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COMPARISON OF OUTCOMES WITH HYPOFRACTIONATED PALLIATIVE RADIOTHERAPY 'CHRISTIE REGIMEN' VERSUS STANDARD PALLIATIVE RADIATION IN HEAD AND NECK SQUAMOUS CELL CARCINOMA- PROSPECTIVE STUDY

Oncology/Radiotherapy

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ABSTRACT

Purpose: The main objective of the study was to compare the efficacy and toxicity profile of patients with Head and Neck Squamous Cell Carcinoma (HNSCC) without curative treatment options treated with Hypo fractionated palliative radiotherapy 'Christie Regimen' versus Standard Palliative radiation. **Methodology:** This was double arm prospective study with 60 patients with biopsy proven stage IV inoperable HNSCC. 30 patients each was taken for arm A and B. All patients were treated on a telecobalt machine. ARM A (control arm) was given 300 cGy /10 # / 30 Gy / 2 weeks and ARM B (study arm) was given 312.5 cGy / 16 # /50 Gy /3.1 weeks. Response to the therapy was assessed six weeks after the completion of treatment using RECIST criteria. **Results:** The mean age of the study participants among the study and control arm was 65 ± 6.18 and 59 ± 6.23 respectively. Complete response was seen among 40% and 30% of the patients in study and control arm respectively. Static response was higher among the control arm (16.7%) than the study arm (3.3%). Acute toxicities for both Study and Control arm are not statistically significant. After 6 months follow up, 3 and 5 participants in the study and control arm group died. Quality of Life are also improved in Study arm but not statically significant. **Conclusion:** Comparing the standard palliative RT schedule with Christie regimen, the present study showed some improved response rates and improved Quality of life in Christie regimen with manageable toxicities.

KEYWORDS

Palliative radiotherapy; Christie regimen; Response, Head and Neck Cancers

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) are the 3rd most common cancer globally including India.(1) Most of the HNSCC present with advanced disease and gives poor results to common standard usual treatment like surgery and radiotherapy.(2) Head and neck cancers always show a significant treatment challenge as the disease will be near several critical tissues, such as the spinal cord, salivary glands, mandible and the organs of speech, swallowing, hearing and respiration.(3) Some of the major symptoms of advanced disease include pain, difficulty and pain during swallowing, earpain, voice change, cough and difficulty in breathing. The symptoms and treatment toxicity for the head and neck cancers always overlap. (4)

Nowadays majority of patients with head and neck squamous cell carcinoma (HNSCC) are unsuitable for aggressive radical treatment with surgery or chemoradiotherapy (CRT) and attempt to cure these cancers with aggressive treatment have not succeeded till date (5) because of a very advanced local and regional disease, co-morbidities, low performance status and distant metastasis. It has been documented that palliative radiotherapy (PRT) provides effective palliation and improved quality-of-life (QOL) in advanced Head and Neck cancers with no curative option (6,7,8) and constitute a part of cancer care globally.

There is a paucity of guidelines in current literature regarding the ideal choice of palliative treatment regimens for these patients with inadequate information on time, dose and fractionation; toxicity of such treatment; and Quality of Life issues pertinent to them.

According to Globacon 2018, Carcinoma of Lip and Oral cavity is first most common malignancy in Males and Third most common malignancy in Females. According to Population Based Cancer Registry (PBCR), during the period 2014-2015, Head and neck cancers in Males 22.35% of all cancer. In Females 7.41% of all cancer. Tongue and Buccal mucosa cases are common about 7% each followed by hypopharynx.

The majority of cancers in the head and neck region are with histology moderately differentiated squamous cell carcinomas. These cancers respond well to standard therapy like surgery or radiotherapy if in the early stage. Unfortunately, in India majority of the patients present with advanced disease which are unresectable and locoregionally bulky disease. Though there are many Quality of Life questionnaires and scales assessing the symptoms and features in head and neck cancers(10,11,12) the majority of them pertain to only for radical treatment for SCCHN. But for Palliative Radiotherapy for head and neck cancers there is still no specific assessment tool specifically incorporating and focusing on symptoms. In Head and neck cancers, the stage of the disease at the diagnosis determines the prognosis. Early stage (I and II) patients have a 60% to 95% chance of cure with local treatment alone, but with advanced disease the cure rate is very minimal and also most of the disease metastasize to distant organ. So the important predictors of prognosis in Head and Neck cancers are lymph node metastases and distant metastases. And also there will be an impact in the Quality of Life with these treatments. For example surgery may lead to facial disfiguration, Loss of voice and Dysphagia. Radiation therapy can also causes dysphagia, dry mouth and altered taste and smell. Ultimately, long-term effects of radiation can lead to pharyngeal or oesophageal stricture and osteoradionecrosis.

Combining chemotherapy with radiation increases this effects leading to severe mucositis and dermatitis. Chemotherapy itself cause alopecia, loss of weight and other effects. From this we can infer that Quality of Life is also an important tool during the treatment of Head and Neck Cancers for both curative and palliative intent.

As majority of head and neck cancer present with advanced disease, some of them are not candidates of curative treatment due to poor general condition or huge neck nodes or gross local disease and palliation is the only way for them. There is no level I evidence regarding the use of palliative head and neck radiotherapy, but several retrospective series, casecontrol studies, single arm prospective trials and one small randomized controlled trial(13,14) affirm that its use is associated with an improvement in outcome. Until recently, there are limited data for palliative radiotherapy in Head and Neck cancers comprising of retrospective series, case-control studies, limited single-institution experiences, and small prospective trials with varying dose-fractionation schedules. And also different form of hypofractionation is tried for. In radiobiological point of view, there will be definite benefit of an increased tumor cell kill because of the large fraction size in a short overall treatment time, by an increased potential for late side effects. So the hypofractionated regimes are used commonly for Head and Neck cancers in palliative setup.

Due to decreased oral intake and lower socioeconomic status leads to

poor nutritional state in majority of patients with advanced disease leading to very poor performance status. Also they need to travel some distance to the radiotherapy treatment centre leading to decreased compliance of patient to radiotherapy. The doses of 30 Gy in 10 fractions of 3Gy/# is considered standard for palliative radiotherapy. The Christie Hospital in Manchester created a 3 weekly regimen in the lace where the radiotherapy treatment centres are limited. Results of the responses and toxicity were more or less similar to the conventional schedules used before for the treatment of head and neck cancers with respect to local control and toxicity. This treatment protocol was then followed in many British RT centres and in the Christie hospital. Most of the randomized and non-controlled trials between conventional and hypofractionated schedules have also shown no difference in local control. Remarkably many of these regimens gave less severe late normal tissue reaction than expected given the short OTT and the high fraction dose. Because of these encouraging outcomes, the Erasmus MC-Daniel den Hoed Cancer Center also tried this palliative radiotherapy regimen in their centre and found good response with comparable toxicity with standard palliative RT(15) .

Objective

To compare the efficacy and toxicity profile of patients with Head and Neck Squamous Cell Carcinoma (HNSCC) without curative treatment options treated with Hypofractionated palliative radiotherapy 'Christie Regimen' versus Standard Palliative radiation

Methodology

Study Design: This was a double arm prospective study
Study Duration: One year
Study Population: Biopsy proven Locally advanced inoperable Head and Neck Cancer

Inclusion Criteria

- Participants aged above 70 years
- Biopsy proven Squamous cell carcinoma of Head and Neck
- Stage IV inoperable locally advanced tumours
- Major comorbidities
- Poor performance status
- Fungating tumor
- Distant metastases
- The combination of one or more of the aforementioned factors

Exclusion Criteria

- Patients with non-squamous histopathology or with tumours of paranasal sinuses, nasal cavity and nasopharynx were excluded from the study.

Sample Size

Totally 60 patients were included in the study. 30 each for Arm A and B were taken.

Procedure

Pre-treatment workup including biopsy confirmation, basic labor investigations and radiological investigations were done for all the participants.

Radiotherapy Technique

All patients were treated on a telecobalt machine with appropriate immobilization using bilateral fields, once daily for five days a week.
ARM A (control arm): 300 cGy /10 # / 30 Gy / 2 weeks
ARM B (study arm): 312.5 cGy / 16 # /50 Gy /3.1 weeks, off cording done at 10 fractions

All patients were monitored weekly during radiotherapy to note the treatment related toxicity. Immobilization was done by thermoplastic masks.

Physical Factors

A Megavoltage equipment, Cobalt-60 unit was used to provide the photon energies, treated at distances of 80 cm SSD.

Localization Requirements

Simulation films were taken and verified. Portals were simulated.

Target Volume

Lateral-opposed fields or single antero-posterior field were used for the primary tumor and involved lymph node disease. All fields given with a 1.5 - 2 cm margin to gross primary and nodal disease.

Dose Calculation

Complete isodose curves were required. The target dose specified in terms of a dose to a point at or near the center of target volume. For two opposed coaxial equally weighted beams: on the central ray at mid separation of beams. The variation did not exceed 10% of the target dose within the target volume. For all patients with post cricoid tumors with cervical esophageal extension, a mediastinal T field was used.

Radiobiology Behind The Study

According to Linear Quadratic model the Biologically Effective Dose (BED) for
50 Gy delivered in 16 # in 3.125 Gy/# is 65.625 Gy
30 Gy delivered in 10# in 3 Gy/# is 39 Gy

Response to the therapy (both clinical and radiological) was assessed six weeks after the completion of treatment. Response assessment was done using RECIST criteria version 2.0 and assessment of complete response, partial response, overall response and toxicities was done.

End Points Of The Study

Response rates using RECIST criteria Complete response (CR) Partial response [PR], and Stable disease. Acute toxicity by RTOG toxicity grading. Assessment of QoL after 6 months Follow-up.

Statistical Analysis

Data was entered in Microsoft excel and was analysed using SPSS version 24. Frequency for each variable was calculated and Pearson Chi square test was done to find the association and p value less than 0.05 was considered significant.

Ethical Consideration and Confidentiality

All the participants were informed regarding the purpose of the study. The study was undertaken after obtaining institutional ethical committee. Informed consent was obtained from all the participants. Confidentiality of the study participants was maintained throughout the study period.

RESULTS

The mean age of the study participants among the study and control arm was 65 ± 6.18 and 59 ± 6.23 respectively. Majority of the study participants in both the groups were male. 43.3% and 53.3% had tumour in oral cavity in control and study arm, followed by 40% and 30% in oropharynx in control and study arm. (Table 1). The stage and grade of the tumour is comparable between the groups. (Table 1).

Complete response was higher among the study group than the control group and static response was higher among the control group. (Table 2).

Acute toxicities for both Study and Control arm are not statistically significant (Table 3).

After 6 months follow up, 3 and 5 participants in the study and control arm group died

Quality of Life with respect to Pain, Performance and Weight loss of the patients in both the arms on follow-up are also improved in Study arm but not statically significant (Table 4).

DISCUSSION AND CONCLUSION

Radiotherapy with or without chemotherapy remains the mainstay of treatment in LAHNC. Because of advanced stage at the time of presentation, the local failure rates are as high as 55-70%, despite improvement in treatment strategies. For palliative treatment there is no definite standard regimen. The patients who are not in the curative intent also needs some sort of treatment as palliation to decrease the disease burden and improve the Quality of Life. Although the information about optimal hypofractionated palliative regimen for incurable HNSCC in the current literature is scanty, an optimal palliative Radiotherapy schedule is one that would provide worthwhile regression of the tumor and local symptoms within a short Overall Treatment Time with minimal toxicity. The advantage of hypofractionation are, the treatment is completed before accelerated repopulation, Second, the less treatment time helps in decrease utilization of resources and compliance, considering that this group of patients are usually of older age and often have poor performance status as well as significant co-morbidities. So if the treatment duration is decreased then with good compliance treatment can be completed and palliation intent can be achieved.

Hypo fractionated radiotherapy utilizes a small number of fractions with a larger dose per fraction. These regimes produce worse late effects than conventional fractionation when used in the curative setting. The acute reactions are acceptable if treatment volumes are kept small and tolerability could be improved by finishing the treatment in shorter time. This type of schedules is most suited to the patient with poor performance status in whom the aim of treatment is to palliate symptoms. These patients have a poor prognosis. There are a number of phase I and II studies that have looked at hypo fractionated palliative radiotherapy for advanced SCC of the head and neck. The QUAD SHOT (9) was developed with the aim of delivering short intense doses of radiation that were below the threshold for mucositis. The protocol consists of 14 Gy in four fractions over 2 days and can be repeated in responders up to a total dose of 42 Gy in 12 fractions. Other palliative schedules include that of Paris, who used 3.7 Gy twice a day for 2 days and repeated this monthly for 3 months. The hypo fractionated schedule involved treating patients twice per week in 6 Gy fractions to a total dose of 30-36 Gy. This is well tolerated in terms of acute reactions and is equivalent to 40 Gy in 2 Gy fractions in terms of tumor and mucosal effects. Comparing these protocols with each other is difficult because of the heterogeneity of advanced SCC of the head and neck and the problems associated with measuring quality of life rather than just survival.

The Christie Hospital in Manchester developed a 3-week schedule of RT during World War II when RT facilities were limited. In these group all patients received a dose of 3.12 to 3.28 Gy per day for total dose of 50 to 52 Gy. The median follow-up period was 5 years and 10 months. With 45% complete response and 28% partial response, an overall response rate of 73% was achieved, 6% had stable disease, and 21% progressed during or directly after completion of treatment. The median survival time was 17 months and 62 patients (40%) survived 1 year after RT. The aute and late toxicities are also comparable when compared to the standard palliative regimen. Results were found not to be different from the conventional schedules used in the previous treatment periods in terms of local control and toxicity. Many randomized and non-controlled trials have also shown no difference in local control between conventional and hypo fractionated schedules. Surprisingly, many of these schedules gave less severe late normal tissue reaction than expected given the short OTT and the high fraction dose.

In our study Comparing the standard palliative RT schedule with Christie regimen, the present study showed improved response rates and improved Quality of life in Christie regimen with acceptable acute toxicities.

Hence, it can be concluded that although there was no significant difference in Response rates, QOL improvement was in favour of Christie regimen schedules with manageable toxicities. But as such this regimen shows a better response than the conventional regimen with no significance. The total time needed in hypofractionated radiotherapy regimen were less, and this radiobiological superiority is beneficial for centers like our hospital where the patient load is higher than the facility available for radiation. Further studies with longer follow-up will be needed for confirmation to establish the long-term effects of this regime.

Conflict of Interest: Nil

Table 1: Profile Of The Study Participants

S no	Variable	Study Control				P value*
		Frequency	Proportion	Frequency	Proportion	
1	Age					0.016
	50-60	7	23.3	18	60	
	61-70	19	63.3	10	33.3	
	>71	4	13.3	2	6.7	
2	Gender					0.718
	Male	26	86.6	25	83.3	
	Female	4	13.4	5	16.7	
3	Smoking					0.278
	Yes	27	90	24	80	
	No	3	10	6	20	
4	Tobacco					0.793
	Yes	12	40	13	43.3	
	No	18	60	17	56.7	
5	Grade	4	13.3	2	6.7	0.751
	Well differentiated					
	Moderately differentiated	17	56.7	18	60	
	Poorly differentiated	5	16.7	4	13.3	
	Undifferentiated	4	13.3	6	20	
6	Stage					0.739
	III	6	20	5	16.7	
	IV	24	80	25	83.3	

*-chi square test applied

Table 2: Response Rate Among The Study Participants

S no	Response rate	Study		Control		P value*
		Frequency	Proportion	Frequency	Proportion	
1	Complete	12	40	9	30	0.210
2	Partial	17	56.7	16	53.3	
3	Static	1	3.3	5	16.7	

*-chi square test applied

Table 3: Acute Toxicity Among The Study Participants

S no	Variable	Study		Control		P value*
		Frequency	Proportion	Frequency	Proportion	
1	Skin toxicity					0.814
	Grade 1	10	33.3	12	40	
	Grade 2	17	56.7	16	53.3	
	Grade 3	3	10	2	6.7	
2	Mucositis					0.857
	Grade 1	12	40	14	46.7	
	Grade 2	14	46.7	12	40	
	Grade 3	4	13.3	4	13.3	
3	Xerostomia					0.959
	Grade 0	5	16.7	6	20	
	Grade 1	12	40	11	36.7	
	Grade 2	8	26.6	9	30	
	Grade 3	5	16.7	4	13.3	
4	Laryngitis					0.868
	Grade 0	6	20	8	26.7	
	Grade 1	12	40	10	33.3	
	Grade 2	10	33.3	9	30	
	Grade 3	2	6.7	3	6.7	
5	Oesophagitis					0.804
	Grade 0	5	16.7	8	26.7	
	Grade 1	12	40	11	36.7	
	Grade 2	10	33.3	9	30	
	Grade 3	3	10	2	6.6	

*-chi square test applied

Table 4: Distribution Of Study Participants According To Pain, Performance And Weight Loss After 6 Months Follow Up

S no	Variable	Study (N=27)		Control (N=25)		P value*
		Frequency	Proportion	Frequency	Proportion	
1	Pain					0.053
	Improved	16	59.3	7	28	
	Worsened	2	7.4	8	32	
	No change	9	33.3	10	40	
2	Performance					0.205
	Improved	17	63	9	36	
	Worsened	4	14.8	8	32	
	No change	6	22.2	8	32	
3	Weight loss					0.498
	Improved	9	33.3	5	20	
	Worsened	5	18.5	8	32	
	No change	13	48.2	12	48	

*-chi square test applied

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