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HYPERFRACTIONATED RADIOTHERAPY WITH CONCURRENT CHEMOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK CANCER – AN OBSERVATIONAL STUDY

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ABSTRACT

ORIGINAL RESEARCH ARTICLE

Introduction: Radiotherapy plays an important role in the multidisciplinary treatment of locally advanced head and neck cancer, but the rates of locoregional recurrence are high and survival is poor. Thus, there was an emergence of altered fractionation. The purpose of this study is to see the treatment overall response of Hyperfractionated Radiotherapy with concurrent chemotherapy in locally advanced Head and Neck Cancer patients.

Material & Methods: This was an observational study conducted in the Department of Radiation Oncology, Pravara Rural Hospital, Loni between September 2018 to September 2019. Fifteen histopathologies proved patients with locally advanced head and neck cancer received Hyperfractionated radiotherapy (HFRT) with concurrent chemotherapy. Patients received 6760cGy to 7260cGy in 66-70 fractions, 110cGy per fraction, 2 fractions per day with 6 hours gap over 7-8 weeks and weekly injection cisplatin 30 mg/m^2.

Results: At the endpoint of 6 months which was the minimum follow up for all patients the overall response and complete response was 86.66% and 66.66% respectively. The complete response rate was 80% and 60% in Stage III and Stage IV patients respectively.

Conclusion: Hyperfractionated Radiotherapy with concurrent chemotherapy gives good local control and improved overall response in locally advanced head and neck squamous cancer. However larger studies should be done to confirm the results.

INTRODUCTION

HNSCC is the sixth leading cancer by incidence worldwide. Head and neck cancer (HNC) is a common and aggressive malignancy with a high morbidity and mortality profile. The annual incidence of head and neck squamous cell carcinoma (HNSCC) worldwide is more than 550,000 cases with around 300,000 deaths each year[1]. The male to female ratio ranges from 2:1 to 4:1. About 90% of all head and neck cancers are squamous cell carcinomas (HNSCC). The majority of them arise in the epithelial lining of the oral cavity, oropharynx, larynx and hypopharynx [2, 3].

Head and neck cancers in India are emerging as major public health problems, which are genetic, environmental and lifestyle-related. In India, 6.5% of the total population is represented by older persons (60 years and above).[4] and has a distinct demographic profile, risks factors, food habits, family and personal history.[5]

According to recent worldwide estimates, one billion men and 250 million women smoke cigarettes, 600-1200 million people chew betel quid, and two billion consume alcohol. An unbalanced diet is a common factor among people in developed and developing countries. [11]Tobacco and alcohol consumption alone is implicated in 75% of all SCCHN cases, and the effect is synergistic rather than simply additive.[7-9]Over 200,000 cases of head and neck cancers occur each year in India. Nearly 80,000 oral cancers are diagnosed every year in our country.[10]Nearly two-thirds of oral cancers are located in the mucogingival sulcus, where the betel quid is kept for long periods in the oral cavity. The location and etiology of this buccogingival cancer may warrant the term 'the Indian oral cancer'.

The 5-year overall survival rate of patients with HNSCC is about 40%-50%. About one-third of patients present with early-stage disease (T1-2, N0) and remaining present with locally advanced stage. In fact, 60-80% of patients present with Stage III & Stage IV HNC in India, as compared to 40% in developed countries, consistent with which, the overall survival is also reduced[18.]

Standard treatment in HNC includes surgery, radiation therapy (RT), chemotherapy (CT), and biological or targeted agents. Radiation therapy (RT) plays a pivotal role in multidisciplinary treatment management of head and neck squamous cell carcinoma (HNSCC). In curative intent radiotherapy of HNSCC, differences in clinical outcomes are accountable to treatment-related variables including total dose, overall treatment time (OTT) and addition of chemotherapy besides tumor-related prognostic factors). Conventional multifractionated RT regimens are largely the result of early radiobiological experiments conducted in the 1920-1930s (51, 52). Although standard conventional fractionation (CF) of delivering five fractions (F) per week, 1.8–2.0 Gy per fraction for 6-7 weeks has been time-tested for many decades, it is more of a convenient approach than a scientific one.

The state of the art regarding radiation dose fractionation has evolved from once-daily treatment to altered fractionation-hyperfractionation and accelerated fractionation.[11-14] These new strategies lead to a 7% to 10% improvement in a locoregional control relative to once-daily treatment schemes. A meta-analysis of randomized trials testing modified fractionation schemes against conventional once-daily fractionation demonstrated that hypofractionation was the most effective strategy, leading to an 8% absolute improvement in 5-year survival.[15] Nonetheless, even the most effective RT regimens result in local control rates of 50% to 70% and disease-free survivals (DFSs) of 30% to 40%.

In Hyperfractionated Radiotherapy more than one fraction is delivered each day, but the overall treatment time remains similar to that for conventional fractionation, with increased total dose, with decreased dose per fraction and increased numbers of fractions. Typically, this means 1.1–1.3 Gy/fraction,

twice daily, with an increase in the total dose of the order of 20%–30% to account for increased repair at the lower dose per fraction.

Most randomized clinical trials show the superiority of combined RT and chemotherapy to RT alone for the treatment of locally advanced, non-metastatic HNC. A meta-analysis of individual patient data from >17,346 participants in 93 trials conducted from 1965-2000(Meta-Analysis of Chemotherapy in Head and Neck Cancer [MACH-NC] demonstrated that use of radiotherapy and concurrent chemotherapy resulted in 19% reduction in the risk of death and an overall 6.5% improvement in 5year survival compared to treatment with RT alone($p<0.0001$).

The purpose of the present study was to access the overall response rate of hyperfractionated radiotherapy with concurrent weekly Injection Cisplatin($30mg/m^2$) in locally advanced carcinoma of head and neck.

MATERIAL & METHODS

This was a single institutional, prospective, observational study in which 15 patients of locally advanced head and neck cancer attending oncology OPD at Pravara Rural Hospital between September 2018 to September 2019 were enrolled.

INCLUSION CRITERIA:

- Histologically proven cases of non-metastatic Head and Neck Squamous cell carcinoma.
- Locally advanced head and neck cancers stage III and IV.
- Either Gender
- Patients with normal haemogram, renal function tests, and liver function tests.
- Age between 25 to 65 years.
- Patients undergoing Hyperfractionated Radiotherapy along with concurrent chemotherapy in locally advanced head and neck cancers.
- Patients were willing to give written informed consent for participation in the study.

EXCLUSION CRITERIA:

- Patients previously operated for Head and Neck cancer.
- Patients who have undergone radiotherapy or chemotherapy in the past.
- Age more than 65 years and less than 25 years.
- Nasopharyngeal cancer, sinonasal sinus cancer, thyroid cancer, and salivary gland cancer
- Cancer of non-squamous pathology.

All patients that fit in the above-mentioned criteria were included in the study after written informed consent.

A detailed history regarding age, sex, occupation, addictions, symptoms at presentation and past history was obtained from each patient. A clinical examination was done for primary disease mapping and regional nodal assessment. The tumors were classified according to the criteria of the American Joint Committee on Cancer Staging eighth edition.

All patient's dental checkup was done and all non-salvageable teeth were removed before radiotherapy. Purpose of treating by Hyperfractionated radiotherapy, treatment duration, side effects was explained to each patient. The Institutional Ethical Committee of Pravara Institute of Medical Sciences approved the protocol.

TREATMENT DELIVERY

All patients received radiotherapy on CLINAC DBX linear accelerator (6MV photons) with a source to axis distance (SAD) of 80-100cm as per the treatment planning system. During radiation treatment patients were placed in the supine position using the thermoplastic head and neck mask on the treatment table with shoulder traction, which was aligned with wall-mounted red lasers using external marks. The patient's position was confirmed by using EPID before the start of the treatment and twice weekly. Initial target volume consisted of the primary tumor, involved lymph nodes and probable subclinical disease. The irradiation field was reduced after

44-46 Gy to spare the spinal cord. As per the Hyperfractionation schedule dose of 110cGy was given twice a day with 6 hours interval. The treatment was given 5 days a week from Monday to Friday. The total dose was 6760 to 7620cGy in 66-70 fractions in six to seven weeks with concurrent cisplatin(30mg/m2) on a weekly basis.

On follow-up, All patients were examined weekly for acute toxicities, primary & nodal response and concurrent weekly Injection Cisplatin (30mg/m2) during the course of radiotherapy. Follow-up examinations for all patients were done at one and a half months and three months thereafter for a period of 6 months to 1 year to assess treatment response and acute as well as late toxicities. Toxicity related to treatment was considered acute if it occurred within the first 90 days from the start of treatment and late if it occurred after 90 days if acute toxicity persisted beyond day 90.

The treatment response was assessed as per the WHO RECIST criteria. [16]

RESULTS

PATIENT CHARACTERISTICS

The age of patients ranged between 40 and 65 years, mean age 55.8 years. Of 15 patients 11 were male and 4 were females. The majority of the cases were of carcinoma larynx and hypopharynx in this study as most of the carcinoma oral cavity patients reported after surgery and were not included which was actually the most common head and neck malignancy reported at our center. Maximum patients were T3, T4 and N2 stage followed by N1. 5 patients were grouped in stage III and 10 patients in Stage IV according to AJCC (8th edition) for staging.

Table 1: Pretreatment characteristics of patients

Patients characteristics		
Age (in years)	**Range**	40-65
	Mean	55.8
Sex (%)	**Male**	11(73.33%)
	Female	4(26.66%)
Site (%)	**Oral cavity**	3(20%)
	Oropharynx	2(13.33%)
	Hypopharynx	4(26.66%)
	Larynx	6(40%)
T stage (%)	**Tx-T1**	1(6.66%)
	T2	3(20%)
	T3	6(40%)
	T4	5(33.33%)
N stage (%)	**N0**	2(13.33%)
	N1	4(26.66%)
	N2	8(53.33%)
	N3	1(6.66%)
Overall TNM stage (%)	**III**	5(33.33%)
	IV	10(66.67%)

TREATMENT RESPONSE

15 biopsy-proven cases of locally advanced HNSCC from the year September 2018 to September 2019 were enrolled for the study. 80% of patients (4/5) of Stage III and 60% of patients (6/10) of Stage IV showed CR. At the endpoint of 6 months follow-up complete response, partial response, stable response, and progressive disease were 66.66%, 20%, 6.66%, and 6.66% respectively.

The overall response rate of this study was 86.66%.

Table no. 2: Stage wise response

Response	Stage III (n = 5)	Stage IV (n = 10)	Total (n=15)
Complete	4(80%)	6(60%)	10(66.66%)
Partial	1(20%)	2(20%)	3(20%)
Stable	0	1(20%)	1(6.66%)
Progressive Disease	0	1(20%)	1(6.66%)

Figure no.1: Stage wise treatment response

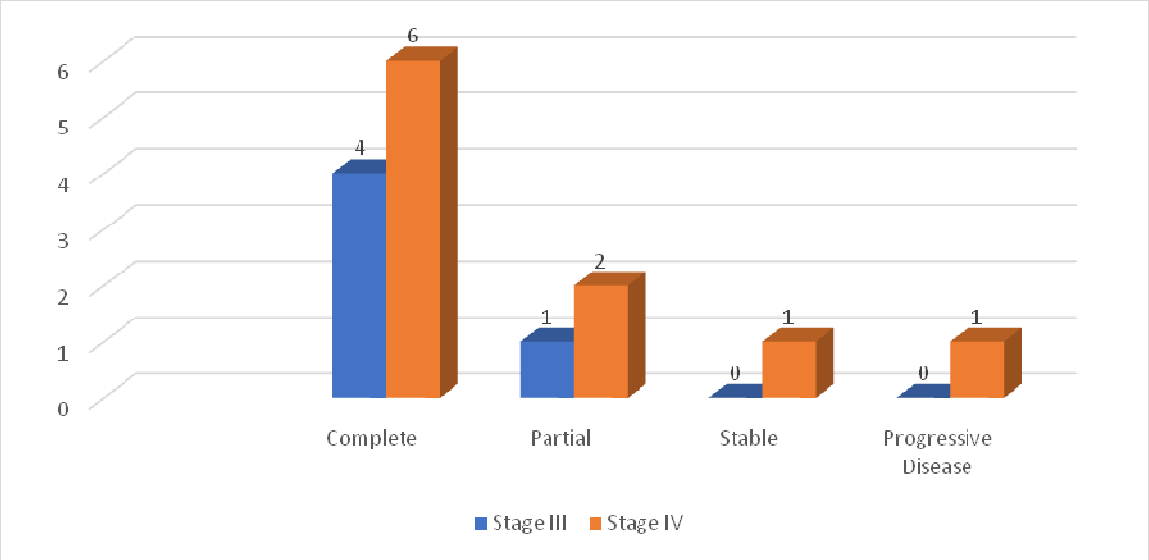
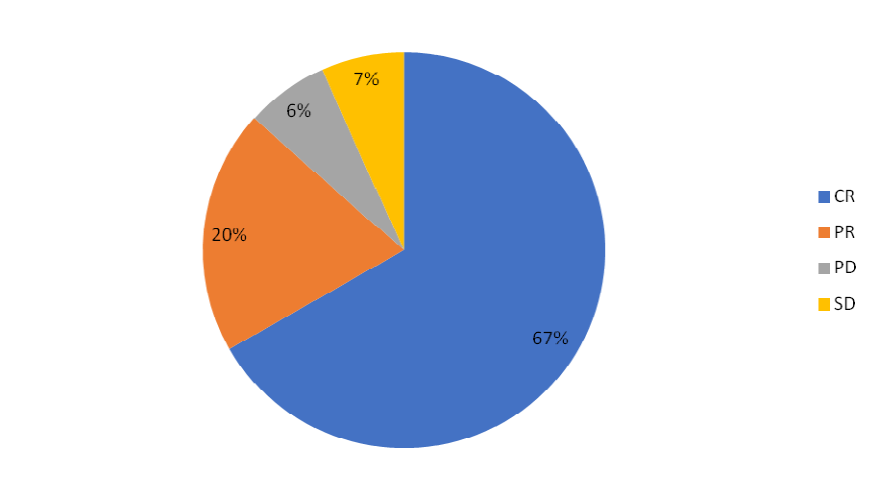


Figure no. 2: overall response rate



DISCUSSION

This study was conducted to evaluate the overall response of hyperfractionated radiotherapy with concurrent weekly Injection Cisplatin(30mg/m2) in locally advanced carcinoma of head and neck.

We enrolled 15 biopsy-proven cases of locally advanced HNSCC, out of which 11(73.33%) patients were males and 4(26.66%) patients were females. In India, it accounts for one-fourth of male cancers and one-tenth of female cancers. The overall male: female ratio of head and neck cancers in the urban population is 2:1 and in rural population is 5:1[6]. Our center is in a rural setting and most patients belonged to a lower socio-economic class. Almost all the participants gave a significant addiction history, attributing to tobacco, areca nut, alcohol, etc thus explaining the difference in sex incidence of locally advanced HNSCC reporting in this study.

From the present study, the most commonly involved site was larynx 40% followed by hypopharynx 26.66%, oral cavity 20% and oropharynx 13.33%. Relatively, smoking is the strongest risk factor for laryngeal and pharyngeal cancer than for oral cavity cancer.[7] Smoking was the major addiction in this study, thus explaining the majority of cases belonging to laryngeal and hypopharyngeal cancers.

In India 60% of the cases present as advanced HNSCC. In my study 5(33.33%) reported in Stage III and 10(66.67%) in Stage IV. Poverty, illiteracy, lack of access to health care, pose a major challenge in reporting cases at an early stage and cause limitations in the management of these cancers.[6]

Out of the 15 patients who completed treatment, 10(66.66%) patients had complete response (CR), 3(20%) patients had partial response (PR), 1(6.66%) had progressive disease and 1(6.66%) patients had stable disease(SD) at last follow up which varied between 6months to 12months. Stage III 4/5(80%) patients had CR and Stage IV (6/10)60% had CR.

These results were comparable to Tallari et al[18]. at 12 months this study showed LRC of 68%, PFS of 87.2% and OS of 93.6%. Similar results were seen in a study by Al-Saleh K et al[19] CR was observed in 40 patients (83.3%) and PR was observed in 8(16.7%) and Aldestein et al[20] at 30months-OS- 59%, LC without surgical resection- 91%, with surgical resection-97% and metastasis was present in8/13 patients.

Several studies have been carried out using hyperfractionated RT. All studies showed an improved tumor control and overall response compared to the conventional treatment schedule.

Table 3: Results of randomized controlled trials of hyperfractionated versus conventional radiotherapy in locally advanced head and neck squamous cell cancer[10]

Study(reference)	Locoregional response		Overall survival	
	HFRT	CFRT	HFRT	CFRT
RTOG 79-13/Marcial et al. 1987	52%	55%	13months	NR(29% at 2yrs)
Datta et al 1989 abstract	85.7%	72.9%	Not recorded(NR)	NR(32.9% at 2years)
Sanchiz et al 1990	86.66%	67.8%	7years	22%
Pinto et al	62%	52%	21months	NR
EORTC 22791/Horiot et al. 1992	86%	86%	3years	40%

Cummings et al., 2000 abstract	NR	NR	NR(40% at 5years)	37%
RTOG 9003/Fu et al. 2000	NR	NR	NR(54.5% at 2years)	NR(46% at 2years)
Current study	66.66%	-	-	-

Shukovsky J.L. et al (1976) [21] reported better control rate with a twice-daily fractionation schedule in 24 patients with advanced HNSCC. Medini E. et al (1980)[22] reported 53% local control in 15 patients with advanced HNC. Jampolis et al (1977)[23] reported a local control rate of 61% and a regional control rate of 95% in 24 patients who had T4 lesions treated with 1.2-1.25cGy twice daily to a total dose of 7200cGy. Hariot et al (1992) reported a similar control rate with locally advanced HNC.

A study by Lacas et al described the role of radiotherapy fractionation in head and neck cancers(MARCH) an updated meta-analysis, searched for randomized trials done between Jan 1, 2009, and July 15, 2015, comparing primary or postoperative conventional fractionation radiotherapy versus altered fractionation radiotherapy (comparison 1) or conventional fractionation radiotherapy plus concomitant chemotherapy versus altered fractionation radiotherapy alone (comparison 2) The results showed-overall survival benefit of 8.1% at 5years and 3.9% at 10years with Hfrx RT(altered fractionation) and worse survival of Hfx RT compared with CRT-5.8% at 5years and – 5.1% at 10years. This update confirms, with more patients and a longer follow-up than the first version of MARCH, that hyperfractionated radiotherapy is, along with concomitant chemoradiotherapy, a standard of care for the treatment of locally advanced head and neck squamous cell cancers. Thus as per the current study interpretation, the overall response and survival is good in patients treated with hyperfractionated RT with concurrent chemotherapy.[25]

Even though the outcome of this study is good and comparable to similar studies, the result must be interpreted with caution due to the small sample size, irregular follow up and short duration of the study.

CONCLUSION

With this study, we conclude that hyper fractionated radiotherapy in combination with chemotherapy seems to be more efficacious than CFRT as compared to other studies in the treatment of unresectable, locally advanced head and neck squamous cell carcinoma in terms of a good locoregional control and improved overall response, thus hyper-fractionated radiotherapy should be practiced more often in cases of locally advanced head and neck cancer.

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