COMPARISON OF TOXICITY PROFILES AMONG HEAD &NECK CANCER PATIENTS UNDERGOING 3D CRT, IMRT & IGRT MODES OF RADIOTHERAPY

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BRANCH IX

ORAL MEDICINE AND RADIOLOGY

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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation titled **"COMPARISON OF TOXICITY PROFILES AMONG HEAD &NECK CANCER PATIENTS UNDERGOING 3D CRT, IMRT & IGRT MODES OF RADIOTHERAPY"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. S. KAILASAM, B.Sc., M.D.S.**, Professor and Head, Department of Oral Medicine & Radiology, Ragas Dental College and Hospital, Chennai.

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CERTIFICATE

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This dissertation is submitted to **THE TAMILNADU Dr. M.G.R.MEDICAL UNIVERSITY,** in partial fulfilment for the degree of **MASTER OF DENTAL SURGERY, BRANCH IX – Oral Medicine & Radiology.**

It has not been submitted (partial or full) for the award of any other degree or diploma.

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LIST OF ABBREVATIONS

S. NO	ABBREVATION	EXPANSION
1	2 D CRT	2 Dimensional Conformal radiotherapy
2	3D CRT	3 Dimensional conformal radiotherapy
3	IMRT	Intensity Modulated Radiotherapy
4	IMRT + SIM	Intensity Modulated radiotherapy+simultaneous integrated boost
5	IGRT	Image guided radiotherapy
6	GTV	Gross tumor volume
7	CTV	Clinical target volume
8	PTV	Planned target volume
9	ICRU	International commission on radiation units and measurements
10	GTV-P	Gross tumour Volume –Primary
11	GTV-N	Gross tumour volume-node
12	CT	Computed tomography
13	MRI	Magnetic resonance imaging
14	CTV-P	Clinical Target Volume – Primary
15	ITV	Internal target volume

16	RTOG	Radiation therapy oncology group
17	EORTC	European organization for research on toxicity criteria
18	ICD	International classification of diseases
19	WHO	World health organization
20	IARC	International agency for research on Cancer
21	PBCR	Population based cancer registry
22	HPV	Human papilloma virus
23	HIV	Human immunodeficiency virus
24	OSCC	Oral squamous cell carcinoma
25	TSG	Tumor suppressor gene
26	DNA	Deoxy ribonucleic acid
27	HNSCC	Head and neck squamous cell carcinoma
28	LOH	Loss of heterozygosity
29	FHIT	Fragile histidine triad
30	APC	Adenomatous polyposis coli
31	FDG	Flourodeoxyglucose
32	PET	Positron emission tomography
33	CT	Computed tomography perfusion
34	CBCT	Cone beam computed tomography
35	STIR	Short inversion time inversion recovery

36	DWI	Diffusion weighted imaging
37	TIRM	Tube inversion recovery imaging
38	SPECT	Single positron emission computed tomography
39	CRT	Cardiac resynchronization therapy
40	NAB	Needle assisted biopsy
41	USG	Ultrasonography
42	V-MAT	Volumetric modulated arc therapy
43	ORN	Osteoradionecrosis
44	MLC	Multileaf collimator
45	OR	Organ at risk
46	PRV	Planning organ at risk volume
47	BTV	Biological target volume
48	GM-CSF	Granulocyte monocyte colony stimulating factor
49	QOL	Quality of life
50	DVH	Dose volume histogram
51	KPC	Kornofsky performance scale

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INTRODUCTION

Oral cancer is a malignant neoplasm which occurs in the lip, floor of the mouth, cheek lining, gingiva, palate, maxillary and mandibular alveolar process or in the tongue. Worldwide oral carcinomas is one of the most prevalent cancer and is one of the ten most common causes of death.[23] In India oral cancer is one among the top three cancers among which 90% - 95% are squamous cell carcinomas. They arise specifically in the squamous epithelium of the various regions in the oral cavity. Severe alcoholism, use of tobacco in any form (smokeless/ those that liberate smoke), poor oral hygiene, oncogenic viruses, especially human papilloma virus and poor dietary habits are directly attributed to the occurrence of oral cancer. The International Agency for Research on Cancer has predicted that in India the incidence of cancer will increase from 1 million in 2012 to more than 1,7 million in 2035.[61]

Since oral cancer remains a major health problem and the incidence is bound to increase by 2030 in both the sexes, early detection, prompt treatment and prevention will reduce the burden in future. The principal objective of treatment is to cure the patient of cancer. The choice of treatment is primarily determined by the cell type, degree of differentiation, size, location and aggressiveness of the primary tumour, extent of nodal involvement and the estimated functional impact of therapy.[37]

Aggressive multimodality treatment with curative intent may include surgery, radiotherapy and chemotherapy. Either surgery or radiation may be

used for many T1 and T2 lesions, however surgery is specifically indicated for tumours involving bone , for recurrent tumours and for tumours that lack sensitivity to radiation.[23]

Radiotherapy may be used alone or as a part of multimodality approach, and often with significant short and long term side effects. In radical radiotherapy though the is intention is to cure the patient, the total dose is high, the course of therapy is prolonged and the early and late radiation effects are common. In palliative care, radiation may provide symptomatic relief from pain, bleeding, ulceration, and oropharyngeal obstruction.[23]

There are various means by which radiation is delivered, the most common being brachytherapy and external beam radiotherapy. In brachytherapy interstitial and intercavitary implants may be used for treating localized tumours in the anterior two thirds of the oral cavity and for boosted doses of radiation to a specific site[23]. The cobalt units have been used for traditional teletherapy equipments and they produce stable dichromatic beams of 1.17 and 1.33 MeV, resulting in an average beam energy of 1.25 MeV. The role of cobalt has been increasingly replaced by the linear accelerator, which can generate higher energy of electrons in the energy range of 4, 6, 15 and 18 MeV.[37]

Radiation therapy designs have evolved over the past 30 years from being based on two dimensional (2D) to three dimensional images, incorporating increasingly complex computer algorithms. The shape and

intensity of the electron beam has to be collimated to attain the highest probability of tumour control or cure with the least amount of morbidity and toxicity to normal surrounding tissues (sometimes referred to as ***organs at risk***).[28]

In **three dimensional conformal radiotherapy** the radiation conforms to the shape of the volume to be treated and is most useful for tumours that are close to important structures like prostrate, spine, oesophagus, lung, bladder, pancreas, head and neck etc. The primary advantage of this imaging modality is dose escalation within the target volume that theoretically should increase the therapeutic ratio.[18] In **Intensity modulated radiotherapy** the physician designates specific doses of radiation (constraints) that the tumour and normal surrounding tissues receive and then uses a computer programme to develop an individualized plan to meet the constraints, called inverse treatment planning.[25] In **image guided radiotherapy** the linear accelerator is equipped with an imaging technology that allows the physician to image the tumour immediately before or even during the time the radiation is delivered, while the patient is positioned on the treatment table.[35]

In stereotactic body radiotherapy, the tumour location can be tracked in four dimensions (including time) using several CT imaging techniques that depend on the platform, tracking on bony structures or implanted fiducials. In proton therapy, high energy, positively charged particles, are used, which

enables physicians to deliver high energy conformal doses to the tumour volume while almost completely sparing normal tissues.[44]

Though radiation delivery methods and beam shaping has evolved continuously with novel methods, it is not without some pitfalls, the most important being acute and chronic toxicities that develop after radiotherapy. Toxicities that develop within 90 days from the beginning of radiotherapy are acute and that developing after 90 days is chronic. The most common acute side effects are mucositis, skin reactions, dysphagia and dysguesia. The chronic toxicities that develop include xerostomia, and difficulty in mouth opening due to fibrosis. Thus acute and late toxicities of radiotherapy in cancer patients represent important clinical outcomes that can substantially reduce quality of life and the ability of individuals to complete the entire planned course of treatment.

The purpose of the present study is to explore the acute and chronic toxicity profiles associated 3DCRT, IMRT and IGRT in oral cancer patients which would help us to further optimize the process and incorporate re planning strategies to obtain an even better locoregional control and thus produce a potential positive impact on the quality of life of the patient.

AIMS AND OBJECTIVES

AIM OF THE STUDY:

To compare and assess the acute and chronic toxicity profiles of head and neck cancer patients undergoing radiotherapy by 3D CRT, IMRT and IGRT modes of treatment.

OBJECTIVE OF THE STUDY:

1. To evaluate the toxicity profiles in patients undergoing 3D CRT.
2. To evaluate the toxicity profiles in patients undergoing IMRT.
3. To evaluate the toxicity profiles in patients undergoing IGRT.
4. To compare and assess the toxicity profiles among 3D CRT, IMRT and IGRT patients.

REVIEW OF LITERATURE

Worldwide, oral carcinoma is one of the most common cancers and one of the ten most prevalent causes of death and the majority of cancers are squamous cell cancers. Other malignant diseases that can occur in the head and neck include tumours of the salivary gland, thyroid gland, lymph nodes and soft tissues.

Approximately 95% of oral squamous cell carcinomas occurs between 25 – 40 years. The majority of oral cancers involve the tongue, oropharynx, and floor of the mouth. The lips, gingival, dorsal tongue and palate are less common sites. African Americans in theUnited States have a higher risk of developing oropharyngeal cancer than do Caucasians. The increased risk appears to be due to environmental factors, although possible genetic factors have not been determined.[23]

EPIDEMIOLOGY OF ORAL CANCER IN INDIA:

Ken Russell Coelho (2012)[33] has put forth a review article which provides a synopsis of the incidence of oral cancer in India by focussing on it's measurement in cancer registries across the country. This paper discusses about the high burden of oral cancer in India, case definition of oral cancer, the systematic search strategy about the literature on oral cancer along with the results, measurement of incidence of oral cancer, about the cancer registry data and comparisons with the IARC sources, trends in oral cancer in India,

variability in incidence, aetiological factors, tobacco usage, global burden of disease, limitations , projections, screening and early detection and future challenges.

HIGH BURDEN OF ORAL CANCER IN INDIA:

Oral cancer is a major problem in the Indian subcontinent. It ranks among the top three types of cancer in the country with the incidence being 20 per 100,000 population and accounts for over 30% of all cancers in the country the main cause being the combined effect of ageing of the population, as well as regional differences in the prevalence of disease-specific risk factors.

CASE DEFINITION OF ORAL CANCER:

Oral cancer is defined as cancer of, mouth, tongue and lip to include the anatomic description of the oral cavity as reported in previous major population based research reports. Based on these criteria, oral cavity cancer is the 8th most frequent cancer in the world among males and 14th among females , the main risk factors being tobacco and alcohol use.

SEARCH STRATEGY:

A systematic search of the literature was accomplished using the Pubmed Database. Medical Subject headings and free text terms included the following:

1. "Oral Cancer" OR "Lip Cancer" OR " Tongue Cancer".
2. "Epidemiology" OR "Descriptive Statistics" OR "Incidence" OR "Prevalence" OR "Longitudinal" OR "Cohort" OR "Case Control" OR "Cross sectional."

Free text terms included,

3. India OR South Asia

SUMMARY OF THE FINDINGS:

Gupta et al. conducted a case-control study; however, this study was nested within a larger study utilising a rural based population registry. **Sankaranarayanan et al** utilised a community based cluster-randomised controlled trial where participants were randomised to either an intervention group or a control group to test the effect of a screening programme on the oral cancer incidence and mortality. **Mehta et al.** utilised a mixed methods approach conducted in different phases. **Malaowalla et al. Gupta et al** and **Cancela et al.** conducted population-based prospective cohort studies to examine the incidence of oral cancer tracked prospectively over a period of time. A number of survey methods were employed, including house-to-house recruitment, interviewing, and data abstraction from medical records.

MEASUREMENT OF DISEASE INCIDENCE:

An increasing trend based on age; however, lower incidence recorded amongst females as compared to males is indicative of gender differences in the lifestyle and behavioural patterns associated with incidence of oral cancer. Different studies reported a range of age-adjusted incidence rates (per 100,000 population) for oral cancer.

INCIDENCE AND TRENDS OF ORAL CANCER IN INDIA:

Oral cancer accounts for over 30% of all cancers in India. The variation in incidence and pattern of oral cancer is due to regional differences in the prevalence of risk factors.

VARIABILITY IN INCIDENCE:

The incidence varies considerably based on study designs, sampling methodology and case ascertainment, as well as by age, gender and location. Variations in age-specific incidence rates also increased with age, which drops at the age of seventy, a trend which is consistent in multiple studies.

AETIOLOGICAL FACTORS:

The use of tobacco (smoking or chewing) or alcohol intake is associated with oral cancer. Several studies discussed the associations between use of tobacco and oral cancer incidence. **Mehta et al.** reported the

regression rate of leukoplakia as significantly higher among those who had stopped or reduced tobacco consumption in rural populations in Kerala, Andhra Pradesh and Gujarat. **Gupta et al** reported an association between the cessation of tobacco habits and a drop in the incidence of leukoplakia implying reduced risk for oral cancer after cessation of tobacco use. **Khandekar et al.** reported tobacco consumption habits among subjects that included chewing (in the form of betel quid, or khaini) and smoking (bidis and cigarettes) as the common cause of oral cancer. Based on the TNM classification, 48% of these oral cancer cases presented in later stages, that is, III and IV.

TOBACCO USE:

57% of all men and 11% of women between 15–49 years of age use some form of tobacco which include the use of ghutks, mawa, zarra, khainni, pan etc. Recently, the trend has also been observed towards increased incidence of oral cancer among young adults. This increase in incidence is observed in patients with tongue cancer.

GLOBAL BURDEN OF DISEASE:

Approximately 12% of deaths worldwide occur due to cancer, and in about twenty years, it is projected to increase from about 6 to 10 million.

LIMITATIONS:

A number of studies may not have been found using the identified search strategy. Secondly, mortality and survival from oral cancer in India have not been described. Finally, the search strategy was also limited to studies published in English, leaving out local language-based Indian journals.

PROJECTIONS:

Oral cancer in particular will continue to be a major problem. Crude incidence projections by Globocan demonstrate that oral cancer crude incidence will increase in India by 2020 and 2030 in both sexes.

SCREENING AND EARLY DETECTION:

Early detection would not only improve the cure rate, but it would also lower the cost and morbidity associated with treatment. Mouth self-examination could further reduce the cost of the screening and increase awareness in high-risk communities in India. Such a simple and cost-effective strategy has the potential to have a significant impact on the awareness of oral cancer in the broader community.

FUTURE CHALLENGES:

There exists a significant gap in the Indian public's knowledge, attitudes, and behaviours and efforts must be made to overcome this. Prevention through

action against risk factors, especially tobacco will be key to reducing the burden amongst these groups

ETIOLOGY AND RISK FACTORS ASSOCIATED WITH CANCER:

Murthy et al (2004)[44] have reviewed on the various aetiological factors related to oral cancer:

TOBACCO USAGE:

The principle impact of tobacco smoking is seen in higher incidence of cancers of the lung, larynx, oesophagus, pancreas and bladder. Bidi smoking is associated with cancer of oropharynx as well as larynx. This could be due to poor combustibility as well as the nicotine and tar content of bidi which exceeds that of cigarette.

ALCOHOL CONSUMPTION:

Epidemiological studies carried out in India and abroad have shown that increased alcohol consumption is causally associated with cancers at various sites, mainly oral cavity, pharynx, larynx, and oesophagus. A prospective study in India has found that alcohol consumption increases the incidence by 49% among current users and 90% in past drinkers. This could be due to residual effect of alcohol consumption or them having quit the habit due to serious illness. Consumption of alcoholic beverages was associated with increased risk for Oral cancer in men but it was not observed in women because very few women consumed alcohol.

INFECTIONS:

There is strong evidence that majority of cervical neoplasia is caused by certain sub types of human papilloma virus (HPV), a sexually transmitted infection. Studies carried out in India have also confirmed the role of HPV and cervical cancer. Other virus–cancer relationships are between Epstein–Barr virus and nasopharyngeal cancer; chronic active infection and hepatitis B virus and primary liver cancer; *Helicobacter pylori* and stomach cancer; HIV and Kaposi's sarcoma and some forms of lymphoma.

DIET AND CANCER:

Increased intake of fat and red meat associated with a higher risk of colorectal cancer and probably prostate cancer. High consumption of fruits and vegetables is associated with reduced risk of several cancers including lung, oral, pancreas, larynx, oesophagus, bladder, stomach and cervical cancers.

SEXUAL AND REPRODUCTIVE FACTORS:

Epidemiological data strongly implicate sexually transmitted agents in the aetiology of cervical cancer . Studies carried out have been shown that early onset of menarche, late age at first child birth, nulli-parity and late natural menopause increase the risk of breast cancer . Early age at first sexual intercourse and multiple sexual partners add to the risk of cancer of the cervix.

Murthy et al (2004)[44] has also focussed on the role of population based cancer registry (PCBR) as the source of data in estimating the incidence and

mortality rate of cancer cases in a defined region. From the PCBR the age adjusted incidence rates vary from 44 to 122 per 100,000 in males and 52 to 128 per 100,000 in females. The population registries also suggest a variation in sitewise distribution among the various regions of India.

PATHOPHYSIOLOGY OF CANCER:

The molecular pathogenesis of OSCC reflects an accumulation of genetic changes that occur over a period of years. 20% of OSCCs are documented arising in or are associated with a clinically visible precursor lesion, such as leukoplakia and erythroplakia. Major genes involved in head and neck squamous cell carcinoma (HNSCC) include proto-oncogenes and tumor suppressor genes (TSGs). Other factors that play a role in the progression of disease may include allelic loss at other chromosome regions, mutations to proto-oncogenes and TSGs, or epigenetic changes such as deoxyribonucleic acid (DNA) methylation or histone deacetylation. Cytokine growth factors, angiogenesis, cell adhesion molecules, immune function, and homeostatic regulation of surrounding normal cells also play a role. Proto-oncogenes associated with HNSCC include ras (rat sarcoma), cyclin-D1, myc, erb-b (erythroblastosis), bcl-1, bcl-2 (B-cell lymphoma), int-2, CK8, and CK19.[23]

Williams H. K. (2000)[63] in his review of the molecular pathogenesis of oral squamous carcinoma delivers details about genetic alterations which could be point mutations, amplifications, rearrangements and deletions

Several oncogenes have also been implicated in oral carcinogenesis. Aberrant expressions of the proto – oncogenes epidermal growth factor receptor, members of the ras gene family, c – myc, int -2, PRAD – 1 and bcl – 1 is believed to contribute towards cancer development. With regards to tumour suppressor genes, mutation of the p53 gene, p21, and retinoblastoma gene results in progression of squamous cell carcinomas.

The author has finally discussed the role of cell adhesion molecules in which there is a loss or reduced expression of beta 1 integrins and alpha 6 beta 4, especially in poorly differentiated carcinomas. The association of viruses with cancer seems to be very important with the fact that oral epithelial dysplasia which is a precursor to squamous carcinoma, is infected with HPV, and type 2, 6, 11, 18, 31, 33, 35 have been detected. Most of the oral squamous cell carcinomas are found to contain HPV – 16 and HPV – 18. These viruses contain gene products (E6 and E7) that bind wild type p53 and Rb proteins and eliminate the ability of these proteins to stimulate DNA repair or apoptosis.

PRESENTING SIGNS AND SYMPTOMS OF ORAL CANCER:

Discomfort is the most common symptom (85% of patients) that lead a patient to seek care. The patient is also aware of a mass in the mouth or neck. Dysphagia, odynophagia, otalgia, limited movement, oral bleeding and neck masses may occur in advanced cases. The patient should be assessed for tissue changes that include a red, white or red/ white lesion, a change in the

surface texture of the lesion producing a granular, smooth , crusted, lesion; or the presence of a mass or ulceration. The lymphatic spread of the carcinoma usually involves the submandibular, digastrics , upper cervical nodes and finally the remaining lymph nodes of the cervical chain. Lymph nodes associated with cancer become enlarged and firm to hard in texture. Accurate node examination is needed before biopsy, and the individual who is performing the procedure must be experienced in lymph node palpation.[23]

CLINICAL FEATURES OF ORAL SQUAMOUS CELL CARCINOMA:

Persons with OSCC are most often older men who have been aware of an alteration in an oral cancer site for 4 to 8 months before seeking professional help, the reason perhaps being that there is minimal pain during the early growth phase. It has a varies clinical presentations which include

1. Exophytic (mass forming; fungating, papillary, verruciform)
2. Endophytic (invasive, burrowing, ulcerated)
3. Leukoplakic (white patch)
4. Erythroplakic (red patch)
5. Erythroleukoplakic (combined red and white patch)

OROPHARYNGEAL CARCINOMAS:

Tumour size is typically greater than that of anterior carcinomas and the proportion of cases with cervical and distant metastases at diagnosis is higher. Three of every four oropharyngeal carcinomas arise from tonsillar area or soft

palate; most other originate on the base of the tongue. The initial symptoms are usually pain or difficulty in swallowing with the pain being dull or sharp and frequently referred to the middle ear.[47]

METASTASES:

The metastatic spread of carcinoma is largely through the lymphatics to the ipsilateral cervical lymph nodes and the consistency of the lymph node is usually stony hard, non tender and enlarged. If the malignant cells have perforated the capsule of the node and invaded the surrounding tissues, the node will feel fixed or not easily movable. Ocassionally, contralateral or bilateral metastatic deposits are seen, and at least 2 % of patients have distant metastases at diagnosis. The most common sites of distant metastases are the lungs, liver and bones but any part of the body may be affected.

Carcinomas from the lower lip and oral floor tends to travel to the submental nodes; tumours from the posterior portions of the mouth travel to the superior jugular and diagastric nodes. Lymphatic drainage from the oropharynx leads to the jugulodigastric chain of lymphnodes or to the retropharyngeal nodes.[46]

DIAGNOSTIC AIDS:

Aids to oral examination include imaging and light technologies, vital tissue staining using toluidine blue, and computer-assisted cytology of oral brush biopsy specimens.

Toluidine blue can be applied directly to suspicious lesions or used as an oral rinse.[23] Use of 1% toluidine blue has been mentioned due to the property of the dye to stain hyperchromatic nuclei[45] . Positive retention of toluidine blue (particularly in areas of leukoplakia, erythroplakia, and uptake in a peripheral pattern of an ulcer) may indicate the need for biopsy. False-positive dye retention may occur in inflmmatory and ulcerative lesions, but false negative retention is uncommon**.**[23]

ViziLite is a disposable chemiluminescent light source, approved by the US Food and Drug Administration (FDA) and used in conjuction with a standard visual examination and toluidine blue.[22] Visual inspection is carried out under chemiluminescent illumination to detect abnormal epithelial changes. Normal epithelium gives a blue hue and altered epithelium appears "acetowhite" under chemiluminescent light.[45]

In exfoliative cytology, smears are stained by standard Papanicolaou's technique and studied for changes of character of cell population and individual cells**.**[45] In conclusion the author delivers that early evaluation of oral pre cancerous lesions can have a dramatic effect on oral cancer mortality rate and hence an attempt has been made to identify oral cancers in the early stages by more precise methods.

IMAGING:

Routine radiology, computed tomography (CT), nuclear scintiscanning, magnetic resonance imaging (MRI), and ultrasonography can provide evidence of bone involvement and can indicate the extent of some soft tissue lesions. Positron emission therapy (PET) using the radiolabeled glucose analog 18-florodeoxyglucose (18FDG) offers a functional imaging approach for the entire body. Imaging to determine bone involvement may include and routine radiology (including dental radiographs for alveolar bone involvement), CT, bone scanning and nuclear scintiscanning. Soft tissue involvement of the antrum and nasopharynx can be assessed with CT and MRI. Each MRI image should include T1-weighted images, which demonstrate normal anatomy with detail and soft tissue defiition, and T2-weighted images, which demonstrate the tumor in comparison with adjacent muscle and other soft tissues. CT and MRI also help in determining the status of the cervical nodes.[23]

Paulina palasz et al (2017)[50] has reviewed the contemporary diagnostic imaging of oral squamous cell carcinoma. The characteristic feature of malignant lesions in plain radiographs include – atrophy of cortical lamina, osteolytic defects – both single and multiloular with an initial osteosclerotic capsule. In later stages, the ridges of bone defects become sharp and the teeth lose their bony support at the site of infiltration.

In panoramic radiographs detection of involvement of bone has sensitivity of 75% and specificity of 100% respectively.

COMPUTED TOMOGRAPHY:

CT is a standard tool for detecting the primary tumours as well as their local bone infiltration. Contrast enhanced computed tomography can accurately determine lymph node metastases .The sensitivity of CT in detecting tumours is 41% - 82% (specificity 82 – 100%) and in determining bone infiltration 63% - 80%(specificity 81 – 100%).In cancers localized in the retromolar triangle with the use of puffed cheek MDCT, the sensitivity and specifity of determining mandible and bone marrow involvement can be increased to 83% - 94%. Perfusion computed tomography is based on the increase in blood volume and blood flow in tumours.

CONE BEAM COMPUTED TOMOGRAPHY:

CBCT is more accurate than panoramic radiography and comparable to MRI, CT and bone scintigraphy. However, it is limited by a poor assessment soft tissues.

CT FLUOROSCOPY GUIDED BIOPSY:

It is a minimally invasive imaging technique that enables a real time assessment. It can be used for taking biopsies of oral cancers.

MAGNETIC RESONANCE IMAGING (MRI):

The protocol of an MRI study includes the following sequences – T1, T2, STIR, TIRM, DWI, perfusion with and without a contrast agent. MRI enables the detection of very small lesions, assessment of local spread of the tumour, planning surgery, evaluation of complications that can occur during and after surgery, involvement of bone marrow and bones as well as vessels and nerves. In case of micrometastases in the lymph nodes, DWI based MRI and hybrid methods can be helpful. Diffusion weighted imaging is used for assessing lymph nodes

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT):

SPECT allows for mapping metabolic activity of the tumour with the use of gamma radiation. The sources of radiation are isotopes such as 3-D 99mTcDPD or 99mTechnetium methoxy isobutyl isonitrile

POSITRON EMISSION TOMOGRAPHY:

PET with 18-fluorodeoxyglucose evaluates tissue metabolic activity. It is used when planning adjuvant treatment and predicting survival without recurrence.. Moreover, PET is used to look for primary tumour site when metastases are found earlier .

ULTRASONOGRAPHY:

Ultrasonography is used to evaluate superficial lesions, lymph nodes and to guide needle aspiration biopsies.(NAB). NAB is used in order to confirm metastatic lymph nodes. In oral cancer, intraoral USG with colour Doppler can also be used in order to assess the involvement of lymph nodes. It can show an increased vascularity within the tumour (blood flow) .

In conclusion the author emphasizes that it is crucial to be aware of the basic clinical data of patients and their tumours when interpreting the results of their imaging studies. The author further adds that all imaging modalities have their advantages and disadvantages and therefore the clinician must judiciously combine them in order to attain the highest possible efficacy and sensitivity, as it cam significantly improve patient outcomes.

BIOPSY – ACQUISITION OF TISSUE SPECIMEN:

In addition to the standard biopsy techniques, tissue can be acquired for histopathology by using fine-needle aspiration (FNA) and exfoliative cytology. Open biopsy of enlarged lymph nodes is not recommended; in such cases, FNA biopsy should be considered. FNA also may aid the evaluation of suspicious masses in other areas of the head and neck, including masses that involve the salivary glands, tongue, and palate.[23]

Oliver et al 2004[49] presents an updated review of biopsies and discusses some of the potential problems with biopsy technique and how to

overcome them. If the reason for biopsy was to exclude malignancy a biopsy of the ulcer to include some adjacent clinically normal epithelium would be desirable. The centre of larger tumours should be avoided as this is often necrotic and will not yield diagnostic material.

The author concludes that a little forward planning and thinking can greatly improve the diagnostic value obtained. Careful handling of the tissue and prompt appropriate fixation will enable a confident histological diagnosis to be reached

STAGING OF ORAL CANCER:

The ***American joint Committee on Cancer[3] (AJCC)*** in cooperation with TNM committee for the International Union against for Cancer, has brought out the sixth edition of the ***AJCC manual for the staging of cancer in the year 2002.*** This classification is based on the premise that cancers of the same histologic site and histology and pattern share similar patterns of growth and similar outcomes.

GENERAL RULES OF THE TNM SYSTEM:

The TNM system is an expression of the anatomic extent of the disease and is based on the assessment of three components:

T The presence or absence of primary tumour

N The presence or absence of regional nodal metastases

M The presence or absence of distant metastases

The use of numerical subsets of the TNM components indicates the progressive extent of malignant disease:

T0, T1, T2, T3, T4

N0, N1, N2, N3

M0, M1

The following general rules apply to all sites:

1. All cases should use the following tome guidelines for evaluating the stage: through the first course of surgery or 4 months whichever is longer.
2. All cases should be confirmed microscopically for TNM classification. Rare cases that do not have a biopsy or cytology of the tumour can be staged but should be analysed separately and should not be included in survival analysis.
3. Four classifications can be described for each site:
    - Clinical classification designated as cTNM
    - Pathologic classification designated as pTNM
    - Retreatment classification designated as rTNM
    - Autopsy classification designated as aTNM

DEFINITIONS OF TNM:

Primary tumour:

Tx Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ

T1 Tumour 2cm or less in greatest dimension

T2 Tumour more than 2cm and less than 4cm in greatest dimension

T3 Tumour more than 4cm in greatest dimension

T4 Tumour invades through cortical bone, inferior alveolar nerve, floor of the mouth or skin of the face i.e ., chin or nose

T4a Tumour invades through cortical bone , into deep (extrinsic) muscles of the tongue, maxillary sinus, skin of the face.

T4b Tumour involves masticator space, pterygoid plates, or skull base and /or encases internal carotid artery

REGIONAL LYMPH NODES:

NX Regional lymph nodes cannot be assessed

N0 No regional lymph nodes metastasis

N1 Metastasis in single ipsilateral lymph nose , 3 cm or less in greatest Dimension

N2 Metastasis in single ipsilateral node more than 3 cm , but less than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes , none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes , none more than 6 cm in dimension

N2a Metastases in single ipsilateral node, more than 3 cm but less than 6 cm in greatest dimension

N2b Metastases in multiple ipsilateral lymph nodes less than 6 cm in greatest dimension

N2c Metastases in bilateral or contralateral lymph nodes none more than 6 cm in greatest dimension

N3 Metastases in lymph node more than 6 cm in greatest dimension

DISTANT METASTASES:

MX Distant metastases can be assessed

M0 No distant metastases

M1 Distant metastases

STAGE GROUPING:

0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVa	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	AnyT	N3	M0
	T4b	AnyN	M0

IVC AnyT AnyN M1

HISTOLOGIC GRADE:

GX Grade cannot be assessed

G1 Well differentiated

G2 Moderately differentiated

G3 Poorly differentiated

RESIDUAL TUMOUR

RX Presence of residual tumour cannot be assessed

R0 No residual tumour

R1 Microscopic residual tumour

R2 Macroscopic residual tumour

In ,reviewing the staging systems, several changes in the T classifications as well as stage groupings are made to reflect current practices of treatment, clinical relevance, and contemporary data. Uniform T staging for oral cavity. oropharynx, salivary and thyroid cancers greatly simplifies the system and will improve compliance by the clinicians.

TREATMENT OF ORAL CANCER:

The principal objective of treatment is to cure the patient of cancer Surgery and radiation are used with curative intent in the treatment of oral cancer. Chemotherapy is an adjunct to the principal therapeutic modalities of radiation and surgery and is now standard combined therapy in management of advanced disease. Either surgery or radiation may be used for many T1 and T2

lesions; however, combined radiation and chemotherapy with or without surgery is usually employed for more advanced disease.[23]

Jelena Prelac et al (2014)[28] has done a review of the different modalities of treatment of oral cancer. The discussion focuses on the specific effects of the different treatment modalities which includes surgery, chemotherapy, radiotherapy combination therapy , targeted therapy on the patient in different stages of cancer. In general, single modalities are more commonly used in early stage SCC (Stages I & II) and carcinoma-*in situ (CIS)*, while patients with advanced disease (Stages III & IV) are treated with a combination of therapies . Tumour characteristics such as site, proximity to bone, the depth of invasion, and stage (tumour size, lymph node involvement, and risk of metastasis) are considered along with the age of the patient, co-morbidities, compliance to treatment, and the desire to make lifestyle changes.

SURGERY AND NECK DISSECTION:

The intent of surgery is to completely remove cancerous tissue, leaving histologically normal tumour margins while attempting to preserve normal tissue and function . Positive or suspicious lymph node involvement may require a radical neck dissection, while elective neck dissections are sometimes undertaken even when the lymph nodes are negative.

CHEMOTHERAPY:

The purpose of Chemotherapy is to destroy dividing abnormal cancer cells rapidly in order to manage spread and metastasis. The delivery of CT can be divided into three categories: induction CT (before surgery), concurrent CRT (in conjunction with radiation treatment), and adjuvant CT (after surgery and/or radiation). Induction therapy is used primarily in patients who have advanced stage disease and nodal involvement, and in patients at the greatest risk of recurrence, second primary tumours, and metastases. By combining a chemotherapeutic agent with radiation, the efficacy of RT is increased and results in better tumour control and survival rates.

RADIOTHERAPY:

The intent of RT is to destroy DNA in dividing cancer cells in a localized region while preserving adjacent tissue and function. The use of surgery and postoperative RT is a common combination in oral cancer treatment, used for large tumours and when surgical margins are positive for cancer. RT combined with CT is the preferred treatment of oropharyngeal cancers. The two main types of RT are external beam radiation and brachytherapy Brachytherapy, a form of internal radiation, involves the precise surgical placement of a radioactive insert into the tumour, directly treating the tumour. However, it is restricted by the size of the field that it can target effectively. External beam radiation is provided as a daily outpatient treatment, over the course of about 6 weeks, using a linear accelerator

(LINAC) that focuses radiation on the tumour site. While it is a very effective cancer treatment, it also unfortunately affects the normal surrounding tissue and the normal tissue through which it travels to reach the tumour site.

TRADITIONAL AND CURRENT RADIOTHERAPY:

In traditional external beam radiation, "shrinking fields" are used in which the most sensitive organs are irradiated fist and blocked, treating the overlying low-risk organs next with more superficial radiation. The high-risk areas surrounding the tumour, grossly involved lymph nodes, and the tumour itself are treated last with the highest dose of tolerable radiation Radiation doses vary; generally 1.8 to 2.0 Gray (Gy) are delivered daily, 5 days a week, Monday to Friday. Treatment continues over the course of 6 weeks for a total of 30 fractions, until a maximum of 60 Gy is provided.

Current approaches to RT include 3-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), and volumetric arc therapy (VMAT).These techniques have been developed both to deliver radiation to the tumour more precisely while protecting normal tissues and to allow for flexibility to alter the dose. 3D-CRT delivers beams from 3 dimensions versus the traditional 2, while IMRT provides even greater control by using beams of different intensities from a variety of dimensions. VMAT is a further extension of IMRT, delivering a higher dose faster to the whole tumour volume simultaneously either in a single arc or series of arcs. Two more recent advances in RT are altered fractionation and concurrent systemic

chemotherapy. Altered fractionation refers to changes in the dose per fraction, the number of fractions delivered per day, and the overall duration of treatment. Altered fractionation can further be divided into hyperfractionation and accelerated fractionation. Hyperfractionation provides smaller doses per treatment but delivers 2 fractions per day for the same or longer time period so that a greater overall dose can be delivered to the tumour. In contrast, accelerated fractionation delivers the total dose over a shorter time period, usually with greater doses per fraction or multiple doses per day. By increasing irradiation intensity, accelerated fractionation reduces the risk of repopulation of cancer cells, which may follow delays in treatment.

SIDE EFFECTS:

The short-term effects of RT are more well known than the late and long-term effects. In the short term, RT can result in mucositis (more than 50% of patients), loss of taste, hoarseness and pain, as well as dermatitis, radiation burn, and an increased susceptibility to infection. For more than 60% of patients, xerostomia will be long term, a major concern for dental professionals as it significantly increases a patient's risk of caries and periodontal disease. Other long-term effects on both soft and hard tissue include poor wound healing, taste impairment, diffiulty swallowing, tissue fibrosis, osteoradionecrosis (ORN), and telangiectasia. ORN, chronic ulcers, and telangiectasia may not appear until many years after RT has been completed. Approximately 40% of patients who receive CRT suffer

from severe late toxicity. The severe toxic effects include hypomagnesaemia, myelosuppression, neutropenia, and general haematologic toxicity, as well as more common outcomes such as mucositis, dermatitis, stomatitis, and xerostomia.

In conclusion, the author emphasizes that the purpose of monitoring patients following therapy is to a) provide care for the sequelae of treatment side effects; b) to coordinate care between specialists and primary care providers to ensure that both oral and overall health needs are met; and c) to prevent and identify recurrence or the development of a second primary tumour.

ADVANCES IN EXTERNAL BEAM RADIOTHERAPY:

Dirk Van Gestal et al (2013)[12] has reviewed the advances in external beam radiotherapy or treatment of head and neck cancer. The discussion gives us an overview of the recent evolution of external beam therapy, which had initially began with 2D CRT, 3D CRT and then has evolved as static beam IMRT, rotational beam IMRT, stereotactic RT which includes cyber knife and particle RT which includes protons IMPT and heavy ions which include carbon ions. In IMRT the use of multileaf collimators (MLC) which causes a rapid change in field configuration and the use of rotational intensity modulated radiotherapy resulting in more conformal dose distribution has also been discussed.

Mehta et al (2010),[37] has reviewed the basic concepts of radiotherapy, and the recent advances and has emphasised that approximately 65% of all patients require radiotherapy as the sole treatment modality and / or in combination with chemotherapeutic drugs and surgery, however a huge gap between the supply and demand of infrastructure and facilities exists, which is of concern. A brief mention has been made about the principles of radiation physics, biology of radiation therapy, different modes of radiotherapy and about the acute and late toxic reactions which are associated with radiotherapy.

Kara . M . Bucci et al (2005)[38] has reviewed the advances in radiotherapy and the way these advances have changed the way the common neoplasms are treated now and in the future. A discussion of the different modes of radiotherapy including 3D CRT, IGRT, IMRT, the pitfalls of each of these methods, which has driven us to a more novel 4 dimensional radiotherapy mode has also been done. The advances in radiotherapy in treating prostrate cancer, head and neck cancer, breast cancer , biological therapies, targeted therapies has also been mentioned. To conclude, the advances in molecular profiling and new imaging techniques may eventually help those fortunate patients in future.

Fig 1: Linear Accelarator Machine

DEFINING THE TUMOUR AND TARGET VOLUMES FOR RADIOTHERAPY:

Neil G Burnrt et al (2004)[46] have proposed a review article to define the tumour and target volumes for radiotherapy. There are three main volumes to be considered in radiotherapy planning. The first of these two volumes is the position and extent of the primary tumour; this is known as the gross tumour volume (GTV). The second volume surrounds the GTV and describes the extent of microscopic, un-imageable tumour spread; this is known as the

clinical target volume (CTV). Once these two volumes are established, the third volume, the planning target volume (PTV), which allows for uncertainties in planning or delivery, must be added, and the normal tissue structures in the vicinity of the target must be considered.

GROSS TUMOUR VOLUME:

This is the easiest volume to define,and is essentially the gross demonstrable location and extent of tumour, can be palpated or imaged.site, involves lymph nodes or spread into adjacent soft tissue. Typically, it is considered that the GTV corresponds to the part of the tumour where the tumour cell density is highest.

CLINICAL TARGET VOLUME:

The CTV contains the demonstrable GTV plus a margin for sub-clinical disease spread which cannot be imaged. This volume must be adequately treated if cure is to be achieved. It is assumed that the tumour cell density in the CTV is lower than in the GTV and consequently the radiotherapy dose may be lower. It requires clinical assessment of risk and extent of spread, normally based on historical series rather than the extent of tumour quantified in an individual patient.

PLANNED TARGET VOLUME:

The PTV is really a geometric concept designed to ensure that the radiotherapy prescription dose is actually delivery to the CTV. It is a volume

related to the isocentre of the linear accelerator rather than to the anatomy of the patient. For this reason, the PTV may extend beyond anatomical barriers such as bony margins, and may even extend outside the patient.

ORGANS AT RISK:

ORs are normal tissues whose radiation sensitivity influences treatment planning or the prescribed radiation dose. Both systematic and random errors apply to OAR just as much as to the CTV. In that case, a margin should be added to the OR, which is analogous to the PTV margin around the CTV, and generates the PRV.

In conclusion the author delivers that the concepts of GTV, CTV and PTV have been enormously helpful in allowing radiation oncologists to develop treatment protocols and all of these volumes are crucially dependent on high quality imaging.

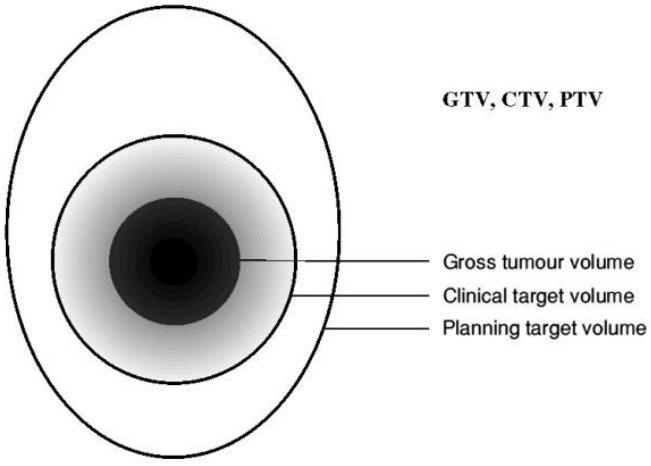


Fig 2: Radiotherapy Planning Volumes

Anca Ligia Grosu et al, (2005)[4] has reviewed the various target volumes and had also discussed about new concepts called biological target volume. Techniques such as PET, SPECT and MRS permit the visualisation of molecular biological pathways in tumours

To conclude the author emphasizes that target volume definition is an interactive process and based on radiological (and biological) imaging, the radiation oncologist has to outline the GTV, CTV, ITV , PTV and BTV.

3 DIMENSIONAL CONFORMAL RADIOTHERAPY:

Zimmerman(1998)[18] has reviewed the basic principles about 3D CRT which explains the concept of Gross Tumour Volume, Clinical Target Volume, Planned Target Volume, various methods of immobilization before radiotherapy, ideal positioning of the target volume, Beam modelling, calculation of dose distribution, Dose-Volume Histograms, the normal tissue complication probability, simulation and treatment procedure. To conclude, the author has delivered that computer controlled treatment delivery will help to reduce treatment and planning time and the treatment quality will be further improved.

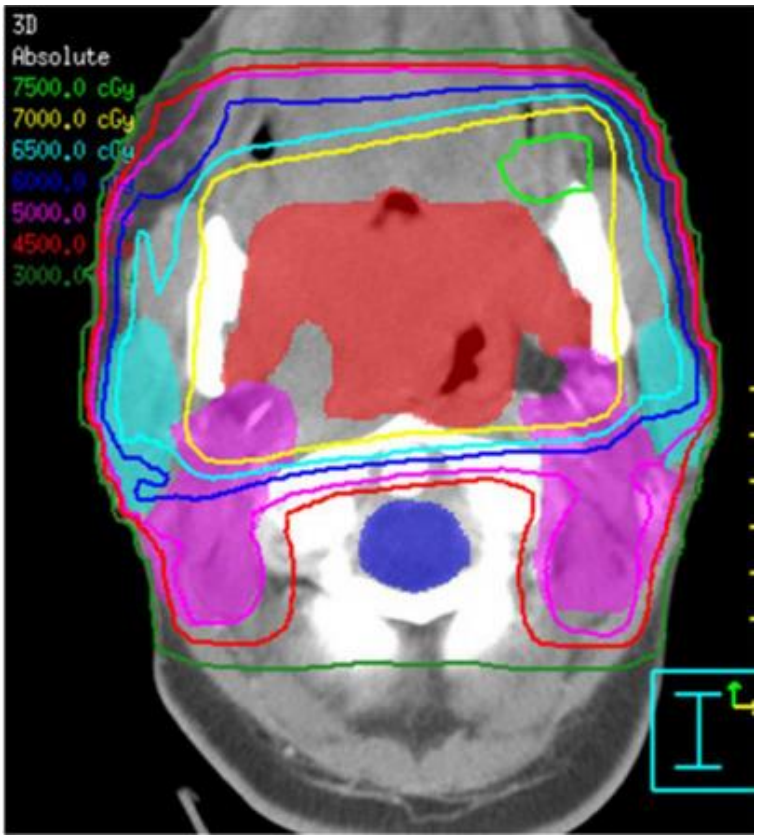


Fig 3: Planning in 3D CRT

INTENSITY MODULATED RADIOTHERAPY:

Bin S The et al (2017)[7] has reviewed the basics of Intensity modulated radiotherapy and describes it as a revolutionary concept. In IMRT the use of multiple treatment fields, choice of beam energies and modalities, weighting of different beams as well as the use of wedges and tissue compensators, has accomplished the goal of keeping the radiation dose to the surrounding normal structures below tolerance level. IMRT combines two advanced concepts to deliver 3D conformal radiation therapy: A) inverse

treatment planning with optimization by computer and B) computer-controlled intensity modulation of the radiation beam during treatment.

A radiation oncologist defines the tumour and the radiation dose that he wants around the tumour. The computer, using a mathematical optimization technique known as simulated annealing, will determine the optimal treatment fields. In addition, one can also define where one does not want the deposition of radiation. IMRT system, starts with the target volume, where it places a uniform, conformal dose around the tumor. The computer then "backprojects" through the patient's tissue to the linear accelerator source and finds the nonuniform radiation exposure that must be delivered by the linear accelerator to give this conformal dose pattern. The system, like the CT scan, uses a slice-by-slice, arc-rotation approach.

The author concludes by saying that IMRT is especially promising in decreasing acute treatment-related toxicity in either definitive or palliative irradiated cases.

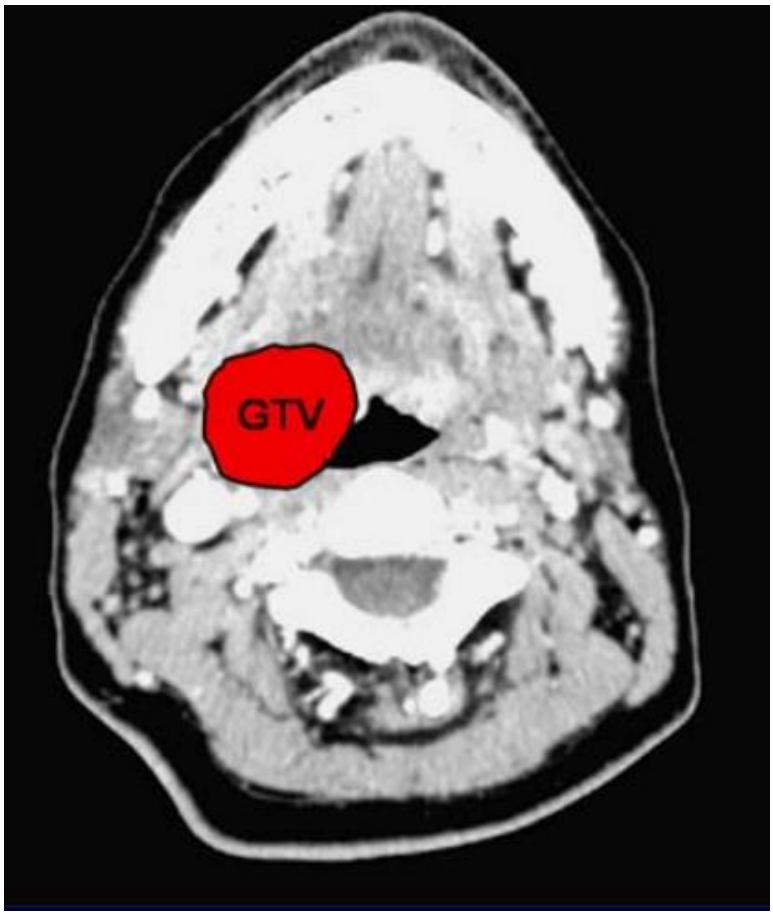


Fig 4:Primary tumor in IMRT

COMPENSATORS IN IMRT:

A.Bakai et al (2001)[6] have described about the different compensators used in IMRT which includes the use of multi- leaf collimators (MLC) for beam shaping. In addition to the use of MLC's there are other compensators used which are highly absorbing materials of varying thickness according to the fluence distribution of varying fields. The author has concluded saying that the compensators could be made much thinner and therefore lighter which would make their usage in everyday's clinical routine practicable.

IMAGE GUIDED RADIOTHERAPY:

Lei Xing et al (2006)[35] has delivered an overview on image guided radiotherapy which describes IGRT as an advanced imaging technology to better define the tumour target and is the key to reducing and ultimately reducing the uncertainities. The review focuses on the IGRT development in four major areas, including (1) biological imaging tools for better definition of tumour volume (2) time resolved 4D imaging techniques for modelling the intra fraction organ motion (3) on board imaging system or imaging devices registered to the treatment machines for inter fraction patient localization (4) new radiation treatment planning or treatment schemes incorporating the information obtained from the mew imaging techniques. Tumour target volume delineation could be done by imaging techniques including CT, MRI, specialized MRI techniques and ultrasound. The role of CBCT in patient localization and dose verification has also been explained. To summarize, the review focuses on the recent efforts put forth in removing the uncertainty in the definition of the target volume and un the determination of the position of the mobile and often deformable organs.

METHODS OF IMMOBILIZATION IN DIFFERENT MODES OF RADIOTHERAPY

For repeated doses of radiation to be applied to the site of treatment, the patient and the area of treatment are immobilized, but using various techniques and materials, including head holders; bandages; laser positioning, using

head and neck "landmarks"or tattoos; and custom acrylic shells (mold room technique). Custom shells provide the best means of immobilization and positioning of patients that are critical in IMRT and IGRT. These techniques may be combined with an oral device to position the mandible, allowing the maxilla or mandible to be moved into or out of the radiation field.[23]

ACUTE AND LATE TOXICIY EFFECTS OF RADIATION:

Supriya Mallick et al (2015)[57] has reviewed the pathophysiology, prevention and management of oral mucositis which is a major limiting acute side effect of radiotherapy of head and neck cancer. The pathophysiology includes five phases , the initiation phase,(DNA strand breaks and damage to the cells), activation phase (role of proinflammatory cytokines),signalling and amplification phase (activation of ceramide and capsases pathways), ulceration phase (breach in the mucosa) and finally the healing phase. The first sign of mucositis is erythema (Grade I) which starts by the end of second week, followed by focal areas of desquamation (Grade II) which develop during the third week of RT, which then progresses to confluent mucositis (Grade III) by fourth to fifth week. Various methods to prevent the development of mucositis like use of mouthwashes, various topical analgesics, sucralfate, GM – CSF, cryotherapy, palifermin, pentoxyphylline, glutamine, beta – carotene, prostaglandins have also been mentioned briefly. To conclude , the author says that adequate management and treatment may improve

patient compliance which may translate into better disease control and survival.

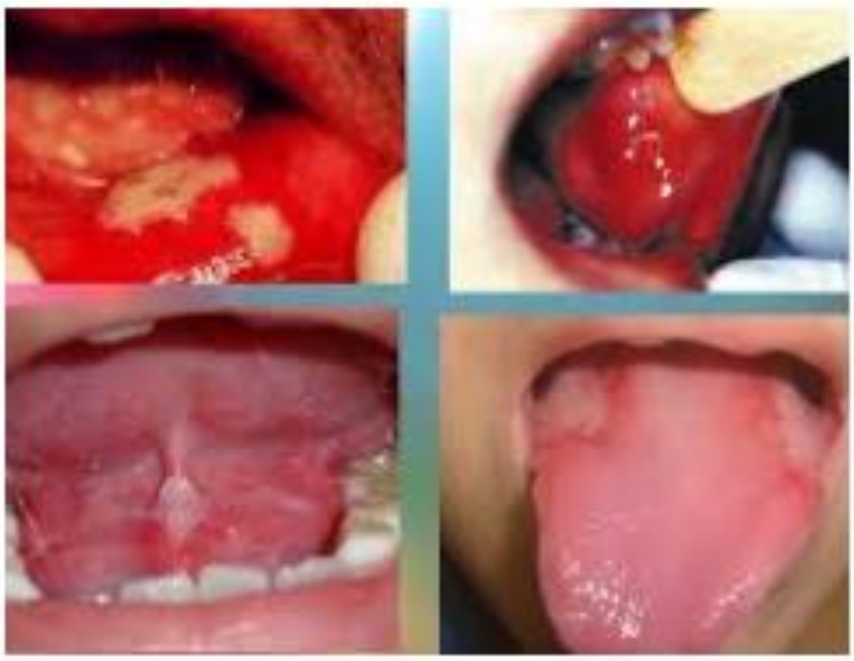


Fig 5: Mucositis in Oral Cavity

Fleta N Brey et al (2007)[19] have in their review article have focussed on the acute and chronic cutaneous reactions to ionizing radiation. Acute changes include erythema and pain and occur within 90 days. Acute reactions start with erythema, edema, pigmentary changes and depilation that correlate with the amount of radiation exposure. Grade 1 changes include dry desquamation with a generalized erythema. Pruritus, epilation, scaling and depigmentation can also occur. With grade 2, there is brisk erythema or localized focal sloughing of the epidermis With moist desquamation, the epidermal layer is lost and there is a high propensity for infection. The

reaction peaks in 1–2 weeks with subsequent healing. Grade 3 presents with extensive moist desquamation outside of skin folds . With grade 4, ulcerations, hemorrhage and skin necrosis are likely to occur. Chronic radiation dermatitis is unlikely to self-repair and may remain indefinitely. The defining features of the late-stage are fibrosis, atrophy, hypo- or hyperpigmentary changes and the development of cutaneous malignancies. Significant cutaneous injury is characterized by persistent dyspigmentation, atrophy, and telangiectasia.The management includes use of low to mid potency topical steroids, hydrophilic moisturizers, use of hydrogel and hydrocolloid dressings and mesenchymal stem cell injections to increase healing.

To conclude, the author emphasizes there is still a great need for novel and developing therapies and supportive care and appropriate wound care continue to be the mainstays of treatment at this time.

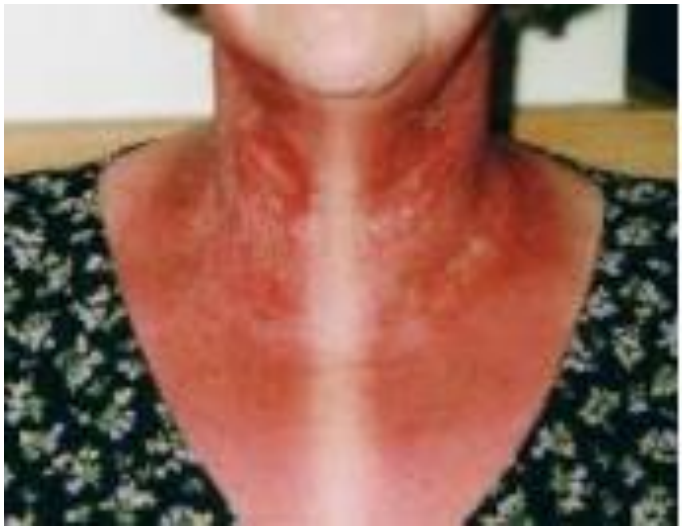


Fig 4: Skin Reactions after Radiotherapy

Roberto pinna et al (2015)[52] have presented a review article which highlights the salivary gland hypofunction and xerostomia after irradiation in head and neck cancer patients which severely hampers the quality of life of these patients. The pathophysiology says that the damage to the oral cavity has been strongly related to the radiation dose, fraction size, volume of irradiated tissue, fractionation scheme, and type of ionizing irradiation, but on the other, it may be difficult to distinguish changes caused by radiotherapy itself from those related to the malignant disease. The submandibular gland is less radiosensitive than the parotid gland. Salivary electrolytes are altered, with an increase in the concentrations of sodium, chloride, calcium, and magnesium, while potassium is only slightly affected. Saliva also reduces the buffering capacity in irradiated patients due to a reduction of bicarbonate concentration in parotid saliva. Saliva becomes, moreover, highly viscous, and reduces its pH from about 7.0 to 5.0 The management includes the use of candy containing xylitol or sorbitol, parasympathomimimetic drugs like cevimeline or pilocarpine , use of cholagogue anathol trithione and yohimbine.

In conclusion the author says the best approach to manage the radiotherapeutic patient begins with a careful clinical assessment of the individual case, followed by preventive therapy aimed to reduce oral complications when possible and hence the clinician must keep this kind of patients under careful control in order to palliate the symptoms of xerostomia and improve their quality of life.

STUDIES CONDUCTED FOR COMPARISON OF TOXICITY PROFILES:

Ibrahim Awad et al (2013)[26] have conducted a study to evaluate the wedged tangential beam three dimensional conformed radiotherapy compared to the previously used (5 years) two dimensionally planned radiotherapy for post mastectomy breast cancer patients. They were assessed for PTV and organs at risk with a prescribed total dose of 50 Gy for 25 fractions. The results showed that the mean percentage dose to the contralateral breast to the prescribed dose was 8.2% for 3D CRT compared to 10.4% for 2D CRT tangential field techniques. On conclusion the author has confirmed that the tangential beam 3D CRT planning demonstrated a significantly better homogeneity index for the PTV of post mastectomy breast cancer patients

Rudd .C .Wortel(2015)[53] et al have conducted a study to assess and compare the acute toxicity profiles among prostrate carcinoma patients. The purpose of the study was to compare dose distribution to organs at risk and acute gastrointestinal and genitourinary toxicity levels of patients treated to 78 Gy with either IG – MRT or 3D CRT. IG – MRT resulted in significantly lower overall RTOG grade > 2 GI toxicity, with a p value of 0.002 and overall GU grade of > 2 toxicity with a p value of 0.009. Hence there is a clinically meaningful reduction in dose to organs at risk and acute toxicity levels was observed in IG – MRT patients as a result of improvement in technique and tighter margins.

Evangelia Paponi et al (2011)[16] have carried out a study to evaluate the subjective and objective long term swallowing function, and to relate dysphagia to the radiation dose delivered to the critical anatomic structures in the head and neck cancer patients treated with intensity modulated radiotherapy (+/- chemotherapy) , using a midline protection contour.Normal tissue effects were graded according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) radiation morbidity scoring criteria. Swallowing dysfunction and dysphagia were additionally graded with subjective patient reported and objective observer assessed instruments. The results showed that at the 32 month follow up evaluation, persisting swallowing dysfunction grade 3 was subjectively and objectively observed in 1 patient. The 5 year local control rate of the cohort rate was 75%, with no medial marginal failures observed. Based on the results it was concluded that sparing the swallowing structures by IMRT is relatively safe in terms of avoidance of persistent grade ¾ dysphagia and local disease control.

Tim J Kruser et al (2013)[59] have conducted a study to compare the acute haematological and mucosal toxicities in patients undergoing head and neck radiotherapy by 3D CRT, IMRT and helical tomotherapy. This analysis was limited to 178 patients receiving ≥ 60 Gy with concurrent weekly cisplatin. Radiation delivery used 3D-CRT in 41 patients (23%), conventional IMRT in 56 patients (31%), and helical tomotherapy in 81 patients (46%).

Acute mucositis rates, weekly hematologic parameters, and ability to deliver planned chemotherapy cycles were examined for each patient during their course of chemoradiotherapy. Analysis showed patients were well balanced with regard to sex, age, and stage. The results showed that among oropharynx patients treated with 3D-CRT, grade 2 mucositis occurred in 12.5% and grade 3 in 83.3%; among LINAC-IMRT patients grade 2 mucositis occurred in 40% and grade 3 in 57.5%; and among helical tomotherapy-treated patients grade 2 mucositis occurred in 30% and grade 3 in 70%. Chemotherapy has been demonstrated to increase the risk of mucosal Grade 3 toxicity approximately 4 times over radiation alone, and is equivalent to an additional 6.2 Gy to the oral mucosa. Through six weeks of chemoradiotherapy, the median decline in hemoglobin was 15.6%, the median decline in platelets was 30.6%, and the median decline in leukocytes was 51.5%, but these drops were not significantly different between treatment cohorts.

Gopa Gosh et al (2016)[20] have conducted a study to compare the toxicity profile of 3D CRT and IMRT modes of radiotherapy in head and neck cancer patients. A total of 80 patients with proven head and neck cancer who underwent radiotherapy on linac 2300 C/D machine were included in the study, IMRT group and 3D-CRT group comprised of 40 patients each. The 3D-CRT group demonstrated signifiantly more acute toxic effects compared with the IMRT group . Acute Grade 3 or greater toxic effects to the skin occurred in 5 of 40 (12.5%), patients in the 3D-CRT group compared with 3 of

40 (7.5%) patients in the IMRT group. Acute Grade 3 or greater toxic effects to the mucous membranes occurred in 23 of 40 (57.5%) patients in the 3D-CRT group and only 16 of 40 (40%) patients in the IMRT group. Statistically significant dysphagia developed in 34 of 40 (85%), patients in 3D-CRT group compared with 23 of 40 (57.5%) patients in IMRT group, while statistically significant xerostomia developed in 29 of 40 patients in 3D-CRT group (72.5%), compared with18 of 40 (45%) patients in IMRT group.

Gupta Tejpal et al (2010)[25] have done a systematic meta analysis on the various studies conducted to analyse the toxicity profiles of 3D CRT and IMRT modes of treatment. In the first study, 69 patients with early oropharyngeal cancer (T1-2, N0-1) on accelerated, hypofractionated IMRT regimen , receiving a dose of 66 Gy to primary tumor and involved nodes and 54–60 Gy to subclinical disease in 30 fractions over 6 weeks were followed up for 2.8 years. The 2- year estimated localregional failure rate was 9%. Maximal late toxicities ≥ grade 2 were dermatitis (12%), mucositis (24%), salivary gland toxicity (67%), esophagitis (19%), and osteoradionecrosis (6%). Grade 2 or worse xerostomia was observed in 55% of patients at 6 months but reduced to 25% and 16% at 1-year and 2-years respectively.

Vergeer et al[62] have done a large prospective non-randomized comparison of conventional radiotherapy (150 patients) with IMRT (91 patients) and Patient-rated xerostomia, RTOG acute and late xerostomia, and QOL scores were measured at baseline (pre-radiotherapy) and at specified

post-radiotherapy intervals. The use of IMRT resulted in a significant reduction of the mean parotid dose (27 vs 43 Gy; P < 0.001). At 6-months, 41% patients treated with IMRT reported moderate or severe xerostomia compared with 67% patients treated with 3D-CRT (P < 0.001). During treatment, significantly more patients in the 3D-CRT group encountered worse acute xerostomia and mucositis. At 6-months, 32% patients treated with IMRT had ≥ grade 2 RTOG late xerostomia compared to 56% patients treated with 3D-CRT (P = 0.002).

Micheal T Spiotto et al (2014)[42] have done a study to compare the outcome of patients treated with 3D CRT and IMRT with or without simultaneous integrated boost during Concurrent chemoradiation for locally advanced head and neck cancers. The study was conducted between 1993 and 2012 with 379 patients with non-metastatic Stage III-IV head and neck squamous cell cancer treated with concurrent chemoradiation using 3D-CRT (n = 125), IMRTseq (n = 120) and IMRT +SIB (Simultaneous Integrated Boost) (n = 134).The results showed that Patients treated with any technique had similar rates of 2y local control, 2y regional control, 2y progression free survival and 2y overall survival. Patients treated with IMRT +SIB had lower rates acute toxicity according to Grade 3 or greater mucositis (3D-CRT: 44.0% vs. IMRTseq: 36.7% vs. IMRT +SIB: 22.4%; P,.0001), dermatitis (3D-CRT: 44.0% vs. IMRTseq: 20.0% vs. IMRT +SIB: 7.5%; P,.0001) and feeding tube placement during radiotherapy (3D-CRT: 80.0% vs. IMRTseq: 50.8% vs.

IMRT +SIB: 44.0%; P,.0001) as well as late toxicity as measured by feeding tube use (P,.0001) and tracheostomy use (P,.0001). On multivariate analysis, IMRT +SIB predicted for less mucositis, dermatitis and feeding tube use compared to 3DCRT and for less dermatitis compared to IMRTseq.

Ajay Singh Choudary et al (2017)[1] have conducted a study comparative study of toxicities during treatment with IMRT Versus 3DCRT in locoregionally advanced Head and Neck Carcinoma. A total of 150 patients of histologically confirmed stage III to IVB squamous cell carcinoma of the oral cavity and oropharynx of either sex were evaluated in the study from July 2015 to June 2016; 58 in IMRT group and 92 in 3DCRT group. All patients received 70 Gy in 35 fractions with 2 Gy per fraction in both groups with 6MV photon beam concurrent with weekly cisplatin 30 mg/m2. The results showed that after median follow-up of 18 months (range, 12 to 24 months), 3D-CRT group demonstrated significantly more acute toxic effects compared with the IMRT group. Significantly higher grade III or worse acute mucositis, dysphagia, acute and late xerostomia occurred in 57.6%, 84.8%, 71.7% & 63% of patients in 3DCRT group compared with 39.7%, 56.9%, 39.7% & 20.7% of patients in IMRT group (P-value 0.23, <0.001, <0.001 and <0.00respectively). Hence IMRT is associated with decreased early and late toxicities as compared to 3DCRT.it offers better normal tissue sparing, and better quality of life.

MATERIALS AND METHODS

The present study attempts to assess and compare the acute and chronic toxicity profiles due to radiotherapy in head and neck cancer patients undergoing 3D CRT, IMRT and IGRT modes.

TYPE OF STUDY: Prospective study

SAMPLE SIZE : 60

STUDY PERIOD: January 2017 to November 2017

PLACES CONDUCTED:

1. Dr. Rai Memorial Cancer Treatment Centre
2. Billroth Hospitals, Shenoy nagar, Chennai
3. V.S. Hospitals - Cancer treatment centre, Chetpet, Chennai

STUDY POPULATION:

1. 20 patients with head and neck cancer undergoing 3D CRT mode of radiotherapy
2. 20 patients with head and neck cancer undergoing IMRT mode of radiotherapy
3. 20 patients with head and neck cancer undergoing IGRT mode of radiotherapy.

INCLUSION CRITERIA:

1. Patients diagnosed with squamous cell carcinoma of oropharynx,nasopharynx, oral cavity, hypopharynx and planned for radiotherapy.
2. Staging T1 – T4,N0 – 2c,M0.
3. Patients receiving 50 – 70 Gy, with or without concurrent chemotherapy.
4. No prior radiotherapy.
5. Kornofsky Performance Scale more than 70.

EXCLUSION CRITERIA:

1. Histopathologically proven cancer other than squamous cell carcinoma.
2. Prior radiotherapy.
3. Kornofsky performance Scale less than 70.

MATERIALS USED:

1) Sterilized set of mouth mirror, probes, kidney trays, metallic scale, divider, vernier callipers, graduated saliva collectors.

ETHICAL APPROVAL:

Ethical clearance was obtained from the Institutional review board.

METHODOLOGY:

A prospective analysis of a total of 60 patients to undergo 3D – CRT, IMRT and IGRT for treatment of squamous cell carcinoma in the head and neck region are to be selected. All patients were treated on linac 2300C/D machine, with immobilization in supine position using a customized thermoplastic device. Treatment planning involved Computerized Tomography Scan of the area of interest, followed by delineation of various target volumes like Gross tumour Volume(GTV),Clinical Target Volume(CTV),Planning Target Volume(PTV) and Organ at Risk volumes. The delineation of various volumes are done as per consensus guidelines. The ICRU report 50 from 1993 and ICRU report 62 from 1999 standardised the nomenclature used for three-dimensional conformal treatment planning and thus gave the community of radiation oncologists a consistent language and guidelines for image based target volume delineation.

The gross tumour volume (GTV) is the macroscopic (gross) extent of the tumour as determined by radiological and clinical investigations (palpation, inspection). The GTV-primary (GTV-P) defines the area of the primary tumour and GTV-nodal (GTV-N) the macroscopically involved lymph nodes (**Anca Ligia Grosu et al).** The GTV was obtained by summarising the area outlined by the radiation oncologist in each section and was multiplied by the thickness of each section. This extension of the GTV is

of major importance for the treatment strategy . The delineation of GTV was based on the data obtained from CT and MRI.

Clinical Target Volume: The GTV, together with the surrounding microscopic tumour infiltration constituted the primary clinical target volume CTV (CTV-P). which included the tumour bed, which has to be irradiated after a complete macroscopic tumour resection, in both R0 (complete microscopic resection) and R1 (microscopic residual tumour on the margin of the tumour bed) situation. As the margins between CTV and GTV are not homogenous, they are adjusted to the probable microscopic tumour spread. CTV dose is calculated as CTVdose = GTVdose + 10-20mm margin

Internal Target Volume: The ITV encompassed the GTV/CTV plus internal margins to the GTV/CTV, caused by possible physiological movements of organs and tumour, due to respiration, pulsation and variation of tumour size. In most cases the observation is impossible or difficult.

Planning Target Volume: The planning target volume (PTV) incorporated the GTV/CTV plus margins due to uncertainties of patient setup and beam adjustment; due to variations in patient positioning during radiotherapy and organ motility. The PTV dose is calculated as

PTVdose = CTVdose + 3 to 5 mm

After delineating the various target volumes and calculating the dose the fractionation is planned such that the total dose in case of squamous cell

carcinomas is between 50 – 70 Gy/ 30 – 35 daily fractions, such that each day the patient would receive 180cGy – 200cGy.

Planning Technique:

3D CRT: The field was chosen to optimize dose coverage, and respect normal tissue tolerance with a single isocentre technique, avoid junction through gross disease. The energy is delivered through 6 MV photons.

IMRT: This includes 6 -9 coplanar fields and energy is delivered through 6 MV photons. The beam intensities are modulated or non uniform in that they resulted in a sharper space dose gradient than 3D CRT technique. The field size, gantry angles and other beam characteristics are well defined to achieve a desired dose distribution.

IGRT: The target volume delineation is done in the same manner as that of IMRT, but additionally frequent imaging was done during the course of radiotherapy, and these images are compared with the reference images taken during simulation and hence radiation beams are adjusted to more precisely target the radiation dose to the tumour.

After a cycle of radiotherapy is delivered by one of the three means the patients were observed to develop toxicities which included mucositis, skin reactions, xerostomia and dysphagia. The toxicity patterns (grades of mucositis, skin reaction, dysphagia, xerostomia) developing within 90 days from the beginning of RT (acute toxicity) are assessed according to Radiation

Therapy Oncology Group (RTOG) and European Organisation 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 sequelae **(Gopa Gosh et al, 2016)** The grading according to the RTOG criteria for acute and chronic toxicities are as such:

RTOG ACUTE Radiation morbidity

Tissue	Grade 1	2	3	4
Skin	Follicular, faint or dull erythema/epilation/dry desquamation/decreased sweating	Tender or bright erythema, patchy moist desquamation/moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Mucous membrane	Irritation/may experience mild pain not requiring analgesic	Patchy mucositis that may produce a serosanguinous discharge/moderate pain requiring analgesia	Confluent fibrinous mucositis/may include severe pain requiring necrotic	Ulceration, hemorrhage, necrosis
Salivary gland	Mild mouth dryness/slightly thickened saliva, may have slightly altered taste such as metallic taste	Moderate to complete dryness/ thick, sticky saliva/markedly altered taste	None	Acute salivary gland necrosis
Pharynx & oesophagus	Mile dysphagia or odynophagia/may require topical anesthetic or non – narcotic analgesics/may require soft diet	Moderate dysphagia or odynophagia/may require narcotic analgesics/ may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss > 15% from pretreatment	Complete obstruction, ulceration, perforation, fistula

			baseline requiring NG feeding tube, IV fluids.	

RTOG/EORTC LATE RADIATION MORBIDITY

TISSUES	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Skin	Slight atrophy; pigmentation change; some hair loss	Patchy atrophy; moderate telangiectasia; hair loss	Marked atrophy; gross telangiectasia	Ulceration
Mucous membrane	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucous	Marked atrophy with complete dryness	Ulceration
Salivary glands	Slight dryness of mouth; good response of stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response to stimulation	Fibrosis
Pharynx & Oesophagus	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semisolid food; dilatation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing	Necrosis/ perforation fistula

GRADING OF TOXICITY PROFILES:

CLINICAL CHARACTERISTICS	POST RT	90 DAYS POST RT
MUCOSITIS		
SKIN REACTIONS		
DYSPHAGIA		
XEROSTOMIA		

STATISTICS TO BE USED:

SPSS for Windows 13.0 (Statistical Package for the Social Sciences, Chicago, IL).

The statistics used include ANOVA, Turkey HSD and Post Hoc methods.

DETAILED BUDGET PLAN:

Rs. 10,000.

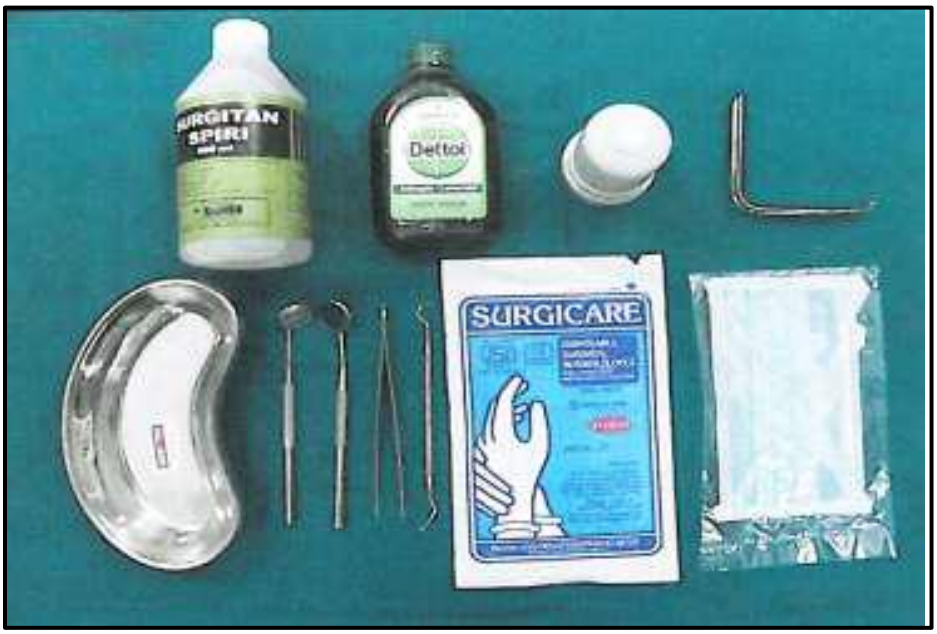


Fig 8 : Armamentarium for Clinical Examination

Fig :Graduated saliva container

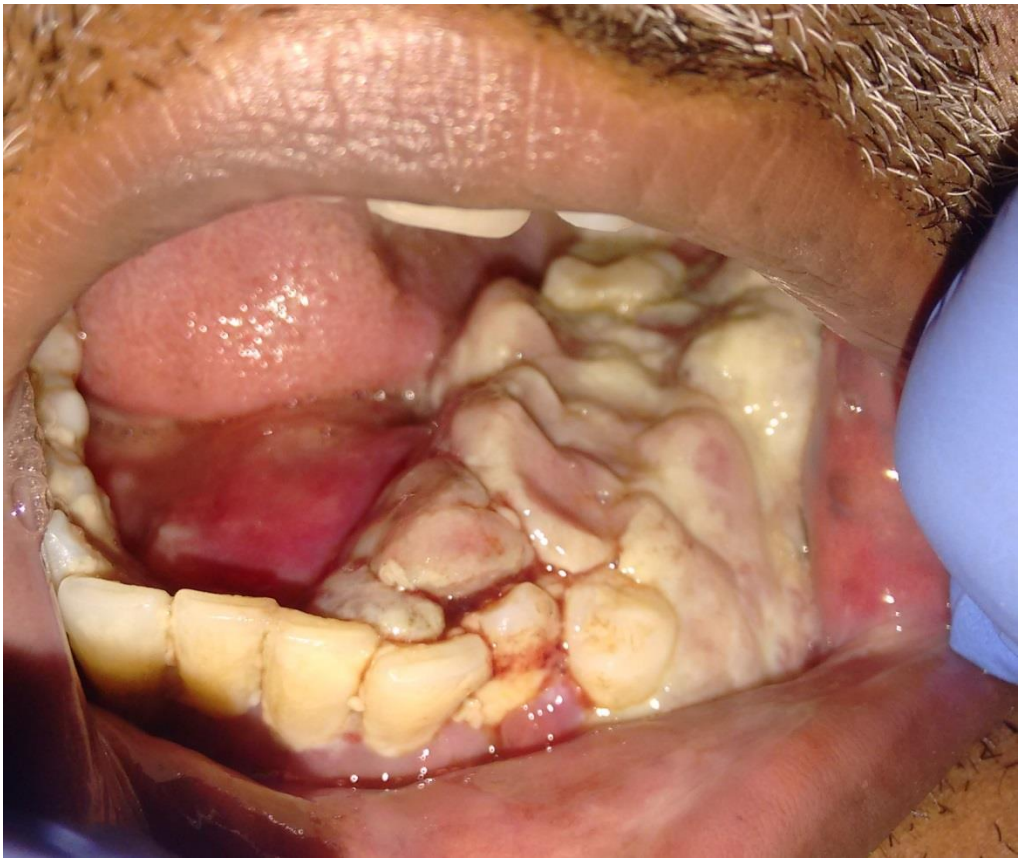


Fig 11 : Patient with OSCC

RESULTS

The present study was conducted to compare the toxicity profiles in head and neck cancer patients undergoing 3D CRT, IMRT and IGRT modes of radiotherapy between January 2017 to November 2017. The results are tabulated and described as follows

TABLE 1: INCIDENCE OF MUCOSITIS POST RT IN 3D CRT, IMRT AND IGRT GROUP OF PATIENTS:

Among the 20 (100%) patients in 3D CRT group, 6 (30%) had grade 2 mucositis, and 14(70%) had grade 3 mucositis. Among the 20(100%) patients in IMRT group, 2(10%) had grade 1 mucositis and 18 (90%) had grade 2 mucositis. Among the 20 (100%) patients in IGRT group, 3(15%) had grade 1 mucositis and 17(85%) had grade 2 mucositis.

TABLE 2: COMPARISON OF MUCOSITIS POST RT IN 3D CRT AND IMRT GROUPS:

On comparing the grades of mucositis between 3D CRT and IMRT groups, out of the 20 patients in 3D CRT group 6(30%) had grade 2 mucositis and 14(70%) had grade 3 mucositis and out of the 20 patients in IMRT group 2 (10%) had grade 1 mucositis and 18(90%) had grade 2 mucositis. The P value was found to be 0.000 which was statistically significant.

TABLE 3: COMPARISON OF MUCOSITIS POST RT IN 3D CRT AND IGRT GROUPS:

On comparing the grades of mucositis between 3D CRT and IGRT groups, out of the 20 patiemts in 3D CRT group 6 (30%) had grade 2 mucositis and 14 (70%) had grade 3 mucositis and out of the 20 patients in IGRT group 3(15%) had grade 1 mucositis and 17(85%) had grade 2 mucositis. . The P value was found to be 0.000 which was statistically significant.

TABLE 4: COMPARISON OF MUCOSITIS POST RT IN IMRT AND IGRT GROUP OF PATIENTS:

On comparing the grades of mucositis between IMRT and IGRT groups, out of the 20 patients in IMRT group, 2 (10%) had grade 1 mucositis, amd 18(90%) had grade 2 mucositis. The P value was found to be 0.912 which was statistically insignificant.

TABLE 5: INCIDENCE OF MUCOSITIS 90 DAYS POST RT IN 3D CRT, IMRT AND IGRT GROUP OF PATIENTS:

Among the 20 (100%) of patients in 3D CRT group, 10 (50%) had grade 1 mucositis ,10 (50%) had grade 2 mucositis. Among the 20 patients in IMRT group, 16 (80%) had grade 1 mucositis, 4 (20%) had grade 2 mucositis. Among the 20 patients in IGRT group, 18(90%) had grade 1 mucositis and 2 (10%) had grade 2 mucositis.

TABLE 6: COMPARISON OF MUCOSITIS 90 DAYS POST RT IN 3D CRT AND IMRT GROUPS:

On comparing the grades of mucositis between 3D CRT and IMRT groups, out of the 20 patients, in 3D CRT group, 10 (50%) had grade 1 mucositis, 10 (50%) had grade 2 mucositis and out of the 20 patients in the IMRT group, 16(80%) had grade I mucositis and 4(20%) had grade 2 mucositis. The P value was found to be 0.069 which was statistically significant.

TABLE 7: COMPARISON OF MUCOSITIS 90 DAYS POST RT IN 3D CRT AND IGRT GROUPS:

On comparing the grades of mucositis between 3D CRT and IGRT groups, out of the 20 patients , in 3D CRT group, 10 (50%) had grade 1 mucositis, 10 50%) had grade 2 mucositis and out of the 20 patients in the IGRT group, 18(90%) had grade1 mucositis and 2(10%) had grade 2 mucositis. The P value was found to be 0.010 which was staristically significant.

TABLE 8: COMPARISON OF MUCOSITIS 90 DAYS POST RT BETWEEN IMRT AND IGRT GROUPS:

On comparing the grades of mucositis between IMRT and IGRT groups, out of the 20 patients in IMRT group, 16(80%) had grade 1 mucositis and 4 (20%) had grade 2 mucositis and out of the 20 patients in IGRT group 18

(90%) had grade 1 mucositis and 2 (10%) had grade 2 mucositis. The P value was found to be 0.732 which was statistically insignificant.

TABLE 9: INCIDENCE OF SKIN REACTIONS POST RT IN 3D CRT, IMRT AND IGRT GROUPS OF PATIENTS:

Among the 20 (100%) of patients in 3D CRT group 13 (65%) had grade 1skin reactions, 5 (25%) had grade 2 skin reactions and 2 (10%) had grade 3 skin reactions. Among the 20 (100%) of patients in the IMRT group, 18(90%) had grade 1 skin reactions and 2(10%) had grade2 skin reactions. Among the 20 (100%) of patients in the IGRT group, 18(90%) had grade 1 skin reactions and 2(10%) had grade2 skin reactions.

TABLE 10: COMPARISON OF SKIN REACTIONS POST RT IN 3D CRT, IMRT GROUPS:

On comparing the grades of skin reactions , between 3D CRT and IMRT groups, out of the 20 patients in 3D CRT group 13(65%) had grade 1 skin reactions, 5 (25%) had grade 2 skin reactions and out of the 20 patients in IMRT group, 18(90%) had grade 1 skin reactions, and 2 (10%) had grade 2 skin reactions. The P value was found to be 0.004 which was statistically significant.

TABLE 11: COMPARISON OF SKIN REACTIONS POST RT IN 3D CRT AND IGRT GROUPS:

On comparing the grades of skin reactions, between 3D CRT and IGRT groups, out of the 20 patients in the 3D CRT group 13(65%) have grade 1 skin reactions, 5(25%) have grade 2 skin reactions and out of the 20 patients in IGRT group 18(90%) have grade 1 skin reactions and 2(10%) have grade 2 skin reactions. The P value was found to be 0.002 which was statistically significant.

TABLE 12: COMPARISON OF SKIN REACTIONS POST RT IN IMRT AND IGRT GROUPS:

On comparing the grades of skin reactions, between IMRT and IGRT groups, out of the 20 patients in the IMRT group 18(90%) had grade 1 skin reactions , 2 (10%) had grade 2 skin reactions and out of the 20 patients in IGRT group, 18(90%) have grade 1 skin reactions and 2(10%) have grade 2 skin reactions. The P value was found to be 0.969 which was not statistically insignificant.

TABLE 13: INCIDENCE OF SKIN REACTIONS 90 DAYS POST RT IN 3D CRT, IMRT AND IGRT GROUPS:

Among the 20 (100%) patients in 3D CRT group, 17(85%) had grade 1 skin reactions and 3(15%) had grade 2 skin reactions. Among the 20 (100%)of patients in the IMRT group, 11(55%) had grade 1 skin reactions, 2 (10%) had

grade 2 skin reactions. Among the 20 (100%) of patients in the IGRT group, 10 (50%) had grade 1 skin reactions and 3(15%) had grade 2 skin reactions.
TABLE 14: COMPARISON OF SKIN REACTIONS 90 DAYS POST RT IN 3D CRT, IMRT GROUPS:

On comparing the grades of skin reactions between 3D CRT and IMRT groups, out of the 20 patients in 3D CRT group 17 (85%) had grade 1 skin reactions and 3(15%) had grade 2 skin reactions and out of the 20 patients in IMRT group, 11(55%) had grade 1 skin reactions and 2 (10%)had grade 2 skin reactions. The P value was found to be 0.000 which was statistically significant.

TABLE 15: COMPARISON OF SKIN REACTIONS 90 DAYS POST T IN 3D CRT , IGRT GROUPS:

On comparing the grades of skin reactions between 3D CRT and IGRT groups, out of the 20 patients in 3D CRT group 17 (85%) had grade 1 skin reactions and 3(15%) had grade 2 skin reactions and out of the 20 patients in IGRT group, 10(50%) had grade 1 skin reactions and 3 (15%)had grade 2 skin reactions. The P value was found to be 0.000 which was statistically significant.

TABLE 16: COMPARISON OF SKIN REACTIONS 90 DAYS POST RT IN IMRT AND IGRT GROUPS:

On comparing the grades of skin reactions between IMRT and IGRT groups, out of the 20 patients in IMRT group 11 (55%) had grade 1 skin reactions and 2(10%) had grade 2 skin reactions and out of the 20 patients in IGRT group, 10(50%) had grade 1 skin reactions and 3 (15%)had grade 2 skin reactions. The P value was found to be 0.679 which was not statistically significant.

TABLE 17: INCIDENCE OF XEROSTOMIA POST RT IN 3D CRT, IMRT AND IGRT GROUPS:

Among the 20 (100%) of patients in the 3D CRT group, 15(75%) had grade 1 xerostomia, 3 (15%) had grade 2 xerostomia. Among the 20(100%) of patients in the IMRT group, 13(65%) had grade I xerostomia, 3(15%) had grade 2 xerostomia. Among the 20 (100%) in the IGRT group, 14(70%) had grade 1 xerostomia and 3(15%) had grade 2 xerostomia.

TABLE 18: COMPARISON OF XEROSTOMIA POST RT IN 3D CT, IMRT GROUPS:

On comparing the grades of xerostomia between 3D CRT and IMRT groups, out of the 20 patients in 3D CRT group, 15(75%) had grade 1 xerostomia, 3(15%) had grade 2 xerostomia and out of the 20 patients in the IMRT group,

13(65%) had grade 1 xerostomia and 3 (15%) had grade 2 xerostomia. The P value was found to be 1.000 which was not statistically significant.

TABLE 19: COMPARISON OF XEROSTOMIA POST RT IN 3D CRT, IGRT GROUPS:

On comparing the grades of xerostomia between 3D CRT and IGRT groups, out of the 20 patients in 3D CRT group, 15(75%) had grade 1 xerostomia, 3(15%) had grade 2 xerostomia and out of the 20 patients in the IGRT group, 14(70%) had grade 1 xerostomia and 3 (15%) had grade 2 xerostomia. The P value was found to be 0.532 which was not statistically significant.

TABLE 20: COMPARISON OF XEROSTOMIA POST RT IN IMRT AND IGRT GROUPS:

On comparing the grades of xerostomia between IMRT and IGRT groups, out of the 20 patients in IMRT group, 13(65%) had grade 1 xerostomia, 3(15%) had grade 2 xerostomia and out of the 20 patients in the IGRT group, 14(70%) had grade 1 xerostomia and 3 (15%) had grade 2 xerostomia. The P value was found to be 0.532 which was not statistically significant.

TABLE 21: INCIDENCE OF XEROSTOMIA 90 DAYS POST RT IN 3DCRT, IMRT AND IGRT GROUPS:

Among the 20 (100%) of patients in the 3D CRT group, 15(75%) had grade 1 xerostomia, 5 (25%) had grade 2 xerostomia. Among the 20(100%) of patients in the IMRT group, 17(85%) had grade I xerostomia, 2(10%) had grade 2

xerostomia. Among the 20 (100%) in the IGRT group, 16(80%) had grade 1 xerostomia and 1(5%) had grade 2 xerostomia.

TABLE 22: COMPARISON OF XEROSTOMIA 90 DAYS POST RT IN 3D CRT AND IMRT GROUPS:

On comparing the grades of xerostomia between 3D CRT and IMRT groups, out of the 20 patients in 3D CRT group, 15(75%) had grade 1 xerostomia, 5(25%) had grade 2 xerostomia and out of the 20 patients in the IMRT group, 17(85%) had grade 1 xerostomia and 2 (10%) had grade 2 xerostomia. The P value was found to be 0.000 which was statistically significant.

TABLE 23: COMPARISON OF XEROSTOMIA 90 DAYS POST RT IN 3D CRT AND IGRT GROUPS:

On comparing the grades of xerostomia between 3D CRT and IGRT groups, out of the 20 patients in 3D CRT group, 15(75%) had grade 1 xerostomia, 5(25%) had grade 2 xerostomia and out of the 20 patients in the IGRT group, 16(80%) had grade 1 xerostomia and 1 (5%) had grade 2 xerostomia. The P value was found to be 0.000 which was statistically significant

TABLE 24: COMPARISON OF XEROSTOMIA 90 DAYS POST RT IN IMRT AND IGRT GROUPS:

On comparing the grades of xerostomia between IMRT and IGRT groups, out of the 20 patients in IMRT group, 17(85%) had grade 1 xerostomia, 2(10%) had grade 2 xerostomia and out of the 20 patients in the IGRT group,

16(80%) had grade 1 xerostomia and 1 (5%) had grade 2 xerostomia. The P value was found to be 0.497 which was not statistically significant.

TABLE 25: INCIDENCE OF DYSPHAGIA POST RT IN 3D CRT, IMRT AND IGRT GROUPS:

Among the 20 (100%) of patients in the 3D CRT group, 11(55%) had grade 1 dysphagia, 7 (35%) had grade 2 dysphagia and 2(10%) had grade 3 dysphagia . Among the 20(100%) of patients in the IMRT group, 19(95%) had grade I dysphagia, 1(5%) had grade 2 dysphagia. Among the 20 (100%) in the IGRT group, 19(95%) had grade 1 dysphagia and 1(5%) had grade 2 dysphagia.

TABLE 26: COMPARISON OF DYSPHAGIA POST RT IN 3D CRT AND IMRT GROUPS:

On comparing the grades of dysphagia between 3D CRT and IMRT groups, out of the 20 patients in 3D CRT group, 11(55%) had grade 1 dysphagia, 7(35%) had grade 2 dysphagia 2(10%) had grade 3 dysphagia and out of the 20 patients in the IMRT group, 19(95%) had grade 1 dysphagia and 1 (5%) had grade 2 dysphagia. The P value was found to be 0.000 which was statistically significant.

TABLE 27: COMPARISON OF DYSPHAGIA POST RT IN 3D CRT AND IGRT GROUPS:

On comparing the grades of dysphagia between 3D CRT and IGRT groups, out of the 20 patients in 3D CRT group, 11(55%) had grade 1 dysphagia

7(35%) had grade 2 dysphagia 2(10%) had grade 3 dysphagia and out of the 20 patients in the IGRT group, 19(95%) had grade 1 dysphagia and 1 (5%) had grade 2 dysphagia. The P value was found to be 0.000 which was statistically significant.

TABLE 28: COMPARISON OF DYSPHAGIA POST RT IN IMRT AND IGRT GROUPS:

On comparing the grades of dysphagia between IMRT and IGRT groups, out of the 20 patients in IMRT group, 19(95%) had grade 1 dysphagia, 1(5%) had grade 2 dysphagia and out of the 20 patients in the IGRT group, 19(95%) had grade 1 dysphagia and 1 (5%) had grade 2 dysphagia. The P value was found to be 0.966 which was statistically not significant.

TABLE 29: INCIDENCE OF DYSPHAGIA 90 DAYS POST RT IN 3D CRT, IMRT AND IGRT GROUPS:

Among the 20 (100%) of patients in the 3D CRT group, 13(65%) had grade 1 dysphagia, 7 (35%) had grade 2 dysphagia . Among the 20(100%) of patients in the IMRT group, 10(50%) had grade I dysphagia, 1(5%) had grade 2 dysphagia. Among the 20 (100%) in the IGRT group, 9(45%) had grade 1 dysphagia and 3(15%) had grade 2 dysphagia.

TABLE 30: COMPARISON OF DYSPHAGIA 90 DAYS POST RT IN 3D CRT AND IMRT GROUPS:

On comparing the grades of dysphagia between 3D CRT and IMRT groups, out of the 20 patients in 3D CRT group, 13(65%) had grade 1 dysphagia, 7(35%) had grade 2 dysphagia and in the IMRT group, 10(50%) had grade 1 dysphagia and 1 (5%) had grade 2 dysphagia. The P value was found to be 0.001 which was statistically significant.

TABLE 31: COMPARISON OF DYSPHAGIA 90 DAYS POST RT IN 3D CT AND IGRT GROUPS:

On comparing the grades of dysphagia between 3D CRT and IGRT groups, out of the 20 patients in 3D CRT group, 13(65%) had grade 1 dysphagia, 7(35%) had grade 2 dysphagia and in the IMRT group, 9(45%) had grade 1 dysphagia and 3 (15%) had grade 2 dysphagia. The P value was found to be 0.000 which was statistically significant.

TABLE 32: COMPARISON OF DYSPHAGIA 90 DAYS POST RT IN IMRT AND IGRT GROUPS:

On comparing the grades of dysphagia between IMRT and IGRT groups, out of the 20 patients in IMRT group, 10(50%) had grade 1 dysphagia 1(5%) had grade 2 dysphagia and in the IGRT group, 9(45%) had grade 1 dysphagia and 3 (15%) had grade 2 dysphagia. The P value was found to be 0.903 which was not statistically significant

TABLE 1:INCIDENCE OF MUCOSITIS POST RT IN 3D CRT , IMRT AND IGRT PATIENTS

Mucositis grade	3D CRT	%	IMRT	%	IGRT	%
1	-	-	2	10%	3	15%
2	6	30%	18	90%	17	85%
3	14	70%	-	-	-	-
4	-	-	-	-	-	-
Total	20	100%	20	100%	20	100%

TABLE 2:COMPARISON OF MUCOSITIS POST RT AMONG 3DCRT AND IMRT

Mucositis grade	3D CRT	%	IMRT	%	P VALUE
1	-	-	2	10%	0.000
2	6	30%	18	90%	
3	14	70%	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 3: COMPARISON OF MUCOSITIS POST RT AMONG 3D CRT AND IGRT

Mucositis grade	3D CRT	%	IGRT	%	P VALUE
1	-	-	3	15%	0.000
2	6	30%	17	85%	
3	14	70%	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 4: COMPARISON OF MUCOSITIS POST RT AMONG IMRT AND IGRT

Mucositis grade	IMRT	%	IGRT	%	P VALUE
1	2	10%	3	15%	.912
2	18	90%	17	85%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 5: INCIDENCE OF MUCOSITIS 90 DAYS POST RT IN 3D CRT, IMRT AND IGRT GROUPS:

Mucositis grade	3D CRT	%	IMRT	%	IGRT	%
1	10	50%	16	80%	18	90%
2	10	50%	4	20%	2	10%
3	-	-	-	-	-	-
4	-	-	-	-	-	-
Total	20	100%	20	100%	20	100%

TABLE 6:COMPARISON OF MUCOSITIS 90 FDAYS POST RT IN 3D CRT AND IMRT GROUPS:

Mucositis grade	3D CRT	%	IMRT	%	P VALUE
1	10	50%	16	80%	.069
2	10	50%	4	20%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 7:COMPARISON OF MUCOSITIS 90 DAYS POST RT IN 3D CRT AND IGRT GROUPS:

Mucositis grade	3D CRT	%	IGRT	%	P VALUE
1	10	50%	18	90%	.010
2	10	50%	2	10%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 8: COMPARISON OF MUCOSITIS 90 DAYS IN POST RT IN IMRT AND IGRT GROUPS:

Mucositis grade	IMRT	%	IGRT	%	P VALUE
1	16	80%	18	90%	.732
2	4	20%	2	10%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 9: INCIDENCE OF SKIN REACTIONS POST RT IN 3D CRT, IMRT AND IGRT GROUPS:

Skin reactions grade	3D CRT	%	IMRT	%	IGRT	%
1	13	65%	18	90%	18	90%
2	5	25%	2	10%	2	10%
3	2	10%	-	-	-	-
4	-	-	-	-	-	-
Total	20	100%	20	100%	20	100%

TABLE 10: COMPARISON OF SKIN REACTIONS POST RT IN 3D CRT AND IMRT GROUPS:

Skin reactions grade	3D CRT	%	IMRT	%	P VALUE
1	13	65%	18	90%	.004
2	5	25%	2	10%	
3	2	10%	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 11: COMPARISON OF SKIN REACTIONS POST RT IN 3D CRT AND IGRT GROUPS:

Skin reactions grade	3D CRT	%	IGRT	%	P VALUE
1	13	65%	18	90%	0.002
2	5	25%	2	10%	
3	2	10%	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 12: COMPARISON OF SKIN REACTIONS POST RT IN IMRT AND IGRT GROUPS:

Skin reactions grade	IMRT	%	IGRT	%	P VALUE
1	18	90%	18	90%	.969
2	2	10%	2	10%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 13: INCIDENCE OF SKIN REACTIONS 90 DAYS POST RT IN 3D CRT, IMRT, IGRT GROUPS:

Skin reactions grade	3D CRT	%	IMRT	%	IGRT	%
1	17	85%	11	55%	10	50%
2	3	15%	2	10%	3	15%
3	-	-	-	-	-	-
4	-	-	-	-	-	-
Total	20	100%	20	100%	20	100%

TABLE 14: COMPARISON OF SKIN REACTIONS 90 DAYS POST RT IN 3D CRT AND IMRT GROUPS:

Skin reactions grade	3D CRT	%	IMRT	%	P VALUE
1	17	85%	11	55%	0.000
2	3	15%	2	10%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 15: COMPARISON OF SKIN REACTIONS 90 DAYS POST RT IN 3D CRT AND IGRT GROUPS:

Skin reactions grade	3D CRT	%	IGRT	%	P VALUE
1	17	85%	10	50%	0.000
2	3	15%	3	15%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 16: COMPARISON OF SKIN REACTIONS 90 DAYS POST RT IN IMRT AND IGRT GROUPS:

Skin reactions grade	IMRT	%	IGRT	%	P VALUE
1	11	55%	10	50%	0.679
2	2	10%	3	15%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 17: INCIDENCE OF XEROSTOMIA POST RT IN 3D CRT, IMRT AND IGRT GROUPS:

Xerostomia grade	3D CRT	%	IMRT	%	IGRT	%
1	15	75%	13	65%	14	70%
2	3	15%	3	15%	3	15%
3	-	-	-	-	-	-
4	-	-	-	-	-	-
Total	20	100%	20	100%	20	100%

TABLE 18: COMPARISON OF XEROSTOMIA POST RT IN 3D CRT AND IMRT GROUPS:

Xerostomia grade	3D CRT	%	IMRT	%	P VALUE
1	15	75%	13	65%	1.000
2	3	15%	3	15%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 19: COMPARISON OF XEROSTOMIA POST RT IN 3D CRT AND IGRT GROUPS:

Xerostomia grade	3D CRT	%	IGRT		P VALUE
1	15	75%	14	70%	.532
2	3	15%	3	15%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 20: COMPARISON OF XEROSTOMIA POST RT IN IMRT AND IGRT GROUPS:

Xerostomia grade	IMRT	%	IGRT	%	P VALUE
1	13	65%	14	70%	.532
2	3	15%	3	15%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 21: INCIDENCE OF XEROSTOMIA 90 DAYS POST RT IN 3D CRT, IMRT AND IGRT GROUPS:

Xerostomia grade	3D CRT	%	IMRT	%	IGRT	%
1	15	75%	17	85%	16	80%
2	5	25%	2	10%	1	5%
3	-	-	-	-	-	-
4	-	-	-	-	-	-
Total	20	100%	20	100%	20	100%

TABLE 22: COMPARISON OF XEROSTOMIA 90 DAYS IN 3D CRT AND IMRT GROUPS

Xerostomia grade	3D CRT	%	IMRT	%	P VALUE
1	15	75%	17	85%	0.000
2	5	25%	2	10%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 23: COMPARISON OF XEROSTOMIA 90 DAYS POST RT IN 3D CRT AND IGRT GROUPS:

Xerostomia grade	3D CRT	%	IGRT		P VALUE
1	15	75%	16	80%	0.000
2	5	25%	1	5%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 24: COMPARISON OF XEROSTOMIA 90 DAYS POST RT IN IMRT AND IGRT GROUPS:

Xerstomia grade	IMRT	%	IGRT	%	P VALUE
1	17	85%	16	80%	0.497
2	2	10%	1	5%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 25: INCIDENCE OF DYSPHAGIA POST RT IN 3D CRT, IMRT AND IGRT GROUPS:

Dysphagia grade	3D CRT	%	IMRT	%	IGRT	%
1	11	55%	19	95%	19	95%
2	7	35%	1	5%	1	5%
3	2	10%	-	-	-	-
4	-	-	-	-	-	-
Total	20	100%	20	100%	20	100%

TABLE 26: COMPARISON OF DYSPHAGIA POST RT IN 3D CRT AND IMRT GROUPS:

Dysphagia grade	3D CRT	%	IMRT	%	P VALUE
1	11	55%	19	95%	0.000
2	7	35%	1	5%	
3	2	10%	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 27: COMPARISON OF DYSPHAGIA POST RT IN 3D CRT AND IGRT GROUPS:

Dysphagia grade	3D CRT	%	IGRT	%	P VALUE
1	11	55%	19	95%	0.000
2	7	35%	1	5%	
3	2	10%	-	_	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 28: COMPARISON OF DYSPHAGIA POST RT IN IMRT AND IGRT GROUPS:

Dysphagia grade	IMRT	%	IGRT	%	P VALUE
1	19	95%	19	95%	0.966
2	1	5%	1	5%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

TABLE 29: INCIDENCE OF DYSPHAGIA 90 DAYS POST RT IN 3D CRT, IMRT AND IGRT GROUPS:

Dysphagia grade	3D CRT	%	IMRT	%	IGRT	%
1	13	65%	10	50%	9	45%
2	7	35%	1	5%	3	15%
3	-	-	-	-	-	-
4	-	-	-	-	-	-
Total	20	100%	20	100%	20	100%

TABLE 30: COMPARISON OF DYSPHAGIA 90 DAYS POST RT IN 3D CRT AND IMRT GROUPS:

Dysphagia grade	3D CRT	%	IMRT	%	P VALUE
1	13	65%	10	50%	0.001
2	7	35%	1	5%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

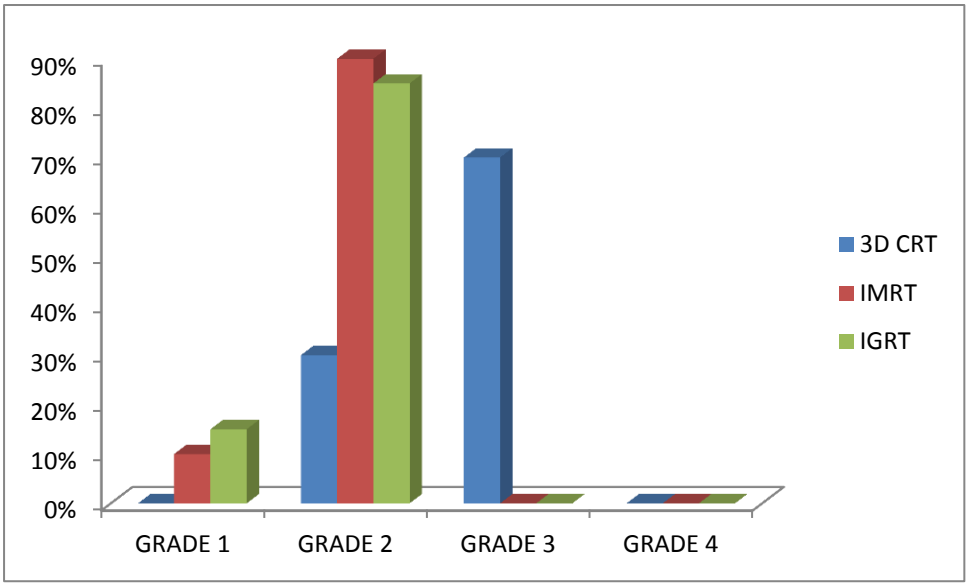
TABLE 31: COMPARISON OF DYSPHAGIA 90 DAYS POST RT IN 3D CRT AND IGRT GROUPS:

Dysphagia grade	3D CRT	%	IGRT	%	P VALUE
1	13	65%	9	45%	0.000
2	7	35%	3	15%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

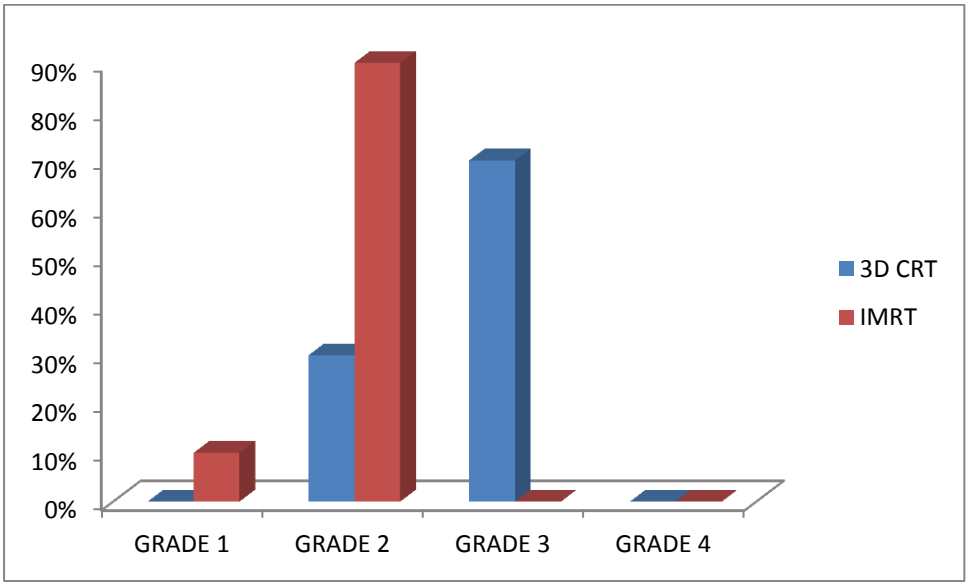
TABLE 32: COMPARISON OF DYSPHAGIA 90 DAYS POST RT IN IMRT AND IGRT GROUPS:

Dysphagia grade	IMRT	%	IGRT	%	P VALUE
1	10	50%	9	45%	0.903
2	1	5%	3	15%	
3	-	-	-	-	
4	-	-	-	-	
Total	20	100%	20	100%	

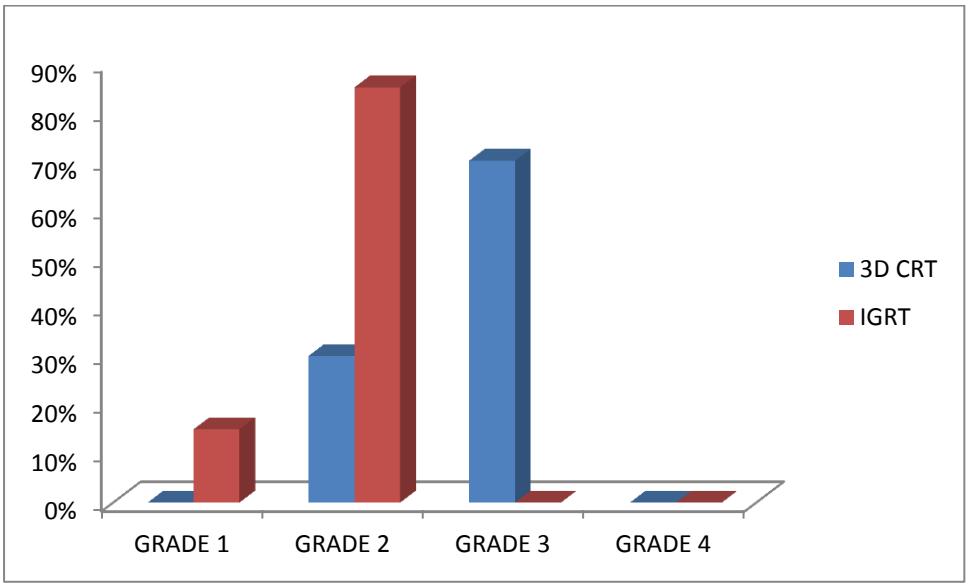
GRAPH 1: INCIDENCE OF MUCOSITIS POST RT IN 3D CRT, IMRT AND IGRT GROUPS:



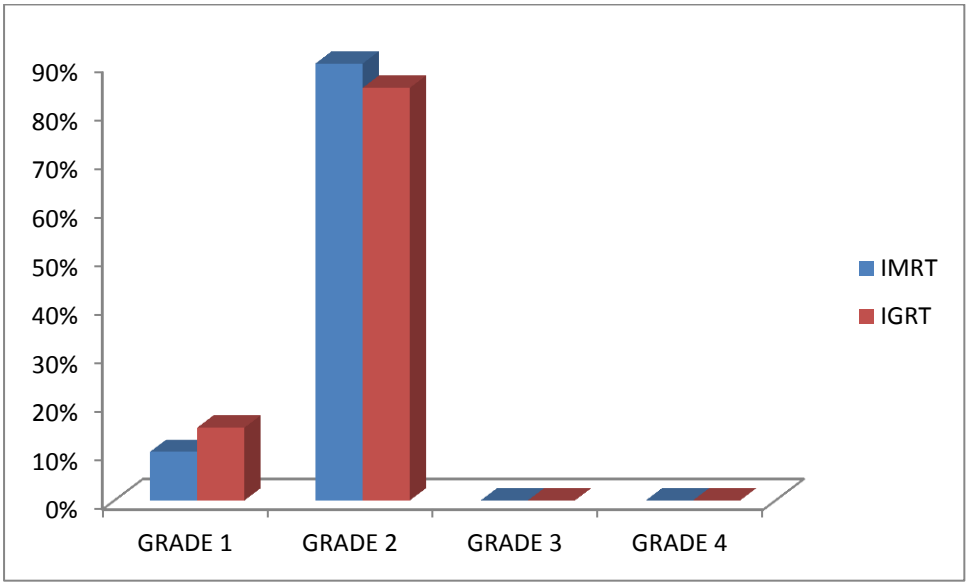
GRAPH 2: COMPARISON OF MUCOSITIS POST RT IN 3D CRT AND IMRT GROUPS:



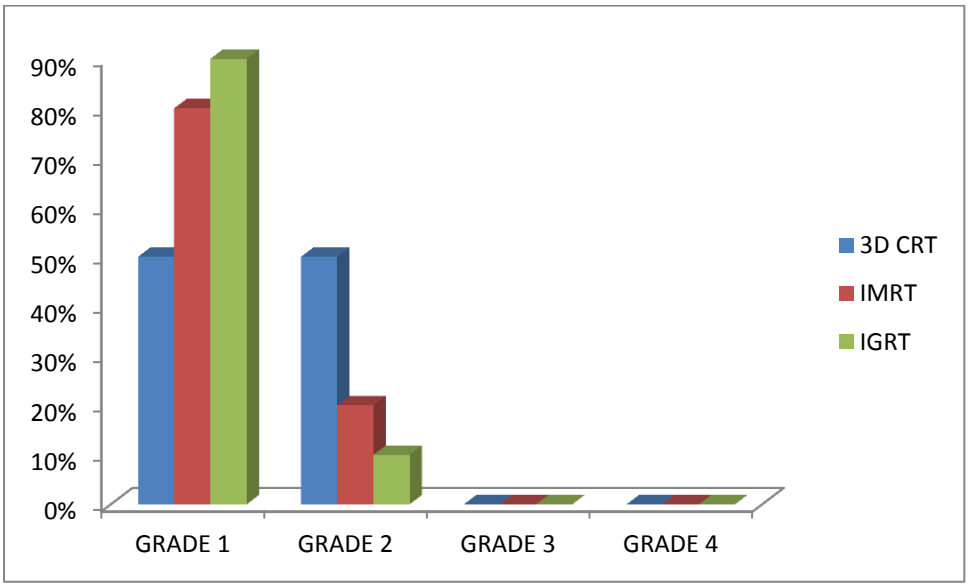
GRAPH 3: COMPARISON OF MUCOSITIS POST RT IN 3D CRT AND IGRT GROUPS:



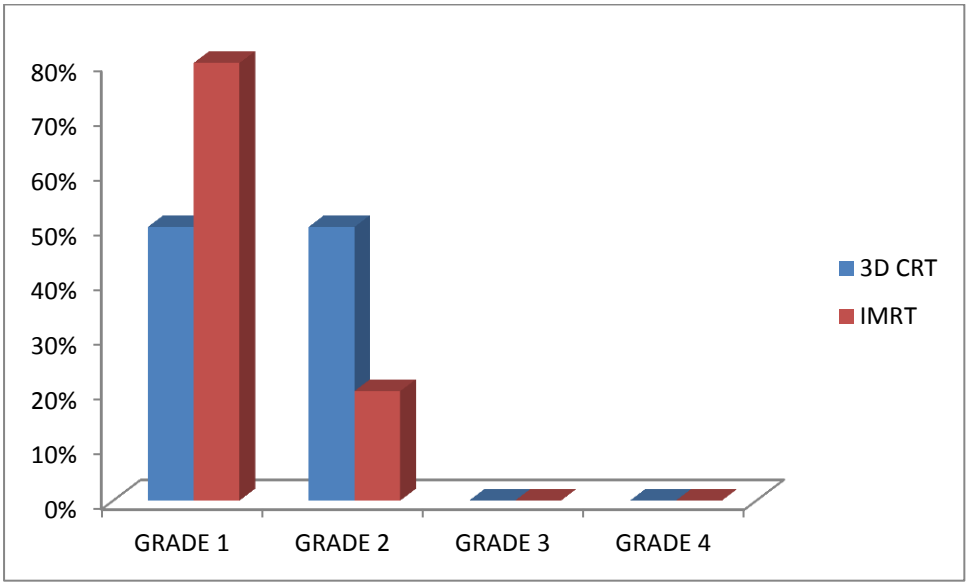
GRAPH 4: COMPARISON OF MUCOSITIS POST RT IN IMRT AND IGRT GROUPS:



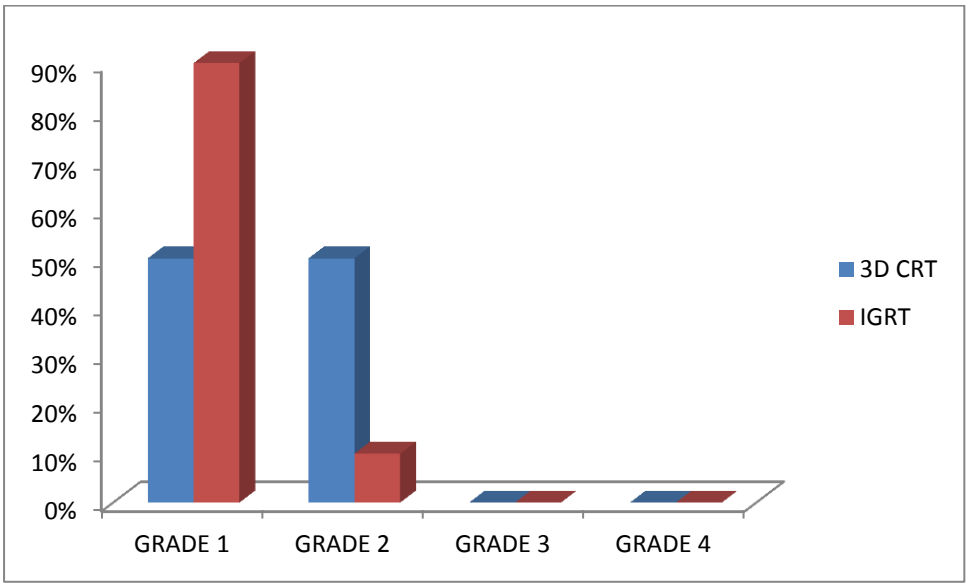
GRAPH 5: INCIDENCE OF MUCOSITIS 90 DAYS POST RT IN 3D CRT, IMRT AND IGRT GROUPS:



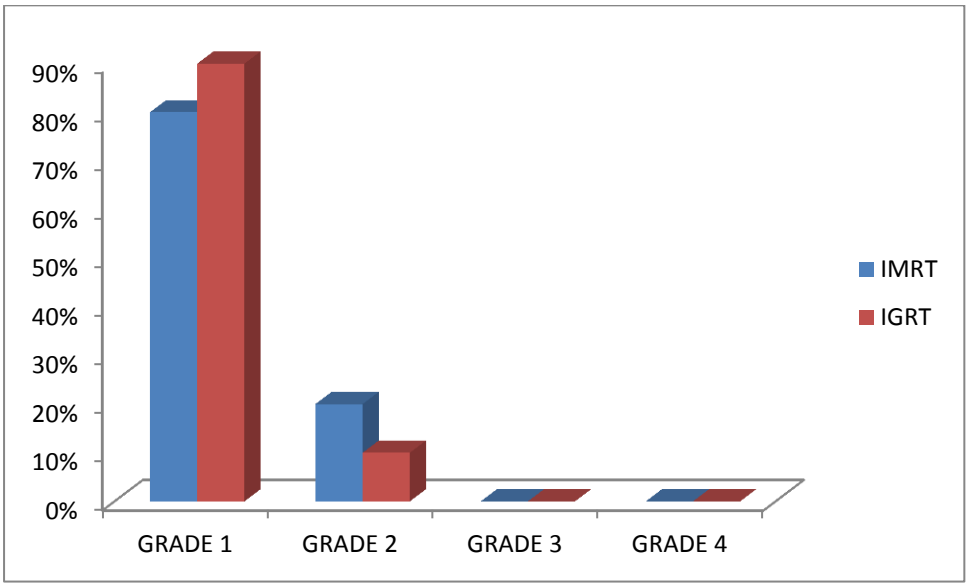
GRAPH 6 : COMPARISON OF MUCOSITIS 90 DAYS POST RT IN 3D CRT AND IMRT GROUPS:



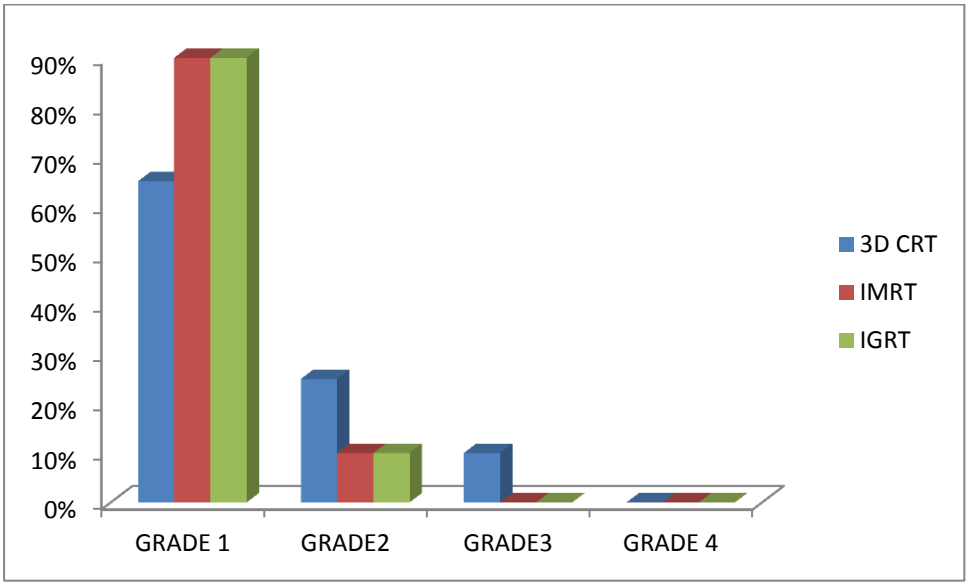
GRAPH 7: COMPARISON OF MUCOSITIS 90 DAYS POST RT IN 3D CRT AND IGRT GROUPS:



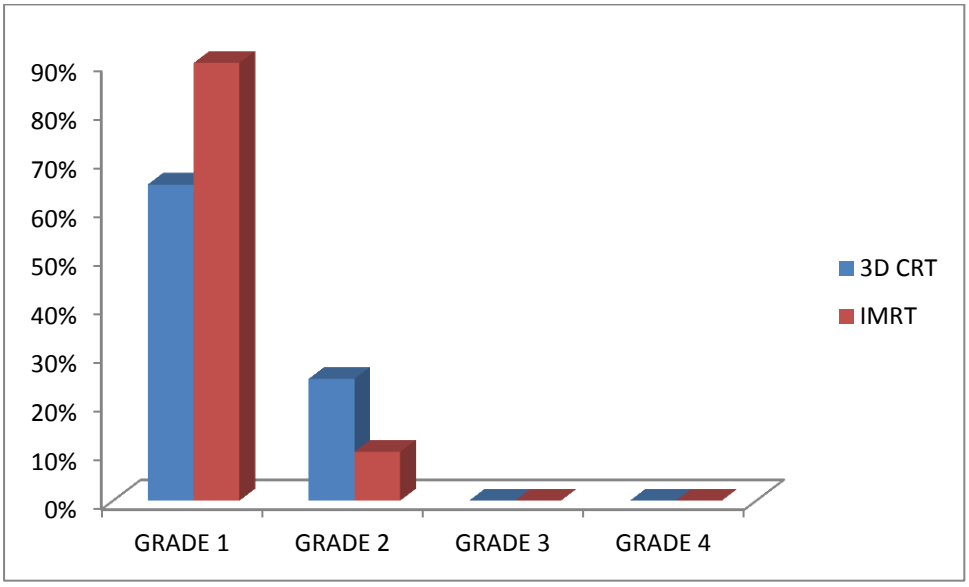
GRAPH 8: COMPARISON OF MUCOSITIS 90 DAYS POST RT IN IMRT AND IGRT GROUPS:



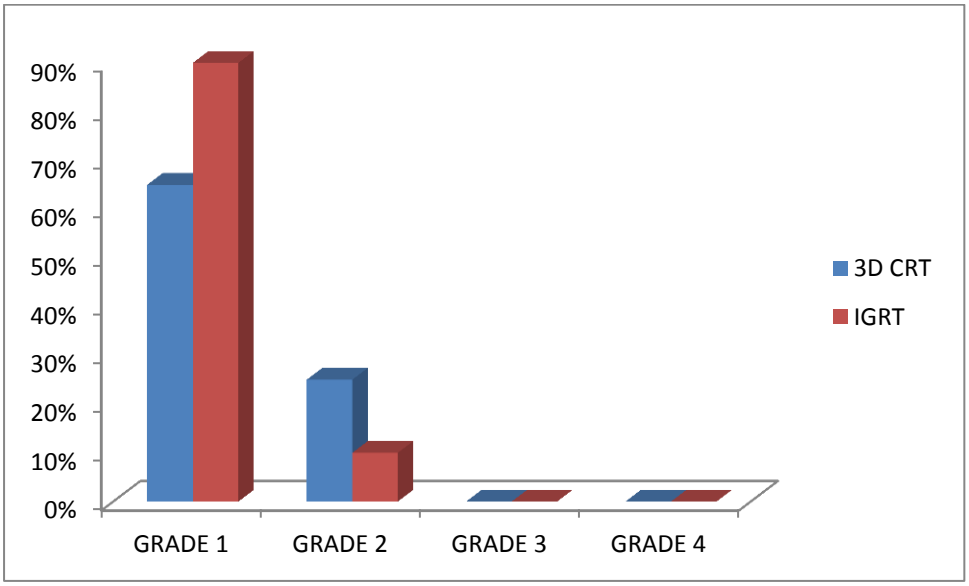
GRAPH 9: INCIDENCE OF SKIN REACTIONS POST RT IN 3D CRT, IMRT AND IGRT GROUPS:



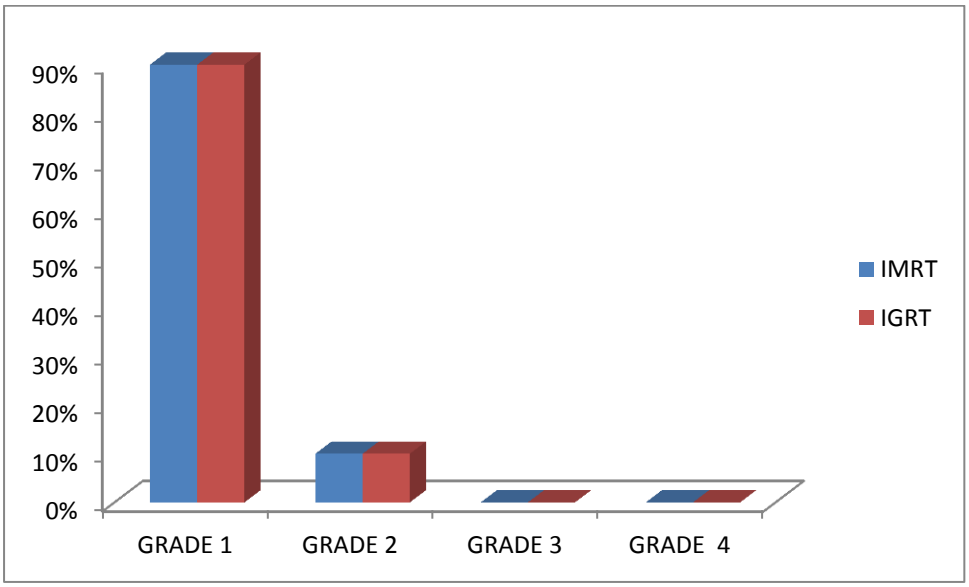
GRAPH 10: COMPARISON OF SKIN REACTIONS POST RT IN 3D CRT AND IMRT GROUPS:



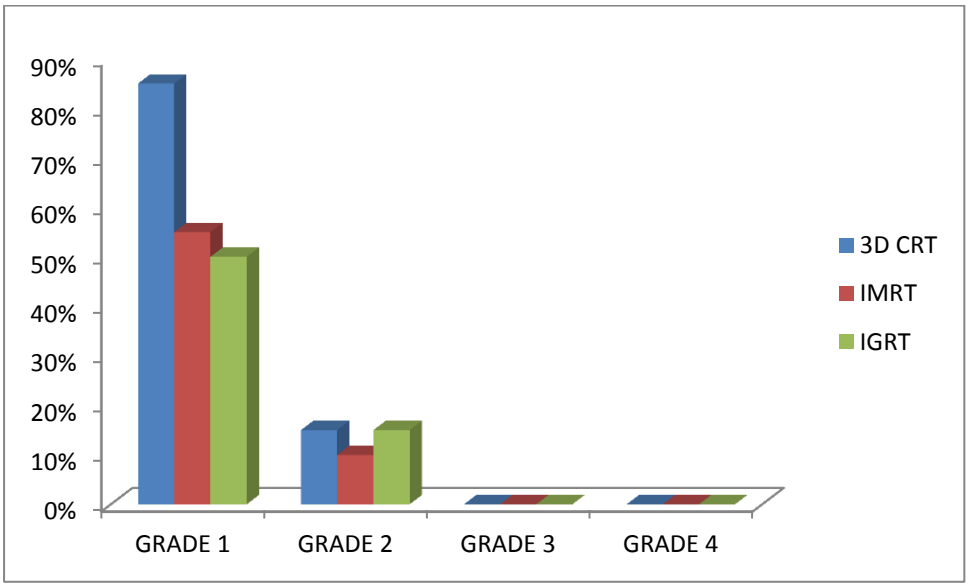
GRAPH 11: COMPARISON OF SKIN REACTIONS POST RT IN 3D CRT AND IGRT GROUPS:



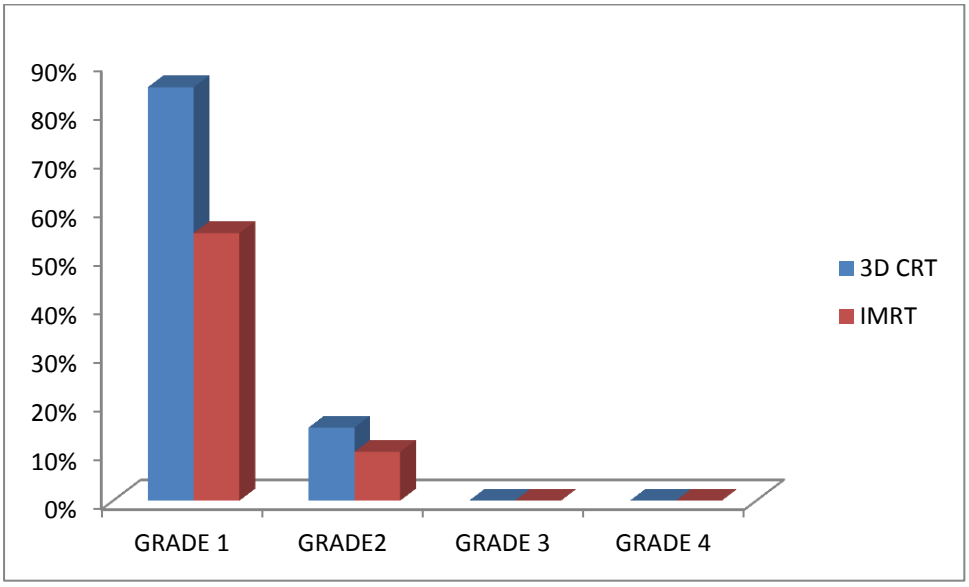
GRAPH 12: COMPARISON OF SKIN REACTIONS POST RT IN IMRT AND IGRT GROUPS:



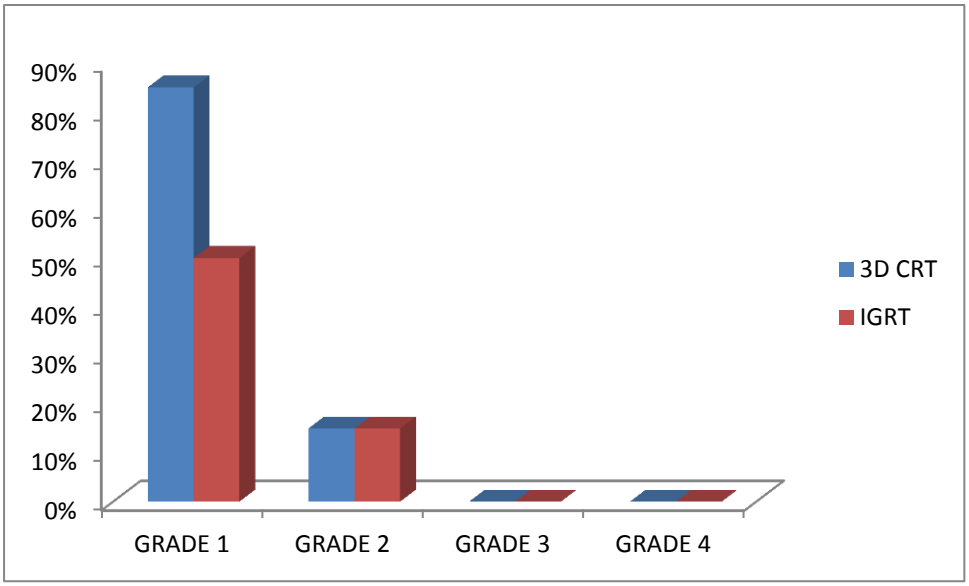
GRAPH 13: INCIDENCE OF SKIN REACTIONS90 DAYS POST RT IN 3D CRT, IMRT AND IGRT GROUPS:



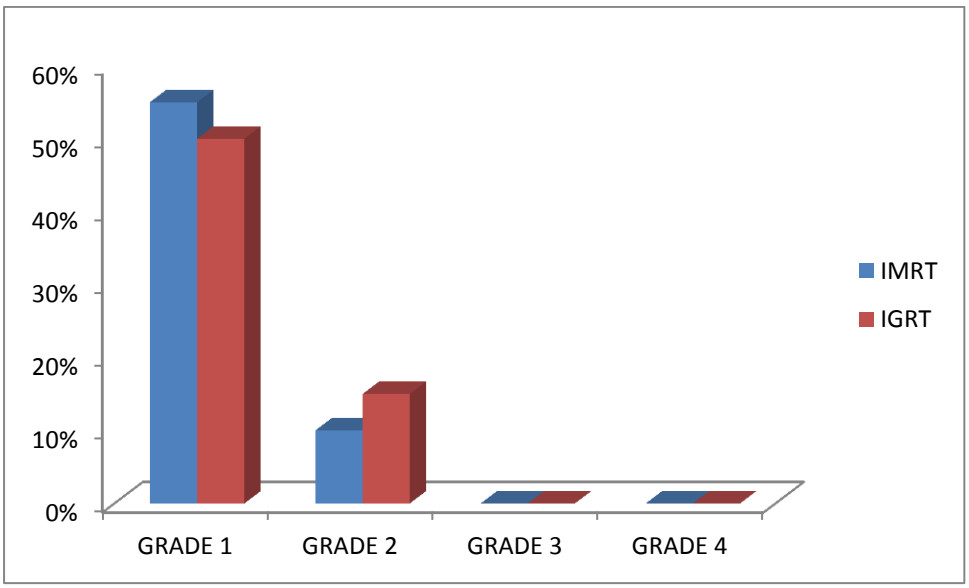
GRAPH 14: COMPARISON OF SKIN REACTIONS 90 DAYS POST RT IN 3D CRT AND IMRT GROUPS:



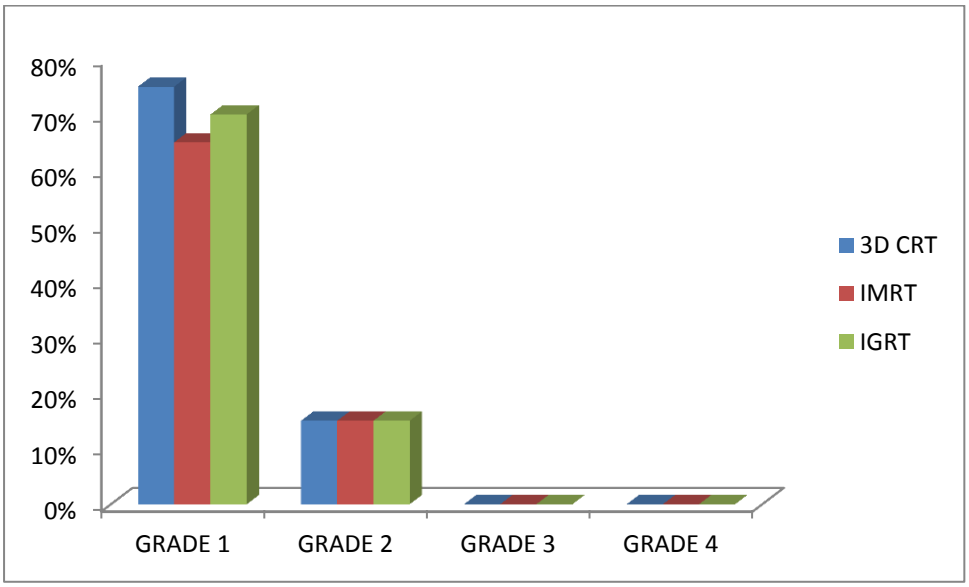
GRAPH 15: COMPARISON OF SKIN REACTIONS 90 DAYS POST RT IN 3D CRT AND IGRT GROUPS:



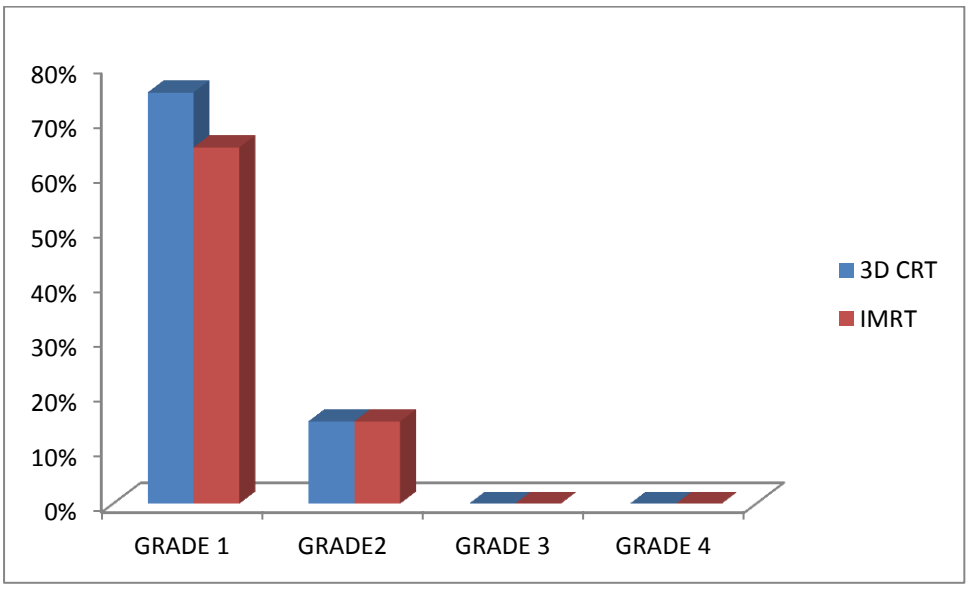
GRAPH 16 : COMPARISON OF SKIN REACTIONS 90 DAYS POST RT IN IMRT AND IGRT GROUPS:



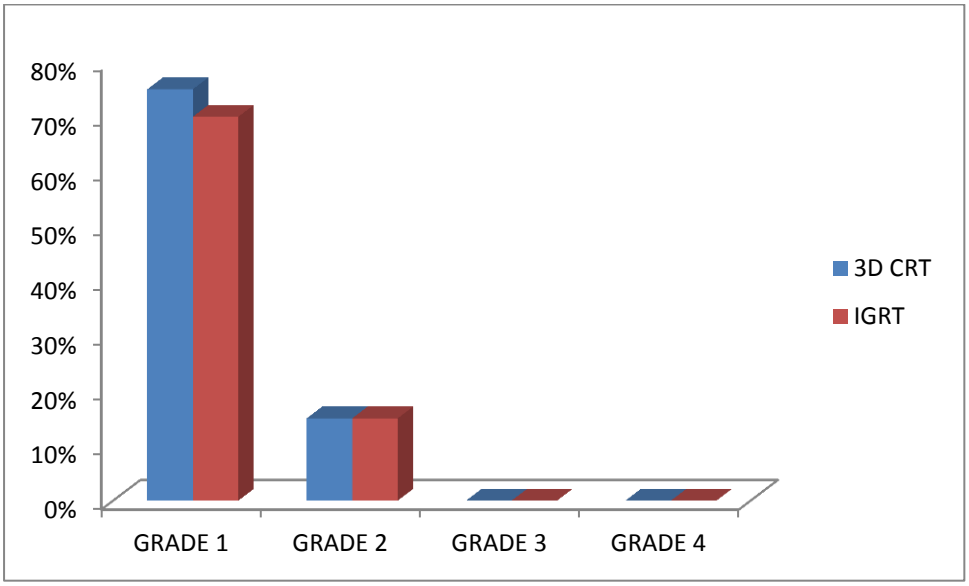
GRAPH 17: INCIDENCE OF XEROSTOMIA POST RT IN 3D CRT, IMRT AND IGRT GROUPS:



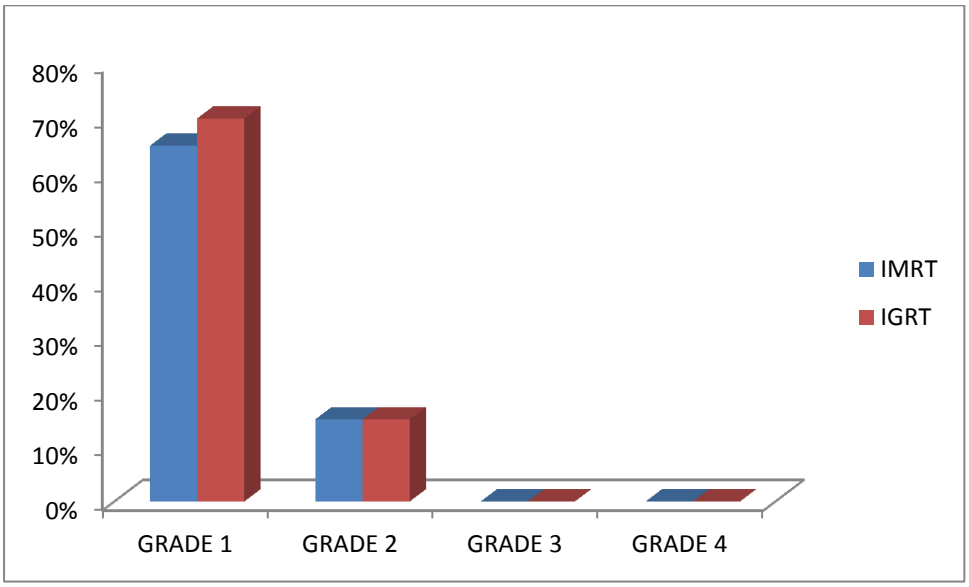
GRAPH 18: COMPARISON OF XEROSTOMIA POST RT IN 3D CRT, IMRT GROUPS:



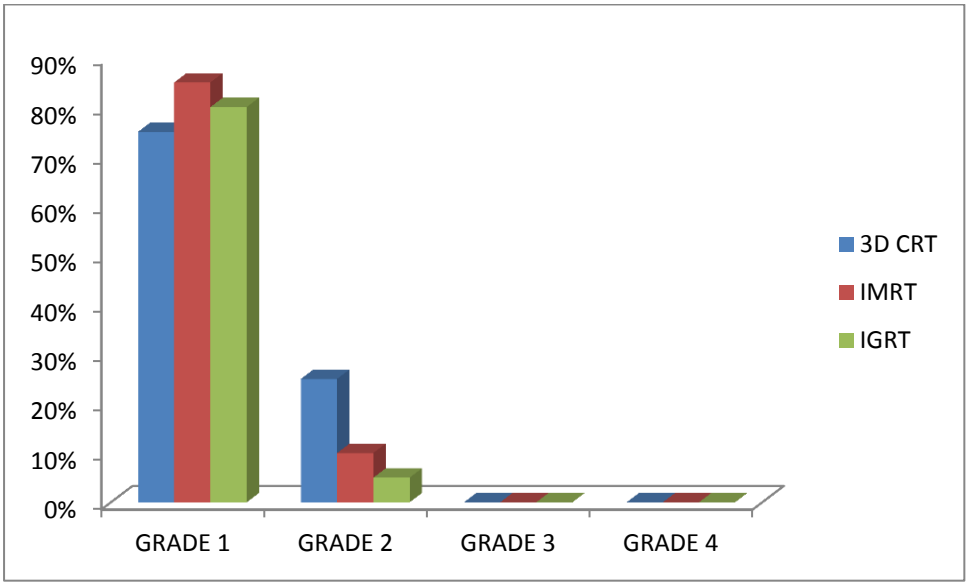
GPAPH 19: COMPARISON OF XEROSTOMIA POST RT IN 3D CRT AND IGRT GROUPS:



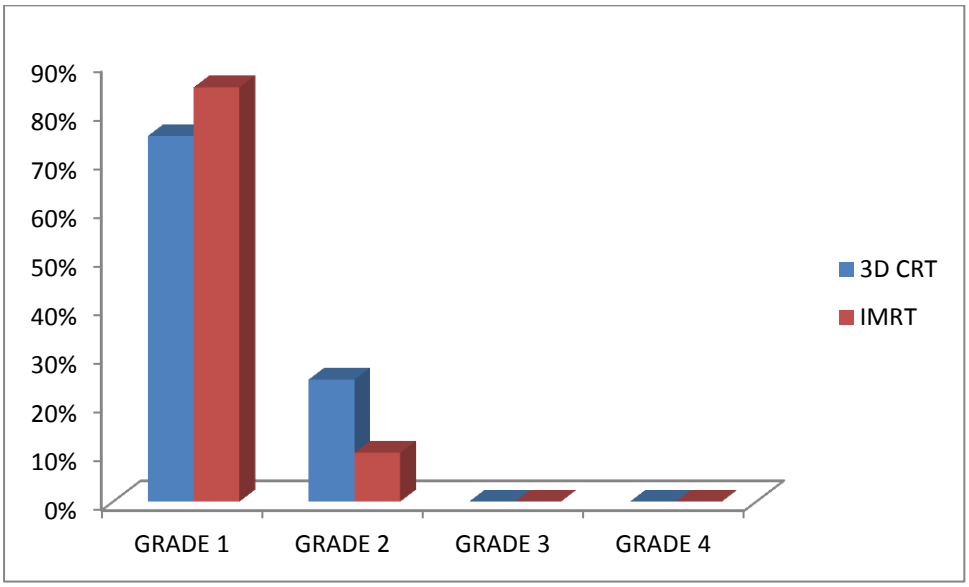
GRAPH 20 : COMPARISON OF XEROSTOMIA POST RT IN IMRT AND IGRT GROUPS:



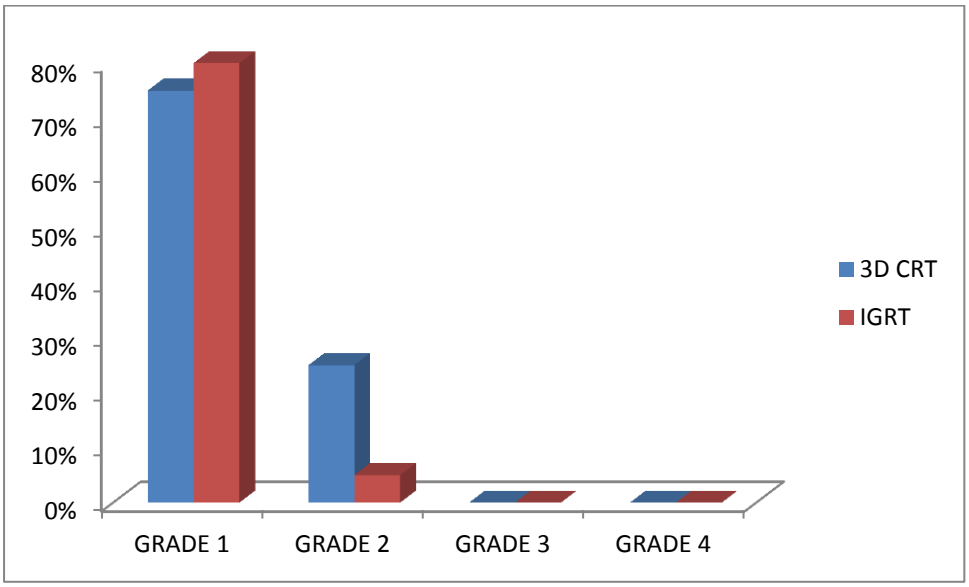
GRAPH 21: INCIDENCE OF XEROSTOMIA 90 DAYS POST RT IN 3D CRT, IMRT AND IGRT GROUPS:



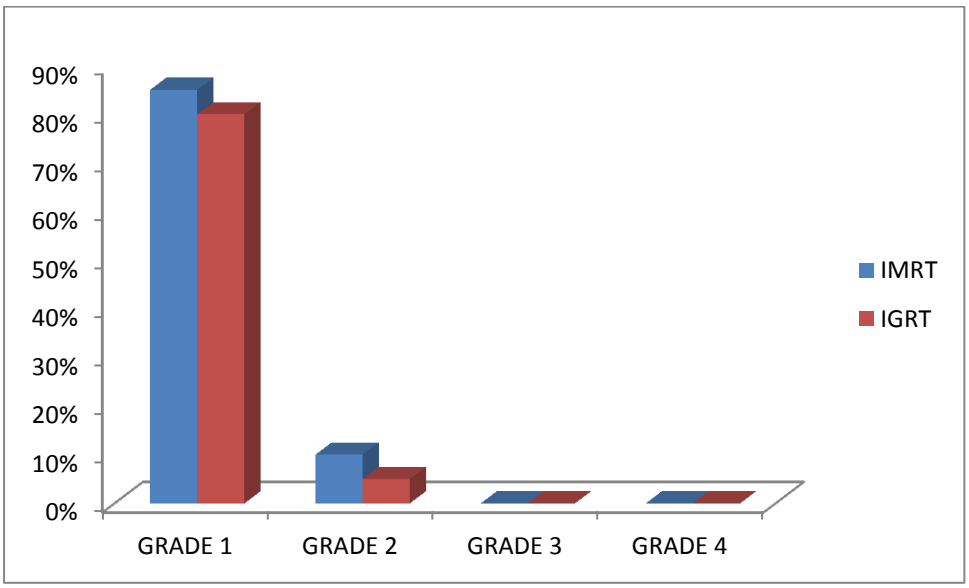
GRAPH 22: COMPARISON OF XEROSTOMIA 90 DAYS POST RT IN 3D CRT, IMRT AND GROUPS:



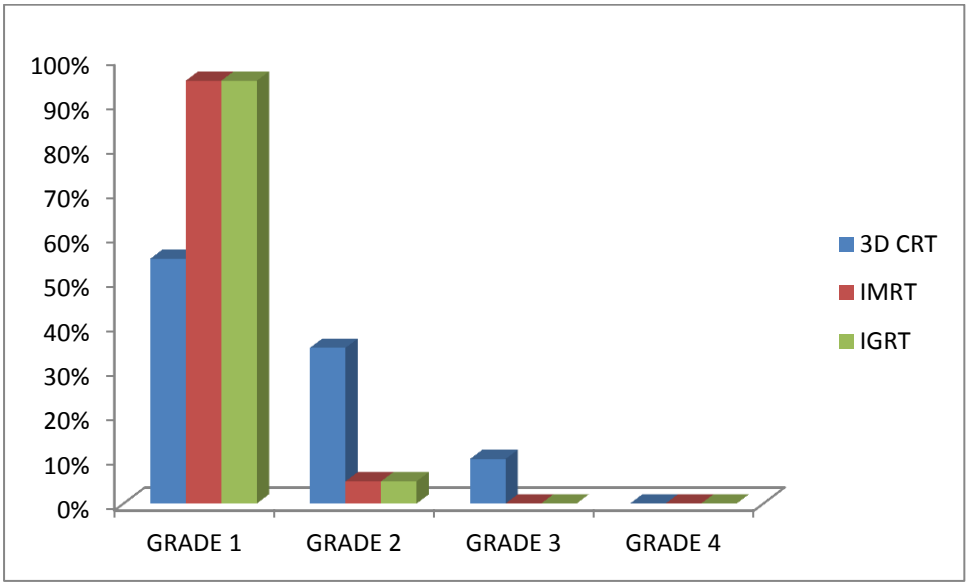
GRAPH 23: COMPARISON OF XEROSTOMIA 90 DAYS POST RT IN 3D CRT AND IGRT GROUPS:



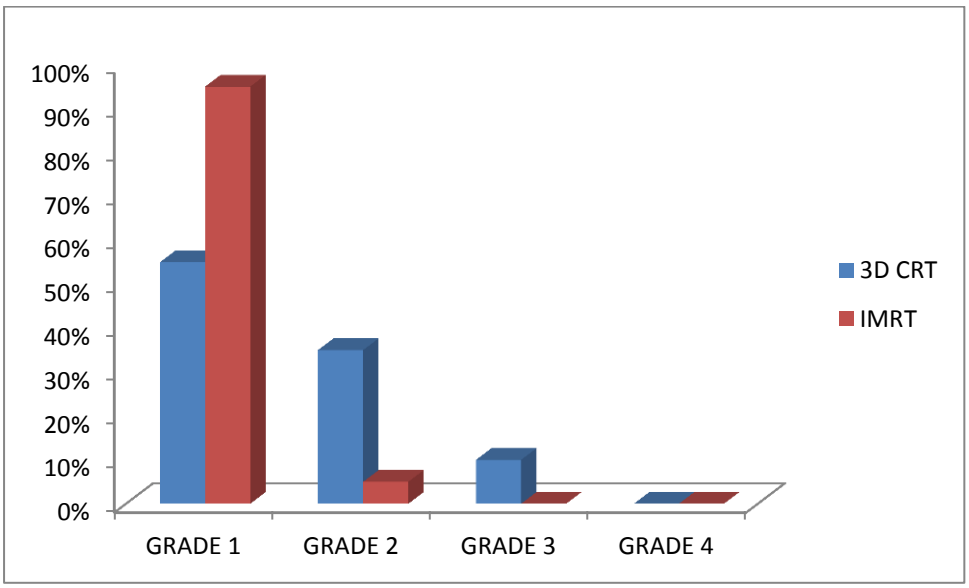
GRAPH 24: COMPARISON OF XEROSTOMIA 90 DAYS POST RT IN IMRT AND IGRT GROUPS:



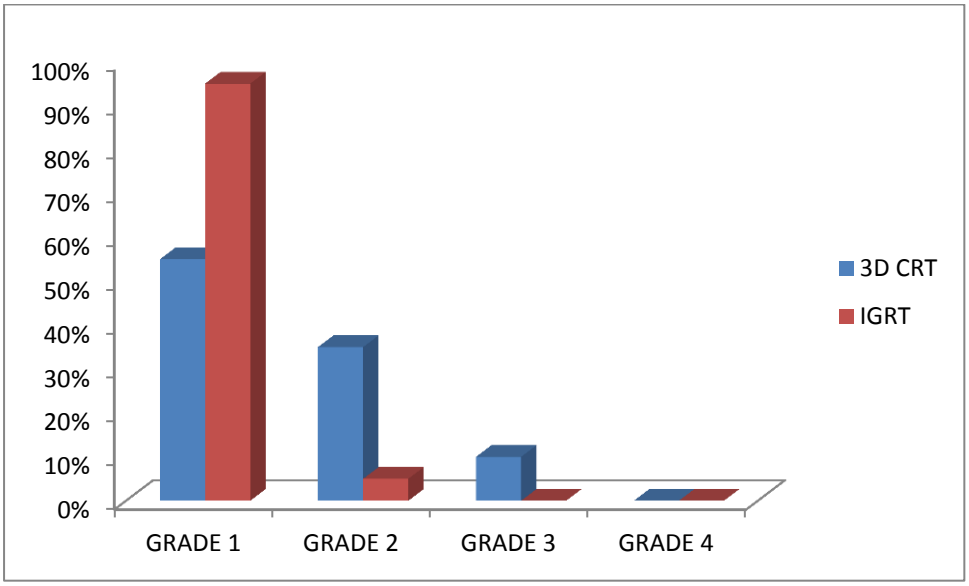
GRAPH 25: INCIDENCE OF DYSPHAGIA POST RT IN 3D CRT, IMRT AND IGRT GROUPS:



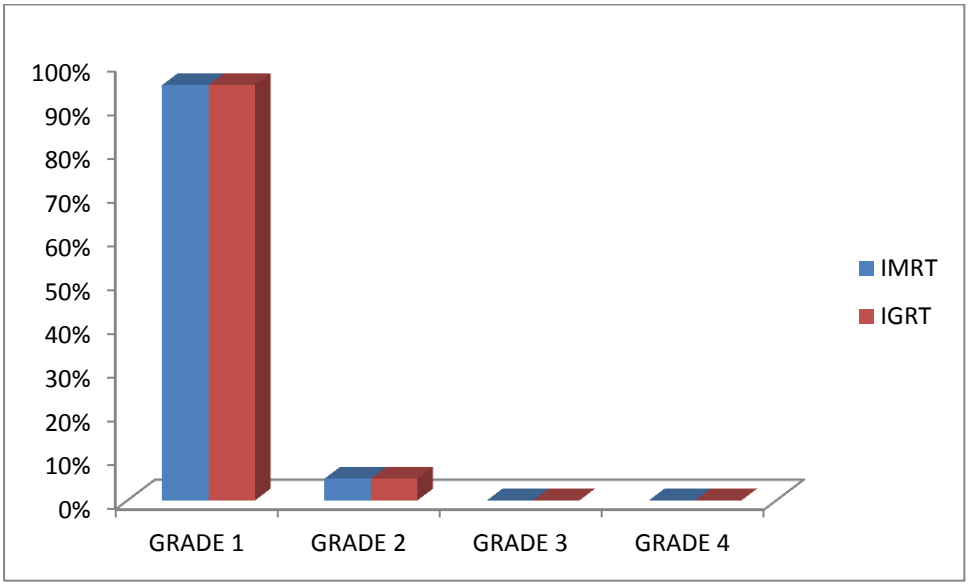
GRAPH 26: COMPARISON OF DYSPHAGIA POST RT IN 3D CRT AND IMRT GROUPS:



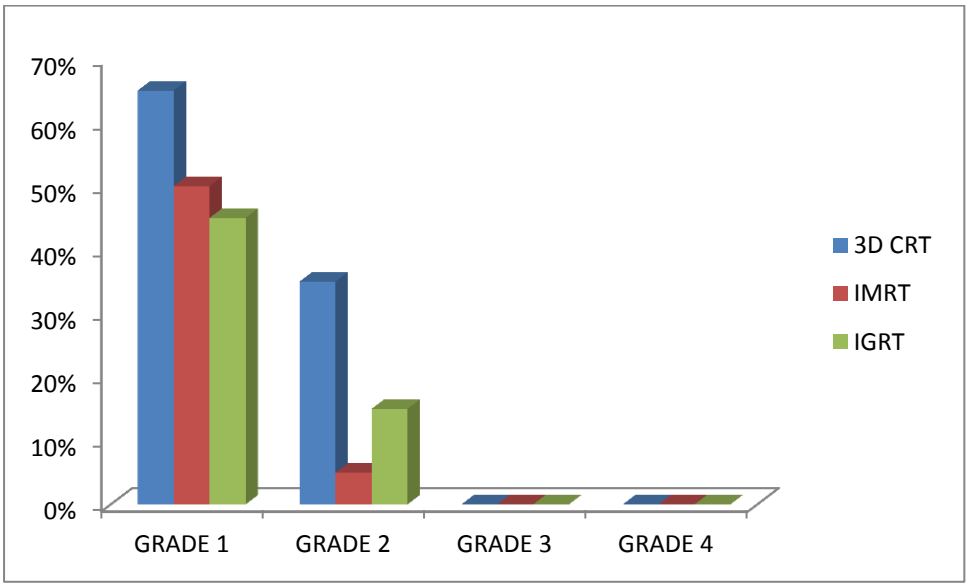
GRAPH 27: COMPARISON OF DYSPHAGIA POST RT IN 3D CRT AND IGRT GROUPS:



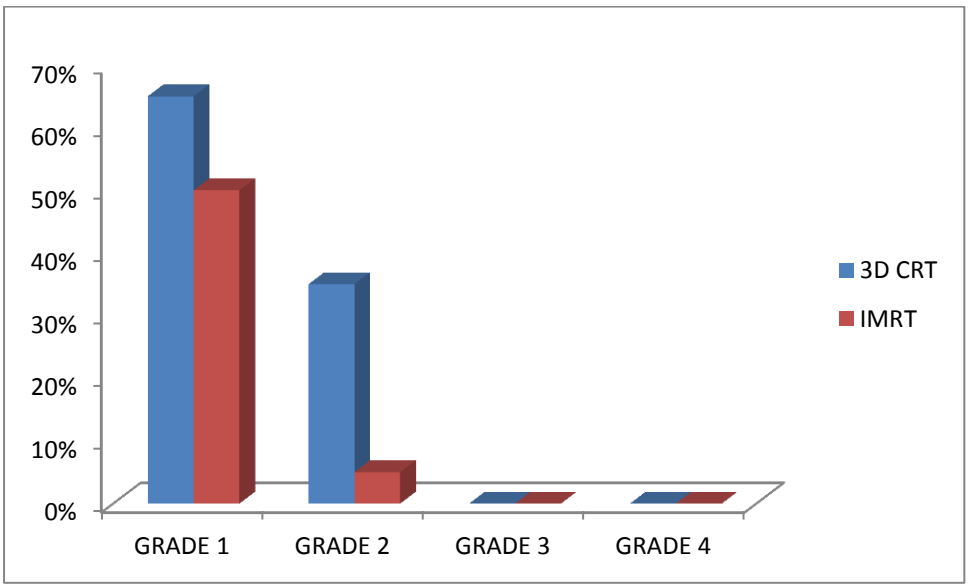
GRAPH 28: COMPARISON OF DYSPHAGIA POST RT IN IMRT AND IGRT GROUPS:



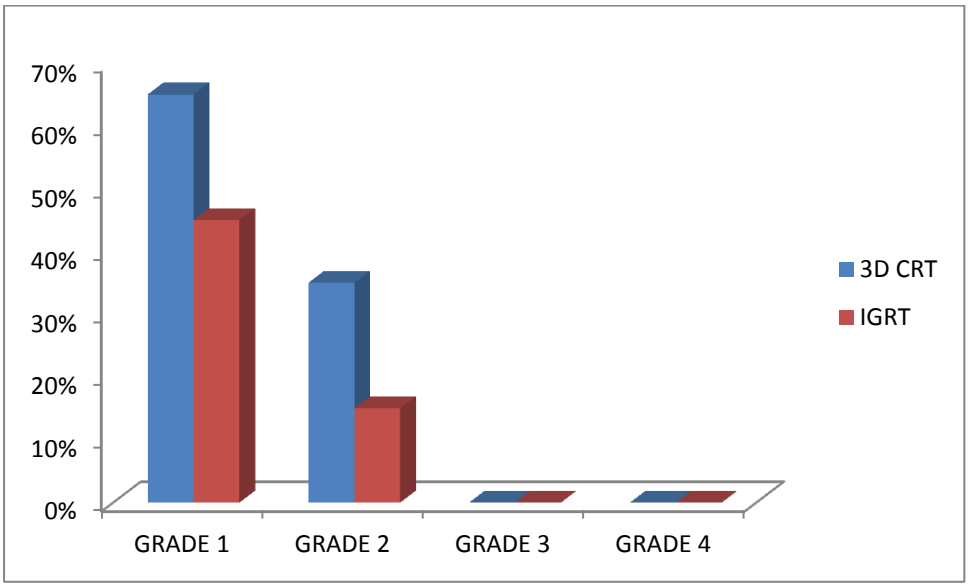
GRAPH 29: INCIDENCE OF DYSPHAGIA 90 DAYS POST RT IN 3D CRT, IMRT AND IGRT GROUPS:



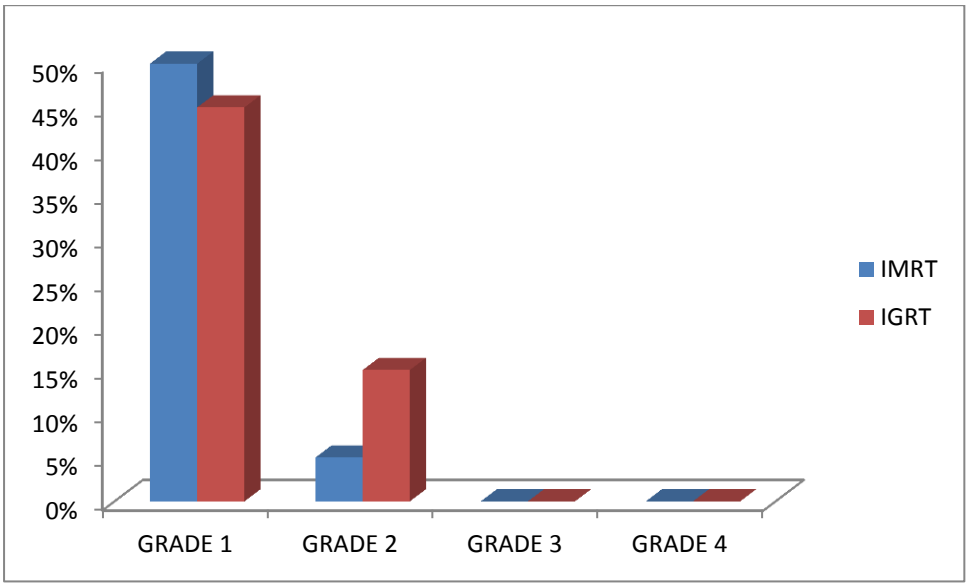
GRAPH 30: COMPARISON OF DYSPHAGIA 90 DAYS POST RT IN 3D CRT, IMRT GROUPS:



GRAPH 31: COMPARISON OF DYSPHAGIA 90 DAYS POST RT IN 3D CRT AND IGRT GROUPS:



GRAPH 32: COMPARISON OF DYSPHAGIA 90 DAYS POST RT IN IMRT AND IGRT GROUPS:



DISCUSSION

Among the different modes of treatment of oral cancer radiotherapy and chemotherapy remain the key modalities. By combining a chemotherapeutic agent with radiation, the efficacy of radiotherapy is increased and results in better tumour control and survival rates. Adjuvant chemoradiotherapy is used as an effort to completely eradicate advanced disease and metastases [28] External beam radiotherapy or teletherapy is the most frequently used form of radiotherapy. The shape and intensity of the electron beam produced by a Linac may be modified or collimated by a variety of means. Thus conventional, conformal, intensity modulated, tomographic and stereotactic RT are all produced by specially modified linear accelerators.

Conformal radiotherapy aims at an optimal dose distribution, which requires a sophisticated planning of radiation treatment. Substantial development and impressing improvements in the planning devices have lead to the advent of a new modality called **3 dimensional conformal radiotherapy (3D CRT)** [18] Here the radiation field conforms to the shape of the volume to be treated. To optimize the dose distribution, the clinical target volume (CTV) and the normal tissue must be defined with very high accuracy by the radiotherapist. The CTV contains the clinically evident tumour **(Gross tumour volume, GTV),** along with a margin of microscopic tumour spread which includes the lymphatics. The CTV has to obtain 100% of the radiation

dose with a dose distribution of highest homogeneity. Macroscopic tumour masses are detected by CT, MRI and biological activity of the tumour is detected by SPECT, PET etc. In order to ensure an optimum of precision and reproducibility in dose delivery and dose distribution, the positioning of the patient has to be identical during the diagnostic procedures, the process of treatment simulation, and the whole radiation treatment. This is achieved by a process called immobilization which includes devices like head holders with masks, foam molds and evacuated bags, so that the movement of almost any anatomical region of a cooperative patient can be reduced to less than 5 mm. External markers are placed on the immobilization device or/and the patient to delineate the coordinates system. After identical positioning of the target volume, the calculation of dose distribution is done. Using the fixation devices, and laser system, it is ensured that every point of the coordinates in the X-ray, CT or MRI device will be at the same coordinates in each scan of the patient. It is possible to study the shape of the different beams in comparison to the contour of the tumour by looking along the central axis of the beam (beam's eye view). Using the beam's eye view, the contour of every beam can be designed very close to the tumour border, after which dose calculation is performed. To compare different treatment plans on a numerical base, integrated dose-volume histograms (DVH) are used. The final procedure is the simulation and treatment procedure which includes the verification of the calculated plan by X-ray control. Following all the procedural steps carefully, a highly precise radiation dose is delivered.[18] However the radiation

intensity is uniform within each beam and the modulation is conferred only by wedges. Hence in order to further improve the therapeutic ratio ,to reduce the dose to the neighbouring normal tissues , and to achieve a better locoregional control there arose a need for the advent of a more conformal form of radiotherapy.

The advent of **intensity modulated radiotherapy (IMRT),** has ushered in a new paradigm that has completely revolutionized contemporary radiotherapy practice. This is a highly précised form of radiotherapy, delivering radiation beams with more than two intensity levels, from a single beam direction and a single source of position in space. It excludes beams that use a transmission block with a single attenuation level, standard dynamic or static wedges, single boost field inside the main field, as well as beams used in conformal arc therapy. The promise of generating highly conformal and concave dose distributions around complex target volumes with steep dose gradients makes IMRT ideally suited to Head and Neck Cancer. The heart of the process is a concept called inverse treatment planning in which the clinical objectives are specified mathematically and a computer optimization algorithm is used to automatically determine beam parameters (mainly beamlet weights) that will lead to the desired dose distribution. Optimization is an iterative process that balances the trade-off between target dose and coverage versus minimization of impact on normal tissues utilization a cost or objective function. The cost function is a mathematical description of criteria

of treatment plan optimization (i.e. clinical objectives) and may be specified in terms of dose-limits, dose-volume limits, dose-response functions, or other formulations.

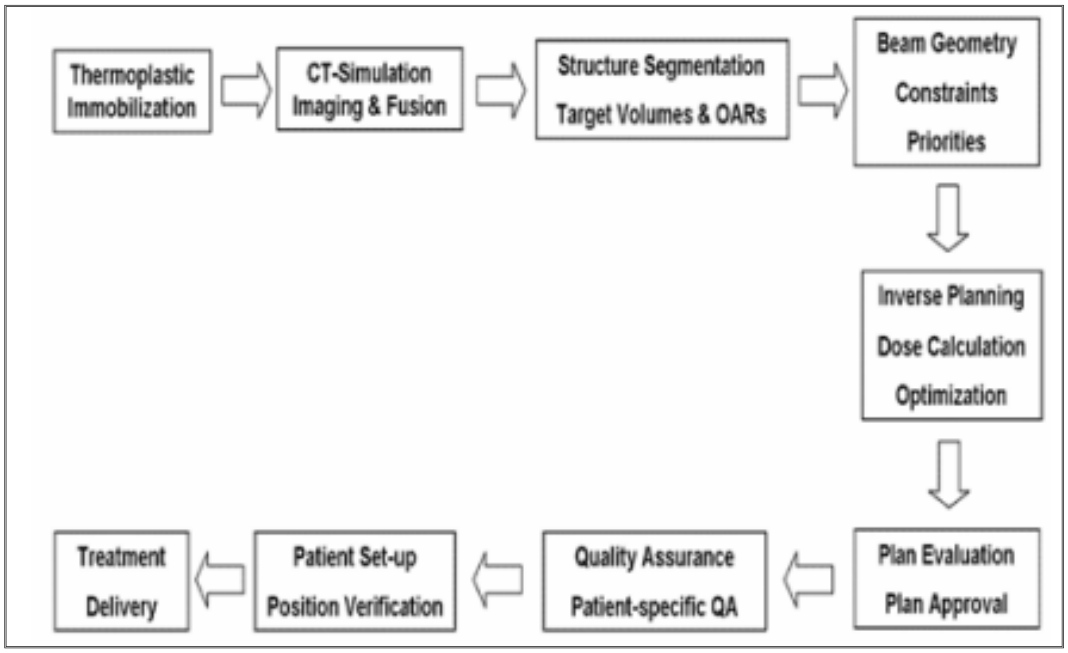


Figure 1:Intensity Modulated Radiotherapy Process Chain

The overall accuracy of IMRT depends upon mechanical isocentric accuracy of the delivery unit (gantry, collimator, couch), beam stability (at low monitor units and small filed sizes), multi-leaf collimator (MLC) system (leaf-travel and position accuracy, reproducibility) and its characterization into the treatment planning system (MLC leaf-end and side leakage, tongue-and-groove effect, penumbra modeling). Well-defined guidelines for tolerance limits and action levels pertaining to various aspects of IMRT dosimetry

including a credentialing mechanism has been proposed to ensure that what is planned is actually delivered**.**[25]

Image guided radiotherapy (IGRT) represents a logical advancement in the field of high precision radiotherapy and is a natural corollary to IMRT.[25] Some linacs have an on board Imager, an automated system that uses a high resolution X rays to produce contrasting images of cancerous tumours and surrounding soft tissue, allowing physicians to target the cancerous tumour more precisely during treatment and decreasing radiation exposure if healthy tissues. Before the on-board imager, physicians would have to treat a larger area of the body near the cancerous tumour to compensate for any tumour movement, exposing healthy tissue to the radiation. This technique is called image guided radiotherapy (IGRT) . The imaging equipment can also be kept inside the treatment room separately (CT on rail) to acquire the scans in the treatment position. Thus IMRT improves the radiation delivery precision by using multiple beam angles and giving distinct dose to each segment and IGRT improves the radiation delivery accuracy; thereby decreasing the volume of normal tissue being irradiated.[37]

Though radiation delivery methods and beam shaping has evolved continuously with novel methods, it is not without some pitfalls, the most important being acute and chronic toxicities that develop after radiotherapy. Toxicities that develop within 90 days from the beginning of radiotherapy are acute and that developing after 90 days are chronic**.** The most common acute

side effects are mucositis, skin reactions, dysphagia and xerostomia. The chronic toxicities that develop include difficulty in mouth opening due to fibrosis.[20] Thus acute and late toxicities of radiotherapy in cancer patients represent important clinical outcomes that can substantially reduce quality of life and the ability of individuals to complete the entire planned course of treatment.

Hence this has formed the basis of our study where we have explored the acute and chronic toxicity profiles associated with 3DCRT, IMRT and IGRT in oral cancer patients which would help us to further optimize the process and incorporate re planning strategies to obtain a even better locoregional control and thus produce a potential positive impact on the quality of life of the patient.

COMPARISON OF MUCOSITIS POST RT BETWEEN 3D CRT Vs IMRT and 3D CRT Vs IGRT GROUPS:

On comparing the mucositis occurring post RT between 3D CRT, IMRT and IGRT groups, among the 20 patients in the 3D CRT group 30% had grade 2 mucositis and 70% had grade 3 mucositis , among the 20 patients in the in the IMRT group 10% had grade 1 mucositis and 90% had grade 2 mucositis and aming the 20 patients in the IGRT group 15% had grade 1 mucositis and 85% had grade 3 mucositis .The P value is statistically highly significant between 3D CRT and IMRT groups (0.000) , and 3D CRT and

IGRT groups (0.000) and statistically insignificant between IMRT and IGRT (0.912).

The results of our study are in accordance with the results of the studies conducted by **Vergeer et al(2009)[62], Micheal J Spitto et al (2014)[42] Gopa Gosh et al (2016)[20], and Ajay Singh Choudhary et al (2017)[1].**

Vergeer et al (2009)[62] performed a study compare the mucositis grading in 91 patients in the IMRT group and 150 patients in the 3D CRT group and found there was a significant difference in acute mucositis in favour of IMRT in weeks 3,4,5 and 12 after treatment with a P value ranging from 0.006 to 0.016

Micheal Spitto et al (2014)[42] did a study to compare the toxicity profiles during treatment with 3D CRT, IMRT with SIB and IMRT without SIB with a statistically highly significant with a P value of <0.001 in favour of IMRT with or without SIB

Gopa Gosh et al (2016)[20] conducted a study to compare the toxicity profiles among 3D CRT and IMRT patients in a sample size of 80 patients , out of the 40 patients in the 3D CRT group, 57.5% were found to have grade 3 mucositis and out of the 40 patients in the IMRT group, 40% were found to have grade 3 mucositis which demonstrated significant results.

Ajay Singh Choudhary et al (2017)[1] compared the toxicity profiles during treatment of head and neck cancer with 3D CRT and IMRT in a sample

size of 150 patients , and found that significantly higher grade 3 or worse mucositis occurred in 57.6% of the 3D CRT group and 39.7% of patients in the IMRT group with a P value of 0.03 which was statistically highly significant.

The results of our study are in contradiction to the results of the studies conducted by **Gupta et al (2012)[24]** and **Tim Kruser et al (2013)[59]** .

Gupta et al (2012)[24] did a study to compare acute mucositis between 3D CRT and IMRT in a group of 60 patients and found no statistical difference between groups, while comparing grade 2 and grade 3 mucositis , but had a statistical difference in grade I mucositis.

This contradiction may be due to the fact that the site of primary tumour also has influence on mucositis. When a more conformal technique such as IMRT is given to primary tumours located in or near the oral cavity, it might result in higher mucositis because of the higher dose given to that region. Moreover in their study a statistical difference was obtained in grade 2 mucositis.

Tim J Kruser et al (2013)[59] compared the acute mucositis grading in patients undergoing 3D CRT, IMRT and helical tomotherapy in a sample of 108 patients, and found that the results of the study were not statistically significant with a P value of 0.20 in contradiction to the results of our study.

COMPARISON OF MUCOSITIS 90 DAYS POST RT IN 3D CRT Vs IMRT GROUPS AND 3D CRT Vs IGRT GROUPS:

On comparing the grades of mucositis occurring 90 days after RT between 3D CRT ,IMRT and IGRT groups, among the of the 20 patients, in 3D CRT group, 50% had grade 1 mucositis, 50% had grade 2 mucositis and out of the 20 patients in the IMRT group, 80% had grade I mucositis and 20% had grade 2 mucositis and among the 20 patients in the IGRT group 90% had grade 1 mucositis and 10% had grade 2 mucositis. The P value is statistically insignificant between the 3D CRT and IMRT groups (0.069) and statistically significant between 3D CRT and IGRT groups (0.010) and statistically insignificant between IMRT and IGRT groups (0.732).

Though statistically insignificant results between the groups of patients were obtained the number of patients affected by grade 2 mucositis in 3D CRT was more when compared to the number of patients in the IMRT group.

COMPARISON OF SKIN REACTIONS POST RT IN 3D CRT Vs IMRT and 3D CRT Vs IGRT GROUPS:

On comparing the skin reactions occurring post RT between 3D CRT, IMRT and IGRT groups, among the 20 patients in the 3D CRT group 65% had grade 1 skin reactions , 25% had grade 2 reactions and out of the 20 patients in the IMRT group 90% had grade I skin reactions and 10% had grade 2 skin reactions and out of the 20 patients in the IGRT group 90% had grade

1 skin reactions and 10% had grade 2 skin reactions. The P value is statistically significant between 3D CRT and IMRT groups (0.004) and statistically significant between 3D CRT and IGRT groups (0.002) and statistically insignificant between IMRT and IGRT groups (0.969).

COMPARISON OF SKIN REACTIONS 90 DAYS POST RT IN 3D CRT Vs IMRT GROUPS AND 3D CRT Vs IGRT GROUPS:

On comparing the skin reactions occurring 90 days post RT between 3D CRT, IMRT and IGRT groups, among the 20 patients in the 3D CRT group 85% had grade 1 skin reactions , 15% had grade 2 reactions and out of the 20 patients in the IMRT group 55% had grade I skin reactions and 10% had grade 2 skin reactions and out of the 20 patients in the IGRT group 50% had grade 1 skin reactions and 15% had grade 2 skin reactions. The P value is statistically highly significant between 3D CRT and IMRT groups (0.000) and statistically highly significant between 3D CRT and IGRT groups (0.000) and statistically insignificant between IMRT and IGRT groups (0.679).

The results of our study are in accordance with the results of the study conducted by **Micheal J Spitto et al (2014)[42] Gopa Gosh et al (2016)[20]** .

Micheal J Spitto et al (2014)[42], performed a study to compare the toxicity profiles of radiotherapy in a sample of 379 subjects, out of the 125 patients treated with 3D CRT, 44% demonstrated grade 3 or greater dermatitis, out of the 120 patients treated with IMRT seq, 20.0% demonstrated grade 3 or

greater dermatitis and out of the 134 patients treated with IMRT +SIB, 7.5% demonstrated grade 3 or greater dermatitis and the result were statistically highly significant with a P value of <0.001.

Gopa Gosh et al (2016)[20] compared the acute and chronic toxicity in a sample of 80 subjects, out of the 40 patients in the 3D CRT group, acute grade 3 or greater toxic effects occurred in 5 (12.5%) of the patients and out of the 40 patients in the IMRT group, acute grade 3 or greater toxic effects to the skin occurred in 3(7.5%) of the patients which showed a significant difference.

The results of our study are not in accordance with the results of the studies done by **Tejpal Gupta et al (2012)[58] , Ajay Singh Choudhary et al (2017)[1]**

Tejpal Gupta (2012)[58] did a study to compare the toxicity profiles in patients with 3D CRT and IMRT modes in a sample of 60, out of the 28 patients in the 3D CRT group, 14.5% developed grade 3 dermatitis and out of the 32 patients in the IMRT group , 6% developed grade 3 dermatitis and the results of the study were not statistically significant.

Though a statistically significant result was not obtained by their study , there were significantly less number of patients affected by dermatitis in IMRT group compared to 3D CRT group.

Ajay Singh Choudhary et al (2017)[1] did a study to compare the toxicity profile in patients with IMRT and 3D CRT modes in a sample of 150 patients, out of the 92 patients in the 3D CRT group, grade 3 or greater dermatitis occurred in 87% of the patients and out of the 58 patient in the IMRT group, 93.1% had grade 3 or greater dermatitis and the results of the study did not give statistically significant results.

This variation may be due to the fact that there was uneven distribution of study population where 3D CRT group has 92 patients and IMRT group has only 58 patients which might have lead to statistically insignificant results.

COMPARISON OF XEROSTOMIA POST RT IN 3D CT Vs IMRT GROUPS AND 3D CRT Vs IGRT GROUPS:

On comparing the xerostomia occurring post RT between 3D CRT, IMRT and IGRT groups, among the 20 patients in the 3D CRT group , 75% had grade 1 xerostomia , 15% had grade 2 xerostomia and out of the 20 patients in the IMRT group, 65% had grade I xerostomia and 15% had grade 2 xerostomia and out of the 20 patients in the IGRT group, 70% had grade 1 xerostomia and 15% had grade 2 xerostomia. The P value is statistically insignificant between 3D CRT and IMRT groups (1.000) and statistically insignificant between 3D CRT and IGRT groups (0.532) and statistically insignificant between IMRT and IGRT groups (0.532).

The results of our study are in contradiction to the results of the studies conducted by **Bramm et al (2006)[8], Tejpal Gupta et al (2012)[58], Gupta et al (2012)[24] and Gopa Gosh et al (2016)[20].**

Bramm et al (2006)[8] conducted a study to compare the salivary flow in a group of 56 patients and the results showed significant difference in the salivary flow with 87% of the patients affected by xerostomia in the 3D CRT group and 55% of the patients affected by xerostomia in the IMRT group with a P value of 0.002.

Tejpal Gupta et al (2012)[58], compared the toxicity profiles in 3D CRT and IMRT patients in a sample of 60 patients, out of the 28 patients in the 3D CRT group, Grade 2 xerostomia was seen in 25(89%) of the patients and out of the 32 patients in the IMRT group, Grade 2 xerostomia was seen in 19 (59%) of the patients which showed statistically significant differences.

Gupta et al(2012)[24] conducted a study in which it was found that 89 % of patients had grade 2 or worse acute xerostomia in the 3D CRT group compared to 59% in the IMRT group and it was statistically significant with a P value of 0.009

Gopa Gosh et al (2016)[20] had conducted a study to compare xerostomia in the 3D CRT and IMRT groups in a sample of 80 patients, out of the 40 in the 3D CRT group, grade 3 xerostomia developed in 72.5% of the patients and

out of the 40 patients in the IMRT group, grade 3 xerostomia developed in 45% of the patients showing statistically significant differences.

The results of our study are in contradiction to the results of the study conducted above as they have included patients where the planned RT has been given in site specific locations sparing the parotids, but in our study all the cancers of the oropharyngeal regions have been included , which could have an effect on the parotid secretions.

COMPARISON OF XEROSTOMIA 90 DAYS POST RT IN 3D CRT Vs IMRT GROUPS AND 3D CRT Vs IGRT GROUPS:

On comparing the xerostomia occurring 90 days post RT between 3D CRT, IMRT and IGRT groups, among the 20 patients in the 3D CRT group, 75% had grade 1 xerostomia, 25% had grade 2 reactions and among the 20 patients in the IMRT group, 85% had grade I xerostomia and 10% had grade 2 xerostomia and among the 20 patients in the IGRT group, 80% had grade 1 xerostomia and 5% had grade 2 xerostomia. The P value is statistically highly significant between 3D CRT and IMRT groups (0.000) and statistically highly significant between 3D CRT and IGRT groups (0.000) and statistically insignificant between IMRT and IGRT groups (0.497).

The results of our study are in accordance with the results obtained in the studies of **Bramm et al (2006)[8], Nutting et al (2011)[48], Ajay Singh Choudhary et al (2017)[1].**

Bramm et al (2006)[8] have conducted a study to compare the chronic toxicity in xerostomia in patients undergoing CRT (2D CRT and 3D CRT) and IMRT and found that after 6 months, the difference in the xerostomia levels was 81% in the CRT group and 56% in the IMRT group with a P value of 0.04 which was statistically significant.

Nutting et al (2011)[48] performed a study to compare the toxicity profiles in patients undergoing 3D CRT and IMRT modes of treatment , in the sample size of 94 patients. A 12 month follow-up demonstrated that grade 2 or worse xerostomia was significantly lower in IMRT group compared to the 3D CRT group with a statistically significant difference with a P value of < 0.001.

Ajay Singh Choudhary et al (2017)[1] did a study compare the toxicity profiles in patients undergoing 3D CRT and IMRT modes of radiotherapy, in a sample of 150 patients, out of the 92 patients in the 3D CRT group, grade 2 or greater xerostomia was seen in 58 (63%) of the patients and out of the 58 patients in the IMRT group grade 2 or greater xerostomia developed in 12 (20.7%) of the patients, which showed a statistically significant difference of < 0.001.

COMPARISON OF DYSPHAGIA POST RT IN 3D CRT Vs IMRT AND 3D CRT Vs IGRT GROUPS:

On comparing the dysphagia occurring post RT between 3D CRT, IMRT and IGRT groups, among the 20 patients in the 3D CRT group, 55% had grade 1 dysphagia , 35% had grade 2 dysphagia, 10% had grade 3 dysphagia and among the 20 patients in the IMRT group 95% had grade I dysphagia and 5% had grade 2 dysphagia and among the 20 patients in the IGRT group 95% had grade 1 dysphagia and 5% had grade 2 dysphagia. The P value is statistically highly significant between 3D CRT and IMRT groups (0.000) and statistically highly significant between 3D CRT and IGRT groups (0.000) and statistically insignificant between IMRT and IGRT groups (0.966).

COMPARISON OF DYSPHAGIA 90 DAYS POST RT IN 3D CRT Vs IMRT AND 3D CRT Vs IGRT GROUPS:

On comparing the dysphagia 90 days post RT between 3D CRT, IMRT and IGRT groups, among the 20 patients in the 3D CRT group,65% had grade 1 dysphagia , 35% had grade 2 dysphagia, and among the 20 patients in the IMRT group 50% had grade I dysphagia and 5% had grade 2 dysphagia and among the 20 patients in the IGRT group 45% had grade 1 dysphagia and 15% had grade 2 dysphagia. The P value is statistically significant between 3D CRT and IMRT groups (0.001) and statistically highly significant

between 3D CRT and IGRT groups (0.000) and statistically insignificant between IMRT and IGRT groups (0.903).

The results of our study are in accordance with the results obtained from the studies of **Manan Trivedi et al (2015)[39], Gopa Gosh et al (2016)[20], Ajay Singh Choudhary et al (2017)[1].**

Manan Trivedi et al (2015)[39] have conducted a study to compare the toxicity profiles in 2D CRT, 3D CRT, IMRT and IGRT modes of radiotherapy and it was found that in the 3rd week after radiotherapy in the 2D CRT and 3D CRT group dysphagia was demonstrated in 33.3% and 54.5% respectively. In the 4th week after radiotherapy, dysphagia was demonstrated in 48.78% in the IMRT and 47.5% in the IGRT group respectively which showed significant difference between 3D CRT with IMRT and 3D CRT with IGRT and insignificant differences between IMRT and IGRT.

Gopa Gosh et al (2016)[20] have done a study to compare the toxicity profiles between patients treated in 3D CRT and IMRT modes of radiotherapy, in a sample of 80 patients, out of the 40 in the 3D CRT group grade 2 dysphagia was seen in 34 (85%) of patients and grade 2 dysphagia was seen in 23 (57.5%) of patients in 3D CRT group which showed a statistically significant results with a P value of 0.013

Ajay Singh Choudhary et al (2017)[1] performed a study to compare the acute dysphagia in patients treated in 3D CRT and IMRT modes of

radiotherapy in a sample of 150 patients, out of the 92 in the 3D CRT group, grade 3 on greater dysphagia occurred in 84.4% of the patients and out of the 58 patients in the IMRT group, grade 3 or greater occurred in 56.9% of the patients which showed a statistically significant result with a P value of < 0.001.

The results of our study are in contradiction to the results of the study conducted by **Tejpal Gupta et al (2012)[58].**

In a study conducted by **Tejpal Gupta et al (2012)[58]** in a sample of 60 patients in the 3D CRT and IMRT groups, out of the 28 patients in the 3D CRT group, grade 3 dysphagia was demonstrated in none of the patients and out of the 32 patients in the IMRT group grade 3 dysphagia was demonstrated in 3 (9.5%) with a P value of 0.21 which was not statistically significant.

Though statistically insignificant results were obtained from the study, the percentage of patients affected by grade 2 or greater dysphagia by 3D CRT is 71.5% and is greater compared that of IMRT where the percentage of patients affected by grade 2 or dysphagia is 59.3% and could be due to the differences in the midline protection contouring and the location of the primary tumour site.

SUMMARY AND CONCLUSION

The present study was conducted to assess and compare the toxicity profiles in head and neck cancer patients undergoing 3D CRT, IMRT and IGRT modes of radiotherapy.

A total of 60 patients were included in the study which included 20 patients in the 3D CRT group, 20 patients in the IMRT group and 20 patients in the IGRT group.

The results of the study could be summarised as follows:

- On comparing mucositis occurring post RT between 3D CRT and IMRT it was found that there was a statistically highly significant difference between the groups with a P value of 0.000 and between 3D CRT and IGRT it was found that there was a statistically highly significant difference between the groups with a P value of 0.000. On comparing mucositis occurring 90 days post RT between 3D CRT and IGRT it was found that there was a statistically significant difference of 0.010.
- On comparing skin reactions occurring post RT between 3D CRT and IMRT it was found that there was a statistically significant difference between the groups with a P value of 0.004 and between 3D CRT and IGRT it was found that there was a statistically significant difference between the groups with a P value of 0.002 . On comparing skin reactions occurring 90 days post RT between 3D CRT and IMRT it

was found that there was a statistically highly significant difference between the groups with a P value of 0.000 and between 3D CRT and IGRT it was found that there was a statistically highly significant difference between the groups with a P value of 0.000.

- On comparing xerostomia occurring 90 days post RT between 3D CRT and IMRT it was found that there was a statistically highly significant difference between the groups with a P value of 0.000 and between 3D CRT and IGRT it was found that there was a statistically highly significant difference between the groups with a P value of 0.000.
- On comparing dysphagia occurring post RT between 3D CRT and IMRT it was found that there was a statistically highly significant difference between the groups with a P value of 0.000 and between 3D CRT and IGRT it was found that there was a statistically highly significant difference between the groups with a P value of 0.000. On comparing dysphagia occurring 90 days post RT between 3D CRT and IMRT it was found that there was a statistically highly significant difference between the groups with a P value of 0.000 and between 3D CRT and IGRT it was found that there was a statistically highly significant difference between the groups with a P value of 0.000.In our study we have compared the toxicity profiles between IMRT and IGRT groups and have not obtained any statistically significant differences between the two groups.

In all the studies conducted so far IMRT and IGRT have been considered together as a single treatment arm and it's toxicity profiles have been compared with other conformal techniques. With the results obtained from the present study though IMRT and IGRT modes of radiotherapy are technically similar the difference in cost between the two modes for treatment delivery is huge and hence it should be justified that IMRT is as efficoaus as IGRT with minimum toxicities.

The results of this study point to the fact that intensity of the side effects of radiotherapy depend not only on the dosage of the therapy but also on the type of radiotherapy being given to the patients. Also, it can be seen that onset of side effects also depends on the stage of radiotherapy. Mucositis is the unavoidable side effect of radiotherapy and occurs in all the patients undergoing any form of radiotherapy. Other acute toxic effects seen were dysphagia and dryness of mouth. Decreased salivation was seen as a minor side effect in all the therapies. Though all these side effects were seen in all therapies, the onset of the effects and the percentage of patients suffering was different and for almost all effects, IMRT and IGRT proved to be a better treatment option as almost all the side effects occurred relatively later as compared to 3D CRT therapy and the number of patients suffering were smaller when compared to 3D CRT. Also, modern IMRT delivery techniques do not appear to result in increased toxicities in HNSCC patients undergoing high dose radiation with concurrent chemotherapy. Within the limitations of

our study, it is suggestive of IMRT being as effective as other treatment strategies for locally advanced head and neck cancer and provides better outcomes in terms of toxicity as compared to conventional techniques. The small number of patients and relatively short follow up remains the major limitations of the present study and further studies with larger group and long term follow up is recommended.

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CLINICAL CHARACTERISTICS OF PATIENTS

NAME		
AGE		
SEX		
SITE		**SUBSITE**
TNM STAGING		
TREATMENT		
MODE OF RADIOTHERAPY		

GRADING OF TOXICITY PROFILES

CLINICAL CHARACTERISTICS	**POST RT**	**90 DAYS POST RT**
MUCOSITIS		
SKIN REACTIONS		
XEROSTOMIA		
DYSPHAGIA		

CONSENT LETTER

I _____ the undersigned hereby give my consent for the performance of diagnostic tests on myself for "**the comparison of toxicity profiles in head and neck cancer patients undergoing 3D-CRT, IMRT and IGRT**" being conducted by Dr. B.Niveditha under the guidance of Dr. S.Kailasam, Professor, Head Of the Department of Oral Medicine, Diagnosis Radiology , Ragas Dental College and hospital, Chennai. I have been informed and explained about the status of my disease, investigation procedure, the proposed treatment procedure, risk involved and likelihood of success. I also understand and accept that as a part of this study protocol, thereby voluntarily, unconditionally, freely give my consent without any fear or pressure in mentally sound and conscious state to participate in the study.

Witness/Representative: Patient's Signature

Date:

ஒப்புதல் கடிதம்

நான்_____ என்னுடைய முழு ஒத்துழைப்பை திருமதி. நிவேதிதா அவர்கள் மற்றும், திரு.S. கைலாசம் தலைமை பேராசிரியர், வாய் மருத்துவம் மற்றும் வாய்நோய் அறிதல் கதிர் வீச்சுத்துறை ராகாஸ் பல் மருத்துவ முதுநிலை படிப்பிற்கான என்னுடைய கடுமையான மற்றும் நாள்பட்டகதிரியக்க சிகிச்சை பக்க விளைவுகள் ஆய்வு பரிசோதனைகள் செய்ய நான் என் முழு சுயநினைவில் யாருடைய வற்புறுத்தல் இல்லாமல், யாருடைய கட்டுப்பாட்டிற்க்கு கீழ்பணியாமலும் என்னுடைய முழு ஒத்துழைப்பையும் இந்த மருத்துவ ஆராய்ச்சிக்காக ஒப்புதலை அளிக்கின்றேன்.

சாட்சிகள்: கையொப்பம்

தேதி :

Karnofsky/Lansky Performance Status

The CIBMTR uses Karnofsky/Lansky performance status to determine the functional status of a recipient. Recipient performance status is a critical data field that has been determined to be essential for all outcome-based analyses. The Karnofsky Scale is designed for recipients aged 16 years and older, and the Lansky Scale is designed for recipients less than 16 years old. Use this scale (see table 1) to determine the score (10-100) that best represents the recipient's activity status at the requested time point.

Table 1. Karnofsky/Lansky Scale

Karnofsky Scale (recipient age ≥ 16 years)		Lansky Scale (recipient age <16 years)	
Able to carry on normal activity; no special care is needed		**Able to carry on normal activity; no special care is needed**	
100	Normal, no complaints, no evidence of disease	**100**	Fully active
90	Able to carry on normal activity	**90**	Minor restriction in physically strenuous play
80	Normal activity with effort	**80**	Restricted in strenuous play, tires more easily, otherwise active
Unable to work, able to live at home cares for most personal needs, a varying amount of assistance is needed		**Mild to moderate restriction**	
70	Cares for self, unable to carry on normal activity or to do active work	**70**	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance but is able to care for most needs	**60**	Ambulatory up to 50% of time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	**50**	Considerable assistance required for any active play, fully able to engage in quiet play
Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly		**Moderate to severe restriction**	
40	Disabled, requires special care and assistance	**40**	Able to initiate quite activities
30	Severely disabled, hospitalization indicated, although death not imminent	**30**	Needs considerable assistance for quiet activity
20	Very sick, hospitalization necessary	**20**	Limited to very passive activity initiated by others (e.g., TV)
10	Moribund, fatal process progressing rapidly	**10**	Completely disabled, not even passive play

Karnofsky/Lansky Performance Score vs. ECOG performance score:
Some transplant centers may prefer to collect and use the ECOG performance score as opposed to the Karnofsky/Lansky score. Although the ECOG and Karnofsky/Lansky performance score systems are based on similar principles, the scales are not the same. **For centers that collect only the ECOG performance score, see the memorandum and worksheet example on the following pages.**

CIBMTR® CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

MEMORANDUM

To: Transplant center primary contacts

From: Debra Christianson and Douglas Rizzo, MD MS

RE: Provision of Karnofsky performance score (KPS) versus ECOG performance score (ECOG PS) to CIBMTR.

Date: January 31, 2009

CIBMTR has collected the Karnofsky performance score for adult transplant recipients at the time of HCT and during the follow-up period for over two decades. This score, reported on an ordinal scale from 0 to 100, provides a rough measure of the patient's well-being, including their ability to conduct activities of daily living and functional capacity. In children, the Lansky score serves a similar purpose.

As a data item, the pre-HCT KPS is included in virtually all analyses performed by the CIBMTR as an adjustment factor for outcomes of HCT. It is a statistically significant pre-HCT patient risk factor in nearly every analysis of outcomes, including the unrelated Center Specific Outcomes reports created by the NMDP. Therefore, CIBMTR believes that accurate collection and reporting of the performance score is very important, and should be included in the routine auditing of data at transplant centers.

Methods to accurately collect and report performance scores vary across transplant programs. In general, it appears best if the performance score is reported in a systematic fashion at the time of assessment by a clinician in a way that is readily available to the data professionals that report the data to CIBMTR. Although the KPS is very commonly used, some institutions have a preference to collect and use the ECOG PS at their center. This may occur because of heavy involvement in ECOG clinical studies, or other institutional preference. **Centers using primarily ECOG PS have asked whether they can report ECOG PS to the CIBMTR, and how to account for differences between ECOG PS and KPS when reporting.**

Although ECOG PS and KPS rest on similar foundations to record performance status, their scales are not alike. KPS is more detailed and is described in 11 categories, whereas the ECOG PS is reported in six categories. Conversion

instruments between ECOG PS (Zubrod-WHO) and KPS exist and have been validated. However, unfortunately, because of differences in the number of categories, there exists an overlap between the categories of functionality included in the two systems. For example, ECOG PS 1 can be mapped to either KPS categories 80 or 90. This lack of 1:1 mapping in the direction of ECOG PS to KPS causes an inherent problem for centers collecting ECOG PS and wishing to report KPS to CIBMTR or other entities.

Because of the greater detail found in the KPS, as well as its reproducible effect in HCT outcomes analyses over the past two decades, CIBMTR plans to continue to collect performance scores using the KPS system, and will also audit source records at transplant centers based upon the KPS system. Since there exists a 1:1 directional mapping of KPS to ECOG PS, we believe some centers that must report ECOG PS to other entities may be accommodated by collecting the KPS primarily, and converting to ECOG PS for those entities that request an ECOG PS. However, for those centers wishing to collect only the ECOG PS, **CIBMTR will make the following accommodations when auditing the source data regarding KPS as reported to CIBMTR:**

- Centers collecting ECOG PS should do so using standard practices to assure its accuracy.

- Conversion of ECOG PS to KPS for the purposes of CIBMTR reporting should follow a standard and reproducible practice to account for the lack of direct 1:1 mapping from ECOG to KPS. This practice should be transparent and reproducible such that an auditor reviewing patient records and center conversion tools can readily reproduce the derived KPS across the full spectrum of patients included in an audit. Although CIBMTR cannot pre-determine whether any particular practice is sufficient, and example “process” might include:
    - A physician records the patient’s ECOG PS at the time of an office visit, along with their actual performance capabilities that would determine the score.
    - The data professional reporting to the CIBMTR takes the recorded ECOG PS, and reads the applicable recorded history about the patient’s functional capacity.
    - Using a standardized worksheet (see attached example), the data professional maps the recorded ECOG PS to a KPS for reporting to the CIBMTR. Such a worksheet may include space for text to record specific statements in the medical record that substantiate the chosen conversion, as well as check boxes to acknowledge the original document where the functional status statements originated. The worksheet might also include both scoring systems, to facilitate conversion.

- The worksheet is signed and dated, then placed in the patient's medical chart and available for future auditing purposes.

As audits reveal "best practices" for those centers where only the ECOG PS is collected, CIBMTR will provide additional suggestions to other centers that may follow this practice at the time of auditing.

Conversion Worksheet: ECOG to Karnofsky/Lansky

Patient Name/ID#:_____
Date/Follow-up period:_____

☐ Pre-transplant ☐ 6 months ☐ Chronic GVHD
☐ 100 days ☐ Annual, specify year:_____ ☐ Other, specify:_____

PERFORMANCE STATUS CRITERIA

ECOG (Zubrod)		Karnofsky		Lansky	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort, some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of, and less time spent in, play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to a bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping, play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.
5	Dead	0	Dead	0	Dead

Supporting documentation from medical record:

Reported ECOG: _____ **Converted KPS:** _____

M.D. Signature: _____

ANNEXURE – VI

RAGAS DENTAL COLLEGE & HOSPITAL

(Unit of Ragas Educational Society)
Recognized by the Dental Council of India, New Delhi
Affiliated to The Tamilnadu Dr. M.G.R. Medical University, Chennai

2/102, East Coast Road, Uthandi, Chennai - 600 119. INDIA.
Tele : (044) 24530002, 24530003-06. Principal (Dir) 24530001 Fax : (044) 24530009

TO WHOMEVER IT MAY CONCERN

Date: 24.01.2018

Place: Chennai

From

The Institutional Review Board,

Ragas Dental College and Hospital,

Uthandi,

Chennai – 600119.

The dissertation topic titled **"COMPARISON OF TOXICITY PROFILES AMONG HEAD AND NECK CANCER PATIENTS UNDERGOING 3D CRT, IMRT AND IGRT MODES OF RADIOTHERAPY"** submitted by **Dr. B NIVEDITHA** has been approved by the Institutional Review Board of Ragas Dental College and Hospital.

Dr. N. S. AZHAGARASAN M.D.S.,

Member secretary,

Institution Ethics Board,

Ragas Dental College and Hospital,

Uthandi, Chennai – 600119.

RAGAS DENTAL COLLEGE Chennai

ANNEXURE – VII

URKUND

Urkund Analysis Result

Analysed Document: toxicity profiles in 3D CRT, IMRT and IGRT modes of treatment..docx (D35009851)
Submitted: 1/25/2018 10:36:00 AM
Submitted By: bniveditha14980@gmail.com
Significance: 3 %

Sources included in the report:

THESIS.docx (D21805488)
Dr.ingersal thesis.docx (D31331013)
Slutversion.Weidenhaijn.Johan.doc (D12944095)
https://www.duo.uio.no/handle/10852/11251
https://www.duo.uio.no/handle/10852/27977
https://www.radiologyinfo.org/en/info.cfm?pg=igrt
https://www.slideshare.net/shatham/imrt-intensity-modulated-radiotherapy

Instances where selected sources appear:

16

Radiation Oncology/Toxicity grading/RTOG

- **Front Page:** Radiation Oncology | RTOG Trials | Randomized Trials

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RTOG/EORTC Radiation Toxicity Grading

- RTOG Common Toxicity Criteria
  - **1995** - PMID 7713792 — "Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC)." Cox JD et al. Int J Radiat Oncol Biol Phys. 1995 Mar 30;31(5):1341-6.

ACUTE

For all: 0 - no symptoms, 5 - death directly related to radiation effects

RTOG ACUTE Radiation Morbidity

Tissue	Grade 1	2	3	4
Skin	Follicular, faint or dull erythema / epilation / dry desquamation / decreased sweating	Tender or bright erythema, patchy moist desquamation / moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Mucous membrane	Irritation / may experience mild pain not requiring analgesic	Patchy mucositis that may produce an inflammatory serosanguinous discharge / may experience moderate pain requiring analgesia	Confluent fibrinous mucositis / may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
Eye	Mild conjunctivitis w/ or w/o scleral injection / increased tearing	Moderate conjunctivitis w/ or w/o keratitis requiring steroids and/or antibiotics / dry eye requiring artificial tears / iritis with photophobia	Severe keratitis with corneal ulceration / objective decrease in visual acuity or in visual fields / acute glaucoma / panophthalmitis	Loss of vision (uni or bilateral)
Ear	Mild external otitis with erythema, pruritus, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline	Moderate external otitis requiring topical medication / serous otitis media / hypoacusis on testing only	Severe external otitis with discharge or moist desquamation / symptomatic hypoacusis / tinnitus, not drug related	Deafness
Salivary gland	Mild mouth dryness / slightly thickened saliva / may have slightly altered taste such as metallic taste / these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness / thick, sticky saliva / markedly altered taste	(none)	Acute salivary gland necrosis
Pharynx & esophagus	Mild dysphagia or odynophagia / may require topical anesthetic or non-narcotic analgesics / may require soft diet	Moderate dysphagia or odynophagia / may require narcotic analgesics / may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss > 15% from pretreatment baseline requiring NG feeding tube, IV fluids, or hyperalimentation	Complete obstruction, ulceration, perforation, fistula
Larynx	Mild or intermittent hoarseness / cough not requiring antitussive / erythema of mucosa	Persistent hoarseness but able to vocalize / referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic / cough requiring antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic / confluent fibrinous exudate, marked arytenoid edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary
Upper GI	Anorexia with ≤ 5% weight loss from pretreatment baseline / nausea not requiring antiemetics / abdominal discomfort not requiring parasympatholytic drugs or analgesics	Anorexia with ≤ 15% weight loss from pretreatment baseline / nausea and/or vomiting requiring antiemetics / abdominal pain requiring analgesics	Anorexia with > 15% weight loss from pretreatment baseline or requiring NG tube or parenteral support. Nausea and/or vomiting requiring tube or parenteral support / abdominal pain, severe despite medication / hematemesis or melena / abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Ileus, subacute or acute obstruction, perforation, GI bleeding requiring transfusion / abdominal pain requiring tube decompression or bowel diversion
Lower GI / Pelvis	Increased frequency or change in quality of bowel habits not requiring medication / rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (e.g. Lomotil) / mucous discharge not necessitating sanitary pads / rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support / severe mucous or blood discharge necessitating sanitary pads / abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
Lung	Mild symptoms of dry cough or dyspnea on exertion	Persistent cough requiring narcotic, antitussive agents / dyspnea with minimal effort but not at rest	Severe cough unresponsive to narcotic antitussive agent or dyspnea at rest / clinical or radiological evidence of acute	Severe respiratory insufficiency / continuous oxygen or

			pneumonitis / intermittent oxygen or steroids may be required	assisted ventilation
Genitourinary	Frequency of urination or nocturia twice pretreatment habit / dysuria, urgency not requiring medication	Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g. Pyridium)	Frequency with urgency and nocturia hourly or more frequenty / dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic / gross hematuria with/without clot passage	Hematuria requiring transfusion / acute bladder obstruction not secondary to clot passage, ulceration, or necrosis
Heart	Asymptomatic but objective evidence of EKG changes or pericardial abnormalities without evidence of other heart disease	Symptomatic with EKG changes and radiological findings of congestive heart failure or pericardial disease / no specific treatment required	Congestive heart failure, angina pectoris, pericardial disease responding to therapy	Congestive heart failure, angina pectoris, pericardial disease, arrhythmias not responsive to nonsurgical measures
CNS	Fully functional status (i.e. able to work) with minor neurological findings, no medication needed	Neurological findings present sufficient to require home care / nursing assistance may be required / medications including steroids/antiseizure agents may be required	Neurological findings requiring hospitalization for initial management	Serious neurological impairment that includes paralysis, coma, or seizures > 3 per week despite medication / hospitalization required
HEME	**1**	**2**	**3**	**4**
WBC	3.0 - < 4.0	2.0 - < 3.0	1.0 - < 2.0	< 1.0
Platelets	75 - < 100	50 - < 75	25 - < 50	<25 or spontaneous bleeding
Neutrophils	1.5 - < 1.9	1.0 - < 1.5	0.5 - < 1.0	< 0.5 or sepsis
Hgb / Hct	11 - 9.5 (28% - < 32%)	< 9.5 - 7.5 (< 28%)	< 7.5 - 5.0 (Packed cell transfusion required)	(none)

LATE

For all: 0 - no symptoms, 5 - death directly related to radiation effects

RTOG/EORTC LATE Radiation Morbidity

Tissue	Grade 1	2	3	4
Skin	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Subcutaneous tissue	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture > 10% linear measurement	Necrosis
Mucous membrane	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucous	Marked atrophy with complete dryness	Ulceration
Salivary glands	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis
Spinal cord	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadraplegia
Brain	Mild headache; slight lethargy	Moderate headache; great lethargy	Severe headache; severe CNS dysfunction (partial loss of power or dyskinesia)	Coma
Eye	Asymptomatic cataract; minor corneal ulceration or keratitis	Symptomatic cataract; moderate corneal ulceration; minor retinopathy or glaucoma	Severe keratitis; severe retinopathy or detachment	Panophthalmitis / blindness
Larynx	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis
Lung	Asymptomatic or mild symptoms (dry cough); slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); low grade fever; patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; dense radiographic changes	Severe respiratory insufficiency / Continuous oxygen / assisted ventilation
Heart	Asymptomatic or mild symptoms; transient T wave inversion & ST changes; sinus tachy > 110 (at rest)	Moderate angina on effort; mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low ORS	Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; EKG abnormalities	Tamponade / severe heart failure; severe constrictive pericarditis
Esophagus	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semisolid food; dilatation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilatation required	Necrosis / perforation fistula
Small/Large intestine	Mild diarrhea; mild cramping; bowel movement 5 times daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement > 5 times daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis / perforation fistula
Liver	Mild lassitude; nausea, dyspepsia; slightly abnormal liver function	Moderate symptoms; some abnormal liver function tests; serum albumin normal	Disabling hepatic insufficiency; liver function tests grossly abnormal; low albumin; edema or ascites	Necrosis / hepatic coma or encephalopathy
Kidney	Transient albuminuria; no hypertension; mild impairment of renal function; urea 25-35 mg/dL; creatinine 1.5-2.0 mg/dL; creatinine clearance > 75%	Persistent moderate albuminuria (2+); mild hypertension; no related anemia; moderate impairment of renal function; urea > 36-60; creatinine clearance 50-74%	Severe albuminuria; severe hypertension; persistent anemia (< 10); severe renal failure; urea > 60; creatinine > 4.0; creatinine clearance < 50%	Malignant hypertension; uremic coma; urea > 100
Bladder	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)	Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria	Severe frequency & dysuria; severe telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (<150 cc)	Necrosis/contracted bladder (capacity < 100 cc); severe hemorrhagic cystitis
Bone	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis / spontaneous fracture
Joint	Mild joint stiffness; slight limitation of movement	Moderate stiffness; intermittent or moderate	Severe joint stiffness; pain with severe limitation	Necrosis / complete fixation

		joint pain; moderate limitation of movement	of movement	