



A prospective study of comparison between concomitant boost radiotherapy and conventional fractionated radiation in treatment of laryngeal cancer in a tertiary care institute of east India.

Oncology

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ABSTRACT

Background:

The increasing incidence of laryngeal cancer is of greater concern because of its potential impact on interpersonal communication skills. Various radiotherapy fractionation regimens are in practice to improve control of disease. Concomitant boost radiotherapy which is a type of modified hyperfractionation regimen has been perceived to provide better control over conventional schedule. This Present study was conducted to analyse the effectiveness and superiority of concomitant boost radiotherapy over conventional fractionated radiotherapy in treatment of carcinoma larynx.

Materials and Method:

Patients with histologically proven squamous cell carcinoma of the larynx in Stage I - IV without distant metastasis were randomly allocated into two arms; Control Arm-A (n=26): conventional external beam radiotherapy (EBRT) of dose 60 Gy in 30#, 2Gy per fraction, 5# per week for 6 weeks. Study Arm-B (n=24): Conventional EBRT of dose 60 Gy/6 weeks + concomitant boost radiation of dose 1.2 Gy/#, 5# / week × 2 weeks during last 2 weeks of the 6 weeks period with total dose of 72 Gy. The two arms were then compared in terms of complete response, locoregional control, disease free survival, acute and chronic radiation induced toxicity with a median follow up period of 24 months.

Results:

Complete response seen in the study was 84% vs. 68%, the locoregional control after a median follow up of 24 months was 68% vs. 44% and the 2 year DFS was 67 % vs 43% in study arm-B versus control arm-A respectively. Acute toxicity including mucositis, dysphagia, dermatitis were increased but tolerable in the study arm but the significant late morbidity like persistent laryngeal edema was comparable in both arms.

Conclusions:

The response to radiotherapy, locoregional control, 2 year DFS of concomitant boost EBRT is better than conventional EBRT in carcinoma of larynx with acceptable local toxicities. Further analysis and follow-up are needed to evaluate if the benefit will translate into prolonged survival.

KEYWORDS

conventional RT, concomitant boost RT, carcinoma larynx

Introduction:

Head and neck cancers are the most significant cause of cancer related mortality and morbidity in India. According to GLOBOCAN 2012, worldwide incidence and mortality of head and neck cancers (lip, oral cavity, pharynx and larynx) are 4.2% and 4.0% respectively.¹ The incidence of laryngeal cancer is only 1–2% of all malignancies much less as compared to carcinoma lung, prostate, breast and cervix.^{1,3} However a substantial amount of literature on it reflects the perceived importance of this disease relative to its potential impact on interpersonal communication skills. Investigations continue therefore, into the methods of conservative laryngeal surgery, different radiation therapy strategies, and combined chemotherapy and radiation therapy protocols designed for laryngeal preservation.^{4,6} Conventional radiotherapy regimens using 1.8 – 2 Gy per day, 5 days per week had developed empirically over the decades. But the realization that it may not be the best fractionation pattern for all situations led to the concept of hyperfractionation and accelerated fractionation.⁷ In recent times, radiation oncologists have developed the technique of concomitant boosting, where in the boost dose to a reduced volume is given concomitantly with the treatment of the initial larger volume rather than as a sequel.⁸⁻¹¹ The boost is given as a second dose with an interfractionation interval of at least 6 hours, preferably during the later part of the treatment when normal tissue regeneration is in full swing.¹² The concomitant boost technique has been tried keeping in mind the radiobiological aspects of accelerated fractionation radiotherapy which gives beneficial results by decreasing the number of clonogenic cells to considerable extent and without doing much harm to the normal cells. Although the cure rates have not been changed dramatically during recent years, the treatment options and the sequencing of those options have an increasing impact on laryngeal preservation and quality of life in return to an acceptable degree of morbidity.¹²⁻¹³

The present study had been conducted to evaluate the impact of concomitant boost radiotherapy and conventional fractionation regimen on locoregional control and normal tissue toxicity in treatment of laryngeal cancer patients.

Materials and Method:

This is a prospective study conducted in Department of Radiotherapy, Acharya Harihar Regional Cancer Center, Cuttack, a tertiary care center in Odisha, east India from August 2006 to July 2008., All patients diagnosed with carcinoma of larynx were screened for inclusion in the study. All patients underwent complete evaluation by history taking, local examination and systemic examination. Histological proof of malignancy was attained through biopsy in all patients. All patients were evaluated by complete blood count, liver function tests, renal function tests, chest radiograph, indirect laryngoscopy, CECT face and neck or MRI neck were done as appropriate. AJCC Staging system was used to stage the patients.. Out of 62 patients that fulfilled the eligibility criteria; 8 patients discontinued treatment and 4 patients were lost to follow up and hence excluded. Finally 50 patients were considered for analysis and were divided in two arms such as Arm-A, n=26 (conventional fractionated radiotherapy) and Arm-B, n=24 (concomitant boost radiotherapy).

Arm A - Conventional fractionated radiotherapy was delivered using Megavoltage Telecobalt unit to whole neck by bilateral opposing portals at 200 cGy /fraction, 5 fractions / week for 6wks. giving a cumulative tumour dose (CTD) of 60 Gy in 6wks.

Arm B - Concomitant Boost Radiotherapy was delivered using Telecobalt by Bilateral Opposing portals as detailed below :

- (i) Initial larger Volume to the whole neck 200 cGy per fraction, 5 fractions per week for 6 weeks.

(ii) Reduced Boost Volume Primary tumour and adjacent clinically palpable lymph node) 120 cGy per fraction, 5 fractions per week during the last 2 weeks as a second dose at an interfraction interval of at least 6 hours.

Thereby giving a CTD of 72 Gy in 6 weeks. Spinal Cord Shielding was applied in both arms after 44 Gy by moving forward the posterior margin of the radiation portal. Both groups have been compared with respect to the local/regional control of disease, compliance to treatment, toxicity profile & disease free survival.

Radiation Portals For the whole Neck the Bilateral Opposing portals were defined as follows in both Arms:

Superior Border	From the tragus to the mentum
Inferior Border	Along the lower margin of the clavicle.
Posterior Border	From the tip of the mastoid along the trapezius
Anterior Border	The field was left open anteriorly allowing the beam to fall off in the air.

For the Boost fields the Bilateral opposing portals were defined as follows as per site of disease.

Supraglottis:

Superior Border	1 cm above the hyoid
Inferior Border	Lower border of thyroid cartilage
Posterior Border	1 cm behind posterior border of thyroid cartilage
Anterior Border	Field was left open anteriorly for the beam to fall in air.

Glottis:

Superior Border	1cm above the thyroid notch.
Inferior Border	Inferior border of cricoid cartilage
Posterior Border	1cm behind posterior border of thyroid cartilage.
Anterior Border	Field was left open anteriorly for the beam to fall in air.

Inclusion Criteria	Exclusion Criteria
Histopathologically Confirmed Squamous Cell Carcinoma Larynx (tnm, stage I-iv).	Presence of synchronous dual primary and subglottic carcinoma larynx.
Patients with Karnofsky Performance Status > 60.	Presence of distant metastasis
No prior history of radiotherapy/chemotherapy/surgery of the neck.	Not willing to sign the informed consent
Willing to sign the informed consent.	Pregnant and lactating mother

Follow up:

Patients were assessed for tumor response after 6 weeks of completion of radiotherapy. Response assessment was done based on RECIST (Response Evaluation Criteria In Solid Tumors) criteria. After completion of treatment, all the patients were advised for follow up regularly at 6 weeks, 3 months, 6 months, 9 months and 1 year and thereafter four monthly during second year. During follow up patients were evaluated for local recurrence, distant failures, early and late toxicity. All patients underwent thorough clinical examination and necessary investigations such as indirect-laryngoscopy and contrast enhanced computed tomography (CECT) were done as appropriate. Early and late radiation toxicity were documented during follow up period and grading was done according to the Radiation Therapy Oncology Group/ criteria.

Statistical analysis:

Statistical analysis was done using SPSS software version 16, the background characteristics were compared using univariate and/ or multivariate tables. Difference in patient characteristics were evaluated using Chi-square test for the categorical variables and t-test for numerical variables.

Results:

The study has been conducted on patients attending OPD of our institute Acharya Harihar Regional Cancer Center, Cuttack, Odisha from August 2006 to July 2008. A total number of 62 cases of laryngeal malignancy have been enrolled during the aforesaid period out of a total number of 3566 new cancer cases registered at the institute during the same period, giving an overall incidence of 1.7% of all

malignancies. 62 patients that fulfilled the eligibility criteria have been enrolled for the study. 8 patients discontinued treatment and 4 patients were lost to follow up and hence excluded. Finally 50 patients were considered for analysis and were divided in two arms such as Arm-A, n=26 (conventional fractionated radiotherapy) and Arm-B, n=24 (concomitant boost radiotherapy).

Table 1 depicts the site specific distribution of disease in conventional (Arm-A) as well as concomitant boost arm (Arm-B).

Table-1: Site Specific Distribution in Carcinoma Larynx

Site of Disease	Total (n=50)	Arm-A (n=26)	Arm-B (n=24)
Supraglottis	36 (72%)	19 (76%)	17 (68%)
Glottis	14 (28%)	6 (24%)	8 (32%)

Majority of the patients (72%) presented with supraglottic disease, the rest (28%) had carcinoma of the glottic larynx.

The Acute Radiation Toxicity was scored according to the RTOG criteria for mucositis, dysphagia and skin reaction and shown in Table-2,3,4 respectively.

Table-2: Acute Mucositis During RT in Carcinoma Larynx

Group	Grade 1	Grade 2	Grade 3	Grade 4
Arm-A	26 (100%)	20 (80%)	9 (36%)	0
Arm-B	24 (100%)	22 (88%)	15 (60%)	0

Acute mucositis (Grade-I RTOG) is found in 100% cases in both arms followed by Grade 2 mucositis 88% in boost arm vs 80% in conventional RT arm. Grade 3 is also higher in boost arm (60% vs 36%). No Grade IV mucositis is found in either arms.

Table-3: Acute Dysphagia During RT in Carcinoma Larynx

Group	Grade 1	Grade 2	Grade 3	Grade 4
Arm-A	26 (100%)	10 (40%)	1 (4%)	0
Arm-B	24 (100%)	15 (60%)	3 (12%)	0

Acute dysphagia Grade I is found 100% in both arms, but Grade II and Grade III dysphagia are more common in boost arm than conventional RT arm (60% vs 40%) and (12% vs 4%) respectively

Table-4: Acute Dermatitis During RT in Carcinoma Larynx

Group (n=25)	Grade 1	Grade 2	Grade 3	Grade 4
Arm-A	26 (100%)	9 (36%)	0	0
Arm-B	24 (100%)	17 (68%)	5 (20%)	0

Acute dermatitis Grade 1 (RTOG) is equal in both arms (100%) but the Grade 2 and Grade 3 reactions are more common in boost arm than Arm B (Cov. RT) i.e. 68% vs. 36% and 20% vs. 0% respectively.

The Tumour Response was first assessed at 6 weeks from end of RT as shown in Table-5.

Table-5 Response Rate of RT in Carcinoma Larynx

Group	Complete Response	Partial Response	No. Response
Arm-A	17 (68%)	8 (32%)	0(0%)
Arm-B	21 (84%)	4 (16%)	3 (12%)

The complete response (CR) after 6 weeks of completion of RT is better in Arm B (84% vs. 64%) and partial response is better in Arm A (32% vs. 16%).

From the above analysis, the clinical complete response is better in Arm B as compared to Arm A. Complete response is found more in the early T lesion (T1, T2) than advanced T (T3, T4). Partial response is more in Arm A than Arm B.

The Response Rate as per site of disease is shown in Table-6.

Table-6: Response rate as per Site of Disease

Site of Disease	Overall (n=50)		Arm-A(n=26)		Arm-B(n=24)	
	CR	PR	CR	PR	CR	PR
Supraglottis	26 (72.2%)	10 (27.8%)	12 (63.1%)	7 (36.9%)	14 (82.3%)	3 (17.7%)
Glottis	12 (85.7%)	2 (14.3%)	5 (83.3%)	1 (16.7%)	7 (87.5%)	1 (12.5%)

The complete response (CR) is more in Arm B than Arm A in both

Carcinoma supraglottis and glottis. Partial response (PR) is more in Arm A than Arm B.

Table-7: Late Morbidity of RT in Carcinoma Larynx

Late Toxicity	Arm-A	Arm-B
Subcutaneous fibrosis	14 (63.6%)	13 (68.4%)
Laryngeal oedema	7 (31.8%)	6 (31.5%)
Skin pigmentation	1 (4.5%)	1 (5.2%)
Cartilage Necrosis	0	0
Airway obstruction	0	0
Myelitis	0	0

The locoregional control, locoregionally diseased, lost of follow up, Distant metastatis and death of patients; all are better in Arm B (Boost) than Arm A.

At 2 years, the Disease Free Survival as estimated by Kaplan Meier method is shown in Table-8

Table-8: DFS at 2 years in Arm-A (Conventional Fractionated Radiotherapy)

Month after study entry	No. of Patient	Lost to FU/ RESI / REC Dist Mets	Death	Exposed to cure COL 2-COL (3+4)	Pro. With Disease COL (3 +4/ COL2)	Prop. Without disease 1-COL6	Probability of DFS
0-6	26	8	1	16	0.36	0.64	0.64
6-12	16	2	0	14	0.12	0.88	0.56
12-18	14	2	0	12	0.15	0.85	0.47
18-24	12	1	0	11	0.08	0.92	0.43

Table-9: DFS at 2 years in Arm-B (Concomitant Boost Radiotherapy)

Month After Study Entry	No. of Patient	Lost to FU/ RESI / REC Dist Mets	Death	Exposed to cure COL 2-COL (3+4)	Pro. With Disease COL (3 +4/ COL2)	Prop. Without disease 1-COL6	Probability of DFS
0-6	24	4	0	21	0.16	0.84	0.84
6-12	21	3	0	18	0.14	0.86	0.72
12-18	18	1	0	17	0.06	0.94	0.67
18-24	17	0	0	17	0.00	1.00	0.67

Discusson:

During the period of patient accrual from August 2006 to July 2008, the total number of new cases of cancer registered at the institute was 3566, of which 62 were diagnosed to have been suffering from laryngeal cancer giving an incidence of 1.7% of all malignancies.

Majority (74%) of the patients in our study population presented with locoregionally advanced disease (stage III & IV), with only 26% of patients having presented early (Stage I & II). The WHO reported the relative incidence of early stage disease versus advanced stage disease in laryngeal cancer at 1:3 in the developing world which is comparable to our study.

The response rate (complete response) at 6 wks from end of RT was higher in the concomitant boost arm. In the conventional RT arm, the CR was 68% and PR was 32% for all sites and stages combined. The corresponding figure in the concomitant boost arm was CR – 84% and PR-16% (p value for CR < 0.05).

The response rate (CR) as per UICC / AJCC stage was 100% for Stage I and II both the arms. For stage III, the CR was 78.5% for the Arm-A as compared to 87.5% for the Arm-B (p > 0.05), not significant). However for stage IV, the CR was 50% in he boost arm as compared to zero in the conventional arm (p < 0.0001).

The patient were followed up for a median duration of 24months (range of 3 -36 months). The loco regional control in the Arm-B was 68% as compared to 44% in the Arm-A (p < 0.01, significant). One distant metastasis was noted in each arm, to the lungs in Arm-A and to the vertebra in the Arm-B. Two patients in the conventional RT arm were lost on follow up while one death occurred. No deaths were reported in the boost RT arm.

The Acute toxicities such as mucositis, dysphagia and dermatitis were more prominent and persistent in the Arm-B. The only significant late morbidity recorded was persistent oedema of the larynx in both arms (31.8%) in the Arm-A versus 31.5%, in the Arm-B . Subcutaneous

fibrosis occurred in 63.6% and 68.4% of the Arm-A and Arm-B respectively. Skin pigmentation was seen in 4.5% and 5.2% of patients respectively. No patients developed cartilage necrosis, airway obstruction or myelitis as late toxicity. Thus late morbidity was comparable in both arms (p > 0.05, not significant).

At 24 months, the disease free survival as estimated by the Kaplan Meier method was 43% in the Arm-A, whereas it was 67% in the Arm-B, thereby implying a significant benefit for the accelerated regiment (p < 0.05, significant).

Several authors have reported variable results for radiation therapy of carcinoma larynx. Mendenhall gave an overall local control rate for supraglottic carcinoma as per T category as T1 -100%, T2 – 85%, T3- 64% and T4 – 36%. He had however used both hyperfractionation and conventional fractionation.¹⁴ Wendt reported a local control rate of 92% for T1 lesions; 81% for T2 lesions; 60% for T3; and 31% for T4 lesions using irradiation alone for supraglottic cancers.¹⁵ Wang et al reported an initial locoregional control rate of 75%; 50%; 38% and 26% for T1 to T4 lesions of supraglottis respectively.⁷ Bataini reported an initial local control rate of 87.5% for T1 and T2 lesions combined and 65% for T3 and T4 lesions combined in carcinoma supraglottis.¹⁶ Harwood et al reported a local control rate of 71%, 68%, 56% and 52% for T1 to T4 node negative patients of supraglottic disease.¹⁷

For glottic cancers, the initial local control reported by most authors is in the range of 80 – 93% for T1 and 70 – 88% for T2 disease. Patients with advanced disease treated with primary radiotherapy have an initial local control rate in the range of 23% to 64% for T3 / T4 tumours. Harwood et al reported an initial local control of 86% and 69% for T1 and T2 lesions respectively of the glottis treated by primary radiation therapy.¹⁷ Fletcher and Colleagues reported 89% and 74% complete response rate for T1 and T2 lesions of glottic larynx respectively. Mendenhall and colleagues reported a somewhat higher initial local control rate of 93% and 75% for T1 and T2 vocal cord carcinoma respectively.¹⁴ Wang et al also reported 90% local control for T1 lesions and 69% for T2 lesions of vocal cord treated by only Radiation therapy. Stewart and Colleagues reported a 57% initial control rate in moderately advanced carcinoma of the glottic larynx treated by primary radiotherapy. Harwood reported an initial local control of 56% and 51% for T3 N0 and T4N0 lesions of glottis treated by RT alone.¹⁷ Van den Bogaert quoted a 23% initial local control rate in 35 patients of T3 / T4 lesions of glottis. Mendenhall using hyperfractionated radiotherapy gave an initial control rate of 64% in locally advanced glottic cancers.¹⁴ Wang et al reported a 32% response rate in 65 patients of T3 / T4; NO / N+ carcinoma of glottic larynx, treated by primary radiotherapy.⁹

The acute toxicities encountered were mucositis, dysphagia and dermatitis. The incidence of Grade 1 and 2 mucositis was similar in both arms. A higher number of patients (60%) developed Grade 3 mucositis in the boost arm as compared to 36% in the conventional RT arm. Also noted was Grade 1 dysphagia which was similar in both arms. It progressed to Grade 2 in 40% of patients in the conventional RT arm as opposed to a 60% incidence in the concomitant boost arm. Only 4% had Grade 3 dysphagia in the conventional arm as compared to a 12% incidence of Grade 3 dysphagia in the boost RT arm. The acute skin reactins were also accentuated in the concomitant boost arm. Only 4% had Grade 3 dysphagia in the conventional arm as compared to a 12% incidence of Grade 3 dysphagia in the boost RT arm. The acute skin reactions were also accentuated in the concomitant boost are. Grade 1 dermatitis was seen in 100% of patients in both arms. Grade 2 skin reaction were 36% and 68% in the conventional RT and concomitant boost RT arm respectively. 20% of patients on concomitant boost developed Grade 3 Skin Reactions whereas no patients on conventional radiotherapy arm had Grade 3 reactions.

Knee et al reported a 35% incidence of severe mucositis (> Grade 3) in 53 patients treated by concomitant boost RT for locally advanced disease of the head and neck. Moderate late effects were reported in 11% of cases.¹⁸ Ang and coworkers⁹ reported a 7% incidence of severe mucositis and a 16% incidence of dysphagia necessitating NG tube feeding (Grade 3) in moderately advanced lesions treated by concomitant boost radiotherapy. The moderate to severe late effects were quoted at 5%.¹⁹ Schmidt-Ullrich and Morris MM et al also reported increased acute morbidity in the accelerated fractionation Arm-B, with an incidence of severe mucositis of 32% at 5 years.^{20,21} The overall late complication rate was comparable with the

conventional radiotherapy arm. Considerable volumes of studies have been conducted emphasizing the fact that concomitant boost radiotherapy is better than conventional fractionated regimen with or without concurrent chemotherapy in accomplishing primary objective of optimal locoregional control with acceptable toxicities to the organs at risk²²⁻²⁷

In conclusion, we can state that concomitant boost radiotherapy gives a significantly higher loco-regional control and 2 year Disease Free Survival as compared to conventional fractionated radiotherapy. There is increased acute morbidity with concomitant boost radiotherapy as compared to conventional fractionated radiation. The late morbidity is comparable in both arms. The use of concomitant boost radiotherapy in appropriately selected cases of carcinoma larynx is justified.

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