Section: Radiation Oncology

Original Research Article

SPARING OF DENTAL STRUCTURES IN HEAD AND NECK CANCERS TREATED WITH INTENSITY MODULATED RADIATION THERAPY DOSIMETRIC EVALUATION AND FUNCTIONAL OUTCOMES IN COMPARISON WITH 3D CONFORMAL THERAPY

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Abstract

Background: Intensity-modulated radiation therapy (IMT), a novel treatment technique for head and neck cancers, aims to improve the functional outcome and quality of life in head and neck cancers, in addition to improving prognosis and overall survival rates achieved by a significant reduction in side effects by sparing normal tissues to a good extent and delivering larger doses to the tumour more accurately. **Aim:** This study aimed to determine the efficacy of IMRT in sparing normal dental structures and analyse the outcomes of 3D conformal therapy (3D CRT) and IMRT in head and neck squamous cell carcinoma patients admitted to the Division of Radiation Oncology, Cancer Institute (W. I. A.), Chennai. **Material and Methods:** Thirty patients with histologically proven head and neck cancers planned for definitive radiation/chemoradiation were prospectively allocated into two groups. IMRT and conformal 3D plans were generated using CT images in the planning software. The average mean and maximum volumetric dose histograms were generated. The site-wise dose distribution was evaluated and compared between the groups. **Results:** The average mean and maximum doses delivered to dental structures in 3DCRT were 3900 cGy and 6300 cGy, respectively, and were relatively lower for the IMRT technique (2600 cGy and 5400 cGy). Most patients developed acute mucositis/gingivitis during treatment, and the subacute complication was xerostomia. Patients treated with the IMRT technique had a lower incidence of morbidities, such as dental caries, loosened teeth, hypersensitivity, and better functional quality than those treated with the conformal technique. **Conclusion:** Treatment-related dental morbidities can be significantly decreased in oropharyngeal, nasopharyngeal, and hypopharyngeal cancers using the IMRT approach by reducing dose delivered to dental structures at risk at specific range.

INTRODUCTION

More than 90% of malignancies in the head and neck region have squamous cell histology and originate in the larynx, nasopharynx, oropharynx, lip/oral cavity, and hypopharynx. Head and neck cancers account for 16.1% of all cancer cases recorded in India and are the most common tumours among males.[1] This tumour is among the most aggressive tumours. India has a unique demographic profile, set of risk factors, dietary habits, and patient history regarding head and neck malignancies. Squamous cell carcinomas account for most head and neck malignancies, whereas other histological categories are less common. When it comes to head and neck cancers, the most frequent risk factors include years of smoking, alcohol consumption, and, in the case of oropharyngeal cancers, human papillomavirus infection.[2]

The head and neck region comprises several delicate, intricately organised structures vital for many functions, including basic physiological needs and crucial for appearance, expression, and social function.[3] Radiotherapy plays an important role in the treatment of head and neck cancer, both in the definitive and palliative aspects. The planning radiation field frequently includes the salivary glands, oral cavity, and mandible. In addition to structural deformities and functional handicaps, it also causes multiple treatment-related morbidities. Mucositis, trismus, dental caries, dysphagia, dysgeusia, skin fibrosis and xerostomia are commonly seen.[4] Radiotherapy kills malignant cells by ionising radiation and damages normal cells also by the same mechanism, thus producing RT-induced morbidity of normal tissues. The main goal of radiotherapy is to provide maximum locoregional tumour control with minimum toxicity.[5]

The most difficult aspect of using RT for head and neck cancer is trying to control the illness as much as possible while minimising side effects and damage to nearby healthy tissues. Acute and late toxicities associated with RT can significantly impair patients' quality of life. Radiation delivery has changed during the last 20 years, moving from two-dimensional external beam radiation therapy (2DRT) to three-dimensional conformal radiation therapy (3DCRT).[6] An even greater development is intensity-modulated radiation therapy (IMRT), which employs computerised optimisation of the intensities of many beams in conjunction with computed tomography-based planning and radiation delivery.[7] This enhances the capacity to precisely adapt the treatment volume to concave tumour forms while reducing dosages to at-risk organs (OAR). It is especially beneficial in the head and neck region, where OAR comprise the optic pathway, parotid glands, brain stem, spinal cord, and inner ear.[8]

Research has indicated that IMRT, instead of 3DCRT, can considerably improve tumour target coverage and preserve sensitive, normal tissue in patients with head and neck malignancies. According to preliminary dosimetric studies, conformal methods, particularly IMRT, might considerably protect parotid glands while potentially lowering the frequency and severity of hypofunction of the salivary glands.[9] Multicentric trials later verified the usefulness of IMRT in lowering xerostomia and enhancing quality of life, matched case-control studies, and prospective longitudinal single-institution studies.[10] A focus on appropriate target volume selection and delineation was placed due to early concerns over marginal failures. This was done to ensure that parotid sparing was not happening at the price of locoregional control or survival.[11]

Studies have separately studied dosimetric patterns in various types of radiation therapy, such as conformal, IMRT, and rapid arc techniques. Some studies have shown radiation's direct and indirect effects on dental structures and their outcomes. Still, comprehensive studies are lacking in correlating between doses received by dental structures and their outcome on treated patients, helping in future treatments.[12]

Aim

This study assessed whether IMRT delivers lower radiation doses to dental structures and provides better outcomes with fewer and milder side effects than conventional 3D radiation therapy. It also aims to determine the most desirable dose range that will cause minimal damage to dental structures. In a particular subset of patients with head and neck cancers, it is feasible to obtain the desired dose range so that they benefit much from the use of IMRT as a standard treatment for head and neck cancers in future settings.

MATERIALS AND METHODS

This prospective study was conducted at the Cancer Institute for two years between November 2017 and October 2019, involving 30 patients who met the following inclusion criteria at the Division of Radiation Oncology, Cancer Institute (WIA), Chennai.

Inclusion Criteria

Patients of both sexes aged >30 years, with histologically proven head and neck cancers in Sites Included-Base of the tongue, Oro pharynx, Nasopharynx, Hypopharynx, and larynx, planned for definitive chemoradiation/definitive radiation, with an ECOG performance status-0/1, and patients with hypertension and diabetes under control were included in the study.

Exclusion Criteria

Patients with poor performance status (PS ≥ 2), initially treated outside, palliative intent treatment, distant metastatic disease, or double primary and uncontrolled comorbid illness were excluded from the study.

Examination of the neck nodes for location, size, number, mobility, tenderness, and persistence was performed. Submental (Level Ia) and sub-mandibular (Level Ib), upper, middle, and lower deep cervical groups of nodes (Level II, III and IV) of the neck were investigated. Indirect laryngoscopy was performed to visualise the base of the tongue, vallecula, median and lateral glossoepiglottic folds, Epiglottis, Vestibular fold, true vocal cords, Trachea, Laryngeal cartilage (in order). Direct laryngoscopy and pharyngoscopy techniques were used to visualise the posterior pharyngeal wall, post-cricoid region, pyriform fossa, larynx with vocal cords, cervical and thoracic oesophagus, and up to the esophagogastric junction.

Pre-treatment evaluation

Direct laryngoscopy, esophagoscopy, and bronchoscopy were performed to assess the extent of tumour relation with surrounding structural involvement and mobility of the vocal cords. Pan-endoscopy in unknown primary cases. Chest radiography was performed to evaluate for infection, malignancy, and metastasis. HR-CT was performed to analyse the tumour thickness, invasion of underlying structures, and lymph node metastasis. MRI was used to analyse the soft tissue details and tissue oedema. Bone scans and ultrasound of the abdomen and pelvis were performed to rule out metastatic spread.

Radiation treatment planning

The patients were immobilised with a thermoplastic head and neck mould. Bite blocks are used. The mask was attached to the couch using an indexed patient positioning system. CT for RT planning was performed from the orbit to the shoulder with 3 mm cuts. Marks like lead shots were placed at bony landmarks, and CT was performed for RT planning.

Target volume description

All clinical and radiological primary and nodal diseases seen on the planning CT scan were included in the gross tumour volume (GTV) (GTV primary – primary tumour, GTV Nodal – metastatic lymphadenopathy, GTV M – other metastases). CTV: Clinical Target Volume-covered subclinical disease extent, 0.5-1.5cm around GTV to cover microscopic disease spread in CTV I and regional lymph nodes were covered for nodal spread in CTV II. The Planning Target Volume (PTV) accounts for all possible geometrical variations and inaccuracies in absorbing the prescribed dose in the CTV. PTV was usually extended 0.3-0.5 cm around the CTV for organ motion, treatment technique, and setup errors, both intra-fractional and inter-fractional.

Internal Margin (IM) denotes the Margin to CTV for compensating expected physiological movements and variation in CTV size, shape, and position during radiation therapy. The ITV refers to the internal target volume (ITV) (ITV-CTV + IM). In the setup margin, SM is the margin that accounts for uncertainties in patient positioning and beam alignment during treatment planning and delivery (PTV – ITV + SM). Organs at Risk (OAR) denote normal tissues whose radiation sensitivity may significantly influence treatment planning and prescribed doses. Radiation morbidity was categorised into three classes based on severity (Class I - severe, Class II - Intermediate/Moderate, and Class III - Mild or no morbidity).

Determination of dose

The dosage was determined according to RTOG guidelines (Table 1). The maximum dose (Dmax) refers to the maximum dose to the PTV and the organ at risk; a volume with a diameter greater than 15 mm is involved. The minimum Dose (Dmin) was the smallest dose in a defined volume. No volume is recommended. The mean Dose (Dmean) is the mean dose value for a specified volume.

Generation of IMRT and 3D CRT plans

3D-CRT was planned using 6MV/15MV photons with 4-9 Co planar beams with MLC-shaping based on the beam's eye-view projection of the planning target volume (PTV) and organs at risk (OARs). The wedges and blocks were used as and, respectively, when required. The beams were weighed appropriately to reduce hot or cold spots. IMRT plans were created using the Eclipse treatment planning system. The IMRT plans consisted of 7-11 Fields with 6/10 MV photon beams for step-and-shoot/dynamic shoot delivery, while the rotational arc plans consisted of two full or partial arcs using 6 MV photons. Dental structures such as the anterior mandible (incisors and canines), right and left posterior mandibles (premolars and molars), and Maxillary and Mandibular bones with maxillary and mandibular teeth were all contoured around the tumour location. They were marked using CT images in the planning software. The mean and maximum doses received in specified areas were calculated. Average mean and maximum volumetric dose histograms were generated for each defined area. The site-wise dose distribution was evaluated and compared with the tumour location and stage in the IMRT and conformal 3D technique groups.

Pre-treatment evaluation and management of dental conditions

Complete dental evaluation including tooth profiling, periodontal probing, cavity and caries check, mobility check, impacted/untrusted tooth, broken/missing tooth, artificial dentures are noted along with trismus. Extraction of deep caries/non vital tooth, dental scaling, smoothing edges, endodontic and periodontic treatments if necessary done. Additionally, mouth opening exercises, mucositis and fluoride prophylaxis also given.

Dental management and post-treatment follow-up

Weekly examinations were performed during the radiation therapy phase. The dental care provided during radiation therapy included examinations during routine check-ups, guard placement, antibacterial rinse usage, treatment for dysphagia, oral candidiasis and mucositis in patients who required it, management, supervision of oral hygiene and diet.

Post-radiation care included monthly follow-ups for the first six months and then three-monthly follow-ups for one year, with a dental examination during each follow-up for up to a year.

Inflammation (mucositis, periodontitis, and gingivitis post-radiation), radiation-related caries development and loosening of teeth, hypersensitivity of the tooth due to erosion and decay, xerostomia indirectly causing dental caries, exposed bone of the maxilla or mandible, dental extractions, or osteoradionecrosis of the mandible, if any, are documented and graded based on the oral assessment guide (Table 2). The RTOG grading was used to assess mucositis and acute toxicity of the salivary gland. (Table 3). Visual pain was evaluated using an analogue scale (0 = no pain and 10 = worst imaginable pain).

Table 1: Dosage determination

CTV	DOSE (GY)
High risk	66 -70
Intermediate risk	59 - 60

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Low risk	52 - 54

Table 2: Oral Assessment Guide

Assessment	Criteria	Score/ Grade
Teeth	Clean and no debris	I
	Plague/Debris in a localised area	II
	Generalised plague/debris along denture-bearing area	III
Gingiva	Pink, stippled, firm gingiva	I
	Oedematous gingiva with or without redness	II
	Spontaneous bleeding/Bleeding with pressure	III

Table 3: RTOG Grading

	Criteria	Grading
Mucositis	No change over baseline	0
	Irritation or slight pain not requiring analgesic	1
	Patchy mucositis with moderate pain requiring analgesics	2
	Confluent mucositis with severe pain requiring narcotic	3
	Ulceration, haemorrhage and necrosis	4
	Death	5
Acute toxicity of the Salivary gland	Mild mouth dryness, thick saliva with no change in feeding behaviour	1
	Moderate to complete dryness with marked altered taste	2
	None	3
	Acute salivary necrosis	4
	Death	5

RESULTS

The mean age of patients included in the study was 52 years, with a predominance of male patients (Table 1). Patient and disease characteristics of the cohort are presented in Table 1. The predominant histopathological finding was squamous cell carcinoma (23), with a smaller percentage of poorly differentiated carcinoma (7). Most patients were in stages 3 (16) and 4 (11) in the locally advanced stages. T3 tumour stage predominates in T staging (16), and both N1 (9) and N2 patients (7) predominate in nodal staging. Of the 30 patients, most (27) received definitive chemoradiation as the treatment modality (Table 4). The radiation techniques used were conformal in 15 patients, and intensity-modulated radiation therapy was used in the remaining 15 patients (Table 4).

One patient had severe renal disease and sensory hearing loss, making the patient unfit for chemotherapy, and one patient was elderly and did not fit for multimodality treatment. One patient had early T2 disease with multiple comorbidities and opted for definitive radiation therapy only (Table 4). The chemoradiation group mostly received cisplatin chemotherapy (18 patients), whereas carboplatin was administered to patients unsuitable for cisplatin treatment (9 patients).

Cisplatin was given in 100mg/meter square dosage in 3 weekly intervals, and all of the patients of the nasopharynx received three adjuvant cycles of cisplatin and 5 Fluorouracil chemotherapy. Two patients in the chemoradiation group who had residual disease post-chemoradiation underwent salvage surgery. [Table 4]

The Dmean values of CRT were relatively higher for all subsites with posterior mandibular regions, both right and left, displaying the highest values of 54.53 and 54.6 GY (Table 5). The lowest Dmean value was observed in the IMRT group with Maxillary teeth (26.13 GY) (Table 5). The Dmax value was higher in the CRT group, with the left posterior mandible displaying the highest GY value of 64.13, and the anterior mandible in the IMRT group displayed the lowest GY of 39.6 (Table 5).

The high-dose region (red) and the target OAR volume (white) in the dose colour wash of the IMRT plan (Figure 1) and conformal plan (Figure 2). Blue indicates the low dose. These images indicated that the posterior mandible received higher doses in IMRT and a much higher dose prevalence in the conformal group in all subsites (Figures 1 and 2). Dental morbidity analysis during radiation was observed in 8 patients in the CRT group and 4 in the IMRT group (Figure 3). No patient above grade 2 was found in the IMRT group. However, in the CRT group, five patients had grade 2 morbidity, and one had grade 3 morbidity (Figure 3).

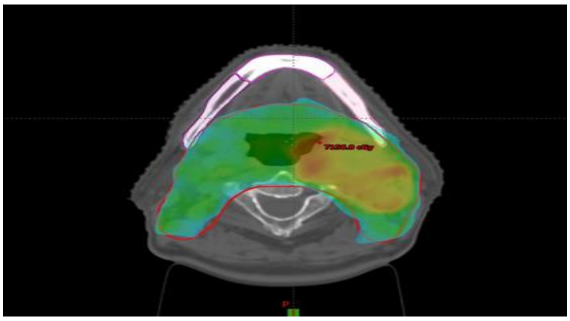

Figure 1: Dose colour wash IMRT Plan

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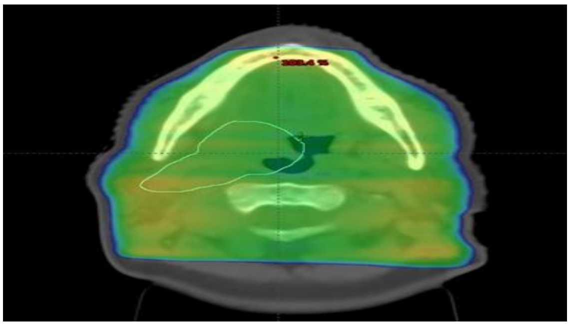

Figure 2: Dose colour wash Conformal plan

Post-radiation morbidities were observed at higher levels in the CRT group (24). However, only eight events of post-radiation morbidities were observed in patients treated with IMRT (Figure 4). Xerostomia and hypersensitivity were the most prevalent morbidity in both groups. However, xerostomia recurrence was observed in eight patients receiving CRT, while only 2 of them with xerostomia were detected in the IMRT group (Figure 4).

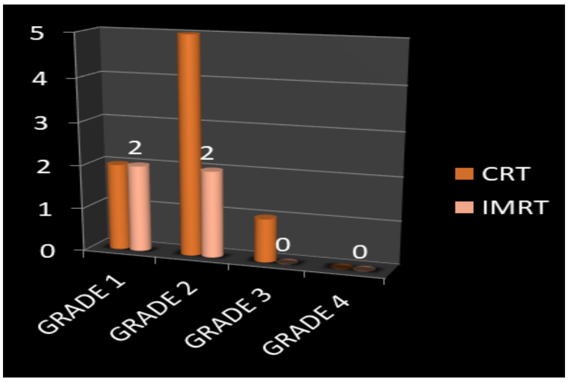

Figure 3: Dental morbidity analysis – during radiation

The IMRT group was divided into three categories based on the mean doses received by the dental structures. One category received a 25-30 Gy mean dose; the other received 30-35 Gy and 35-40 Gy mean doses. Dental events were noted and charted in each category. [Table 6]

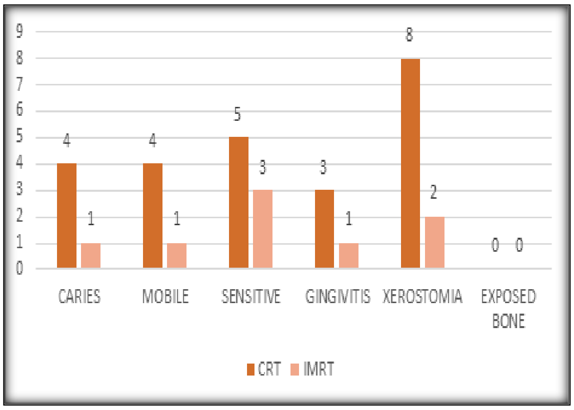

Figure 4: Dental structure morbidity - post-radiation

Table 4: Patient, disease, and treatment characteristics

Variables		Number of patients
Gender	Male	23
	Female	7
Primary site	Oropharynx	14
	Hypopharynx	10
	Larynx	6
Histopathology	SCC	23
	PDC	7
Overall stage grouping	1	0
	2	3
	3	16
	4	11
T stage	T1	4
	T2	9
	T3	16
	T4	1
N stage	N0	10
	N1	9
	N2	7
	N3	4
Treatment technique		
Radiation technique	CRT	15
	IMRT	15
Radiation therapy	CTRT	27
	CDDP	18
	CARBO	9

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Table 5: Dosimetric details of patients in CRT and IMRT

Subsite	Dosimetry (GY)			
	Dmean		Dmax	
	CRT	IMRT	CRT	IMRT
Mandibular teeth	37.4	31	53.13	46.9
Maxillary teeth	39.6	26.13	56.8	46.66
Anterior mandible	32.7	27.46	44.26	39.6
Right posterior mandible	54.53	39.1	60.4	52.4
Left posterior mandible	54.6	39.6	64.13	53.1

Table 6: Correlation between mean doses and dental events in IMRT

MEAN DOSE (GY)	DENTAL CARIES	MOBILE TOOTH	SENSITIVE TOOTH	GINGIVITIS	XEROSTOMIA
25-30	0	0	1	0	0
30-35	0	0	1	0	0
35-40	1	1	1	1	2

DISCUSSION

Based on a substantial amount of excellent data, definitive chemoradiotherapy (i.e. radiation combined with concurrent systemic chemotherapy) is the current gold standard of care for nonsurgical treatment of head and neck squamous cell carcinoma (HNSCC). High-precision radiotherapy techniques, such as 3D CRT and IMRT, have recently become extremely popular due to imaging, planning, and delivery advancements. This is especially true in HNSCC, where the techniques promise to improve locoregional control, reduce acute and late treatment morbidity, and improve quality of life and survival.[11] Given comparing and correlating between the dose delivered to dental structures through IMRT technique and conformal 3DCRT technique and its early outcomes in terms of dental events and quality of life of patients in post-radiation follow-up for one year, in HNSCC patients admitted to cancer institute, the current study was carried out.

As expected, when analysed, the mean and maximum volumetric doses achieved by dental structures in IMRT techniques were lower than those in conformal techniques. The subsites that received low doses in IMRT and conformal radiotherapy were the anterior mandible, maxillary teeth, and maxilla. By contrast, the posterior mandible received higher doses of IMRT and higher doses in the conformal group. The lowest mean dose received in the IMRT group is 26.[13] Gy in the maxillary teeth site. In contrast, the highest mean dose recorded in the IMRT group was at the left posterior mandible, 39.6 Gy, lower than the conformal dose of the left posterior mandible, 54.6 Gy. Similarly, the highest Dmax recorded in the IMRT group was 53.1 Gy in the left posterior mandible region, whereas in the conformal group, it was 64.13 in the left posterior mandible region. Similar low doses in IMRT compared to CRT were reported by Pow et al., who performed a randomised controlled trial in assessing xerostomia and quality of life in patients post-treatment by IMRT and CRT for early-stage nasopharyngeal carcinoma.[13]

Because of the low doses, the dental morbidity events, both acute and sub-acute during radiation and in the post-radiation period, were lower in the IMRT group. Grade 4 mucositis was not recorded in the two techniques, demonstrating its superiority over conventional techniques. Grade 3 mucositis was not recorded in the IMRT group, and only four patients developed grade 2 mucositis. Using parotid-sparing techniques has resulted in a significant reduction in the incidence of moderate to severe late xerostomia (> grade 2), as reported by Jensen et al. in his A systematic review of analysing the severity of cancer therapies on salivary gland hypofunction and xerostomia induced by cancer therapies.[14]

Eight patients in the conformal group complained of mucositis. One of those 8 had grade 3 mucositis. The post-radiation period dental morbidity analysis showed multiple dental events, such as dental caries, mobile tooth, hypersensitivity of the tooth and mucosal inflammation in the form of gingivitis or periodontitis. Extreme morbidities like exposed bone and osteoradionecrosis were not documented in our study. Gradual but partial recovery over time manifests as subjective and objective improvement of late xerostomia-related symptoms, leading to a preserved or improved quality of life. Multicentric cooperative group clinical studies have since been used to investigate and confirm IMRT's parotid-sparing capabilities, as reported by Lee et al. and Eisbruch et al. in their studies of IMRT therapies for naso and oro-pharyngeal carcinoma.[15,16]

Among the IMRT and conformal groups, only eight dental events were recorded in 4 patients in the IMRT group. The conformal group had 24 dental events in 11 of the 15 treated patients. Further analysis of the mean doses received by dental structures and dental events recorded in the IMRT group showed that most of the dental events (6) were in the group that had achieved mean doses of 35-40 Gy. Dental events were almost nil (1) in the mean doses of 25-30 Gy group and also the same outcome (1) recorded in 30 -35 Gy mean dose group. A similar study also reported a lower incidence of xerostomia > grade 2 in the IMRT group of oropharyngeal squamous cell cancer patients after one year of follow-up post-IMRT and

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CRT therapies.[17] The same study also showed that IMRT dramatically increased salivary function recovery, leading to clinically meaningful gains in dry-mouth-specific and overall quality of life ratings. Despite all the restrictions and limitations, it has been possible to show that IMRT, as opposed to 3D-CRT, reduces acute and late dental structures related morbidities in a statistically significant and clinically useful way.

Limitations

This study has the drawbacks of a small sample size and a short follow-up period. Hence, prospective studies with larger sample sizes and longer follow-up periods must validate these results.

CONCLUSION

With newer techniques such as image-guided radiotherapy, adaptive radiotherapy, and simultaneous integrated boost, IMRT has achieved well adequate target doses to a tumour with greater normal tissue sparing. Sparing of dental structures can be easily achieved with advanced radiotherapy IMRT treatment. It is not considered for a longer time owing to deficits in analysing the importance of doses received and the morbidity encountered. In this study, treatment-related morbidity was considerably reduced in oropharyngeal, nasopharyngeal, and hypopharyngeal cancers, where there was no compromise in the dose delivered to the tumour despite sparing dental structures, with the help of the IMRT technique unlike oral cavity cancers. Xerostomia is a prevalent and toxic side effect of extensive head-neck radiation exposure that may negatively impact the quality of life. IMRT dramatically lowers the incidence and severity of xerostomia and dental morbidity events when compared to 3D-CRT. A notable recovery over time bolsters its broad acceptance in modern radiation practice without compromising local control or survival.

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