Original Article

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Oncology Section

Accelerated Fractionation versus Concomitant Chemoradiation in Locally Advanced Head and Neck Cancer- A Prospective Study

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ABSTRACT

Introduction: Cancers of head and neck region is one of the most common cancer type found in Indian population. Concomitant chemoradiation is the standard treatment for locally advanced head and neck cancer. Different altered fractionation regime has been tried to optimise the outcome.

Aim: To compare the response, treatment outcomes and toxicities between accelerated fractionation and concomitant chemoradiation in locally advanced squamous cell cancer of head and neck region.

Materials and Methods: This prospective study was conducted at College of Medicine and Sagore Dutta Hospital, West Bengal, Kolkata, India, from March 2020 to December 2020. The study evaluated total of 45 patients of histologically proved locally advanced Tumour (T) Node (N) Metastasis (M) of T_{2-4} N_{1-3} M_0 squamous cell carcinoma of head and neck region (larynx, oropharynx, hypopharynx and oral cavity). The patients were divided into two groups- Group A (n=22) and Group B (n=23) according to the treatment decided in each subject based on their clinical details and risk factors. Patients in group A received only radiation with accelerated fractionation with 2 Gray (Gy)/fraction, single fraction/day, 6 days/week. Patients allotted in the group B were treated with external beam radiotherapy in conventional fractionation. Concomitant cisplatin was administered at the dose of 100 mg/m^2 of Body Surface Area (BSA) in first, fourth and seventh week of radiation. In both the groups, 66-70 Gy of total dose of radiation was prescribed. Patients were followed-up at monthly interval for first three months and at three monthly intervals thereafter. The collected data was tabulated in Microsoft excel sheet and frequency and percentage analysis was done. The significance between two variables was calculated by two tailed Fisher's-Exact test.

Results: Total of 45 patients (43 males and 2 females) were evaluated. The 22 patients (median age 60 years) were included in group A and 23 patients (median age 58 years) in group B. The median overall treatment time observed was 45 days and 59 days in group A and B. The prolongation of treatment was significantly different in between the both groups (p-value=0.0001). A total of 3 (13.04%) patients of group B and 1 (4.54%) patients of study arm could not complete the prescribed radiation (p-value=0.607). Complete Response (CR) was achieved in 8 (36.36%) patients in group A vs 8 (34.78%) patients in the group B and Partial Response (PR) was achieved in 11 patients (50%) vs 10 patients (43.48% cases) of group A and B respectively. Grade II/III vomiting noted in 10 patients (45.45%) vs 18 patients (78.26% cases) (p=0.03) in group A and B respectively. Grade III mucositis was observed in 16 patients (72.73%) vs 18 patients (78.26%) cases (p-value=0.513) in group A and B respectively. Grade III anaemia was observed in 6 patients (27.27%) in group A while in 15 patients (65.22%) in group B (p-value=0.016). No significant difference in late toxicity could be documented.

Conclusion: The response rate with accelerated fractionation is not inferior to concomitant chemoradiation. Accelerated fractionation was tolerated well by patients of the present study.

Keywords: Body surface area, Chemotherapy, Cisplatin, Dose, Radiotherapy, Squamous cell carcinoma

INTRODUCTION

Worldwide, nearly 6,50,000 people develop head and neck cancer each year [1,2]. Around 60% of the patients present with locally advanced but non metastatic disease [3]. The extensive use of tobacco products is one of the reasons behind the ever increasing number of head and neck cancers in the developing nations who can least afford to treat them [4,5]. In India also, cancers of oral cavity, tongue, pharynx, and larynx contribute a major share [5,6]. The age adjusted incidence for these sites in Indian male population range from 10.8 to 38.8 per 1,00,000 populations and in 6.4 to 14.9 in 1,00,000 female populations and there are 3,50,000 deaths from this disease [7].

Treatment of advanced squamous cell cancer of head and neck has been the subject of intensive investigations in last few decades [3,4]. Radiotherapy (RT) alone was the standard non surgical treatment for advanced disease for long time. But it was observed that radiotherapy alone resulted in local control of 50-70% and disease free survival of 30-40% [5]. Multiple trials established the superiority of concurrent chemoradiotherapy for the locally advanced head and neck cancers with improvement of survival. Among the cytotoxic drugs, cisplatin is one of the corner stones [5].

Although daily, weekly and three weekly schedules with concurrent radiation have been studied, the three weekly regime is the one most studied and widely accepted. Though concomitant chemoradiation had been able to show improved response, it was associated with increased toxicities. Typically, the acute mucositis arising from these regimens is greater than that seen with RT alone. It is the most significant impediment to the timely delivery of concurrent therapy [3,5]. Because prolongation of total treatment time adversely affects the success of RT in Head and Neck Cancer (HNC).

In purely fractionated regime, total dose is delivered in half the overall time without changing the size of the fraction. But in practice, it is difficult to follow it because of acute toxicities [8,9,10]. In the present study, a modest acceleration regime by giving six fractions of radiotherapy per week was followed The aim of the present study was to determine and compare the treatment outcomes, acute and late toxicities in accelerated fractionation regime with the conventional radiation fractions with concomitant chemotherapy in squamous cell carcinoma of head and neck cancer patients.

MATERIALS AND METHODS

The present study was a prospective study conducted on the patients who attended the Outpatient Department (OPD) in the Department of Radiotherapy at College of Medicine and Sagore Dutta Hospital, West Bengal, Kolkata, India, from March 2020 to December 2020. According to the study Institutional policy, patients were included in the present study only after obtaining informed consent.

Inclusion criteria: All histologically proven male and female patients of age 18-60 years of locally advanced non metastatic squamous cell cancer of head and neck region (T_{2-4},N_{1-3},M_0) i.e. carcinoma of larynx, oropharynx, hypopharynx, oral cavity, with adequate performance status (Karnofsky performance status >60) [11] were included in the study.

Exclusion criteria: Patient with Carcinoma of Nasopharynx, orbit, Paranasal Sinus (PNS), skin, salivary glands, lymphoma and those patients having evidence of uncontrolled systemic disease eg, renal, cardiac or respiratory, were excluded from the study.

All the patients attending the OPD of the study Institute during the given time period and fulfilling the inclusion and exclusion criteria were included in the study. Out of total 50 accrued patients, five patients were eliminated because of poor compliance and withdrawal of consent and development of systemic metastases. A total of 45 patients were evaluated, including cases of carcinoma of larynx (n=10), oropharynx (n=18), hypopharynx (n=11) and oral cavity (n=6). All these patients were divided into two groups according to the treatment schedules planned-

- Group A (n=22) and
- Group B (n=23).

Procedure

All the patients were thoroughly examined clinically. All general haematological, biochemical, radiological investigations, endoscopic evaluation was carried out for the subjects to rule out presence of metastasis as only patients with no metastasis were planned for inclusion in the study. Fine Needle Aspiration Cytology (FNAC) or excisional biopsy was done, whenever indicated. Contrast Enhanced Computerised Tomography (CECT) scan of head and neck region extending up to clavicle was acquired in every case for the radiation planning purpose. Staging was done according to the American Joint Committee on Cancer (AJCC) staging system 8th edition (TNM) [12]. The histopathological differentiation [13] was done for all patients on the basis of histological reports.

Group A (n=22): Prescribed with external beam radiation with accelerated fractionation regime. The dose schedule was 2 Gy per fraction, single fraction daily, and six days per week without administration of any chemotherapy. The total dose prescribed in both the groups was 66-70 Gy, according to the stage of the disease. Sparing of the spinal cord was done after 44 Gy. Proper immobilisation in thermoplastic mask was done in all the cases.

Group B (n=23): Prescribed with concomitant chemoradiation. Patients in this group were treated with conventional fractionation radiation, i.e. 2 Gy per fraction, single fraction daily given over five days per week. Along with this, injection (inj.) Cisplatin was given concurrently at the dose of 100 mg/m^2 of body surface area on first, fourth and seventh week of treatment. This was administered with proper hydration and premedications.

Treatment planning was done in the three dimensional (3D) Treatment Planning Systems (TPS). External beam radiotherapy was done in Cobalt-60 (Theratron-780C) machine. Patients in both groups were evaluated weekly during treatment by clinical examination. All the features of acute toxicities were noted according to the Common Terminology criteria for adverse events version 4.0 [14]. All patients were followed-up and evaluated at one monthly interval initially, then at three monthly interval. Response assessment was done at the end of treatment and after one month of competition of treatment. Response was assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) [15]. Acute toxicity noted during the treatment and immediate follow-up period. Late toxicity noted at six months. Gap in radiation was allowed for managing any grade III/IV toxicity.

STATISTICAL ANALYSIS

Statistical analysis was done by two-tailed Fisher's-Exact test. The p-value <0.05 was considered as statistically significant.

RESULTS

Amongst the 45 patients evaluated, median age of presentation was 60 years and 58 years group A (n=22) and group B (n=23) respectively. Only two female patients could be included. The 40 (88%) of the patients had addiction to tobacco in various form. Detail distribution of the patients according to demographic details, histological character and site specifically involved is depicted in [Table/Fig-1,2].

Parameters	Group A (N=22)	Group B (N=23)
Median age	60 years	58 years
Sex		
Male	21	22
Female	1	1
Tobacco use		
Yes	20	20
No	2	3
T stage		
T1	0	0
T2	3	2
T3	17	17
T4	2	4
N stage		
N1	4	3
N2	7	9
N3	11	11
Histopathology		
Well differentiated carcinoma	9	8
Moderately differentiated carcinoma	13	15

[Table/Fig-1]: Distribution of patients in two groups.
T: Tumour; N: Node; Metastasis was absent (M0) in all subjects

Site	Group A (N=22)	Group B (N=23)
Larynx	6 (27%)	4 (17%)
Oral cavity	2 (9%)	4 (17%)
Oropharynx	8 (36%)	10 (43%)
Hypopharynx	6 (36%)	5 (21%)

[Table/Fig-2]: Site specific distribution of all subjects in both the groups.

One patient in accelerated fractionation group A and three patients in chemoradiation therapy group B could not complete the prescribed radiation. Gap in treatment was allowed to control toxicities. Alteration of prescribed dose of radiation was not done. Median overall treatment time in group A was 45 days and in group B this was 49 days. Prolongation of treatment was significantly different in two groups (p-value=0.0001) [Table/Fig-3]. At the completion of the treatment, 8 (36%) patients in group A and 8 (40%) patients in group B achieved complete response. Partial response was achieved in 11 (52%) patients in group A and 10 (50%) patients of group B. Overall response was 90% vs 90% in group A and B respectively (p-value=1.0) [Table/Fig-3]. Site specific overall response are shown in [Table/Fig-4].

Clinical parameters	Group A (N=22)	Group B (N=23)	p- value
Median overall treatment time	45 days	49 days	-
Prolongation of treatment (beyond 3rd week of treatment)	4 (18.18%)	8 (78.26%)	0.0001
Incomplete treatment	1 (4.54%)	3 (13.04%)	0.607
Overall response	19 (86.36%)	18 (78.26%)	1
Complete response	8 (36.36%)	8 (34.78%)	1
Partial response	11 (50%)	10 (43.48%)	1
Stable disease	2 (9.09%)	2 (8.69%)	1

[Table/Fig-3]: Treatment and response analysis of all subjects in both the arms.
p-values calculated by two tailed Fisher's-Exact test

Site	Group A	Group B	p-value
Larynx	6/6	4/4	1
Oral cavity	2/2	3/4	1
Oropharynx	6/8	7/10	0.215
Hypopharynx	5/6	4/5	1

[Table/Fig-4]: Site specific overall response in all subjects of both groups.
p-values calculated by two tailed Fisher's-Exact test

Acute toxicities were documented according to the Common Terminology Criteria for adverse events version 4.0 [14] during the treatment and at immediate follow-up period. In accelerated fractionation group, acute toxicities noted are oral mucositis, dryness of mouth and skin toxicities. Grade III mucositis was observed in 16 (72.73%) of the cases in group A and 18 (78.26%) (p-value=0.513) cases of group B. Grade II vomiting was noted in 10 (45.45%) vs 18 (78.26%) (p-value=0.03) cases in group A and B. Incidence of grade III anaemia was 6 patients (27.27%) vs 15 patients (65.22%) (p-value=0.016) respectively in group A and B. Blood transfusion was needed in 1 patient (4.54%) vs 10 (43.48%) (p-value=0.0041) cases in group A and B respectively [Table/Fig-5].

Toxicity	Group A (N=22)	Group B (N=23)	p-value
Anorexia	20 (90.90%)	22 (95.65%)	0.617
Vomiting (Grade II)	10 (45.45%)	18 (78.26%)	0.03
Diarrhoea	4 (18.18%)	10 (43.48%)	0.10
Mucositis (All grade)	22 (100%)	23 (100%)	1.00
Mucositis (Grade III)	16 (72.73)	18 (78.26%)	0.513
Dermatitis	18 (81.82%)	15 (65.22%)	0.315
Dryness of mouth	16 (72.73%)	19 (82.61%)	0.490
Anaemia (Grade III)	6 (27.27%)	15 (65.22%)	0.016
Neutropenia	1 (4.54%)	3 (13.04%)	0.6331
Blood transfusion	1 (4.54%)	10 (43.48%)	0.0041

[Table/Fig-5]: Acute toxicity and adverse events reported in all subjects.
Noted during the treatment and at immediate follow-up period; Grading and diagnosis according to the Common Terminology Criteria for adverse events version 4.0 [14]

Late toxicities were noted at sixth month of follow-up. However late toxicities noted in both groups were xerostomia, subcutaneous tissue fibrosis, oedema. No grade III or higher toxicity were noted [Table/Fig-6].

Late toxicity	Group A (N=22)	Group B (N=23)	p-value
Xerostomia	7	6	1
Fibrosis of subcutaneous tissue	8	8	1
Laryngeal oedema	3	1	0.606

[Table/Fig-6]: Late toxicities as observed in subjects of both arms.
Noted at sixth month of follow-up ; p-values calculated by two tailed Fisher's-Exact test

DISCUSSION

The present study was conducted with a modest acceleration regime treatment plan by giving six fractions of radiotherapy per week and analysing the treatment response, acute toxicities and late toxicities. About two-third of the patients with head and neck cancers present with locally advanced disease [1]. The present study also comprised of population of locally advanced head and neck cancer patients. In past the radiotherapy had long been used as the standard non surgical treatment modality of patients of these cases. But unfortunately, the even the most effective radiotherapy regime has been able to achieve 50-70% local control [1]. So search is still continuing to find out an optimum treatment regime to achieve better outcome with acceptable toxicity profile.

There are list of factors which are responsible for the poor outcome of the single modality of treatment with radiation, specially while treating locally advanced solid tumours [4]. The phenomenon of accelerated repopulation is one of reason of treatment failure in cancers of head and neck. This refers to the triggering of the surviving tumour cells clonogens to divide more rapidly, as a tumour shrinks after irradiation or chemotherapy. It starts after about four weeks of radiation in head neck cancers. About 0.6 Gy/day is needed to compensate for this repopulation. This suggests that treatment should be completed as soon as possible once it is started [3,5].

Accelerated treatment strategy aims to deliver the same total dose over a shorter time, as was planned in the present study at moderate level. The patients in the group A were exposed to the accelerated fractionation radiotherapy while the group B patients were prescribed the conventional chemoradiotherapy.

The tendency of larger tumours to have hypoxic cells are well established and has serious implications. Adding two different modalities prevents development of resistant population of tumour cells. So it is imperative to add chemotherapy with radiation in some fashion in treating this advanced tumours [3,8,9].

Most randomised clinical trials show superiority of combined chemoradiation to radiation alone in treating locally advanced squamous cell cancers of head and neck region [4]. Comparison of concurrent radiation and induction chemotherapy followed by radiation alone are few but they confirm the superiority of the former regime [2,3,5]. But at the same time, the present study showed significant increase in acute toxicity. Severe acute cutaneous and haematological toxicity with poor nutritional status had been reported in the past studies in chemoradiotherapy treated patients [4,9].

So it is evident from present data, that, radiation in conventional fractionation as a single modality is not optimum for treating advanced head and neck cancers. Whether chemoradiation is superior to altered fractionation regimen is still not established. Acute and late toxicities are increased significantly with use of concurrent chemotherapy. Often this leads to the undue prolongation of the treatment, favouring the accelerated repopulation of clonogens to start. This ultimately results in poor treatment outcome [6].This problem becomes more prominent in head and neck cancer patients as these patients generally present with poor nutritional status and associated anaemia. Poor socio-economic status of most of these patients adds to the problem [6,10]. In the present study, also significant prolongation of overall treatment time was observed in concomitant chemoradiation group. In most cases, interruption in treatment occurred beyond third week of treatment. Significant number of patients could not complete the prescribed treatment. As now it is clearly known, that cure rate of squamous cell cancer are highly dependant upon overall treatment time, this prolongation of treatment was detrimental [10]. In group B subjects of the present study, most of the interruptions were observed during this phase and no significant difference was observed in overall response between two groups. In group A, authors prescribed pure acceleration which led to moderate shortening of the overall treatment time. Total dose of radiation was same to CTRT arm (70 Gy). Expected duration of radiation was 42 days. The median duration of overall radiation came out to be 45 days. Discontinuation of radiation was lower in the group A.

Intensity of acute reaction is determined primarily by the rate of dose accumulation or weekly dose rate [9,10]. So increased incidence of acute toxicity was expected in accelerated fractionation group in the present study. Toxicities noted in this group were vomiting, oral mucositis, dryness of mouth, radiation dermatitis, and anaemia. But none were life threatening and were managed adequately. Incidence of blood transfusion was significantly lower in comparison to group B.

The late toxicities were xerostomia, subcutaneous tissue fibrosis, laryngeal oedema. But, probably these were the consequential effects to acute reactions. No significant difference was observed in the incidence of late toxicity profile of the two groups.

Limitation(s)

Survival data could not be assessed in the present study considering the short duration. As the duration of the study was short and the follow-up period too, only few late effects were documented. Statistical power of the present study was low as the number of patients were less.

CONCLUSION(S)

Concomitant chemoradiation is the standard modality of treatment in locally advanced squamous cell cancers of head and neck region. But most of the patients of present study failed to tolerate this because of toxicities associated with the treatment. This was reflected in increased incidence of interruption in radiation and treatment discontinuation. Radiation with accelerated fractionation as a single modality has produced equal response in this group of patients. Toxicities were better tolerated by present patient population. So, radiation with accelerated fractionation may be practiced in treating these patients. Long term study with greater number of patients is recommended in future to find out the statistical significance of the outcome.

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