Original Article

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Toxicities and Outcome of Intensity Modulated Radiotherapy Vs 2D Conformal Radiotherapy in Head and Neck Cancers

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Abstract

Aim: To compare toxicities and outcome in head and neck cancers patients treated with IMRT and 2D conformal radiotherapy along with concurrent chemotherapy. *Materials and Methods:* Patients presenting to the Department of Radiation oncology with head and neck squamous cell cancers TNM staging T1-4 N0-3 M0. Twenty patients of head and neck cancer and 20 undergoing conventional 2DConformal Radiotherapy alone served as controls were included in this study. *Results:* Most of these patients were found to be in highly advanced stage of disease with poor nutritional status and poor performance status (stage III and IVA) at the time of diagnosis. All the 40 patients received concurrent cisplatin chemotherapy. All the patients were examined and graded for mucositis, dysphagia, xerostomia, skin reactions and tumor response. This study was conducted to compare whether Simultaneous Integrated Boost-Intensity Modulated Radiotherapy (SIB-IMRT) could reduce radiotherapy induced acute mucositis, dysphagia, xerostomia and increase tumor response and tolerance to it in head and neck cancer patients compared to standard conventional Radiotherapy. IMRT may have had a role in reducing the incidence, delaying the onset & diminishing the severity of mucositis in some patients. However it did not completely prevent the occurrence of mucositis. Our study demonstrated that the IMRT may not reduce the incidence of dysphagia. It may be because of high dose per fraction in IMRT delivered to swallowing apparatus. IMRT reduced the incidence of xerostomia. Also the duration of xerostomia was decreased by IMRT. IMRT was also able to reduce the dose to parotids along with adequate coverage of planning target volume. Submandibular glands received less doses, particularly in hypopharyngeal and nasopharyngeal cancers. The contralateral parotid in all IMRT patients were within the tolerance dose of 26 Gy of mean dose. In few selected IMRT patients depending on the primary site, ipsilateral parotid were confined to their tolerance doses of 26 Gy of mean doses. Our study did not show any benefit for tumor response due to IMRT. However the incidence of recurrence is reduced due to IMRT. *Conclusion:* IMRT offers a safe, effective, reduction of normal tissue dose in head and neck cancer patients undergoing radiotherapy & was generally well tolerated. Hence we recommend using IMRT in head and neck cancer patients undergoing radiotherapy in order to reduce RT induced acute mucositis and xerostomia.

Introduction

Head and neck cancers are one of the most common malignancies in both and males and females [1,2]. In India, head and neck constitutes 25% to 30% in males and 15% in females .The patients of head and neck cancers should be dealt with by a multi-disciplinary. Surgery and radiotherapy with or without chemotherapy are most frequently used therapeutic modalities in head and neck cancers. Radiotherapy with or without chemotherapy offer higher rates of organ preservation, and for some cancers, where function is important, it is the treatment of choice. The choice of treatments depends on individual factors, including patient preference. Surgery or radiotherapy has shown good comparable results in early stage cancers (T1, T2). For advance stage disease (stage III / IV) with large primary tumors and or regional nodal involvement, the primary curative

modalities are surgery, radiotherapy and chemotherapy. Whenever two modalities show similar results in terms of control and survival, quality of life and cosmesis becomes important. Standard conventional radiotherapy protocol calls for a total dose of 66 – 70 Gy, 2 Gy per fraction, once daily for five days a week for 6 – 7 weeks. The conventional RT to head and neck cancers typically involves irradiation of major salivary glands and large area of normal mucosal irradiation. It leads to mucositis, dysphagia and xerostomia. Xerostomia is most prevalent late side effect of head and neck malignancy. Also xerostomia is cited by patient as major cause of decreased quality of life [2]. Careful planning of RT fields with appropriate blocks for critical anatomical structures is essential, hence the adverse effects on normal tissue are dependent on total dose delivered, the fractionation schedule, the volume treated and the fields employed. An adverse effect to normal tissue is the major treatment limiting factor in RT [4]. The radiation induced adverse events manifest as either acute reactions (i, e occurring within 90 days of RT) or late/delayed reactions (i.e occurring months to years after RT). The acute reaction includes mucositis, difficulty in swallowing food & xerostomia. The delayed effect includes nocturnal dry mouth, difficulty in swallowing food, speech, dental caries, periodontitis & osteoradionecrosis. Acute reactions occur during the course of RT because of direct tissue injury and possible secondary bacterial irritation, inflammatory reactions in the mucosal, epidermal and glandular tissues within the radiation field leading to acute mucositis, dermatitis & xerostomia which may become dose limiting.

Oral mucositis begins to manifest at doses of 10 to 20Gy (one to two weeks of therapy) and is limited to the field of radiation. Initial signs may include mucosal whitening due to transient hyperkeratinization followed by erythema or erythema may occur first. Ulceration then occurs typically at doses over 30Gy. The patient also receives concurrent chemotherapy to increase locoregional control [5]. This, in addition, increases acute reactions like mucositis, pharyngitis, neutropenia, secondary bacterial infection, etc. The effect on mucosa is of epithelial atrophy, altered vascular supply fibrosis in connective tissue resulting in reduced in atrophic and friable mucosa. The potential sequelae of mucositis consists of severe pain, increased risk for local and systemic infection, compromising oral and pharyngeal function, oral bleeding that effects quality of life leading to increased duration of hospitalization and cost of care [6]. RT to head and neck cancer usually involves irradiation of salivary glands, Salivary gland damage has been shown to be dose dependent & patients receiving less than 50 Gy had significantly increased salivary flow when compared to patients receiving more than 66 Gy [7]. The threshold dose above which salivary gland (particularly parotid gland) will permanently be damaged is said to 26 Gy [8]. During RT, the serous acini are affected earlier than the mucous acini, resulting in a thick viscous secretion causing food and bacteria to adhere to the teeth resulting in significant dental sequelae like plaque formation, periodontal disease, dental caries, tooth loss, dysphagia, difficulty in speaking, loss of taste acuity, increased incidence of oral opportunistic infections and with secondary risk of osteoradionecrosis, fissures on lips & tongue. Saliva production rapidly decreases by 50% after 1 week of standard fractionation radiotherapy [9]. Changes in composition of saliva also occurs resulting in decrease in secretory immunoglobulin, & buffering capacity. The potential oral sequelae also alter food choice, leading to nutritional compromise & weight loss [6]. Primary objective of the study is to compare toxicities and outcome in head and neck cancers patients treated with IMRT and 2D conformal radiotherapy along with concurrent chemotherapy .

Materials and Methods

Patients presenting to the Department of Radiation oncology with head and neck squamous cell cancers TNM staging T1-4 N0-3 M0, MNJIO RCC Hyderabad. This study was conducted between December 2014 to August 2016. The Sample size has been estimated in consultation with a biostatistician. The sample size chosen is 20. This was estimated based on data obtained with the historical studies . Twenty patients of head and neck cancer were included in this study.

Inclusion Criteria was that patients should have age of 18 to 75 years, Performance Status-0-2(ECOG Criteria), Patients who are Radiation with/without chemotherapy in head and neck cancers TNM Stages from T1-4, N0-3, M0, renal parameters with serum creatinine <1.5.

Exclusion Criteria was patients who had metastatic disease, ECOG performance status more than 2, post-operative cases, patients who received neo-adjuvant chemotherapy, previously irradiated. Treatment planning system was varian. Comparison of dosimetric analysis using dose volume histogram (DVH) and comparison of radiation induced toxicities in the patients between both the arms using RTOG acute toxicity grading criteria.

Investigations done were a standardized data collection proforma was used for the study, all the cases underwent biopsy or FNAC for confirmation of malignancy, clinical examination, Computer tomography (CT) or Magnetic Resonance Imaging (MRI) with contrast was carried out for staging, X-ray Chest, complete blood count. Renal Function Test.

When all the investigations were within the normal limits, patient's written consent was taken after explaining the nature of the disease, its treatment options and side effects in the own vernacular language. Patients were also explained about the clinical trial in depth. Patient was counseled about ill effect of tobacco and alcohol consumption and asked to discontinue the same. They were also explained regarding oral hygiene, nutrition and precautions to be taken throughout the treatment.

Results

The patients were selected according to the inclusion and exclusion criteria as mentioned earlier. 20 out of 40 patients were treated with Simultaneous Integrated Boost-IMRT (SIB-IMRT) Technique with concurrent cisplatin chemotherapy served as cases. The other 20 patients were undergoing conventional radiotherapy with 2 DCRT & concurrent cisplatin chemotherapy served as controls.

The follow up was taken of median range of 2-4 months after treatment.

IMRT Target Volumes

PTV 1 was prescribed to doses ranging from 6600 cGy. The dose per fraction was from 200-220 cGy and the number of fractions was 30–33 fractions. PTV 2 received doses ranging from 6000 cGy. The dose per fraction was 200 cGy. PTV 3 received doses from 5400cGy and dose per fraction was 180 cGy. PTV 1, PTV 2 and PTV 3 were treated simultaneously, one fraction each day, five days a week for 6 – 61/2 weeks. At least 95% of prescribed isodose was seen covering 95% volume of PTV in all the cases. Two patients had > 107% prescription dose within the PTV. It was 0.9% and 0.8% of PTV in those patients. None of them had >107% and >110% isodose coverage outside the PTV. The maximum, minimum and mean doses for PTV 1 were 7144cGy, 6400cGy and 6712cGy respectively. *Parathyroid glands:* Mean dose to ipsilateral parotid was 3327.88 cGy in IMRT patients. Mean dose to contralateral parotid was 1948.3 cGy in IMRT patients. Mean dose to ipsilateral parotid was 5184.79 cGy in 3DCRT patients. Mean dose to contralateral parotid was 4731.5 cGy in 3DCRT patients.

Out of forty patients, 26 (65%) patients were male, 14 (35%) patients was female, 37(92.5%) patients gave a history of using tobacco and or alcohol. The patients selected for the study aged from 15 – 65 years: 2(5%) patients were of the age less than 20, 14(35%) patients were in the age group of 21-40, 21(52.5%)were in the age group of 41-60 and 3(7.5%) were of the age above 60.

Table 1: Demographic distribution between the two groups

Age groups (years)	IMRT Group, N (%)	2D CRT Group, N (%)
<20	01 (5%)	01 (5%)
20-40	07 (35%)	07 (35%)
41-60	10 (50%)	11 (55%)
>60	02 (10%)	01 (5%)
Total	20	20
Mean±SD	44.3±13.31	41.75±11.62
Stage		
II	3(15%)	3(15%)
III	8(40%)	7(35%)
IV	9(45%)	10(50%)
Total	20	20

Using Chi-square test, we found that on comparing the two groups, at week 2,4 and 7 there was a difference in number of patients having reduced severity of mucositis in the case group ($p<0.05$) Thus we infer that IMRT may have had a role in reducing severity of mucositis in more number of patients.

Dysphagia in 2 groups "p value" was not statistically significant at week 3, 6, 7 and 1 month ($p>0.05$). Hence we may infer that IMRT may not reduce dysphagia compared to conventional RT

At week 7, there no significant difference between IMRT and RT groups ($p>0.05$).Even 1 month after completion of treatment there was no statistically significant difference between two groups. But at 3 months after treatment there was statistically significant difference between conventional RT and IMRT groups ($p<0.05$)

Table 2: Shows mucositis and dysphagia after treatment

Mucositis		**Grade 1**		**Grade 2**		**p-value**
Week 2	IMRT	8		11		0.01
	RT	1		19		
Week 4		Gr 1	Gr 2	Gr 3	Gr 4	<0.0001
	IMRT	4	14	2	0	
	RT	0	2	16	2	
Week 7	IMRT	0	12	8	0	<0.0001
	RT	0	1	14	5	
Dysphagia		**Grade 1**		**Gr 2**	**Gr 3**	**p-value**
Week 2	IMRT	3		17(Gr 2)		0.2
	RT	6		14(Gr 2)		
Week 7	IMRT	1		14	5	0.5
	RT	0		15	5	
1 month	IMRT	0		11	9	0.1
	RT	0		6	14	

Table 3: Xerostomia and skin reactions at week 2, 4 and 7

Xerostomia		**Grade 1**	**Gr 2**	**Gr 3**	**p-value**
Week 2	IMRT	3	13	4	0.4
	RT	1	16	3	
Week 4	IMRT	11	9	0	0.06
	RT	6	10	4	
Week 7	IMRT	15	5	0	0.0000007
	RT	0	7	13	
Skin Reactions		**Grade 1**	**Gr 2**	**Gr 3**	**p-value**
Week 2	IMRT	14	3	0	0.006
	RT	8	12	0	
Week 4	IMRT	6	13	1	0.04
	RT	1	14	5	
Week 7	IMRT	2	13	5	0.08
	RT	0	9	11	

Table 4: Shows tumour response in 7 weeks, 1 month and 2 months

		CR	**PR**	**PD**	**p-value**
7 weeks	IMRT	8	10	0	0.5
	RT	7	13	0	
1 month	IMRT	15	3	0	0.1
	RT	12	8	0	
2 months	IMRT	17	1	0	0.3
	RT	17	3	0	

Tumor response was assessed at the completion of Rt and on follow up at 1 month and 2 months post RT. Tumor response in control arm were as below, After 7 weeks of RT- complete response was seen in 35%, after one month, 60% had complete response, after two months-85% patients had complete response, Tumor response in IMRT arm were as below, After 7 weeks 40% had complete response, after 1 month 60% had complete response, after 2 months 85% had complete response.

Discussion

Head and neck cancer is one of the commonest malignancy affecting males and females in developing countries and is implicated as a major contributor to the burden of cancer of India [1]. Radiotherapy plays a significant role in management of head and neck cancer as the primary treatment modality. The most common and clinically significant adverse effects arising from head and neck irradiation are acute mucositis, and acute and chronic xerostomia, the last of these being lifelong in duration. Xerostomia, thus affects the quality of life-disrupting normal activities such as eating, speaking and leads to sequelae including radiation induced dental caries and tooth loss with secondary risk of osteonecrosis. Hence strategies for the prophylaxis of xerostomia and mucositis were needed. This study was undertaken to prevent radiotherapy induced adverse effects such as mucositis, dysphagia, skin reactions and xerostomia and thereby improving patient's quality of life. Many studies have been reported on radiotherapy in neck and head cancers.

Mehrotra et al (2005) [10] observed that head and neck neoplasia constitute one of the commonest cancers in India. Use of smokeless tobacco (Pan Masala, Zarda etc.) was on the increase in North India . Data was collected year-wise using the tumor registry data. It was a retrospective study of 11 years from 1990 to 2000 was designed . A comparison of the age-specific prevalence rates of cancer during the study period showed that the prevalence was highest in patients belonging to the 50-59 years age group and squamous cell carcinoma Grade II was the most prevalent type.

Konings AW, Coppes RP, Vissink A (2005) [11] analyzed appropriate literature, especially with respect to mechanisms of action of early radiation damage, and supplied information on the possibilities of amelioration of radiation damage to the salivary glands after radiotherapy of head-and-neck cancer. Massive apoptosis was suggested, the leakage of granules and subsequent lysis of acinar cells was thought to be responsible for the acute radiation-induced function loss of the salivary glands. Literature shows that the compromised cells suffer selective radiation damage to the plasma membrane, disturbing signal transduction primarily affecting watery secretion. They concluded that the most probable mechanism of action, explaining the enigmatic high radiosensitivity for early effects, is selective radiation damage to the plasma membrane of the secretory cells, disturbing muscarinic receptor stimulated watery secretion. Later damage is mainly due to classical mitotic cell death of progenitor cells, leading to a hampered replacement capacity of the gland for secretory cells, but is also caused by damage to the extra cellular environment, preventing proper cell functioning.

Jen YM, Lin YC, Wang YB, et al (2006) [12], evaluated (1) the change in whole salivary secretion rates of nasopharyngeal carcinoma patients before, during, and after radiotherapy, especially during the first week of irradiation; (2) the recovery capability of salivary glands up to 2 years post irradiation; and (3) the possible prognostic factors affecting salivary gland function. Fifty patients who completed conventional radiotherapy technique were included. They observed that salivary glands were very radiosensitive and responded to radiation very early. After 7200 cGy at the fourth day of the 8-week treatment, the unstimulated and stimulated salivary flow rates had decreased by 40%-50%. The nadir was reached in many patients after 3600 cGy (4 weeks). A second phase of decrease in salivary secretion was noted after completion of radiotherapy. They suggested that different mechanisms may be responsible for salivary response after low and high dose of radiation. This study showed no recovery of salivary secretion during thefollow-up period, and the best strategy for managing radiation-induced salivary gland damage may be reduction of radiation dose to the glands. Schwartz et al (2007) [13] determined the feasibility and toxicity profile of accelerated radiotherapy with a simultaneous integrated boost fractionation scheme with intensity-modulated radiotherapy (SIB-IMRT) with or without chemotherapy. Forty-nine patients with advanced head and neck cancer underwent SIB-IMRT. Concomitant chemotherapy was administered in 29 patients. Grade 3 acute toxicities included 55% mucositis, 20% odynophagia, 12% nausea, 18% hematologic, and 8% skin. There were no grade 4 toxicities or treatment-related deaths. With a median follow-up of 25 months, locoregional control was 83%, and overall survival was 80%. Of patients with grade 3 late toxicities, two patients (4% of the total) required a permanent percutaneous endoscopic gastrostomy tube, and osteonecrosis occurred in one patient (2% of the total). They concluded that SIB-IMRT is a feasible technique that shortens the overall treatment time in the radical treatment of patients with advanced head and neck cancer while maintaining acceptable rates of acute toxicity. Daly E Megan et al (2007) [14], correlated patterns of failure with target volume delineations in patients with head and neck squamous cell carcinoma (HNSCC) treated with intensity modulated radiation therapy (IMRT) and reported subjective xerostomia outcomes after IMRT as compared with conventional radiation therapy (CRT). Between January 2000 and April 2005, 69 patients with newly diagnosed nonmetastatic HNSCC underwent curative parotid-sparing IMRT at Stanford University. Sites included were oropharynx (39), oral cavity (8), larynx (8), hypopharynx (8) and unknown primary (6). Forty-six patients received definitive IMRT (66 Gy, 2.2 Gy/fraction), and 23 patients received postoperative IMRT (60.2 Gy, 2.15 Gy/fraction . At a median follow-up of 25 months for living patients (range, 10–60), 7 locoregional failures were observed, 5 in the gross target or high-risk postoperative volume, 1 in the clinical target volume, and 1 at the junction of the IMRT and supraclavicular fields. The 2-year Kaplan–Meier estimates for locoregional control and overall survival were 92% and 74% for definitive IMRT and 87% and 87% for postoperative IMRT patients, respectively. The mean total xerostomia questionnaire score was significantly better for IMRT than for CRT patients ($p = 0.006$). They concluded that predominant pattern of failure in IMRT treated patients is in the gross tumor volume. Parotid sparing with IMRT

resulted in less subjective xerostomia and may improve quality of life in irradiated HNSCC patients. CM van Rij et al (2008) [15] assessed the impact of intensity modulated radiotherapy (IMRT)versus conventional radiation on late xerostomia and Quality of Life aspects in head and neckcancer patients.

They found that Parotid gland sparing IMRT for head and neck cancer patients improves xerostomiarelated quality of life compared to conventional radiation both in rest and during meals. Laryngealcancer patients had fewer complaints but benefited equally compared to oropharyngeal cancerpatients from IMRT. An Indian study by Chakraborty Santam et al (2009) [16], Simultaneous Integrated Boost (SIB-IMRT) was planned for 20 patients. 14 patients were treated with the SIB-72 schedule delivering a dose of 7200 cGy, 6600 cGy, and 5700 cGy to the PTV_{GTV}, PTV_{CTV1}, and PTV_{CTV2} in 33 fractions.6 patients were treated with the SIB-66 schedule delivering 6600 cGy, 6000 cGy, and 5400 cGy to the above-mentioned volumes in 30 fractions. Patients were monitored for toxicity. They concluded that SIB-IMRT schedules evaluated were found to be safe and effective and are being subjected to further prospective studies.

Conclusion

IMRT definitely has a role in reducing radiation inducing toxicities like oral mucositis, xerostomia, skin reactions, dysphagia etc.

It also has a significant role in reducing the incidence of severity of acute and chronic xerostomia in patients undergoing RT in addition to decreased incidence of mucositis. Hence, RT induced secondary complications like oral discomfort, speech, dental caries, periodontitis & osteoradionecrosis could be prevented. Though, IMRT did reduce incidence of severity of dysphagia slightly it was not very effective in preventing dysphagia altogether.

IMRT was generally well tolerated and offered a safe and effective means of salivary gland sparing in head and neck cancer patients. Although our study consisted of a small number of patients, most of the cases in both arms were locally advanced the clinical response was not was not as expected although it has shown favorable improvement in quality of life for patients both during and after RT. Hence we recommend the usage of IMRT in head and neck cancer patients.

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