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Original Article

Treatment of Locally Advanced Squamous Cell Carcinoma of Head and Neck with Hybrid Accelerated Radiotherapy and Concurrent Chemotherapy

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Abstract

Introduction: Head and neck cancer is the most common cancer in India. Overall, 57.5% of global head and neck cancers occur in Asia, especially in India. Even though anatomical subsites of head and neck regions are accessible to clinical examination, 60–80% of patients in India report with locally advanced disease in comparison with developed countries which is 40% only. Concurrent chemoradiation remains the standard treatment approach in locally advanced head and neck cancers. Conventional radiation schemes with 3 weekly cisplatin produce a response rate of 50–60% only in locally advanced head and neck cancer. Studies reveal that tumor clonogen repopulation might be one of the most important factors determining treatment outcome. Various retrospective studies and clinical trials have shown that an increase in tumor control can be achieved by shortening treatment time using altered fractionation schemas.

Aim: In this present work, we made an attempt to improve the therapeutic ratio by hyperfractionation and accelerated radiation regimens.

Methods: To achieve the above, 30 patients of locally advanced squamous cell carcinoma with different disease status were chosen. Patients subjected to hybrid accelerated radiotherapy with total dose of 72 Gy along with cisplatin 100 mg/m^2 were given on day 1 and day 22. Complete response rate in primary T2, T3, and T4 tumors is 100%, 86.95%, and 16.67%, respectively.

Results: Complete response rates attained by N0, N1, and N2 nodes are 100%, 100%, and 50%, respectively. 16.6% had Grade 2 mucositis and 50% had Grade 3 mucositis. 80% had Grade 3 and 20% had Grade 2 skin toxicities. No Grades 3 and 4 hematological toxicities such as anemia, leucopenia, or thrombocytopenia were observed.

Conclusion: Hence, we suggest that combination of hybrid accelerated radiotherapy and cisplatin mono-chemotherapy, with manageable, although substantial, toxicity as an effective alternative regimen to treat head and neck cancer.

Key words: Head and neck cancer, Hybrid accelerated radiotherapy, Locally advanced squamous cell carcinoma, Telecobalt acceleration radiation, Tumor clonogen repopulation

INTRODUCTION

Overall, 57.5% of global head and neck cancers occur in Asia, especially in India, for both sexes.[1] Head and neck cancers in India accounted for 30% of all cancers in males. In females, they constitute 11–16% of all sites of cancers. 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.[3] Regional differences in the prevalence of risk factors are the reason behind the variability in incidence and pattern of head and neck cancer. Anatomical subsites of head and neck region though highly accessible to clinical examination, in India, 60–80% of patients report with locally advanced disease in comparison with developed countries which is 40% only.[2]

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Head and neck cancer is the most common cancer presenting to our oncology department. 25–30% present in the early stage of disease, with 70–80% in advanced stage of presentation. Conventional radiation schemes with 3 weekly cisplatin produce a response rate of 50–60% in locally advanced head and neck cancer. Evidence-based oncology has shown that local control can be increased by altered fractionation schemas, by making use of the differential response of tumor cells and normal cells to radiation.[4] Hybrid accelerated radiation schema employs reduced treatment duration, with alteration in fraction size, total dose, and number of fractions per day. The study protocol delivers a total dose of 72 Gy over 5.5 weeks, where a single dose of 2 Gy is delivered daily up to 40 Gy, and then, radiation dose is accelerated by delivering two doses of 1.6 Gy per day after the 28th day, as significant measurable accelerated tumor repopulation starts by 28 days in squamous cell carcinoma of the head and neck (SCCHN)[5] and extra dose of 0.5–0.8 Gy/day is needed to tackle the repopulation during fractionated radiotherapy.[6-9] Start of hyperfractionation after the 28th day produces enhanced tumor cell kill by exploiting the R's of radiobiology, namely Reoxygenation, Repopulation, and Redistribution. Thus, entire treatment is completed within 5.5 weeks as compared to 7 weeks in conventional radiation, with a total dose of 72 Gy aiming to increase the locoregional control by challenging accelerated tumor repopulation. Cisplatin a platinum analog an established radiosensitizer effectively gets rid of tumor cells along with radiation by fixing the sublethal damage also. Cisplatin has equivalent cytotoxic effect on the micrometastasis. The use of concomitant (platinum based) chemotherapy has an absolute survival benefit of 6.5% at 5 years.[10]

Aim

This study aims to assess the immediate locoregional response rates of locally advanced unresectable squamous cell carcinomas of the head and neck treated with hybrid accelerated radiotherapy and concurrent cisplatin days 1 and 22.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Radiotherapy, Madras Medical College in previously untreated patients with locally advanced squamous cell carcinomas of head and neck from March 2013 to October 2013. The study population consisted of 30 patients with histologically proven locally advanced squamous cell carcinoma, registered in our department. Recruitment of patients was started after obtaining approval from ethics committee of our institute. Information sheet was provided to all 30 patients with explanation about the study design, risks, and benefits of study. Patient consent was obtained from all patients included in the study in their local language.

Inclusion Criteria

Biopsy-proven squamous cell carcinoma of the head and neck, primary tumor sites eligible: oral cavity, oropharynx, hypopharynx, larynx, age <70 years, Stage III or IV disease, non-metastatic disease (AJCC staging manual 7th, edition 2010), ECOG PS 0–2, diabetes, and hypertension under control were included in the study.

Exclusion Criteria

Patient not consenting to chemotherapy at any point in the treatment, previously received treatment for any other malignancy, tumors of nasal cavity, paranasal sinuses, salivary glands and nasopharynx, non-squamous histopathology, primary tumor involving bone or cartilage, recurrent tumors, inadequate hepatic, renal functions, bone marrow reserve, and pregnant females were excluded from the study.

Pre-treatment Investigations

The study population underwent pretreatment investigations which included complete history and physical, Biopsy from tumor, Complete blood count (CBC), WBC >4000/cu mm, Hb >11 g%, Platelet count >1,00,000/cu mm, Renal Creatinine Clearance ≥50 ml/min calculated by COCKGROFT AND GAULT FORMULA, Serum creatinine ≤1.2 mg/dl, liver function tests (LFT) serum total bilirubin ≤1.2 mg/dl, Blood Grouping and Typing, computed tomography (CT) scan Neck (From base of skull to Root of Neck) – Plain and Contrast, Chest X ray – posteroanterior view, Dental evaluation, Weekly CBC, renal function tests, LFT during radiotherapy and chemotherapy, staging was done based on American Joint Committee staging manual 7th edition (for head and neck cancers).

Therapeutic Protocol

Equipment: Telecobalt machine (Theratron Phoenix).

Patients received total dose of 72 Gy which was delivered by 20 daily fractions of 2 Gy (40 Gy) followed by 20 fractions of 1.6 Gy twice daily (32 Gy). Patients received radiation 5 days a week and cisplatin 100 mg/m^2 was given on day 1 and day 22. External beam radiation was delivered by telecobalt at SSD of 80 cm.

Radiation Regimen

Three-phase dose prescription

Phase I: Treatment field included the primary tumor plus 2 cm margin, nodal volume which included clinical and radiologically involved nodes and those nodal levels that have high risk of subclinical disease in the drainage area.

FIELD I was delivered a dose of 40 Gy by 20 fractions of a single dose of 2 Gy per fraction.

Phase II: On day 29 and 30, FIELD I was delivered 1.6 Gy twice a day with a time interval of 6 h between two fractions. Dose delivered to FIELD I by Phase II was 6.4 Gy.

Phase III: Boost treatment volume included primary tumor and significant nodes (clinically palpable and radiologically significant) plus 1 cm margin. The dose for boost is 1. 6 Gy twice a day for 8 days. Boost volume received a dose of 25.6 Gy.

Total dose = 72 Gy = Phase I (40 Gy) + Phase II (6.4 Gy) + Phase III (25.6 Gy)

Uninvolved lymph node stations were delivered a prophylactic dose of 46.4 Gy while the confirmed nodal disease received 72 Gy as for the primary.

Maximum allowed OTT = 6 weeks.

Chemotherapy Regimen

Drug cisplatin: Total dose per cycle 100 mg/m^2 on day 1 and day 22 in three divided doses (50 mg × 3 mg).

Procedure of chemotherapy administration

Patients were advised to have 2 L of oral fluids on the previous day of chemotherapy. 500 ml of ringer lactate was given as prehydration.

Patients were reassessed clinically and radiologically with contrast CT from base of skull to root of neck 6 weeks after completing hybrid chemoradiation based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1 version) criteria.

RESULTS

A total of 30 patients were enrolled into the study. 26 patients of the study sample were male and four patients were female. 63.66% of patients were in ECOG Status I and 36.66% of patients were in ECOG status II. 18 of 30 patients had oropharyngeal primary (60%), among which tonsil primary was observed in 12 patients, five patients had involvement of base of tongue and one patient had soft palate primary. 5 of 30 patients had hypopharyngeal primary (10%), among which pyriform fossa primary was observed in four patients and one patient had post-cricoid primary. Oral cavity primary was noted in four patients and laryngeal primary was observed among three patients, all of which had supraglottic involvement. 76% of patients belonged to T3 stage, followed by T4 stage among 20% of patients and 3% of patients belonged to T1 stage. 76% of patients belonged to T3 stage followed by T4 stage among 20% of patients and 3% of patients belonged to T1 stage. 43.34% of patients were grouped as Stage III, 50% of patients as Stage IV A, and 6.66% of patients in Stage IV B. 70% of patients had moderately differentiated tumor, 16.67% had well differentiated, and 13.33% had poorly differentiated tumor. Among 30 patients treated with hybrid accelerated chemoradiotherapy, 73% of the study population showed complete response and 26% of patients showed partial response. People aged <50 years achieved a higher complete response as compared to people ≥50 years. Patients with ECOG 1 status achieved 85% complete response and patients with ECOG 2 status attained only 54% complete response. T2 tumors produced 100% complete response. T3 tumors produced 86.95% complete response and the response of 16.67% was seen for T4 tumors. Higher complete responses were seen in N0 and N1 nodes and lesser complete responses were seen in N2 nodes. Highest complete response was seen in oropharyngeal (88.89%). Oral cavity cancers showed 50% complete and 50% partial response. In this study, laryngeal and hypopharyngeal cancers showed partial response only. Moderately differentiated cancers responded better to chemoradiation. Moderately differentiated cancers showed 85.7% complete response rates and 14.29% partial response rate; poorly differentiated cancers showed equal complete and partial response rate. Well-differentiated tumors showed 40% complete and 60% partial response rate.

About 33.33% of patients developed minimal injection of the mucosa (Grade 1), 16.67% of patients developed patchy mucositis (Grade 2), and 50% of patients developed confluent mucositis (Grade 3). 80% of the study population showed Grade 2 toxicity and 20% showed Grade 3 toxicity. 26% had Grade 1 and 73% had Grade 2 xerostomia. 26.67% of patients developed Grade 2 laryngitis. 60% and 23% of the study population had Grade 3 and Grade 2 pharyngitis, respectively. Nasogastric tube insertion was done for 60% of the study population. 25 patients had hemoglobin >11 gm% (Grade 0 anemia); five patients had a fall during treatment with hemoglobin between 9.5 and 11 gm% (Grade 1 anemia). 73.34% of patients had loss of appetite without alteration in food habit (Grade 1); 26.66% of patients had diminished oral intake without significant weight loss and dehydration due to nausea (Grade 2). 66.66% of patients had once or twice vomiting on the day of chemotherapy (Grade 1) and rest of the patients had 3–5 episodes of vomiting in 24 h. None had Grade 3 vomiting (6 times).

DISCUSSION

Concurrent chemoradiation remains standard treatment approach in locally advanced head and neck cancers. The standard regimen of concurrent chemoradiation in head and neck delivers a total radiation dose of 66–70 Gy along with single-agent chemotherapy using cisplatin 100 mg/m^2 D1, D22, and D43. Conventional radiotherapy has a local control of 40–50% in locally advanced head and neck squamous cell carcinoma. Therefore, attempts have been made to improve the therapeutic ratio by hyperfractionation and acceleration radiation regimens. Various retrospective studies and clinical trials have shown that an increase in tumor control can be achieved by shortening treatment time.[11,12] It indirectly suggests that tumor clonogen repopulation might be one of the most important factors determining treatment outcome. The present results of this study also support this suggestion. In comparison with chemoradiation treatment strategies attempted in this institution, this treatment protocol showed comparable outcome. A concurrent chemoradiation study conducted in this institution with conventional radiation and concurrent chemotherapy using cisplatin (3 cycles) had yielded a complete response rate of 69% and acute Grade-III toxicity rates of 61.6%. Another study that evaluated hyperfractionated radiation therapy and concurrent cisplatin-5FU chemotherapy (2 cycles, weeks 1 and 5) recorded a complete response of 73.1% and acute Grade-III toxicity of 62%. Thus, with a marginally increased, but acceptable level of toxicity the response rate and feasibility achieved in this study is improved by about 6–10%. A study which evaluated accelerated radiotherapy 6Fx/Wk along with cisplatin as radiosensitizer (20 mg/m^2) once a week for 6 weeks in advanced HNSCC showed a complete response of 80% and Grades III and IV acute toxicity in 48%. So far, hybrid accelerated radiotherapy has been tried in head and neck in two trials. Leuven *et al.*, in 2001, enrolled 73 patients with SCCHN and treated them with hybrid accelerated radiotherapy, delivering a total dose of 72 Gy. Hybrid accelerated radiotherapy had complete response in 90.4% of patients, with partial response in 9.6% of patients. Leuven *et al.*, in 2004, treated 90 patients with SCCHN with hybrid accelerated radiotherapy along with two cycles of cisplatin every 21 days. However, improvement in outcome through the intensification of RT regimens and/or the addition of chemotherapy comes at the cost of increased acute and perhaps also late toxicity. In our study, the increase in both acute mucositis and dysphagia (leading to higher pain rates) since the use of concomitant chemotherapy was noted. Soon after the introduction of this regimen, it became evident that feeding support was required in almost all patients (82%) and percutaneous endoscopic gastrostomy tube placement before the start of treatment would be advantageous.

CONCLUSION

These data show that it is feasible to combine hybrid accelerated radiotherapy and cisplatin mono-chemotherapy, with manageable, although substantial, toxicity. The hospital stay is reduced. Hence, it is an effective alternative regimen in centers with high work overload.

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