Research Article

Palliative head-and-neck radiotherapy with cyclical hypofractionated radiotherapy (Quad Shot): A single-institutional experience

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ABSTRACT

Background: This study aims to report on our institutional experience of palliative radiotherapy (RT) in the locally advanced head and neck by cyclical hypofractionated RT (Quad Shot) which is a short-course palliative regimen with good patient compliance, low rates of acute toxicity, and good response rates. **Objectives:** The objectives of the study were to review the use of the Quad Shot technique at our institution to quantify the palliative response in locally advanced head-and-neck cancer. **Materials and Methods:** Between April 2017 and July 2019, 45 patients with biopsy-proven squamous cell carcinoma of the head-and-neck region at the Department of Radiotherapy, Nil Ratan Sircar Medical College, Kolkata, which were deemed to be fit for palliative RT by departmental tumor board were given cyclical hypofractionated palliative RT as 14 Gy in four fractions over 2 days, twice daily, repeated every 4 weeks for a maximum of 3 cycles. Retrospective assessment was done for improvement in pain and dysphagia and also response to treatment. **Results:** Pain response occurred in 66.7% of the patients. The mean pain scores decreased significantly from pre- to post-treatment, 47.4 to 21.5 ($P < 0.0001$). The mean initial dysphagia score improved from 21.9 to 38.2 ($P = 0.0002$). About 60% of patients developed mucositis (≤ Grade 2), while no Grade 3 mucositis was reported. A total of 30 patients had partial response (66.67%) and 6 patients had stable disease. However, a total of nine patients had progressive disease which included those patients that were given fewer courses of Quad Shot. **Conclusion:** In locally advanced head-and-neck cancer patients particularly with poor performance status or elderly patients who are in dire need of some form of local therapy for symptom control and palliation, the hypofractionated palliative RT regimen (Quad Shot) offers an effective and quick treatment option which is beneficial both clinically and in logistics issue.

KEY WORDS: Head-and-Neck Cancers; Hypofractionated Radiotherapy; Quad Shot

INTRODUCTION

Head-and-neck malignancy in recent years has emerged as a major health problem all over the world. Asia contributes to 57.5% of the global head-and-neck malignancy among which more than 30% is contributed by India.[1-3] Head-and-neck malignancies rank as the sixth most common disease in males and seventh in females. It has wide variation with respect to demographic profile, food habits, etiological factors, and personal and family history making it a very unique. Head-and-neck malignancies are in the rise in India due to various factors as increasing longevity of population and increasing habit of consumption of tobacco-related products. This has led to the development of varying degrees of structural and functional deformities and dysfunctions depending on the site and size of head-and-neck malignancy. This ultimately leads to mutilation and decreases in quality of life (QOL). It is estimated that around 2 lakh head-and-neck malignancies occur every year in India.[4,5] Nearly 80,000 are diagnosed

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every year in the country.[6] It has been found that increased expression of p53 and Ki-67 is related to the progression of oral epithelial to neoplasia.[7] In comparison to developed countries, about 60–80% of patients in India present in advanced stage among all the patients of head-and-neck cancer. These patients have poorer prognosis compared to the less advanced stage patients. For these advanced-stage patients, radical which is often mutilating surgery and radiation therapy is generally advocated. External beam radiotherapy (RT) has been the mainstay for inoperable tumors; it, however, had a dismal 20% 5-year survival rate. Additional benefit though minimal has been achieved through change in fractionation schedule (accelerated or hyperfractionated) and different agents of radiosensitizers. The benefit of chemo-RT is put into debate by the severe toxicity encountered and the resultant morbidity, particularly in patients with other associated medical conditions. It has been found out that various scales of functional and symptomatic domains of QOL were significantly impaired at the end of RT and which, however, was either restored to or improved in comparison to pre-RT level, at 6 months after completion of RT. However, social functioning, nausea vomiting, appetite loss, dry mouth, and sticky saliva remained significantly deteriorated at the final assessment as compared to pre-RT level.[8] In general, a significant number of head-and-neck cancer population are unsuitable for aggressive definitive treatment due to other medical comorbidities, and their metastatic status or very advanced locoregional disease, or a combination of these factors. However, they require some form of treatment for their locoregional disease, for symptoms relief. For these patients, conventional chemo-RT is not a reasonable option due to the side effect profile. These patients are ideal candidate of palliative treatment. Usually, the most effective palliation regimen generates symptom reduction with minimal treatment-related side effects. Hypofractionated/split-course regimens are frequently used in elderly patients, especially the most fragile and critically ill patients so that the burden of a relatively long treatment, which generally is associated with tiring daily transportation, can be avoided. Several prospective studies have reported an association between the use of hypofractionated regimens and significant clinical benefit with minimal toxicities in the management of head-and-neck cancer. A cyclical hypofractionated palliative RT regimen, which had been successfully implemented for advanced pelvic malignancies (RTOG 8502),[9,10] has been successfully adapted for palliative treatment of head-and-neck cancers.[11] This protocol is implemented with 3.7 Gy twice-daily fractions given over 2 consecutive days per cycle with a rest period of 2–4 weeks between the 3 (maximum) prescribed cycles for a total dose of 44.4 Gy. As each cycle consists of four fractions over 2 days, this regimen has become widely known as the "QUAD SHOT regimen." The RTOG 8502 regimen for head-and-neck cancer palliative RT demonstrated tumor response rates of 53–77% with palliation or response achieved in over 80% of patients.[11-13] Minimal toxicity was reported among which Grade 3 toxicity ranged from 0% to 9%, of which mostly were mucositis.[11-13] Similar regimen of "QUAD SHOT" has been used successfully by S. Ghoshal *et al.* at PGIMER, Chandigarh. They had a radiation dose schedule of 14 Gy/4 fractions/2 days with a gap of 6 h between consecutive fractions. They showed an objective response rate of around 50%.[14,15]

This study in our institution with similar cyclical hypofractionated palliative RT regimen as palliative RT is to show the response rate and palliative/symptoms relief in selected locally advanced squamous cell carcinoma of the head-and-neck region. In our institution, elderly patients of advanced head-and-neck cancer who are put on longer duration palliative RT course face difficulty in daily commuting and often fail to complete the course. Hence, this short-course 2 days RT was started as it would be beneficial to these patients. This short-course cyclical hypofractionated palliative RT also has an advantage of decreasing the logistic burden on the telecobalt machine which is very beneficial in our setup with huge patient burden.

The limitations of our study and similar studies published are that they are single-armed studies with a short follow-up period and small number of patients. This prevents any comparative analysis with conventional schedules of radiation.

MATERIALS AND METHODS

Between April 2017 and July 2019, 45 patients of the head-and-neck malignancy (all histologically proven as squamous cell carcinoma) at the Department of Radiotherapy, Nil Ratan Sircar Medical College, Kolkata, which were deemed to be fit for palliative RT by departmental tumor board were given cyclical hypofractionated palliative RT regimen after proper informed consent. The data regarding the treatment and response of those patients were retrospectively analyzed.

The Institutional Ethical Committee was informed regarding this and consent was taken for the publication of the study.

The inclusion criteria were histologically proven squamous cell carcinomas of the head-and-neck cancer, Stage IV A/B (AJCC Staging System) with Karnofsky performance score between 50 and 70 which were deemed to be fit for palliative RT by departmental tumor board.[16] Prior radiation to the head-and-neck region was taken as exclusion criteria to prevent unacceptable toxicity to organs at risk. The "Quad Shot" radiation dose schedule was 14 Gy/4 fractions/2 days as described by Corry *et al*.[12] All the patients were treated in cobalt-60 teletherapy units and the gross tumor volume (including the primary tumor and involved nodes) with 2 cm margin was irradiated. Two fractions of radiation were delivered daily for 2 consecutive days with a minimum gap of 6 h between the two fractions, that is, total four fractions of radiation in 2 consecutive days. Patients were reviewed

approximately 3 weeks after each radiation for response and toxicities. Relief of presenting symptoms was compared after treatment completion. The tumor response was assessed by the WHO criteria,[17] while the Common Terminology Criteria for Adverse Events Ver. 4.0 was used for grading mucosal and dermal toxicities.[18] The summation of the length and breadth of the residual tumor mass was taken for measurement and comparison with the pre-treatment size. If the response was more than 50%, the "Quad Shot" dose was repeated. The biologically equivalent dose (BED) for one Quad Shot was 18.9 Gy10 and 30.33 Gy3 for tumor and late-reacting tissues. If the second Quad Shot was to be delivered, then the BED for the two shots together was 37.8 Gy10 and 60.66 Gy3 for tumor control and late complications, respectively. If the third Quad Shot was to be delivered, then the BED for the three shots together was 56.7 Gy10 and 91 Gy3 for tumor control and late complications, respectively. This is assuming that there is no repopulation between two fractions considering the small time interval. Assessment was done for improvement in pain using a verbal numeric pain rating scale (range 1–10, 10 being severe pain) and dysphagia using the dysphagia outcome and severity scale (range 1–7, level 1 being most severe), and also response to treatment. For pain and dysphagia, a linear transformation to 0–100 was applied to the raw scores. Score after linear transformation = ([Raw score – 1]/Range) × 100. Statistical analysis was done with SPSS ver. 25.

RESULTS

After receiving the first four fractions of radiation, an objective response of more than 50% was observed in 42 of 45 patients, and these patients were selected for the second course of this treatment. Incidentally, the response was applicable for both tumor and the nodal burden. Out of these 42 patients, 25 showed more than 50% response after the second Quad Shot course. When assessed 6 weeks after completion of radiation which included either single or multiple courses of radiation, 30 patients showed partial response to the Quad Shot regime, while 6 patients demonstrated stable disease. However, nine patients had progressive disease [Table 1].

A total of 27 patients reported having mucositis among which 18 were Grade 1 and 9 were Grade 2, but no reported incidence of any higher grade of mucositis was found. Only 20 patients were found to have Grade 1 dermatitis. Before radiation, pain and difficulty in swallowing were the chief complaints in most of the patients. After "Quad Shot," pain score improved in 30 of 45 patients and 15 patients had a static score. After applying a linear transformation to 0–100 to the raw score, the mean pain scores decreased significantly from pre- to post-treatment, 47.4 to 21.5 ($P < 0.0001$). Before treatment, 42 of 45 patients required narcotic analgesics (step II and III analgesics); post-radiation, this number was reduced to 12. The score for swallowing remained stable in 30 patients and improved in 15 patients. The mean score of dysphagia improved from 21.9 to 38.2 ($P = 0.0002$) (After applying a linear transformation to 0–100, to the raw score) [Table 2]. None of these patients reported any increase in pain or severity of dysphagia, which is associated with radiation-induced mucositis.

DISCUSSION

The primary purpose of palliative radiation for any inoperable and advanced cancer is to relieve the symptoms as much as possible while keeping the side effects of the treatment as low as possible. In addition, the radiation course should be completed as quickly as possible to decrease the hospital stay of the patients. In our study, 42 patients of the 45 initial patients responded after the first Quad Shot while 25 of these patients showed response after the second Quad Shot course. At the time of review at 6 weeks after completion of radiation which included either single or multiple courses of radiation, 30 patients showed partial response to the Quad Shot regime, while 6 patients demonstrated stable disease. However, nine patients had progressive disease which included those patients that were given fewer courses of Quad Shot. Twenty-seven patients reported having mucositis among which 18 were Grade 1 and 9 were Grade 2, but no reported incidence of any higher grade of mucositis was found. Only 20 patients were found to have Grade 1 dermatitis. After "Quad Shot," pain score was found to be improved in 30 of 45 patients

Table 1: Change of tumor dimension and response after Quad Shot RT

Before RT	Tumor dimension (cm) (mean±standard error)			Response		
	After Quad Shot RT			PR	SD	PD
	1 cycle	2 cycles	3 cycles			
11.09±0.17	4.67±0.14*	2.48±0.09* (42 patients)	1.16±0.07* (25 patients)	30 (66.7%)	06 (13.3%)	09 (20%)

*Means statistically significant, RT: Radiotherapy

Table 2: Pain score (before and after RT), dysphagia (before and after RT), and mucositis and dermatitis (after RT)

Pain score (mean±S.E.)		Dysphagia score (mean±S.E.)		Mucositis			Dermatitis	
Before RT	After RT	Before RT	After RT	NIL	Grade 1	Grade 2	NIL	Grade 1
47.4±1.48	21.5±1.91*	21.9±1.16	38.2±4.02*	18	18	09	25	20

*Means statistically significant, RT: Radiotherapy, SE: Standard error

and 15 patients had a static score. The score for swallowing remained stable in 30 and improved in 15 patients. The cyclical hypofractionated palliative RT regimen (Quad Shot) given for the present study revealed that this short course of hypofractionated radiation is an effective tool for palliation and patients responded quite well to the treatment. As per the protocol, those patients who showed lesser than 50% response were spared any further radiation, while the patients who showed the desired response were given the 2nd cycle "Quad Shot." In this regard, our study showed comparable outcome to that done by Corry *et al*., and we were able to give the 3rd cycle to 25 of our patients who showed the desired response after the 2nd cycle.[12]

The result of our study in regard to response to treatment and symptom relief is almost similar to the study done by Corry *et al*. (80% and 77%). This palliative treatment has been very effective in pain relief and control of dysphagia in the patients, with no evidence of increase in these symptoms after radiation. None of the patients in the present study or in Corry trial[12] or trial of Ghoshal *et al.* [15] had Grade 3 mucositis, but another hypofractionated RT trial for similar patients reported 26% Grade 3 mucositis and 11% Grade 3 dermatitis.[19] Similarly, in another large Indian study of 505 patients, mucositis of varying degrees in almost all patients was reported after receiving 20 Gy in five fractions.[20] The difference in severity of acute toxicities in our study can be attributed to the short time of radiation and the larger fraction size of radiation. During the follow-up period, evaluation was done as per departmental protocol and that revealed very little to almost no change in salivation; however, taste sensation was reported to be altered or diminished by almost all patients. Corry *et al*. in their study reported change in quite a few numbers of patients which was probably due to increased dose delivered to the salivary glands.[12]

An important significance of this study is the variety of advantages offered by this cyclical hypofractionated palliative RT regimen (Quad Shot). As previously explained, patient comorbidities and other logistic issues prevent prolonged treatment in these patients; here in this very short course of RT, this problem is almost non-existent. Moreover, due to the structuring of the regime in such a manner that response to the treatment is taken in account for further subsequent therapy planning, unnecessary treatment delivery is not done. In our study, we found that even a single cycle of hypofractionated palliative RT regimen (Quad Shot) provided benefit in some patients; however, patients who received the full 3 cycles of RT attained greater benefit. Elderly patients of advanced head-and-neck cancer when put on longer duration palliative RT course face difficulty in daily commuting and often fail to complete the course. This short-course 2 days RT has been found to be more patient friendly and compliant as well as effective. This short-course cyclical hypofractionated palliative RT also has an advantage of decreasing the logistic burden on the telecobalt machine which is very beneficial in our setup with huge patient burden.

CONCLUSION

Head-and-neck cancer patients present in most centers of India at late advanced stages which make them unsuitable for definitive treatment. In these patients who are in dire need of some form of local therapy for symptom control and palliation, the hypofractionated palliative RT regimen (Quad Shot) offers an effective and quick treatment option which is beneficial both clinically and in logistics issue. This regime will definitely benefit outstation patients as the duration of stay away from home will be shorter. In addition, the shorter course of radiation would be logistically better for the treating center. For appropriately selected patients, this regimen is our one of the accepted institutional schedules for patients requiring palliative radiation for incurable cancers of the head and neck. In future, this regime may find its justified place along with the conventional regimes for the treatment of selected advanced staged head-and-neck cancer patients.

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