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A Prospective study to evaluate the response and quality of life with Quad shot Radiotherapy in locally advanced or Metastatic Head & Neck Cancer.

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Abstract:
This prospective observational study investigates the impact of palliative radiotherapy on patient-reported outcomes (PRO) in individuals with head and neck cancer (HNC). The study enrolled 44 patients, with 42 included in the analysis, focusing on evaluating the effectiveness, tolerability, and toxicity of three different schedules of palliative radiotherapy. The participants, predominantly with advanced-stage HNC, completed questionnaires, including the University of Washington Quality of Life (UWQOL) questionnaire, at multiple time points during and after radiotherapy. The study aimed to assess changes in quality of life, pain intensity, patient satisfaction, and overall survival. Results indicated that while there were no significant improvements in predefined areas of health-related quality of life (HrQoL) at the group level, most patients experienced a substantial improvement in their main symptoms, surpassing the minimum important difference (MID). Common toxicities included dysphagia and mucositis, with significant mucositis decreasing within one week post-radiotherapy. The study highlights challenges in patient enrollment and attrition rates. Although limitations such as a small sample size and participant dropout exist, the findings suggest a discernible benefit of palliative radiotherapy in reducing pain and improving specific HrQoL domains for selected HNC patients. Further prospective studies are recommended to validate these results.

Keywords: Head and Neck Cancer, Palliative Radiotherapy, Patient-Reported Outcomes (PRO), Health-related Quality of Life (HrQoL), Mucositis.

INTRODUCTION

Head and neck cancer comprises 4.8% of the total worldwide cancer cases and 14.3% of all cancer cases in India [1]. In the context of India, over 70% of patients are diagnosed at an advanced stage, resulting in local failure rates ranging from 50% to 70% [2, 3]. Radiotherapy (RT) is the established primary treatment for locally advanced head and neck cancer (LAHNC), without the need for surgery. Regarding LAHNC, the local control rates achieved by the most efficient RT regimens range from 50% to 70%, whereas disease-free survivals range from 30% to 40% [4, 5]. Due to the presence of severe disease upon first diagnosis, certain individuals are only eligible for palliative radiation therapy. The objective of treating these patients is to promptly alleviate uncomfortable symptoms, and an essential determinant of therapy success is the quality of life (QOL). Due to the majority of these patients having a low performance status, the extended duration of therapy and frequent hospital visits negatively impact their quality of life. Given that enhancing symptoms and quality of life (QOL) is a crucial element of palliative care, a study without these outcomes is deemed insignificant. Several studies have examined the use of hypofractionated radiation therapy (RT) for palliative treatment of locally advanced head and neck cancer (LAHNC). However, most studies suffer from methodological flaws, as they lack comprehensive toxicity data and fail to measure the impact on quality of life (QOL). There is currently no universally accepted protocol for dividing the total radiation therapy (RT) dose into smaller fractions for the purpose of palliative treatment of locally advanced head and neck cancer (LAHNC). This study aimed to compare the effectiveness, tolerability, and toxicity of three different schedules of palliative radiation therapy (RT) in locally advanced head and neck cancer (LAHNC). Additionally, it sought to examine the quality of life (QOL) before and after RT in all groups using the University of Washington Quality of Life (UWQOL) questionnaire.

MATERIALS AND METHODS

Study design and setting

We conducted a prospective observational study. We planned an overall sample size of 122 patients who were evaluated, 70 were found to be ineligible and four declined to take part in the study. The study comprised a total

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of 44 patients. The recruitment period was from June 2020 until June 2022. Inclusion criteria were i) mucosal squamous cell carcinoma of the head and neck, ii) any form of palliative radio(chemo)therapy prescribed for head and neck cancer, iii) ability to complete questionnaires, iv) age ≥18 years, and v) written informed consent. Exclusion criteria were i) prescription of radical radiotherapy for the current radiotherapy course (defined as EQD2Gy ≥ 60 Gy; $\alpha/\beta = 10$) and ii) cutaneous primary.

Variables and outcomes

We collected data using an case report form. Variables included patient and treatment characteristics, the age-adjusted Charlson Comorbidity Index, toxicity per Common Terminology Criteria for Adverse Events (CTCAE) v5.0, overall survival, patient-reported head and neck cancer pain intensity per Numeric Rating Scale (NRS 0-10), patient satisfaction, and the patient-reported questionnaires EORTC were asked to indicate their two most burdensome symptoms (hereafter termed primary or secondary symptom) related to the head and neck cancer if present . Patients could choose to complete the questionnaires electronically on a personal device or paper-based. Time points of data collection at clinical encounters were baseline, first fraction of radiotherapy, last fraction of radiotherapy, one week after radiotherapy, and eight weeks after radiotherapy . Subsequent remote PRO data collection was planned. However, results after eight weeks were not analyzed due to a limited number of available questionnaires at various following time points. The follow-up date at one week after radiotherapy was included due to concerns of a delayed onset of acute toxicity in anticipation of the use of hypofractionated radiotherapy regimens. Data for survival was collected until October 2022. Concerning questionnaire data, we predefined to report in detail the domains “Global health status/quality of life”, “Physical functioning”, “Pain in the mouth”, “Swallowing”, and “Fatigue” at eight weeks after radiotherapy in comparison to the first fraction of radiotherapy. We hypothesized that these domains and the time frame should be relevant for the majority of the patients based on previous studies. Primary and secondary symptoms were linked to a coherent questionnaire domain prior to statistical analysis. For two symptoms, the coherent symptom domain was ranked zero (=absence of the symptom) by the respective patient and the analysis was therefore deemed infeasible for those symptoms.

RESULTS

Enrollment and demographic information of patients

Out of the 122 patients who were evaluated, 70 were found to be ineligible and four declined to take part in the study. The study comprised a total of 44 patients. Out of these, one patient underwent radical radiotherapy, leading to a total of 42 patients included in the analysis. Three centres failed to enrol patients within a one-year period and were subsequently closed for recruitment. The average duration of observation was 20.4 months for the assessment of overall survival. Table 1 displays the attributes of the patients and the features of palliative radiotherapy. The patient cohort had a median age of 73 years, with males accounting for 71% (30 out of 42) of the total. The predominant radiotherapy regimens consisted of 45 Gy administered in 15 fractions (48%; 20/42) and 36 Gy administered in 12 fractions (14%; 6/42), with each fraction being administered five times per week. Each of the remaining eight radiotherapy regimens was prescribed only once. In 95% (40/42) of the cases, the target volume was limited to the visible tumour. Seven out of twenty-one individuals, which is equivalent to thirty-four percent, had received radiotherapy treatment for head and neck cancer before. The reasons for prescribing palliative radiotherapy instead of radical radiotherapy included advanced age (n=20), comorbidity (n=14), local extent (n=14), and recurrent disease (n=12) . Multiple factors contributed to the condition in 62% (26/42) of the patients.

One patient, accounting for 5% (2 out of 42), opted to complete the questionnaires electronically rather than using paper-based forms. In relation to the EORTC patient-reported outcomes questionnaires QLQ-C30 and EORTC QLQ-H&N43, there were a total of 18 questionnaires available during the initial fraction of radiotherapy, 13 during the final fraction of radiotherapy, 10 one week after radiotherapy, and eight eight weeks after radiotherapy . The results of all questionnaire domains are summarised in Supplementary Table 2. We conducted a detailed analysis of the domains "Global health status/quality of life", "Physical functioning", "Pain in the mouth", "Swallowing", and "Fatigue" as initially specified. Specifically, we compared the data from the first fraction of radiotherapy with the data from eight weeks after radiotherapy in patients who had data available for both time points. None of these domains met the minimum important difference (MID) of 10 points when analysed based on the mean values across patients.

Out of the patients who completed questionnaires both at the beginning of radiotherapy and eight weeks later, five individuals reported experiencing both a primary and secondary symptom, two patients reported only a primary symptom, and one patient was unable to identify either a primary or secondary symptom. At the level of each individual patient, the main symptom showed improvement of over 10 points in 71% (10/14) of cases, and there were no patients whose symptoms worsened by more than 10 points (Fig. 3). 40% (4/10) of the patients

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experienced an improvement of more than 10 points in the secondary symptom, while none of the patients experienced a worsening of more than 10 points.

The average NRS score for pain resulting from head and neck cancer was 3.2 initially (n=42) and decreased to 0.8 after eight weeks of radiotherapy (n=18) (Supplementary Table 3). At eight weeks after radiotherapy, there was no observed augmentation in the consumption of opioid analgesics (Supplementary Table 3). A Wilcoxon rank test indicated that the disparity in average NRS scores was not statistically significant (p = .065). Nevertheless, there is a disparity in the average NRS.

Table 1 displays the characteristics of the 42 patients who underwent palliative radiotherapy. Numerical values are provided in absolute terms, while percentages are shown in brackets, unless otherwise specified. The sum of the numbers may deviate from 100% due to rounding inaccuracies or the absence of certain values. Abbreviations: CCI stands for Charlson Comorbidity Index; ECOG stands for Eastern Cooperative Oncology Group; HNC stands for head and neck cancer; IQR stands for interquartile range; PEG stands for percutaneous endoscopic gastrostomy; SD stands for standard deviation.

TABLE 1

Patient characteristics			Total number of patients(42)
Age			Median: 73; IQR: 17
Sex	Female:		12
	male		30
ECOG	1		12 (29%)
	2		22(52%)
	3		8(19%)
Age-adjusted CCI			Median: 4;
			IQR: 4
Smoking status	Current or former smoker		32 (76%)
	Never smoked		10 (24%)
History of risky alcohol use [a]			18 (43%)
Tracheostomy in place			8 (19%)
PEG tube in place			18 (43%)
HNC site	Oral cavity		16 (38%)
	Oropharyngeal		14 (33%)
	Laryngeal		6 (14%)
	Other		6 (14%)
UICC stage (TNM v8)	II		2 (5%)
	III		4 (10%)
	IV		34 (81%)
HPV-positive disease			p16
Recurrent HNC	HNC treatment prior to pall. RT	Surgery	28 (33%)
		Radiochemotherapy	10 (24%)
		Radiotherapy	4 (10%)
	HNC treatment after pall. RT	Immunotherapy	4 (10%)
		Immunotherapy	6 (14%)
		Re-Radiotherapy	4 (10%)
Global health status/ quality of life	Per EORTC QLQ-C30		Mean: 66.7
			SD: 20.3
Radiotherapy characteristics			
Radiotherapy regimen	45 Gy/15fx 36 Gy/12fx		20 (48%)
	45 Gy/15fx 36 Gy/12fx		6 (14%)
	Other		16(38%)

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Radiotherapy completed as prescribed		26 (62%)
Radiotherapy technique b	VMAT or IMRT	34(81%)
	3DCRT	6 (14%)
GTV volume (ml)		Mean: 95.45
		SD: 102.6
Concurrent systemic therapy	Immunotherapy	4(10%)
	Chemotherapy	2 (5%)

a History of hazardous alcohol consumption is characterised as males consuming more than 2 glasses per day and females consuming more than 1 glass per day for a duration exceeding 3 months. (1 glass is equivalent to 0.3 litres of beer, 0.125 litres of wine or 4 centilitres of spirits). b One patient expired before the completion of radiotherapy planning.

The statistical significance, as determined by the Wilcoxon signed rank test, was observed only in patients who had data available at eight weeks after radiotherapy ($p = 0.041$). The initial average pain score for these nine patients was 3.6, with a standard deviation of 3.6. Regarding patient satisfaction, all of the patients (18/18) with available data at eight weeks after radiotherapy expressed a desire to undergo radiotherapy again if given the opportunity to reconsider.

Supplementary results

At eight weeks after radiotherapy, the Eastern Cooperative Oncology Group (ECOG) performance status score remained stable in 56% (10/18) of the patients and declined in 44% (8/18) of the patients, as shown in Supplementary Table 4. Furthermore, after eight weeks of radiotherapy, the body weight of 78% (14/18) of the patients remained stable, while it declined in 22% (4/18) of the patients (Supplementary Table 4). The toxicity according to CTCAE v5.0 is displayed in Table 2. At the final fraction of radiotherapy, 44% (16/32) of the patients had mucositis of grade 3 or higher. One week after radiotherapy, this condition was present in 33% (6/18) of the patients, and no patients had mucositis of this severity eight weeks after radiotherapy.

No unforeseen hospitalisations occurred during the radiotherapy treatment. However, another patient was hospitalised within the time frame that occurred after the previous treatment session and one week later. The reasons for hospitalisation were cachexia, pain, pneumonia, and the advancement of pulmonary metastases. A cerebrovascular accident necessitated the admission of another patient within a timeframe ranging from one to eight weeks following radiotherapy. The median overall survival was 11 months.

Toxicity according to the Common Terminology Criteria for Adverse Events v5.0 (related and unrelated to radiotherapy). Absolute numbers are given and percentages are displayed in brackets. Abbreviations: RT, radiotherapy.

Table 2

	Baseline, n = 40		Last fraction of RT, n = 32		1 week after RT, n = 18		8 weeks after RT, n = 18	
	◦ 2	≥◦ 3	◦ 2	≥◦ 3	◦ 2	≥◦ 3	◦ 2	≥◦ 3
Mucositis	4 (10%)	0 (0)	10 (28%)	16 (44%)	8 (44%)	6 (33%)	2 (11%)	0 (0)
Dermatitis	0 (0)	0 (0)	2 (6%)	0 (0)	2 (11%)	2 (11%)	0 (0)	0 (0)
Dysphagia	6 (15%)	12 (30%)	10 (28%)	18 (50%)	8 (44%)	4 (22%)	4 (22%)	4 (22%)
Xerostomia	2 (5%)	0 (0)	2 (6%)	2(6%)	6 (33%)	0 (0)	0 (0)	0 (0)
Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	4 (2%)	0 (0)	0 (0)	0 (0)

DISCUSSION

In this prospective observational study examining the effects of palliative radiotherapy on patient-reported outcomes (PRO) in individuals with head and neck cancer, we encountered challenges related to limited patient enrollment and significant rates of participant attrition. Patient-reported health-related quality of life (HrQoL) improvements were not observed in specific areas for patients following palliative radiotherapy. Individually, the majority of patients experienced a significant improvement in their main symptom resulting from the head and neck cancer.

Regarding the treatment patterns of palliative radiotherapy for head and neck cancer, 71% of the patients had an ECOG performance status of 2 or higher, indicating a moderate to severe level of physical functioning, and 81%

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of the patients had UICC stage IV disease, indicating an advanced stage of cancer. Prior groups of prospective studies investigating palliative radiotherapy for head and neck cancer have documented an ECOG performance status of 2 or greater in 25% to 71% of the patients [6-10]. The studies found that UICC stage IV disease was present in 53% to 97% of the patients. Hence, our study group comprises patients with a performance status that is below average, yet remains representative in comparison to previous trials. However, we discovered that the use of palliative radiotherapy was uncommon among head and neck cancer patients at the participating centres. There are two possible reasons for this situation. One reason is that a patient may be deemed "too fit" for palliative radiotherapy, which would lead to a more aggressive treatment approach. The other reason is that a patient may be considered "too frail," in which case the best course of action would be to provide supportive care. This was highlighted by the fact that one patient underwent radical radiotherapy and that two patients passed away before starting the recommended palliative radiotherapy treatment. Indeed, two additional patients succumbed prior to the designated time frame of our primary analysis, which was eight weeks following radiotherapy. Three patients experienced a deterioration in their health condition, preventing them from completing the HrQoL questionnaires. Regrettably, the restricted accumulation of data in our observational study is a common occurrence, particularly in trials investigating palliative radiotherapy for head and neck cancer carried out in Europe. A Dutch randomised controlled trial, which aimed to compare two treatment plans of palliative radiotherapy for head and neck cancer, was terminated prematurely due to a low number of participants. The trial had only enrolled 34 patients before it was closed [6].

Regarding the feasibility of utilising PRO (Patient-Reported Outcomes), it is worth noting that only one patient opted to electronically complete questionnaires on a personal device. Despite the majority of patients being elderly with a median age of 73 years, we anticipated a greater inclination towards electronic Patient-Reported Outcomes (ePRO). This study was conducted based on a prior German study that provided breast cancer patients with the option to use either an electronic or paper-based version of Patient-Reported Outcomes (PRO) [11]. Among the participants aged 70-80 in this study, a significant majority of 88% expressed a preference for the electronic version. In addition, a prior investigation on the use of electronic patient-reported outcome (ePRO) monitoring in head and neck cancer patients undergoing radical radiotherapy revealed a high compliance rate of 94% [12]. However, in our study, a more unfavourable performance status in the palliative setting may have hindered the use of ePROs. Ongoing research is being conducted to determine the significance of ePROs [13]. Collectively, our observational study provides a warning regarding the use of electronic patient-reported outcomes (PRO) in the context of head and neck cancer patients receiving palliative radiotherapy.

Regarding longitudinal Health-related Quality of Life (HrQoL) outcomes, there were no significant improvements observed in predefined areas at the eight-week mark following radiotherapy among the patients. The findings remain inconclusive in this regard, possibly due to the limited number of patients. Prior studies with limited patient samples [6] have previously reported inconclusive mean values for PRO. When examined on an individual basis according to predetermined criteria, most patients showed significant improvement in their primary symptom, surpassing the minimum important difference (MID). Some of the symptoms included "neck swelling," "mouth pain," and "difficulty swallowing." Previous studies have demonstrated the potential for improvement in the latter two conditions following palliative radiotherapy for head and neck cancer. Fortin and colleagues found that 83% of the 32 patients experienced either improvement or stability in head and neck pain, as assessed by the EORTC QLQ-H&N35 questionnaire, following palliative radiotherapy [7]. In addition, Porceddu and his colleagues found that 81% of the 37 patients experienced either improved or stable swallowing, as measured by the FACT-H&N questionnaire, after receiving palliative radiotherapy [9]. However, these previous studies primarily documented the improvement of symptoms without reporting the Minimal Important Difference (MID). Indeed, the documentation of patient-reported outcome (PRO) data in clinical trials involving palliative radiotherapy seems to be inadequate, as demonstrated by a recent comprehensive analysis conducted by our research team [14]. The primary tumor-induced pain, as assessed by the Numeric Rating Scale (NRS), is a frequently used measure of patient-reported outcomes (PRO) [15]. Patients who responded to the pain question at eight weeks after radiotherapy exhibited significantly lower values of pain per NRS in our cohort. This finding aligns with prior retrospective and prospective studies that have also documented a notable enhancement in pain levels as measured by the NRS or Visual Analogue Scale [10,16]. Collectively, our study provides evidence at the individual patient level that palliative radiotherapy may exert a beneficial influence on crucial symptoms experienced by patients with head and neck cancer.

The most common toxicities observed in our group were dysphagia and mucositis. Mucositis of grade 3 or higher was absent at the beginning but developed in 44% of the patients during the final stage of radiotherapy. The occurrence of mucositis significantly decreased within one week following radiotherapy, which provided reassurance considering the use of hypofractionated radiotherapy regimens. However, the incidence of acute mucositis remains significant in a palliative setting and has also been documented in other research studies. In

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our study, the prevailing radiotherapy treatment consisted of 15 sessions, with each session delivering a dose of 3 Gy. These sessions were administered five times per week, resulting in a cumulative dose of 45 Gy. In the mentioned randomised trial, 16 fractions of 3.125 Gy were administered in four fractions per week, resulting in a total dose of 50 Gy in one group. This group reported that 43% of the patients experienced acute mucositis of grade 3 or higher [6]. Alternative treatment protocols, such as the "Quad Shot" which involves administering 25 Gy in five daily fractions, or using 6 fractions of 6 Gy twice per week, have been found to have lower toxicity rates, specifically mucositis of grade 3 or higher, which is below 10% according to studies [6,7,17]. These treatment plans may be favoured when toxicity is a particular concern. Nevertheless, an increased dosage of radiotherapy may be linked to enhanced overall survival. The cohort's median overall survival was 11 months. Research on less aggressive radiotherapy treatments, such as the "Quad Shot" or 25 Gy in five daily fractions, found that the median survival time was approximately 6 months [7,8]. However, research on more rigorous radiotherapy treatments has indicated a median overall survival of up to 17 months [18]. The Dutch randomised controlled trial demonstrated a significantly longer median overall survival when using a more intensive radiotherapy regimen lasting 15 months, compared to a less intensive regimen lasting 9 months [6]. Nevertheless, this discrepancy did not have a statistically significant impact. Conversely, a methodical

The review found a negative relationship between the amount of radiation received and the overall survival rate in older patients who underwent palliative radiotherapy for head and neck cancer [19]. The association between the dose of radiotherapy and survival is still uncertain in this context, but the overall survival of our group aligns with the findings reported in existing literature.

Our study is limited by the small sample size of patients and the significant rate of participant attrition. While we established key elements of our analyses in advance, the outcomes may be influenced by selection bias and diminished representativeness. Furthermore, we did not gather data regarding local control or radiographic response rates, which prevents us from conducting analyses on progression-free survival. However, this approach was pre-defined as PRO (patient-reported outcomes) data and overall survival are widely regarded as patient-centered endpoints in prospective studies [20,21]. Moreover, a distribution-based minimal important difference (MID) across symptom domains has frequently been employed in previous research and provides a logical and easy-to-understand starting point [22]. Additional sophisticated methods for calculating MID have been recently suggested [23,24].

CONCLUSION

Our study demonstrates a discernible advantage of palliative radiotherapy for head and neck cancer, as assessed by patient-reported outcomes (PRO). The advantage was evident in terms of pain reduction and in the individual domains of Health-related Quality of Life (HrQoL). Additional prospective studies are necessary to confirm these findings, however, palliative radiotherapy is a viable choice for meticulously chosen patients with head and neck cancer.

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