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RESEARCH ARTICLE

TOXICITY PROFILE OF IMRT vs. CONVENTIONAL RADIOTHERAPY HEAD AND NECK CANCER: A PROSPECTIVE STUDY

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ABSTRACT

Objectives: The main aims of study were to compare toxicity profile of IMRT with conventional Radiotherapy (2D RT) in head and neck cancer. **Methods**: The Study was a prospective one in which we included Eligible patients known case of head and neck cancer like oral cavity, nasopharaynx, oropharaynx, and hypopharyanx to received either definitive chemoradiation alone or adjuvant. Eligible patients in conventional group randomized to receive radiotherapy with parallel opposed lateral fields and one direct anterior lower neck. In IMRT group patients received either 7 fields or 5 fields or parotid sparing radiation. Patients Toxicity pattern (grades of mucositis, skin reaction, xerostomia, odynophagia) of both groups was noted down. Toxicity of Radio-Therapy (RT) developing within 90 days and more than 90 days from the beginning of RT assessed according to Radiation Therapy Oncology Group (RTOG) and European Organization for the Research and Treatment of Cancer (EORTC) criteria. **Results:** A total of 30 patients were available for the analysis, 15 patients were in conventional group and 15 were in IMRT group. Patients who developed toxicity was compared both groups. Acute toxicity as well as late toxicity is concern in present study, it has been found that in conventional group toxicity is more common other than skin toxicity as compared to IMRT group. **Conclusion**: Although for some side-effects, the benefit of IMRT on conventional RT cannot be easily proven, the majority and present study show a reduction in toxicity when using IMRT in head and neck cancer. IMRT should be used in all head and neck cancer patients, in order to try to reduce the devastating side effects. Continuous prospective data collection on toxicity and outcome will provide us more data in the future, supporting this technological progress.

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INTRODUCTION

Head and neck cancer (HNC) is the seventh most common cancer worldwide with 550,000 new cases every year. It is furthermore, the seventh most common cause of death, resulting in 380,000 deaths annually (Fitzmaurice *et al*., 2017). Risk factors for the development of cancers occurring in the head and neck region are a history of smoking and alcohol exposure. In developed countries where a decrease is seen in smoking and alcohol exposure, there is a decrease in HNC incidence in general. However, the incidence of oropharyngeal cancer (OPC) at first stagnated, and is now, even increasing due to a different etiology, namely infection with Human papilloma virus type 16 (HPV-16) (Pytynia *et al*., 2014). The usual time of diagnosis is after the age of 40, except for salivary gland and nasopharyngeal cancers (NPCs), which may occur in younger age groups. HNC is usually diagnosed in a locally advanced but curable or potentially curable stage. This frequently requires a multimodal treatment approach comprising surgery followed by radio-chemotherapy or radiotherapy alone as definitive treatment. The treatment of choice depends on multiple factors such as tumor grade, stage and localization, nodal involvement, patient characteristics and impact of the treatment (Pfister, 2011). Radio or radio chemotherapy holds the potential for better functional outcomes compared to surgery. Most head and neck malignant neoplasm's arise from the surface epithelium and are squamous cell carcinoma or one of its variants, including lymphoepithelioma, spindle cell carcinoma, verrucous carcinoma, and undifferentiated carcinoma. Conventional Radiotherapy Techniques, simple-shaped radiation fields based on bony anatomy were aimed at the tumor to be sure the tumor was irradiated sufficiently. This was the so-called two-dimensional radiotherapy (2DRT). Large volumes of normal tissue were irradiated using this technique, causing important toxicity acute or chronic such as xerostomia, dysphagia and fibrosis of the skin. Advancement in imaging techniques, improved identification of target volume, 3D image reconstruction, computer optimized algorithms have led to

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evolution of radiation delivery from 2D Radiotherapy to Three Dimensional Conformal Radiotherapy (3D CRT) with geometric modulation of beam shape that conform as closely as possible to the target volume in terms of adequate dose to the tumor and minimal possible dose to normal tissue (Bucci MK *et a*l.,2005). Further progress in conformal radiotherapy led to logical evolution of Intensity Modulated Radiation Therapy (IMRT) where simultaneous geometric and intensity modulation of radiation beams allows delivery of non-uniform fluence from any given position of the treatment beam to optimize the composite dose distribution. The intensity modulated radiotherapy (IMRT) allows not only sparing of OARs, but also makes it possible to deliver inhomogeneous doses which allows simultaneous boosting of the tumor, and could facilitate dose escalation in certain regions of the tumor. Xerostomia, skin toxicity, mucositis, fibrosis are the most troubling side effects of RT-based treatment. The use of radiation therapy, often integrated with chemotherapy must deal with severe acute and chronic skin toxicity often associated with pain, discomfort, itching, and burning, heavily affecting patients' quality of life (Russi EG *et a*l., 2012). Significant acute skin toxicity may affect up to 95% of these patients, which sometimes impacts negatively on the proper adherence to the treatment protocol (Porock D *et a*l., 2002).

MATERIALS AND METHODS

The Study was a prospective one in which we included Eligible patients known case of head and neck cancer like Oral cavity, Nasopharaynx, Oropharaynx, Hypopharyanx to receive either definitive chemo radiation alone or adjuvant. A prospective analysis of total 30 patients was done who underwent IMRT (15 patients) and conventional (15 patients) for head and neck squamous cell cancer between January 2017 to may 2018. Eligible patients in conventional group randomized to receive radiotherapy with parallel opposed lateral fields and one direct anterior lower neck. In IMRT group patients received either 7 fields or 5 fields or parotid sparing radiation. Patients in conventional group received radiation in two phases; in second phase spinal card is out of field after 46 Grays. Convention group treated under cobalt machine, while as IMRT group treated under Linac machine. All the patients received 70Gy in 35 fractions, 2Gy per fraction. All patients were treated with immobilization in supine position using a customized thermoplastic device. Treatment planning involved Contrast enhanced planning Computerized Tomography (CT) scan of the area of interest with 2-3 mm slices on CT scan that is networked to the treatment planning system (ECLIPSE), followed by delineation of various target volumes like, Gross Tumor Volume (GTV), Clinical Target Volume (CTV), Planning Target Volume (PTV) and organ at risk volumes contoured on each slice. An isometric margin of 5mm provided to the CTV for final PTV and 3mm to organs at risk for Planning Organ at Risk Volume (PORV).The delineation of the various volumes was done as per consensus guidelines. Toxicity pattern (grades of mucositis, skin reaction, xerostomia, odynophagia) of both groups was noted down. Toxicity of Radio-Therapy (RT) developing within 90 days from the beginning of RT (acute toxicity) assessed according to Radiation Therapy Oncology Group (RTOG) and European Organization for the Research and Treatment of Cancer (EORTC) criteria. RT toxicity developing after 90 days (chronic/ late toxicity) is graded with the same scale for late squeal.

Statistical analysis: The data was analyzed statistically with the statistical software version 20. All the continuous variables of the study were represented by descriptive statistics and the entire categorical variable in terms of frequency and percentage. Depending on the variable of interest, mean (SD), median (range) and frequency (percentage) were used to summarize data in a descriptive manner. Nonparametric Wilcoxon rank-sum tests, two-sample t-tests and chi-square tests (or Fisher's exact tests) were used to compare two groups. Also the appropriate statistical charts were used to represent the data. The main of study was to compare toxicity profile of IMRT with conventional Radiotherapy (2D RT) in head and neck cancer especially skin toxicity.

RESULTS

A total of 30 patients were available for the analysis, 15 patients were in conventional group and 15 were in IMRT group. Patients who developed toxicity was compared both groups. Table 1,2 illustrates patients characteristics, in conventional group most commonly observed age group was in between 51-60years (46%) closely followed by age group of 41-50 years (33%) and 41- 50 years (43%) followed by 31-40 years (33%) was in IMRT group.

Table1. Distribution of Study Subjects According To Demographic Profile

Age (Years)	N	
	Conventional group	IMRT group
21 – 30	0 (0%)	1 (6.6%)
31 – 40	2 (13%)	3 (20%)
41 – 50	5 (33.3%)	8 (53%)
51 – 60	7 (46%)	2 (13%)
61+	1 (6.6%)	1 (6.6%)
Mean ± SD	49.7 (8.34)	44.3 (9.61)
Gender		
Male	9 (60%)	10 (66%)
Female	6 (40%)	5 (33%)
Total	**15**	**15**

Table 2. Case Distribution According To Site of Primary Malignancy

Site	N	N
	Conventional group	IMRT group
Tongue	3 (20%)	2 (13%)
Tonsils	2 (13%)	1 (6.6%)
Hypopharynx	3 (20%)	2 (13%)
Nasopharynx	7 (46.6%)	10 (66.6)
Total	15 (100%)	15 (100%)

P value 0.718

Table 3.Acute Toxicity

Acute toxicity	Conventional group	IMRT group	P Value
Skin toxicity grade			
i	6 (40%)	2 (13%)	
ii	5 (33.3%)	4 (26%)	
iii	3 (20%)	6 (40%)	0.319
iv	0 (0%)	3 (30%)	
Xerostomia grade			
i	2 (13%)	5 (30%)	
ii	4 (26%)	7 (46.6%)	0.123
iii	6 (40%)	3 (20%)	
iv	3 (20%)	0 (0%)	
Mucositis grade			0.565
i	4 (26%)	6 (40%)	
ii	3 (20%)	5 (30%)	
iii	6 (40%)	3 (20%)	
iv	2 (13%)	1 (6.6%)	

Table 4. Late toxicity

Late toxicity	Conventional group	IMRT group	P VALUE
Odynophagia grade	N %	N %	
i	3 (20%)	1 (6.6%)	
ii	1 (6.6%)	0 (0%)	
iii	0 (0%)	0 (0%)	
iv	0 (0%)	0 (0%)	>0.999
Skin /subcutaneous Thickening grade			
i	3 (20%)	4 (26%)	
ii	2 (13%)	2 (13%)	
iii	0 (0%)	0 (0%)	0.567
iv	0 (0%)	0 (0%)	
Xerostomia grade			
i	9 (60%)	2 (60%)	
ii	4 (26%)	4 (26%)	0.009
iii	7 (46.6%)	1 (6.6%)	
iv	2 (13%)	0 (0%)	

Majority of patients were males in both group. Most of the patients were having nasopharyngeal cancer as their primary site of malignancy in both the groups followed by tongue cancer. Most patients were having ECOG performance score 1 (73%), followed by 20% patients had ECOG performance score 2 in conventional group, however in IMRT group 8 patients (53%) had ECOG performance 1 followed by 26% of patients had ECOG Performance 0. Most of the patients had advanced stage at presentation and eligible patients underwent surgery with neck dissection prior to chemo radiotherapy.

Toxicity: So for as acute toxicity is concern**,** The IMRT group demonstrated significantly higher grade acute skin toxic effects compared with the Conventional group in our analysis. Table 3 illustrates acute toxicity, Six patients (40%) had grade 3 skin toxicity in IMRT group than 3 patients in conventional group, However Acute grade I and ii toxicity is concern, conventional groups had more however this was statistically insignificant (p-0.319). Xerostomia was more commonly significant in conventional than IMRT Group, Grade iii 40% of patients and grade iv 20% patients in conventional group however grade ii (46.6%) and grade I 30% patients more common in IMRT group, this was statically insignificant (p- value 0.123). Acute grade 3 or greater toxic effects to the mucous membranes occurred in 6 of 15 (40%) patients in the conventional group and only 3 of 15 (20%) patients in the IMRT group.

This was statically insignificant (p- value 0.565). The conventional group demonstrated significantly more late toxicity as shown in table 4, like odynophagia and xerostimia effects compared with the IMRT group in our analysis; however skin/ subcutaneous thickening grade more in IMRT group. Late toxicity grade 1 odynophagia occurred in 3 of 15 (20%) patients in the conventional group and only 1 of 15 (6.6%) patients in the IMRT group, this was statically insignificant (p value->0.999). Late Grade 2 toxic effects to the skin occurred in 4 of 15 (26%) patients in the IMRT group compared with 2 of 15 (13%) patients in the conventional group however this was statically insignificant (p value-0.567).Statistically significant (p value 0.009) xerostomia grade 3 developed in 7 of 15 (46%), patients in conventional group compared with 1 of 15 (6.6%) patients in IMRT group.

DISCUSSION

Radiotherapy has played a significant role in the treatment of head and neck cancers. More than two third of head and neck cancer patients need to undergo either definitive or post-operative radiation therapy (Ling *et al*., 2000).

Conventional radiotherapy is associated with significant acute and late toxicities and to overcome this, newer techniques have evolved with the aim of delivering cancericidal dose to the tumor while delivering minimum dose to surrounding normal tissues. As compared to conventional radiotherapy, IMRT technique offers better sparing of normal tissue thus minimizing toxicity. The radiation beam can be adjusted to the irregularly shaped target volumes with extremely high precision while reducing the radiation delivered to the surrounding healthy tissue and critical structures e.g., spinal cord, brain stem, parotid glands, eyes etc. in case of head and neck cancer (Ezzell *et al*., 2003; Nutting, 2000). In conventional group, most commonly observed age group was in between 51-60 years(46%) closely followed by age group of 41-50 years (33%) and 41- 50 years (43%) followed by 31-40 years (33%) was in IMRT group. Majority of patients were males in both group, and only 5 females were in IMRT group and 6 in conventional group. This was different with the study done by *Brandi n. and reeves, M.D,* (Reeves, 2012).

Acute toxicity is concern in present study; it has been found that in conventional group acute toxicity is more come other than skin toxicity as compared to IMRT group. The grade 3 or higher skin toxicity concern in IMRT group explained by following reasons first is multiple field, second is angle of oblique which decreased skin sparing effect. Acute grade 3 or greater skin toxic effects occurred in 6 of 15 (40%) patients in the IMRT group and only 3 of 15 (20%) patients in the conventional group. This was statically insignificant, however late skin or subcutaneous toxicity are also more in IMRT group than conventional group. Our study was contradicted to study conducted by Gosh-Laskar *et al*. (2016) acute dermatitis did not differ significantly between the two treatment arms, late subcutaneous fibrosis was significantly less frequent in patients treated with IMRT compared to patients in the 3DCRT-arm at all time points. So far as late toxicity concern was more in conventional groups except skin or subcutaneous toxicity. Late grade 1 or greater toxic effects to the odynophagia occurred in 3 of 15 (20%) patients in the conventional group and only 1 of 15 (6.6%) patients in the IMRT group ,however Statistically significant xerostomia grade 3 developed in 7 of 15 (46%) patients in conventional group compared with 1 of 15 (6.6%) patients in IMRT group, our study is similar to study conducted by Nutting *et al*. (2011), a phase 3 multicentre randomized controlled trial, Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT). Their primary objective was to assess late side-effects of radiotherapy by looking at the proportion of patients with

xerostomia grade 2 or worse in conventional group. The limitation of the study was its small sample size.

Conclusion

The conclusion drawn from this study, although for some side-effects, the benefit of IMRT on conventional RT cannot be easily proven, the majority and present study show a reduction in toxicity when using IMRT in head and neck cancer. IMRT should be used in all head and neck cancer patients, in order to try to reduce the devastating side effects. Continuous prospective data collection on toxicity and outcome will provide us more data in the future, supporting this technological progress.

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