SSR Institute of International Journal of Life Sciences
ISSN (O): 2581-8740 | ISSN (P): 2581-8732
Mishi *et al*., 2024
DOI: 10.21276/SSR-IIJLS.2024.10.5.16

Original Article

open access

Comparative Study of Hypofractionated vs. Conventional Chemoradiation in Locally Advanced Head and Neck Cancer

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Received: 29 May 2024/ Revised: 03 Jun 2024/ Accepted: 02 Aug 2024

ABSTRACT

Background: Head and neck squamous cell carcinomas are the sixth most common cancer, with 830,000 new cases and 430,000 deaths annually. India accounts for 30% of global cases, with 119,992 new cases and 72,616 deaths in 2018. Locally advanced cancers (stage III or higher) have a high recurrence rate despite treatment advances. Hypofractionated radiotherapy, offering larger doses in shorter durations, shows promise for better tumor control and patient compliance, prompting a randomized study on its efficacy and tolerance.

Methods: A total of 70 patients (15 months study) who were willing to give informed consent and fulfilling the specified inclusion and exclusion criteria were enrolled for the study. This 15-month study at the State Cancer Institute, Jabalpur, enrolled 70 head and neck squamous cell carcinoma patients. Eligible participants were aged 18-70, treatment-naive, and had an ECOG score of 0-2. Patients were randomized into two treatment arms, both receiving weekly cisplatin. Treatment response and adverse reactions were monitored weekly, with evaluations based on WHO and RTOG criteria.

Results: Both arms had similar male dominance (~87-89%) and rural representation (~80-82.5%). Tobacco use was high in both groups (~77-80%), with Arm B showing higher alcohol and dual addiction rates (65.71% vs. 41.67%). Arm A had a higher complete response rate (77.1% vs. 62.8%), and fewer cases of progressive disease (0% vs. 20%). Toxicities were manageable, with similar dysphagia rates, but Arm B showed more severe mucositis.

Conclusion: The study concluded that hypofractionated radiation therapy can be preferred over conventional chemoradiation therapy because it offers a comparable clinical response with manageable toxicities.

Key-words: Cancer treatment, Definitive chemoradiotherapy (dCRT), Early-stage cancers, Head and neck squamous cell carcinomas (HNSCC), Oral cancers

How to cite this article
Tiwari M, Singotia L, Jain R, Rawat S, Saxena A, et al. Comparative Study of Hypofractionated vs. Conventional Chemoradiation in Locally Advanced Head and Neck Cancer. SSR Inst Int J Life Sci., 2024; 10(5): 6229-6235.

Access this article online
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INTRODUCTION

Squamous cell carcinomas of the head and neck are the sixth most common type of cancer globally, accounting for 830,000 new cases and about 430,000 deaths annually [1,2] Speaking of the situation in Asia and India, Asia is home to 57.5% of all HNCs worldwide, with India leading the way with 30% of all HNC cases. [3,4] India has the highest number of oral cavity cancer patients

DOI: 10.21276/SSR-IIJLS.2024.10.5.16

worldwide, accounting for 72,616 deaths and 1,19,992 new cases of oral cancer in 2018. [5].

At the time of initial presentation, 10% of patients with locally advanced disease already had distant metastases [6] and it is also well known that patients often ignore their symptoms during initial stages, leading to further advancement in disease and making it even more difficult to achieve cure rates. The clinical stage at hospital presentation and early detection are the main indicators of survival for head and neck cancers. According to AJCC version 7, locally advanced HNSCC is classified as stage III or higher. Therefore, the disease is deemed locally advanced in patients whose primary tumor stage is T3 or higher and/or whose regional nodal stage is N2 or higher. The rate of locoregional failure remains high despite advances in cancer treatment. Advanced cancers (stages III and IV) have a greater than 50% chance of distant metastases and recurrence, while early-stage cancers (stages I and II) have a 60%–95% chance of recovery from local treatment alone [7,8].

dCRT standard of care for locoregionally advanced HNSCC is definitive chemoradiotherapy. The patients will receive 2 Gy of radiation per fraction, or a total of 70 Gy in 35 fractions, five times a week, according to the traditional fractionation technique used to deliver radiation to the patients. Patients with locally advanced squamous cell carcinoma of the head and neck are usually treated with radiation therapy for up to seven weeks. Given the improved tumor growth control, convenience, and compliance to short course RT regimens, trials testing altered fractionation schedules are currently underway in several countries, providing evidence in favor of altered fractionation in several solid cancers (breast, lung, and headneck). In hypofractionated regimens, we deliver a larger dose per fraction with a total decreased dose and in a shorter amount of time [3,9]

Radiobiological evidence supports the use of hypofractionated radiation therapy for tumor control. The duration of treatment has a significant impact on the cure rates of squamous cell carcinomas. The likelihood of tumor control may rise with a shorter treatment duration overall. On the other hand, increased tumor cell repopulation is assumed to be the cause of a decline in tumor control with extended treatment durations. During fractionated radiation therapy, surviving tumor changes clonogens regenerate quickly after a viable lag period. Therefore, adding 0.2 Gy daily in the form of mild hypofractionation may improve the effectiveness of tumor control.

The safety and viability of hypofractionated radiation therapy (HFRT) for head and neck (HN) tumors have been documented in an increasing amount of literature in recent years [10,18]. We carried out a randomized study to compare the effectiveness, response rate, toxicity tolerance in patients, patient compliance, and treatment completion rate of hypofractionation radiation therapy in locally advanced head and neck cancer. The study was supported by robust evidence-based trials and considered all the factors above.

MATERIALS AND METHODS

This was conducted in the Department of Radiation Oncology State Cancer Institute, Netaji Subhash Chandra Medical College Jabalpur, for 15 months, starting from February 2021 to May 2022. A total of 70 patients who were willing to give informed consent and fulfilling the specified inclusion and exclusion criteria were enrolled for the study.

Inclusion Criteria:

- Age >18 years and <70 Years.
- Pathologically proved head and Neck squamous cell carcinoma
- Eastern Cooperative Oncology Group PS 0-2
- Treatment naive except for biopsy or cytology
- Signed study-specific informed consent given by the patient before randomization.

Exclusion Criteria:

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

Pre-treatment evaluation- All patients were evaluated with history taking, complete physical and local examination including endoscopy and laryngoscopy guided examination for laryngopharyngeal growth, complete blood count, renal function and liver function tests. Preventive dentistry and biopsy of the primary

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tumour were mandatory for all patients. Radiological investigations included CECT face and neck, chest radiography, and ultrasound of the abdomen. All the patients were staged according to TNM staging system (AJCC 8th edition).

After pre-treatment evaluation and staging, patients were randomized into two arms by sequential randomization according to their first visit in our department. Patients were planned for external beam radiotherapy delivered by Co-60 teletherapy machine. The radiation therapy planning technique was the same and standardized for both groups of patients. Each group of patients received concurrent chemotherapy with cisplatin 35 mg/m2 weekly after normal blood investigations.

Arm A Received 2.2 Gy dose per fraction, 5 fractions a week, with concurrent cisplatin 35mg/m2 weekly with a total dose of 66 Gy/ 30 fractions, for a total duration of 6 weeks, with cord shielding at 44.2 Gy. Arm B Received 2 Gy per fraction, 5 fractions in a week, with concurrent cisplatin 35mg/m2 weekly with a total dose of 70 Gy /35 fractions, for 7 weeks with cord shielding at 46 Gy.

Response evaluation- Response evaluation was performed at the end of the treatment and monthly till three months after completion of chemotherapy by physical examination, indirect laryngoscopy, and CECT face and neck wherever feasible. Additional investigations were performed whenever necessary. Clinical and radiological responses were evaluated as per WHO criteria. Response was evaluated in terms of Stable disease (SD), Partial responses (PR), Progressive disease (PD) OR Complete response. Patients in both arms were assessed weekly for adverse reactions such as diarrhea, skin mucosal reactions, nausea, vomiting, dysphagia, acute renal toxicity and heamatological toxicity. Grading of adverse reactions as done as per RTOG criteria of adverse events and treatment response was assessed as per WHO criteria,

Statistical Analysis- The statistical analysis for this study was performed using SPSS version 27**.** The data was analyzed using the Chi-Square test and Fisher's exact test to assess the correlation between variables. These tests were applied to compare categorical variables, such as treatment responses (complete, partial, or progressive disease) and the incidence of treatment-related toxicities (e.g., mucositis, dysphagia). A p-value of less than 0.05 was considered statistically significant.

RESULTS

In both arms, the majority of patients were male, with Arm A having 87% male participants and Arm B slightly higher at 89%. Most patients came from rural areas (82.5% in Arm A and 80% in Arm B). Tobacco use was prevalent in both arms (80% in Arm A and 77% in Arm B), with 60% of participants in each group being smokers. Alcohol consumption was more common in Arm B (46%) than in Arm A (37.3%). Interestingly, the combination of both alcohol and smoking was much higher in Arm B at 65.71% compared to 41.67% in Arm A (Table 1).

Table 1: Patient Demographics and Addiction Profile Across Treatment Arms

Characteristics	Arm A	Arm B
Median age	53 years	51 years
Male	87.00%	89.00%
Female	13.00%	11.00%
Rural/urban	82.5% Rural	80% Rural
Addiction		
Tobacco	80.00%	77.00%
Smoking	60.00%	60%
Alcohol	37.30%	46%
Both alcohol and smoking	41.67%	65.71%

Oral cavity tumors were the most common in both groups, though more prevalent in Arm A (54.2%) compared to Arm B (45.7%). Oropharyngeal tumors were more frequent in Arm B (37.14%) than Arm A (22.85%). A small proportion of patients in Arm A had hypopharyngeal tumors (2.28%), with none in Arm B. Most patients in both arms had stage 3 tumors, but Arm B had a slightly higher percentage (85%) compared to Arm A (74.2%). Regarding lymph node status, Arm B had a higher proportion of patients with free lymph nodes (45.71%) compared to Arm A (30.56%), while the percentage of patients with fixed lymph nodes was similar in both arms (Table 2).

Table 2: Tumor Site, Stage, and Lymph Node Status Distribution

Tumor site	Arm A	Arm B
Oral cavity	54.2% (19)	45.7% (16)
Oropharynx	22.85% (8)	37.14% (13)

DOI: 10.21276/SSR-IIJLS.2024.10.5.16

Hypopharynx	2.28% (1)	0.00%
Larynx	20% (7)	17.14% (6)
Stage wise distribution		
Stage 3	74.2% (26)	85% (30)
Stage 4	25.8% (9)	15% (5)
Lymph node status		
Free	30.56%	45.71%
Fixed	47.22%	48.57%

At 3 months post-chemoradiotherapy, Arm A had a higher complete response rate (77.1%) compared to Arm B (62.8%). The partial response rate was slightly higher in Arm A (22.8%) than in Arm B (17.1%). Notably, no patients in Arm A experienced progressive disease, while 20% of patients in Arm B showed disease progression (Table 3).

Table 3: Treatment Response and Toxicity at 3-Month Follow-Up After Chemoradiotherapy

Response at 3 months after chemoradiotherapy	Arm A	Arm B
Complete response	27(77.1%)	22(62.8%)
Partial response	8(22.8%)	6(17.1%)
Progressive disease	0.00%	7(20%)

In terms of skin reactions, Arm A had a higher proportion of patients with Grade 1 reactions (71.4%) compared to Arm B (62.8%), while Arm B had more patients with Grade 2 reactions (25.7% vs. 14.2% in Arm A). Vomiting was more prevalent in Arm B, with more patients experiencing Grade 1 vomiting (62.8%) compared to Arm A (51.4%), although Grade 2 vomiting was more frequent in Arm A (14.2% vs. 5.7% in Arm B). Dysphagia was evenly distributed in both arms, with 42.8% of patients in each arm experiencing Grade 3 dysphagia. Mucositis was slightly more severe in Arm B, with more patients experiencing Grade 3 mucositis (25.7%) than in Arm A (20%) (Table 4).

Table 4: Comparative Analysis of Acute Toxicities Between Treatment Arms

Skin reactions	Arm A	Arm B
Grade 1	25(71.4%)	22(62.8%)
Grade 2	5(14.2%)	9(25.7%)
Vomiting		
Grade 1	18 (51.4%)	22(62.8%)
Grade 2	5(14.2%)	2(5.7%)
Dysphagia		
Grade 2	12(34.2%)	8(22.8%)
Grade 3	15(42.8%)	15(42.8%)
Mucositis		
Grade 2	16(45.6%)	17(48.5%)
Grade 3	7(20%)	9(25.7%)

DISCUSSION

As mentioned earlier, head and neck squamous cell carcinomas, or HNSCCs, are the sixth most common cancer type globally. Nearly 30% of all cases registered in a given year at our institution, the Netaji Subhash Chandra Bose Medical College and Hospital in Jabalpur, Madhya Pradesh, are related to head and neck cancer. The year our study was conducted, 2021, saw a total of 2641 cases registered at our institute; of those, 851 cases were for head and neck cancers, or approximately 32.226%, or nearly one-third of all cases registered. In locally advanced head and neck cancer, this study compares a single-centered experience with a modest hypofractionation dose of 2.2 Gy/fraction for five fractions per week to a total dose of 66 Gy / 30 fraction with concurrent weekly cisplatin treatment [15-17].

Out of the 70 patients, 49, or 70% of the patients, had a complete response that was assessed at the end of three months using the racist criteria. In our study, the control arm demonstrated a complete response in 22 patients, or 62.28% of the total patients, while the study arm demonstrated a complete response in 27 cases, or 77.14% of the study [18]. The study arm demonstrated a better competitive response than the control arm. Eight patients in the study arm—or 22.85% of the patients—saw a partial response, and six patients in the control arm—or 17.14% of the patients—saw a partial response. Twenty percent of the patients in the control arm experienced a progressive disease [14,15]. The P-value of 0.0194 was determined to be significant. In a study by Meena et al., patients with HNC were treated with either a conventional dose and fractionation (CDF) schedule (70 Gy at 2.0 Gy per fraction) to the gross tumor (primary and nodal) with reduced dose to the elective neck lymphatics, or a moderate hypofractionation (MHF) schedule (66 Gy total dose with 2.2 Gy per fraction to the gross tumor (primary and nodal) with standard dose fractionation (54–60 Gy at 1.8–2.0 Gy per fraction). The

DOI: 10.21276/SSR-IIJLS.2024.10.5.16

study's results were analyzed [18,19] The results of this study were similar to those of our study [20]. During the COVID-19 pandemic, Shao et al. conducted a study wherein they observed similar outcomes using hypofractionated radiation therapy alone, administering 2.4 Gy per fraction for head and neck cancer. The findings of this study suggested that hypofractionated radiation therapy be taken into consideration as an alternative to traditional chemoradiation therapy [21-23]. In addition to the obvious logistical benefits, radiobiological modeling indicates that standard 2.0 Gy fractionation is not as effective for controlling H&N tumors and reducing late effects as up to 3.0 Gy per fraction. Therefore, it would be very beneficial to follow a hypofractionation schedule to be radical or to achieve prolonged local control (LC), which can be accomplished without causing excessive discomfort or toxicity [21].

If we go deeper into radiobiology, we find that the α/β ratio is a measure of fractionation response; normal tissues that respond slowly are associated with low ratios (high α/β). In comparison to tumors, which typically have higher α/β ratios, a low ratio indicates a greater capacity for repair between fractions and greater relative sparing with smaller fraction sizes. For the majority of tumor types, under these circumstances, an improved therapeutic ratio can be obtained with multiple small fractions. The α/β ratios are thought to be related to tumors; however, they are usually 8 or higher, while the analyses of many experimental and some clinical outcome studies suggest values on the order of 3 or 4 or slightly less for late-responding normal tissues. However, there seem to be some exceptions to this general tumor response to fractionation. Effective cell cycle time, also known as growth fraction, has been frequently linked to the fractionation response. Generally, slowly proliferating normal tissues and certain tumors that proliferate slowly exhibit larger than expected fraction size responses or low α/β ratios. Because of this rationale, hypofractionated radiation therapy (HFRT), which uses a single 2.1–3.5 Gy fraction administered five days a week for approximately four weeks, has attracted a lot of attention recently [22].

Radiation therapy, whether administered with a conventional or hypofractionation regimen, inevitably results in toxicity. The total dose, the dose per fraction, and the amount of treatment time all affect the response of tumor and normal tissue to therapy as well as the probability of acute and late side effects. Radiation damage can rarely be repaired in a single exposure if the dose is given rapidly and at a high dose rate; additionally, the damage per unit of absorbed dose is high. Assuming the use of daily fractions, the hypofractionated regimen's overall treatment time (OTT) will be shorter than its conventionally fractionated comparator, potentially worsening acute toxicity. In our investigation, grade 2 dysphagia affected the greatest number of patients in both the study and control groups. Forty-five percent of the patients in both the study and control arms had grade 2 dysphagia. Just 10% of patients in the control arm had grade 3 dysphagia, compared to 25.71% of patients in the study arm. Similar findings were observed in the Behnmida *et al.* study, where grade 1, 2, and 3 dysphagia were present in 12 (16%), 13 (17.3%), and 2 (2.7%) of the patients [23].

Nonetheless, patients receiving treatment for dysphagia were frequently advised to maintain good oral hygiene, support their nutrition, and have a ryles tube inserted. The majority of patients who received treatment with a hypofractionated regimen were dependent on a feeding tube; in the study arm, 22% of patients had dependence for one month, 28.5% for two months, and 5% for three months. This is similar to findings from a study by Alexander et al. that showed rates of mucositis and grade 3 dermatitis with spontaneous resolution of 30% and 40%, respectively. Fifteen patients (75%) were offered nasogastric tubes during their treatment; four patients (20%) required feeding tubes after two months, and only one patient required a feeding tube after a year [24]. This was in contrast to the outcome in the control group, where patients relied less on ryles for nutrition because they did not have as severe dysphagia and oral ulceration. Patients in both groups experienced radiation-induced dermatitis, but the control arm experienced a greater skin reaction. The majority of patients in both groups—71.4% in the study arm and 62.8% in the control arm-suffered from grade 1 toxicity. In the study arm, 14.2% of patients experienced grade 2 toxicity, while in the control arm, 25.7% of patients experienced the same condition. There were no patients in either arm experiencing grade 3 toxicity [23,24].

CONCLUSIONS

The study concluded that hypofractionated radiation therapy can be preferred over conventional

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chemoradiation therapy because it offers a comparable clinical response with manageable toxicities. Additionally, its shorter treatment duration makes it particularly beneficial in resource-limited settings like India, especially during the COVID-19 pandemic or similar situations where minimizing hospital visits and stays is crucial. The hypofractionated regimen showed a higher complete response rate, although it caused prolonged but manageable radiation-induced mucositis. Dysphagia rates were similar between both treatment arms. Due to limited time and sample size, conclusions on overall survival and disease-free survival could not be drawn, requiring longer follow-up. However, the shorter treatment duration of the hypofractionated regimen is advantageous, particularly in resource-limited settings like India, where outpatient load is high. The study's relevance is underscored by the COVID-19 pandemic, which strained healthcare systems and increased the need to reduce hospital visits, as advised by ASTRO ESTRO guidelines. This makes hypofractionated radiation therapy an ideal choice during pandemics and similar situations, offering comparable efficacy with manageable toxicity.

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