

## **Original Article**

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# **Clinical and radiobiological comparison of two palliative regimens of radiotherapy in advanced squamous cell carcinoma of head and neck: a prospective randomized study**

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### **Abstract:**

*Objective: The aim of this study is to compare two different palliative radiotherapy regimes - standard hypofractionated regime and split course hypofractionated regime in advanced head and neck cancer.*

*Methods: 60 untreated patients of advanced squamous cell carcinoma of head and neck who were treated with palliative intent were randomized into two arms: Arm A (n=30) patients received 30 Gy in 10 fractions in two weeks; Arm B (n=30) patients received 1750 cGy in 5 fractions followed by a three weeks gap and then again 1750 cGy in 5 fractions, treatment completed in 5 weeks.*

*Result: The response was comparable in both the arms. Symptom palliation was also similar; pain relief was 76% in both arms and relief of dysphagia 73% in arm A vs 79% in arm B. Partial response rate was equivalent (69% vs 62%). Mucositis and upper GI toxicity did not show any significant difference. Patient drop out was only 1 in arm B compared to 4 in arm A. The  $BED_{10}$  values are 39 and 37.84 in arm A and B respectively; whereas the  $BED_3$  values are 60 and 75.8.*

*Conclusion: We conclude that the second regime can also be used in palliative setting in some selected patients.*

**Key words:** Advanced head and neck cancer, Palliative Radiation.

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### **Introduction:**

Squamous cell carcinoma of head and neck (SCCHN) is one of the commonest cancers seen in India, constituting around 25% of the overall cancer burden. It is the commonest cancer among males in India. The vast majority of them present with loco-regionally advanced disease where achievement of cure is difficult. Advanced SCCHN bears a poor prognosis and patients usually die of uncontrolled loco-regional disease. The five-year survival of advanced SCCHN even with

aggressive treatment is less than 20%, with a median survival of around 12 months. Moreover by aggressive therapy, these patients suffer from radiation toxicities that further compromise their quality of life.

It is widely recognized that palliative radiotherapy (PRT) provides effective palliation and improved quality of life in advanced incurable malignancies and accounts for a significant portion of cancer care across the world. But insufficient information precludes estimations of the frequency, degree or duration of symptomatic relief from palliative radiation of head and neck cancer. The medical literature is flooded with radiotherapy of curative intent – varieties of dose, fractionation and concomitant chemotherapy. But very few publications are available in palliative setting. Naturally, there is a paucity of guidelines in current literature regarding the optimal choice of palliative regimens for these patients with inadequate information on time, dose, fractionation and toxicity of such palliative regimens. Keeping this in view, we have designed this trial of palliative regime for these patients.

In India, the patients either have to travel a considerable distance to the treatment centre daily or have to stay for a long period outside their native place for receiving radiation therapy. This is due to limitation in resources both in terms of personnel and radiation equipment. Moreover, arrangement for staying of patient and relative is not readily available in many big cities. Hence, compliance of the standard two week regime of PRT is not good. In this context, we have tested a split course radiotherapy regime in these patients.

We are aware that unnecessarily extended treatment times could theoretically reduce the duration of tumor regression and symptomatic relief. As in the case of radical radiotherapy, continued tumor cell repopulation over the

period of the gap can be expected to reduce the effectiveness of radiotherapy as treatment time increases. The present study considers the issues associated with this clinical situation by including the radiobiological analysis of palliative treatments.

In this setting, we report our experience with a hypofractionated radiotherapy regimen and a split course radiotherapy regimen for palliation of loco-regionally advanced and incurable SCCHN; both radiobiologically as well as by clinical outcomes.

### **Methods:**

#### **Patient selection:**

From Jan 2008 to June 2010, a randomized prospective study was performed with 60 patients who met the following inclusion criteria:

- Age 18 year or more
- Patients of histology proved squamous cell carcinoma of head and neck
- Stage III or IV disease
- Previously untreated
- Performance status: Eastern Co operative Oncology Group ~1 and 2
- Signed informed consent

#### **Treatment protocol:**

They were randomized into two arms by sequential randomization according to their attendance in OPD:

- Arm A - (n=30) patients received 30 Gy in 10 fractions in two weeks.
- Arm B - (n=30) patients received 1750 cGy in 5 fractions followed by a three weeks gap and then again 1750 cGy in 5 fractions, treatment completed in 5 weeks.

The primary endpoints of the study included symptom palliation (dysphagia and pain), compliance and toxicity profile while the

secondary end point was the assessment of response.

#### Patient evaluation:

All the patients have undergone detailed history taking, thorough physical examination, complete blood count, liver Function Test, kidney Function Test, chest skiagram and USG abdomen as baseline evaluation.

Radiation was given by Telecobalt machine with conventional planning. The portals were mostly lateral parallel opposed fields; occasionally direct anterior field was also given. Patients were monitored weekly during radiotherapy for compliance, toxicity and nutritional support. After completion of therapy, follow up was done every week for first month and then monthly to evaluate response and toxicities. Symptom palliation (pain and dysphagia) was recorded 4 weeks after completion of radiotherapy.

Toxicity was recorded according to Radiation Therapy Oncology Group Acute Radiation morbidity Criteria and tumor response by Response Evaluation Criteria in Solid Tumor (Complete Response, Partial Response, Stable Disease and Progressive Disease). For symptom palliation, subjective response was considered. The following grades were used: Grade 0 – no improvement, Grade 1 – slight improvement, Grade 2 – moderate improvement, Grade 3 – remarkable improvement.

All significance tests were done using Student's unpaired t test and Fisher's exact test and statistical significance was accepted for a calculated p-value less than 0.05.

#### Evaluation of treatment regime:

Two regimes of radiotherapy were compared radiobiologically by Linear-Quadratic model, applying the formula  $BED = nd [1+d/(\alpha/\beta)]$ . Here, BED= Biologically Effective Dose, n= number of fractions, d= dose per fraction.  $\alpha$  and  $\beta$  are measures of the relative importance of lethal and sub lethal damage. The ratio  $\alpha/\beta$

is the dose in which the linear and quadratic components of the cell damage are equal.

The BED, which is proportional to the cell kill, will be reduced during the gap period due to repopulation of tumor cells. To allow for this, the formula will be  $BED = nd [1+d/(\alpha/\beta)] - \ln 2 (T-T_a)/\alpha T_p$ , where  $T_p$  = potential doubling time in days,  $T_a$  = time of beginning of accelerated repopulation and T = overall treatment time in days.

During calculation, the accepted values of  $T_p$ ,  $T_a$  and  $\alpha$  are 4 days, 2 weeks & 0.35 respectively, for head and neck cancer. The comparison was done regarding both acute and late effects between two regimes. The standard value of  $\alpha/\beta$  for acute effects is accepted as 10 and that of late effect is 3.  $BED_{10}$  (considering  $\alpha/\beta$  value 10) predicts acute effects and tumor control. For late effects the BED is designated as  $BED_3$  (considering  $\alpha/\beta$  value 3).

#### Results:

##### Demography:

The characteristics of the two arms are summarized in Table I. All the baseline profiles in two arms were comparable.

**Table-I**  
*Demography*

Characteristic	Arm A (n=30)	Arm B (n=30)
Age		
Range	51 yr - 83 yr	52 yr - 75 yr
Median Age	68 yr	69 yr
Sex		
Male	28 (94%)	27 (92%)
Female	2 (6%)	3 (8%)
Mean ECOG	2	2
Site		
Larynx	4 (13%)	5 (17%)
Oropharynx	16 (54%)	14 (48%)
Hypopharynx	10 (33%)	11 (35%)
Stage		
III	6 (20%)	5 (17%)
IV	24 (80%)	25 (83%)

**Treatment compliance:**

In arm A, 4 out of 30 patients did not complete the radiation. Two patients left after 5th fraction, whereas other two after 7th and 8th fraction, respectively. The cause was 'could not tolerate radiation' for two cases and no place to stay near hospital and urgent work at home for other two. In arm B, only one patient failed to comply. He didn't come for second half of radiation. [Table-II]

**Table-II**  
*Treatment Compliance*

	Arm A (n= 30)	Arm B ( n=30)
Drop out	4	1
Completed	26	29

**Symptom palliation:**

Excluding the drop out cases, evaluable patients were 26 in arm A and 29 in arm B. Symptom palliation was excellent and similar in both the arms. Moderate to good relief of pain was observed in 76% patients of both arms (p value 1.00). [Table III] The corresponding figures are 73% and 79% for relief of dysphagia in arm A and arm B. (p value 0.73). [Table-IV]

**Table-III**  
*Symptom Palliation: Pain relief*

	Arm A (n=26)	Arm B (n=29)
Grade 3	12 (46%)	13 (45%)
Grade 2	8 (30%)	9 (31%)
Grade 1	6 (24%)	7 (24%)

**Table-IV***Symptom Palliation: Dysphagia relief*

	Arm A (n=26)	Arm B (n=29)
Grade 3	10 (38%)	13 (45%)
Grade 2	9 (35%)	10 (34%)
Grade 1	7 (27%)	6 (21%)

Duration of symptom control was also similar in two arms, median duration of symptom control being 4 and 5 months in arm A and arm B respectively. [Table-V].

**Table-V***Duration of symptom control (in months)*

	Arm A	Arm B
Range	2 to 9	3 to 11
Median	4	5

**Tumor Control:**

Majority of the patients had partial response and none had complete response. The response was comparable in both the treatment arms (69% vs 62%; p value 1.00). [Table-VI].

**Table-VI**  
*Tumor Control*

	Arm A (n=26)	Arm B (n=29)
PR	18 (69%)	18 (62%)
SD	7 (27%)	9 (31%)
PD	1 (4%)	2 (7%)

**Toxicities:**

All 60 patients were considered for toxicity since all of them had received at least one fraction of radiotherapy. The most important toxicities were mucositis and upper

gastrointestinal. Pain and dysphagia were not considered as toxicity since they were present at baseline in majority of patients. The incidence of toxicity did not show any significant difference. [Table VII]

**Table-VII**  
*Toxicity profile*

Toxicities	Arm A (n=30)	Arm B (n=30)
Mucositis: (Grade 2 & above)	10 (67%)	8 (27%)
Upper GI (Grade 2 & above)	13 (43%)	9 (30%)

**Radiobiological comparison:**

BED<sub>10</sub> values which predict tumor control and acute effects are comparable in both the arms. For late effects BED<sub>3</sub> predicts increased late effects in arm B. [Table VIII].

**Table-VIII**  
*Radiobiological Comparison*

	Arm A	Arm B
Acute effects (BED <sub>10</sub> )	39	37.84
Late effects (BED <sub>3</sub> )	60	75.8

**Discussion:**

In the absence of reliable and robust prognostic factors, it is often difficult to identify subsets of patients with advanced disease best suited for palliative therapy alone as compared to those in whom radical treatment could still be considered. The factors which we have considered in choosing patients for palliative intent treatment alone are i) inoperable, fixed and unresectable disease; ii) very advanced loco-regional disease not amenable to cure; iii) poor physical condition and medical co-morbidities and vi) short life-expectancy.

Best supportive care alone is associated with a median survival of three to six months in advanced SCCHN<sup>1</sup>, and there is no definite guideline regarding the use of palliative head and neck radiotherapy, but several retrospective series<sup>2,3,4</sup>, case-control studies, single arm prospective trials<sup>5,6,7</sup> affirm that its use is associated with an improvement in outcome in the form of symptom palliation.

In the last decade or so, clinical trials and consensus guidelines utilizing short-course PRT have evolved for several incurable solid tumors such as bone metastases,<sup>8</sup> and lung cancer.<sup>9,10</sup> No such large prospective randomized controlled trial has been done for PRT in advanced incurable SCCHN. It has been argued that a higher total dose is needed for growth restraint and sustained palliation in head-neck cancers. Various dose-fractionation schedules that have been used in the aforementioned sites have been extrapolated for use in palliative head-neck radiotherapy. Although the quality of evidence is not very robust, the weight of evidence favors a short-course fractionated regimen (20 Gy/5 fractions or 30 Gy/10 fractions) as compared to single fraction or protracted courses of radiotherapy.

Most of the trials reported retrospective data or single arm prospective study. A study used a higher dose regimen for palliation in inoperable head and neck cancer patients.<sup>11</sup> They treated 58 patients with split-course radiotherapy, 50 Gy/20 fractions with concurrent bleomycin and a 2-week break after the first 25 Gy. This regimen was associated with a local control rate of 69% with median response of seven months. Symptomatic improvement was seen in 81% of patients, but grade 3 toxicity was found in 79% patients.<sup>11</sup>

Twenty five patients with advanced SCCHN were treated with a short course of PRT (30

Gy / 10 fractions/2 weeks.<sup>5</sup> Baseline symptoms were assessed with an 11-point numerical scale for pain, dysphagia, cough, insomnia and dyspnea. At 1-month post treatment, all patients with pain and more than 90% patients with dysphagia, dyspnea and insomnia experienced significant symptom relief. The median duration of response was 3 months. No patients experienced grade 3 or worse toxicity.<sup>5</sup>

In a study 40 Gy used in 16 fractions to treat 110 patients of advanced head and neck carcinoma with palliative intent where 57% of the patients had moderate & 17% had good symptomatic improvement.<sup>12</sup> Another series used a split course regime of 20 Gy in 5 fractions over one week, a two week gap and then a further 20 Gy in 5 fractions. They have reported a symptomatic improvement in 79% of patients.<sup>13</sup>

Our trial is unique in that we have compared the split course regime with the standard palliative regime in a prospective randomized fashion. Here, symptom palliation in both the arms was good and comparable. There was no dose limiting toxicity. Compliance to therapy is better in split course regime due to shorter out station-stay at a time and some relief of radiation toxicity during the gap period.

In our split course regime,  $BED_{10}$  is comparable with that of standard regime which means acute effects and tumor response will be same. Higher value of  $BED_3$  with split course radiation predicts increased late effects, but since the treatment was given in palliative settings and the patients did not have prolonged life expectancy, it did not have any clinical significance.

#### **Conclusion:**

To conclude, this split course palliative regime is an alternative to standard palliative regime and can be better accepted in our country.

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