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ORIGINAL ARTICLE

Dosimetric and Radiobiological Analysis of VMAT Treatment Plan with Flattened and Flattening Filter-free Photon Beams for Postoperative Oral Cavity Cancer Treatment

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OBJECTIVE

The study objective was to assess the dosimetric and radiobiological characteristics of flattened filter (FF) and flattening filter-free (FFF) beam techniques in volumetric modulated arc therapy (VMAT) for patients with postoperative oral cavity cancer.

METHODS

20 patients with oral cavity cancer underwent treatment for VMAT_FF. Subsequently, retrospective VMAT_FFF treatment plans were developed using the eclipse treatment planning system. Both treatment plans adhered to a Simultaneous Integrated Boost (SIB), delivering 60Gy to PTV60 and 54Gy to PTV54 in 30#. The assessment encompassed biological indices (e.g., NTCP) and physical dose metrics, including target coverage, conformity, dose homogeneity, and doses to organs at risk.

RESULTS

The dosimetric evaluation revealed negligible differences between the both techniques. The conformity index was similar for VMAT_FF (0.975±0.017) and VMAT_FFF (0.975±0.019, p=0.813). The monitor units required for VMAT_FFF (583±52.1) were significantly greater than VMAT_FF (530±69.9, p=0.001). NTCP values for critical structures, including the spinal cord, brainstem, and optic chiasm, were consistent at 0.00±0.00 for both techniques. For the parotid glands, NTCP values related to xerostomia show insignificant variation: 17.8±8.17 (right) and 20.3±11.2 (left) for VMAT_FF compared to 17.9±8.29 (right) and 20.7±11.4 (left) for VMAT_FFF.

CONCLUSION

Both VMAT_FF and VMAT_FFF techniques exhibited comparable dosimetric and radiobiological results for the treatment of oral cavity cancer. Although VMAT_FFF required a higher number of monitor units, it demonstrated similar clinical effectiveness, suggesting its appropriateness for therapeutic application.

Keywords: Dosimetric analysis; flattening filter-free; normal tissue complication probability; oral cavity cancer;radiotherapy; volumetric modulated arc therapy.

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INTRODUCTION

Oral cavity cancer presents a significant global health issue, marked by its intricate epidemiological characteristics and a rising incidence in developing countries. Data from GLOBOCAN 2022 reveals a concerning global cancer burden, with 377,713 new cases and 177,757 deaths attributed to cancer reported worldwide.[1] This condition exhibits a notable male predominance, with a gender ratio of 3:1, and is particularly prevalent in populations from South and Southeast Asia.[2] The development of oral cavity carcinoma is influenced by a multifaceted interaction between environmental carcinogens and genetic predispositions. Prominent risk factors include tobacco use, which is widely acknowledged as a primary contributor to oral cancer, as highlighted in numerous epidemiological studies.[3] Additionally, alcohol consumption not only poses an independent risk but also works in conjunction with tobacco, thereby increasing the likelihood of developing the disease.[3] The role of human papillomavirus (HPV) infection, particularly the high-risk variants, has gained recognition as a crucial etiological factor, especially among younger demographics.[4,5] Furthermore, genetic factors, including inherited mutations and polymorphisms, play a significant role in determining individual susceptibility to oral cavity cancer, often interacting with these external carcinogenic agents.[6]

Postoperative radiotherapy is a crucial treatment modality that plays a significant role in improving local disease management and substantially reducing the likelihood of recurrence. In this context, Volumetric Modulated Arc Therapy (VMAT) has emerged as a groundbreaking radiotherapy technique, providing exceptional accuracy in dose administration and enhanced treatment effectiveness when compared to traditional radiation methods.[7] In VAMT, the flattening filter (FF) is employed; however, it presents several drawbacks. The FF extends the duration of on-beam times, results in reduced treatment doses, diminishes photon intensity, and increases the scattering of the treatment dose.[8,9] Recently, research has focused on the application of flattening filter-free (FFF) beams in VAMT.[10–13] Extensive research[14,15] shown that FFF beams can significantly decrease the total body dose and alleviate acute radiation toxicity.

The role of radiobiological analysis is vital in refining radiotherapy techniques, employing metrics such as Normal Tissue Complication Probability (NTCP) to obtain critical insights into the risks linked to radiation-induced complications. The Eclipse Planning System offers comprehensive tools for evaluating biological parameters, facilitating the development of customized treatment plans that optimize the equilibrium between tumor control probability (TCP) and the protecting normal tissues.

The objectives of the current study were to explore the therapeutic benefits of the Flattening Filter-Free (FFF) mode in Volumetric Modulated Arc Therapy (VMAT) in comparison to the Flattened Filter (FF) mode for patients who have undergone surgery for oral cavity cancer. Furthermore, the study sought to analyze the variations in dosimetric parameters and Normal Tissue Complication Probability (NTCP) values by utilizing Eclipse Planning System biological plan evaluation tools for both radiation beam types.

MATERIALS AND METHODS

The study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Indira Gandhi Institute of Medical Science Office of Ethics Committee (No: 35/IEC/IGIMS/2024, Date: 17/05/2024).

Patient Selection and CT Simulation

This retrospective analysis involved a cohort of 20 patients diagnosed with oral cavity cancer, sourced from our institutional database. The study focused on histopathologically confirmed cases of individuals aged between 18 and 70 years, all possessing a Karnofsky Performance Status exceeding 70. Patients were excluded if they had residual disease, metastatic conditions, prior radiotherapy exposure, or uncontrolled medical issues.

CT simulation was performed using a Revolution EVO (GE Healthcare) system, with patients positioned in a supine and immobilized with a thermoplastic mask. A standard and contrast-enhanced computed tomography (CT) scan was performed with a slice thickness of 2.5 mm, encompassing the area from the top of the skull to the mid-thoracic region. The obtained CT data were then transferred to the treatment planning system for comprehensive volumetric delineation.

The contouring process meticulously defined the Gross Tumor Volume (GTV), Clinical Target Volume (CTV), and Planning Target Volume (PTV) in accordance with institutional protocols. Critical organs at risk (OARs), including the spinal cord, brainstem, parotid glands, mandible, and structures within the oral

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Table 1 The biological functions selected for the biological evaluation of the oral cavity patient plans

Structure	Volume type	Model	D_{50}	γ	α /β [Gy]	Seriality	Endpoints
Parotid gland	Normal	NTCP	4600	1.8	3	1	Xerostomia
Spinal cord	Normal	poisson-	6860	1.9	3	4	Myelitis necrosis
Mandible	Normal	LQ	7030	3.8	3	1	Joint dysfunction
Brain stem	Normal		6510	2.4	3	1	Necrosis/infraction
Optic chiasm	Normal		6500	2.3	3	1	Blindness
Eye	Normal		6500	1.8	3	1	Blindness

D_{50}: The dose at which 50% of patients would experience a specific complication; γ: The steepness of the dose-response curve; α/β: A parameter describing the relative effectiveness of low and high radiation doses; Seriality: Seriality factor; NTCP: Normal tissue complication probability; LQ: Linear-quadratic

cavity, were accurately contoured to ensure precise treatment planning and minimize the risk of radiation-induced complications.

Treatment Planning

This retrospective investigation involved a thorough treatment planning methodology for patients diagnosed with oral cavity cancer. A total of 40 treatment plans were formulated for 20 individuals, utilizing both Flattened Filter (FF) and Flattening Filter Free (FFF) photon beam techniques within the framework of Volumetric Modulated Arc Therapy (VMAT).

Multiple dose levels were allocated to the Planning Target Volumes (PTVs) utilizing the Simultaneous Integrated Boost (SIB) methodology. The dosage for PTV60, which included the high-risk Clinical Target Volume (CTV) and the nodal CTV, was established at 60Gy in 30 fractions @ 2 Gy per fraction. In contrast, the dosage for PTV54, which addressed the low-risk CTV, was determined to be 54 Gy over 30 fractions @ 1.8 Gy per fraction.

The treatment planning process was carried out utilizing the Eclipse Treatment Planning System (version 16.1), with final dose calculations performed through the Anisotropic Analytical Algorithm (AAA). The beam characteristics were clearly specified, with a dose rate of 600 MU/min for flattened fields (FF) and 1400 MU/min for flattening filter-free (FFF) beams. All treatment plans were developed and executed using a True Beam SVC linear accelerator (Varian Medical Systems, a subsidiary of Siemens Healthineers) equipped with a 120 millennium multileaf collimator (MLC). The VMAT treatment planning approach utilized a sophisticated arc rotation configuration. Three distinct arcs of rotation were meticulously crafted, encompassing angles of 181°–179°, 179°–181°, and 181°–179°, with collimator angles precisely established at 30°, 330°, and 30°, respectively. To minimize potential bias and ensure methodological consistency, all planning and optimization parameters were uniformly applied across both FF and FFF photon beam plans. The plan optimization objective was 95% of the PTVs received the prescribed dose, while concurrently reducing exposure to the Organs at Risk (OARs) including Spinal cord: ≤45 Gy, Brainstem: Dmax≤54 Gy, Optic chiasm: Dmax≤54 Gy, Eyes: Dmax≤45 Gy, Parotid glands: Dmean≤26 Gy, D50%≤30 Gy, V30Gy≤50%, V40Gy≤30%, V50Gy≤20%.

The VMAT plans generated by VMAT_FF and VMAT_FFF can be accessed through the integrated dose-volume analysis tool available in the Eclipse system. Furthermore, the Normal Tissue Complication Probability (NTCP) value for Organs at Risk (OARs) can be evaluated using a biological assessment tool, which is not included as a standard feature but is instead an additional software component created by RaySearch Laboratories. Additionally, the NTCP for each OAR was determined utilizing the Poisson model, relying on the parameters and endpoints specified in Table 1.

Treatment Plan Evaluation

In the assessment of radiotherapy treatment plans, various dosimetric indices play a vital role in evaluating the quality and efficacy of dose distribution within the target volume, as well as the protection of organs-at-risk (OARs).

Coverage Index: It is defined as ratio of minimum dose within target volume to prescribed dose.[16]

C=Dmin / PD

The prescribed dose (PD) represents the minimum dosage required for tumor volume. A treatment plan is deemed compliant with protocol if the target volume is entirely encompassed by 90% of the prescribed isodose. A minor deviation occurs when the target is covered by 80% of the prescribed dose. Con-

versely, if 80% of the PD fails to fully cover the target, it is classified as a major deviation.[17]

Uniformity Index: UI = D5% / D95%,

D5% and D95% denote the doses administered to the highest and lowest 5% of the target volume, respectively.[18] A reduced UI signifies an improved dose distribution throughout the target volume. The categorization of UI values is as follows: Excellent for UI≤0.95, Moderate for 0.95<UI≤1.0, and Poor for UI>1.0.

Homogeneity Index: HI=Dmax / PD,

Where, Dmax is the maximum dose delivered to the target and PD is the prescribed dose.[18] A reduced HI value signifies improved dose uniformity within the target area. The categorization of HI values is as follows: Excellent for HI≤1, Moderate for 1.1<HI≤1.5, and Poor for HI>1.5.

Conformity Index: CI=Vreference volume/PTV volume

Where, Vreference volume is the volume receiving the reference dose, and PTV volume is the planning target volume. The theoretical ideal for the CI is 1.[19] A CI value falling between 1 and 2 indicates that the treatment aligns with the prescribed treatment plan.

The dose gradient index (GI) assesses the efficacy of dose reduction beyond the planning target volume (PTV). It is determined by the ratio of the volume that receives the prescribed isodose line to the volume that receives half of that dose, allowing for the comparison of treatment plans that exhibit similar dose conformity yet differ in their gradients.[20]

The unified dosimetry index (UDI) serves as a thorough assessment tool for radiotherapy treatment plans by integrating key dosimetric factors: Coverage (C), Conformity Index (CI), Homogeneity Index (HI), and Gradient Index (GI). The calculation is expressed as follows:

UDI = C×CI×HI×GI

A UDI value approaching 1 signifies an optimal quality of the treatment plan, whereas values exceeding 1 are generally deemed unsatisfactory. This index plays a crucial role in determining the most effective techniques for treatment planning.[20]

Gamma Analysis

Patient-specific quality assurance (PSQA) plans were created for 20 treatment plans, with each techniqueby performing calculations on a CT scan of the ArcCHECK phantom within the Eclipse Treatment Planning System (Varian Medical Systems, Palo Alto, CA) and subsequently recalculating doses based on the phantom's geometry. These PSQA plans were then exported as DICOM files to facilitate patient-specific QA measurements. The measurements utilized a Sun Nuclear ArcCHECK phantom (Sun Nuclear Corporation, Melbourne, FL), which is equipped with 1386 Sun Point diode detectors. All patient-specific QA treatment plans were administered using a Varian True Beam SVC linear accelerator, and the measurements were analyzed with the SNC ArcCHECK and Patient software program. A quantitative assessment of the measured doses in comparison to the doses calculated by the treatment planning system (TPS) was conducted through gamma index analysis. The parameters for absolute gamma analysis were established at a 3 mm distance-to-agreement, a 3% dose difference, and a 10% dose threshold. Gamma passing rates (GPR) of 95% or higher were acceptable.

Statistical Analysis

Statistical analyses were conducted utilizing Jamovi software (version 1.6). The mean values along with standard deviation (SD) for the VMAT_FF and VMAT_FFF plans were computed. The Student's paired t-test was employed to assess the significance of the differences between these two plans. A probability value (p) of ≤0.05 is regarded as indicative of statistically significant differences between the two methods.

RESULTS

Physical Analysis for PTV

Table 2 presents a summary of the comparison between PTV coverage and dosimetric parameters for VMAT_FF and VMAT_FFF in patients with oral cavity cancer. This evaluation encompasses essential planning parameters, including the minimum dose (Dmin), maximum dose (Dmax), and the homogeneity index (HI), as well as other pertinent metrics. An analysis of the differences in these parameters between the two techniques was conducted to evaluate their effects on treatment planning and dose distribution.

For the PTV: 60Gy, the minimum dose administered to the PTV for both VMAT_FF (50.0±4.19 Gy) and VMAT_FFF (50.1±4.26 Gy) is nearly the same, with no statistically significant difference (p=0.710). Likewise, the average dose to the PTV is almost identical for both methods, exhibiting minimal variations—VMAT_FF provides 60.1±0.134 Gy while VMAT_FFF offers 60.1±0.119 Gy. This difference is not statistically significant (p=0.123). The maximum dose is also comparable between the two methods (VMAT_FF: 64.3±0.976 Gy, VMAT_FFF:

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Table 2 Comparison of PTV dosimetric parameters between FF and FFF VMAT plans

Parameters	Dosimetric parameters	VMAT_FF (mean±SD)	VMAT_FFF (mean±SD)	p
PTV -60Gy	Minimum dose(Gy)	50.0±4.19	50.1±4.26	0.710
	Mean dose (Gy)	60.1±0.134	60.1±0.119	0.123
	Maximum dose (Gy)	64.3±0.976	64.4±1.00	0.537
	D95%	96.4±0.773	96.4±0.867	0.993
PTV-54Gy	Mean dose (Gy)	54.2±0.217	54.3±0.217	0.011
Plan evaluation	UI	1.077±0.013	1.07±0.016	0.438
	Coverage	0.834±0.07	0.835±0.07	0.710
	HI	1.07±0.016	1.07±0.017	0.537
	CI	0.975±0.017	0.975±0.19	0.813
	GI	1.21±0.120	1.21±0.118	0.769
	UDI	1.05±0.015	1.05±0.014	0.712
MU		530±69.9	583±52.1	0.001
GPR (%) (3%/3mm)		98.8±0.359	98.5±0.346	0.001

PTV: Planning target volume; FF: Flattenting filter; FFF: Flattening filter free; VMAT: Volumetric modulated arc therapy; SD: Standard deviation; Gy: Gray; D95%: Dose received by 95% of the PTV; UI: Uniformity index; HI: Homogeneity index; CI: Conformity index; GI: Gradient index; UDI: Undefined dosimetric index; MU: Monitor units; GPR (%): Gamma passing rate in percentage

64.4±1.00 Gy), with no significant difference observed (p=0.537). The D95% values for both VMAT_FF (96.4±0.773%) and VMAT_FFF (96.4±0.867%) are virtually the same, indicating no significant difference (p=0.993). These findings, as presented in Table 1, imply that both techniques are equivalent in delivering the minimum, mean, and maximum doses, as well as in providing similar coverage for 95% of the PTV. For PTV-54Gy, the average dose administered to the PTV is 54.2±0.217 Gy for VMAT_FF and 54.3±0.217 Gy for VMAT_FFF. The disparity between the two methods is statistically significant (p=0.011).

The evaluation of the plan dosimetric parameters reveals that the uniformity index (UI) for VMAT_FF (1.077±0.013) and VMAT_FFF (1.070±0.016) does not exhibit a significant difference (p=0.438). This suggests that both techniques achieve comparable dose uniformity throughout the PTV. The coverage index values for the two techniques are closely aligned, with VMAT_FF measuring 0.834±0.07 and VMAT_FFF at 0.835±0.07, showing no significant difference (p=0.710). Regarding the homogeneity index (HI), both VMAT_FF (1.07±0.016) and VMAT_FFF (1.07±0.017) are nearly the same, with no significant difference (p=0.537). This finding suggests that both techniques provide comparable homogeneity in dose distribution, ensuring an even dose within the PTV. The conformity index (CI) is also very similar for both methods, with VMAT_FF at 0.975±0.017 and VMAT_FFF at 0.975±0.019, again showing no significant difference (p=0.813). Both techniques exhibit equivalent conformity. In terms of the gradient index (GI), the values for both techniques are comparable (VMAT_FF: 1.21±0.120, VMAT_FFF: 1.21±0.118), with no significant difference (p=0.769). This indicates that the dose fall-off outside the PTV is similarly pronounced for both techniques. Lastly, the undefined dosimetric index (UDI) for both techniques is nearly identical (VMAT_FF: 1.05±0.015, VMAT_FFF: 1.05±0.014), with no significant difference (p=0.712). This implies that both techniques possess similar dosimetric characteristics that are not reflected in the other indices, thereby maintaining equivalent treatment quality.

The monitor units (MU) were notably higher in the VMAT_FFF plans (583±52.1) compared to the VMAT_FF plans (530±69.9, p=0.001), indicating improved delivery efficiency in the VMAT_FF plans. The mean Gamma Passing Rate was significantly higher for VMAT_FF (98.8±0.359%) compared to VMAT_FFF (98.5±0.346%), p<0.001.

Table 3 summarizes the details of the dosimetric parameters and NTCP values associated with different organs at risk (OARs) in the comparison between flattened field (FF) and flattened filter-free (FFF) VMAT plans. The maximum dose delivered to the spinal cord was identical for both the VMAT_FF (31.8±3.29 Gy) and VMAT_FFF (31.8±3.28 Gy) treatment plans, demonstrating no statistically significant difference (p=0.834). Similarly, the brainstem received a maximum dose of 22.1±10.4 Gy in the VMAT_FF plan and 22.4±11.0 Gy in the VMAT_FFF plan, with no significant variation noted (p=0.582). Furthermore, the max-

Table 3 Comparison of OAR physical and biological dose analysis between FF and FFF VMAT plans

Organ at risks (OAR)	Dosimetric parameter	VMAT_FF (mean±SD)	VMAT_FFF (mean±SD)	p
Spinal cord	Maximum dose (Gy)	31.8±3.29	31.8±3.28	0.834
	NTCP poisson-LQ (myelitis necrosis)	0.00±0.00	0.00±0.00	–
Mandible	Maximum dose (Gy)	62.2±0.725	62.3±0.757	0.694
	NTCP poisson-LQ (joint dysfunction)	0.656±0.376	0.686±0.369	0.072
Brainstem	Maximum dose (Gy)	22.1±10.4	22.4±11.0	0.582
	NTCP poisson-LQ (necrosis/infraction)	0.00±0.00	0.00±0.00	–
Optic chiasm	Maximum dose (Gy)	2.52±1.98	2.45±1.99	0.278
	NTCP poisson-LQ (blindness)	0.00±0.00	0.00±0.00	–
Eye (right)	Maximum dose (Gy)	3.45±3.37	3.33±3.66	0.190
	NTCP poisson-LQ (blindness)	0.00±0.00	0.00±0.00	
Eye (left)	Maximum dose (Gy)	5.99±10.7	5.64±10.5	0.005
	NTCP poisson-LQ (blindness)	0.00±0.00	0.00±0.00	–
Parotid glands (right)	Mean dose (Gy)	24.6±4.64	24.1±4.52	0.001
	D50	20.6±7.93	19.6±7.41	0.003
	V50	11.3±6.95	11.6±7.41	0.326
	V40	24.2±10.3	24.2±9.72	0.863
	V30	36.3±12.7	35.3±10.9	0.178
	NTCP poisson-LQ (xerostomia)	17.8±8.17	17.9±8.29	0.788
Parotid glands (left)	Mean dose (Gy)	24.9±5.16	24.5±5.27	0.005
	D50	20.7±7.94	19.8±7.74	0.037
	V50	13.8±8.55	14.3±8.92	0.236
	V40	26±10.1	25.9±10.4	0.880
	V30	38±12.4	36.9±11.8	0.098
	NTCP poisson-LQ (xerostomia)	20.3±11.2	20.7±11.4	0.316

FF: Flattening filter; FFF: Flattening filter free; SD: Standard deviation; Gy: Gray; NTCP: Normal tissue complication probability; LQ: Linear-quadratic; D50: Dose received by 50% of the volume; VyyGy: Percentage volume of an organ that receives at yyGy of radiation

imum dose to the optic chiasm was slightly lower in the VMAT_FFF plan (2.45±1.99 Gy) compared to the VMAT_FF plan (2.52±1.98 Gy), although this difference was not statistically significant (p=0.278).

Regarding the mandible, no significant difference was observed (p=0.694), with doses of 62.2±0.725 Gy for the VMAT_FF plan and 62.3±0.757 Gy for the VMAT_FFF plan. For the Right Parotid Gland, the average dose delivered by VMAT_FF is 24.6±4.64 Gy, whereas VMAT_FFF provides a dose of 24.1±4.52 Gy. The observed difference is statistically significant (p=0.001), indicating that VMAT_FF delivers a marginally higher mean dose. Regarding D50, which represents the dose received by 50% of the parotid volume, VMAT_FF administers 20.6±7.93 Gy, in contrast to VMAT_FFF, which delivers 19.6±7.41 Gy. This difference is also statistically significant (p=0.003), suggesting that VMAT_FF results in a greater dose to 50% of the parotid gland compared to VMAT_FFF. However, no substantial differences were found in specific dose-volume metrics, such as V50 (11.3±6.95% in VMAT_FF versus 11.6±7.41% in VMAT_FFF, p=0.326), V40 (24.2±10.3% in VMAT_FF versus 24.2±9.72% in VMAT_FFF, p=0.863), and V30 (36.3±12.7% in VMAT_FF versus 35.3±10.9% in VMAT_FFF, p=0.178).

A similar trend was observed for the left parotid gland, where the mean dose was significantly lower in the FFF plan (24.9±5.27 Gy) compared to the FF plan (25±5.19 Gy, p=0.003), For the Left Parotid Gland, the average dose administered by VMAT_FF is 24.9±5.16 Gy, whereas VMAT_FFF delivers an average dose of 24.5±5.27 Gy, with a statistically significant difference observed (p=0.005). Regarding D50, which represents the dose received by 50% of the parotid volume, VMAT_FF provides a dose of 20.7±7.94 Gy, in contrast to VMAT_FFF, which delivers 19.8±7.74 Gy, also showing a significant difference (p=0.037). This suggests that VMAT_FF administers a higher dose to 50% of the left parotid gland compared to VMAT_FFF. While the dose-volume parameters V50, V40, and V30 did not show significant differences.

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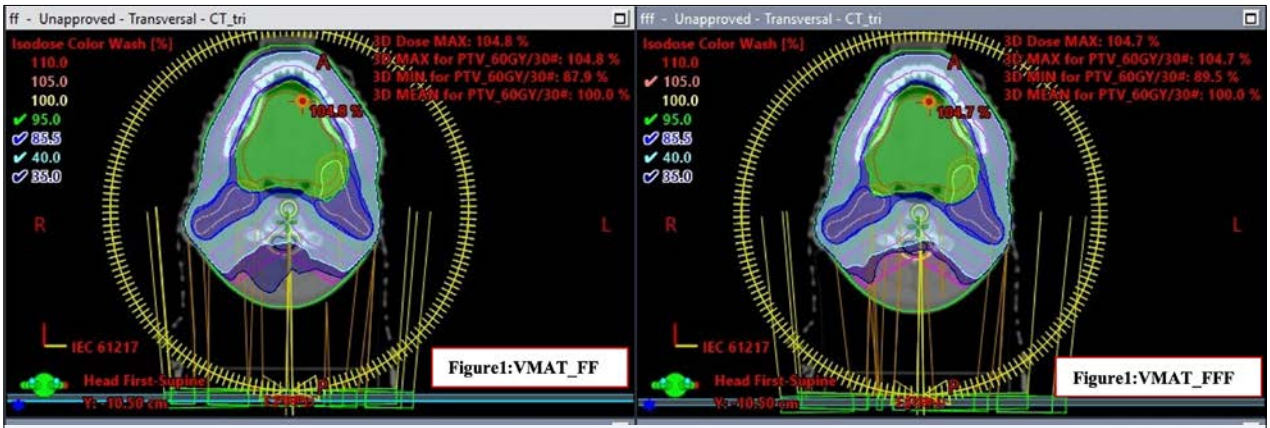

Fig. 1. Axial slice showing isodose distribution for VMAT_FF and VMAT_FFF, with isodose lines up to 35% of the maximum dose and color wash depicting overall dose distribution.
VMAT: Volumetric modulated arc therapy; FF: Flattening filter; FFF: Flattening filter free.

A comparison of the maximum dose delivered to the eyes revealed no significant difference for the right eye, with values of 3.45±3.37 Gy in the VMAT_FF plan and 3.33±3.66 Gy in the VMAT_FFF plan (p=0.190). However, a significant reduction in the maximum dose to the left eye was observed in the VMAT_FFF plan, which recorded a dose of 5.64±10.5 Gy, in contrast to the VMAT_FF plan's dose of 5.99±10.7 Gy (p=0.005).

The comparison of NTCP values between VMAT_FF and VMAT_FFF plans indicated that there were no significant differences for most organs at risk (OARs). In particular, the NTCP values for the spinal cord, brainstem and optic chiasm, eye related to myelitis necrosis, necrosis/infarction and blindness were both recorded as 0.00±0.00 for the VMAT_FF and VMAT_FFF plans. Furthermore, although the NTCP values for joint dysfunction in the mandible were slightly higher in the VMAT_FFF plans (0.686±0.369) compared to the VMAT_FF plans (0.656±0.376), this difference did not reach statistical significance (p=0.072). Concerning the parotid glands, The NTCP values for Xerostomia, derived from the Poisson-LQ model, exhibited minimal differences between VMAT_FF and VMAT_FFF. For the right parotid, the values recorded were 17.8±8.17 and 17.9±8.29, while for the left parotid; the values were 20.3±11.2 and 20.7±11.4. These findings indicate that there is no significant difference, implying that the NTCP values remain consistent across both treatment modalities (p>0.05).

DISCUSSION

In this study, we assessed the radiobiological and dosimetric effects of the FFF photon beam in comparison to the FF photon beam, utilizing VMAT planning techniques for the treatment of oral cavity cancer. Figure 1 illustrates the axial slice isodose distribution in the different dose levels for VMAT_FF and VMAT_FFF. The isodose lines represent the maximum dose levels up to 35%, and the color wash depicts the overall dose distribution and Figure 2 illustrates the dose volume histogram (DVH) curves between the VMAT_FF and VMAT_FFF techniques. This indicates that the overall dose distribution to the target volumes (PTVs) and organs at risk (OARs) between the two VMAT approaches.

In our study, dosimetric analysis of PTV-60Gy, the maximum and mean doses delivered to the target volume were observed to be comparable in both VMAT_FF and VMAT_FFF techniques. Furthermore, the conformity index (CI) in the FFF mode demonstrated a significant similarity to that of the FF mode, indicating that the dose distribution conformity between the two methods is alike. These results are consistent with earlier research that has examined the dosimetric properties of flattening filter-free (FFF) linear accelerators. For instance, Zwahlen et al.[21] reported that FFF beams, while offering benefits such as reduced treatment duration and enhanced dose delivery efficiency did not markedly change the dose distributions within the target volume when compared to FF beams, especially regarding the mean and maximum doses to the target.

Dosimetric indices of dose distribution, the uniformity index (UI), homogeneity index (HI), gradient index (GI), and undefined dosimetric index (UDI) in our study revealed no significant differences between the two modalities. This suggests that both VMAT_FF and VMAT_FFF exhibit similar characteristics in dose distribution regarding uniformity and homoge-

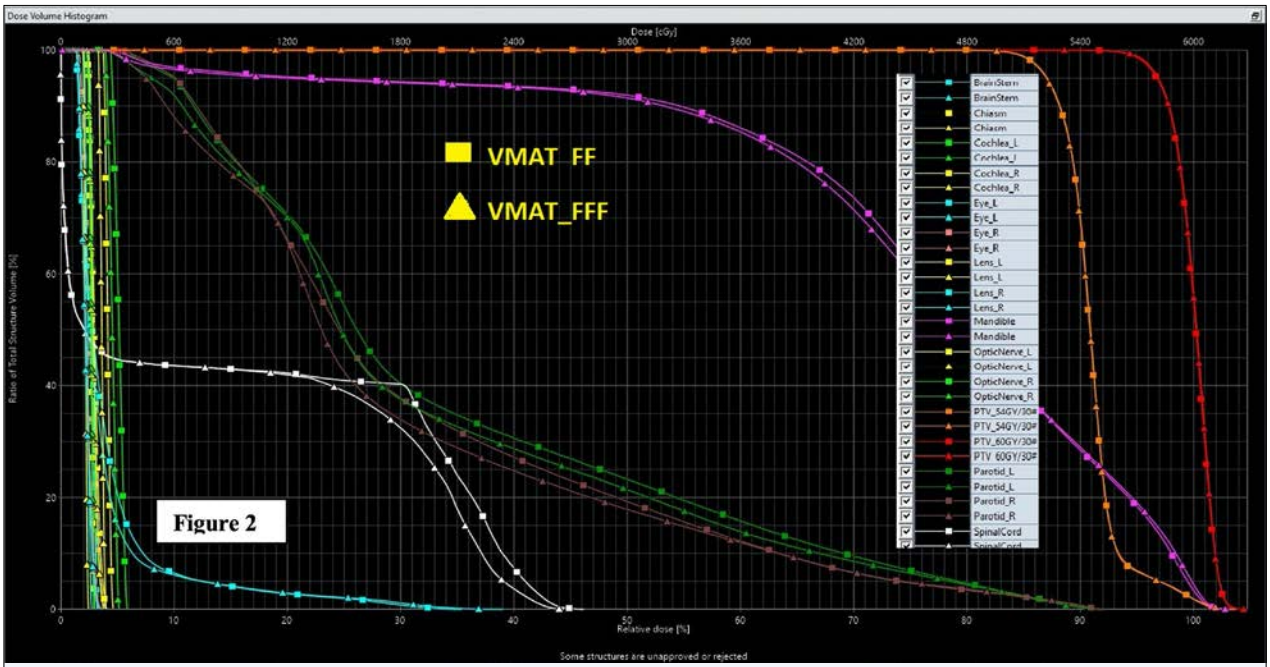

Fig. 2. Dose volume histogram (DVH) curves comparing VMAT_FF and VMAT_FFF, showing dose distribution to planning target volumes and organs at risks.
VMAT: Volumetric modulated arc therapy; FF: Flattening filter; FFF: Flattening filter free.

neity. These results align with the findings of earlier studies conducted by Kim et al.[22] and Hrbacek et al.,[23] which indicated that FFF techniques deliver comparable dose uniformity and target coverage, while also enhancing treatment efficiency through shorter beam delivery times.

A minor variation in the mean dose for the PTV-54Gy was noted between the two techniques, with VMAT_FF administering a slightly lower dose (54.2±0.217 Gy) compared to VMAT_FFF (54.3±0.217 Gy), which was statistically significant (p=0.011). Although this difference is minimal, it may indicate the influence of the lower energy and the more rapid off-axis dose reduction associated with the FFF mode, as previously highlighted in the research conducted by Sarma et al.[24] and Low et al.[25]. These studies proposed that FFF beams might encounter difficulties in achieving the same depth of dose distribution in larger target volumes due to the accelerated dose fall-off, thereby complicating the delivery of uniform dose coverage across the entire target.

Monitor units (MU) employed in FFF VMAT planning were observed to be significantly higher than those used in FF VMAT planning (583±52.1 compared to 530±69.9, p=0.001). This observation aligns with previous studies, such as that conducted by Zwahlen et al.,[21] which suggested that FFF beam delivery requires a greater number of MUs due to the absence of a flattening filter. However, despite the elevated MU associated with FFF plans, no significant difference in treatment duration was observed between the two planning methods. This can be attributed to the administration of a consistent single dose of 2Gy in both FFF and FF modalities, which alleviated any potential impact of MU discrepancies on treatment time. These findings indicate that while FFF plans necessitate a higher quantity of MUs, they do not compromise therapeutic effectiveness.

Figure 3 illustrates the correlation between the Equivalent Dose in 2 Gy/Fraction (Gy) and the LQ Scaled DVH, which serves as an indicator of radiation dose distribution, for multiple types of Normal Tissue Complication Probabilities (NTCPs) in a single patient. The graph presents the NTCP curves corresponding to various organs and tissues, such as the Mandible, Spinal Cord, Brain Stem, Parotid Gland, among others. A significant insight derived from this graph is the divergence observed in the NTCP curves across various organs and tissues, which reflects their distinct sensitivities to radiation exposure. The NTCP curves for the Spinal Cord and Brain Stem exhibit steeper inclines, implying that these tissues are more susceptible to increases in radiation dosage. In contrast, the NTCP curves for the Mandible and Parotid Gland display shallower slopes, suggesting

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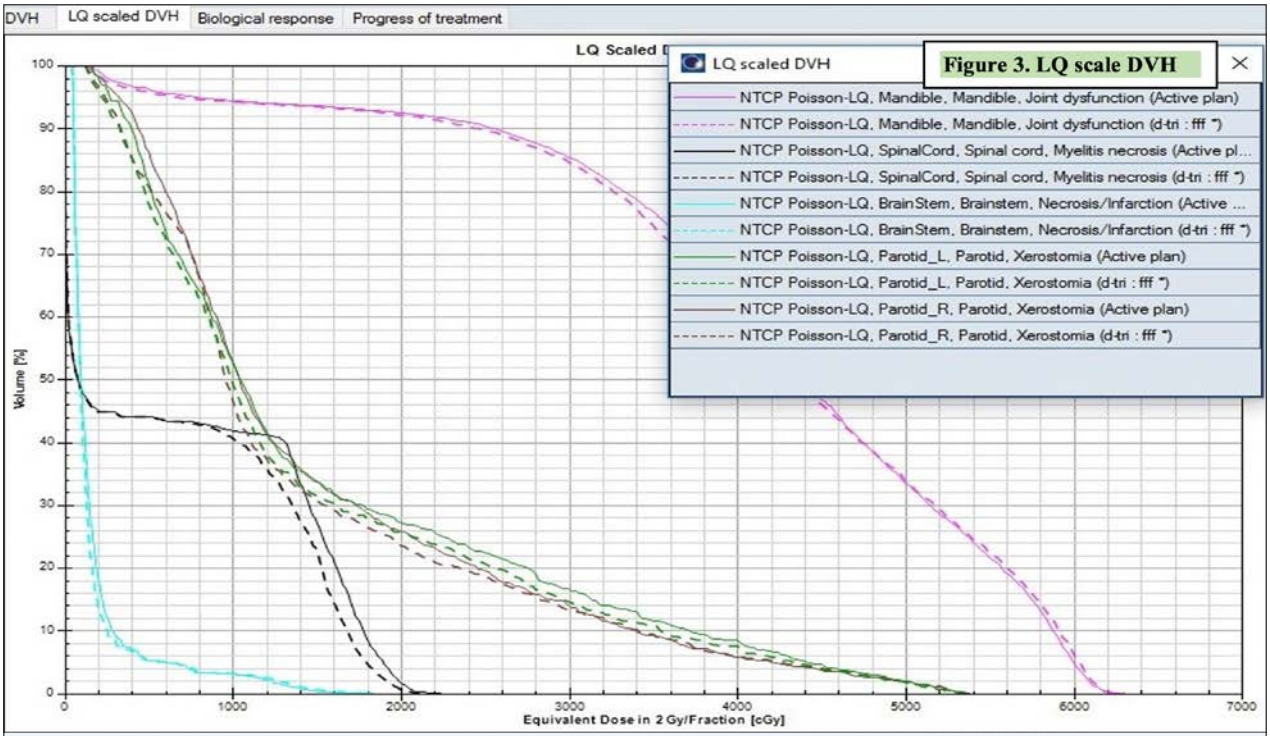

Fig. 3. Linear-quadratic (LQ) scale DVH showing biologically scaled dose-volume histograms for OAR structures used in NTCP analysis.
DVH: Dose volume histogram; OAR: Organ at risks; NTCP: Normal tissue complication probability.

that these tissues possess a greater resistance to radiation-induced damage. This variation in sensitivity is a crucial factor in treatment planning, as healthcare professionals must strive to deliver an effective therapeutic dose to the tumor while concurrently minimizing the potential for unacceptable toxicities to adjacent healthy tissues.

The graph further illustrates that specific normal tissues, including the Parotid Gland and Xerostomia, exhibit two separate NTCP curves, which are distinguished by the labels VMAT_FF and VMAT_FFF. This indicates that the selection of the radiation beam whether a VMAT_FF or a VMAT_FFF beam can influence the likelihood of normal tissue complications in these organs for the patient. The variation between the NTCP curves for VMAT_FF and VMAT_FFF suggests that the type of beam may significantly affect the risk of toxicities, with the VMAT_FFF beam potentially presenting a reduced probability of complications for certain organs when compared to the VMAT_FF beam at the same equivalent dose level. These results underscore the critical role of beam selection in radiation treatment planning and emphasize the necessity of integrating this understanding into the optimization process to enhance patient outcomes and quality of life.

Organ-specific Finding

The mean dose and D50 for the left parotid gland were decreased by 1.61% and 4.35%, respectively, in the VMAT_FFF technique when compared to VMAT_FF. However, the NTCP Poisson-LQ (Xerostomia) exhibited a slight increase of 1.93%, which was not statistically significant. In a similar manner, the right parotid gland experienced reductions of 2.03% in mean dose and 4.85% in D50, accompanied by a non-significant increase of 0.56% in NTCP. In alignment with previous research, doses to the parotid glands that exceed 25–30 Gy significantly elevate the risk of xerostomia. [26–29]. Our results further support the notion that minimizing parotid doses can lead to a decrease in xerostomia incidence, underscoring the critical need for dose optimization to mitigate side effects and enhance treatment outcomes.

Mandibular dysfunction, which encompasses conditions such as trismus and osteoradionecrosis, exhibits a strong association with the maximum radiation dose absorbed by the mandible. Previous studies have indicated that doses surpassing 60–65 Gy

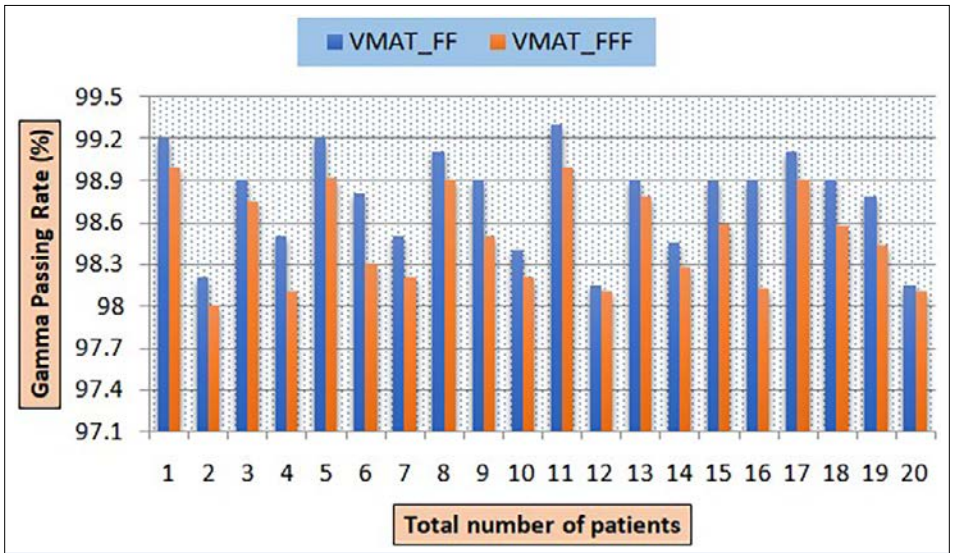

Fig. 4. Gamma passing rate (%) comparison between VMAT_FF and VMAT_FFF.
VMAT: Volumetric modulated arc therapy; FF: Flattening filter; FFF: Flattening filter free.

significantly elevate the likelihood of these complications.[30,31]. In our evaluation found the maximum dose delivered to the mandible in the FF plan exhibited a negligible reduction of 0.16% when compared to the FFF plan, accompanied by a 4.37% decrease in the NTCP for joint dysfunction. These results indicate that the risk profiles for mandibular dysfunction remain consistent between the two techniques; however, the marginally elevated NTCP observed in FFF plans necessitates additional examination.

Kirkpatrick et al.[32] conducted a study on the radiation tolerance of the spinal cord and determined that the likelihood of developing myelitis necrosis significantly increases when radiation doses surpass 45–50 Gy using conventional fractionation (2 Gy per fraction). This dosage threshold indicates the onset of irreversible damage to the spinal cord, which can result in complications such as radiation myelopathy. Their research underscored the necessity of adhering to stringent dose limits to reduce neurological risks. In our investigation, both VMAT_FF and VMAT_FFF techniques demonstrated comparable maximum doses to the spinal cord, achieving a dose reduction of 29.33% in relation to the established tolerance limit.

The brainstem, similar to the spinal cord, exhibits a restricted tolerance to radiation owing to its essential neurological roles. Doses surpassing 54 Gy markedly elevate the likelihood of necrosis and vascular injury.[33,34] In this study, the NTCP values associated with brainstem complications were minimal, with the maximum doses in both FF and FFF plans remaining within permissible thresholds, thereby providing adequate protection to the brainstem without undermining the therapeutic dose. These results underscore the necessity of following dose limitations to reduce radiation-related damage while preserving clinical effectiveness.

The optic chiasm exhibits a significant sensitivity to radiation, with a tolerance dose estimated at around 55 Gy when utilizing conventional fractionation (2 Gy per fraction) to reduce the likelihood of complications such as blindness. Clinical research, including the work of Emami etal.,[35] indicates a TD5/5 of 50 Gy for the optic chiasm. These parameters have become essential components of contemporary radiotherapy protocols aimed at preventing radiation-induced optic neuropathy. Surpassing these limits can lead to irreversible damage to the optic pathways, highlighting the importance of adhering to dose limitations during the treatment planning process. In our study, the maximum dose (Gy) in the VMAT_FFF plan demonstrated a 2.78% decrease compared to the VMAT_FF plan; however, this difference lacks statistical significance. The NTCP Poisson-LQ (Blindness) revealed no difference, with both values recorded at 0.

Radiation exposure has the potential to cause ocular complications, including cataracts, retinopathy, and optic neuropathy. Cataracts are generally observed at radiation doses exceeding 2 Gy, while optic neuropathy is associated with doses greater than 45 Gy. To mitigate these risks, radiotherapy

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protocols are designed to keep the maximum dose to the eyes below 45 Gy. In our investigation, the maximum doses administered to both the right and left eyes remained within these established limits, suggesting a minimal risk of clinically significant visual impairment. This finding is consistent with guidelines that advocate for rigorous dosimetric control to safeguard ocular structures while delivering effective treatment. Research conducted by Mayo et al.[36] and Bhandare et al.[37] reinforces these dose limitations, underscoring the necessity of keeping doses significantly below 50 Gy to prevent complications. Furthermore, studies referenced asand have identified comparable thresholds for radiation-induced ocular toxicity.[38] The percentage difference in maximum doses for both eyes were negligible, with the right eye receiving 3.48% and the left eye 5.84% lower doses in VMAT_FFF compared to VMAT_FF, while the NTCP Poisson-LQ for blindness indicated no difference (0%).

Figure 4 illustrates the comparison of the Gamma Passing Rate (GPR) between VMAT_FF and VMAT_FFF for a cohort of 20 patients. Both techniques exhibited clinically acceptable GPR values exceeding 97%. However, VMAT_FF consistently demonstrated marginally higher passing rates than VMAT_FFF. This indicates slightly enhanced delivery accuracy with FF beams, although both methods met high standards for quality treatment delivery.

Limitation of the Study

The retrospective nature of the study, along with its restricted sample size, limits both its statistical power and the ability to generalize the findings. Although the Normal Tissue Complication Probability (NTCP) analysis employing the Poisson Linear Quadratic (LQ) model offers important insights, it may not fully encompass the intricate nature of clinical toxicity.

CONCLUSION

Our research indicates that VMAT_FFF techniques provide similar dosimetric and radiobiological properties to VMAT_FF techniques in the treatment of oral cavity cancer. The slight variations in dosimetric parameters do not meaningfully impact the overall effectiveness of treatment or the associated risk profiles. These results advocate for the clinical use of FFF VMAT, highlighting the critical role of meticulous treatment planning in enhancing patient outcomes.

Ethics Committee Approval: The study was approved by the Indira Gandhi Institute of Medical Science Office Ethics Committee (no: 35/IEC/IGIMS/2024, date: 17/05/2024).

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209–49.
2. Gupta B, Johnson NW. Systematic review and meta-analysis of association studies of alcohol, tobacco, and other risk factors for oral cancer. J Oral Pathol Med2014;43(9):635–47.
3. Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of human papillomavirus-positive head and neck squamous cell carcinoma. J Clin Oncol2015;33(29):3235–42.
4. Castellsagué X, Alemany L, Quer M, Halec G, Quirós B, Tous S, et al. HPV involvement in head and neck cancers: Comprehensive assessment of biomarkers in 3680 patients. J Natl Cancer Inst 2016;108(6):djv403.
5. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009;45(4–5):309–16.
6. Hunte SO, Clark CH, Zyuzikov N, Nisbet A. Volumetric modulated arc therapy (VMAT): A review of clinical outcomes—what is the clinical evidence for the most effective implementation? Br J Radiol 2022;95(1136):20201289.
7. Georg D, Knoos T, McClean B. Current status and future perspective of flattening filter free photon beams. Med Phys 2011;38(3):1280–93.
8. Jank J, Kragl G, Georg D. Impact of a flattening filter-free linear accelerator on structural shielding design. Z Med Phys 2014;24(1):38–48.
9. Cashmore J. The characterization of unflattened photon beams from a 6 MV linear accelerator. Phys Med Biol 2008;53(7):1933–46.

10. Almberg SS, Frengen J, Lindmo T. Monte Carlo study of in-field and out-of-field dose distributions from a linear accelerator operating with and without a flattening filter. Med Phys 2012;39(9):5194–203.
11. Akino Y, Ota S, Inoue S, Mizuno H, Sumida I, Yoshioka Y, et al. Characteristics of flattening filter free beams at low monitor unit settings. Med Phys 2013;40(11):112101.
12. Patil D, Zope M, Madhawi R, Raj S, Kishor K, Devi S, et al. Physical and radiobiological dosimetric comparison of volumetric arc treatment plans with or without flattening filter in synchronous bilateral breast cancer. Turk J Oncol 2024;39(4):411–22.
13. Zwahlen DR, Lang S, Hrbacek J, Glanzmann C, Kloeck S, Najafi Y, et al. The use of photon beams of a flattening filter-free linear accelerator for hypofractionated volumetric modulated arc therapy in localized prostate cancer. Int J Radiat Oncol Biol Phys2012;83(5):1655–60.
14. Alongi F, Fogliata A, Clerici E, Navarria P, Tozzi A, Comito T, et al. Volumetric modulated arc therapy with flattening filter-free beams for isolated abdominal pelvic lymph nodes: Report of dosimetric and early clinical results in oligometastatic patients. Radiat Oncol 2012;7:204.
15. Krishna GS, Srinivas V, Ayyangar KM, Reddy PY. Comparative study of old and new versions of treatment planning system using dose volume histogram indices of clinical plans. J Med Phys 2016;41(3):192–7.
16. Murphy MJ, Chang S, Gibbs I, Le QT, Martin D, Kim D. Image-guided radiosurgery in the treatment of spinal metastases. Neurosurg Focus 2001;11(6):e6.
17. International Commission on Radiation Units and Measurements. Prescribing, recording, and reporting photon-beam intensity-modulated radiation therapy (IMRT). Available at: https://www.icru.org/report/prescribing-recording-and-reporting-intensity-modulated-photon-beam-therapy-imrticru-report-83/. Accessed Mar 21, 2025.
18. Paddick IA. A simple scoring ratio to index the conformity of radiosurgical treatment plans. J Neurosurg 2000;93(Suppl 3):219–22.
19. Krishna GS, Srinivas V, Ayyangar KM, Reddy PY, et al. Comparative study of old and new versions of treatment planning system using dose volume histogram indices of clinical plans. J Med Phys 2016;41(3):192–7.
20. Akpati H, Kim C, Kim B, Park T, Meek A. Unified dosimetry index (UDI): A figure of merit for ranking treatment plans. J Appl Clin Med Phys 2008;9(3):99–108.
21. Zwahlen DR, Lang S, Hrbacek J, Glanzmann C, Kloeck S, Najafi Y, et al. The use of photon beams of a flattening filter-free linear accelerator for hypofractionated volumetric modulated arc therapy in localized prostate cancer. Int J Radiat Oncol Biol Phys2012;83(5):1655–60.
22. Kim JW, Cho BC, Lee SW. A comparison of flattening filter-free and flattening filter photon beams in breast cancer treatment. Radiat Oncol 2018;13(1):89.
23. Hrbacek J, Lang S, Zwahlen DR. The use of photon beams of a flattening filter-free linear accelerator for hypofractionated volumetric modulated arc therapy in localized prostate cancer. Int J Radiat Oncol Biol Phys 2014;83(5):1655–60.
24. Sarma R, Kumar S, Yadav R. Dosimetric comparison of flattening filter-free and flattening filter beams in treatment of head and neck cancer. Med Phys 2015;42(6):3519–26.
25. Low DA, McCullough EC. The impact of flattening filter-free beams on radiation therapy: A review of clinical dosimetric studies. J Radiat Oncol 2013;28(3):235–42.
26. Deasy JO, Moiseenko V, Marks L, Chao KS, Nam J, Eisbruch A. Radiotherapy dose-volume effects on salivary gland function. Int J Radiat Oncol Biol Phys 2010;76(3):S58–63.
27. Eisbruch A, Ten Haken RK, Kim HM, Marsh LH, Ship JA. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 1999;45(3):577–87.
28. Pow EH, Kwong DL, McMillan AS, Wong MC, Sham JS, Leung LH, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: Initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys 2006;66(4):981–91.
29. Dijkema T, Terhaard CH, Roesink JM, Braam PM, van Gils CH, Moerland MA, et al. Large cohort dose-volume response analysis of parotid gland function after radiotherapy: Intensity-modulated versus conventional radiotherapy. Int J Radiat Oncol Biol Phys 2012;82(2):652–9.
30. Gomez DR, Estilo CL, Wolden SL, Zelefsky MJ, Kraus DH, Wong RJ, et al. Correlation of osteoradionecrosis and dosimetric parameters after intensity-modulated radiotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2011;81(4):e207–13.
31. Tsai CJ, Hofstede TM, Sturgis EM, Garden AS, Lindberg ME, Wei Q, et al. Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer. Int J Radiat Oncol Biol Phys 2013;85(2):415–20.
32. Kirkpatrick JP, van der Kogel AJ, Schultheiss TE. Radiation dose-volume effects in the spinal cord. Int J Radiat Oncol Biol Phys 2010;76:S42–9.
33. Lawrence YR, Li XA, el Naqa I, Hahn CA, Marks

Turk J Oncol 2025;40(2):120–132
doi: 10.5505/tjo.2025.4496

L, Merchant TE, et al. Radiation dose-volume effects in the brainstem. Int J Radiat Oncol Biol Phys 2010;76(1):S20–7.
34. Schultheiss TE, Kun LE, Ang KK, Stephens LC. Radiation response of the central nervous system. Int J Radiat Oncol Biol Phys 1995;31(5):1097–108.
35. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21(1):109–22.
36. Mayo C, Martel MK, Marks LB, Flickinger J, Nam J, Kirkpatrick J, et al. Radiation dose-volume effects of optic nerves and chiasm. Int J Radiat Oncol Biol Phys 2010;76(3):S28–35.
37. Bhandare N, Monroe AT, Morris CG, Bhatti MT, Mendenhall WM. Does altered fractionation influence the risk of radiation-induced optic neuropathy? Int J Radiat Oncol Biol Phys 2011;81(2):S11–8.
38. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76(3):S10–9.