Original Article

Comparison of the Locoregional Outcome, Toxicities, and Compliance between Hypofractionated and Conventional Chemoradiotherapy for Head-and-Neck Cancers

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Abstract

Introduction: Head-and-neck cancer (HNC) treatments are elusive, and the hunt for an appropriate radiation strategy continues. Hypofractionation has the potential to provide several advantages, including a shorter overall duration that reduces rapid repopulation, dosage escalation with a higher biologically effective dose, and patient convenience. Hypofractionation is also beneficial in minimizing the danger of catching an infectious agent by reducing the number of hospital visits during the height of the COVID-19 epidemic. **Materials and Methods:** Between January 2020 and August 2021, 120 patients with squamous cell carcinoma of the head-and-neck subsites were randomly allocated to either the hypofractionated arm A (n = 60) or the standard fractionation arm B (n = 60) with concomitant treatment. **Results:** Locoregional tumor response, acute and late toxicity, and compliance were the study's endpoints. The normal tissue toxicities of each patient undergoing radiation were monitored weekly. Clinical and radiographic evaluations of locoregional control were conducted. **Conclusion:** Hypofractionation effectively overcomes tumor repopulation in rapidly growing tumors such as HNC, and we conclude in our study that the hypofractionated chemoradiation schedule appears to be more efficacious, with relatively superior locoregional control when compared to conventional chemoradiation with comparable normal tissue toxicities and compliance.

Keywords: Conventional, head-and-neck cancers, hypofractionation

Introduction

Cancer is one of the prime factors for morbidity and mortality across the world. Head-and-neck cancers (HNCs) have been prominent in the top ten malignancies worldwide, accounting for one-quarter of male cancers and one-tenth of female cancers in India.

Before 1980, the most common treatment for locally advanced head-and-neck squamous cell carcinomas (HNSCC) was surgical resection followed by postoperative radiotherapy.[1-4] Today, Concurrent Chemoradiation (CCRT) has replaced surgery in locally advanced HNC, with the added benefit of protecting both organs and functions.

Radiotherapy is provided in the fractionated form, splitting doses into numerous fractions to maximize tumor destruction while preserving normal tissues as much as possible. A variety of treatments have been explored to enhance the outcomes of locally advanced HNC treatments. As a solo modality, one method is to utilize changed fractionated radiation with and without concomitant chemotherapy. Hypofractionation and other rapid fractionation regimens have been studied in several research.[5]

Typically, fractionated radiation is delivered in 1.8–2.0 Gy increments. Various changes in the irradiation regimens studied during clinical trials are now reckoned as conventional therapeutic choices while understanding radiation with tumor biology. Another form is hyperfractionation, which uses a reduced treatment dosage to deliver radiation. Accelerated fractionation radiation reduces the time it takes to

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administer treatment by increasing the number of treatments given each day. Finally, by increasing daily treatment dosages, hypofractionation reduces the number of fractions administered.[6]

The advent of the COVID-19 new coronavirus pandemic in late 2019/early 2020 prompted a quick social response, which is essential in primary medical care. Patients suffering from head-and-neck pain are treated.[7]

Hypofractionation has the potential to provide several advantages, including a shorter overall duration that reduces rapid repopulation, dosage escalation with a higher biologically effective dose, and patient convenience. Although individual treatment sessions are a little longer, it may minimize the demand on radiotherapy resources by utilizing fewer fractions.

The study's main goal was to compare tumor response, normal tissue toxicities, and compliance in HNSCC patients who received hypofractionated radiation and concurrent chemotherapy to patients who received standard fractionation and concurrent chemotherapy.

Materials and Methods

Study design

From August 2020 to June 2021, prospective randomized comparative research was conducted in which all eligible patients attending the department of radiation oncology outpatient department treatment were randomly allocated to one of two study arms using the chit box method.

Sample size

There were 120 patients in all, 60 in each arm, with biopsy-proven head-and-neck malignancies.

Study setting

Sixty patients received conformal radiotherapy with a hypofractionated regimen in Arm A (test arm) with a total dose of 66 Gy/30# (in 6 weeks), i.e., 2.2 Gy per fraction with concurrent chemotherapy.

In Arm B (control arm), 60 patients were treated with conformal radiotherapy following a conventional schedule with concurrent chemotherapy (CCRT) with a total Dose 70 Gy/35# (in 7 weeks).

Appropriate approval has been taken from the concerned IRB (Letter No.MGMCH/IEC/JPR/2020/165).

Inclusion criteria

The patients were according to the following eligibility criteria: (1) biopsy-proven, nonmetastatic, squamous cell carcinoma of the larynx, oropharynx, hypopharynx, and oral cavity; (2) Karnofsky performance score/scale more than 70; (3) aged from 18 to 70; (4) no history of previous malignancy; (5) and normal laboratory investigations – Complete blood count, renal function test, liver function test, and normal chest X-ray.

Exclusion criteria

(1) Patients who do not give consent; (2) patients with ages <18 years and >70 years; (3) patients with distant metastasis; (4) prior head-and-neck irradiation and neoadjuvant chemotherapy; and (5) histologically other than squamous cell carcinoma and tumors affecting sinonasal and nasopharyngeal sites.

Each patient undergoing radiotherapy was assessed weekly for normal tissue toxicities – acute mucositis, acute dermatitis, and dysphagia using CTCAE criteria 5.0. Moreover, RTOG guidelines and assessment of locoregional control were done clinically by direct laryngoscopy every month for 6 months and radiologically by contrast-enhanced computed tomography scan NECK after 3 months (if required) and at 6 months using RECIST criteria 1.1.

Statistical analysis

The Chi-square statistical test was utilized for statistical analysis, with $P = 0.05$ adjudged as significant.

This medical research involving human subjects follows the guidelines laid down in the Declaration of Helsinki.

Observation and Results

Table 1 indicates similar patient and tumor characteristics in both arms, with 62 years as the median age and male preponderance in both. Similarly, the majority of patients had performance scores of 80–90 and Grade II histopathologic differentiation, indicating that they had locally advanced disease (Arm A – 86.6% and Arm B – 90%), with the larynx as the primary site in the arm A (40%) and the oropharynx as the primary site in arm B (43.3%).

Table 2 shows a similar pattern of acute mucositis and dysphagia in both arms, with Grade III toxicity in Arm A and Grade II toxicity in Arm B, as well as an equivalent Grade I dermatitis. Grade I xerostomia was observed in both arms, followed by Grade I dysphagia and mucositis, a major part of late toxicities included Grade I xerostomia, Grade I dysphagia, and Grade I mucositis.

Table 3 shows a comparable outcome in both arms at 6 months, with 80% complete response (CR) in Arm A and 76.6% CR in Arm B, and nonsignificant *P* values in patients displaying a partial response (PR), stable disease, and advancing disease.

Table 4 compares the compliance outcomes of the two arms, revealing that 83.3% of the patients in Arm A and 80% of the patients in Arm B completed radiation therapy without gaps, with equal numbers of defaulters and patients who died.

Discussion

In recent years, several radiotherapy strategies have emerged which improve response and/or decrease the side effects of the therapy.[8]

Several randomized trials have demonstrated the critical role of concomitant chemoradiation in the literature. It is

Table 1: Baseline patient and tumor attributes

Patient parameters	Arm A (%)	Arm B (%)
Gender		
Male	54 (90)	58 (96.6)
Female	6 (10)	2 (3.4)
Age		
21-30	0	2 (3.4)
31-40	8 (13.3)	10 (16.6)
41-50	18 (30)	10 (16.6)
51-60	14 (23.3)	18 (30)
61-70	20 (33.4)	20 (33.4)
Histopathologic differentiation		
WDSCC	26 (43.3)	16 (26.6)
MDSCC	30 (50)	40 (66.7)
PDSCC	4 (6.7)	4 (6.7)
KP score		
70	6 (10)	6 (10)
80	36 (60)	28 (46.7)
90	16 (26.6)	24 (40)
100	2 (3.4)	2 (3.4)
Sites		
Oral cavity	10 (16.6)	10 (16.6)
Oropharynx	22 (36.6)	26 (43.3)
Larynx	24 (40)	20 (33.4)
Hypopharynx	4 (6.7)	4 (6.7)
Stage		
I	2 (3.4)	0
II	6 (10)	6 (10)
III	16 (26.6)	26 (43.3)
IV	36 (60)	28 (46.7)

KP: Karnofsky performance, SCC: Squamous cell carcinomas, WDSCC: Well-differentiated SCC, MDSCC: Moderately difference SCC, PDSCC: Poorly difference SCC

Table 2: Comparison between acute and late toxicities

Acute toxicities	Arm A (%)	Arm B (%)
Mucositis		
I	0	0
II	24 (40)	34 (56.67)
III	32 (53.34)	24 (40)
IV	4 (6.6)	2 (3.3)
Dermatitis		
I	34 (56.7)	40 (66.7)
II	24 (40)	18 (30)
III	2 (3.3)	2 (3.3)
IV	0	0
Dysphagia		
I	0	0
II	28 (46.67)	42 (70)
III	30 (50)	18 (30)
IV	2 (3.33)	0
Late toxicities	**Arm A (%)**	**Arm B (%)**
Mucositis		
I	4 (6.67)	4 (6.67)
II	1 (1.6)	4 (6.67)
III	0	0
IV	0	0
Dysphagia		
I	10 (16.6)	12 (20)
II	6 (8.3)	6 (8.3)
III	0	0
IV	0	0
Xerostomia		
I	12 (20)	14 (23.34)
II	8 (13.3)	12 (20)
III	4 (6.6)	4 (6.6)
IV	0	0

becoming progressively apparent that incorporating systemic therapy with radiotherapy amplifies locoregional outcomes and supplements overall life expectancy in patients with locally progressed HNSCC.

We show here that using a systematic optimization approach, new hypofractionated procedures for HNCs may be created that improve tumor control while reducing late normal tissue problems.

In our study, the frequency of Grade 3 mucositis in Group A was higher, i.e., 32 patients (53.3%) compared with 24 patients in Group B (40%), and was statistically significant ($P = 0.033$). The incidence of Grade 2 mucositis was observed in 24 patients (40%) compared with 34 patients (56.67%). Most patients who develop Grade 3 or 4 mucositis are hospitalized and are therefore treated supportively with parenteral nutrition and appropriate fluid supplementation. One of the studies demonstrated that coadministration of cisplatin with hypofractionation was associated with improved disease-free survival (DFS), whereas mucosal toxicity was high (G2 and above). Similarly, an observational study found that Grade 1, 2, 3, and 4 mucositis were found in 1% of the patients, 25% of the patients, 69% of the patients, and 5% of the patients, respectively.

The incidence of Grade 1 acute dermatitis was seen in 34 patients (56.7%) in the test arm and 40 (66.7%) in the control arm; Grade 2 dermatitis was more in arm A (24 patients- 40%) than in arm B (18 patients – 30%), and none developed Grade 4 dermatitis.

Similarly, we found in a study, Grade 1 dermatitis in 53% of the patients, followed by Grade 2 dermatitis in 41%, and 6% of the patients showed Grade 3 dermatitis with no Grade 4 dermatitis.[9]

Arm A patients had more incidence of Grade 3 dysphagia (30 patients – 50%) as compared to arm B patients who had more incidence of Grade 2 (40 patients – 70%). In Arm A, the incidence of Grade 3 and Grade 2 dysphagia is comparable. Similarly, we can compare this outcome with a study that shows Grade 1 dysphagia in 2.4% of the patients and Grade 2 dysphagia in 43.2%, followed by Grade 3 dysphagia in 54.4% of the patients.

Table 3: Response evaluation at 3 and 6 months

	Arm A		Arm B	
	At 3 months	At 6 months (%)	At 3 months	At 6 months (%)
CR	47	48 (80)	44	46 (76.6)
PR	7	6 (10)	10	8 (13.3)
SD	4	4 (6.6)	2	2 (3.3)
PD	2	2 (3.4)	4	4 (6.6)

CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

Table 4: Compliance

Parameters	Arm A (%)	Arm B (%)
Completed treatment	50 (83.3)	48 (80)
Treatment with gap	6 (10)	6 (10)
Defaulted	2 (3.3)	2 (3.3)
Died	2 (3.3)	4 (6.6)

In our study, the clinical response rates obtained after 6 months of treatment revealed that the CR rate was found in 48 patients, i.e., 80% of the patients in the hypofractionated chemoradiotherapy arm, and 46 patients, i.e., 76% of the patients in the conventional chemoradiotherapy arm. The PR rates were 10% (6 patients) in the hypofractionated chemoradiotherapy arm and 13.3% (8 patients) in conventional chemoradiotherapy. Overall response OR rates (CR + PR) were 90% in the hypofractionated chemoradiotherapy arm and 89.9% in the conventional chemoradiotherapy arm which results in a nonsignificant outcome methodically.

A similar study observed that hypofractionated radiotherapy combined with systemic therapy can be considered a potential alternative to conventional fractionation regimen. In this study, a significant locoregional control resulted from hypofractionated arm and systemic chemotherapy.[10]

In another study by Pignon *et al.*, it was determined that no major complications of RTOG/EORTC Grade 3 or higher were noticed. Cutaneous toxicity Grades 1 or 2 were the ones frequently accepted. No notable variation was detected in the incidence of acute or late cutaneous, mucosal, or laryngeal toxicity between the two treatment groups.[11] A dose rate similar to our study was used in one more study. Therefore, our study's findings of acute and late toxicity were no exception and were familiar to the reported data. The daily dosage that was moderately increased can be reduced throughout the treatment period without adversely affecting the local area or toxicity profile of early glottic cancer. In our study, the HYPO group had a 5-year LPFS rate of 88.5%, which was not statistically significant but higher than the CONV group (77.8%). The 5-year LCR was 77% in the standard group and 92% in the test group, according to the same study. There was no significant difference in the incidence of acute or late side effects, just as there was in our study. They discovered that using a hypofractionation schedule with a shorter overall treatment time resulted in better local control than traditional fractionation, with no side effects from increased fractionation.[12]

Late toxicities, defined as side effects lasting more than 4 weeks, were investigated in our study. Xerostomia, dysphagia, and mucositis were all taken into account. Grade 1 dysphagia was seen in 10 patients (16.7%) in arm A and 12 patients (20%) in arm B in late toxicities; Grade 2 dysphagia was seen in six patients (8.3%) in arm A and six patients (8.3%) in arm B in late toxicities, with no Grade 3 dysphagia. These findings were nearly identical to those of a trial that found Grade 1 dysphagia in 6.2% of the patients and no Grade 2 or 3 toxicities.[13]

Late Grade 1 mucosal toxicity was seen in four patients (6.67%) in arm A and four patients (6.67%) in the arm B; Grade 2 in arm A seen in one patient (1.6%) and the arm B seen in four patients (6.67%) with 0 patients showing Grade 3 mucositis in both the arms. Similarly, we see in one of the studies that no mucositis was found in any of the patients.[14]

Many radiotherapy departments had to examine chemoradiation methods during the peak of the COVID-19 pandemic and adjust them based on local viral risk and health-care capability. The ASTRO-ESTRO consensus statement and the Royal College of Radiologists' recommendation of mild hypofractionation are supported by the indistinguishability in effectiveness and quality of life endpoints between the 6- and 7-week arms at baseline (acute effects) and 2 years (passive effects).[15]

The use of a 6-week program merely reduces the number of health examination visits to the doctor. For T1-T3 N0-N2c HPV positive and T1-T2 N0 HPV-negative tumors, a hypofractionated radiation alone schedule of 60 Gy/25# over 32 days has been recommended based on single-center data. In terms of fewer patient visits and capacity use, this regime may be more advantageous. In two recent randomized trials, however, the absenteeism synchronous cisplatin in HPV-positive individuals was shown to be detrimental to overall survival.[16]

This report provides corroboration for the widespread use of 6 weeks expedited mildly hypofractionated chemoradiation during the COVID-19 pandemic.

Conclusion

In fast-growing tumors such as HNC, hypofractionation effectively overcomes tumor repopulation. Although this is not a novel concept, practical applications to HNC malignancies have been limited in the past due to the risk of increased early and late complications.

Thus, a comparative study was undertaken to evaluate the compliance, toxicities, and locoregional control between hypofractionated chemoradiation versus conventional chemoradiation regimens.

Overall response odd ratio (OR) rates (CR + PR) were 93.3% in the hypofractionated chemoradiotherapy arm and 89.9% in the conventional chemoradiotherapy arm.

Both the CR and OR rates were determined to be nonsignificant ($P = 0.63$).

Treatment toxicities in terms of acute mucositis and dysphagia were experienced more in the hypofractionated chemoradiation arm than the conventional chemoradiation arm, where the difference in mucositis of Grade III was statistically significant ($P = 0.033$).

Other acute toxicities such as dermatitis were comparable in both groups (statistically not significant) and were managed with general supportive care. The treatment compliance was also similar in both arms. One of the studies states that mild hypofractionated schedules are becoming more important in early laryngeal cancer. According to one study,[14] there was no increased toxicity in the low fraction group. The conventional fraction group had a 5-year LPFS of 77.8%, and the low fraction group had an LPFS of 88.5% ($P = 0.213$). As a result, they concluded that the hypofraction had a similar toxicity profile to the standard fraction in T1 and T2 glottic cancers and was not inferior to it. The hypofractionated schedule's role in T12 laryngeal and hypopharyngeal cancer was investigated in a separate study. In comparison to previous controls, they found that implementing this process improved local control in T1 laryngeal and hypopharyngeal cases. With a median follow-up of 47 months and no ongoing Grade II toxicity, the treatment was well tolerated.

Hypofractionated chemoradiation concurrent cisplatin chemotherapy in HNSCC is safe and efficacious with superior LRC with comparable compliance and toxicities to the conventional chemoradiation regimen. Large sample size and longer follow-up are needed for better evaluation and to draw inference on LRC, DFS, and overall survival.

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Conflicts of interest

There are no conflicts of interest.

References

1. Kulkarni MR. Head and Neck Cancer Burden in India. Int J Head Neck Surg 2013;4:29-35. [doi: 10.5005/jp-journals-10001-1132].
2. Rodgers LW, Stringer SP, Mendenhall WN, Parsons JT, Cassisi NJ, Million RR, *et al*. Management of squamous cell carcinoma of the floor of the mouth. Head Neck 1993;15:16-9.
3. Weber RS, Gidley P, Morrison WH, Peters LJ, Hankins P, Wolf P, *et al*. Treatment selection for carcinoma of the base of the tongue. Am J Surg 1990;160:415-9.
4. El Badawi SA, Goepfert H, Fletcher GH, Herson J, Oswald MJ. Squamous cell carcinoma of the pyriform sinus. Laryngoscope 1982;92:357-64.
5. Chow LQ. Head and neck cancer. N Engl J Med 2020;382:60-72.
6. Perez CA, Holtz S, Ogura JH, Dedo HH, Powers WE. Radiation therapy of early carcinoma of the true vocal cords. Cancer 1968;21:764-71.
7. Fletcher GH, Jessee RH. The place of irradiation in the management of the primary lesion in head and neck cancers. Cancer 1977;39:862-7.
8. Eisbruch A, Harris J, Garden AS, Chao CK, Straube W, Harari PM, *et al.* Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). Int J Radiat Oncol Biol Phys 2010;76:1333-8.
9. Gupta NK, Swindell R. Concomitant methotrexate and radiotherapy in advanced head and neck cancer: 15-year follow-up of a randomized clinical trial. Clin Oncol (R Coll Radiol) 2001;13:339-44.
10. Lacas B, Bourhis J, Overgaard J, Zhang Q, Grégoire V, Nankivell M, *et al*. Role of radiotherapy fractionation in head and neck cancers (MARCH): An updated meta-analysis. Lancet Oncol 2017;18:1221-37.
11. Pignon JP, le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4-14.
12. Petit C, Pignon JP, Landais C, Trotti A, Gregoire V, Overgaard J, *et al.* What is the most efective treatment for head and neck squamous cell carcinoma? An individual patient data network meta-analysis from the MACH-NC and MARCH collaborative groups. Eur J Cancer 2017;72 Suppl 1:S140.
13. Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, Phillips TL, *et al.* A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: First report of RTOG 9003. Int J Radiat Oncol Biol Phys 2000;48:7-16.
14. Beitler JJ, Zhang Q, Fu KK, Trotti A, Spencer SA, Jones CU, *et al.* Final results of local-regional control and late toxicity of RTOG 9003: A randomized trial of altered fractionation radiation for locally advanced head and neck cancer. Int J Radiat Oncol Biol Phys 2014;89:13-20.
15. Cummings B, Keane T, Pintilie M, Warde P, Waldron J, Payne D, *et al.* Five year results of a randomized trial comparing hyperfractionated to conventional radiotherapy over four weeks in locally advanced head and neck cancer. Radiother Oncol 2007;85:7-16.
16. Bourhis J, Blanchard P, Overgaard J, Ang KK, Saunders M, Bernier J, *et al*. Hyperfractionated or accelerated radiotherapy for head and neck cancer: A meta-analysis. Lancet 2006;368:843-54.