IMRT technique resulting in less toxicity. Complete response is seen in 50% of the patients clinically and radiologically. No patient died during treatment or at follow up.

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