Main Article

COMPARISON OF SEQUENTIAL CHEMORADIATION WITH RADIATION ALONE IN THE TREATMENT OF ADVANCED HEAD AND NECK CANCERS

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ABSTRACT: ***Objectives****: To compare locoregional control with alternating chemo radiation and radiation alone in patients with locally advanced head and neck carcinoma.* ***Study Design****: A prospective randomized study.* ***Setting****: Tertiary academic referral center.* ***Patients****: 50 patients of biopsy proven locally-advanced carcinoma of head and neck.* ***Intervention****: 25 patients were kept in Group I or study group (i.e. alternating chemo-radiation) and 25 patients in Group II or control group (i.e. radiation alone). In the study group, patients were given 3 cycles of chemotherapy (Cisplatin 20 mg/m[2] and Inj. 5-FU 200 mg/m[2] from day 1-5 of each week) during weeks 1,5 and 9 alternated with radiation dose of 10Gy/week was given during weeks 2,3,4 and 6,7,8. In the control group, patients were given a total dose of 60Gy in 6 weeks.*
Outcome measures*: The response rate at the primary site and nodal site was better in study group as compared to control group.* ***Results****: On comparing the response at the primary and nodal site together, 72% (18/25) patients of group I and 44% (11/25) patients of group II showed CR. PR was seen in 28% (7/25) and 36% (9/25) patients in group I and II respectively. No response was seen in 5/25 (20%) of patients in Group II.* ***Conclusion****: Our study has revealed that alternating/ sequential chemoradiation is a promising and feasible approach for patients in advanced head and neck cancer.*

Key Words: *Chemoradiation, head and neck cancer*

INTRODUCTION

Cancer arising in the head and neck area is particularly devastating both to the patient and the treating physician.[1] The term "head and neck cancer" describes a diverse collection of cancers of varying histologies arising from a variety of anatomic sites that comprise the upper aerodigestive tract.[2] Approximately 90% of head and neck cancer occur after exposure to known carcinogens like tobacco and alcohol, since both are known to act synergistically.[2]

Epidemiology

The head and neck malignancies constitute 5% of all the cancers worldwide.[3] In India, the most common head and neck cancer are those of the oral cavity and pharynx. The age adjusted incidence for these sites, in the Indian males range from 10.8 to 38.8 per 100,000 males; and for the females it is 6.4 to 14.9 per 100,000 females.[3] The overall male-female ratio is nearly 4:1; with the exception of carcinoma of postcricoid region in which there is almost a total reversal of rates with females predominating.[4] Incidence of head and neck squamous cell carcinoma increases with age and usually present in patients older than 50 years.[2,5] Nasopharyngeal and salivary gland tumors are exceptions which may occur in the younger age group.[3]

Etiopathogenesis

The commonest known etiological factor is cigarette smoking.[3] Case control studies calculated increase in relative risk by 5-25 folds for the smokers.[3] Cigarette smoking induces carcinoma of larynx and lung; pipe and cigar smokers have higher incidence of lip and oral cavity cancers; cancer of hard palate is found in reverse chutta smoking; while chewing of tobacco has increased risk of buccal mucosa and oropharyngeal cancers.[3] Pathogenesis of alcohol induced cancer is not yet established, although it is synergistic with cigarette smoking and also with malnutrition, vitamin deficiency etc. Low nutritional status and poor vitamin intake are associated with higher risk of head and neck cancer for it is believed that retinoic acid has important preventive effect. Other factors like poor orodental hygiene, illfitting dentures, occupational exposure to wood dust, textile fibers, nickel and radium has also been implicated.[3] Exposure to Epstein-bar virus increases the risk of nasopharyngeal carcinoma.

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Histopathology

Squamous cell carcinoma (epidermoid) constitute about 90% of head and neck carcinoma.[6] This can be graded as well, moderately and poorly differentiated; and more than 75% of these are of keratinizing type.[3] Other histological types include verrucous carcinoma, adenocarcinoma, adenoid cystic carcinoma, lymphomas and rare variants like melanomas, esthesioneuroblastomas, sarcomas etc.

Majority of these patients i.e. 70-80% are diagnosed with locally advanced disease with lymphnode involvement in upto 30-50% of patients.[7] Because of high incidence of advanced disease at presentation and locoregional recurrences, the management of these patients is very disappointing and remains to be a great challenge.[7,8] Historically the carcinoma of head and neck has been treated with surgery and/or radiotherapy alone. These days concomitant chemoradiation has been designed to be a third definitive treatment for locally advanced head and neck squamous cell carcinoma. The concept of combined modality approach aims at improved survival, local control, reduction of distant metastases and above all preservation of organ-function without jeopardizing the overall outcome.[7]

MATERIALS AND METHODS

This randomized trial was conducted on 50 patients of biopsy proven squamous cell carcinoma of head and neck referred to the Radiotherapy department of PGIMS Rohtak from 1998-2000. The patients with good performance status (KPS score 70 or above) and whose financial condition allowed for chemotherapy were selected for alternating chemoradiation (study) group I, while the remaining patients were put in the radiation alone (control) group II. Written consent was obtained from the patients for this trial; and approval was taken from the ethical committee of the institution. All patients were within the normal range of biochemical tests. The patients were having locally advanced disease without distant metastases. All patients were subjected to thorough and detailed clinical examination and workup and details recorded in proformas.

Treatment delivery and schedule

In the study group, patients were given 3 cycles of chemotherapy during weeks 1,5 and 9. Chemotherapy given was Inj Cisplatin 20 mg/m^2 and Inj. 5-FU 200 mg/m^2 from day 1-5 of each course with adequate hydration, forced diuresis and antiemetics schedule. Total radiation dose of 60Gy (10Gy/week) was given during weeks 2,3,4 and 6,7,8 alternated with chemotherapy during weeks 1,5,9. In the control group, patients were given a total dose of 60Gy in 6 weeks, 2gy/fraction and 5 fractions in a week. In both the groups, external beam radiotherapy was given on telecobalt Theratron-780C machine by two parallel-opposed lateral fields. Spinal cord was shielded after a total dose of 45Gy. The patients were weekly assessed for treatment toxicities using WHO toxicity criteria. The response was assessed 4 weeks after completion of treatment using WHO response criteria. All patients underwent regular general physical, local and systemic examination every month for 6 months.

OBSERVATIONS AND RESULTS

The median age at presentation was 53 years in both the groups (range 41-60 years). The majority of patients were in 4th and 5th decades of life. The male-female ratio was 9:1. The most common primary site was oropharynx (mainly base of tongue and tonsil) in both the groups (29/50). Other common sites were supraglottic larynx, hypopharynx and oral cavity respectively. Moderately differentiated squamous cell carcinoma was the most common histopathology noted (32/50). 26/50 patients presented in stage III, the remaining in stage IV. The most common symptom at presentation was dysphagia followed by pain throat, hoarseness of voice and swelling neck respectively. 44/50 patients had a history of smoking for more than 20 years, while chronic alcohol consumption was seen in 68% in both the groups.

Response to the treatment

Table 1 shows the response at primary site and nodal site individually. The complete response (CR) at primary site in group I was seen in 20/25 (80%) patients, compared with 13/25 (52%) in control group. The partial response (PR) at primary site for Group I and Group II was seen in 20% (5/25) and 28% (7/25) patients respectively. 5/25 (20%) of patients in Group II showed no change in disease status after treatment.

The complete response at nodal site for Group I and II was seen in 19/25 (76%) and 15/25 (60%) of patients respectively; while the partial response was 6/25 (24%) and 3/25 (12%) respectively. 7/25 (28%) of patients in group II showed no response at the nodal site. Table 2 shows the response at

Table 1: Response at primary and nodal site individually (WHO response criteria)

WHO response criteria		Study group (n=25)	Control group (n=25)	*P* value
Response at primary site	CR	20 (80)	13 (52)	*P* <0.05
	PR	5 (20)	7 (28)	
	NC	0	5 (20)	
Response at nodal site	CR	19 (76)	15 (60)	*P* <0.05
	PR	6 (24)	3 (12)	
	NC	0	7 (28)	

Figures indicates in parenthesis are percentage

Table 2: Response rate together at primary and nodal site (WHO response criteria)

WHO response criteria		Study group (n=25)	Control group (n=25)	*P* value
Response at primary and nodal site	CR	18 (72)	11 (44)	*P* <0.05
	PR	7 (28)	9 (36)	
	NC	0	5 (20)	
Overall RR	CR+PR	25 (100%)	20 (80%)	

Figures indicates in parenthesis are percentage

primary site and nodal site together. On comparing the response at the primary and nodal site together, 72% (18/25) patients of group I and 44% (11/25) patients of group II showed CR. PR was seen in 28% (7/25) and 36% (9/25) patients in group I and II respectively. No response was seen in 5/25 (20%) of patients in Group II.

The overall response rate (PR and CR combined) at primary and nodal site was 25/25 (100%) in study group compared with 20/25 (80%) in control group, *P* value < 0.05. Thus the response rate at the primary site and nodal site was better in study group as compared to control group.

Status at last follow-up

All patients completed 6 months of follow-up (range 6-24 months) and the observations are tabulated in [Table 3]. The disease status at 6 months for Group I and Group II was: No evidence of disease (NED) in 68% and 32%, residual disease in 20% and 52% and recurrent disease in 12% and 16% patients respectively. In the control group, 3 patients had progressive disease while 2 had metastases in lung and brain; no patient of study group showed progression of disease or metastatic disease.

DISCUSSIUON

Chemotherapy in head and neck cancer has historically been given in neoadjuvant, adjuvant, or concomitant with radiation; now a days concomitant chemoradiation is fast emerging as a third definitive treatment for selected locally advanced head and neck squamous cell carcinoma. Schedules of concomitant administration of chemotherapy and radiation can be.

Table 3: Status at last follow-up (6 months)

Status at 6 months	Study group (n=25)	Control group (n=25)
NED	17 (68)	8 (32)
Residual	5 (20)	13 (52)
Recurrence	3 (12)	4 (16)

Figures indicates in parenthesis are percentage

1. Synchronous, both modalities given close together.
2. Sequential/alternating, both administered in a non-overlapping fashion.[2,9]

Basis of alternating chemo-radiotherapy

1. The sequential administration of the former therapy induces cell recruitment making the latter more effective.[10]
2. Goldie and Coldman hypothesis suggests that alternating delivery of two active, non-cross resistant treatments could increase the cure rate because of the possibility of each treatment extinguishing the residual resistant cell clones, avoiding the development of double resistant cell clones.
3. Unlike the split course radiotherapy, in sequential chemo-radiotherapy there is no true gap because chemotherapy fills the pause between the radiation courses.

Various trials have shown better locoregional control with alternating chemo radiation compared to either radiotherapy alone or neoadjuvant chemotherapy.[11-13] Hence this prospective study was undertaken to study and compare the locoregional control with alternating chemo radiation and radiation alone in patients with locally advanced head and neck carcinoma. The study results proved that sequential chemoradiation is a better treatment option compared with radiation alone for the control of primary and nodal disease in locally advanced head and neck cancers.

CONCLUSION

There is definitely a beneficial role of chemotherapy along with radiotherapy in patients of locally advanced head and neck squamous cell carcinoma. Our study has revealed that alternating/ sequential chemoradiation is a promising and feasible approach for patients in advanced head and neck cancer.

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