Original Research Article

A comparative study of weekly versus daily schedule of hypofractionated palliative radiotherapy with concurrent chemotherapy in the treatment of locally advanced head and neck cancer

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Abstract

Background: Most head and neck cancer cases and deaths are due to both individual predispositions linked to certain genetic characteristics, and exposure to carcinogens caused by lifestyle behaviors. We compared weekly versus daily schedule of hypofractionated palliative radiotherapy with concurrent chemotherapy in the treatment of locally advanced head and neck cancer.**Materials & Methods:**Fifty patients, randomly selected were divided in to two groups of 25 patients each. Group A: - These patients received injection Cisplatin 40 mg/m 2 given intravenously 2 hrs infusion six hour before radiation and repeated weekly for 6 cycles. Group B: - This group consisted of randomly selected, previously untreated 25 patient of squamous cell carcinoma of head and neck. Thesepatients received injection Cisplatin 40mg/m 2 given intravenously 2 hrs infusion six hour before radiation and repeated weekly for 3 cycles. **Results:** Incidence of well differentiated histology was 20% in both arm, poor differentiated was 8 % and 4% respectively in arm-A and Arm-B, undifferentiated was 52% and 44% respectively in arm-A and arm-B. It was observed that moderately differentiated squamous cell carcinoma was the commonest in both arm-A and arm-B i.e. 13(52%) in arm-A and 11(44%) in arm-B. The P value was insignificant in each group. Among the arm-A and arm-B the complete response is 20% and 36% ($\chi 2$ = 4.571, p=0.032), the partial response is 52% and 44% ($\chi 2$ = 0.667, p=O.414). Stable disease in the arm-A and in arm-B was 12% and 8% ($\chi 2$ = 0.800, p=O.371) respectively and progressive disease was 16% and 12% respectively ($\chi 2$ = 0.571 p=O.449).**Conclusion:** Hypofractionated radiotherapy with either 600cGy per fraction given weekly or 300cGy per fraction given daily along with concurrent chemotherapy are feasible options for palliation in advanced head and neck cancers. 300cGy given daily schedule is associated with slightly higher acute reactions but increases the chances of complete response. The 300cGy daily arm patients completed treatment in 3 weeks as against 6 weeks for 600cGy weekly arm. 600cGy weekly radiotherapy given on Saturday is a feasible alternative to daily 300cGy schedule with lesser burden to the busy radiotherapy department.

Keywords: Hypofractionated,Palliative,Radiotherapy

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Introduction

Among Indian population, head and neck cancer leads to an estimated incidence of 12.48 cases per 100,000 population for males and 5.52 per 100,000 populations in females. The estimated mortality is about 3.48 per 100,000 in males and 1.34 per 100,000 in females. Most of head and neck cancers are histologically squamous cell carcinomas (90-95%)[1].Most head and neck cancer cases and deaths are due to both individual predispositions linked to certain genetic characteristics, and exposure to carcinogens caused by lifestyle behaviors. In addition, exposure to two or more of the following risk factors has a synergistic effect on increasing oral cancer risk[2]. Tobacco smoking in the form of cigarettes, bidis, cigars /chutta / cheroot, dhumti (Goa), the water pipes/hookah (north India), reverse chutta smoking (coastal regions of Andhra Pradesh and Orissa), hookli (Gujarat) and chillum (northeastern parts of India)[3]. Around 57% of all men and 11% of women in India, between 15 and 49 years of age use tobacco in some form. Results from the global youth tobacco survey in India show that about 10 to 20% of students in 8th to 10th grades (about 13- 15 years), currently use tobacco in some form[4].Squamous cell carcinoma of the head and neck region constitute approximately 25% of the total cancer patient population treated at our center, and about 30% of these patients are treated with only palliative intent[5]. Conventionally, recent phase II trials have suggested alternative hypo-fractionated schedules for palliation where the overall treatment duration is further reduced[6]. It was assumed that such hypo-fractionated concurrent radiotherapy would be cost effective and equally efficacious and would ensure better patient compliance[7].In present study we compared weekly versus daily schedule of hypofractionated palliative radiotherapy with concurrent chemotherapy in the treatment of locally advanced head and neck cancer.

Materials & Methods

The present study was conducted on a total of 50 patients of locally advanced carcinoma of head and neck. All patients will be histologically proved squamous cell carcinoma at Acharya Tulsi

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Regional Cancer Treatment and Research Institute, Sardar Patel Medical College and associated group of hospitals, Bikaner. Inclusion criteria was patients with histologically proven advanced squamous cell carcinoma of the head and neck(Stage III /IV), age: ≤70years, European Co-operative Oncology Group (ECOG) performance status (0-1-2), no prior malignancy oriented treatment and adequate base line organ function (Hematological, RFT, LFT& Other).Complete history and general physical examination with an assessment of the patient's clinical performance status, and dental status. Quality of Life assessments was done prior to the start of treatment. Local examination of oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx was done under aseptic conditions. Primary site of malignancy was inspected for site, size, shape, surface, borders, margins, base, infiltration to surrounding structures and any signs of inflammation. All the findings of inspection was confirmed by palpation. Careful examination of lymphatic system of head & neck was performed for the level of lymph nodes (level 1to 5) involved, number, size, consistency, mobility, and any sign of inflammation. All patients were staged according to the American Joint committee on cancer staging, 2011 staging system. Fifty patients, randomly selected were divided in to two groups of 25 patients each. The randomization scheme (Appendix V) was generated by using the web site Randomization. com (http://www.randomization.com). The groups were as under:

Group A: - This group consisted of randomly selected previously untreated 25 patients of squamous cell carcinoma of head and neck. These patients received injection Cisplatin 40 mg/m^2 given intravenously 2 hrs infusion six hour before radiation and repeated weekly for 6 cycles. All patients received 36Gy(BED-54.4Gy) concurrent radiation at the rate of 6 Gy/fraction 1fraction /week, 6 fraction in 6weeks by cobalt-60 Theratron -780 E/780C or Bhabhatron-II telecobalt units by bilateral parallel opposed portals.

Group B: - This group consisted of randomly selected, previously untreated 25 patient of squamous cell carcinoma of head and neck. These patients received injection Cisplatin 40mg/m 2 given intravenously 2 hrs infusion six hour before radiation and repeated weekly for 3 cycles. All patients received 42Gy (BED-54.6 Gy) concurrent radiation at the rate of 3 Gy/ fraction 1 fraction /day, 5 fractions /week, 14 fractions in 3weeks (18 days) by cobalt-60 Theratron -780 E/780C or Bhabhatron-II telecobalt units by bilateral parallel opposed portals.Treatment fields included both primary tumor site plus neck nodes region. Parallel opposed bilateral fields & unilateral field (in unilateral disease) was planned. The dose was prescribed at midline. Surface bolus was used where there is dermal involvement or skin fungation. Patients in both arms received concurrent chemo-radiation were accessed weekly for local disease response & development of any acute skin or mucosal & haematological reactions. Treatment response were assessed as per the WHO Tumor Response Criteria (Appendix-III).

Acute mucosal and skin toxicity were assessed. The result of both arm were analyzed & compared in terms of various aspects like drug toxicity profile, tumor response (primary), & local disease (nodal) status. The data thus collected was analyzed by using Chi-Square test for co-relation.

Results

Table 1: Gender distribution

Sex	No. of patients		Percentage (%)		P value
	Arm-A	Arm-B	Arm-A	Arm-B	
Male	24	22	96	88	0.42
Female	1	3	4	12	

Table 1 shows that majority of the patients enrolled in arm-A as well arm-B were males.

Table 2:ECOG(performance status) grade

Grade	Arm-A (%)	Arm-B (%)	χ^2	P value
1	14 (56)	17 (68)	1.161	0.281
2	11 (44)	8 (32)	1.895	0.168

Table 2 shows that 14 (56%) patients in arm-A and 17(68%) in arm-B were of ECOG -1and. 11 (44%) patients in the arm-A and 8 (32%) in arm-B were of ECOG –II respectively.

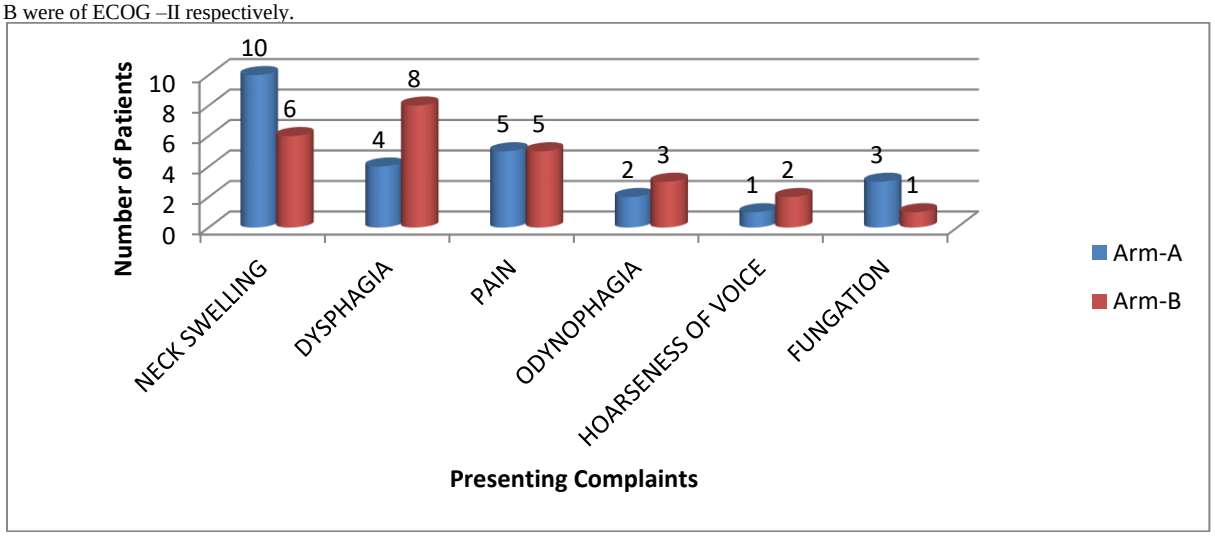

Fig 1: Complaints of patients

Fig 1shows that 10(40%) patients in the arm-A and 6(24%) patients in the arm-B presented with neck swelling, 4(16%) patients in the arm-A and 8(32%) patients in the arm-B presented with dysphagia, 5(20%) patients in the arm-A and 5(20%) patients in the arm-B presented with pain, 2(8%) patients in the arm-A and 3(12%) patients in the arm-B presented with odynophagia and 1(4%) from the arm-A and 2 (8%)in arm-B presented with hoarseness of voice. Neck swelling Dysphagia (40%) was the most common symptom in the arm-A, whereas dysphagia (32%) was common among controls. Above all neck swelling (40%) was the most common among all patients.

Table 3:Histological differentiation of primary tumor

Differentiation of Squamous Cell Carcinoma	Arm-A	Arm-B	χ^2	*P value*
Well differentiated	5 (20)	5 (20)	0.00	-
Moderately Differentiated	13 (52)	11 (44)	0.667	0.4140
Poorly Differentiated	2 (8)	1 (4)	1.333	0.248
Undifferentiated	5 (20)	8 (32)	2.769	0.0961
Total	25	25	-	-

Table 3 shows that incidence of well differentiated histology was 20% in both arm, poor differentiated was 8 % and 4% respectively in arm-A and Arm-B, undifferentiated was 52% and 44% respectively in arm-A and arm-B. It was observed that moderately differentiated squamous cell carcinoma was the commonest in both arm-A and arm-B i.e. 13(52%) in arm-A and 11(44%) in arm-B. The P value was insignificant in each group.

Table 4:Primary response based on t-status (at end of radiotherapy)

T-Status	CR		PR		SD		PD	
	Arm-A	Arm-B	Arm-A	Arm-B	Arm-A	Arm-B	Arm-A	Arm-B
T3	4(16)	7(28)	3(12)	3(12)	2(8)	0	2(8)	1(4)
T4	3(12)	5(20)	6(24)	4(16)	3(12)	3(12)	2(8)	2(8)

Table 4 shows that among the arm-A and arm-B the complete response for the primary based on T-stage was T3:16% and 28% (χ2=3.273,p=0.070)and T4: 12% and 20%(χ2=2.00,p=1.531), the partial response was T3:12% and T4:24% and 16%(χ2= 1.600, p=0.205)respectively. Stable disease was T3:8% in the arm-A and T4:12% in both arm. At end of radiotherapy progressive disease was T3:8% & 4% in arm-A and arm-B (χ2=1.33,p=0.248) respectively and T4:8% in both arm.

Table 5:Treatment response (at end of radiotherapy)

Response	No of Patients (%)		χ^2	*P value*
	Arm-A	Arm-B		
CR	6 (24)	11(44)	5.882	0.015
PR	12 (48)	8 (32)	3.200	0.073
SD	4 (16)	4 (16)	0.000	-
PD	3 (12)	2 (8)	0.800	0.371

Table 5 shows that at end of sixth week of treatment, 6(24%) patients had complete response in arm-A and 11(44%) patients in arm-B (χ2=5.882, p=0.0152). Partial response in arm-A and arm-B was 48% and 28% respectively (χ2=3.200, p=0.073). Stable disease in arm-A and arm-B was 16% in both arms. Progressive disease in arm-A and arm-B was 12% and 8% respectively (χ2=0.800, p=0.371).

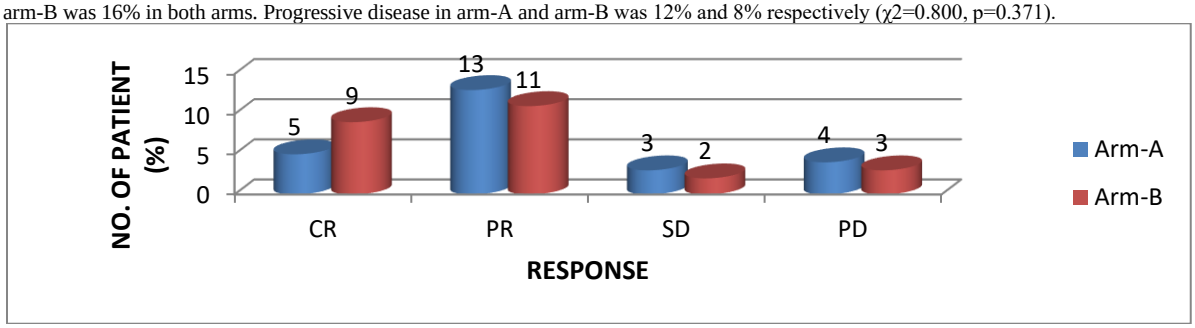

Fig 2:Overall treatment response

Fig 2 shows that among the arm-A and arm-B the complete response is 20% and 36% (χ2 = 4.571, p=0.032), the partial response is 52% and 44% (χ2 = 0.667, p=O.414). Stable disease in the arm-A and in arm-B was 12% and 8% (χ2 = 0.800, p=O.371) respectively and progressive disease was 16% and 12% respectively (χ2 = 0.571 p=O.449).

Discussion

The aim of palliative radiation in any advanced cancer is to relieve the symptoms quickly while minimizing the side-effects[8]. In addition, the treatment should be delivered in the shortest possible time considering the patients and caregivers convenience[9]. Squamous cell carcinoma of the head and neck region constitute approximately 25% of the total cancer patient population treated at our center, and about 30% of these patients are treated with only palliative intent[10,11]. Hence, we undertook this study to identify the best possible palliative radiation schedule in such patients.In present study, arm- A had 24 males and arm- B had 22 males. We found that 14 (56%) patients in arm-A and 17(68%) in arm-B were of ECOG -1and. 11 (44%) patients in the arm-A and 8 (32%) in arm-B were of ECOG –II respectively.Vikram et al[12] has suggested that advanced cancers of head and neck from developing countries do not show favorable outcomes and it would seem prudent to explore novel ways of providing relief to these patients. It is now realized that a proportion of advanced stage IV patients have life-limiting disease.

We found that 10(40%) patients in the arm-A and 6(24%) patients in the arm-B presented with neck swelling, 4(16%) patients in the arm-A and 8(32%) patients in the arm-B presented with dysphagia, 5(20%) patients in the arm-A and 5(20%) patients in the arm-B presented with pain, 2(8%) patients in the arm-A and 3(12%) patients in the arm-B presented with odynophagia and 1(4%) from the arm-A and 2 (8%)in arm-B presented with hoarseness of voice. Porceddu et al[13] in a multicentric study reported on 35 patients treated with a novel hypofractionated radiotherapy regimen (30 Gy/5fractions /2fractions per week, at least 3 days apart with additional boost of 6 Gy for limited volume disease. The overall objective response rate was 80%. In present study an overall objective response (CR+PR) of 72% and 80% were found in arm-A and arm-B, respectively. When primary site evaluation was done for arm-A patients, 7(28%) and in the arm-B 11(44%) had CR, 9 (36%) in the arm-A and 8 (32%) in the arm-B had PR, 5 (20%) and 3 (12%) had SD in the arm-A and arm-B respectively, PD had 4(16%) and 3(12%), respectively. When nodal status were assessed out of arm-A and arm-B patients, 9(36%) and 13 (52%) had CR, 9 (36%) in the arm-A and 6 (32%) in the arm-B had PR, 5 (20%) and 2 (8%) had SD in the arm-A and arm-B, respectively PD had 5(20%) and 2(8%), respectively. We found that neck swelling and dysphagia (40%) was the most common symptom in the arm-A, whereas dysphagia (32%) was common among controls. Above all neck swelling (40%) was the most common among all patients.We found that incidence of well differentiated histology was 20% in both arm, poor differentiated was 8 % and 4% respectively in arm-A and Arm-B, undifferentiated was 52% and 44% respectively in arm-A and arm-B. It was observed that moderately differentiated squamous cell carcinoma was the commonest in both arm-A and arm-B i.e. 13(52%) in arm-A and 11(44%) in arm-B.Weissberg et al[14] compared the efficacy of high fractional dose(400 cGy/10-12 fractions/2-3week/4fractions per week) and conventional radiotherapy (60-70 Gy/30-35 fractions/6-7 weeks). No statistical differences of results were found in either arm.

We observed that among the arm-A and arm-B the complete response for the primary based on T-stage was T3:16% and 28% and T4: 12% and 20%, the partial response was T3:12% and T4:24% and 16%respectively. Stable disease was T3:8% in the arm-A and T4:12% in both arm. At end of radiotherapy progressive disease was T3:8% & 4% in arm-A and arm-B respectively and T4:8% in both arm.We found that at end of sixth week of treatment, 6(24%) patients had complete response in arm-A and 11(44%) patients in arm-B. Partial response in arm-A and arm-B was 48%and 28% respectively. Stable disease in arm-A and arm-B was 16% in both arms. Progressive disease in arm-A and arm-B was 12% and 8% respectively. Paris et al [15] analyzed 37 patients in a non-randomized Phase I-II trial, used twice a day fraction (370 cGy per fraction) for 2 consecutive day's total dose of 1480 cGy per course. Previously untreated malign-ancies were present in 24 lesions, primary recurrent diseases in six patients, metastasis to the head and neck in five patients and skin primaries in the remaining two cases. At presentation, 15 of 37 patients (or 17 of 39 lesions) were inoperable due to poor medical status, eight patients were considered technically in operable due to extent of disease, 10 patients had distant metastasis and four patients refused surgery. Three courses were given at 3-week intervals for a final tumor dose of 4,440 cGy in twelve fractions over 8-9 weeks. After completion of therapy, 11/39 (28%) complete response; 19/39(49%) partial response; 4/39(10%) no response and 3/39(8%) had progressive disease.

Conclusion

Authors found that hypofractionated radiotherapy with either 600 cGy per fraction given weekly or 300 cGy per fraction given daily along with concurrent chemotherapy are feasible options for palliation in advanced head and neck cancers. 300cGy given daily schedule is associated with slightly higher acute reactions but increases the chances of complete response. The 300cGy daily arm patients completed treatment in 3 weeks as against 6 weeks for 600cGy weekly arm. 600cGy weekly radiotherapy given on Saturday is a feasible alternative to daily 300cGy schedule with lesser burden to the busy radiotherapy department. This has an advantage that the radiotherapy machine can be used for curative radiation treatment during weekdays.

Conflict of Interest: Nil
Source of support:Nil

References

1. Rohde S, Kovacs et al. Intra-arterial high-dose chemotherapy with cisplatin as part of a palliative treatment concept in Advanced oral cancer. AJNR Am J Neuroradiol. 2005; 26(7):1804-9.
2. D.I. Hodson, E. Bruera, L. Eapen et al., The role of palliative radiotherapy in advanced head and neck cancer. Can J Oncol 1996; 6(1)S: 54–60.
3. Erkal HS, Mendenhall WM, Amdur RJ, Villaret DB, Stringer SP. Squamous cell carcinomas metastatic to cervical lymphnodes from an unknown head and neck mucosal site treated with radiation therapy with palliative intent. Radiother Oncol 2001;59:319–21.
4. Al-mamgani A, Tans L, Van rooij PH, Noever I, Baatenburg de jong RJ, Levendag PCHypofractionated radiotherapy denoted as the "Christie scheme": an effective means of palliating patients with head and neck cancers not suitable for curative treatment. Acta Oncol. 2009; 48(4):562-70.
5. Isaacs JH Jr, Schnitman JR. Outcome of treatment of 160 patients with squamous cell carcinoma of the neck staged N3a. Head Neck. 1990;12(6):483-7.
6. Corry J, Peters LJ, Costa ID, Milner AD, Fawns H, Rischin D, et al. The Quad shot: A phase II study of palliative radiotherapy for incurable head and neck cancer. Radiother Oncol. 2005;77:137–42.
7. Schiff PB, Fant J, Horwitz SB. Promotion of microtubule assembly in vitro by Taxol. Nature 1979;277:665-7.
8. Hong A, Saunders Ml, Dische S, Gosch E, Fermont D, Ashford RFU, Maher EJ. An audit of head and neck cancer treatment in a regional centre for radiotherapy and oncology. Clin Oncol. 1990; 2 :130-137.
9. Al-mamgani A, Tans L, Van rooij PH, Noever I, Baatenburg de jong RJ, Levendag PC Hypofractionated radiotherapy denoted as the "Christie scheme": an effective means of palliating patients with head and neck cancers not suitable for curative treatment. Acta Oncol. 2009;48(4):562-70.
10. Jones GW, Browman G, Goodyear M, Marcellus D,Hodsond D lan. Comparison of the addition of T and N integer scores withstage groups in head and neck cancer. 1993;15:497-503.
11. Vikram B. Editorial—cancers of the head and neck region in developing countries.Radiother Oncol 2003;67:1–2
12. Porceddu SV, Rosser B, Burmeister BH, et al. Hypofra-ctionated radiotherapy for the palliation of advanced head and neck cancer in patient unsuitable for curative treatment-hypo trial. Radiother Oncol 2007;85:456-62
13. Weissberg JB, Pillsbury H, Sasaki CT et al High fractional dose irradiation ofadvanced head and neck cancer. Implications for combined radiotherapy and surgery Arch Otolaryngol. 1983 ;109(2):98-102
14. Paris KJ, Spanos WJ et al Phase I-II study of multiple daily fractions for palliation of advanced head and neck malignanc-ies, Int J Radiat Oncol Biol Phys. 1993;25(4):657-60.