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MANAGEMENT OF ADVANCED STAGE OF CARCINOMA LARYNX

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ABSTRACT

AIM: The aim of this study was to analyze the efficacy and safety of concurrent chemotherapy with Cisplatin, Paclitaxel and radiotherapy on survival, functional and quality of life outcomes in locally advanced carcinoma of larynx.

MATERIALS & METHODS: From June 2004 to Sep 2006, seventy four inoperable, previously untreated, histopathologically proven, locally advanced patients of carcinoma larynx were planned to be treated with radical EBRT- 56 Gy and concurrent weekly chemotherapy with Cisplatin 30 mg/m^2 and 5FU 400 mg/m^2 placed in Group A and Group B patients were given RT with concomitant chemotherapy Cisplatin30 mg/m^2, Paclitaxel 60 mg/m^2 IV weekly up to 4 weeks and after a gap of two weeks all patients were given 20 Gy by reduced field without chemotherapy in both groups .

RESULTS: Follow up of patient was done up to September 2008. The duration of follow up was in the range of 16-18 months. Parameters studied were local control, complication, recurrence and mortality. Nearly 79% of patients of Group B had complete response after completion of one-month of treatment. Local control was better in patients of Group B.

CONCLUSION: Concomitant chemo radiation with Paclitaxel and Cisplatin would be a better choice in advanced stage of laryngeal cancer, which also provides laryngeal organ preservation together with enhanced response as well as satisfactory survivors.

INTRODUCTION: Now a day after cardiac disease carcinoma is the second most common cause of death worldwide. Carcinoma larynx has become a very common malignancy among males especially metros of our country [1]. In Delhi Cancer Registry Program cancer of larynx is 2nd most common cancer among males and according to Bombay Cancer Registry Program, it is the 3rd most common cancer among males [1]. Laryngeal tumors constitute 2% of total cancer risk [2]. The laryngeal cancer occupies an important position amongst all head & neck cancer. Incidence of laryngeal cancer varies in different parts of the world. In India the incidence is very high more than 10/100000 population [3]. Since it affects the voice organ, the disease and treatment both can alter functional aspect of larynx i.e. voice, most precious gift of nature. The early history of laryngeal cancer is relatively obscure although medical records from sixteen century onwards mention about patients who developed malignant tumors of larynx.

Various radical and voice conserving procedures of laryngectomy have evolved during the last 50 years. Management has improved dramatically due to endolaryngeal surgery and laser treatment [23]. From 1950, Cobalt 60 teletherapy has improved the survival of carcinoma larynx. Currently the megavoltage telecobalt and linear accelerator have become the accepted treatment modality. The high risk of loco regional failure and probability of distant metastasis are responsible for the emerging importantance of chemotherapy [16].

The concept of combined modality approach aims at improved survival, local control, reduction of distant metastasis and above all preservation of organ function [3]. Desirable mode of action of the chemotherapeutic drugs in such combination is direct action on malignant cells as well as its action as a Radiosensitizer [22]. Keeping in view of these considerations Paclitaxel and Cisplatin was used in present study. Combined surgery and chemo radiation is now an established practice for advanced tumors [4, 9]. In advanced and extensive disease, radiotherapy is often used for palliating. More than 2/3rd of patients present themselves in advanced stage of their disease, and requiring chemotherapy [10, 20].

However, combination of chemotherapy and irradiation in advanced stage laryngeal cancer has shown success in preservation of larynx, improved loco regional control as well as increased toxic effect [3, 14, 19]. Therefore, this trial to assess the effect of chemotherapy and radiation therapy was planned in the hope of finding better treatment outcome for preserving larynx.

Tobacco smoking is the indisputable risk factor & seen to act synergistically with alcohol. Smoking increase the risk of developing cancer by 4 times & maximum risk is seen in those men who smoke over 30 cigarettes/bidi a day for 10 years. The risk decreases only after 4 yrs of cessation of smoking. Other etiological factors are asbestos, wood dust, solvents, sheet metal workers, previous irradiation, and dietary deficiency of vitamin A. Viral agents include HPV1, 11, 16, HSV type 1, premalignant lesion leukoplakia, and erythroplakia etc [11, 12, 13, 15].

MATERIALS AND METHODS

This randomized study was carried out for the management of advanced stage of carcinoma of larynx, conducted on the patients attending the department of Radiotherapy and ENT, PMCH, Patna. Patients were selected for a period of 21 months starting from June 2004 to march 2006. These patients have been followed up to September 2008.

During this period, 74 patients of carcinoma larynx were selected for randomized study; all of them completed follow up. Characteristics of those patients are shown in Table 1.

TABLE 1: PATIENT CHARACTERISTICS

PATIENT CHARACTERISTICS	
Age distribution	50-59, maximum (33.78 %)
Sex wise distribution	Male: Female (62:12)
Inhabitation area	Rural : Urban (59:15)
Symptoms	Hoarseness of voice > Neck mass >Respiratory distress **(74:70:31)**
Sub site	Supraglottic (55) > glottic (19)
Histological grading	WDSCC (49) >MDSCC (19) >PDSCC (6)
Tumor size	T4 (32) >T3 (30) >T2 (12), T4 and N2 more common
Regional lymph node involvement	N2 (39) >N1 (25) >N3 (10)
Staging	IVA- 64.86% (48) IVB- 13.5% (10) III- 21.62% (16)

Total 38 patients enrolled in Study group (Group B) and 36 patients in Control group (Group A). Criteria for selection were histological confirmed patients of squamaous cell carcinoma, stage III, IVA, & IVB according to AJCC / UICC staging system [7], patients who have not received any antimalignant treatment, karnofsky performance status more than 60, age between 20 to 75 yrs, patients with normal hepatic & renal function tests.

Treatment protocol included Group A patients who received chemotherapy with regimens Cisplatin 30 mg/m^2/week and 5Fu 400 mg/m^2/week intravenously. Group B patients received Paclitaxel 60mg /m^2/week and Cisplatin 30 mg/m^2/week. All patients received external beam radiotherapy in dose of 50-56 Gy /27-30 fractions over 5 to 6 weeks for 5 days / week, spinal cord was excluded from the radiation field after a dose of 44 Gy. After a gap of 7-14 days , patients were further planned by reduced field through wedge pair or bilateral parallel opposed field in dose of 15-20 Gy/8-12 fraction over 2-3 weeks without concomitant chemotherapy. For N3 lesion direct applied field was used. Both Groups of patients received 4 cycles of concomitant chemotherapy with EBRT. All patients were encouraged to take fluids liberally and high protein diet. Patients were allowed a gap of 7-14 days in planned Treatment, whenever it was considered that further treatment might be detrimental to them. Both group of patients were expected to suffer from mucositis so a prophylactic treatment with Clorhexidine mouth wash, Sucralfate suspension & Vitamins containing (E&A) prescribed from 2nd week till completion or subsidence of mucositis. Patients were evaluated for radiation reactions, effects of treatment on the primary tumor site along with local extension and regional metastasis. The usual statistical methods had been utilized to assess, analyze, compare and evaluate the observations and data for study group.

RESULTS

Maximum Percentage (33.78) of patients (n=25) in both the Group (n=62) was of 50-59 years of age. More number of male patients is mainly due to the smoke habit (Bidi), more prevalent among males. Rural population is more in our total, which is

reflected in table 1. Most frequently reported symptom was hoarseness of voice followed by neck mass and respiratory obstruction. Glottic Carcinoma is about three times more common than supraglottic. But in our study most of the patients had developed supraglottic extension of the disease with metastatic cervical lymph nodal enlargement. Most of the carcinoma larynx is of well-differentiated grade. Tumor size T4 and Nodal size N2 was most prevalent in both groups.

Total 39 (52.70%) patients of both group A and B were having Nodal status N2 and 25 (33.78%) had Nodal status N1 and remaining 10 (13.51%) had Nodal involvement N3. Major part of patients of both group i.e. 32 (43.24%) has tumor size T4, 30 (40.54%) had T3 tumors. Out of 74 patients 48 (64.86%) were in stage A, 10 (13.51%) in stage IVB and 16 (21.62%) were in stage III as shown in Table 1. The patients showing objective response as stage wise after one month is shown in Table 2.

TABLE 2: PATIENT SHOWING QBJECTIVE RESPONSE STAGEWISE AFTER TREATMENT AT 1 MONTH

STAGE	Gr. A	%	Gr. B	%
III	CR	85.71	CR	77.77
	PR	14.28	PR	22.22
IV A	CR	66.66	CR	79.16
	PR	33.33	PR	20.83
IV B	CR	60.00	CR	80.00
	PR	40.00	PR	20.00

Stage III patient of Group A had complete response 85.71% and that of Group B 77.77%, respectively in Stage IV A 66.66% vs. 79.16% and in Stage IV B 60.00% vs. 80.00%. So, obviously Group B patients have better CR and OR than Group A patient. Although, stage wise partial response was better in Stage IV A (33.33% vs. 20.83%) and Stage IV B (40.00% vs. 20.00%) in Group A patient. Patients showing response as group wise after 1 month of completion of treatment is shown in Table 3.

TABLE 3: PATIENT SHOWING RESPONSE IN GROUP WISE AFTER TREATMENT AT 1 MONTH

GROUPS → RESPONSE ↓	Group A		Group B	
	N	%	N	%
CR	25	69.44	30	78.94
PR	11	30.55	8	21.05
OR	36	99.99	38	99.99
NR	0	0	0	0
Total(CR+PR)	36	100	38	100

At first follow up 25 patients in Group A i.e. 69.44 % was in complete response while 30 patients (78.94%) in Group B were in CR. Similarly 11 patients in Group A and 8 patients in Group B i.e. 30.55% vs. 21.05% were in partial response. Group B patients had better CR than Group A patients. Status of patient at 6 month after completion of treatment is shown in Table 4.

TABLE 4: STATUS OF PATIENTS AFTER TREATMENT AT 6 MONTHS

Status	Group A		Group B	
	N	%	N	%
Disease free survival	22	61.11	28	73.68
Stable Disease	12	33.33	9	23.68
Progressive Disease	2	5.55	1	2.63
Dead	0	0	0	0
Total	36	100	38	100

28 patients in Group B and 22 patients in Group A i.e. 73.68% vs. 61.11% had disease free survival.

While 9 patients in Group B and 12 patients in Group A (23.68% vs. 33.33) having stable disease, although progressive disease was present in 1 patient in Group B and 2 patient in Group A. No death reported in any group. Status of patient at 18 month after completion of treatment is shown in Table 5. 17 patients in Group A and 21 patients in Group B ie 47.22 vs 55.26% were disease free while stable disease was present in 10 and 11 patients (27.77% vs 28.94%) respectively. Death was reported in both group, 4 patient in Group A and 3 in Group B. Toxicity during or after treatment in both the group is shown in Table 6.

TABLE 5: STATUS OF PATIENTS AFTER TREATMENT AT 18 MONTHS

GROUPS → STATUS ↓	Group A		Group B	
	N	%	N	%
Disease Free survival	17	47.22	21	55.26
Stable Disease	10	27.77	11	28.94
Progressive Disease	5	13.88	3	7.89
Dead	4	11.11	3	7.89
Total	36	100	38	100

TABLE 6: TOXICITY DURING OR AFTER TREATMENT IN BOTH THE GROUP

Toxicity		Group A				Group B			
		Grade I	Grade II	Grade III	Grade IV	Grade I	Grade II	Grade III	Grade IV
Mucositis	N	17	3	1	0	20	5	2	0
	%	47.22	8.33	2.77	0	52.63	13.88	5.26	0
Mylosuppression	N	16	3	1	0	12	2	1	0
	%	44.44	8.33	2.77	0	31.57	5.26	2.63	0
Xerostomia	N	24	12	0	0	28	10	0	0
	%	66.66	33.33	0	0	73.68	26.31	0	0
Weight loss	N	4	1	0	0	3	1	0	0
	%	11.11	2.77	0	0	7.89	2.63	0	0
Dermatological	N	34	2	0	0	31	7	0	0
	%	94.44	5.56	0	0	80	20	0	0
Peripheral Neuropathy	N	5	1	0	0	8	1	0	0
	%	13.88	2.77	0	0	21.05	2.63	0	0
Nephrological	N	0	0	0	0	0	0	0	0
	%	0	0	0	0	0	0	0	0
Nausea/Vomiting	N	32	4	0	0	34	4	0	0
	%	90	10	0	0	90	10	0	0

Nearly half of the patients in both Group A & B (47.22% vs. 52.63%) had Grade I oral mucositis. Major number of patient i.e. 16 patients in Group A and 12 patient in Group B (44.44% vs. 31.57%) having myelosuppression of Grade I. Xerostomia Grade I was present in 24 patient and of Grade II was present in 12 patient of Group A, while in Group B it was present in 28 & 10 patients respectively. Peripheral neuropathy was present in 9 patient of Group B in comparison to 6 patients of Group A. Nephrological complication was nil in both group and nausea and vomiting & dermatological reaction was present in almost all patient.

DISCUSSION: Carcinoma larynx is predominantly a disease of male; more than 80% of patients were male in both groups. Nearly 80% of patients were from rural areas & nearly all the patients had hoarseness of voice as presenting symptom and 90% of patients had cervical lymph node enlargement. In this study 75% of patients were of supraglottic carcinoma mostly due to extension of glottic carcinoma and 95% of patients had cervical nodal enlargement due to supraglottic nature of disease. In our study nearly 65% of patients of both the groups were stage IV A. Nearly 85% patients of Group A and 77% patients of Group B of stage III disease had complete response after completion of one-month period of treatment. Stage IV A patients of Group A had complete response in more than 65%, where as that of Group B pts had achieved complete response in nearly 80% of patients. Taking all patients of both groups the response after one month showed almost 100% overall survivors and no Non-responders. No death had occurred in either of the Group patients after 6 month of completion of treatment. After 18 months of follow up the stable disease was just less than 30% in both the groups. However, progressive disease in Group A was around 14% where in Group B it was about 7%. Toxicities of chemotherapeutic agents were present in all the patients of our study, but mostly were confined to Grade II & I. Conserving procedures of larynx have evolved during the last 50 yrs. From 1950 cobalt 60, teletherapy have improved the survival of carcinoma larynx [5, 8]. Carcinoma larynx is predominantly a disease of male due to prevalence of smoking mainly Bidi. Sqamous cell histology of well differentiated is the commonest histological type among these patients. Supraglottic extension from glottic disease with cervical lymph nodal involvement was found in our study.

Pfister DG et al[8] reported that larynx is preserved with combined chemotherapy & radiotherapy in advanced but resectable head and neck cancer. Concomitant chemotherapy and irradiation results in an improved possibility of cure compared to radiation alone. Benaso M et al [17] used Cisplatin and 5FU in the treatment of locally advanced head and neck cancer concurrently with conventional radiation dose of 60 Gy. They reported 51% complete response and 70% overall response. This study demonstrated increase in survival among responders in the concurrent chemo radiation setting. Hitt R et al [18] reported Paclitaxel and Cisplatin is an effective first line regimen for loco regionally advanced head and neck cancer. Preliminary results showed 18 patients evaluable for response, 39% achieved a complete response, and 33% achieved a partial response. The overall response rate was 72%. Chougule PB [21] et al stated that concurrent Paclitaxel, Carboplatin and External beam radiotherapy (72Gy) yielded excellent clinical and pathological response. Clinical complete response occurred in 20 patient (60%) and partial response occurred in 10 (30%) for an overall response rate of 90%.

CONCLUSION: Concomitant chemo radiation achieved encouraging response and a satisfactory survival with an added advantage of laryngeal organ preservation. Toxicity of chemotherapy as well as radiation therapy occurred in almost all patients but was up to grade I and in some cases grade II. Response and its statistical significance at first follow up in Group B patients were better in complete response & overall response than Group A patients. At six month of follow up survival was better 12.57% in-group B. At 18 months disease free survival was better by 8.04 % in-group B. Concomitant chemoradiation with Paclitaxel and Cisplatin could be a better choice in advanced stage of Supraglottic laryngeal cancer as well as Glottic carcinoma, which also provides laryngeal organ preservation together with enhanced response as well as satisfactory survivors.

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