

**Original Article**

## Palliative single agent Methotrexate followed by Hypo-fractionated Radiotherapy in Advanced Inoperable Head and Neck Cancer not suitable for definitive treatment

Authors

**Dr Jitendra Kumar Verma<sup>1</sup>, Dr SN Prasad<sup>2</sup>, Dr Pramod Kumar Singh<sup>3</sup>,  
Dr Mangesh Korde<sup>4</sup>, Dr Dharmaraj<sup>5</sup>**

<sup>1</sup>MD Radiotherapy, FAROI. Assistant Professor, JK Cancer Institute, Kanpur

<sup>2</sup>MD Radiotherapy, HOD and Professor, JK Cancer Institute, Kanpur

<sup>3</sup>MD Radiotherapy, Assistant Professor, JK Cancer Institute, Kanpur

<sup>4</sup>MD Radiotherapy

<sup>5</sup>Junior Resident, MD Radiotherapy, JK Cancer Institute, Kanpur

**Abstract**

**Context:** *Locally advanced oral cavity cancer with fungating mass or fistula formation are incurable. The number of cases with such advanced stage are increasing due to late diagnosis or negligence. Also, these patients have limited life expectancy.*

**Aim:** *To evaluate the symptomatic response, improvement in Quality of Life and acute toxicity after Injection Methotrexate followed by Palliative Radiotherapy.*

**Methods and Material:** *total of 54 Patients registered in our institute who were histo-pathologically proven as squamous cell carcinoma of oral cavity with inoperable stage IV and KPS > 70 were chosen for study. All patients received 6 doses of weekly injection Methotrexate followed by Palliative dose of 16Gy with 4Gy single fraction weekly for 4 consecutive weeks. Patients were evaluated after 4 weeks of completion of Radiotherapy for disease response (WHO criteria), symptomatic response, acute toxicities (RTOG) and quality of life (UW-QOL).*

**Results:** *Most common presenting complaint was pain followed by dysphagia and discharge from fun gating mass. Majority of patients (70-80%) got 90% relief from their presenting symptom. In our study, we observed Partial Response (PR) in majority of patients i.e. 89%. RTOG toxicity grading of the patients showed grade one and two acute skin and mucosal toxicities one month after completion of treatment about 41% and 18% respectively.*

**Conclusion:** *Combined MTX with Palliative weekly Radiotherapy proved good for symptomatic response and relief and improved Quality of Life and also helpful in decreasing burden of machine.*

**Keywords:** *Palliative Methotrexate, Hypofractionation in Advanced Head and Neck.*

**Introduction**

Head and neck cancer is one of the highly prevalent cancers in developing countries like India<sup>[1,2]</sup>.

The epidemiology and biology of head and neck cancer in developing countries are different from that of developed countries.<sup>[4]</sup> Therefore, the treatment data from Western literature should be

extrapolated with caution in developing countries like India.

Also In the developing world, approximately 75% of patients with head and neck malignancies present with locally advanced disease.

Among Indian population, incidence of head and neck cancer had estimated 12.48 and 5.52 per 100,000 populations in male and female respectively. Estimated mortality is about 3.48 and 1.34 per 100,000 in male and female, respectively<sup>[3]</sup>.

In most cases, due to extensive locoregional involvement, poor general condition of the patient, or comorbid conditions curative treatment is not possible. Therefore, the relevance of aggressive treatment in unresectable locally advanced head and neck cancer has been questioned<sup>[4,5,6,7]</sup>.

The intent of treatment in such cases is to improve the quality of life of the patients keeping their socioeconomic condition in mind and judiciously utilizing the precious resources for curable conditions

At our center, the registry of year 2011 recorded 1106 new cases of head and neck cancer which constitute about 24.7% of total registered patients. The common malignancies registered were carcinoma of tongue: 287 (25.94%), Buccal mucosa: 254 (22.96%), palate: 84(7.5%), Lip:60 (5.4%), Gingivo Buccal Sulcus :69(6.2%), Alveolus: 31(2.8%) ,tonsil: 160 (14.46%), laryngopharynx: 66 (5.9%), nasopharynx: 24 (2.16%) and post cricoid 71(6.41%).

Majority of head and neck cancer patients present with advanced, incurable stage and around 50% dying from uncontrolled locoregional disease..

This prospective observational study is designed to report the feasibility of a short duration, hypofractionated, palliative radiotherapy schedule along with Methotrexate for locally advanced inoperable head and neck cancer for palliation of cancer-related distressing symptoms. Occurrence of acute treatment-related toxicities (RTOG criteria) and improvement in quality of life (based

on UW-QOL v4) a baseline and at completion of radiotherapy is also compared

### Subjects and Methods

In our study, 54 previously untreated patients with histopathologically proved locally advanced inoperable head and neck squamous cell carcinoma with hard fixed cervical node(s) were included from December 2014 to July 2015.

Patients with stage IV AJCC (American Joint Committee on Cancer) with hard fixed cervical nodes, Karnofsky Performance Status,>70 with life expectancy <1year were included. Patients were treated by Intramuscular Methotrexate 50mg weekly for six cycles followed by external beam radiotherapy delivered by Cobalt-60 teletherapy machine (Theratron 780E/780C). A total dose of 16Gy was given in 4 fractions on weekly basis (every Saturday) with a dose of 4Gy per fraction. Treatment volume included primary tumor site plus neck region. Bilateral Parallel-opposed fields were planned where disease crossing the midline and had bilateral presentation and dose was being prescribed to midline. Surface bolus was used in fun gating mass or lymph nodes. These patients were evaluated weekly during Radiation and on completion of Radiation and 4 weeks after completion of radiation and assessed for treatment response in terms of disease control (tumor regression) using WHO criteria<sup>[8]</sup> and palliation of symptoms using symptomatic response grading. Acuteskin and mucosal reactions grading was done as per RTOG (Radiation Therapy Oncology Group) toxicity criteria. Further treatment of patients was done according to tumor regression status.

Quality of life assessment was done by obtaining baseline details and compared with assessment done after completion of treatment. QOL questionnaire were being validated in local language (Hindi).

### Results

The baseline characters of the patients were represented in Table 1. Overall, the number of

male patients is much higher than the female patients. Median age was 55 years and ranges from 40 to 65 years. Most of patients had KPS 70. Most common presenting complaint was pain followed by dysphagia. Buccal mucosa was most commonly involved sites. Commonly observed histology was moderately differentiated squamous cell carcinoma.

Treatment related toxicities are shown in Table 2. None of the patients experienced radiation toxicities that required hospitalisation. Almost all

patients showed grade one and two acute skin and mucosal toxicities at one month after completion of treatment.

Symptom burden at presentation and symptomatic relief on follow-up visits are shown in table 3. Majority of patients (70-80%) had appreciable relief in their presenting symptoms.

Overall treatment response at one month follow-up is shown in Table 4. In our study, we observed Partial Response (PR) in majority of patients (89 %) and no patient had progressive disease.

**Table 1** Patient Characteristics

| Variables               |   | Number of Patients |
|-------------------------|---|--------------------|
| Sex                     | Male  | 53 (88.33)         |
|                         | Female  | 07 (11.66)         |
| Main Complaint          | Pain  | 60 (100%)          |
|                         | Dysphagia                                       | 43 (71.66)         |
|                         | Discharge                                       | 46 (76.66)         |
| Primary site of disease | Right buccal Mucosa                             | 22 (36.66)         |
|                         | Left buccal mucosa                              | 19 (31.66)         |
|                         | Lip   | 02 (3.33)          |
|                         | Alveolus + Gingivobuccal sulcus + Buccal mucosa | 17 (28.33)         |

**Table 2** Acute toxicity evaluation at 14<sup>th</sup> day

|                  | Grade I      | Grade II    | Grade III  | Grade IV |
|------------------|--------------|-------------|------------|----------|
| Skin Toxicity    | 41 (75.92%)  | 13 (24.07%) | 0          | 0        |
| Mucosal Toxicity | 18 (33.33 %) | 32 (59.25%) | 04 (7.40%) | 0        |

**Table 3:** Symptomatic Response in Main Complaints

| Main Symptom at Presentation | Symptom Relief |                              |                                  |
|------------------------------|----------------|------------------------------|----------------------------------|
|                              | No Relief      | Partial Relief (~50% relief) | Significant Relief (~90% relief) |
| Pain                         | 02 (4%)        | 12 (22%)                     | 40 (74%)                         |
| Dysphagia                    | 02 (5%)        | 07 (16%)                     | 34 (79%)                         |
| Discharge                    | None           | 05 (10%)                     | 41 (90%)                         |
| Otalgia                      | 05 (20%)       | 04 (16%)                     | 15 (62.5%)                       |

**Table 4:** Overall Treatment Response on Day 30th

|                        |             |
|------------------------|-------------|
| Complete Response (CR) | 04 (7.40%)  |
| Partial Response (PR)  | 48 (88.88%) |
| Stable Disease (SD)    | 02 (3.70%)  |

## Discussion

In developing countries like India Locally advanced head and neck cancer constitutes about 25% of cancer burden in clinical practice.<sup>[09]</sup> While aggressive treatment with chemo-radiotherapy in inoperable locally advanced head and neck cancer is poor and with significant treatment related toxicities.<sup>[10]</sup>

In India, about 70-75% cases of head and neck cancer present in a locally advanced stage with a significant portion of patients in an inoperable stage<sup>[11]</sup>. So, Palliation of distressing presenting symptom like painful ulcer, throat pain, swallowing difficulty, and breathing difficulty remains the main objective of treatment,<sup>[12]</sup> with minimal treatment-related toxicities. Also

improvement of quality of life and cost benefit issues are more important than increasing the life expectancy in such cases.<sup>[10]</sup> In India, most of the government tertiary cancer centers like that of ours are overloaded with patients. Also the number of newly registered and untreated patients are increasing yearly according to our patient registry data of last few years which indirectly signifies the increasing number of cases in state like Uttarpradesh.

So In order to strike a balance between radiobiologically effective dose and overall treatment duration, the present dose fractionation scheme was selected. High Dose per fraction was selected based on the only previous randomized study of palliative radiotherapy in advanced head and neck cancer, which showed equivalent results between Hypofraction vs conventional Radiotherapy<sup>[13]</sup>.

In "Hypo Trial" twice weekly treatment was given to reduce the number of hospital visits, so we planned once weekly treatment schedule as prior Injection Methotrexate was also given and improve patient compliance.<sup>[14]</sup>

Also an optimal dose fractionation schedule for palliative radiotherapy in head and neck cancer is yet to evolve even though there are some guidelines for curative settings.<sup>[15]</sup>

Weissberg et al.<sup>[13]</sup> evaluated conventionally fractionated versus hypofractionated palliative External Beam Radiation Therapy (EBRT) schedules for patients with locally recurrent or advanced head and neck cancers. That study compared 60 Gy to 70 Gy in 6 to 7 weeks versus 40 Gy to 48 Gy in 64 patients with stages III and IV surgically unresectable squamous cell carcinoma of the head and neck. No differences were noted in tumor control, acute side effects, or long term sequelae.

Current evidence seems to favor short course palliative radiotherapy schedule than single fraction or protracted course of radiation.<sup>[09]</sup>

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<sup>[16]</sup>. Various hypofractionated palliative radiotherapy schedules have been reported in the literature from Western countries as well as from India.

In a large study, on 505 patients with stage IV head and neck squamous cell carcinoma, Mohanty et al gave a uniform regimen of 20 Gy/5 Fractions, once daily over 1 week. They reported good symptomatic relief (>50% for pain, 53% for dysphagia, 57% hoarseness, 47% otalgia, 76% for respiratory distress and 59% for cough ). At one month assessment, 189 (37%) achieved a partial response and had ambulatory physical state suited for further curative-dose radiotherapy. The main acute toxicity of palliative radiotherapy was patchy oro-pharyngeal mucositis and dermatitis. Median overall survival was 200 days. One hundred fifty three patients who went on to receive further curative dose had significantly overall survival of 400 days<sup>[17]</sup>.

At Tata Memorial Hospital, Agarwal *et al.*,<sup>[11]</sup> used a schedule of 40 Gy in 16 fractions. Patients who had partial response had a dose escalation up to 50 Gy in 20 fractions. The incidence of grade III mucositis was 69%. About 74% patients had more than 50% symptom relief. Overall progression-free survival was 55% at 1 year. The cohort had 22% less than T4 disease, 17% less than N2 disease. Weight (>50 kg) and radiotherapy dose (>40 Gy) were significant prognostic factors for progression-free survival. Two palliative radiotherapy schedules were reported from PGI Chandigarh for a small group of patients (30 Gy in 10 fractions for  $n = 25$  and Quad Shot regimen for  $n = 15$ ). In the former study, all the 22 out of 25 patients had relief of pain which lasted for about 3 months. Only 16 patients came for follow-up and more than 50% patients had to travel over 50 km. to come to the hospital.<sup>[5]</sup> So This is a real situation in India especially in UP and our experience parallels to that of the above authors.

Our study which was also conducted in similar way, reported good symptomatic relief (more than

74% for pain, 79% for dysphagia, 90% discharge and otalgia 62%). The main acute toxicity of palliative radiotherapy was similar to above studies. At one month assessment 88.88% patients achieved partial response. Thus our protocol leads to no hospital stay for patients and better patient compliance. Also in a setup like ours it helped in reducing the patient burden on machine and increasing more slots on machine for curative patients. The rate of hospitalization due to treatment was reasonably low. The median survival was 6 months which is comparable to that in the literature.

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