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Study of Hypofractionated Radiotherapy Regime for Locally Advanced Head and Neck Cancer

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Abstract
The aim of this study is to evaluate the response rates and toxicity of hypofractionated radiation therapy in locally advanced head & neck cancer patients who are not fit for concurrent chemoradiation or surgery.
Material and Methods: *Thirty patients were eligible for radical treatment (metastatic excluded) were received a total dose of 50 Gray (Gy) in 16 fractions, 3.125 Gy per fraction, total treatment time 3 weeks.*
Results: *The overall response rates (CR + PR) were 70% and Stage wise [III, IVA and IVB] overall response were 90.9%, 66.66% & 42.8%. Of all primaries. The hypopharyngeal cancer patients had the worst response rates with progressive disease in 20-33% of patients and laryngeal cancer patients having best response rates. Only one patient develop grade 4 mucositis for which he was hospitalized for conservative management. Despite the high rate of acute skin and mucosal toxicities, There were no dropouts or treatment breaks more than 7 days due to adequate nutritional and supportive management provided to the patients. The chronic grade 2 and 3 toxicities were higher for skin and mucous membrane.*
Keywords: *hypofractionated radiotherapy, locally advanced head and neck cancer.*

Introduction

The International Agency for Research on Cancer (IARC) estimate that one-in-five men and one-in-six women worldwide will develop cancer over the course of their lifetime, and that one-in-eight men and one-in-eleven women will die from their disease. A number of factors appear to be driving this increase, particularly a growing and ageing global population and an increase in exposure to cancer risk factors linked to social and economic development. Asia accounts for nearly half of the new cancer cases and more than half of cancer deaths. Estimated suggest that Asia and Africa have a higher proportion of cancer deaths (7.3% and 57.3% respectively) compared with their incidence (5.8% and 48.4% respectively)[1].

Head and neck cancers account for 8.04% (1.4 million) of the total cancer cases and 4.9% (0.47 million) of cancer related deaths worldwide based on GLOBOCAN2018 estimates. In India, currently Head and neck cancers is the leading cause of cancer including lips and oral cavity (at top), larynx, hypopharynx, thyroid, oropharynx, salivary glands & nasopharynx; accounting for nearly 17.74% (2.05 million) of all registered new cancer cases and related to 16.3%(1.27 million) deaths in the country[1]. Among males, it is the leading cause of cancer mortality, accounting

for 19.9% (0.073 million) of all male cancer deaths, while in female it accounts 5.03%(0.0218 million) mortality.[1]

Nearly 60% of patients of head and neck cancer present with locally advanced but nonmetastatic disease. Locoregional failure constitutes the predominant recurrence pattern. Results of treatment of these tumors are inversely proportional to the extent of the disease[2].

Squamous cell carcinoma histology in the head and neck is predominant and the primary treatment modalities for it are surgery and radiotherapy.[3] Radiotherapy alone is used in nonoperable, existing co-morbidities, poor performance status, distant metastatic disease and patients who refuses surgery for the locally advanced disease.[4,5,6] Radiation dose fractionation has evolved from once daily to hyperfractionation and accelerated fractionation. Nonetheless, even the most effective radiation regimens result in local controls rates of 50% to 70% and disease-free survivals of 30% to 40%. So that the combined modality concurrent chemoradiotherapy is used as the standard care of treatment for locally advanced head and neck cancer. [7, 8, 9]

The optimum treatment time for locoregional control is not clear. A reduction in the locoregional control by lengthening the treatment time has been observed and possible cause for it is radiation-induced accelerated proliferation of clonogenic tumor cells. Furthermore, reduction in the total treatment time has improved local tumor control in several clinical studies.[10] A shorter treatment time may be accomplished by applying a higher dose per fraction or by increasing the daily number of radiation fractions with a minimum 6 hrs time interval between two fractions. But the short overall treatment time leads to potential increased late side effects. However, late radiation toxicity is often less relevant in patients treated in advanced stage setting due to poor overall survival.

The aim of this study is to evaluate the response rates, toxicity and survival benefits of hypofractionated radiation therapy in locally advanced head & neck cancer patients who are not fit for concurrent chemoradiation or surgery followed by adjuvant therapy. Second aim of our study was to determine the toxicity profiles and the disease-free survival and overall survival.

Materials and Method

This was a prospective study conducted at Acharya Tulsi Regional Cancer Treatment And Research Institute, Sardar Patel Medical College and associated group of hospitals, Bikaner.

The study protocol includes 30 patients of locally advanced carcinoma of head and neck, histological proven squamous cell carcinoma, who were enrolled from June 2018 to May2019. The inclusion criteria were primary malignancies of Head and neck region i.e. starting from base of the skull to the thoracic inlet, age: >18 years, no prior treatment of malignancy. normal base line organ function (CBC, RFT, LFT & others), and without Significant comorbidities.

The protocol was approved by hospital's institutional ethical committee and all patients were properly informed and consent was taken for treatment. 30 patients eligible for radical treatment (metastatic excluded), and received a total dose of 50 Gray (Gy) in 16 fractions, 3.125 Gy per fraction, total treatment time 3 weeks.

BED calculation-

BED = D [1+ d/ (α/β)]

Where D is the total dose and d is dose per fraction.

BED Calculation for hypofractionated arm

BED for early effects =

3.125×16 (1+3.125/10) = 65.625Gy

BED for late effects =

3.125×16(1 + 3.125/3) = 102.08Gy

Treatment volume were included primary tumor site plus neck node region. Parallel opposed bilateral fields were planned. The dose was prescribed at midline. External beam radiotherapy was given with radiation therapy parameter on Cobalt-60 machines Theratron 780E / 780C/

Bhabhatron II with photon energies of 1.25 MeV. Minimum treatment distance was >= 80 cm SSD (or SAD for iso-centric techniques).

During treatment patients were assessed for treatment response, control of symptoms and any treatment related morbidity by doing complete blood counts, biochemistry profile consisting of RFT&LFT, chest X-ray, USG Abdomen. Nutritional status was maintained with all patients encouraged to liberal oral food intake and in the case of difficulty, the feeding tube was inserted either through the nasal route, percutaneously, or endoscopically. For patients with respiratory distress, it was sometimes elected to perform tracheostomy before starting radiation.

The primary end point of the study was the response rate (complete response (CR), partial response (PR), and overall response rate (ORR = CR+PR)) (assessment was done by WHO criteria). The secondary end points were acute (within 90 days of radiation) and late toxicity (beyond 90 days after radiation) (graded according to the RTOG/EORTC Acute and Chronic Radiation Morbidity Scoring).

Patients were evaluated 6-8 weeks after completion of treatment by the ENT surgeon and radiation oncologist. All patients underwent detailed ENT examination with a directed biopsy performed in patients with clinical suspicion of persistent primary and/or nodal disease. Wherever feasible, patients with residual disease were sent for salvage chemotherapy with combination of taxanes, platinum, and 5-fluorouracil. Salvages surgery for the removal of primary and/or nodal disease was not possible due to co-morbid conditions. After initial assessment, the patients with no evidence of residual primary and nodal disease were evaluated every 3 months till the end of the study to assess the toxicity. On subsequent follow up in 3rd, 6th month, detailed systemic examination, CBC, LFT, RFT, chest x-ray and USG Abdomen was done to evaluate for distant metastasis and complications RT like mediastinitis, esophagitis and radiation pneumonitis.

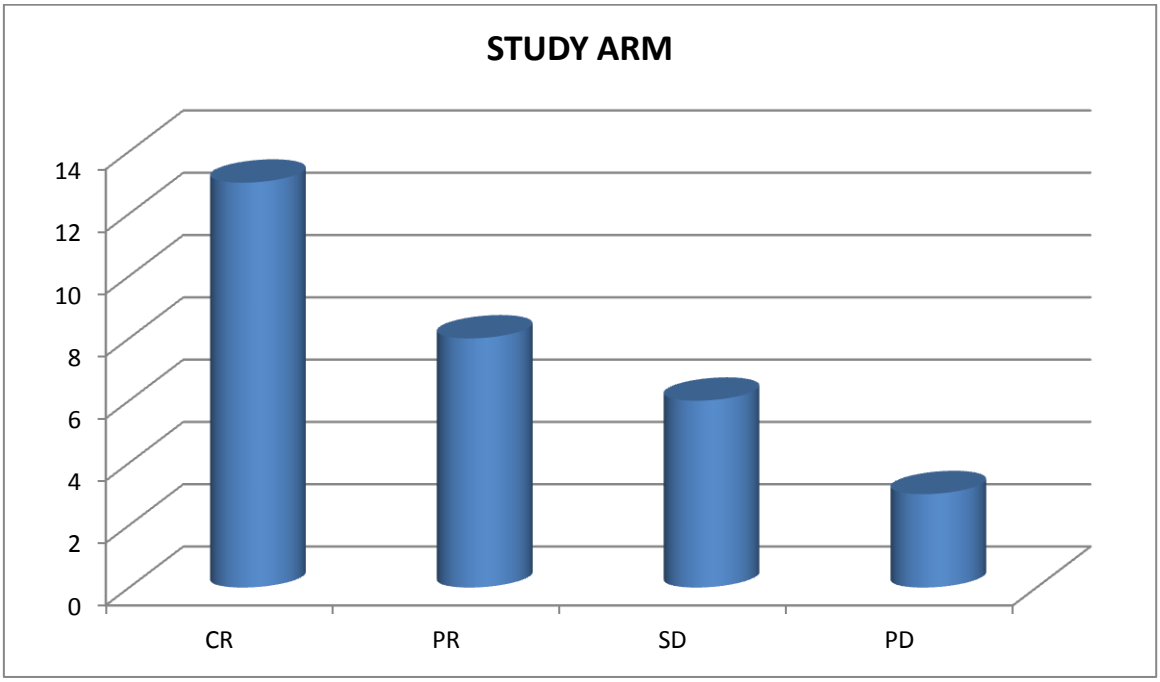
Results

Table 1 Patient Characteristics

		No. of Patients (%)
		Study Arm 30 (100%)
Age	51-59 yrs	13
	≥ 60 yrs	17
SEX	Male	26 (88.4%)
	Female	4 (11.6%)
Socioeconomic Status	rural	28
	Urban	2
Habbit	Tobacco chewer	28
	Non-tobacco chewer	2
ECOG	3	23 (76.66%)
	4	7 (23.33%)
Primary site	Oral cavity	6 (20%)
	Oropharynx	14 (46.66%)
	Larynx	7 (23.33%)
	Hypopharynx	3 (10%)
T -STAGE	2	02
	3	10
	4	18
N- STAGE	1	11
	2	13
	3	06
Overall Stage	III	11
	IV A	12
	IV B	07

Table 2 Treatment Response

	NO.OF PATIENTS (%)
	STUDY ARM 30 (100%)
COMPLETE RESPONSE (CR)	13 (43.33%)
PARTIAL RESPONSE (PR)	08 (26.66%)
STABLE DISEASE (SD)	06 (20%)
PROGRESSIVE DISEASE(PD)	03 (10%)



Graphical represtation of Treatment Response

Table-3 Stage Wise Response Assessment Using RECIST Criteria at the End of the Treatment

STAGE	RESPONSE USING WHO criteria	STUDY ARM
STAGE III	CR	07 (63.6%)
	PR	03 (27.2%)
	SD	00 (0%)
	PD	01 (9.1%)
STAGE IV A	CR	06 (50%)
	PR	02 (16.66%)
	SD	04 (33.33%)
	PD	00 (0%)
STAGE IV B	CR	00 (0%)
	PR	03 (42.8%)
	SD	02 (28.5%)
	PD	02 (28.5%)

Table-4. Toxicities

Toxicities	ACUTE SKIN REACTION	ACUTE MUCOSITIS	LATE SKIN REACTION	LATE MUCOUS MEMBRANE REACTION
Grade 0	05(16.66%)	05(16.66%)	08(26.66%)	06(20%)
Grade I	03(10%)	05(16.66%)	08(26.66%)	11(36.66%)
Grade II	11(36.66%)	12(40%)	10(33.33%)	08(26.66%)
Grade III	11(36.66%)	07(23.33%)	04(13.33%)	05(16.66%)
Grade IV	00(0.0%)	01(03.33%)	00(0.0%)	00(0.0%)

30 patients were eligible and enrolled for this study.88.4% & 11.6% of patients were male and females respectively, median age 61 years (range: 50-73 years). 93.33% of individuals were tobacco chewers. Largest proportion of was oropharyngeal cancer and belongs to stage IV A, (40%). The overall response rates (CR + PR) were 70% and Stage wise [III, IVA and IVB] overall response were 90.9%, 66.66% & 42.8%.Of all primaries, the hypopharyngeal cancer patients had the worst response rates with progressive disease in 20-33% of patients and laryngeal cancer patients having best response rates.

Only one patient develop grade 4 mucositis for which he was hospitalized for conservative management. Despite the high rate of acute skin and mucosal toxicities, there were no dropouts or treatment breaks more than 7 days due to adequate nutritional and supportive management provided to the patients.

Discussion

A considerable number of patients with squamous cell carcinoma of the head and neck (HNSCC) are not suitable for aggressive radical treatment with surgery or chemoradiotherapy (CRT) because of a very advanced loco-regional disease, significant co-morbidities, poor performance status, distant metastatic disease, or a combination of these factors. However, this group of patients still requires some form of treatment to control their loco-regional disease and to alleviate their troublesome symptoms.[9]

Historically, patients with unresectable HNSCC treated by RT alone have LRC rates between 50 and 70% [11, 12, 13] and 5-year survival rates of 10 - 20%. A large portion of these patients die of locoregional disease progression.Patients with untreated advanced stage HNSCC have a median survival of approximately 100 days.

In a curative setting, the addition of CT in different regimens has improved disease control and long-term survival [14, 16].RTOG 81-17 attempted concurrent chemoradiotherapy (cisplatin based) to treat 134 patients who had unresectable carcinomas of the head and neck.[17] The response and survival rates were favorable to concurrent cisplatin-based chemoradiation. Concurrent chemoradiotherapy in contrast with radiotherapy alone was suggested on the basis of other RTOG trials to treat unresectable carcinomas of the head and neck as it favors to amplify the local control for patients.

Acceleration can produce equivalent results to conventional radiation even when significant reductions in overall dose occur as demonstrated in Continuous Hyperfractionated Accelerated Radiotherapy Trial (CHART) [18]. 54 Gy in 36 fractions over 12 days was compared with a conventional arm of 66 Gy in 33 fractions over six-and-a-half weeks. Except for advanced laryngeal tumors there was no difference in locoregional control compared to the conventional arm. Acute morbidity was increased in CHART but the reduction in total dose and dose per fraction was associated with a reduction in later morbidities including osteochondritis, skin telangiectasia, mucosal ulceration, and laryngeal edema.

Thus Increased hyperfractionation strategy is expected to improve the probability of cancer control by delivery of a higher total dose of radiation without increasing dose for serious late normal tissue complications. Randomized trials of a 4-week hyperfractionated radiation schedule and of two other regimens of accelerated hyperfractionation were recently completed and their early results confirm to some degree the biological hypotheses on which this strategy is based. [19]

A small number of fractions with a larger dose per fraction is used in hypofractionated radiotherapy. The general time is normally shorter than an accelerated protocol. These regimes produce worse late effects than conventional fractionation when used in the curative setting.[20] The intense responses are satisfactory if treatment volumes are kept little and tolerability can be improved by bringing treatment breaks into the protocol.

Eight randomized trials without dose reduction and five with a total dose reduction were undertaken to perform a meta-analysis of accelerated protocols.[21] The hazard ratio for death for first and second group was 0.97 (0.89 - 1.05) and 0.92 (0.86 - 0.97) respectively. The trials resulted in 2% and 1.7% respectively of the absolute survival improvement at 5 years. With that 7.3% and 2.3% improvements in locoregional control at 5 years respectively were observed too.

Some accelerated form of treatment is required for the patients with inoperable conditions. Patients who do not fit to endure the burden of CRT require treatment even if it is with palliative intent to control their locoregional disease and to lessen their acute symptoms. Hypofractionated schedule is more suitable as, the treatment is completed before accelerated repopulation turns into a critical radiobiological factor. Further, the reduced number of fractions permits an increasingly effective utilization of assets, which can help avoid long waiting times for other patients and finally, it is practically required to keep the OTT as short as could be allowed for the fact that this group of patients are usually of older age and often have a poor performance status as well as significant co-morbidities. A hypofractionated schedule would be the most suitable and reasonable option from radiobiological, economic, and logistical points of view,patients having poor prognosis with a median survival of 4-8 months found fit to hypofractionated radiotherapy.[22] As for these patients with poor performance status, the aim of treatment is to palliate symptoms and cause as little as possible in the ways of side-effects.

During World War II, when RT facilities were limited the Christie Hospital in Manchester developed a 3-week schedule of RT. In one of randomized trial for locally advanced head and neck cancer the Christie hospital treated patients with hypofractionated radiation (50 - 55 Gy in 15 or 16 fractions) with concurrent single agent methotrexate (MTX) 100 mg/m^2 given at the commencement of and after 2 weeks of a 3-week course of treatment. Mucositis was significantly greater in the patients receiving MTX, but there was no difference in long-term toxicity. The addition of MTX increased local control from 50% to 70% (P = 0.02) and survival from 37% to 47% (P = 0.07). The significant benefit was seen among patients with oropharyngeal primaries which constituted 33% of the study population. [23]

To overcome accelerated repopulation of tumourclonogens to control tumour in head and neck carcinoma, it is advantageous to use shorter overall treatment time[24].In SIB, the approach of using a higher dose/fraction conveniently adds the advantage of a shorter course of treatment. Overall, IMRT schedules surveyed showed a considerably shorter overall treatment time (median 39 days) than the conventional 70 Gy delivered over 7 weeks (46 days).

Various limitations affected the present investigation. It was recognized that there was selection bias in the present study due to inclusion of patients with early-stage laryngeal cancer deemed unsuitable for curative options because of high age, poor performance and/or co-morbidity. This incorporation predisposition would halfway clarify the phenomenal LRC-rates. However, most of these patients died of intercurrent disease which explains the relatively lower OS rates.

Within these confinements the present investigation gives significant information on response rates, toxicity and survival in the patients treated according to the “Christie scheme”. The results referenced in this paper are helpful for clinicians to implement suitable fraction size to treat this group of patients.

Based on the encouraging results of the present examination, it is presumed that the hypofractionated scheme has radiobiological, economic and logistic advantages and can be adopted for patients with HNSCC who are unsuitable for curative treatment options as surgery or CRT. Hypofractionated schedule is considered for significant tumor regression and symptom control within a short overall treatment time (OTT) with minimal side effects. From

radiobiological point of view, the large fraction size in a short OTT is counteracted which benefits in an increased tumor cell kill with increased potential for late side effects.

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