BENEFITS OF INTENSITY-MODULATED RADIOTHERAPY (IMRT) IN PATIENTS WITH HEAD AND NECK MALIGNANCIES- A SINGLE INSTITUTION EXPERIENCE

Sherry Seasor Abraham[1], Binitha Tresa Thomas[2], Rema Padanayil Lekshmikutty[3], Flowerlit Thomas[4], Nabeel Yahia[5], Anil kumar[6], Ancy joseph[7], Seeja Joseph[8]

[1]Consultant, Department of Radiation Oncology, Government Medical College, Kottayam.
[2]Assistant Professor, Department of Radiation Oncology, Government Medical College, Kottayam.
[3]Professor, Department of Radiation Oncology, Government Medical College, Kottayam.
[4]Assistant Professor, Department of Radiation Oncology, Government Medical College, Kottayam.
[5]Associate Professor, Department of Radiation Physics, Government Medical College, Kottayam.
[6]Consultant, Department of Radiation Oncology, Government Medical College, Kottayam.
[7]Assistant Professor, Department of Radiation Physics, Government Medical College, Kottayam.
[8]Statistical Assistant, Department of Radiotherapy, Government Medical College, Kottayam.

ABSTRACT

BACKGROUND

Radiotherapy and surgery are the principal curative modalities in treatment of head and neck cancer. Conventional two-dimensional and three-dimensional conformal radiotherapy result in significant side effects and altered quality of life. Intensity-Modulated Radiotherapy (IMRT) can spare the normal tissues, while delivering a curative dose to the tumour-bearing tissues. This study reveals the role of IMRT in head and neck cancer in view of normal tissue sparing with good tumour control.

MATERIALS AND METHODS

Radical radiotherapy was given using linear accelerator up to a dose of 66 to 70 gray in 30 to 33 fractions (intensity-modulated radiotherapy with simultaneous integrated boost) over 6 to 7 weeks to 56 eligible patients. Concurrent cisplatin was given to patients with locally-advanced disease up to a dose of 40 mg/m^2 weekly once along with radiation. The patients were monitored weekly once during the treatment for acute skin and mucosal toxicities using the RTOG scoring criteria. After the treatment, locoregional response was assessed and recorded at 6 weeks, 3 months and 6 months intervals.

RESULTS

Severe skin toxicity (grade III or more) was seen in approximately 7% patients. Severe mucosal toxicity (grade III or more) was seen in approximately 80% of patients. IMRT technique showed better skin sparing compared to 3D conformal radiotherapy. Severe mucosal toxicity was slightly higher in this study due to the simultaneous integrated boost technique used for dose intensification to the mucosa, which results in better primary tumour control. At the end of 6 months, 75% patients achieved locoregional control and residual/recurrent disease was seen in 25% of patients. IMRT offered good locoregional control with less skin toxicity and acceptable mucosal toxicity. The results were similar to the previous study reports using IMRT.

CONCLUSION

IMRT is a better treatment option in locally-advanced head and neck malignancies providing good locoregional control with acceptable toxicities.

KEYWORDS

IMRT, Head and Neck Cancer, 3D Conformal Radiotherapy.

HOW TO CITE THIS ARTICLE: Abraham SS, Thomas BT, Lekshmikutty RP, et al. Benefits of Intensity-Modulated Radiotherapy (IMRT) in patients with head and neck malignancies- A single institution experience. J. Evid. Based Med. Healthc. 2017; 4(72), 4305-4309. DOI: 10.18410/jebmh/2017/857

BACKGROUND

Radiotherapy is the main nonsurgical treatment for Head and Neck Squamous Cell Carcinoma (HNSCC).[1] High rates of local control of disease can be achieved with more than 85% for stage 1 and 2 and 60-70% for stage 3 and 4 at 5 years.[2] Conventional two-dimensional and three-dimensional conformal radiotherapy results in significant side effects and altered quality of life. Intensity-Modulated Radiotherapy (IMRT) is a conformal radiotherapy technique that can spare the normal tissues, while delivering a curative dose to the tumour-bearing tissues. The sharp dose fall off gradient of this technique permits the administration of a highly conformal and more homogeneous dose to the Planning Target Volume (PTV)[3] than conventional and conformal radiotherapy. This allows better sparing of the organs at risk

Financial or Other, Competing Interest: None.
Submission 19-08-2017, Peer Review 26-08-2017,
Acceptance 05-09-2017, Published 07-09-2017.
Corresponding Author:
Dr. Binitha Tresa Thomas,
Pampackal House, Arpookara East P. O.,
Panampalam, Kottayam- 686008.
E-mail: drbinithaabey@gmail.com
DOI: 10.18410/jebmh/2017/857

(e.g., parotid glands, submandibular and minor salivary glands, larynx and swallowing structures) leading to a decrease in acute and late side effects.[4,5] This may open a window for treating patients with intensification of radiotherapy alone or combined with chemotherapy and/or targeted therapy. In addition, IMRT permits the administration of differential dose ("dose painting") to different parts of the treatment volume (risk zones) at the same time. Nutting et al[6] reported the first phase-III multicentre randomised-controlled trial in patients with HNC showing significantly less xerostomia (grade 2 or more) at 12 and at 18 months in the IMRT group compared to conventional radiotherapy group of patients, both without concurrent chemotherapy. However, a clear survival benefit of IMRT over the more classic three-dimensional conformal radiation therapy has not been shown.[7] There are some concerns about the theoretically higher risk of induction of secondary cancers by IMRT because of the increased low-dose irradiated volume.[8] Therefore, more trials and experiences with IMRT with and without induction and/or concurrent chemotherapy are required to be reported and shared. Hence, this prospective single arm study is to share the role of IMRT in head and neck cancer in relation to normal tissue sparing and tumour control.

Aims and Objectives

Prospective single arm study-

1. To assess the locoregional control of tumour in patients receiving IMRT for head and neck malignancies.
2. To assess the acute skin and mucosal toxicities associated with treatment.

MATERIALS AND METHODS

All head and neck cancer patients attending the Department of Radiation Oncology, Government Medical College, Kottayam, seen between January 2015 to October 2015 were screened for this prospective single arm study by using the following inclusion and exclusion criteria.

Patients with more than 18 yrs. and less than 75 yrs. of age with histological proven primary squamous cell cancer of head and neck region, Karnofsky performance status greater than or equal to 70, normal haematological parameters, LFT and RFT were included in the study.

Patients with other than squamous cell carcinoma, evidence of distant metastases, history of previous surgery/radiotherapy/ chemotherapy having tracheostomy, synchronous primaries and pregnancy are excluded from study.

Study Procedure- This prospective single-arm study included 56 eligible patients with head and neck malignancies. Pretreatment evaluation included complete history, physical examination, body surface area and performance status were recorded. Laboratory studies were done. Biopsy of primary tumour was done for confirmation. Radiographic studies such as chest x-ray, contrast-enhanced CT scan/MRI were obtained. Staging was done according to TNM staging system (AJCC 7th Edition 2010). Dental prophylaxis was advised.

Patients were simulated in a CT simulator with thermoplastic shell as immobilisation. Once the CT data set has been acquired, it was transferred to a computer workstation for normal tissue and tumour/target volume delineation, which completed image acquisition and data input.

Contouring was done as per the RTOG contouring guidelines for head and neck carcinoma. This was done with the help of SomaVision software in our Varian Clinac machine. The contours for target volumes and organs at risk were defined and displayed. Tumour and target volumes were defined based on the conventions of the International Commission on Radiation Units and Measurements (ICRU). The GTV, CTV and PTV for high risk, intermediate risk and low-risk volumes were defined.

All patients were given radical radiotherapy (Intensity-Modulated Radiotherapy - IMRT) with simultaneous integrated boost technique up to a dose of 66 to 70 gray in 30 to 33 fractions over 6 to 7 weeks using linear accelerator (Varian Clinac 2100) with 6MV energy.

Concurrent cisplatin at a dose of 40 mg/m^2 was given weekly once along with radiation for patients with locally-advanced disease. Specific dose prescription were given for planning target volumes. Dose limits were assigned to normal tissues. High-risk volume was prescribed 66 to 70 Gy intermediate risk volume 60 Gy and 54 Gy to the low-risk volume. These were delivered at different dose per fractions using Simultaneous Integrated Boost (SIB) technique. Beam optimisation was done by the Eclipse treatment planning system of Varian machine by the process of iteration.

The target volumes and critical structures are analysed for adequate dose coverage and dose limits and plan was analysed subjectively by evaluating an isodose plot or objectively by reviewing cumulative dose volume histograms. For all patients, a minimum of 95% prescribed coverage to the highest PTV and 99% coverage to the CTVs subs was required for a plan approval. Plan was modified based on the evaluation of dose distributions. Quality assurance was done with portal dosimetry system of Varian machine. The computer generated dosimetric data was compared with the machine generated dosimetric data (3 mm, 3%) is taken as the maximum disparity that can be allowed.

The drug cisplatin was used as a radiation sensitiser with a dose of 40 mg/m2 weekly for 6 to 7 cycles for all patients with T3 or N+ disease.

All patients were examined once in a week during the treatment. Acute mucosal and skin toxicity was assessed and graded as per the RTOG acute radiation morbidity scoring system. The highest grade of skin and mucosal toxicities were noted for each patient during the weekly assessment. At the completion of treatment, both the primary and the node were assessed clinically and noted.

At follow-up, patients underwent thorough clinical examination including ENT evaluation for detection of locoregional disease. The first follow-up was done at 6

weeks after completion of treatment. During follow up, patients were assessed for response of the primary and the node separately and noted down. Patients were scheduled for further follow-up at 3 months and at 6 months. Response rate for the primary tumour and lymph nodes were assessed separately. Complete Response (CR) indicates complete disappearance of all detectable lesions and presence of detectable residual lesion will be labelled as Residual Disease (RD).

RESULTS

This study included 50 male and 6 female patients and 12 cases in 40-50 yrs. age group, 22 in 50-60 yrs. group and 20 in 60-70 yrs. group. Performance status was 70 in 12 cases, 80 in 20 and 90 in 26 cases. Clinical disease stage distribution is shown in Table I and site wise distribution in Table II.

After completion of radiotherapy, 36 patients (64.3%) were with grade II, 16 patients (28.4%) with grade I and 4 patients (7.1%) with grade III skin toxicity. No grade IV toxicity was observed (Table IV). Mucosal reactions after radiotherapy were seen in 44 patients (78.6%) with grade III, 2 patients (3.6%) with grade IV, 8 patients (14.3%) with grade II and 2 patients (3.6%) with grade I toxicity.

Follow up clinical evaluation 6 weeks after post treatment showed complete response in 48 patients (85.7%) and residual disease in 8 patients (14.3%). Among the patients with residual disease, 4 patients had T4 and 2 patients each with T2 and T3 tumour. T1 tumours had no residual disease. Residual disease was seen in 2 patients each with primary in oral cavity, hypopharynx, nasopharynx and larynx. Patients with primary in oropharynx had no residual disease. Histologically, 4 patients with well-differentiated tumours and 4 patients with poorly-differentiated tumours had residual disease. Patients with moderately-differentiated tumours had no residual disease. Patients with N0 nodal status had no residual disease, whereas 4 patients each with N1 and N2 nodal status have shown residual disease. Considering the composite stage, 8 patients with residual disease were having initial stage 4A disease.

After 3 months, 2 more patients, primary in hypopharynx with T4A-N1 disease and moderately-differentiated histology developed locoregional disease. 46 patients (82.1%) were disease free and 10 patients (17.9%) had locoregional disease. Among these patients with locoregional disease, both had T4A and N1 tumours with their primary in the hypopharynx. They were having moderately-differentiated histology.

At the end of 6 months, 4 more patients developed residual/recurrent disease. Initially, two patients had T3 and other two patients were T4A with N1 and N2 lesions with primary in nasopharynx and larynx. Histologically, 2 patients had moderately-differentiated and 2 patients had poorly-differentiated tumours. All those patients were of composite stage 4A.

Tumour Stage	No. of Patients	Nodal Status	No. of Patients	Composite Stage	No. of Patients	Grade	No. of Patients
T1	2	N0	18	II	8	WD	22
T2	18	N1	20	III	20	MD	24
T3	24	N2	18	IV	28	PD	10
T4	12	N3	0				

Table 1. Tumour Characteristics- Grade, T Stage, N Stage, Composite Stage

Tumour Stage	No. of Patients		Nodal Status	No. of Patients		Composite Stage	No. of Patients	
	CR	RD		CR	RD		CR	RD
T1	2	0	N0	18	0	Stage 2	8	0
T2	16	2	N1	12	8	Stage 3	20	0
T3	20	4	N2	12	6	Stage 4A	14	14
T4A	4	8						

Table 2. Clinical Response at 6 Months Post Treatment

CR - Complete Response; RD - Residual Disease.

Subsite	6 Months Complete Response	6 Months Residual Disease
Oral cavity	12	2
Oropharynx	8	0
Hypopharynx	10	4
Nasopharynx	2	4
Larynx	10	4
Total	**42**	**14**

Table 3. Assessment of Local Control According to the Subsite at 6 Months

DISCUSSION

Radiation therapy remains the standard of nonsurgical treatment of head and neck cancers, especially in case of locally-advanced head and neck tumours. Different strategies have been applied to improve treatment outcome such as altered fractionation radiotherapy,[8,9,] concurrent chemoradiotherapy, bioradiation (i.e., concurrent use of radiation and cetuximab)[10] and recently, the use of a more effective induction chemotherapy followed by chemoradiation (i.e., sequential therapy).[11,12]

Radiotherapy techniques have evolved strongly during the last decade with the implementation of Intensity-Modulated Radiotherapy (IMRT). The sharp dose fall-off gradient of this technique permits the administration of a highly conformal and more homogeneous dose to the

Planning Target Volume[13] (PTV) than conventional and conformal radiotherapy. This allows better sparing of the organs at risk (e.g. parotid glands, submandibular and minor salivary glands, larynx and swallowing structures) leading to a decrease in acute and late side effects.

At the end of study, the local control rate was 75%. Van Gestel et al[4] using IMRT in 48 patients reported locoregional control rate of 66% at 3 yrs. Whereas, Chao et al[14] in his study using IMRT in 52 patients reported 85% at 2 years. The 75% locoregional control observed in this study though comparable to the above reports may not be significant due to the short follow up period and limited number of study patients. Gupta et al[15] comparing 3D CRT with IMRT have shown equivalent locoregional control rates with regard to the two arms. Shivangi Lohia et al[13] in their study compared the disease-free survival of patients randomised to treatment with 3D CRT and IMRT reported equivalent disease-free survival rates for both the arms at 2 years follow up.

Acute skin and mucosal toxicity was assessed and analysed weekly during radiotherapy. In this present study, it was seen that 64.3% had grade II, 28.4% grade I and 7.1% grade III skin toxicity. No patients had grade IV skin toxicity. Whereas Van Gestel et al[4] reported acute skin toxicity scoring (RTOG grade III) in 5 cases (6%). Shivangi Lohia et al[13] compared the outcomes using IMRT and 3D CRT in the treatment of oropharyngeal cancers and reported acute grade III or greater skin toxic effects in 9 of 39 patients in the 3D-CRT group (23%), compared to 7 of 97 patients in the IMRT group (7%). These results of acute skin toxicity are comparable with present study results. IMRT technique showed better skin sparing compared to 3D conformal radiotherapy.

In this study, 78.6% patients had grade III, 3.6% grade IV, 14.3% grade II and 3.6% had grade I mucosal toxicity. Overall, approximately 80% of patients had severe mucosal toxicity (grade III or IV). In his study, Van Gestel et al[4] reported 83% acute mucosal toxicity scoring (RTOG grade III or IV). Shivangi Lohia et al reported acute grade III or greater mucosal toxic effects in 37 of 49 patients in the 3D-CRT group (76%) and only 37 of 101 patients in the IMRT group (37%). These results are almost similar to the results of our study. Late toxicities associated with the treatment could not be assessed due to the short follow up period.

A descriptive analysis was made by Vassilis Kouloulias et al in terms of the radiation induced acute and late mucositis and xerostomia along with survival and tumour control rates in head and neck carcinomas with either 2DRT and 3D conformal (3DCRT) or IMRT and reported incidence of acute mucositis (>= RTOG grade II) varying from 68% to 90%. In another randomised study, Nutting et al[15] compared IMRT with conventional radiotherapy and reported 90% clinical mucositis (>= CTCAE grade II). These results are slightly higher than the results from our study maybe due to defining severe mucositis as grade III or IV in this study.

The updated MACH-NC[2] meta-analysis of concurrent chemoradiation in HNSCC confirms that either single agent chemotherapy utilising a platin compound or combination chemotherapy improves efficacy outcomes. In our study, all patients received weekly cisplatin. The haematological, neurological and ototoxicities with the concurrent use of radiosensitiser were not studied. The concurrent use of cisplatin might have contributed to the increased mucosal toxicities seen in our study.

Xerostomia is the most common late side effect of radiotherapy to the head and neck region. Lack of saliva affects speech and swallowing and can accelerate dental caries. Compared with conventional radiotherapy, Intensity-Modulated Radiotherapy (IMRT) can reduce irradiation of the parotid glands.[15] This has been proven in large number of studies. We could not assess the incidence of xerostomia in our study short follow up period.

CONCLUSION

The following conclusions are drawn from this institutional prospective single-arm study- IMRT is a better treatment option than 3D conformal radiotherapy in patients with head and neck malignancies in order to have minimum normal tissue complication probability without compromising tumour control. Conventional RT with 2D planning has been the standard treatment for head and neck cancer for many years. The technique evolution of conformal RT has emerged with 3D CRT followed by IMRT, which has gained increasing popularity in the treatment of head and neck cancers. In this study with IMRT, the locoregional control in head and neck malignancies obtained was high. Severe skin toxicities were markedly reduced with acceptable mucosal toxicities. IMRT represents the potential for a quantum leap forward in the treatment of head and neck cancers for improvements in targeting and sparing of normal tissue toxicity translating into better quality of life. We followed up our patients for a maximum duration of 6 months post-treatment. Longer duration of follow up is needed to clearly assess the locoregional control of the disease and long-term toxicities.

ACKNOWLEDGMENT

We are extremely thankful to Dr. Rema P.L., Professor, Head of the Department of Radiotherapy for the valuable suggestions and guidance. We also thank faculty members of Radiation Physics Department and all the patients who participated in the study. We also express our sincere thanks to Mrs. Ancy Joseph, Statistical Assistant Department of Radiotherapy.

REFERENCES

[1] Bhide SA, Nutting CM. Advances in radiotherapy for head and neck cancer. Oral Oncol 2010;46(6):439-441.
[2] Pignon JP, le Maître A, Maillard E, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol J 2009;92(1):4-14.
[3] Webb S. Contemporary IMRT: developing physics and clinical implementation. CRC Press 2004: p. 502.

[4] Grégoire V, De Neve W, Eisbruch A, et al. Intensity-modulated radiation therapy for head and neck carcinoma. The Oncologist 2007;12(5):555-564.
[5] Bhide SA, Newbold KL, Harrington KJ, et al. Clinical evaluation of intensity-modulated radiotherapy for head and neck cancers. Br J Radiol 2012;85(1013):487-494.
[6] Corvò R. Evidence-based radiation oncology in head and neck squamous cell carcinoma. Radiother Oncol J Eur Soc Ther Radiol Oncol 2007;85(1):156-170.
[7] Pati Destimates of radiation-induced malignancies after intensity modulated radiotherapy [Internet]. [cited 2017 Jul 23]. http://www.cancerjournal.net/article.asp?issn=0973-1482;year=2010;volume=6;issue=4;spage=442;epage=447;aulast=Patil
[8] Budach W, Hehr T, Budach V, et al. A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. BMC Cancer 2006;6:28.
[9] Pignon JP, Bourhis J, Domenge C, et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative group. meta-analysis of chemotherapy on head and Neck Cancer. Lancet. 2000;355(9208):949-955.
[10] Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354(6):567-578.
[11] Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. - PubMed - NCBI [Internet]. [cited 2017 Aug 6]. https://www.ncbi.nlm.nih.gov/pubmed/17960012
[12] Cisplatin and Fluorouracil Alone or with Docetaxel in Head and Neck Cancer - NEJM [Internet]. [cited 2017 Aug 6]. http://www.nejm.org/doi/full/10.1056/NEJMoa070956#t=article
[13] Lohia S, Rajapurkar M, Nguyen SA, et al. A comparison of outcomes using intensity-modulated radiation therapy and 3-dimensional conformal radiation therapy in treatment of oropharyngeal cancer. JAMA Otolaryngol Head Neck Surg 2014;140(4):331-337.
[14] Kouloulias V, Thalassinou S, Platoni K, et al. The treatment outcome and radiation-induced toxicity for patients with head and neck carcinoma in the IMRT era: a systematic review with dosimetric and clinical parameters [Internet]. BioMed Research International. 2013 [cited 2017 Aug 6]. https://www.hindawi.com/journals/bmri/2013/401261/
[15] Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol 2011;12(2):127-136.