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Repurcussions of Concurrent Chemoradiotherapy for Head and Neck Cancers.

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ABSTRACT

Background: Cancer is a potentially lethal disorder with abnormal cell growth and metastasis, warranting multimodal treatment owing to its diversity and complexity. Head and neck cancers are physically and emotionally devastating disease, with profound impact on the most fundamental activities of the subjects' daily life such as the ability to speak, breathe, eat, drink, and socialize. The side-effects of radiotherapy and chemotherapy get superimposed on the existing problems and cause new problems resulting in significant morbidity and suffering. **Methods:** This Prospective Observational study was conducted at the Department of ENT, Southern Railway Headquarters Hospital, Chennai, India. All subjects were evaluated for toxicities using RTOG/EORTC toxicity criteria and Common Toxicity Criteria (CTC). **Results:** Hypopharynx was the most common site of malignancy observed (31.6 %). Pain (90%) and appetite loss (84.2%) secondary to Mucositis and Xerostomia were the most predominant, serious and lasting adverse effects noted. Subjects also experienced markedly altered smell (63%) and taste (78%). Skin changes and alopecia was observed in all the subjects. Overall treatment duration was prolonged in 78.9% owing to severe toxicities, which necessitated withholding of last few cycles of chemotherapy. **Conclusion:** Subjects receiving concurrent Chemo-Radiotherapy experience a substantial number of treatment related adverse events, which had considerable effect on their Quality of life.

Keywords: Concurrent chemoradiotherapy, mucositis, quality of living, xerostomia.

INTRODUCTION

Cancer refers to a large group of potentially lethal disorders characterized by abnormal cell growth and metastasis. Because of its diversity and complexity, cancer has no single treatment, nor can it be attributed to a single etiologic agent. The disease process, treatment options and methods of prevention changes virtually every-day,[1] thus Cancer continues to be a menace despite advances in diagnosis and treatment protocols. Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries.[2] In India, Head and Neck cancers account for 25.3% of all cancers among males and 8.8% of all cancers among females.[3] Overall, cancers of the oral cavity and lip (10.6%) are the second most common followed by cancers of pharynx (8.5%) among males in India.[2] Majority of Head-Neck cancers are preventable. Tobacco and alcohol play an important role in the aetiopathogenesis of Head-Neck cancers.[4,5]

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Why this study?

Head and neck cancer is a physically and emotionally devastating disease, which has a profound impact on the most fundamental activities of the subjects' daily life such as the ability to speak, breathe, eat, drink, and socialize.[6] Unlike other forms of cancer, the disease and side-effects of treatment cannot be hidden, as tumours of the head and neck affect the most visible area of the body. The side-effects of radiotherapy and chemotherapy get superimposed on the existing problems and cause new problems resulting in significant morbidity and suffering.

MATERIALS AND METHODS

This Prospective Observational study was conducted in the Department of ENT, Southern Railway Headquarter Hospital, Perambur, Chennai from May 2011 to May 2012.The present study was planned for a short period of about 1 year and it was a prospective study including all the subjects who fulfilled the criteria during the study period.

Inclusion Criteria

a) Subjects aged 18 years and above.
b) Subjects with histologically proven cancer of the head and neck.
c) Karnofsky's Performance Scale[7] ≥ 70.
d) Normal Hematological investigations, Renal/Liver function and chest X ray.

Exclusion Criteria

a) History of previous radiotherapy / chemotherapy / surgery.
b) Patient with distant metastases.
c) Associated co-morbid conditions (untreated tuberculosis, uncontrolled diabetes mellitus/hypertension, HIV/HBsAg positive subjects).

Nineteen subjects who fulfilled the eligibility criteria were enrolled for the study.

Pre-Treatment Evaluation

A detailed history was taken with emphasis on personal habits like tobacco and alcohol consumption. General physical / systemic / local examination was done followed by blood investigations, biopsy of the tumor, dental / chest evaluation. CT / MRI scan was taken. Written and informed consent was taken after explaining the nature of disease, its treatment and side effects in their own vernacular language.

Treatment Scheme

1. **Radiotherapy**

Depending on the primary tumor site subjects were treated with Linear accelerator using ipsilateral / anterolateral wedge pair technique or two parallel opposed lateral fields or three field technique i.e., two parallel opposed lateral fields and a low neck field (AP). Simulation x-ray film was taken for verification of radiation portals and necessary corrections were made before the start of treatment.

Dose Fractionation - The radiation dose delivered in 30 fractions (5 days in a week) over a period of 6 weeks. The spinal cord was shielded after 46 Gy in 23 fractions in some cases depending upon the initial treatment technique used.

2. **Chemotherapy Protocol**

The drug Cisplatin was used as a single agent concurrently with radiotherapy. The dosage used was 40 mg/m2 weekly for 6 cycles. Premedication with dexamethasone, pantoprazole and anti-emetics (ondansetron) were given before cisplatin infusion. Cisplatin was given as intravenous infusion over 2 to 3 hrs. Adequate hydration with isolyte E was given before and after cisplatin infusion to prevent renal toxicity.

3. **Treatment Monitoring**

All subjects were closely monitored during their entire treatment course. Hydration, protein and caloric intake and oral hygiene were adequately maintained for all the subjects during the entire treatment course. All subjects were also examined clinically every week during the treatment. The toxicities were assessed using RTOG / EORTC toxicity criteria[8] and Common Toxicity Criteria (CTC) .[9]

4. **Follow Up**

The first follow-up was done at 6 weeks or immediately after the completion of treatment chemo-radiotherapy. An attempt to follow-up the patient was made once in 3 months and the subjects reassessed for late toxicities at 6 months (second followup).

5. **Questionnaire**

All subjects were given Quality of Living Questionnaire (QLQ-C30)[10] after translating it into their own vernacular language.

The EORTC quality of life questionnaire (QLQ) is an integrated system for assessing the health related quality of life (QoL) of cancer subjects. The QLQ-C30 version 3.0 (QLQ-C30(V3)) incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea / vomiting), a global health status scale, and a number of single items assessing additional symptoms commonly reported by cancer subjects (dyspnoea, loss of appetite, insomnia, constipation, diarrhea) and perceived financial impact of the disease. Each question has a response category ranging from 1 to 4 namely "Not at all", "A little", "Quite a bit" and "Very much" except for Global health status which has the response category ranging from 1 to 7, where 1 represents "Very poor" and 7 represents "Excellent".[11] The General principles of scoring were followed as described in QLQ-C30.[10]

The scores obtained for quality of life questionnaire were tabulated and analysed in SPSS 19 by applying Student's paired 't' test or Wilcoxon signed rank test based on the pattern of distribution for P value. The clinically assessed toxicity grades were analyzed for significance using Chi-square/Fisher's test.

RESULTS

The various demographic and the treatment characteristics of the subjects are summarized in Table 1. Majority of the subjects were in their 6th decade (78.9%) and were males (94.7%). The commonest site of malignancy observed was hypopharynx (31.6%), in contrast to the study by Givens et al[12] wherein oropharynx (69.2%) was the commonest site of malignancy. Sizeable difference was noted in the Stage at presentation as well; In our study 42.1% presented in stage IV, whereas Givens et al[12] observed it to be 75%. This can be attributed to advancement in diagnostic tools and high clinical vigil, which could in a way improve the survival rate among the diseased [Table 1].

All the subjects had squamous cell carcinoma (histopathological), of which, moderately differentiated (Grade II) grade was observed the

most (68.4%). Smoking and alcohol intake are known and proven risk factors associated with head and neck cancers which was evident in this study; 89.5% of subjects were smokers and 84.2% consumed alcohol. Only 10.5% of the study population had co-morbidities (diabetes mellitus and essential hypertension), which were under control and constant monitoring. 37.8% of the subjects were tracheostomised before commencing the treatment, indication being stridor.

All the subjects received concurrent chemoradiotherapy. Though all the subjects completed radiotherapy in the stipulated time of 6 weeks, the duration of treatment varied widely; The prolongation of treatment beyond 6 weeks was attributable to withholding of chemotherapy cycles in view of toxicities. Treatment duration was prolonged in 78.9% of subjects, which was way higher than that observed in the study by Givens et al (40%).[12] In our study, one of the subjects succumbed to his illness before completion of chemotherapy regimen in comparison to Givens et al,[12] who had reported 2 treatment related deaths.

On analysis of the Quality of life scores the parameters found to be significantly affected were fatigue, pain, insomnia, appetite loss and financial difficulties; although there was worsening of all the symptom scales at the first follow-up [Table 2]. Significant improvement was noted in Global health status and all the functional scales as well at the second follow up. The Symptom scales (fatigue, pain, dyspnoea, insomnia and appetite loss) also had significant improvement [Table 2]. So, overall it was evident that the quality of life showed a brief period of worsening following commencement of treatment protocol, and improved significantly at the second follow-up.

Among the clinical parameters assessed pre-treatment, pain was the most common (90%). Majority of the subjects had loss of appetite (84.2%) and occasional difficulty in sleeping not interfering with function (73.7%). 36.8% of subjects had mild intermittent hoarseness, 15.8% of subjects had moderate dysphagia requiring puree diet [Table 3].

At the first follow-up, all the subjects experienced pain out of which 21.1% had severe pain interfering with activities of daily living. Skin changes were observed in all subjects yet 10.5% had severe confluent moist desquamation with pitting edema. Mucositis was the most debilitating adverse effect observed. Though all subjects had mucositis, 63.2% had confluent fibrinous mucositis with severe pain requiring narcotics. Both pain and mucositis had a profound negative effect on smell, taste and eating, accentuating dysphagia and anorexia [Table 3]. 42.1% of subjects had profound hair loss in the face and neck regions [Table 3], whereas alopecia was reported in 7% of the subjects in a study by Raafat et al.[13]

The second follow-up was done to look for late adverse effects following chemo-radiotherapy. Changes involving the skin, mucus membrane, salivary glands and subcutaneous tissues were the most common and were seen in all the subjects. Xerostomia was observed in all the subjects, as compared to 78% in literature.[14] Dysphagia had greatly improved. Pronounced hair loss persisted in 23.5% of subjects. Markedly altered smell persisted in 58.8%. Taste disturbance persisted in all the subjects but was markedly altered in 47.1%. Pain adequately subsided in all the subjects [Table 3].

Table 1: The demographic and treatment characteristics.

	No. Of subjects	percentage (N=19)		No. Of subjects	Percentage (N=19)
Age			**Sex**		
41-50	2	10.5	Female	1	5.3
51-60	15	78.9	Male	18	94.7
71-80	2	10.5			
Tumour Site			**Tumour Type**		
Glottis	3	15.8	Squamous Cell Carcinoma	19	100
Hypopharynx	6	31.6			
Nasal Cavity	1	5.3			
Oropharynx	5	26.3			
Supraglottis	4	21.1	Tumour Grade		
Tumour Stage			Carcinoma in situ	1	5.3
I	1	5.3	I	2	10.5
II	6	31.6	II	13	68.4
III	4	21.1	III	3	15.8
IV	8	42.1	IV	0	0
Smoking			**Comorbities**		
No	2	10.5	YES	2	10.5
Yes	17	89.4	NO	17	89.5
Dose Of Cisplatin (In mg)			**Radiation Dose (in cGy)**		
31-40	2	10.5	4400	1	5.3
41-50	14	73.7	6000	16	84.2
51-60	3	15.8	6800	1	5.3
			7000	1	5.3
Total Duration Of Chemo-Radiotherapy			**Tracheostomy**		
10 weeks	2	10.5	No	12	63.2

9 weeks	1	5.3	Yes	7	37.8
8 weeks	3	15.8			
7 weeks	9	47.4			
6 weeks	4	21.1			

Table 2: Comparison of Quality of Life scores with the reference values

Function		Reference Scores[16]		Pre-Treatment		First Follow Up		P Value Pt:Ff	Second Follow Up		P Value Pt:Sf
		Mean	Sd*	Mean	Sd*	Mean	Sd*		Mean	Sd*	
Global health status	QL	64.1	22.7	50.4	22.0	31.6	19.8	<0.05 (0.02)	75.0	13.5	<0.05 (0.000)
Physical functioning	PF	81.2	20.4	78.6	22.8	62.1	25.7	<0.05 (0.0000)	87.5	17.3	<0.05 (0.038)
Role functioning	RF	78.9	28.1	78.1	26.1	59.6	31.6	<0.05 (0.003)	86.3	21.4	0.09
Emotional functioning	EF	72.5	24.1	42.5	20.4	25.9	18.4	<0.05 (0.001)	76.5	18.2	<0.05 (0.000)
Cognitive functioning	CF	85.9	19.7	92.1	15.1	82.5	19.6	<0.05 (0.012)	96.1	12.5	0.216
Social functioning	SF	82.6	24.7	50.9	33.1	28.9	33.7	<0.05 (0.002)	54.9	28.7	0.621
Fatigue	FA	26.9	24.9	51.5	26.2	90.1	15.2	<0.05 (0.000)	37.3	18.0	<0.05 (0.018)
Nausea and vomiting	NV	5.3	13.7	12.3	27.7	16.7	28.9	0.371	2.9	8.8	0.109
Pain	PA	23.2	26.1	51.8	20.7	79.8	21.2	<0.05 (0.000)	17.6	23.2	<0.05 (0.000)
Dyspnoea	DY	18.2	26.9	28.1	29.9	33.3	29.4	0.774	9.8	19.6	<0.05 (0.017)
Insomnia	SL	27.3	31.8	47.4	27.9	61.4	27.8	<0.05 (0.009)	33.3	28.9	<0.05 (0.017)
Appetite loss	AP	17.7	28.2	43.9	33.4	57.9	31.1	<0.05 (0.023)	21.6	28.7	<0.05 (0.004)
Constipation	CO	11.1	22.6	17.5	25.7	19.3	23.1	0.564	15.7	17.1	0.527
Diarrhoea	DI	6.1	16.9	3.5	10.5	5.3	16.7	0.371	2.0	8.1	0.317
Financial difficulties	FI	18.2	29.6	52.6	37.4	86.0	25.6	<0.05 (0.002)	66.7	28.9	0.111

Pt: Pretreatment ;
Ff: First followup ;
Sf: Second followup

Table 3: Analysis and comparison of the clinically assessed toxicity grades

Clinical Parameter	Pre-Treatment		First Follow UP		P Value Pt:Ff	Second Follow UP		P Value Pt:Sf	P Value Ff:Sf
	Grade <2	Grade ≥2	Grade <2	Grade ≥2		Grade <2	Grade ≥2		
Skin	100	0	5.3	94.7	< 0.0001	64.7	35.3	0.0064	0.0002
Mucous membrane	100	0	0	100	< 0.0001	58.8	41.2	0.0023	<0.0001
Subcutaneous tissue	100	0	100	0	1.00	70.6	29.4	0.0164	0.0164
Eye	100	0	100	0	1.00	100	0	1.00	1
Ear	100	0	89.5	10.5	0.4865	100	0	1.00	0.4873
Salivary glands	100	0	10.5	89.5	< 0.0001	52.9	47.1	0.0008	0.0103
Pharynx & oesophagus/ dysphagia	84.2	15.8	5.3	94.7	< 0.0001	94.2	5.8	0.6052	<0.0001
Larynx	84.2	15.8	21	79	< 0.0001	94.2	5.8	0.6052	<0.0001
Brain	100	0	100	0	1.00	100	0	1.00	1
Spinal cord	100	0	100	0	1.00	100	0	1.00	1
Alopecia	100	0	57.9	42.1	0.0031	76.5	23.5	0.0404	0.3020
Anorexia	100	0	52.6	47.4	0.0011	100	0	1.00	0.0012
Constipation	94.7	5.3	94.7	5.3	1.00	100	0	1.00	1
Dehydration	100	0	79	21	0.105	100	0	1.00	0.1062
Diarrhoea	100	0	94.7	5.3	1.00	100	0	1.00	1
Nausea	100	0	94.7	5.3	1.00	100	0	1.00	1
Smell	100	0	36.8	63.2	< 0.0001	41.2	58.8	0.0004	1
Stomatitis	100	0	10.5	89.5	< 0.0001	100	0	1.00	<0.0001
Taste disturbance	100	0	21	79	<	52.9	47.1	0.0008	0.08100

(dysguesia)					0.0001				
Vomiting	100	0	100	0	1.00	100	0	1.00	1
Insomnia	100	0	100	0	1.00	100	0	1.00	1
Memory loss	100	0	100	0	1.00	100	0	1.00	1
Neuropathy motor	100	0	100	0	1.00	100	0	1.00	1
Neuropathy sensory	100	0	100	0	1.00	100	0	1.00	1
Pain	79	21	0	100	< 0.0001	100	0	0.1062	<0.0001

Pt: Pretreatment ;
Ff: First followup ;
Sf: Second followup

DISCUSSION

The management of patients undergoing radiotherapy requires a multidisciplinary approach as there are multiple significant adverse effects associated, and it increases many fold when combined with concurrent chemotherapy. The orofacial adverse effects were dose dependent and severe when the doses exceeded 45 Gy, as documented by Rothwell.[15] In our study majority (95 %) received at least 60 Gy of radiation and we observed severe orofacial adverse effects at the first follow up (6 weeks).

There exists an exhaustive list of adverse effects to concurrent chemo-radiotherapy, and discussing all these effects in detail is beyond the scope of this article. Our prime focus is on some of the major and inter-related events which if adequately addressed could significantly alter the magnitude of morbidity and quality of living of patients undergoing concurrent chemo-radiotherapy for head and neck cancers.

The salivary glands have multitude of function like lubrication, antimicrobial properties, cleansing action, digestion, facilitating taste and maintaining mucosal integrity.[16] Major salivary glands account for 70-80% of salivary flow and the rest is contributed by the minor salivary glands throughout. A rapid irreversible loss of salivary flow due to glandular tissue damage following exposure to ionizing radiation is well documented.[17] The replacement of glandular architecture by ductal remnants, fibrous tissue, lymphocytes and plasma cells results in atrophy and fibrosis of salivary glands despite their slow mitotic rate due to high radiosensitivity. The sensation of dryness occur early following radiotherapy because the acini of parotid glands are more radiosensitive than the other two major salivary glands. With the treatment progress saliva becomes thick, vicid and ropy.[18]

Xerostomia induced altered oral microflora results in serious complications. Commonest being candidial infection or colonization of oral cavity and oropharynx, sometimes extending to larynx and hypopharynx. The acute form of infection is clinically indistinguishable from mucositis, presenting as erythema and burning sensation. Symmetrical and bilateral lesions should arouse suspicion of candidial infection.[19]

Other functions of saliva namely cleansing action and digestive enzymes also affected. Dysguesia or altered taste is common sequel to radiotherapy due to loss of salivary facilitation of taste and microvilli damage (secondary taste loss). The progression of dysguesia is rapid and plateaus slowly after all taste sensation is reduced to zero.[20]

Wingard,[21] observed that, the overall effect of xerostomia, dysguesia and mucositis leads to anorexia and weight loss which necessitates hospitalization for parenteral therapy, thereby increasing the financial burden and the risk of nosocomial infections. A similar picture was perceived in our study as well. We observed significant anorexia in both quality of living scores and in clinical assessment scores leading to significant financial difficulties at the first follow up, and all these scores improved significantly at the second follow up.

CONCLUSION

Patients receiving concurrent chemo-radiotherapy encounter considerable amount of treatment related adverse effect, predominantly affecting the oral cavity, oropharynx and larynx, which in turn had significant effect on their Quality of life. We hope that our study serves as an important piece of work in devising strategies to minimize the repercussions of concurrent chemo-radiotherapy for head and neck cancers.

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