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Comparative Study Between Accelerated Fractionation with Concomitant Chemotherapy Versus Conventional Chemoradiation in Unresectable Locally Advanced Head and Neck Cancer

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ABSTRACT

Background: Most head and neck cancers arise from the mucosal epithelium of the oral cavity, pharynx, and larynx, and are collectively referred to as head and neck squamous cell carcinoma (HNSCC). Early-stage HNSCC are managed by surgery alone where whereas locally advanced cancers require multimodal treatment which involves surgery followed by adjuvant radiotherapy(RT) or chemoradiotherapy(CRT).

Methods: The present study was conducted at the State Cancer Institute, Department of Radiation Oncology, Netaji Subhash Chandra Bose Medical College, Jabalpur, MP, India. About 60 patients of either sex, randomized into two groups of 30 patients in each group fulfilling the inclusion and exclusion criteria were scheduled to undergo radiation with Cisplatin. Arm A patients received accelerated fraction, while Arm B received conventional fraction.

Result: Most patients in both arms were males aged 50-60. In both arms, most patients had primary lesions in the oral cavity and were classified as stage III. Mucositis was more severe in Arm A than in Arm B. All of the patients in both arms were suffering from dysphagia during treatment. Complete response was achieved by 55.56% of patients in Arm A and 48.57% in Arm B.

Conclusion: It was concluded that an accelerated regimen could be preferred over a conventional one per the clinical response observed and toxicity management. Disease-free survival can be predicted using a large sample size and time.

Key-words: Benign, Dysphagia, Head & Neck Squamous cell carcinoma (HNSCC), Radiotherapy (RT), Tumor

INTRODUCTION

It is projected that by 2030, the incidence of HNSCC will have increased by 30%, or 1.08 million new cases yearly [1–3].

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The management of locally advanced HNSCC has developed from a poorly successful single modality therapy to an integrated, highly effective multidisciplinary approach. In contrast to HNSCC's early stages, all three treatment modalities, radiation and surgery, have important roles.

The rise of concomitant chemoradiation was proven by RTOG 91-11 trial and the benefit of concurrent chemoradiotherapy in cases with unresectable head and neck cancers was proven by EORTC 22931 and RTOG 9501. These studies were remarkable and proved the

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role of concurrent chemoradiation in unresectable locally advanced head and neck cancer.

A meta-analysis by Bourhis *et al.* [4] titled "Meta-Analysis of Radiotherapy in Squamous Cell Carcinoma of Head and Neck (MARCH)" showed that modified fraction schedules are a helpful substitute for standard radiation because they yield comparable reductions in overall mortality when compared to standard radiation alone in the definitive therapeutic setting. More recently, accelerated radiation therapy regimens have been created to prevent tumor cell repopulation during radiotherapy (RT) [5–15].

One of the most noticeable and important advantages of the accelerated radiation therapy regime is the lesser overall treatment completion time as accelerated radiation therapy completes treatment 1 week earlier than conventional therapy. This tracks its core repercussion in the form of benefits not only from the radiobiological point of view in tackling accelerated repopulation of tumor cells but also from the overall feasibility of providing medical care and utilization of resources, particularly the overburdened government medical institutes. From patients' perspective, since most of our patients here in government institutes are reported to be daily wage workers, overall, less treatment time means less missing out on daily income and fewer dropouts from treatment. Above all, living in a world with epidemics of infectious diseases such as the coronavirus pandemic has a great advantage regarding earlier treatment completion, as fewer hospital visits and lesser in-patient treatment are incredibly beneficial.

A limited number of studies have been conducted in the central India region since most of the studies have been conducted in the Western world. Our hospital, the State Cancer Institute, Jabalpur, Madhya Pradesh, hospitalizes and encompasses nearly 20 districts in the surrounding regions, of which head and neck cancer account for almost 1/3 of total cases registered in a year. For the year 2021 total number of cases at our institute was 2641, out of which 851 were of head and neck cancers, accounting for approximately 32.23%, nearing one-third of the total cases registered. This study represents single-centered experiences of comparing two different fractionation regimens of delivering definitive chemoradiation in unresectable locally advanced head and neck cancer. The study compared the efficacy and toxicity profile of an accelerated fraction regimen of 6 fractions per week with concurrent cisplatin with a conventional regimen of 5 fractions per week with concurrent cisplatin.

MATERIALS AND METHODS

This study was conducted at the State Cancer Institute, Department of Radiation Oncology, Netaji Subhash Chandra Bose Medical College, Jabalpur, MP, India. Registered and histologically proven cases of head and neck cancer were screened and considered for appropriate inclusion criteria to be considered for the study. The study was conducted for 18 months from approval from the ethics committee from March 2021 to August 2022. Thirty patients in each group, 60 of whom had fulfilled the inclusion and exclusion criteria and were ready to give written informed consent, were taken for the study.

Inclusion criteria

- Age >18 years and < 70 years.
- Pathologically proved head and neck carcinoma.
- Squamous cell carcinoma.
- Unresectable tumor.
- Treatment naive except for biopsy or cytology.
- Signed study-specific informed consent given by the patient before randomization.
- ECOG performance status 0-1-2.

Exclusion criteria

- Patients with uncontrolled comorbidity.
- Patients already receiving treatment in the form of CRT radiation or surgery.
- ECOG 3 or more.
- Pregnancy or lactation.
- Hypersensitivity to Cisplatin.
- Distant metastasis.
- Other synchronous malignancy.

Methodology- A prospective randomized comparative study was conducted in a tertiary-level hospital after obtaining approval from the institutional ethics committee and informed patient consent. A minimum of 60 patients of either sex of head and neck cancer were scheduled to undergo Concurrent Chemoradiation with Cisplatin. Patients were randomly allocated into two study groups of 30 patients each as per a computer-generated random number list. The radiation planning

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technique standardized for both groups of patients was the same. Arm A patients received accelerated fraction, dose 2 Gy per fraction, one fraction daily from Monday to Saturday for a total dose of 70 Gy/35 fraction with cord shielding at 50 Gy with concurrent CRT weekly Cisplatin 35 mg/m^2 with proper hydration.

Arm B patients received conventional fraction, dose 2 Gy per fraction, 1 fraction daily from Monday to Friday for a total dose of 70 Gy/ 35 fraction with cord shielding at 50 Gy with concurrent CRT weekly Cisplatin 35 mg/m^2 with proper hydration.

Every week, all patients were examined in the outpatient department to evaluate the toxicity and response to treatment. Haematological toxicity (haemoglobin, total leucocyte count, and platelet count), upper and lower gastrointestinal toxicity (vomiting and nausea), acute renal toxicity, and mucositis, and acute skin reaction were included. Toxicity was graded according to the RTOG criteria.

Following one month of chemoradiotherapy completion, response evaluation was carried out every three months through physical examination, ENT examination, and, if necessary, CECT face and neck. Additional investigations were performed whenever necessary. The response was assessed clinically and radiologically using the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.

Statistical analysis- SPSS 27 was used for statistical analysis. The continuous data were expressed as mean±standard deviation, while the discrete data were expressed as frequency and its respective percentage.

Ethical approval- The ethical committee of State Cancer Institute, Department of Radiation Oncology, Netaji Subhash Chandra Bose Medical College, Jabalpur, M.P., India, approved the study method.

RESULTS

Patient's Characteristics- Most patients were males in both Arms. In Arm A, males comprised 86.11%; in Arm B, males were 88.57% of the total patients, and the majority of patients fall in the age range of 50-60 years. Almost 50% of patients in both arms were residents of rural areas.

In Arm A majority of patients had primary lesions in the oral cavity (52.78%), followed by the oropharynx (22.22%), followed by the larynx (19.44%) and hypopharynx (5.56%). In Arm B, the majority of patients had primary lesions in the oral cavity (45.71%), followed by oropharynx (37.14%) and larynx (17.14%).

In Arm A, 50% of patients were in stage III, while 50% of patients had stage IV disease and thus had locoregionally advanced disease. In Arm B, 62.86% of patients were in stage III while 37.14% had stage IV disease.

Treatment and Toxicity Characteristics- Mucositis was found to be more severe in Arm A than Arm B. Grade 2 mucositis was developed in 41.67% of patients of Arm A while 51.43% in Arm B. Grade 3 mucositis was developed in 58.33% of patients of Arm A while 45.71% of Arm B. During treatment, Grade 2 mucositis was managed on OPD basis and Grade 3 mucositis patient was admitted and managed with proper hydration.

In Arm A, Grade 2 dysphagia was found in 41.7% of patients, while Grade 3 dysphagia was found in 52.5% of patients. In Arm B, Grade 2 dysphagia was found in 58.3% of patients, while Grade 3 dysphagia was found in 47.5% of patients. The patients with Grade 2 dysphagia were managed on OPD basis and a ryles tube was inserted for feeding. Patients with Grade 3 dysphagia were admitted and appropriately managed.

All patients developed skin reactions in both arms which were managed on an outpatient basis. Other notable toxicities, such as CRT-induced nausea and vomiting, leukopenia and anemia were found to be insignificant.

The response was assessed clinically in 4th week after treatment, and it was found that complete response was achieved by 55.56% of patients in Arm A while 48.57% in Arm B. While after 3 months of completion of treatment, the response was assessed clinically and radiologically if needed. Arm A showed a higher complete response (61.11%) than Arm B (48.57%). These results were comparable with other landmark studies and were statically non-significant because of the small sample size. Patients with progressive disease and response were managed by surgery or Metronomic chemotherapy or palliative chemotherapy.

Table 1: Characteristics of cohort.

Characteristics	Arm A (%)	Arm B (%)
Male	86.11	88.57
Female	13.89	11.43

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Rural/Urban	50 each	51.43 Rural 48.47 Urban
Addiction		
Tobacco	77.78	85.71
Smoking	61.11	80
Alcohol	52.78	60
Both Alcohol and Smoking	41.67	65.71
Nasmanjan	55	65.2

Table 2: Distribution according to site.

Tumor site	Arm A (%)	Arm B (%)
Oral cavity	52.78	45.71
Oropharynx	41.67	65.71
Hypopharynx	5.56	0.00
Larynx	19.44	17.14
Stage-wise distribution		
Stage 3	50	62.86
Stage 4	50	37.14
Lymph node status		
Free	30.56	45.71
Matted	47.22	48.57

Table 3: Toxicity profile.

Nausea	Arm A (%)	Arm B (%)
Toxicity		
Grade 2	45.50	53.10
Grade 3	54.50	46.90
p-value= 0.557		
Vomiting		
Grade 1	2.785	5.71
Grade 2	2.78	14.29
p-value= 0.147		
Dysphagia		
Grade 2	41.70	58.30
Grade 3	52.50	47.50
p-value= 0.492		
Mucositis		
Grade 2	41.67	51.43
Grade 3	58.33	45.17
p-value =0.405		

Table 4: Response assessment.

Response at 1 month	Arm A (%)	Arm B (%)
Complete response	55.56	48.57
Progressive disease	44	51.43
Stable disease	0.00	0.00
Response at 3 months	Arm A (%)	Arm B (%)
Complete response	61.11	48.57
Progressive disease	25	34.29
Stable disease	13.89	17.14

p-value=0.228

DISCUSSION

The majority of patients in Arm A had primary lesions in the oral cavity (52.78%), followed by the oropharynx (22.22%), larynx (19.44%), and hypopharynx (5.56%). In Arm B, the majority of patients had primary lesions in the oral cavity (45.71%), followed by the oropharynx (37.14%), and the larynx (17.14%). Most patients fall in the age range of 50–60 years. The majority of patients were males in both arms. In Arm A, males comprised 86.11%, while in Arm B, males were 88.57% of the total patients.

According to a study published by Silva *et al*. [16], excess tobacco use (65.6%) and/or alcohol consumption (61%) were considered to be risk factors for head and neck cancer. Besides cigarettes and alcohol, smokeless tobacco, such as Pan masala, Chheni, Gudaku, etc, also causes cheek and tongue cancers, which are very prevalent in Madhya Pradesh. In our study in Arm A, 77.78% of patients had a tobacco addiction, 61.11% of patients had a smoking addiction, 52.78% of patients were addicted to alcohol, and 41.67% of patients were addicted to both tobacco and smoking. In Arm B, 85.71% of patients had tobacco addiction, 80% of patients had a smoking addiction, 60% of patients had alcohol addiction, and 65.71% were addicted to both tobacco and smoking.

Independently published work by Kulkarni [17] Singh *et al*. [18] reported 60-90% of head and neck cancer at the late stage of the disease in India. Delays in cancer diagnosis and treatment adversely impact survival, treatment cost, recurrence rate, and quality of life of patients. Qualitative data presented by Ganesan *et al*. [19], identified the reasons for the diagnostic delay from the

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patients' perspective. This data is completely comprehended by the current study, where in Arm A, 50% of patients were Stage III. In comparison, 50% of patients had Stage IV disease and thus had locoregionally advanced disease. In Arm B, 62.86% of patients were in Stage III, while 37.14% had Stage IV disease.

During head and neck radiation therapy, dysphagia is a common and debilitating adverse effect.

1476 head and neck cancer patients qualified for primary radiation therapy alone were involved in the DAHANCA 6&7 randomized research. According to DAHANCA grades, acute dysphagia 1, 2, 3, and 4 occurred in 83%, 71%, 43%, and 23% of cases, respectively.

The patient of the present study had complained of dysphagia beginning at around the second week of radiation. The following variables showed up as independent predictors of severe acute dysphagia in multivariate analysis—rapid radiation therapy, age > median, baseline dysphagia > 1, T3–T4 tumours, N-positive disease, non-glottic cancer, and accelerated RT. In our study also, in Arm A, Grade 2 dysphagia was found in 41.7% of patients, while Grade 3 dysphagia was found in 52.5% of patients. In Arm B, Grade 2 dysphagia was found in 58.3% of patients. In comparison, Grade 3 dysphagia was found in 47.5% of patients, which was comparable with these landmark studies and statically non-significant because of the small sample size.

Numerous trials with varying schedules, such as accelerated fractionation, which shortens the treatment duration by applying more than five fractions per week, have examined the function of modified fractionated RT in HNSCC. The Meta-Analysis of Radiotherapy in Squamous Cell Carcinoma of Head and Neck (MARCH) published by Bourhis *et al*. [4] demonstrated that altered schedules are a valuable alternative to standard radiation as they provide similar gains in reduction of overall mortality as compared to standard radiation alone in the definitive therapeutic setting. Similarly, the famous DAHANCA study supported accelerated fraction over conventional radiation therapy regimes. This strategy is justified by the possibility that reducing the total treatment duration could lead to better local tumour control rates by preventing tumour repopulation. There are also economical and patient convenience arguments to shorten the overall treatment time in conventional RT planning slots. Most of the patients in our center were from low socioeconomic conditions and they couldn't afford multimodality treatment.

In our study, in 4th week after treatment, response was assessed and it was found that complete response was achieved by 55.56% of patients in Arm A while 48.57% in Arm B; partial response was achieved by 44.44% of patients in Arm A, and 51.43% in arm B. After 3 months of completion of treatment, Arm A showed a higher complete response (61.11%) compared to 48.57% in Arm B. In Arm A, 25% of patients had progressive disease and 13.89% had stable disease; in Arm B, 34.29% had progressive disease and 17.14% had stable disease. These results were comparable with other landmark studies and statically non-significant because of the small sample size. The patients with progressive disease and patients with partial response are managed by surgery or CRT as per standard protocol.

LIMITATION

Furthermore, the time constraint and many more limitations, such as the study's small sample size and multiple challenges faced during the coronavirus pandemic limited the challenge of further assessment among study patients.

CONCLUSIONS

The study concluded that complete response to treatment was seen more in the accelerated regimen than in the conventional regimen arm. It was found that accelerated RT regime had more significant acute radiation-induced dysphagia for a longer duration of time, but they were manageable. Radiation-induced mucositis was more common in the accelerated regimen than in the conventional regimen. During the COVID era, the American Society for Radiation Oncology and European Society for Medical Oncology (ASTRO-ESTRO) consensus recommended shortening overall treatment time, decreasing the number of hospital visits, and decreasing the period of overall hospital stay. Shortened overall treatment time duration in accelerated regime resulted in minimal hospital stay.

An extended follow-up period is needed to establish a relationship between overall survival and disease-free survival. Hence, we conclude that an accelerated regimen can be preferred over a conventional one because it gives a comparable clinical response with manageable toxicities. Thus, it can be considered ideal

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for a developing country like India, which has a larger outpatient load and limited resources.

CONTRIBUTION OF AUTHORS

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