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ACUTE TOXICITY PROFILE IN HYPERFRACTIONATION VERSUS CONVENTIONAL CHEMO-RADIATION REGIMEN IN ADVANCED HEAD AND NECK CANCER - A TERTIARY CENTRE EXPERIENCE

Oncology

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ABSTRACT

Aim- To compare the onset and severity of acute toxicities in advanced head and neck cancer patients undergoing hyperfractionation as compared to conventional CT-RT (concurrent chemo-radiation). **Method-** 100 patients with squamous cell carcinoma of head and neck region were randomly assigned to either hyperfractionation or conventional CT-RT. Hyperfractionation arm received 74.8 Gy \ 68 fractions, 1.1 Gy per fraction, 2 fractions per day with an interval of 6 hours. While standard arm received 66.6 Gy \ 37 fractions, 1.8 Gy per fraction with concurrent Cisplatin 40mg/m2 .Onset and severity of acute toxicity were observed weekly. **Result-** Onset of acute toxicity like dermatitis, mucositis and laryngitis was within 1st week of treatment in hyperfractionation arm which was statistically significant (P=0.001, P=, 0.01, P=0.04 respectively). No significant difference in the onset of pharyngitis or xerostomia was observed between the 2 arms. In terms of severity, statistically significant grade 3 toxicity were observed in the hyperfractionation arm (dermatitis P=0.045, mucositis P=0.001, laryngitis P=0.002, pharyngitis P=0.002 and xerostomia P= 0.02). Grade 4 toxicity was observed in the pharynx, larynx and mucous membrane in the hyperfractionation arm. **Conclusion-** Hyperfractionation leads to earlier onset and more severe acute toxicity (grade 3 or above) in advanced head and neck cancer which leads to treatment delays and loss of therapeutic gain.

KEYWORDS

Acute toxicity, hyperfractionation, chemo-radiation, advanced head and neck cancer

INTRODUCTION

Head and neck cancer (HNC) includes cancers of lip, oral cavity, oropharynx, hypopharynx and larynx. They contribute to 3.9 % (18.1 million) of the total new cancer and 3.8% (9.6 million) of total deaths worldwide. [1]

The main difference in India (compared to world) is the late and locally advanced presentation of disease. Patients with advanced disease (stage III-IV) have a dismal disease control with conventional therapy which warrants a more aggressive treatment.

Radiation dose of 75 - 80 Gy or more may be needed for disease control in large (T3 or T4) cancers. [2] But, this escalation of dose can produce radiation-induced toxicity although loco regional control is better. Attempts have been made to treat these tumors more effectively by modifying fractionation schedule of radiotherapy.

Both hyperfractionated and accelerated radiotherapy schedules produce better local control (7-10%). But MARCH analysis (2006) [3] - concluded that hyperfractionation had the greatest benefit in improving survival.

Hyperfractionation is based on the difference between the early and late responding tissues so as to increase total radiation dose without an enhancement of late toxicity. However, radiation related acute normal tissue toxicity is a major concern when treating HNC patients.

They have a debilitating effect on the quality of life of patients and contribute to treatment interruptions.

Acute adverse effects are defined as changes in tissues or symptoms associated with it occurring within 90 days from initiation of radiotherapy. [4] Mucositis, dysphagia and xerostomia are the major contributors of acute toxicity.

Material and methods

The study was carried out in the Department Of Radiation Therapy in a Tertiary Care Institute from a period of October 2017- March 2018 with 100 patients.

Study Design-Prospective randomized controlled 2 arm un-blinded study.

Inclusion Criteria-

- Histologically proven squamous cell carcinoma of head and neck region
- Locally advanced, unresected primary or nodal disease (Stage III and IV)
- Primary site- oral cavity, oropharynx, glottis and hypopharynx.
- Age > 18 and < 70 years
- ECOG score >2

Study Procedure-

Approval was taken from Institutional Ethics Committee. Written informed consent was obtained from all patients.

They were stratified by site of cancer origin, ECOG performance score, and stage of disease and then randomly assigned to either treatment arms.

ARM – A (HYPERFRACTIONATION ARM) - 50 patients

- 74.8 Gy \ 68 fractions, 1.1 Gy per fraction, 2 fractions per day with an inter-fraction interval of 6 hours, 5 days a week over 7 weeks .

ARM – B (CONVENTIONAL CT-RT ARM) - 50 patients

- 66.6 Gy \ 37 fractions, 1.8 Gy per fraction, 5 days a week over 7.5 weeks with concurrent chemotherapy consisting of inj. Cisplatin 40mg/m2 i.v. weekly.

Onset and severity of acute reactions were evaluated according to COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) and scored weekly.

Results

All patient characteristics were matched with no statistically significant difference in both the arms.

Mean age in ARM A and B was 43.66 and 43.54 years respectively. Majority of the patients were male (76% both arms).Maximum patients had primary in the oral cavity and belonged to stage IV A.

Table 1- Pre- treatment patient characteristics

	HFRT (ARM A) NO. (%)	CONVENTIONAL CT-RT(ARM B) NO. (%)
Sex -Male -Female	 38(76%) 12(24%)	 38(76%) 12(24%)
Age (years) -<40 ->40	 19(38%) 31(62%)	 20(40%) 30(60%)

ECOG -0 -1 -2	23(46%) 23(46%) 4(8%)	22(44%) 24(48%) 4(8%)
Primary site -Oral -oropharynx -larynx -hypopharynx	34(68%) 12(24% 4(8%) 0	29(58%) 10(20%) 8(16%) 0
Stage -III -IV a -IV b	7(14%) 35(70%) 8(10%)	10(20%) 35(70%) 5(10%)

TABLE 2- Onset of acute toxicity

Week of onset	ARM A NO. (%)	ARM B NO. (%)	P- value
DERMATITIS 1 (week) 2 3 4	 23(46%) 19(38%) 8(16%) 0	 3(6%) 30(60%) 14(28%) 3(6%)	 <0.001 0.03 0.15 0.08
Mucositis 1 2 3 4	 12(24%) 26(52%) 12(24%) 0	 0 18(36%) 20(52%) 6(12%)	 <0.01 0.11 <0.01 0.01
Laryngeal 1 2 3 4	 4(8%) 31(62%) 15(30%) 0	 0 13(26% 32(64%) 5(10%)	 0.04 <0.01 <0.01 0.02
Pharyngeal 1 2 3 4	 6(12%) 31(62%) 13(26%) 0	 2(4%) 25(50%) 20(40%) 3(6%)	 1.41 0.23 0.14 O.08
Xerostomia 1 2 3 4	 2(4%) 24(48%) 21(42%) 3(6%)	 3(6%) 24(48%) 23(46%) 0	 0.64 1 0.69 0.08

In ARM A onset of dermatitis was within the 1st week of treatment affecting 46% patients as compared to 6 % in ARM B which was statistically significant (P< 0.001).In ARM B maximum patients 60% had onset of dermatitis in 2rd week of treatment (P- 0.03).

In ARM A the onset of mucositis was within 1st week of treatment affecting 24 % patients as compared to none in arm B (P- <0.01).In ARM B patients started developing mucositis in 2nd week while majority developed at 3rd week 52 % as compared to ARM B 24 %(P- <0.01, 0.01 respectively).

Onset of laryngitis was within 1st week of treatment 8% in ARM A and maximum developed during 2nd week as compared to arm B- 0% in 1st week and 26% in 2nd week (P- 0.04 and P < 0.01 respectively). In ARM B-most of the patients 64% developed laryngitis during the 3rd week of treatment.

Onset of pharyngitis during 1st week of treatment in ARM A was 12% while in ARM B was 4% with no significant difference. Most of the patients had onset of pharyngitis in the 2nd week

Onset of xerostomia was within 1st week in both arms. Majority had onset in the 2nd week- 48 %.

TABLE 3- Severity of acute toxicity

Grade of toxicity	ARM A NO. (%)	ARM B NO. (%)
1. Dermatitis Grade-1 2 3 4	 13(26%) 26(52%) 14(28%) 0	 8(16%) 36(72%) 6(12%) 0
2.Mucositis 1 2 3 4	 2(4%) 18(36%) 28(56%) 2(4%)	 3(6%) 35(70%) 12(24%) 0
3.Laryngeal 1 2 3 4	 3(6%) 17(34%) 28(56%) 2(4%)	 8(16%) 29(58%) 13(26%) 0
4.Pharyngeal 1 2 3 4	 3(6%) 17(34%) 29(58%) 1(2%)	 8(16%) 28(56%) 14(28%) 0
5.Xerostomia 1 2 3 4	 14(28%) 31(62%) 5(10%) 0	 31(62%) 9(18%) 0 0

In ARM A 28 % patients had grade 3 dermatitis compared to ARM B 12% which was statistically significant (P- 0.045).

Mucositis developed in 56% in ARM A as compared to 24% in ARM B (P-0.001).

Grade 3 laryngitis developed in 56% patients in ARM A while 26% in ARM B which was statistically significant (P- 0.002).

4% patients in ARM A developed grade 4 laryngitis and pharyngitis while none developed in ARM B.

Statistically significant (P-0.002) grade 3 pharyngitis developed in ARM A. 3 patients required nasogastric tube insertion while 1 developed grade 4 pharyngitis which required urgent medical management.

Majority of patients in ARM A had grade 2 xerostomia .Grade 3 toxicity developed in ARM A (10 %) beyond 4 weeks of treatment while none in ARM B (P-0.02).

DISCUSSION

The incidence and mortality rates of head and neck cancers (HNC) vary drastically among developed and developing countries with India accounting for 20-30% of all the cases. [5]
In our study the mean age of patients was 43 years. Oral cavity was the major primary site (which reflects the primary site in India) and majority presented in stage IVA.

A. DERMATITIS

Majority of patients in HFRT arm had acute skin reaction within the 1st week of treatment (P < 0.001). Statistically significant (P- 0.045) severe toxicity (grade 3) was more with HFRT which warranted stopping the treatment.

Krstevska et al [6] observed moderately enhanced grade 2 acute skin reactions in hyperfractionation group compared with conventional fractionation group (P = 0.054).

B. MUCOSITIS (Oral)

We observed acute mucosal reaction earlier in HFRT arm- within 1st week which was statistically significant (P- <0.01) .Grade 3 and 4 toxicity developed in hyperfractionation arm more. The incidence of grade ≥3 mucositis increased from 20 - 50% to 66 - 86% in several trials where altered fractionation was used. [7] Oral mucositis is the most common and clinically significant acute adverse effect of radiotherapy for HNC.

C. PHARYNGITIS

Significant (P-0.002) difference was seen with severity of toxicity – grade 3 toxicity were observed more in the HFRT arm which warranted nasogastric tube insertion and admission .
The findings are in accordance with several studies that concluded that most common site of grade 3 acute reaction was pharynx. [6]

D. LARYNGITIS

The onset of laryngitis was earlier hyperfractionation arm (P-

0.04).Grade 3 toxicities were seen with HFRT schedule more commonly as compared to CTRT arm (P-0.002). Krstevska et al. [6] also observed increased grade of laryngeal toxicity in hyperfractionation arm (P = 0.039).

E. XEROSTOMIA/ Acute salivary gland hypofunction

Statistically significant Grade 3 toxicity developed with hyperfractionation (P-0.02).It was more prominently seen in patients who had bilateral treatment fields leading to irradiation of both parotid glands.

Salivary flow from the parotid gland is markedly reduced following a cumulative dose of 30 - 50 Gy using conventional fractionation and higher with HFRT due to greater cumulative total dose.

To conclude presently, advanced tumors appear to be best treated with conventional chemo-radiation. Hyperfractionation is being used as a tool to enable dose escalation for better local control without an increase of severe late toxicity. However early onset and higher severity of acute toxicity makes it a less encouraging option.

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