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A Prospective Study to Evaluate Tumour Response and Quality of Life with QUAD Shot Radiotherapy in Locally Advanced or Metastatic Head and Neck Cancer

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ABSTRACT

Background: Locally advanced or metastatic patients with head and neck cancer may have a heavy symptom burden and poor performance status, rendering these patients unsuitable to be treated curatively. Palliative radiotherapy is indispensable in a reduction in symptoms and quality of life (QoL). A solution to this scenario is the QUAD shot regimen, a hypofractionated cyclical radiotherapy program utilized in this scenario which has proved to be a convenient and effective treatment option. **Purpose:** The aim is to prospectively study tumour response, symptom relief, and quality of life of patients with advanced head and neck cancer who receive QUAD shot radiotherapy. **Methods:** It was a prospective, single-arm study in a tertiary care facility with 52 patients known to have histologically-proven locally advanced or metastatic head and neck cancer and who were not fit to receive curative care. Radiotherapy QUAD Shots Patients were given 14.8 Gy in four fractions given over two continuous days repeated every 3-4 weeks up to three cycles. RECIST criteria were used to measure the tumour response. They were clinically symptom relief, and QoL with EORTC QLQ-C30 and QLQ-H&N35. The toxicity was graded using CTECAE version 5.0. **Results:** Among the 48 patients with whom it was possible to make an assessment, 62.5 was the total response rate (complete response and partial response). They were found to have considerably improved their symptoms, particularly on pain, dysphagia and bleeding. The statistical significance was present between the quality of life with the global health status, functional scales and symptom domains ($p < 0.05$). No severe adverse events and the majority of the adverse events Grade 1-2 with minimal Grade 3 toxicities. No Grade 4 toxicities or Death due to treatment. **Conclusion:** QUAD shot radiotherapy is a safe, effective and well-tolerated palliative therapy in patients of head and neck cancer with advanced cancer. It provides valuable tumour response, high symptom relief and a considerable quality of life gain at a low toxicity.

INTRODUCTION

Head and neck cancer (HNC) is one of the largest health issues of most countries in the world, and it is often diagnosed at an advanced stage especially in low- and middle-income countries. Advanced illness is strongly associated with severe symptoms of pain, difficulty in swallowing (dysphagia), bleeding, and obstruction of the airway that would are major determinants of the quality of life (QoL) and functional state [1]. Nowadays, many patients are unable to receive curative intent therapy because of a high level of the disease (metastasis), unsatisfactory performance status, or comorbidity, even with the introduction of multimodality treatment, surgery, chemotherapy, and radiotherapy [2]. Once this happens, instead of attempting to cure the patient, the management will focus on palliative goals, including alleviation of symptoms, preservation of dignity and quality of life.

Palliative radiotherapy (RT) has been the key to these patients as it gives effective control of symptoms and local stabilization of the disease. But standard schedules of fractions (e.g. 30 Gy in 10 fractions) can be linked to long-term fractions and large-scale toxicity, and can be less applicable to frail patients [3]. Moreover, patient compliance and overall well being can be negatively affected by the treatment burden and frequent hospital visits. This has led to increased interest in hypofractionated regimes giving a fast response with a low toxicity.

QUAD shot regimen with its initial origin in Radiation Therapy Oncology Group (RTOG) protocols is a cyclical hypofractionated regimen with 14-14.8 Gy given in four fractions each over two consecutive days, with a balance of the 3-4 week intervals [4]. This method enables cytoreduction of tumour with

sufficient recovery time in normal tissues between the cycles. More recent trials have shown encouraging results using this regimen, such as a high response rate of tumors and good palliation of symptoms in patients with incurable HNC [5]. Response of the tumor at percentages of 40 percent and even greater than 80 percent have been reported depending on selection of patients and the number of treatment cycles [6].

Besides tumor control, the quality of life has become an important endpoint measure in palliative oncology. There is an indication that, QUAD shot radiotherapy is associated with substantial reduction in pain, swallowing performance and general health status globally, with majority of patients reporting mild to moderate levels of toxicity [7]. Imperatively, the regimen is applicable to patients with limited life expectancy or poor performance status owing to its short time span and ability to repeat [8].

ES has been investigated further as recent prospective and retrospective studies examine the combination of the QUAD shot radiotherapy with systemic therapies including immunotherapy and chemotherapy, and shows increased local control without significant excess toxicity [9]. In addition, its performance in resource-limited condition underlines its applicability in areas where highly developed cancer presentation occurs frequently [10].

With these benefits, QUAD shot regimen is a promising palliative care approach in patients with head and neck cancer that has spread to the local regions or peripheral areas. In this prospective investigation outcomes in tumor response and quality of life in the case of QUAD shot radiotherapy are being assessed and thus viewed to add to the cumulative evidence regarding its clinical use.

METHODOLOGY

This prospective, single arm observational study, involving patient recruitment, treatment and follow-ups was done by the Department of Radiation Oncology, Shaukat Khanum Memoria Cancer Hospital and Research Center in Peshawar from 5th January 2024 to 4th July 2024. Ethical approval was obtained before coming into action by the Institutional Review Board and everything was performed according to the Declaration of Helsinki. All participants gave informed written permission. The patients included were those of 18 year and above and locally advanced (Stage III-IV) or metastatic squamous cell carcinoma of the head and neck region who were deemed to be inappropriate to receive curative therapy. The reasons were significant comorbidities, a high illness burden, or even low performance status because drastic therapy was not appropriate. Only those patients who had unpleasant symptoms like pain, dysphagia, bleeding or airway impairment, and those who had an Eastern Cooperative Oncology Group (ECOG) performance level of 2-3 were included. Those patients who had uncontrolled systemic diseases, ECOG performance status equal or above 4, radiation to the same location before, were not included, as well as pregnant or lactating patients.

A total of 40-60 patients were planned to be included based on the practicality. The baseline examination included a detailed clinical history, physical examination, and staging according to the AJCC TNM classification. The region of the head and neck was scanned with either magnetic resonance imaging or contrast-enhanced computer tomography, where positron emission tomography-CT was used when available. Liver/kidney and complete blood count tests were done as baseline laboratory tests. Dysphagia was clinically graded at the baseline, and bleeding and other symptoms in the local area were noted, pain was measured using Visual Analog Scale. Quality of life was measured by using validated questionnaires, the European Organization of Research and Treatment of Cancer QLQ-C30 and the head and neck-rated validation questionnaires, the QLQ-H&N35.

The palliative radiation was administered to all patients during two consecutive days via the QUAD shot regimen that entails the total dose of 14.8 Gy in four fractions of 3.7 Gy each with a minimum separation of six hours. Treatment was done using either intensity-modulated radiation or three-dimensional conformal radiotherapy depending on the availability in the institution. The proper margins were added to come up with the planned target volume based on the clinical and radiological outcomes. Each tumor response, symptom relief, and patient tolerance, the treatment cycle was repeated after every three or four weeks up to three cycles.

Patients had their acute toxicities scored using the Common term issue version 5.0 of the criteria of adverse event which was determined at the end of the therapy in a period of one week. Tumor response was assessed on the basis of the RECIST version 1.1 criteria (four weeks after each of the cycles and end of treatment). Quality of life evaluation was again done after every cycle, and a month following the cessation of the therapy. Subsequently, patients were followed at four week intervals and two or three months afterward until the disease progress or death. The main goals were tumor response rate and quality of life scores changes; the secondary goals were symptom alleviation, treatment-related toxicity, and compliance. Statistical analysis was performed using SPSS software. Baseline variables were described using descriptive statistics and appropriate comparative tests were used to determine the alterations of quality of life with a p-value of less than 0.05being taken to be statistically significant.

RESULTS

In the study, there were from 52 patients who were enrolled, 48 of which were assessable in response and quality of life assessment upon the completion of at least one cycle of QUAD shot radiotherapy. The study population was exhausted by 58 median age with a strong dominance of males (38-78 years). The oral cavity was the site of the most frequent primary tumor location, followed by the oropharynx and larynx. Most patients were stage IV disease (with the average performance status of ECOG 2-3) which is an indicator of a population with a high disease stage and low response to the curative therapy. (Table I).

Most of the patients were tolerant to the regimen in areas of treatment compliance. The number of patients

who completed one cycle, two cycle and three planned cycles were 48 (92.3), 36 (69.2), and 24 (46.2) respectively. Primary causes of non-completion of all cycles were the advancement of the disease, general condition worsening or logistic problems. (Table II).

RECIST 1.1 criteria were used to determine tumor response at 4 weeks after each cycle. Out of the assessable patients, complete response (CR) was noted in a low percentage with most displaying partial response (PR). Some portion of patients had stable disease (SD), and only a small fraction of patients had progressive disease (PD). The response rate (CR + PR) hit 62.5% which shows that the use of this palliative regimen was a success in terms of achieving favorable tumor control. (Table III).

Great improvement was observed in the presentation after treatment. At the most typical symptom baseline, pain was revealed to have significantly decreased in intensity in over half of the patients. In the same manner, dysphagia, bleeding and foul discharge were also improved, which led to enhanced patient comfort and daily functioning. (Table IV).

The quality of life measured with the EORTC QLQ-C30 and QLQ-H&N35 questionnaires revealed the statistically significant improvement in the several domains. The scale of global health status and functional scale which included physical/emotional functioning increased substantially. There was a great improvement in symptom scales that included pain, fatigue and difficulty in swallowing after the treatment. These results underline the efficiency of QUAD shot radiotherapy to enhance the clinical symptoms and patient-reported outcome. (Table V).

The therapy was overall satisfactory. The majority of the side effects were Grade 1-2, which consisted of mucositis, dermatitis, and mild dysphagia. There were minimal cases of Grade 3 toxicity, mainly mucositis, which were easily treated with supportive care. Notably, there were no Grade 4 toxicities or mortality related to treatment. (Table VI).

Table I

Baseline Characteristics of Study Participants (n = 52).

Variable	Number	Percentage (%)
Age (years)		
<50	12	23.1
50–65	26	50.0
>65	14	26.9
Gender		
Male	38	73.1
Female	14	26.9
Primary Site		
Oral cavity	19	36.5
Oropharynx	13	25.0
Larynx	10	19.2
Hypopharynx	7	13.5
Others	3	5.8
Stage		
Stage III	10	19.2
Stage IV	42	80.8
ECOG Status		
ECOG 2	31	59.6
ECOG 3	21	40.4

Table II

Treatment Compliance.

Treatment Cycles Completed	Number (n=52)	Percentage (%)
One cycle	48	92.3
Two cycles	36	69.2
Three cycles	24	46.2

Table III

Tumour Response (n = 48)

Response	Number	Percentage (%)
Complete Response (CR)	4	8.3
Partial Response (PR)	26	54.2
Stable Disease (SD)	12	25.0
Progressive Disease (PD)	6	12.5

Table IV

Symptom Relief

Symptom	Baseline (%)	Post-Treatment (%)	Improvement (%)
Pain	88.5	38.5	50.0
Dysphagia	71.2	34.6	36.6
Bleeding	40.4	11.5	28.9
Foul discharge	32.7	9.6	23.1

Table V

Quality of Life (EORTC QLQ-C30)

Parameter	Baseline (Mean ± SD)	Post-Treatment (Mean ± SD)	p-value
Global Health Status	42.3 ± 10.5	64.7 ± 12.2	<0.001
Physical Functioning	51.2 ± 11.3	62.8 ± 10.9	0.002
Emotional Functioning	48.6 ± 12.1	66.4 ± 11.7	<0.001
Pain	72.5 ± 9.8	38.6 ± 10.2	<0.001
Fatigue	68.3 ± 11.5	49.7 ± 10.8	0.004

Table VI

Toxicity Profile

Toxicity	Grade 1–2 (%)	Grade 3 (%)	Grade 4 (%)
Mucositis	54.2	10.4	0
Dermatitis	48.0	6.2	0
Dysphagia	32.5	8.3	0
Xerostomia	29.2	0	0

DISCUSSION

The current prospective trial has shown that QUAD shot radiotherapy as a treatment regimen offers valuable tumour response, good symptom palliation and high quality of life (QoL) with reasonable toxicity levels to patients with locally advanced or metastatic head and neck cancer. These results agree with the accumulating evidence hypofractionated palliative radiotherapy is an effective method to use in the advanced-disease setting and which is patient-friendly.

The response rate (62.5) was overall in this study is in line with the recent literature. One of the more recent analyses has displayed tumour response rates of 50-80% depending on patient selection and the number of cycles administered [11]. Likewise a potential multicentre assessment showed that cyclical hypofractionated QUAD shots regimens lead to massive tumour regression with long lasting local control in a major percentage of individuals. A similar recent review also found that QUAD shot radiotherapy to give meaningful tumour regression, particularly when multiple cycles are undergone, which supports our finding that then patients who underwent more cycles performed better [12].

Our response rates are also quite similar to those of the study by Upadhyay et al., in which the inclusion of systemic therapy only continued to improve tumour control but did not lead to a substantial rise in the toxicity. Likewise, an early 2026 trial comparing QUAD shot-like

regimens with concomitant chemotherapy indicated higher response rates and indicated that combination regimens can further enhance the efficacy of treatments [13]. Nonetheless, in the current study, QUAD shot was administered in a form of independent palliative modality, but still yielded good results, which confirms its independent efficacy.

A very important endpoint in palliative oncology is symptom relief and, according to our results, the pain, dysphagia, bleeding, and discharge symptoms were significantly improved, as reported by the previous reports. A recent trial showed prompt palliation of the symptoms in most of the patients with a most eminent benefit of pain relief. A second clinical assessment noted that over 50 percent of patients showed significant improvement in swallowing and bleeding symptoms, after QUAD shot treatment [14]. These results are very consistent with our results, where the pain decreased by more than 50 percent, and dysphagia improved significantly, which means that this regimen can help to eliminate the key symptom burden in advanced head and neck cancer.

The improvement of quality of life is beginning to be viewed as an important outcome measure in palliative care. Global health status, functional domain, and symptom scales were significantly enhanced in the current study. These results are corroborated by recent prospective evidence that QUAD shot radiotherapy results in statistically significant change in QoL scores which improves especially in the pain domain and in the emotional functioning domain [15]. Equally, a recent study reported another study showing that hypofractionated regimens is beneficial in terms of rapid symptoms relief and a small treatment burden resulting in better patient-reported outcomes [16]. This is because the duration of QUAD shot and its periodicity enable patients to rest between the cycles, thus resulting in long term improvement of QoL.

The treatment of our study was fairly good whereby more than 90 percent of the patients completed at least one cycle. This compares to other studies, where the good compliance is mentioned because of the short duration of using treatment and less frequent visits to the hospital. Nonetheless, all three cycles were done less frequently (46.2%), similar to literature where the progression of the disease and deteriorating performance status may frequently restrict therapy continuation [17]. This emphasizes patient selection and initiation of palliative radiotherapy early before the patient becomes severely ill.

The toxicity profile was acceptable in this study as majority of the adverse events were Grade 1 and Grade 2 and there were very few adverse events of Grade 3. Grade 4 toxicities and treatment mortality were not reported. These findings held true to the previous reports that showed that QUAD shot radiotherapy is not only tolerated, but even in frail and elderly patients [18]. Recent QUAD shot adaptive study also documented a small adverse toxicity rate, indicating the safety of the regimen even available with repeated cycles. Relative to traditional palliative regimens, which could be linked to an increase in toxicity owing to a longer duration of treatment, QUAD shot has a good therapeutic ratio.

Comparing to other schedules of hypofractionation, it can be concluded that QUAD shot is able to effectively deliver similar or better results at a better tolerability. In a randomised comparative trial comparing the schedules of various types of palliative radiotherapy treatments, those using QUAD shot were found to produce similar tumour control as a result but was more convenient and less toxic. Moreover, the recent trials conducted on optimal dose fractionation on palliative head and neck cancer have highlighted shorter and patient-focused regimens of dose fractionation with longer support of QUAD shot [19].

There is also some emerging evidence that there may be a benefit to QUAD shot radiotherapy with immunotherapy. Cases of the experiment of immune checkpoint addition have demonstrated improved local and systemic outcomes, which may have been the consequence of immunomodulatory impact of hypofractionated radiation [20]. Clinical trials are being carried out to further evaluate this synergy, and this means a bright future of enhancing the outcomes in advanced head and neck cancer.

The third point of concern that has been identified by this research is the system of QUAD shot that applies in resource constrained environments. It has fewer visits to hospitals, machine time, and the entire treatment is less expensive and is specially applicable in high burden areas, where patients commonly come to hospitals with advanced disease [21]. This advantageous aspect is also practical and strengthens its position as a desirable palliative treatment modality.

Although the results are encouraging, it is important to note some drawbacks. The single-arm nature and kind of limited sample size restrict the extrapolation of findings. In addition, the limited follow up period does not allow evaluation of the long-term outcomes and long-term benefits with regard to survival benefits. Other study articles have found similar constraints pointing to the need of larger randomized controlled trials in order to implement standardized treatment procedures [22].

On the whole, results of this research align with that of modern literature indicating that QUAD shot radiotherapy is an effective, well-tolerated and patient-friendly approach to palliative radiotherapy. It offers quick relief of symptoms, meaningful tumour response and a big enhancement in quality of life, and so is especially useful in patients who have a limited life expectancy or a poor performance status.

CONCLUSION

Results of this prospective study indicate that QUAD shot radiotherapy is a safe and effective option of palliative modal of radiotherapy successfully used in patients with locally advanced or metastatic head and neck cancer unsuitable to curative therapy. It was found that the regimen had a good response rate of tumour overall, and a high percentage of patients had either partial or total tumour regression. Notably, it produced significant symptom alleviation, especially in pain, dysphagia, and bleeding, which are some of the most uncomfortable complaints of this patient group. Another important aspect of the QUAD shot program evident in this study is its effect on quality of life. Significantly, statistical changes were

observed in various areas, such as global health condition, physical and emotional functioning, and symptom load. The brief course of treatment and cyclic nature of the regimen made it more (particularly in patients with poor performance status or limited life expectancy) patient adherent and provided reduced treatment loads. It must be highly regarded as an alternative choice in the palliative treatment of advanced head and neck cancer and especially in situations of resource dearth. It has the potential to be optimized by further large-scale, randomized studies and understanding of combination strategies with systemic therapies to better harness its therapeutic potential and expand its clinical applicability.

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