INTRODUCTION:

Locally advanced head and neck carcinomas are treated with multimodality approaches like surgery, radiation and chemoradiation, but substantial number of patients with squamous cell carcinoma of the head and neck (HNSCC) are unsuitable 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.

Considerations for an optimal radiotherapy (RT) schedule are significant tumor regression and symptom control within a short overall treatment time (OTT) with minimal side effects. Frequently some form of hypofractionation is opted for. The benefit of an increased tumor cell kill because of the large fraction size in a short OTT is counteracted, from radiobiological point of view, by an increased potential for late side effects. Several trials have demonstrated improvements in loco-regional tumor control from altered fractionation radiotherapy as compared with conventional fractionation. Studies have shown that although most centers adopt conventional 2 Gy fractionation, a substantial proportion of patients receive a hypofractionated prescription with larger doses per fraction, such as 48 Gy in 16 fractions.

COMPARATIVE STUDY ON CONVENTIONAL VERSUS HYPOFRACTIONATED RADIOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK CANCER.

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Abstract

Aim: A prospective comparative study To assess Treatment response, Toxicities and Survival in locally advanced Head and Neck squamous cell carcinoma (HNSCC) who are unfit for surgery with hypofractionated radiotherapy. Material and Methods: In this trial, hundred patients attending our OPD with locally advanced Head and Neck Cancers excluding nasopharynx, unfit for surgery, treated between 2010 - 2012 were taken for the study. Among 100 patients, 50 patients were randomly allocated to receive conventional radiotherapy, of total dose 66 Gy RT at 2 Gy per fraction over 6.3 weeks, with or without concurrent chemotherapy. 50 patients received hypo-fractionated RT of total dose 48 Gy at 3 Gy per fraction over 3 weeks with or without concurrent chemotherapy. The end points were treatment response, toxicities and survival. Results: Fifty patients (male: 37, female: 13) were included in the analysis in Arm1 (Conventional RT). Among 50 patients in Arm2 (Hypofractionated RT), 39 males and 11 females. All patients in both arms had advanced head and neck cancers who are not fit for surgery (60% IVA, 40% stage III, 9%). Planned radiotherapy without any interruptions was completed by all patients in both arms. patients. Fifty patient selected in conventional radiotherapy 58% had complete response, 20% had partial response, 12% had static response and 6% progressed at one year which shows comparable treatment response favouring hypofractionated RT. However, significant differences in incidence of toxicity (mucositis, skin reactions, late grade ≥ 2 dysphagia, laryngeal edema, xerostomia, etc) were found, with higher occurrence in Hypofractionated RT that is 22%, and 10% in conventional RT arm. Severe late toxicity was 38% in hypofractionated RT and 24% for conventional RT. The median survival was 19 months and 40% survived ≥1 year after RT in hypofractionated RT. In conventional RT arm the median survival was 22 months nearly 52% survived more than one year. The actuarial rates of loco-regional control, disease-free survival and overall survival were 70%, 32% and 40% at 1-year, respectively and 32%, 14% and 17% at 3-years, respectively for hypofractionated RT and for conventional RT locoregional control rate, DFS, OS were 80%, 36%, 44% At one year, 40%, 15%, 20% At 3years, which is comparable with conventional RT. Conclusion: Hypofractionated Radiotherapy in a shorter treatment duration can achieve similar treatment response to conventionally fractionated radiotherapy in locally advanced Head and Neck Cancers, with manageable toxicities. Key words : Hypofractionated RT, Conventional RT, HNSCC

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(3 Gy/fraction). This regimen has the theoretical advantage that the treatment is completed before accelerated repopulation becomes a significant radiobiologic factor. The objective of this study was to investigate tumor response in HNSCC using hypofractionated radiotherapy compared with conventional fractionation with or without concurrent chemotherapy.

**SUBJECTS AND METHODS:**

**Study design**: Randomized controlled trial  
**Study setting**: Department of Radiotherapy, Madras Medical College.  
**Inclusion criteria followed were:**  
Biopsy proven newly diagnosed loco regionally advanced squamous cell carcinoma of the head & neck.  
Primary tumor sites: oral cavity, oropharynx, hypopharynx, larynx.  
Age 20-60 years  
Stage IV A locally advanced squamous cell carcinoma.  
Patients unfit for surgery (due to co-morbidity and poor performance status).  
Previously not exposed to any chemo or radiotherapy  
**Exclusion criteria followed were:**  
Non Squamous Histopathology  
Tumors of nasal cavity, paranasal sinuses and nasopharynx.  
Previously received treatment for any other malignancy.  
Stage IVB and stage IVC  
**Radiotherapy**  
All patients underwent simulation, and treatment was delivered with Theratron Phoenix Tele Cobalt-60 using conventional two-dimensional treatment planning. Patients were immobilized in a supine treatment position in a custom-made head-and-neck mask manufactured in the mould room. All patients underwent simulation, using conventional X-ray simulation. The radiation field encompasses the gross disease (primary tumor and/or nodal disease) with a 1 cm margin. Two lateral fields were mostly used to treat the primary tumor and/or upper neck with a matched anterior field, as needed for the supra clavicular region. The intended radiation dose was 60 Gy in 30 fractions of 2 Gy, given 5 days a week in conventional RT arm and patients with hypofractionated arm treated with 3Gy/day for 16 fractions 5 days a week total of 48Gy (biologically equivalent to 60 Gy in 2 Gy fractions using an α/β ratio of 10). After 10 fractions, the spinal cord was shielded by field shifting in hypofractionated arm and for conventional RT arm field spinal cord shielded after 20 fractions. (Surface bolus was used for nodal disease with skin invasion or fungation and treatment was delivered with Theratron Phoenix Tele Cobalt-60 using conventional two-dimensional treatment planning)  
**Endpoints**  
End points of the study were response rates (complete response [CR], partial response [PR], and overall response rate [ORR]) (ORR = CR + PR), loco-regional control (LRC), disease-free survival (DFS), overall survival (OS), acute and late toxicity. The treatment response was evaluated radiation oncologist 6-8 weeks after completion of RT and was done by clinical examination and by CT of the head and neck. Given the potential for differential response at primary and nodal sites in the same patient, the treatment response was recorded as CR only when both primary and nodal disease disappeared completely. If there was any residual disease (either locally or regionally), the case was recorded as PR. Patients in whom the primary tumor and/or nodal disease did not respond to RT were recorded as stable disease (SD), while patients who progressed during or directly after the treatment were recorded as progressive disease (PD). LRC were reported. Local and/or regional failures were recorded as events. Patients died from intercurrent disease without evidence of loco-regional failure were censored at the moment of death. DFS was measured from the date of completion of treatment to the date of first relapse (locoregional or distant metastases) or death. Acute and late toxicities were evaluated by the radiation oncologist during each visit of patients to the outpatient clinic of our hospital according to the RTOG/EORTC acute and chronic radiation morbidity scoring criteria. All patients were encouraged to maintain oral food intake and in case of difficulty, 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 RT.  
**Follow-up**  
Following completion of treatment, patients were followed up 2-monthly for the first year, 3-monthly for the second and third year and 6-monthly thereafter. At each visit, medical history and routine clinical ENT-examination were performed, including flexible naso endoscopy, when indicated.  
**Statistical analysis**  
Survival rates were calculated from the completion of
treatment using Kaplan-Meier technique. Possible predictive clinical factors for ORR, DFS and OS (tumor site, tumor stage, age, sex, use of chemotherapy, RT-schedule, performance status, and co-morbidity), were tested using the χ² test. All significance tests were two-sided and statistical significance was accepted for a calculated p-value of < 0.05.

RESULTS:

Patient, tumor, and treatment-related characteristics
In each Arm 50 pts were selected with a total of 100 patients. Arm1, 37 were males and 13(74% male and 26% female) were females. 78% male and 22% female. The mean age was 57.88 years (Range: 30-70 years). 80 % was addicted to some form of tobacco. Among them, 54% were addicted to smoking and 8% to chewable tobacco, 20% to both smoking and alcohol. Oral cavity tumors tumors were (26%), followed by oropharynx 24% and larynx 14% in Arm1. 22% oral cavity, 44%oropharynx, hypopharynx 16% and larynx 18%. Histologically, 54% of the tumor was moderately differentiated, 24% well-differentiated and 22% in arm1 and 56%, 28%, and 16% in Arm2.

Treatment-related toxicities and feasibility
The radiotherapy schedule was well-tolerated about 75% of the patients completed the planned radiation therapy without any break during the treatment. As per the assessment of toxicity (RTOG) grade >3 mucositis and dermatitis occurred in 22% and 9%, respectively in hypofractionated RT and 10% in conventional RT. The severe late toxicity was 38% in hypofractionated RT, 24% in conventional RT. One-fourth of the patients experienced severe pain which was treated as per the WHO pain ladder. Only two patients (5%) needed morphine for pain relief during the course of radiotherapy. Remaining patients had only mild to moderate pain.

<table>
<thead>
<tr>
<th>ACUTE TOXICITIES</th>
<th>Grade 0,1,2</th>
<th>Grade &gt;3</th>
</tr>
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<tbody>
<tr>
<td>ARM 1</td>
<td>40%</td>
<td>10%</td>
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<tr>
<td>ARM 2</td>
<td>60%</td>
<td>22%</td>
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Table-1 incidence of acute toxicities

Response assessment
Response evaluation was done periodically after completion of treatment based on clinical examination and contrast enhanced CT scan of head and neck, at one year and at 3yrs after completion of RT.

Patients were then categorized as per Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1) as having complete response (CR), partial response (PR), stable disease (SD), and progressive disease.

<table>
<thead>
<tr>
<th></th>
<th>Conventional RT</th>
<th>Hypofractionated RT</th>
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<tbody>
<tr>
<td>Complete response</td>
<td>38%</td>
<td>68%</td>
</tr>
<tr>
<td>Partial response</td>
<td>20%</td>
<td>16%</td>
</tr>
<tr>
<td>Static disease</td>
<td>12%</td>
<td>10%</td>
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<tr>
<td>Progressive disease</td>
<td>6%</td>
<td>6%</td>
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</tbody>
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Table-2 : Response assessment

Survival
The median was 22 months in conventional RT (52% survived for 1 year) and 19 months in hypofractionated RT (40% survived for 1 year). locoregional response rate were 80% in hypofractionated RT, 70% in conventional RT arm favouring hypofractionation.

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<thead>
<tr>
<th></th>
<th>Conventional RT</th>
<th>Hypofractionated RT</th>
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<tbody>
<tr>
<td>LRR</td>
<td>70%</td>
<td>80%</td>
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<tr>
<td>DFS</td>
<td>32%</td>
<td>15%</td>
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<tr>
<td>OS</td>
<td>40%</td>
<td>20%</td>
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</tbody>
</table>

Table-3 : 36 months survival

DISCUSSION:
Locally advanced head and neck cancer constitutes about 25% of cancer burden in clinical practice in developing countries like India. Response of inoperable locally advanced head and neck cancer to aggressive treatments including chemoradiotherapy is poor and is associated with significant treatment-related toxicities. In India, about 70-75% cases of head and neck cancer present in a locally advanced stage with a significant portion in an inoperable stage. Instead of Palliation of distressing presenting symptom like painful ulcer, throat pain, swallowing difficulty, and breathing difficulty, The main objective of treatment is to extend the DFS (Disease free survival), with minimal treatment-related toxicities.

In order to strike a balance between radio biologically effective dose and overall treatment duration, the present dose fractionation scheme was selected. Total dose selected was based on the only randomized study of
hypofractionated radiotherapy in advanced head and neck cancer. The scheme had a high patient compliance rate. It also had the advantage of less opportunity of tumor repopulation. From radiobiological, economic and logistical points of view, hypofractionated schedule would be the most suitable option. First, the treatment is completed before accelerated repopulation becomes a significant radiobiologic factor. Second, the reduction in the number of fractions also allows a more efficient use of resources, which can help avoid long waiting times for other patients and lastly, considering that this group of patients are usually of age and often have a poor performance status as well as significant co-morbidities, it is almost mandatory to keep the OTT (overall treatment time) as short as possible. Because of the aforementioned advantages of a hypofractionated treatment schedule, we treated this group of HNSCC unsuitable for surgery, options with 16 fractions of 3 Gy per fraction comparable with conventional fractionation.

An optimal dose fractionation schedule with hypofractionated radiotherapy in head and neck cancer is yet to evolve even though there are some guidelines for curative settings. Current evidence seems to favor short course palliative radiotherapy schedule than single fraction or protracted course of radiation. Historically, during the World War II, 3-5 weeks regimen was shown to be superior to 1-4-8 days regimen (28% vs. 3% control rate at 3 years for laryngopharyngeal cancer) in Christie Hospital, Manchester as highlighted by Paterson in the Mackenzie Davidson Memorial lecture in 1952. Patients treated with palliative intent decision on dose and fractionation is often based on the feasibility, quality of life, and palliation rather than on survival or radiobiological considerations. Various hypofractionated palliative radiotherapy schedules have been reported in the literature from Western countries as well as from India. A detailed review of the palliative radiotherapy schedules for locally advanced head and neck cancer and their major findings are as follows: One randomized study reported by Weissberg et al., compared conventionally fractionated radiation of 60-70 Gy (over 6-7 weeks) with 40-48 Gy (over 2-3 weeks). Hypofractionated schedule was found to be equivalent to the conventional fractionation, in terms of palliative benefits and response with about 75% incidence of grade III mucositis. Various dose escalation schedule were tried for hypofractionated schedule tried for palliative setting. In our schedule, about almost all patients completed the planned treatment without any interruption. The incidence of grade III or more mucositis was acceptable. More than 80% patients achieved complete response with better LRR with the median survival of 19 months. The protocol leads to significant reduction in hospital stay time for patients and machine time for treatment. The rate of hospitalization due to treatment was reasonably low, which is comparable to that in the literature. The study by Weisberg et al. and the present study clearly shows the relevance, benefit, and feasibility of hypofractionated short course radiotherapy in this condition.

**CONCLUSION:**

In conclusion, our hypofractionated RT regimen of 3Gy in 16 fractions with a dose of 48 Gy is an effective ATTEMPT CURATIVE schedule controlling symptoms and disease in patients with advanced HNSCC who were deemed unsuitable for curative surgery in view of poor performance status. Centres with large volume of patients treated with the single cobalt machine favoring hypofractionated RT with shorter duration and beneficial for treating larger volume than conventional methods. Despite this pessimistic starting-point of the study, excellent local and symptom control was achieved in the majority of patients. As we proceed with an agenda of improving outcomes for our HNSCC patients.

**REFERENCES:**


Acknowledgement:
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