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Comparison of 70 Gy 3DCRT with Concurrent Chemotherapy versus Conventional 66 Gy Radiotherapy with Concurrent Chemotherapy in Locally Advanced Squamous Cell Carcinoma of Larynx

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Abstract

Background: Laryngeal cancer is the most common malignancies of head neck region. The search for optimal treatment option for locally advanced laryngeal cancer is on throughout the world.

Methodology: This was a prospective quasi experimental study carried out in the department of Radiation Oncology of NICRH, Dhaka and Square Hospitals Limited, Dhaka from July 2013 to May 2014.

Result: Thirty patients each were accrued to arm A and arm B purposively to receive 3DCRT and conventional radiotherapy respectively. The patients age ranged from 30 to 60 years; 61.7% patients were male. Among the total patient 43.3% patients were in stage III and 56.7% patients in stage IVA. All radiation related toxicities were found significantly higher in 3DCRT arm (arm A) than conventional arm (arm B). Complete response was found in 40% patients in 3DCRT arm while in conventional arm it was only 10%. Partial response was 36.7% and 46.7% respectively. No response was seen in 8 patients, 3 in arm A and 5 in arm B. More patients in arm B (26.7%) were reported with progressive disease.

Conclusion: It could be said from this study that three Dimensional 70 Gy Conformal Radiotherapy (3DCRT) with concurrent chemotherapy offers higher treatment outcome then conventional 2D radiotherapy with 66 Gy although which was statistically significant and toxicities were reported more in intervention group which need to be managed effectively.

Keywords: Locally advanced squamous cell carcinoma of larynx; 3DCRT; Conventional radiotherapy; Concurrent chemotherapy

Introduction

Head and neck cancers which arise from the lining epithelium of upper aero-digestive tract account for about 3% to 5% of all cancers in the United States [1]. In Indian subcontinents due to more use of smoking and chewing tobacco the incidence is more than 30% of all malignancies [2]. There is no population based cancer registry in our country to provide reliable data on cancer incidence, prevalence and mortality. An institute based study conducted on 27281 new cancer patients at National Institute of Cancer Research and Hospital (NICRH) during the period of 1st January 2008 to 31st December 2010 revealed that laryngeal cancer is the 4th most common cancer (3.01%) in male [3]. Approximately one fourth of all head-neck cancers originate in larynx.

Laryngeal cancer can be cured if treated early. Surgery and radiation therapy are the main treatment modalities. All or part of larynx may need to be removed (total or partial laryngectomy) to achieve surgical control, which creates cosmetic and functional defects. Radiotherapy provides scope of organ preservation and keeps surgery reserve for salvage therapy. Early lesion can be treated with definitive irradiation or surgery. But more advanced disease requires combined treatment. Although chemotherapy by itself is not considered curative, it enhances the effect of irradiation based treatment and thus, is used as part of combined modality treatment, particularly in patients with stage III or IV disease [4].

The major goal of administering chemotherapy concurrently with radiation is to radio-sensitize the tissue in the radiation field. Concurrent chemo-radiation improves the loco-regional control and the survival. It also lowers incidence of distant metastasis and provides better relapse free survival than radiotherapy alone, but has a higher grade of toxic effects.

This study was supposed to provide a comparison between the treatment responses of conformal radiotherapy (3DCRT) and conventional radiotherapy in locally advanced laryngeal cancer with concurrent chemotherapy.

Materials and Methods

This prospective quasi experimental study was carried out in the

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department of Radiation Oncology of NICRH, Dhaka and Square Hospitals Limited, Dhaka from July 2013 to May 2014. The study was approved by the Ethical Review Committee of NICRH and informed consent was taken from each patient before their enrollment in the study. Total study population was 60 among which 30 were in the intervention arm (arm A, 3D CRT) and 30 were in the control arm (arm B, conventional).

Results

The mean age of the conventional group was 43.73 (SD ± 7.741) years and that of the 3D CRT group was 46.8 (SD ± 7.513) years. In arm A 17 (57%) patients were male. in arm B of the number of male were 20 (67%). About 43% patients were in stage III and about 57% patients were in stage IV-A. In group A the percentage of stage III and IV-A were 36.7% and 76.3% respectively. Nineteen patients in group B were staged as III (63.3%) and the rest 7(40%) patients were staged as IV-A. The comparison of oral mucositis and hematological toxicities are given in the Table 1. Starting from 2nd week onward oral mucositis was significantly higher in arm B than arm A ($p<0.05$). Regarding and hematological toxicities, at the end of the 1st, 2nd, 4th and 7th week of treatment no significant differences were noted between these two groups. However, at the end of the 5th and 6th week of treatment significantly more patients experienced hematological toxicities in arm B than arm A. Opposite finding was noted at the end of 3rd week where more patients had such toxicities in arm A than arm B. Table 2 shows radiation toxicity in seven different periods of time. At the end of the 1st and 2nd week of the treatment all the patients in both arms showed grade 0 toxicity but subsequently significantly more number of patients experienced radiation induced toxicities in arm A than arm B ($p<0.05$). Pharynx and esophagus toxicity is compared in seven different periods of time in the Table 2 also. After 1st, 2nd, 3rd, 5th and 6th weeks of treatment no statistically significant differences were noted between these groups regarding pharynx and esophagus toxicity. But after 4th and 7th weeks of treatment significantly more patients had Pharynx and esophagus related toxicities in arm B than arm A. Regarding radiation induced pain perceived by the patients no significant differences are noted after 1st, 2nd, 4th and 7th weeks of treatment. However, after 3rd, 5th and 6th weeks of treatment significantly more patients had this type of toxicity in arm A than arm B ($p<0.05$) (Table 3). After 6 weeks, patients experienced constitutional symptoms almost identically except dysphagia which was slightly higher in arm A. At this point Fiber Optic Laryngoscopy (FOL) revealed post treatment residues in about 67% in arm A and 80% instances in arm B. After 12 weeks of treatment completion no significant shift occurred in symptoms. But FOL found more patients with normal findings in arm A than arm B. This difference was statistically significant ($\chi^2= 9.77$ (df=1); $p=0.002$) (Table 4). In arm A 12 patients (40.0%) showed complete response where in arm B complete response was noticed in 3 patients (10.0%). This difference was statistically significant ($p<.05$); partial responses were 11 (36.7%) and 14 (46.7%) in the two arms respectively. No response was noticed in 3 patients in arm A and 5 patients in arm B. Four patients in arm A and 8 patients in arm B were found with progressive disease. Arm B patients had significantly more progressive disease than arm A patients. However, regarding partial and no response no statistically significances were found between these two arms ($p=0.109$) (Table 4).

Discussion

For many years radiotherapy was considered as the standard treatment for patients with locally advanced laryngeal cancer. Recently, concurrent chemoradiotherapy has been demonstrated to increase survival to a greater degree than induction chemotherapy followed by radiotherapy [5]. A meta-analysis of studies showed that addition of chemotherapy to radiotherapy yielded an absolute benefit of 8% at five years in term of overall survival compared with radiotherapy alone [6,7]. Single agent bolus cisplatin in every three weeks at a dose of 100 milligram per square meter is accepted as standard reference regimen in the setting of definitive chemoradiation [8].

In the present study in arm A patients were given a total dose of 70

Week	Grade	Oral mucositis toxicity				*p*-value	Hematological toxicity				*p*-value
		3D CRT (Arm A)		Conventional (Arm B)			3D CRT (Arm A)		Conventional (Arm B)		
		n	%	n	%		n	%	n	%	
2nd week	Grade 0	10	33.3	20	66.7	0.01	20	66.7	24	80	0.243
	Grade 1	20	66.7	10	33.3		10	33.3	6	20	
3rd week	Grade 0	0	0	14	46.7	<0.001	7	23.3	21	70	0.001*
	Grade 1	21	70	15	50		22	73.3	8	26.7	
	Grade 2	9	30	1	3.3		1	3.3	0	0	
4th week	Grade 0	0	0	1	3.3	0.024	0	0	1	3.3	0.148*
	Grade 1	13	43.3	22	73.3		1	3.3	7	23.3	
	Grade 2	17	56.7	7	23.3		20	66.7	16	53.3	
5th week	Grade 1	2	6.7	19	63.3	<0.001	7	23.3	6	20	0.001
	Grade 2	24	80	10	33.3		2	6.7	1	3.3	
	Grade 3	4	13.3	1	3.3		0	0	10	33.3	
6th week	Grade 1	0	0	15	50	<0.001	18	60	16	53.3	0.002
	Grade 2	15	50	9	30		12	40	4	13.3	
	Grade 3	15	50	6	20		0	0	9	30	
	Grade 4	-	-	-			15	50	18	60	
7th week	Grade 0	0	0	2	6.7	<0.001	13	43.3	3	10	
	Grade 1	0	0	3	10		1	3.3	0	0	
	Grade 2	6	20	20	66.7		1	3.3	0	0	
	Grade 3	24	80	5	16.7		0	0	4	13.3	

* Fisher's Exact Test

Table 1: Distribution of the patients by oral mucositis and hematological toxicity.

Week	Grade	Radiation dermatitis toxicity				*p*-value	Pharynx & esophagus toxicity				*p*-value
		3D CRT (Arm A)		Conventional (Arm B)			3D CRT (Arm A)		Conventional (Arm B)		
		n	%	n	%		n	%	n	%	
2nd week	Grade 0	30	100	30	100		22	73.3	24	80	0.542
	Grade 1	-	-	-	-		8	26.7	6	20	
3rd week	Grade 0	18	60	29	96.7		8	26.7	8	26.7	
	Grade 1	12	40	1	3.3	<.001	21	70	22	73.3	0.600*
	Grade 2	-	-	-	-		1	3.3	0	0	
4th week	Grade 0	1	3.3	18	60		0	0	6	20	
	Grade 1	29	96.7	12	40	<.001	24	80	19	63.3	0.036*
	Grade 2	-	-	-	-		6	20	5	16.7	
5th week	Grade 0	0	0	6	20		0	0	1	3.3	
	Grade 1	27	90	22	73.3		24	80	19	63.3	
	Grade 2	3	10	2	6.7	0.035	4	13.3	10	33.3	0.104*
	Grade 3	-	-	-	-		2	6.7	0	0	
6th week	Grade 0	-	-	-	-		0	0	1	3.3	
	Grade 1	8	26.7	24	80		10	33.3	18	60	
	Grade 2	22	73.3	6	20	<.001	19	63.3	11	36.7	0.093*
	Grade 3	-	-	-	-		-	-	-	-	
	Grade 4	-	-	-			1	3.3	0	0	
7th week	Grade 0	-	-	-	-		1	3.3	1	3.3	
	Grade 1	0	0	15	50		8	26.7	19	63.3	
	Grade 2	27	90	13	43.3	<.001	20	66.7	9	30	0.034
	Grade 3	3	10	2	6.7		1	3.3	1	3.3	

*Fisher's Exact Test

Table 2: Distribution of the patients by radiation dermatitis and pharynx and esophagus toxicity.

Radiation induced pain during treatment		3D CRT (Arm A)		Conventional (Arm B)		*p*-value
		N	%	n	%	
1st week	Grade 0	27	90	28	93.3	
	Grade 1	0	0	2	6.7	0.17
	Grade 2	1	3.3	0	0	
	Grade 3	2	6.7	0	0	
2nd week	Grade 0	24	80	25	83.3	0.739
	Grade 1	6	20	5	16.7	
3rd week	Grade 0	2	6.7	16	53.3	
	Grade 1	27	90	14	46.7	<0.001*
	Grade 2	1	3.3	0	0	
4th week	Grade 0	4	13.3	6	20	
	Grade 1	23	76.7	21	70	0.782*
	Grade 2	3	10	3	10	
5th week	Grade 1	12	40	24	80	0.002
	Grade 2	18	60	6	20	
6th week	Grade 0	0	0	2	6.7	
	Grade 1	5	16.7	20	66.7	
	Grade 2	24	80	7	23.3	<0.001*
	Grade 3	1	3.3	1	3.3	
7th week	Grade 1	3	10	9	30	
	Grade 2	23	76.7	17	56.7	0.134
	Grade 3	4	13.3	3	10	

*Fisher's Exact Test

Table 3: Distribution of the patients by radiation induced pain.

Gy three dimensional conformal radiotherapy with concurrent weekly injection cisplatin 7 doses in 7 weeks for 47 days while in arm B patients were treated with 66 Gy conventional radiotherapy in 33 fractions (200 cGy per fraction) in a total of 45 days with concurrent weekly injection cisplatin 30 mg/m^2 weekly for 6 weeks.

The mean age of the 3D CRT group was 46.8 (SD ± 7.513) years and that of the conventional group was 43.73 (SD ± 7.741) years. No significant difference was observed between these two groups (p=0.125). Male dominance was found in both groups with 57% in arm A and 67% in arm B. This finding is near similar to the Cancer

Follow-up findings		3D CRT (Arm A)	Conventional (Arm B)
		n (%)	n (%)
After 6 weeks			
Anorexia		23 (76.7)	19 (63.3)
Dysphagia		12 (40.0)	17 (56.7)
Cough		4 (13.3)	4 (13.3)
Odynophagia		3 (10.0)	2 (6.7)
Others		4 (13.3)	3 (10.0)
FOL			
Post treatment fibrosis with residue		20 (66.7)	24 (80.0)
Normal		10 (33.3)	6 (20.0)
After 12 weeks			
Anorexia		20 (66.7)	18 (60.0)
Weakness		13 (43.3)	11 (36.7)
Dysphagia		12 (40.0)	7 (23.3)
Odynophagia		3 (10.0)	2 (6.7)
FOL *			
Normal		19 (63.3)	13 (43.3)
Minimal residue		11 (36.7)	17 (56.7)
Status at last follow-up	**(Arm A)**	**(Arm B)**	**p-value**
Complete response	12 (40.0)	3 (10.0)	0.02
Partial response	11 (36.7)	14 (46.7)	0.459
No response	3 (10.0)	5 (16.7)	0.48
Progressive disease	4 (13.3)	8 (26.7)	0.051
Complete response	12 (40.0)	3 (10.0)	0.02

FOL= Fiber Optic Laryngoscopy

Table 4: Distributions of the patients by follow up findings.

Registry Report of NICRH 2008-2010 [3]. Some female patients who had refused to get enrolled in this study may have caused this deviation.

Considering the staging 7 patients in arm A were staged as III (23.3%) and in arm B the percentage of stage III was 63.3%. On the other hand 23 patients in arm A were suffering from stage IVA disease. This number in arm B was 11. Significant statistical difference was found between the two arms (p=0.002) .i.e. more patients of stage III being given conventional radiotherapy while stage IVA patients got 3D CRT treatment frequently.

Oral mucositis was compared in seven different periods of time. At the end of the 1st week of the treatment all the patients in both arms showed grade 0 toxicity. From 2nd to 7th week of treatment significantly more patients suffered from high grade mucositis in arm A than arm B patients (p<.05). This finding is in agreement with the study findings by Jamshed et al. [9].

Regarding hematological toxicity, at the end of the 1st week of the treatment there were twenty-eight grade 0 toxicity, one grade 1 toxicity and one grade 2 toxicity in arm A in contrast to thirty grade 0 toxicity in arm B. This difference was not statistically significant (p=0.355). After 2nd week of treatment this toxicity pattern also did not changed significantly (p=0.243). However, at the end of 3rd week of treatment significantly more patients suffered from high grade haematological toxicities in arm A than arm B patients. This statement is also applicable for 5th and 6th week toxicities comparison but not for 4th week and 7th week of treatment. This finding is in agreement with the study findings by Kose et al. [10].

Like other toxicities radiation dermatitis was compared in seven different periods of time as well. At the end of the 1st and 2nd week of the treatment all the patients in both arms showed grade 0 toxicity. From 2nd week on ward significantly more patients developed high grade radiation dermatitis in arm A than the patients of arm B (p<0.05).

Regarding pharynx and esophagus toxicity, at the end of the 1st week of the treatment all the patients in both arms showed grade 0 toxicity. After 2nd week of treatment there were twenty-two grade 0 and eight grade 1 toxicities in arm A while these numbers were 24 and 6 respectively in arm B. This difference was not statistically significant also (p=0.542). But in the 5 successive weeks thereafter, significantly more patients developed high grade pharynx and esophagus toxicity in arm A than the counterpart of arm B (p<0.05). In our study, the rate of ≥ 3 Grade oesophagitis was higher than other studies [11]. This is probably due to the setup error and generous volume taken for treatment. Poor nutritional status of our study subjects and faulty technique could be causes for such higher rate. Meijer et al. in a study showed that setup error caused about 10% addition toxicity in esophagus [12].

Radiation induced pain was significantly higher in arm A patients than arm B patients at 3rd, 5th and 6th week of treatment (p<.05). In 1st, 2nd, 4th and 7th weeks no significant differences of radiation induced pain was noted.

Regarding follow up, after 6 weeks patients experienced constitutional symptoms almost identically except dysphagia which was slightly higher in arm A. At this point Fiber Optic Laryngoscopy (FOL) revealed post treatment residues in about 67% in arm A and 80% instances in arm B. After 12 weeks of treatment completion no significant shift occurred in symptoms. But FOL found more patients with normal findings in arm A than arm B. This difference was statistically significant (p=0.002).

In arm A 12 patients (40.0%) showed complete response where in arm B complete response was noticed in 3 patients (10.0%). This difference was statistically significant (p<.05); partial responses were 11 (36.7%) and 14 (46.7%) in the two arms respectively. No response was noticed in 3 patients in arm A and 5 patients in arm B. Four patients in arm A and 8 patients in arm B were found with progressive disease. Arm B patients had significantly more progressive disease than arm A patients. However, regarding partial and no response no statistically significances were found between these two arms (p=0.109). Considerable differences in responses are noted between these two groups. i.e. patients getting 3D CRT showed more clinical response than patients got conventional radiotherapy which was statistically significant (p<.05).

Conclusion

In conclusion, it could be said from this study that three Dimensional 70 Gy Conformal Radiotherapy (3DCRT) with concurrent chemotherapy offers higher treatment outcome than conventional 2D radiotherapy with 66 Gy if the toxicity could be managed effectively.

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