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Comparative study of concurrent chemo-radiation in locally advanced head and neck carcinoma treated with 3DCRT versus telecobalt (2D) therapy in relation to toxicity and response

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***Abstract*---**Background: Radiotherapy techniques in Head and neck cancers have evolved over years from 2D RT to conformal techniques. As conformal radiotherapy planning is more time consuming, costly and not available in every radiotherapy centre in India, we can consider Conventional 2D radiotherapy for patients in a country like India where we get large number of patients with low economic profile and with locally advanced stages. Aims: To compare the clinical response along with acute and late treatment related toxicity between two treatment modalities namely 3DCRT versus Telecobalt therapy during and after completion of Radiotherapy. Materials and Methods: 50 patients of Head and Neck cancer were enrolled in the study and were divided into two arms. Arm A consists of the patients planned for conventional EBRT and Arm B consists of the patients planned for 3DCRT. Statistically analysis was performed with the help of Epi Info (TM) 3.5.3. Chi Square(X2) test was used to test the association of

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different study variables with the study groups. T-test was used to compare the means. z-test was used to test the significant difference between the two proportions. Results: The study was performed with 50 patients of Stage III and IVA of head and neck cancer, 25 patients in Arm A and 25 patient in arm B. Arm A-Conventional Telecobalt RT 66/33 fraction and Arm B -3DCRT 60/33 fraction. In both the Arms concurrent weakly cisplatin 40 mg/m2 was given along with radiotherapy. At the end of radiotherapy, 6 weeks, 3 months acute and late toxicities were assessed by RTOG scoring criteria for the skin reaction, mucositis, dysphagia, laryngeal toxicity and xerostomia. Clinical assessment, Radiological criteria and Fiber optic laryngoscopy were used to assess response after 6 weeks, 3months of Radiation completion. At 3 months of follow up-Both Arm A and B complete response rates were 64% and 68% respectively and at one year of follow up were 64% each respectively .There was no superiority of 3DCRT over Conventional Telecobalt therapy. At the end of RT, most of the patients had Grade 2 mucositis, 60% in Arm A and 56% in Arm B. 80% of patients in Arm A and 70% of patients in developed grade 2 Dysphagia at the end of radiotherapy. Arm B has less number of patients who developed Grade 3 dysphagia and need of Ryle tube feeding (12% vs 20% in Arm A). At the end of RT, 92% of patients in Arm A and 88% patients in Arm B developed grade 1 skin reaction and no patient developed grade 3 skin reaction . The results are comparable in both the Arms. Conclusion: Thus in the end it can be stated that both RT techniques resulted in similar outcomes and toxicities were not significantly different. However, this study showed a strong trend suggesting that 3D conformal RT results in less xerostomia. The most appropriate dose distribution with 3-D conformal RT allows partial sparing of parotid glands, in particular, in patients with No/N1 disease, because most of these patients not all cervical lymph node areas must be irradiated.

***Keywords*---**comparative, locally advanced, telecobalt, 3DCRT, radiotherapy, response, toxicity.

Introduction

Squamous cell carcinoma of Head and Neck remains a significant global health problem, with more than 450,000 new diagnoses worldwide each year.[1]Cancers of oral cavity and oropharynx are among the most common cancer HNC worldwide with an estimated 400,000 incident cases and 223,000 deaths.[2]Concurrent chemo radiation has been advocated as a part of organ preservation protocol with good outcomes in cancers of oropharynx andlaryngopharynx.[3] Radiotherapy techniques have evolved over the past 30 years from being two-dimensional(2D) to three-dimensional(3D) images, incorporating increasingly complex computer algorithms.[4] We can use either conventional simulator based Telecobalt therapy or CT scan /3D TPS based planning where the cost is much higher and mostly concentrated in metropolitan cities, on the other hand, conventional Telecobalt RT

machine is much easily available, economic and comparable results documented in locally advanced head and neck cancers.

Aims and Objective

To compare the clinical response between the treatment modalities at 6weeks, 3 months and 1year of treatment completion. To compare the toxicities (in regard to mucositis, dysphagia, skin toxicity, xerostomia at the end of radiation, at 6 weeks, 3months and one year of follow up.

Material and Methods

Methodology

Source of Data

This prospective observational study was conducted between December 2018 to December 2019.

Pretreatment Evaluation

Complete clinical history, examination (both local and systemic). Examination of Lymph nodes was also done. Patients were investigated with routine blood investigations like complete hemogram/RFT/LFT, Chest X-Ray, Dental evaluation and Contrast enhanced CT Scan of Head and Neck Region. Patients were also evaluated at ENT department by routine Fiber optic Laryngoscopy examination and biopsy from the lesion. All patients were staged according to the AJCC TNM staging Manual 8th edition.

Consent of the patient

Patients informed written consent was obtained in their own language. Patients information leaflet was provided to every patient.

Inclusion Criteria

Patients with age >18 years and <70years including both sexes.
Patients with histologically proven Squamous cell carcinoma of oral cavity and oropharynx with stage III and non metastatic Stage IV.
Normal haematological tests.
Normal liver and renal function test.
Patients with controlled hypertension and diabetes mellitus.
Written informed consent.
Patients with ECOG ≤ 2.
No prior history of radiation to head and neck region.

Exclusion criteria

- Patient with distant metastasis.
- Patient with stage 1 and stage 2 tumour.

- ECOG>2
- History of previous treatment with surgery, radiotherapy, chemotherapy.
- Pregnant and breast feeding women.
- Medically unfit patients including patients suffering from severe cardiopulmonary disease, uncontrollable diabetes, residual paralysis from CVA, immune compromised patients.

Parameters of study

Response

After radiotherapy the response was evaluated by clinical, direct oropharyngoscopy, Laryngoscopy at end of RT, 6 weeks, 3 months and at one year.

Toxicities

Toxicity studies were done weekly during treatment, at the end of RT and at 6weeks, 3 months and one year of completion of treatment. Toxicities studies include
Mucositis
Dysphagia
Dermatitis
Xerostomia
Grading was done according to RTOG grading system.

Study design

A prospective observations non-randomized comparative study.

Grouping of patients

The Arm 'A' consisted of patients planned for the Conventional Telecobalt RT and Arm 'B' consisted of patients planned for 3DCRT.

Treatment plan

- **Arm A:** Radiotherapy Protocol -
  Depending upon the Primary tumor site, patients were treated with two parallel opposed fields or three field technique. Telecobalt Theratron Elit-80 has gamma energy of 1.25 Mev, maximum field size of 35×35 cm^2 and minimum field size of 5×5 cm^2 Simulation was taken from verification of radiation portals and necessary connections were were made before start of treatment . The spinal cord was shielded after 46Gy .The radiation dose delivered was 66Gy in 33 fractions.
- **Arm B:**
  Patients were treated with 6MV linear accelerator machine with MLC (3DCRT planning).Target volume for oral cavity and oropharyngeal cancer patients are based on ICRU 50. GTV includes the primary tumor and metastatic lymph nodes. This is usually expanded to include a margin of 1.5 cm for microscopic

extension forming the Clinical target volume. CTVs are expanded to account for organ motion and set-up uncertainity to form Planning target volume. RTOG currently recommends 5 to 10 mm for patients treated with standard linear accelerators. During plan evaluation, target is 95% of the isodose (treated volume) should cover 100% of the PTV. Seimens Primus Accelerator has single photon energy of 6MV and six electron energies such as 5,7,8,10,12 and 14Mev used for the treatment and Oncentra 4.3 computed software was used for planning purpose.

Treatment Monitoring

Acute Toxicity were assessed once weekly. Response was assessed clinically by oropharyngoscopy/RECIST criteria. Toxicities were assessed by CTCAE.

Follow-up

The first follow-up was done after completion of treatment. During follow-up patients were assessed for response and toxicities.

Result and Analysis

Data Analysis: For statistically analysis data were entered into a Microsoft excel spreadsheet and then analysed by SPSS 20.0.1 and Graph Pad Prison version 5. Data have been summarized as mean and standard deviation for numerical. Variables and Count and percentage for categorical variables. The median and interquartile range have been stated for numerical variables that are not normally distributed. Student's independent samplest-test was applied to compare normally distributed numerical variables between groups, unpaired proportions, were compared by Chi-Square test, as appropriate z-test (standard normal deviation) was used to test the significant difference between two proportions. Once a t value is determined, p value can be found using a table of values from student-t distribution. If the calculated p value is below the threshold chosen for statistical significance (usually 0.10, the 0.05or 0.01 level) then the null hypothesis is rejected in favour of the alternate hypothesis.

P value<=0.05 was considered for statistically significant. In this study, 50 patients (25 patients in each arm) were taken for final analysis. Evaluation of overall response (Table-1). At 6 weeks of follow up, Both Arm A and Arm B complete response (CR) rates were 60% and 56% respectively. This difference was not statistically significant (p>0.05). Arm A had partial response (PR) rate of 32% and Arm B had partial response rate of 24% .This difference was not statistically significant (p>0.05). At 3months of follow-up, Arm A had a complete response rate of 64% vs 68% in Arm B respectively. This difference was not statistically significant (p value>0.05). And one year of follow-up, complete response rates were 64% in both Arm A and Arm B respectively (difference not statistically significant p value>0.05). Progressive Disease or Death was present in 36% of patients in Arm A vs 28% Arm B (p value>0.05).

Table 1
Evaluation of Overall Response to treatment in two arms

Response evaluation	Response	Arm-A		Arm-B		p value
		No.	%	No.	%	>0.05
6 weeks response	CR	15	60	14	56	>0.05
	PR	8	32	6	24	>0.05
	SD	2	8	3	12	>0.05
	PD	0	0	2	8	>0.05
3 months response	CR	17	68	16	64	>0.05
	PR	6	24	1	4	>0.05
	SD	2	8	2	8	>0.05
	Death	0	0	6	24	>0.05
1 year response	CR	16	64	16	64	>0.05
	PR	2	8	0	0	>0.05
	Death	7	28	9	36	>0.05

Evaluation of overall Mucosal Toxicity (Table-2): At the End of Radiotherapy, Mucositis Grade1: 2(8%), Grade2:8(32%), Grade 3:15(60%) in Arm A and was Grade 1:1(4%), Grade 2:10(40%),Grade 3:14(56%) in Arm B. Arm B had higher Grade 2toxicitylocalised to area of treatment but this was not statistically significant($p>0.05$). At 3months Grade 0:23(92%), Grade1:2(8%) in Arm A and was Grade 0.16(84.2%), Grade 1:3 (15.8%) in Arm B. At 6months Grade 0:23(100%) in Arm A and Grade0:16(100%) in Arm B with no Grade 1 and 2 toxicity in both groups. In both the groups, most of the patients had Grade 0 late toxicity of mucous membrane noted at 3months, 6 months of follow-up. Also, there was no statistically significant difference in late toxicity level of mucous membrane between two groups ($p>.05$).

Table 2
Overall mucosal toxicity in two arms

Overall Mucosal Toxicity	Grade	Arm-A		Arm-B		p value
		No.	%	No.	%	
At completion of Radiotherapy	Grade 1	2	8	1	4	>0.05
	Grade 2	8	32	10	40	>0.05
	Grade 3	15	60	14	56	>0.05
3 months post EBRT	Grade 0	23	92	16	84.2	>0.05
	Grade 1	2	8	3	15.8	>0.05
	Grade 2	0	0	0	0	>0.05
6 months post EBRT	Grade 0	23	100	16	100	>0.05
	Grade 1	0	0	0	0	>0.05
	Grade 2	0	0	0	0	>0.05

Evaluation of overall Dysphagia Toxicity (Table3): End of RT Dysphagia Grade 1:3(12%), Grade 2:17(68%), Grade 3:5(20%) in Arm A and was Grade 1:2(8%), Grade 2:20(80%), grade 3:3(12%) in Arm B. Arm B had lower grade 3 toxicity but was not statistically significant(p>0.05). At 3 months Grade 0:16(64%), Grade1:7(28%), Grade 2:2(8%) in Arm A and was Grade 0:16(84.2%), Grade1:3(15.8%) in Arm B. At 6months Grade 0:23(100%) in Arm A and Grade 0:16(100%) in Arm B with no Grade 1& 2 toxicity in both arms. In both the arms most of the patients had Grade 0 late toxicity of pharynx and esophagus at 3months, 6 months of follow-up. Also there was no statistically significant difference between the Arms in respect of late toxicity of pharynx and esophagus (p>0.05)

Table 3
Overall dysphagia toxicity in two arms

Overall DysphagiaToxicity	Grade	Arm-A		Arm-B		p value
		No.	%	No.	%	
At completion of Radiotherapy	Grade 1	3	12	2	8	>0.05
	Grade 2	17	68	20	80	>0.05
	Grade 3	5	20	3	12	>0.05
3 months post EBRT	Grade 0	16	64	16	84.2	>0.05
	Grade 1	7	28	3	15.8	>0.05
	Grade 2	2	8	0	0	>0.05
6 months post EBRT	Grade 0	23	100	16	100	>0.05
	Grade 1	0	0	0	0	>0.05
	Grade 2	0	0	0	0	>0.05

Evaluation of overall skin toxicity (Table-4): At the completion of Radiotherapy Arm A had Grade 1:22(88%), Grade 2:3(12%) while Arm B had Grade1:23(92%), Grade 2:2(8%). There was no Grade 3 or higher Skin Toxicity observed in both the Arms. At three months, late skin toxicity was Grade 0:16(64%), Grade 1:9(36%) in Arm A and Was Grade 0:18(94.7%), Grade1:1(5.3%) in Arm B. At 6 months, Grade 0:23(100%) in Arm A and Grade 0:16(100%) in Arm B while no Grade 1or2 toxicity in both the arms. In both the Arms, most of the patients has Grade 0 late toxicity of skin at different times of follow-up. Higher %age of patients in Arm A developed Grade 1 skin toxicity at three months of follow-up (36% vs 5.31%).There was no significant difference between the two arms in respect of late toxicity of skin in all follow-up (p>0.05).

Table 4
Overall dermatitis in two arms

Overall Skin Toxicity	Grade	Arm-A		Arm-B		p value
		No.	%	No.	%	>0.05
At completion of Radiotherapy	Grade 1	22	88	23	92	>0.05
	Grade 2	3	12	2	8	>0.05
	Grade 3	0	0	0	0	>0.05

3 months post EBRT	Grade 0	16	64	18	94.7	>0.05
	Grade 1	9	36	1	5.3	>0.05
	Grade 2	0	0	0	0	>0.05
6 months post EBRT	Grade 0	23	100	16	100	>0.05
	Grade 1	0	0	0	0	>0.05
	Grade 2	0	0	0	0	>0.05

Evaluation of overall Salivary gland toxicity (Xerostomia)(Table-5): End of RT acute salivary toxicity in Arm A, Grade1:20(80%), Grade 2:4(16%) and was Grade1:21)(84%), Grade2:2(8%) in Arm B . Grade2 acute toxicity was higher in Arm A but this was not statistically significant (p>.05).No patients in both arms developed grade 3 toxicity. At three months, Xerostomia Grade 1:6(64%), Grade2:6(24%) in Arm A and was Grade 1:13(68.4%), Grade2:2(10.5%) in Arm B. At 6 months Grade1:13(56.5%), Grade 2:2(8.7%) in Arm A and was Grade 0:8(80%) and Grade1:8(50%) in Arm B. In both the arms, most of the patients had grade 1 xerostomia at different periods of follow-up. Higher percentage of patients in Arm A developed Grade2 Xerostomia than Arm B at 3 months and 6 months of follow-up but this was not statistically significant (p>.05).No patients in both the arms had grade 3 Xerostomia.

Table 5
Overall Xerostomia (dry mouth) in two arms

Overall Salivary Toxicity	Grade	Arm-A		Arm-B		p value
		No.	%	No.	%	>0.05
At completion of Radiotherapy	Grade 0	1	4	2	8	>0.05
	Grade 1	20	80	21	84	>0.05
	Grade 2	4	16	2	8	>0.05
3 months post EBRT	Grade 0	3	12	4	21.1	>0.05
	Grade 1	16	64	13	68.4	>0.05
	Grade 2	6	24	2	10.5	>0.05
6 months post EBRT	Grade 0	8	34.8	8	50	>0.05
	Grade 1	13	56.5	8	50	>0.05
	Grade 2	2	8.7	0	0	>0.05

Discussion

Conventional Radiotherapy (2DRT) is still the standard technique for head and neck cancer in many higher centres in India, while other centres have replaced this technique by 3D Conformal RT or other forms of conformal radiation like IMRT (Intensive Module Research Therapy) which is associated with comparable target coverage with normal tissue sparing. Conventional RT can be planned and determine more quickly, allowing beginning RT earlier if the patient load is high, which may ultimately influence prognosis. This assumption is supported by Ang et al[5] who demonstrated that an interval> 6 weeks between surgery and radiation resulted in impaired outcomes.

Response evaluation

Concurrent chemo-Radiation treatment with Platinum containing regimens has proven to be superior to radiotherapy alone in term of overall survival, disease-free survival and local control as shown in literature by Pignon etal[6], Zhu etal[7,] and Baykara etal.[8] In our study, we reported the overall response rates between the Conventional 2DRT arm and 3D-CRT arm after 6 weeks of completion of treatment, at 3 months and 1 year of follow-up. At 6 weeks, Arm A had 60% CR and 32% PR while Arm B had 56% CR and 24% PR respectively. There was no statistical significant difference between the arms studied. At 1 year of follow-up, CR rates were 64 % in both arms A &B respectively. Progressive disease or recurrence was present in 36% of patients in arm A and 28% in arm B. This difference was not statistically significant (p>H>0.05). Rhades etal[9] in his retrospective study compared to loco-regional control rates, metastasis free survival and overall survival between 2DRT and 3D-CRT at 1 year, 2 year and 3 year of follow up. At 1 year, loco-regional control rate was present in 82% in 2DRT group and 76% in 3D-CRT group. A study by Jen etal[10] compared 72 patients treated with 3D conformal technique and 108 patients treated with 2D technique. A significant improvement in 3 year LRFR for T4 (86% vs 47%) and event-free survival for both stage III (80% vs 56%) ad stage IV (82% vs 33%) was observed. Furthermore, the incidence of Xerostomia at 3 years was significantly less with 3D conformal treatment (69.2% vs 98%) although the most other late toxicities little difference was seen. In our study, the loco-regional control was present in 64% of patients in both arms at 1year which is comparable to the above quoted studies.

Toxicity Profile

During radiation, some acute (during and at the end of RT) and late (3months, at 6 months) toxicities were observed and documented in both arms. In our study, acute mucositis grade 2-3 was reported in 92 % patients in 2DRT and 96% of patients in the 3D-CRT arm which is comparable to the results reported by Rhades etal[9] who reported grade 2-3 acute mucositis in 90-93% of patients in 2 DRT and 87-92% in the 3D-CRTgroup. In our study, late mucosal toxicity grade 1 was reported in 8% in 2DRT arm and 15.8% in 3D-CRT arm with no difference in two arms. Chen et al[11] compared late mucositis in patients treated with 2DRT and 3D-CRT with or without concurrent chemotherapy in advanced head and neck cancers. Grade 3 or worse late mucositis was reported in 16-17% of patients with no difference in two arms. The results are comparable with our study.

Dysphagia

In our study, most of the patients had grade 2 acute toxicity of pharynx& esophagus in both the arms. Grade 3 acute toxicity developed in only 20% of patients in 2DRT arm and 12% in 3D-CRT arm. At 3 months of follow-up, 28% in 2DRT and 15.8% in 3D-CRT arm had grade 1late toxicity of pharynx& esophagus which is similar in incidence as reported by Palazzi et al.[12] Thus, in our study, we reported no difference between the two arms in development of acute and latetoxicity of pharynx & esophagus.

Skin Toxicity

Rhades et al[9] in his retrospective analysis reported that grade 2-3 acute skin toxicity was present in 88% in 2DRT and 84% in 3D-CRT groups. Late skin toxicity was present in 19% in both the groups. Chen et al[11] reported late skin toxicity in patients of stage III and IV HNSCC treated with 2DRT and 3D-CRT along with concurrent chemotherapy. Grade 3+ late skin toxicity was present in 18% in 3D-CRT group versus 27% in 2DRT group. In our study, approximately 90% of patients in both the groups developed grade 1 acute skin toxicity. Grade 2 acute skin toxicity was reported in 12% in 2DRT arm and 8% in 3D-CRT arm. At 3 months of follow-up, 36% in 2DRT arm and 5.3% in 3D-CRT arm had grade late toxicity of skin with no patient having grade 2 toxicity. Thus, in our study we reported less grade 2-3 acute and late toxicity of skin which can be explained by the skin sparing effect of the megavoltage beams used in both the arms and better skin care taken during the treatment. Also, the prospective nature of our study should also be considered while correlating the results with the studies mentioned.

Xerostomia

In our study, grade 2 acute toxicity of salivary gland developed in 16% in 2DRT as compared to 8% in 3D-CRT arm. At 3 months, grade 2 late xerostomia was noted in 24% in 2DRT and 8% in 3D-CRT arms. At 1 year of follow-up, 44% in 2DRT and 31.2% of patients in 3D-CRT arm had grade 1 late xerostomia. Our study shows a trend towards reduced late xerostomia in the 3D-CRT arm. A study by Jenet al[13] compared 3D-CRT and 2DRT in patient receiving primary radiotherapy for nasopharyngeal cancer. There was reduced risk for severe late xerostomia in the 3D-CRT relative to 2DRT. The incidence of severe xerostomia was 39% in 3D-CRT group versus 87% of 2DRT group. A large retrospective study by Rhades et al[80] compared 2DRT with 3D-CRT in stage III and IV oropharyngeal cancer along with concurrent chemotherapy. Grade 2-3 late xerostomia was reported in 63-73% 2DRT group and 43-58% of the 3D-CRT group. The study showed a strong trend suggesting that 3D Conformal RT technique resulted in less xerostomia.

Conclusion

Thus in the end it can be stated that both RT techniques resulted in similar outcomes and toxicities were not significantly different. However, this study showed a strong trend suggesting that 3D conformal RT results in less xerostomia. The most appropriate dose distribution with 3-D conformal RT allows partial sparing of parotid glands, in particular, in patients with No/N1 disease, because most of these patients not all cervical lymph node areas must be irradiated. Parotid gland sparing is often not possible in patients with advanced nodal disease, because most cervical lymph node areas should be irradiated. The best way to reduce xerostomia is IMRT (Intensity modulated radiotherapy) but IMRT is available in limited centres in India. Our study was observational in nature and had limited number of patients and duration of follow-up was also limited. A prospective randomised study with large number of patients and long period of follow-up is needed to extract safe conclusion about the superiority of conformal RT versus 2DRT for tumor control as well as radiation morbidity.

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