What Did the Pandemic Teach Us About Palliative Radiation in Head and Neck Cancer?

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Abstract

Objective: To assess the feasibility and efficacy of palliative radiotherapy dose regimens for patients with locally advanced head and neck cancer.

Methods: Fifty patients of previously untreated, inoperable, stage IVA and IVB squamous cell carcinoma of the head and neck, deemed unfit for radical treatment, were included in the study from May 2020 to June 2020. Two palliative radiotherapy regimens were used. First was a single fraction radiation with 8 Gy for patients with limited life expectancy and poor performance status, which was repeated after 4 weeks in case of good symptom relief. The second regimen was used for patients with good performance status and consisted of fractionated radiation with 30 Gy in 10 fractions over 2 weeks, which was followed by supplementary radiation with 25 Gy in 10 fractions over 2 weeks in patients with good symptomatic response at 2 weeks. Symptoms were assessed at baseline and at the end of 4 weeks after treatment completion using the numerical rating score. Patients were followed up for a median of 4.5 months and assessed for symptom control and overall survival.

Results: Forty-eight patients completed treatment and were included for analysis. Of the 24 patients who received single fraction radiation, 13 (54.2%) were given the second dose. Improvement in pain and dysphagia were reported in 57.9% and 60% patients, respectively. A total of 55.5% noted decrease in size of the neck node. Twenty-four patients received fractionated radiation and 15 (62.5%) were given the second course after 2 weeks. Relief in pain and dysphagia was reported in 68.2% and 63.6% patients, respectively. There were no grade 3/4 toxicities. Symptom control lasted for at least 3 months in 30% of the patients who received single fraction radiation and 54.2% of the patients who received fractionated radiation. The estimated 6-month overall survival of the entire cohort was 51.4%. Conclusion: Judicious use of palliative radiation in advanced incurable head and neck cancers provides effective and durable symptom relief and should be used after careful consideration of patient prognosis, logistics of treatment, and goals of care.

Keywords
head and neck cancer, palliation, radiotherapy, pandemic, symptoms

Introduction

Patients with locally advanced head and neck cancer (HNC) often present with extensive locoregional involvement, poor performance status, and comorbid conditions that preclude aggressive curative therapy. These patients experience a range of distressing symptoms including pain, dysphagia or odynophagia, airway compromise, bleeding, and cosmetically distressing tumor bulk. The overall prognosis remains poor, and definitive curative-intent therapy is usually associated with significant toxicity, in addition to the burden of daily treatment fractions over several weeks. Such toxicity negatively affects the quality of life (QoL) and outweighs the benefits of potentially curative treatment.

Palliative, hypofractionated radiotherapy for locally advanced inoperable HNC provides high chance of symptom control with low treatment-related toxicities and short treatment time. There is no international consensus on the schedule of palliative radiotherapy and many different regimens have been proposed, often based on local practices and infrastructure settings.

The importance of palliative short-course radiotherapy became more pronounced amid the COVID 19 pandemic, which, accompanied by difficulties in transportation, limited availability of staff and resources for supportive care, made it difficult for Radiation Oncology departments to execute prolonged treatment courses for all patients. Therefore, we conducted a prospective study to assess the feasibility and efficacy of palliative radiotherapy dose regimens for patients with locally advanced HNC. The primary objective was to estimate the extent of symptom relief at the end of 4 weeks after the last fraction of radiotherapy. Secondary objectives were to

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evaluate the duration of symptom relief, treatment toxicity, and overall survival (OS).

**Methods**

This prospective study was conducted at a tertiary care center in North India with approval from the departmental ethics committee. Patients of previously untreated, inoperable, stage IVA and IVB (American Joint Committee on Cancer (AJCC) eighth edition) squamous cell carcinoma of the head and neck, deemed unfit for radical treatment were recruited in the study from May 1, 2020, to June 30, 2020. Subsites included were the oral cavity, oropharynx, larynx, and the hypopharynx. Written informed consent was taken from all study participants prior to start of radiotherapy.

**Patient Selection**

Treatment regimen was chosen by the treating physician and directed by the performance status, disease extent, symptom burden, prognosis, and goals of care. In addition, availability of social support, travel, and accommodation facilities were important considerations that determined regimen selection.

Two dose regimens were used in this study. Patients with poor performance status and prognosis, distressing tumor bulk, and symptoms (bleeding/fungating tumors, airway compromise, and pain causing difficulty in positioning) were assigned to a single fraction regimen with a dose of 8 Gy, which was repeated after 4 weeks if there was a good symptomatic response. This regimen was also chosen for patients in need of reduced travel and hospital burden amid the pandemic. Symptom relief and comfort with minimal risk of treatment-related toxicity was the primary goal of care in these patients.

In patients with better performance status and intermediate prognosis, who were candidates for durable palliation and were willing to undertake daily hospital visits for a period of 2 weeks, a fractionated dose regimen of 30Gy/10#/2weeks was used. Supplementary radiation with 25Gy/10#/2weeks was delivered to patients with good symptom relief at 2 weeks, after sparing the spinal cord. Treatment toxicity was assessed using the Common Terminology Criteria for Adverse Events v5. Radiation portals were marked manually and covered the gross primary and nodal disease with a 2 cm margin. All patients were treated on telecobalt machine with 2D-conventional technique using parallel-opposed lateral fields.

**Symptom Assessment**

Symptoms were assessed at baseline and at 4 weeks after the last treatment fraction using an 11-point numeric rating scale. Symptoms were rated by the patient on a scale of 0 to 10 and graded as mild (score 1-3), moderate (4-6), and severe (>6). Analgesics were prescribed in accordance with the World Health Organisation (WHO) pain ladder. The percentage reduction in size of neck nodes was also recorded. Patients who were not able to come for follow-up were contacted telephonically and assessed for symptom control. For patients who received the second course of fractionated or single fraction radiation, symptoms were assessed at 4 weeks from the completion of second course. Patients who received fractionated radiation and were deemed unsuitable for second course at 2 weeks were reassessed for symptom control at 4 weeks from the last fraction.

**Follow-Up**

Patients were followed up at 4 weeks after treatment completion and at 2 monthly intervals thereafter. The duration of symptom control was noted.

**Statistical Analysis**

Descriptive statistics were used to analyze the demographic profile of patients, treatment characteristics, and the percentage symptomatic response. Symptom response (no response/worsening vs response) in both groups was compared using the $\chi^2$ test. Kaplan-Meier curves were used to estimate the OS, which was calculated from the date of start of therapy to the date of death due to any cause or the date of last follow-up. Log
rank test was used to compare OS in both treatment groups. All statistical analyses were carried out using the statistical package for social sciences (SPSS) v25.

**Results**

Fifty patients were enrolled in the study. Of these, 2 patients failed to complete treatment due to difficulty in transportation and were excluded from the analysis. Forty-eight patients completed treatment and were followed up for a median of 4.5 months (range 2-7 months). Majority of the patients (81%) were males and the median age was 57 years. The most common site was the oropharynx (37.5%) followed by the oral cavity (31.3%). All patients had a Karnofsky performance status between 50 and 70. Patient and disease characteristics have been included in Table 1.

**Baseline Symptom Assessment**

The most frequent complaints were dysphagia (87.5%) and pain (85.4%). Pain was graded as mild in 1 patient, moderate in 11 patients, and severe in 29 patients. Similarly, dysphagia was reported as mild in 9 patients, moderate in 18 patients, and severe in 15 patients. Neck swelling was reported in 13 (27%) patients. Of these, 8 patients had N3 disease.

**Dose Regimens**

Twenty-four patients received single fraction radiation with a dose of 8 Gy. Of these, 13 (54.2%) were given a second dose of 8 Gy after a gap of 4 weeks. Twenty-four patients received fractionated radiotherapy with a dose of 30Gy/10#/2 weeks. Fifteen (62.5%) patients went on to receive supplementary radiation with 25Gy/10#/2 weeks after a gap of 2 weeks.

**Post Treatment Symptom Control**

**Single fraction group.** In the single fraction group, 11 (57.9%) of the 19 patients who presented with pain had some form of pain relief. Of these, 7 (36.8%) patients had >50% relief. Five patients did not experience any change in severity while worsening was reported only in 3 patients. Of the 20 patients who complained of dysphagia, 12 (60%) experienced an improvement in severity and 9 (47.4%) of these showed >50% improvement. Worsening of dysphagia was seen in 5 (26.3%) patients. Among the 9 patients with neck nodes, nodal size reduced by >50% in 3 (33.3%) patients, by <50% in 2 (22.2%) patients and was unchanged in 2 (22.2%) patients. Only 2 patients had progression at the nodal site without any bleeding or ulceration (Table 2).

**Fractionated group.** In the fractionated arm, 15 (68.2%) of the 22 patients who presented with pain reported some degree of pain relief, along with the reduction in analgesic requirement. Of these, 9 (41%) patients had >50% improvement. Two patients did not experience any pain relief while it worsened in 5 patients. Fourteen (63.6%) of 22 patients with dysphagia experienced symptomatic relief, with >50% improvement in 10 (45.5%) patients. Worsening of dysphagia was seen in 6 patients. One of the 4 patients with neck nodes had >50% decrease in size after treatment while it remained stable in 2 patients (Table 2). There were no unscheduled treatment breaks and no grade 3/4-skin or mucosal toxicity.

The percentage symptom relief was comparable in both treatment groups (P = .360), indicating that single fraction radiation was equally effective in terms of providing symptom relief. Overall, symptom relief persisted for at least 3 months in 30% patients in the single fraction group and 54.2% patients in the fractionated group. Strong opioids were required only in 4 patients throughout the course of treatment and follow-up.

**Survival.** At a median follow-up of 4.5 months (range 2-7 months), 16 (33%) patients had died (11 patients in the single fraction group and 5 patients in the fractionated group). The median OS was 5 months (range 4-6 months) in patients who received single fraction radiation, while it was not reached in the fractionated group. The estimated 6-month OS in the fractionated group was 54% (Figure 1A). The OS was higher in patients who received fractionated radiation (P = 0.046). This is attributed to the criteria guiding treatment selection. Patients with worse baseline prognosis were chosen to receive single fraction radiation rather than the fractionated schedule. The responders in the fractionated group were given an additional supplementary radiation to maximize the durability of local control and OS. The estimated 6-month OS of the entire cohort was 51.4% (Figure 1B).

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**Table 2. Percentage Symptomatic Response After Radiotherapy in Both Treatment Groups.**

| Symptom             | Single fraction radiation (N = 24) | Fractionated radiation (N = 24) |
|---------------------|-----------------------------------|---------------------------------|
| **Pain**            |                                   |                                 |
| ≥50% improvement    | 7 (36.8)                          | 9 (40.9)                        |
| <50% improvement    | 4 (21.1)                          | 6 (27.3)                        |
| No change           | 5 (26.3)                          | 2 (9.1)                         |
| Worse               | 3 (12.5)                          | 5 (22.7)                        |
| P value             | .526                              |                                 |
| **Dysphagia**       |                                   |                                 |
| ≥50% improvement    | 9 (45)                            | 10 (45.5)                       |
| <50% improvement    | 3 (15)                            | 4 (18.2)                        |
| No change           | 3 (15)                            | 2 (9.1)                         |
| Worse               | 5 (25)                            | 6 (27.3)                        |
| P value             | .942                              |                                 |
| **Neck swelling**   |                                   |                                 |
| ≥50% improvement    | 3 (33.3)                          | 1 (25)                          |
| <50% improvement    | 2 (22.2)                          | 1 (25)                          |
| No change           | 2 (22.2)                          | 2 (50)                          |
| Worse               | 2 (22.2)                          | 0 (0)                           |
| P value             | .067                              |                                 |
| **Overall symptom relief (P value)** | .360                              |                                 |
Discussion

Patients with advanced incurable HNC usually have poor prognosis with a limited life expectancy of 5 to 7 months.\(^\text{10,11}\) In such patients, treatment regimens consisting of radical chemoradiation are generally futile and are associated with significant morbidity that negatively impacts QoL. The primary goal of radiotherapy in such patients is effective palliation, which should provide symptom control, with minimal acute toxicity. Hypofractionated palliative radiotherapy regimens for HNC allow patients to complete treatment within a relatively short duration without significant unscheduled treatment breaks and offer tumor and symptom response with lesser toxicity than higher dose regimens.\(^\text{7,8}\) There is little high-level evidence and lack of consensus to direct the selection of an optimal palliative radiation regimen, which is often based on individual patient assessment and institutional practices.

This study was conducted during the ongoing COVID 19 pandemic, which was accompanied by a nation-wide lockdown, travel curbs, lack of public transport, and shutting down of patient shelters and financial aids, posing significant challenges for cancer treatment. Moreover, in a country like India, where patients mostly travel >100 km from home, belong to the lower socioeconomic strata and have negligible social support,\(^\text{12}\) it was important to optimize treatment schedules, keeping in mind the associated risks and benefits.

We used 2 palliative radiotherapy regimens, the selection of which was guided by the patient’s performance status, comorbidities, disease burden, risk of acute toxicity, and logistics regarding treatment delivery.

More than 55% of the patients who were treated with 1 or 2 courses of single fraction radiotherapy reported improvement in symptoms, with 60% reporting improvement in pain and dysphagia. Single fraction radiation was as effective as the fractionated regimen in providing symptom relief. The median OS in this group of patients was 5 months.

There have been numerous large trials comparing a single fraction of 8 Gy or 10 Gy with multiple-fraction, higher dose regimens in palliation of bone metastases and have documented equivalence in terms of symptom control.\(^\text{13-16}\) Single fraction regimens have also been studied in advanced cervical, endometrial, and other pelvic tumors.\(^\text{6}\) However, there is lack of published data on single fraction schedules for palliation of locally advanced HNCs.

The symptomatic response observed in our study with single fraction radiation is comparable with and even higher than studies that used other short-course palliative radiotherapy regimens like Quad Shot or 20 Gy in 5 fractions. In the Quad Shot approach used by Corry et al., 56% of the patients experienced pain relief and 33% had improvement in dysphagia. Median OS was 5.7 months.\(^\text{2}\) Ghoshal et al. reported improvement in scores for pain and dysphagia in 66% and 33% patients, respectively, after Quad Shot with significant improvement in QoL scores.\(^\text{17}\) No grade 3 toxicities were observed. In both prospective studies, the cyclical nature of the dose regimen enabled response assessment after each course, which guided the decision to proceed with another course. The same was possible with the single fraction regimen used in our study and 54% patients went ahead to receive the second dose. Some patients who were deemed suitable for the second course were still not able to receive treatment due to difficulties with transportation during the pandemic. These patients, however, still benefitted from the initial cycle of treatment. In a large retrospective study, Mohanti et al. reported 50% symptom response rate in patients treated with 20 Gy in 5 fractions. Patients with >50% tumor response were given further radiation till 70 Gy. Median OS was 6 months and all patients had patchy mucositis after treatment.\(^\text{3}\) Another regimen from Canada delivered 24 Gy
in 3 weekly fractions to 110 patients, majority with stage IV disease. The authors reported complete relief of symptoms in 40% and partial relief in 42% patients. 18 The “Hypo Trial” conducted by Porceddu et al. used 30 Gy in 5 fractions, with 2 fractions administered at least 3 days apart weekly. Sixty-two percent patients reported an overall improvement in QoL and 67% experienced improvement in pain. Median survival was 6.1 months. However, grade 3 mucositis was observed in 26% of patients, and 11% patients experienced grade 3 dermatitis and dysphagia. 19 Moreover, the overall treatment time in both schedules was long and not suited for outstation patients.

In HNC patients with a limited lifespan and poor performance status, single fraction treatment provides symptom palliation as effectively as multiple fraction schedules, as shown in our study. This regimen is an optimal intervention for such a group of patients because it involves one visit that includes consultation, dose planning, and delivery of a single fraction treatment. This was especially useful during the pandemic because it enabled us to reduce the number of hospital visits for these already frail and undernourished patients. Moreover, this regimen is also better suited for those who have difficulty with the positioning required for radiation delivery (ie, difficulty in breathing or severe, difficult-to-control pain while lying flat in a thermoplastic cast) and is more cost effective.

More than 68% of the patients who received fractionated radiotherapy experienced pain relief and 63% had improvement in dysphagia. All patients completed treatment with no grade 3 or 4 toxicity. Moreover, symptom control was durable and symptom relief persisted for at least 3 months in 54% of the patients. Patients who responded well to the first course were planned for supplementary radiation to maximize the durability of local control, and hence, improve survival. The estimated 6-month OS in this group of patients was 54%, which is in agreement with previous studies. 7, 8

This schedule with 30 Gy in 10 fractions has been reported previously in a prospective study by Ghoshal et al. which included patients of stage III and IV HNC. There was >50% improvement in symptoms in 90% of the patients, which is higher than in the present study. Relief of pain and other symptoms persisted for at least 3 months in 64% of the patients and no grade 3 toxicities were observed. 20 Ali et al. reported similar outcomes with the regimen of 30 Gy in 10 fractions in a prospective study of 30 patients. All patients had >50% pain relief and improvement in baseline dyspnea. A similar toxicity profile was also observed, with all patients having grade 1 or 2 mucositis. Twenty-seven percent of patients in the cohort went on to receive further radiation in 2 Gy fractions to a cumulative biologically effective dose of 66 Gy. 21

There are many limitations to this study. Tumour response was not assessed in our patients, as a detailed clinical and endoscopic assessment was not possible due to the ongoing pandemic and a radiological evaluation was irrelevant in the palliative care setting. Quality of life assessment was not done. The follow-up period was relatively short. Randomization was not performed and the treatment regimen was directed by the performance status, disease extent, symptom burden, prognosis, and goals of care. Symptom relief is a far more important goal of palliative treatment and we were able to provide effective palliation in a good proportion of patients with advanced HNC during the pandemic. We also demonstrated that single fraction radiation was as good as other multifraction regimens in providing symptom relief and should be considered optimal for patients with poor performance status and lower expected survival, who are likely to benefit from lesser number of hospital visits and reduced travel burden.

Conclusion

Judicious application of palliative radiation can provide effective and durable symptom relief. This study demonstrates the role of 2 palliative radiation regimens in the treatment of patients with advanced HNC. Both approaches are effective for symptom palliation and should be used after careful consideration of patient prognosis, logistics of treatment, and goals of care.

Authors’ Contributions

Concepts and design: SG; Data acquisition: AKS, NB; Data analysis: AKS, AG; Manuscript preparation: AG, AKS; and Manuscript editing and review: SG, AG

Declaration of Conflicting Interests

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