

Comparison of Three Dimensional Conformal Radiotherapy with Cobalt-60 Teletherapy in Squamous Cell Carcinoma of Larynx

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ABSTRACT: Aim: The aim of the study was to compare the results of radical radiotherapy performed by three-dimensional conformal radiotherapy (3D-CRT) and two-dimensional radiotherapy (2DRT) realized with Cobalt-60 (780-E) teletherapy for squamous cell carcinoma of larynx.

Materials and Methods: Between January 2008 to December 2010 (3 years) a total of 98 newly diagnosed cases of Stage-I to IV-B of the carcinoma larynx were considered for study. All cases were staged according to the TNM-Staging system. Ninety eight patients with previously untreated were irradiated with curative intent at our institute. Radical Radiotherapy with the cobalt-60 teletherapy unit was performed on 56 patients and 42 patients were treated with a Linear Accelerator using 3D-CRT and were analyzed for overall survival, local recurrence rate, acute & late radiation reactions, lost to follow up & deaths.

Results :- The 2 & 3 years Overall Survival rates for control group irradiated with the telecobalt therapy were 75.0% & 71.4% and for the study group treated with 3D-CRT were 76.2% & 73.8%, respectively (p=0.823, 0.908). The 2 & 3 years Local recurrence rates for control group irradiated with the telecobalt therapy were 66.0% & 69.6% and for the study group treated with 3D-CRT were 66.7% & 69.0% respectively. The grade of acute reactions of the skin and the larynx differed significantly between the accomplished radiotherapy techniques.

Conclusion :- According to the confirmed advantage of 3D-CRT in terms of reduced treatment toxicity observed in the our study, we consider conformal techniques being a basis in definitive radiotherapy of squamous cell carcinoma of the larynx until the new revolutionary techniques are clinically available.

Keywords: Laryngeal carcinoma, squamous cell carcinoma, three-dimensional conformal radiotherapy (3D-CRT), cobalt-60 teletherapy (2DRT).

INTRODUCTION

Laryngeal cancer comprises 2% to 5% of all malignant disease diagnosed annually worldwide. Annually, approximately 50,000 individuals are diagnosed with head and neck cancer in the United States, and over 11,000 die of the disease. Most patients with head and neck cancer have metastatic disease at the time of diagnoses (regional nodal involvement in 43% and distant metastasis in 10%)⁽¹⁾. In United States about 12,630 new cases of laryngeal cancer (10000 in men and 2,630 in women) and about

3,610 people (2,870 men and 740 women) will die from it in 2013⁽²⁾. In our India there are 25,170 cases male and 4,038 cases of female were diagnosed of laryngeal cancer, which by the year 2,020 will rise to 29,089 in male and 4,796 case in female⁽³⁾. More than 95% cases of laryngeal cancer are squamous cell carcinoma. Most commonly about 60% start in the glottis, while about 35% develop in the supraglottic area and rest develop in either the subglottic or overlap more than one area. The peak incidence is highest in men aged between 55 to 65 years and commonly in smokers and alcoholics.

Squamous cell carcinoma of the larynx is a common malignancy of the head and neck. Patients with stage I-II laryngeal cancer have a favorable prognosis after operation or radiotherapy, but the curative effect and prognosis of stages III-IV are not satisfactory, and their treatment is also controversial^(4,5). The initial treatment of patients with a locally advanced stage of laryngeal cancer consisted of surgery and/or radiotherapy where the choice of treatment was dependent on the tumor site, its resectability, and the patient's comorbidities and working ability⁽⁶⁾. Radical radiotherapy forms the cornerstone of therapy in advanced laryngeal cancers which are not considered suitable for surgery because of medical inoperability, unresectability or potential adverse effects on the functional (speech and swallowing) and cosmetic outcome.⁽⁷⁾ Radical radiotherapy is now being increasingly used in conjunction with cisplatin-based chemotherapy for definitive non-surgical management of advanced squamous cell carcinoma of the larynx.^(8,9)

Advanced laryngeal cancers require, for radical radiotherapy, the delivery of relatively high doses to the planning target volume (PTV). Because doses of about 50Gy are known to eradicate microscopic subclinical disease, the shrinking field technique is used to deliver this dose level to the gross tumor and subclinical disease, before a boost irradiation up to 66 to 72Gy to the primary tumor and metastatic node(s) is applied. Since treatment requires the irradiation of lymphatic regions in the neck. It is evident that planning of such treatments is one of the most demanding tasks for conventional radiotherapy. The conformal approach to irradiation was the first viable solution to obtain dose distributions encompassing adequately the PTV while sparing as much as possible all organs at risk.^(10,11)

The aim of our retrospective study was to compare the results of radical radiotherapy in patients with squamous cell carcinoma of the larynx with regard to treatment outcome in terms of overall survival, local recurrence rates and death and treatment toxicity in terms of acute radiation reactions of skin, mucosa and larynx and late radiation reaction like skin, mucosa, subcutaneous tissue and larynx between the two radiotherapy techniques in two and three years observation obtained when 3D-CRT was performed with those obtained with 2DRT realized with telecobalt therapy.

MATERIAL AND METHODS

The present study was conducted in the department of radiotherapy at <deleted for peer review> over a period of 3 years (from 1st January 2008 to 31st December 2010). Total of 98 newly diagnosed carcinoma larynx (Squamous cell carcinoma) were considered for study. Patients enrolled in our study had either unresectable tumors, or in the cases of technically resectable lesions, surgical treatment was not realized because of patient's co-morbidities, functional morbidity of the procedure or patients refusal. Our retrospective study included two groups of patients. The first group consisted of 56 patients treated from 1st January 2008 to 31st December 2010 with 2DRT in the form of gamma rays delivered by telecobalt unit (780-E). The 3D-CRT proposed to minimize the involvement of organ at risk while preserving target coverage in radical radiotherapy of laryngeal carcinoma. The second group consisted of 42 patients who were irradiated using a linear Accelerator in accordance with a 3DCRT plan from (1st Jan. 2008 to 31st December, 2010). The follow up in both groups was 36 months (3 years). Those patients who had other histopathology, post operated cases, EBRT at other institute, patient who discontinued/expired during treatment and those patients who are treated

by chemo-radiation or surgery are out of this study and treat separately.

Pretreatment evaluation: It included physical examination, complete blood count, serum biochemistry, chest X-Ray, direct laryngoscopy, and biopsy to obtain histological proof. Cytological Proof of cervical neck node metastases was obtained by fine needle biopsy. The majority of patients have radiographic visualization of the larynx by computed tomography (CT-scan). Patients were staged according to TNM-Staging system. ⁽¹²⁾

Radiotherapy protocol: In the first group of patients treated from 1st January 2008 to 31st December 2010 radiotherapy was performed utilizing a telecobalt therapy by 780E unit with a conventional fractionation schedule and a dose of 66-70Gy in 6.5-7 weeks (one fraction of 2Gy per day, 5 fractions per week, Lateral opposing fields were used to treat the primary tumor and the lymph nodes in the upper neck. Elective low neck irradiation was realized through a single anterior field. There was no elective nodal irradiation in patients with early glottic cancer (T_1N_0). Shrinking field technique with appropriate immobilization was used. The lateral field reduction off the spinal cord occurred at 50Gy. A total of 50Gy was given for management of the clinically negative neck. The dose to the lower neck was 50Gy. Electrons or partial semi field technique was used for posterior neck boost, whenever indicated.

In the second arm patients irradiated between the period from 1st January 2008 to 31st December 2010, radiotherapy was performed on a linear accelerator Clinac Dual Energy (PALO-ALTO) U.S.A. in accordance with 3D-CRT plan. Patients were immobilized in a supine position with a thermoplastic head mask. For each patient, CT scan was performed in treatment position 0.5 cm spacing, from the vertex to 5 cm below the sterno-clavicular

joints. The definition of volumes was in accordance with the International Commission on Radiation Units and Measurements (ICRU) guidelines.⁽¹³⁾ Target volumes and organs at risk were delineated on the CT data set by the radiation oncologist. The contour of the gross tumor volume (GTV) according to the extension of the primary laryngeal tumor (GTV_p) and the gross nodal disease (GTV_n) revealed by physical examination and by imaging procedures. The clinical target volume CTV was delineated following recommendations of Gregoire et al^(14,15) and included bilateral nodal level for elective irradiation depending on the tumor site and stage. This volume also included the site of potentials microscopic extensions of the primary tumor. The planning target volumes were PTV70 and PTV50 determined adding a safety margin of 5 mm in every direction (related to the organs and patients movements and positioning to the clinical target volume CTV70 and CTV50, respectively.

The classical technique of conventional mixed electron-photon beams are used. The field set up for PTV50 consisted of two isocentric lateral photon field, including nodal regions and irradiating the spinal cord up to 44Gy, and two isocentric lateral photon fields excluding the spinal cord and two electron field (Skin Surface Distance (SSD)=100 cm, energy 6 MV) to deliver the remaining dose to the spinal chains up to 44Gy. Separate anterior and posterior fields with 6MV photons were used for the lower part of the neck. Two isocentric lateral or oblique opposed photon fields, avoiding the spinal cord, combined when necessary, with matched appositional electron beams to nodal areas overlying the spinal cord were used for the electrons beams to nodal areas overlying of the used the coverage of PTV 70 all field shapes were conformed using the multileaf collimator (MLC). The dosimetric calculation was

performed using the eclipse treatment planning system beams were weighted to confirm the dose, distribution, satisfying dose requirement and constraints. The prescribed doses were 50Gy and 70Gy for the PTV50 and PTV70, respectively. The prescribed dose per fraction was 2Gy. Treatment was delivered once daily, 5 fractions per week. The maximum dose the spinal cord did not exceed 44Gy.

Follow up: During the treatment, patients were examined weekly. The first assessment of tumor response was performed three months after completion of radiotherapy by physical examination, fiber-optic endoscopy and CT-scan of head and neck. Complete responders were followed up every 2 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Suspected sites of loco-regional recurrence were evaluated with a CT scan and confirmed by aspiration cytology or biopsy. A complete response as defined as complete disappearance of the loco-regional disease. Patients who initially achieved only partial response to radiotherapy were considered failures on day I of the commencement of treatment. Patients who achieved a complete response were considered as failures on the day when a recurrence either in the primary or the node was first reported. Local recurrence rate was defined as persisting tumor clearance above the clavicles after a complete response at the end of radiotherapy.

RESULTS

Ninety eight patients were included for this retrospective analysis with follow up period of 3 years (up to 31st December 2013). Table 1 shows the baseline characteristics of the patients.

Characteristics		Observation			
		Group Treated with Telecobalt 780-E n=56		Group Treated with 3D-CRT n=42	
		Percentage	Percentage	Percentage	Percentage
Age	40-60 Yrs.	21	37.5	19	45.2
	60-80 Yrs.	35	62.5	23	54.8
Sex	Male	52	92.8	37	88.0
	Female	4	7.2	5	12.0
KPS-Score	70	20	35.7	14	33.3
	80	24	42.8	10	23.8
	90	12	21.5	18	42.9
T-Stage	T1	2	3.6	3	7.1
	T2	18	32.1	15	35.7
	T3	25	44.6	10	23.8
	T4	11	19.7	14	33.3
N-Stage	N0	20	35.7	38	90.5
	N1	25	44.6	1	2.4
	N2	6	10.7	3	7.1
	N3	5	8.9	0	0
AJCC-Stage	I	2	3.6	3	7.1
	II	18	32.1	15	35.7
	III	21	37.5	9	21.4
	IV A	10	17.85	15	35.7
	IV B	5	8.9	0	0
Histopathology (Sq.Cell Ca)	Well Differentiated	18	32.1	15	35.7
	Moderately Differentiated	30	53.6	23	54.8
	Poorly Differentiated	8	14.3	4	9.5

The results were calculated from the date of initiation of treatment to the occurrence of any event lost to follow up.

Survival Rates:- Table No.2 & 3

The 2 & 3 years O.S. (Overall Survival) rates for control group

(2D RT) irradiated with the telecobalt therapy (780-E) unit were 75.0% & 71.4% and for the study group treated with 3D-CRT were 76.2% & 73.8%, respectively (p=0.823, 0.908). The analysis of the results showed no statistical difference (Figure 1).

TABLE NO.2
COBALT- TELEETHERAPY (780-E)
Overall Survival (O.S.)

TNM Stage	No. of Pt.	Follow-up									
		3 Months		6 Months		12 Months		2 Years		3 Years	
		No. of Pt.	%								
I	2	2	100	2	100	2	100	2	100	2	100
II	18	18	100	18	100	18	100	17	94.4	17	94.4
III	21	21	100	20	95.2	19	90.5	18	85.7	18	85.7
IV-A	10	8	80	8	80	7	70	5	50	3	30
IV-B	5	2	40	1	20	0	0	0	0	0	0
Total	56	51	91.1	49	87.5	46	82.1	42	75.0	40	71.4

TABLE NO. 3
3D-CRT (LINEAR ACCELERATOR)
Overall Survival (O.S.)

TNM Stage	No. of Pt.	Follow-up									
		3 Months		6 Months		12 Months		2 Years		3 Years	
		No. of Pt.	%								
I	3	3	100	3	100	3	100	3	100	3	100
II	15	15	100	15	100	15	100	15	100	14	93.3
III	9	9	100	8	88.9	7	77.8	6	66.7	6	66.7
IV-A	15	12	80	11	73.3	10	66.7	8	53.3	7	46.7
IV-B	0	0	0	0	0	0	0	0	0	0	0
Total	42	39	92.9	37	88.1	35	83.3	32	76.2	31	73.8

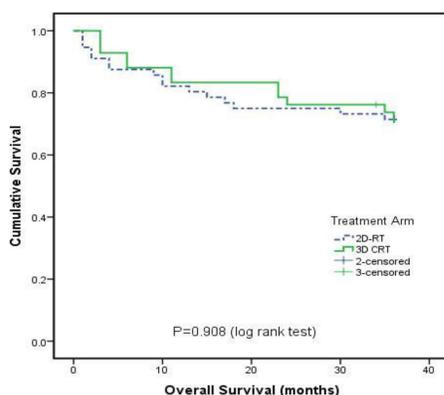


Figure 1: Kaplan-Meier Survival analysis of the Overall survival of the patients treated by 2D-radiotherapy versus 3D-CRT (p=0.908).

Local recurrence Rates:- Table No. 4 & 5 (Depicted at last of manuscript) The 2 & 3 years Local recurrence rates for control group (2D RT) irradiated with the telecobalt therapy (780-E) unit were 66.0% & 69.6% and for the study group treated with 3D-CRT were 66.7% & 69.0% respectively. The analysis of the results should no statistical difference

Lost to follow up and Death:- The 2 and 3 years lost to follow up total patients were 9 & 11 for telecobalt therapy and 7 for linear accelerator respectively and 2 and 3 years total deaths were 5 for telecobalt therapy and 4 & 5 for 3D-CRT Linear Accelerator respectively.

Radiation Reaction

Treatment related adverse effects were categorized as acute (occurring with in 90 days after the start of radiotherapy) or late continuing or occurring after 90 days) and scored according to Radiation Therapy Oncology Group (RTOG) criteria⁽¹⁵⁾ Table No. 6 shows the site and grade of the worst acute adverse effects by treatment group. The skin was the most common site of Grade 3 acute side effects. We did not find any statistically significant difference in the distribution of acute reactions of the mucous membrane between the two treatment groups. There was a significant difference in the grade of acute reactions in the skin between the accomplished radiotherapy techniques. There was also a significant difference in the grade of acute reactions in the larynx between the radiotherapy techniques. Compared to the group irradiated with 3D-CRT, the group treated with telecobalt tel-etherapy has significant enhancement of acute reactions of the skin and the larynx. The sites and grade of worst treatment-related late adverse effects were noted according to radiotherapy technique. No statistically significant difference existed between the two treatment groups with respect to late reactions in the mucous membrane and the larynx. There was a significant differ-

ence in the grade of late effects in the skin between radiotherapy techniques (p=0.001). There was also a statistically significant difference in the grade of late effects in the subcutaneous tissue between the two treatment groups (p=0.035). Grade 2 late reactions in the skin and in the subcutaneous tissue were significantly increased in the group treated with telecobalt teletherapy as compared with the group treated with 3D-CRT.

Statistical Analysis

The two treatment groups were compared with respect to baseline characteristics. Estimates of local recurrence rates and overall survival were computed using the Kaplan-Meier method.⁽¹⁶⁾ Outcomes were measured from the first date of radiation treatment to the date of failure for local recurrence rates, and the last date of follow up or the date of death for survival analysis. For local recurrence rate, the first occurrence of primary or neck relapse was scored. Patients who did not achieve a complete response after treatment were assigned a local recurrence rate of 0 month. For overall survival, all causes of death were considered. Acute and late treatment effects were also assessed. The follow up period was of 3 years.

TABLE NO. 6
Acute Radiation Reactions
(RTOG-Criteria)

Organ/Tissue	Grade	Group treated with				P.
		Teletherapy (780-E)		3D-CRT (L.A.)		
		No. of Patients	%	No. of Patients	%	
Skin	1	28	50	20	47.6	0.012
	2	6	10.7	20	47.6	
	3	22	39.2	2	4.8	
Mucous Membrane	1	21	37.5	32	76.2	0.226
	2	34	60.7	9	21.4	
	3	1	1.8	1	2.3	
Larynx	1	3	0	5	11.9	0.001
	2	18	32.1	25	59.5	
	3	38	67.9	12	28.6	

TABLE NO. 7
Late - Radiation Reactions
(RTOG-Criteria)

Organ/Tissue	Grade	Group treated with				P.
		Teletherapy (780-E)		3D-CRT (L.A.)		
		No. of Patients	%	No. of Patients	%	
Skin	0	2	3.6	23	54.8	0.001
	1	35	62.5	4	9.5	
	2	19	33.9	15	35.7	
Mucous Membrane	0	34	60.7	22	52.4	0.188
	1	18	32.1	13	30.9	
	2	4	7.2	7	16.7	
Subcutaneous tissue	1	35	62.5	35	83.3	0.035
	2	21	37.5	7	16.7	
Larynx	0	18	32.1	16	38.1	0.770
	1	38	67.9	26	61.9	

Discussion

Radical radiotherapy is an effective treatment modality for early-stage squamous cell carcinoma of the larynx, offering a high rate of local control and cure.⁽¹⁹⁻²⁰⁾ Excellent outcomes with local control rates of 90-95% for T1 laryngeal lesion and 75-80% for T2 lesions produced by 2DRT using telecobalt teletherapy or 6MV photons were reported by Gomez et al.⁽²¹⁾ In the retrospective study of Manzo et al.⁽²²⁾, the reported 5-year and 10-year O.S. rates for patients with T1 laryngeal carcinoma with glottic presentation treated with 2DRT radiotherapy were 85.8% and 69.4%, respectively. Retrospectively analyzing patients with T1-T2N0 squamous cell carcinomas of the glottic larynx treated with radical radiotherapy. Jones et al⁽²³⁾ reported 5-year local control rates of 91%, 95%, 96% and 100% for T1a, T1b, T2a and T2b, respectively. Radical radiotherapy was also supported as a reliable treatment option for T3-T4 laryngeal carcinoma by Nguyen-Tan et al⁽²⁴⁾. Data revealed that more than one half of patients treated with radiotherapy alone achieved LRC (the overall 5-year LRC was 56%) and OS in appropriate selected patients was not compromised (the 5-year OS was 44%). Chijiwa et al.⁽²⁵⁾ found that following radical radiotherapy in patients with advanced supraglottic laryngeal cancer treated with radical radio-

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therapy, the 5-year survival rate was 89% in patient with stage III disease and 75% in stage IV patients. Spector et al.⁽²⁶⁾ found a 5-year disease specific survival rate of 50% in patients with stage IV glottic squamous cell carcinoma treated with radical radiotherapy. In the study of Chedid et al.⁽²⁷⁾, the 5-year disease free survival for the whole group of patients with laryngeal cancer undergoing radiotherapy was 38%. Gourin et al.⁽²⁸⁾ reported a 5-year survival rate of 14% in patients with laryngeal cancer stage IV disease treated with radical radiotherapy. Krstevska V et al.⁽²⁹⁾ showed that 2 & 3 year LRC rate for group telecobalt therapy were 73.8% and 70.73% and for group with 3DCRT were 83.2% & 66.8% respectively and overall survival rates for group teletherapy were 78.7% & 68.7% and for 3DCRT were 81.3% and 60.7% respectively.

Radical radiotherapy represents as important part of the therapeutic approach in locally and/or regionally advanced squamous cell carcinoma of the larynx. The improvements in radiotherapy techniques by introducing 3D-CRT are considered as significant factors for the substantial change in the management of laryngeal cancer especially for the greatly diminished role of the open surgery during the past decade^(30, 31). Recent advanced in 3D-CRT have led to better dose distributions for sparing normal organs while treating target volumes with full dose.⁽³²⁾ Since 3D-CRT has become available in the clinical setting during the past decade the possibility of increasing the therapeutic gain by escalating the dose to the tumor with maintained volume weighted dose burden to normal tissues or by minimizing the irradiated normal tissue volumes with unchanged target dose, has been markedly enabled by using the potential of 3D-CRT for tailoring iso-dose surfaces to the shape of the tumor (PTV) on all there dimensions⁽³³⁾.

Patients enrolled in our retrospective study

were treated with radical radiotherapy delivered either using a cobalt-60 (780-E) machine or performed on a linear accelerator in accordance with a 3D-CRT plan. In the analytics of treatment outcome we did not find any statistical difference in the response to treatment between the two treatment groups. The result of our retrospective study also between to two treatment groups. The result of our retrospective study also showed no statistical difference in LRC and O.S. between the group of patients treated with telecobalt teletherapy and those irradiated with 3D-CRT. The only statically difference revealed between the two radiotherapy techniques existed in the treatment related toxicity. In our study there was significant enchantment of acute reaction of the skin and the larynx in the group irradiated with telecobalt teletherapy. In his group of patients late adverse effects in the skin and in the subcutaneous tissue were also significantly increased. These results imply that by using 3DCRT we succeeded in improving the therapeutic ratio through reducing treatment induced morbidity by dose constraints to organs at risk. On the other hand, the absence of any statistically significant advantage in LRC could indicate that dose uniformity within the PTV being one of the requirement in the protocols dedicated to head and neck radiotherapy was not satisfactory fulfilled in order to further improve result achievable with 3D-CRT a new planning technique called four field photons only treatment for advanced laryngeal cancers was started in future.

Conclusion

Although the results of our study did not show any decrease in local recurrence rate and overall survival in patients treated with 3D-CRT, they confirmed the advantage of 3D-CRT in terms of reduced treatment toxicity. We consider conformal techniques that are readily assessable

in our radiotherapy department should be a cornerstone in definitive radiotherapy of squamous cell carcinoma of the larynx until the new revolutionary techniques are clinically available.

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