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Radiobiological analysis of VMAT treatment plan with flattened and flattening filter free photon beam: an EUD and TCP based comparative study

Dinesh Kumar Saroj[1, 3], Suresh Yadav[2], Neetu Paliwal[3], Subhash Haldar[4], Ravindra B. Shende[1], Gaurav Gupta[1], Veenita Yogi[2]

[1]Department of Radiotherapy, BALCO Medical Center, A Unit of Vedanta medical Research Foundation, New Raipur, Chhattisgarh, India
[2]Department of Radiation Oncology, Gandhi Medical College, Bhopal, India
[3]Department of Physics, Rabindranath Tagore University, Raisen, Madhya Pradesh, India
[4]Department of Radiotherapy, Saroj Gupta Cancer Centre and Research Institute, Kolkata (West Bengal), India

ABSTRACT

Background: This study aimed to evaluate the dosimetric and radiobiological differences between 6MV flattened filter (FF) and flattening filter free (FFF) using volumetric modulated arc (VMAT) technique for head and neck (H&N) cancer patients.

Materials and methods: Fifteen patients with H&N carcinoma were selected and treated with VMAT with FF ($VMAT_{FF}$) treatment plan. Retrospectively, additional VMAT treatment plans were developed using FFF beams ($VMAT_{FFF}$). Radiobiological parameters, such as equivalent uniform dose (EUD), tumor cure probability (TCP), and normal tissue complication probability (NTCP), were calculated using Niemierko's model for both $VMAT_{FF}$ and $VMAT_{FFF}$. Correlation between dosimetric and radiobiological data were analyzed and compared.

Results: The conformity index (CI) was 0.975 ± 0.014 ($VMAT_{FF}$) and 0.964 ± 0. 019 ($VMAT_{FFF}$) with $p \geq 0.05$. Statistically, there was an insignificant difference in the planning target volume (PTV) results for TCP (%) values, with values of 81.20 ± 0.88% ($VMAT_{FF}$) and 81.01 ± 0.92 (%) ($VMAT_{FF}$). Similarly, there was an insignificant difference in the EUD (Gy) values, which were 71.53 ± 0.33 Gy ($VMAT_{FF}$) and 71.46 ± 0.34 Gy ($VMAT_{FFF}$). The NTCP values for the spinal cord, left parotid, and right parotid were 6.54×10^{-07}%, 8.04%, and 7.69%, respectively, in the case of $VMAT_{FF}$. For $VMAT_{FFF}$, the corresponding NTCP values for the spinal cord, parotids left, and parotid right were 3.09×10^{-07}%, 6.57%, and 6.73%, respectively.

Conclusion: The EUD and Mean Dose to PTV were strongly correlated for $VMAT_{FFF}$. An increased mean dose to the PTV and greater TCP were reported for the $VMAT_{FF}$, which can enhance the delivery of the therapeutic dose to the target.

Key words: volumetric modulated arc therapy; tumor cure probability; normal tissue complication probability; equivalent uniform dose; flattened filter free

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Introduction

Modern technological advancements have resulted in significant improvements in radiotherapy planning and execution. Rapid Arc is a volumetric modulated arc treatment (VMAT) technique that produces modulated radiation beams by simultaneously altering the multi-leaf collimator

Address for correspondence: Dinesh Kumar Saroj MSc (Physics), Dip.R.P., Department of Radiotherapy, BALCO Medical Center, A Unit of Vedanta Medical Research Foundation, New Raipur, Chhattisgarh, India-49366, tel: (+91)-9869691303; e-mail:dinesh.saroj@ymail.com

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(MLC) field aperture, dose rate, and gantry rotation speed. The primary objective of VMAT treatment is to minimize the dose to the organs at risk (OARs) while producing a conformal radiation dose distribution to the target [1, 2]. On the other hand, a number of variables, including the technique for treatment planning and the algorithms employed in Treatment Planning Systems (TPS), have an effect on dose distribution. Previous research has determined that VMAT stands out as the most efficient treatment technique across various clinical sites. It excels in terms of achieving superior dose conformity, sparing critical organs (OARs), and reducing treatment duration compared to other contemporary treatment methods [3]. The treatment planner meticulously developed the treatment plan using an iterative optimization procedure, taking into account various crucial variables, such as the number of beams, arc angles, collimator rotation, and dose restrictions. These considerations were critical when developing the approach that fit the essential therapeutic objectives. As a result, the VMAT planning optimization method enables the planner to generate a wide range of treatment plans. A comprehensive strategy comparison is used to select the best plan from among these. Notably, there is increased interest in TPS that use a radiobiological model for plan optimization and evaluation [4, 5].

The flattening filter's primary objective was to deliver flattened dose profiles at specified depths.

To minimize the scatter contribution from the flattening filter (FF), it would seem reasonable to remove the FF from the photon beam route [6–8]. Clinical linear accelerators (LINACs) operation in flattening filter-free (FFF) mode has increased in popularity since the creation of more modern options for treatment. Interest in the FFF mode of operation of LINAC has lately increased due to VMAT and other cutting-edge, effective treatment methods.

The forward peaked dose profile of the FFF beam is its most distinguishing feature [9–12]. Additionally, it has a higher dose rate than the flattened photon beam [13], lower doses for the OARs [14], and is less likely to contaminate neutrons for energy beams above 15 MV. As a result, the clinical use of an FFF photon beam for patient treatment will lead to a shorter treatment session, an increased surface dose and a decreased likelihood of radiation-induced secondary cancer [15, 16]. Previous studies have shown that the VMAT treatment techniques are suitable for sites like the brain, head and neck (H&N), prostate, pelvis, etc. [17–19]. It has also been shown that when FFF beams are compared to FF, they create dose distributions comparable to those of FF with better OARs sparing and shorter treatment time [20, 21].

Most of these comparative studies have examined the high dose rate of the FFF beam compared to the FF beam in terms of time efficiency. There is a very limited study available on the comparison of physical dose indices to the radiobiological indices for H&N cases with VMAT treatment plans. The objective of this research is to compare the dosimetric and radiobiological characteristics of the FFF photon beam treatment plan and the FF photon beam treatment plan for squamous cell cancer using the VMAT planning technique. By comparing both the physical dose parameters and radiobiological parameters between the FF and FFF VMAT treatment plans, the study aimed to assess the overall plan quality, target coverage, and sparing of critical structures. This comprehensive evaluation allowed for a more thorough understanding of the differences and potential advantages between the two treatment techniques. Moreover, the study investigated the way these radiobiological estimates of Tumor Cure Probability (TCP) and Normal Tissue Complication Probability (NTCP) correlated with the physical dose metrics for the VMAT treatment plan with both FF and FFF photon beams.

Materials and methods

Patient simulation and selection

15 patients with squamous cell carcinoma were selected for our study from our institutional registered patient's database. All patients underwent treatment employing a 6 MV FF VMAT treatment plan on a Varian True Beam medical LINAC (Varian Medical Systems, Palo Alto, CA). The LINAC consists of up to 5 electron beams with energies of 6 MeV, 9 MeV, 12 MeV, 15 MeV, and 18 MeV as well as 6 MV, 10 MV, and 15 MV photon beams. There is also an FFF mode available for a 6 MV photon beam. For the FF and FFF photon modes, the highest dose rates of 600 MU/min and 1400 MU/min are possible. The MLC on the LINAC has 60 pairs,

with the inner 40 pairs having leaves with a thickness of 5 mm and the outer 20 pairs having leaves with a thickness of 10 mm at the isocenter. For better patient positioning on the couch, on-board imaging with KV, MV, and computed tomographic volumetric images can be performed with an existing LINAC.

Treatment planning

For all patients included in the study, treatment plans were generated on Eclipse TPS (Varian Medical Systems, Palo Alto, CA, USA), version 16.1, using the Anisotropic Analytical Algorithm (AAA) for dose calculation. All patients planned to receive a treatment dose of 70 Gy in 35 fractions, with 2 Gy per day per fraction for 5 fractions in a week.

Retrospectively, additional VMAT plans were designed for all selected patients with FFF photon beams. A total of 30 treatment plans for 15 patients were used in this study for analysis. Three full arcs of rotation from 181°–179°, 179°–181°, and 181°–179° with collimator angles of 30°, 330°, and 45° were used, respectively, for designing both types of the competing treatment plan. While designing the VMAT treatment plan with FFF, all the planning and optimization parameters were kept the same as the VMAT plan with FF photon beam to avoid the bias. The dose was normalized in such a way that 95% of the PTV (Planning Target Volume) should receive the 100% of the prescription dose. While optimizing the treatment plan, the following constraints were used: brainstem (max. dose) < 54 Gy, spinal cord (max. dose) < 45 Gy, lens (max. dose) < 10 Gy and optic chiasm < 55 Gy. Parotids (mean) < 26 Gy, cochlea (mean) < 45 Gy, and larynx (mean) < 45 Gy.

Radiobiological planning

To compare treatment plans, a radiobiological plan evaluation was also performed. For TCP and NTCP, there are a number of models that may be found in the literature [22, 23]. In the present study, we employed radiobiological modelling based on equivalent uniform dose (EUD), which is excellent at predicting the impact of more complex dose distributions. EUD is the dose that, when delivered across the same number of fractions as the non-uniform dose distribution of interest, has the same radiobiological effect. According to Niemierko's model, the EUD is given by [24, 25]:

$$EUD = \sum_i (v_i\, D_i^{\,a})^{\frac{1}{a}} \quad (1)$$

where 'a' is a constant parameter that is different for a specific normal tissue or tumour type. '*Vi*' is that ith partial volume that receives a dose of D*i* in Gy.

The TCP and NTCP are calculated by the following equations

$$TCP = \frac{1}{1+\left(\frac{TCD_{50}}{EUD}\right)^{4\gamma_{50}}} \quad (2)$$

$$NTCP = \frac{1}{1+\left(\frac{TD_{50}}{EUD}\right)^{4\gamma_{50}}} \quad (3)$$

where γ50 = slope of the dose response curve at a dose of 50% complication or control probability; TCD_{50} = tumour dose for 50% TCP; and $TD_{50/5}$ = normal tissue dose for 50% complication probability in 5 years.

The EUDMODEL.m is a MATLAB (The Math Works, Inc., Natick, MA, USA) based program for EUD, TCP, and NTCP calculation [24]. A total of 30 cumulative dose volume histograms (c-DHVs) were exported from TPS and used as input for the above program. Table 1 shows the various radiobiological factors used to calculate the EUD, TCP, and NTCP for tumours and different normal structures [24, 25].

Treatment plan evaluation

For treatment plans with hot and cold regions, a qualitative assessment is necessary. The quantitative analysis includes all DVHs. The DVHs were created to estimate the dose to various structures in various treatment plans. Dose coverage is the percentage of the PTV that receives the prescribed dose of 100%. It is a figure that illustrates how effectively the dose prescribed covers the PTV. Plans covering 92% of the recommended dosage are acceptable [26].

$$Coverage\ Index\ (C) = PTV_{PI}/PTV \quad (4)$$

where PTV_{PI} is the PTV receiving the Prescribed Isodose.

In accordance with ICRU Report No. 62 [27], conformity index (CI) is defined as follows

Table 1. Biological Parameter used for equivalent uniform dose (EUD)-based calculation of tumor cure probability (TCP) and normal tissue complication probability (NTCP) for planning target volume (PTV) and various organs at risk (OARs)

Structure	Volume type	a	γ_{50}	TD_{50} [Gy]	TCD_{50} [Gy]	α /β [Gy]	End points
Target	Tumor	–13	3.2	–	63.8	10	
Spinal Chord	Normal	7.4	4	66.5	–	3	Mylelitis/necrosis [24, 25]
Optic Nerve	Normal	25	3	65	–	3	Blindness [24, 25]
Lens	Normal	3	1	18	–	1.2	Cataract [24, 25]
Brainstem	Normal	7	3	65	–	3	Necrosis [24, 25]
Optic Chiasm	Normal	25	3	65	–	3	Blindness[24, 25]
Parotids	Normal	0.5	4	46	–	2	Xerostomia [24, 25]
Larynx	Normal	12.5	4	70	–	3	Laryngeal edema [24, 25]
Cochlea	Normal	31	3	65	–	3	Chronic serous Otitis [24, 25]

A — unit less parameter; γ_{50} — slope of dose response curve; TD_{50} — normal tissue dose for 50% complication; TCD_{50} — tumor dose for 50% TCP; α/β — alpha-beta ratio; Gy — Gray

$$Conformity\ index\ (CI) = V_{IR}/TV \quad (5)$$

where V_{IR} is the reference dose volume, and TV is the Total target volume.

CI value ranges have been defined in order to evaluate the degree of conformity. The theory suggests that the optimal CI value is 1. If the CI is between 1 and 2, the treatment is considered to be in compliance with the treatment plan. In 1993, RTOG provided rules for frequently assessing plans on a variety of various elements and the homogeneity index (HI). The idea of HI was developed based on the results of a dosimetric study of the proposed treatment [28].

$$Homogeneity\ index\ (HI) = I_{max}/RI \quad (6)$$

where I_{max} is the target's maximal isodose and RI is the reference isodose.

If HI value is:

- $0 < HI \leq 2$ — no violation;
- $2 < HI \leq 2.5$ — a minor violation;
- $HI \geq 2.5$ — major violation.

Plans with various dose gradients but the same dose conformity can be compared using the dose gradient index (GI). The effectiveness of dose fall-off outside the PTV is assessed by GI. The dose GI is defined as the ratio of the volume getting the prescribed isodose line to the volume receiving half of the recommended isodose line (29).

$$Dose\ gradient\ index\ (GI) = D_{50\%}/D_{100\%} \quad (7)$$

where $D_{100\%}$ is volume of the prescribed dose and $D_{50\%}$ is volume of half the prescribed dose.

The unified dosimetry index (UDI) is a useful tool for selecting the most effective technique for a treatment plan. The CI, HI, GI, and C are the best parameters to assess the quality of a treatment plan. The UDI includes each of the four previously mentioned criteria [30]. Any one of the four components may experience changes that affect UDI's value. A UDI number close to 1 is ideal; however, values above 1 are not taken into account.

$$UDI = CN\ X\ CI\ X\ HI\ X\ GI \quad (8)$$

Statistical analysis

Microsoft Excel was used for the statistical calculations. The significance of the differences was determined using a Student's paired t-test with two tails. The mean and 95% confidence interval for $VMAT_{FF}$ and $VMAT_{FFF}$ were assumed to be the same. Therefore, the differences between the two methods are statistically significant if the probability value $(p) \leq 0.05$.

Results

Both $VMAT_{FF}$ and $VMAT_{FFF}$ treatment plans were compared against each other on the basis of physical and radiobiological dose analysis using the DVH. All evaluation parameters had their mean and standard deviation given for all patients.

Table 2. Various dosimetric indices and their comparison between flattened filter (FF) and flattened filter free (FFF) volumetric modulated arc therapy (VMAT) treatment plan for planning target volume (PTV)

Variables	$VMAT_{FF}$ (Mean ± SD)	$VMAT_{FFF}$ (Mean ± SD)	p-value
D_{max} [Gy]	73.95 ± 0.93	74.25 ± 0.97	0.33
D_{mean} [Gy]	71.31 ± 0.27	71.29 ± 0.30	0.22
CI	0.975 ± 0.014	0.964 ± 0.019	0.07
C	1.096 ± 0.025	1.100 ± 0.025	0.62
HI	1.056 ± 0.013	1.061 ± 0.014	0.30
GI	1.025 ± 0.015	1.037 ± 0.021	0.07
UDI	1.158 ± 0.371	1.167 ± 0.365	0.47
MU	510.79 ± 48.46	603.74 ± 53.16	0.01
EUD (Gy)	71.53 ± 0.33	71.46 ± 0.34	0.49
TCP (%)	81.20 ± 0.88	81.01 ± 0.92	0.54

D_{Max} — maximum point dose; D_{Mean} — mean dose; CI — conformity index; C — coverage index; HI — homogeneity index; GI — gradient Index; UDI — unique dosimetric index; MU — Monitor unit; EUD — equivalent uniform dose; TCP — tumor cure probability; SD — standard deviation; $VMAT_{FF}$ — VMAT plan with flattened filter photon beam; $VMAT_{FFF}$ — VMAT plan with flattened filter free photon beam; Gy — Gray

Physical and radiobiological dose analysis for PTV

In Table 2, we see a comprehensive evaluation of the physical and biological characteristics of PTV, together with their corresponding p values. There is no statistically significant difference between the $VMAT_{FF}$ (73.95 ± 0.93 Gy) and the $VMAT_{FFF}$ (74.25 ± 0.97 Gy) regarding the maximum dose (Dmax) to the PTV. According to the data, the PTV received a mean dose (Dmean) of 71.31 ± 0.27 Gy from $VMAT_{FF}$ and 71.29 ± 0.30 Gy from the $VMAT_{FFF}$ treatment plan. With a p-value greater than 0.05, for $VMAT_{FF}$ coverage index (C) was 1.096 ± 0.025, and for the $VMAT_{FFF}$ treatment, the C value was 1.100 ± 0.025. The CI for $VMAT_{FFF}$ is reported to be 0.975 ± 0.014, while that for $VMAT_{FFF}$ is 0.964 ± 0.019. The HI values for FF and FFF photon beams used in VMAT therapy were 1.056 ± 0.013 and 1.061 ± 0.014, respectively. Insignificant ($p > 0.05$) GI values of 1.025 ± 0.015 and 1.037 ± 0.021 were found for $VMAT_{FF}$ and the $VMAT_{FFF}$ treatment plan, respectively. $VMAT_{FF}$ and treatment $VMAT_{FFF}$ plans had UDI scores of 1.158 ± 0.371 and 1.167 ± 0.365, respectively ($p > 0.05$). The MU values reported for the $VMAT_{FF}$ and $VMAT_{FFF}$ were 510.790 ± 48.460, and 603.740 ± 53.160, respectively ($p < 0.05$).

The EUD values for the PTV show the statistically insignificant dose difference between $VMAT_{FF}$ (71.53 ± 0.33 Gy) and the $VMAT_{FFF}$ (71.46 ± 0.34 Gy) treatment plan. With a p-value of 0.54, the TCP value for PTV was 81.20 ± 0.88 % ($VMAT_{FF}$) and 81.01 ± 0.92 % ($VMAT_{FFF}$).

OARs physical dose analysis

Table 3 shows the comparison of the physical doses to the OARs for the $VMAT_{FF}$ and $VMAT_{FFF}$ plans. The Dmax for spinal cord, lens left (L), lens right (R), brainstem, and optic chiasm in $VMAT_{FF}$ were 32.09 ± 1.96 Gy, 3.92 ± 3.10 Gy, 3.80 ± 2.88 Gy, 21.25 ± 13.65 Gy, and 13.13 ± 10.81 Gy, respectively. In $VMAT_{FFF}$ plans, the Dmax for the spinal cord, lens left (L), lens right (R), brainstem, and optic chiasm were 31.92 ± 2.54 Gy, 3.17 ± 2.65 Gy, 3.11 ± 2.53 Gy, 20.39 ± 14.02 Gy, and 13.16 ± 10.27 Gy, respectively. The mean doses reported in $VMAT_{FF}$ treatment plans for the Parotid (L), Parotid (R), Larynx, Cochlea (L), and Cochlea (R) were 29.45 ± 12.75 Gy, 29.45 ± 12.75 Gy, 42.25 ± 4.72 Gy, 10.57 ± 11.96 11.96 ± 10.57 Gy, and 10.25 ± 9.87 Gy respectively, whereas in $VMAT_{FFF}$ treatment plans, the mean doses were 29.20 ± 12.90 Gy, 25.39 ± 10.55 Gy, 42.25 ± 4.72 Gy, 9.83 ± 12.29 Gy, and 10.68 ± 9.05 Gy, respectively.

EUD and NTCP analysis for OARs

Table 4 shows the comparison of observed EUD and NTCP values for various OARs. For the spinal cord, the average EUD values reported for $VMAT_{FF}$ and $VMAT_{FFF}$ were 18.114 Gy and 17.525 Gy, respectively, with insignificant dose differences ($p = 0.72$). NTCP values of the spinal cord for $VMAT_{FF}$ and $VMAT_{FFF}$ treatment plans were 6.54×10^{-07}(%) and 3.09×10^{-07}(%), respec-

Table 3. Comparison of various dosimetric parameters for organs at risk (OARs) between flattened filter (FF) and flattened filter free (FFF) volumetric modulated arc therapy (VMAT) treatment plans

OARs	$VMAT_{FF}$ (Mean ± SD) [Gy]	$VMAT_{FFF}$ (Mean ± SD) [Gy]	p-value
Spinal cord (Max.)	31.92 ± 2.54	32.09 ± 1.96	0.72
Lens (L) (Max.)	3.92 ± 3.10	3.17± 2.65	0.47
Lens (R) (Max.)	3.80 ± 2.88	3.11 ±2.53	0.42
Brainstem (Max.)	21.25 ± 13.65	20.39 ± 14.02	0.86
Optic chiasm (Max.)	13.13 ± 10.81	13.16 ± 10.27	0.92
Parotid (L) (mean)	29.45 ± 12.75	29.20 ± 12.90	0.95
Parotid (R) (mean)	25.90 ± 10.49	25.39 ± 10.55	0.90
Larynx (mean)	42.25 ± 4.72	42.09 ± 4.28	0.92
Cochlea (L) (mean)	11.96 ± 10.57	12.29 ± 9.83	0.87
Cochlea (R) (mean)	10.25 ± 9.87	10.68 ± 9.05	0.86

Max — maximum point dose inside the organ; Mean — average dose; L — left side; R — right side; $VMAT_{FF}$ — VMAT plan with flattened filter photon beam; $VMAT_{FFF}$ — VMAT plan with flattened filter free photon beam; SD — standard deviation

Table 4. Comparison of the equivalent uniform dose (EUD), normal tissue complication probability (NTCP) and Pearson correlation coefficient (r) values for different organs at risk (OARs)

OARs	Radiobiological parameter	$VMAT_{FF}$ (Mean)	$VMAT_{FFF}$ (Mean)	p-value	Pearson correlation coefficient (r)	
					$VMAT_{FF}$	$VMAT_{FFF}$
Spinal cord	EUD [Gy]	18.11	17.53	0.72	0.7589	0.761
	NTCP (%)	6.54×10^{-7}	3.09×10^{-7}	0.79		
Lens (L)	EUD [Gy]	1.57	1.29	0.64	0.9844	0.9435
	NTCP (%)	5.00×10^{-2}	2.75×10^{-2}	0.46		
Lens (R)	EUD [Gy]	1.58	1.18	0.48	0.9822	0.9773
	NTCP (%)	5.41×10^{-2}	1.45×10^{-2}	0.18		
Brainstem	EUD [Gy]	10.18	9.67	0.18	0.7376	0.7302
	NTCP (%)	2.73×10^{-5}	2.53×10^{-5}	0.91		
Optic chiasm	EUD [Gy]	7.16	6.88	0.95	0.7870	0.7971
	NTCP (%)	9.38×10^{-3}	9.47×10^{-3}	0.99		
Parotid (L)	EUD [Gy]	21.34	19.66	0.73	0.8127	0.7853
	NTCP (%)	8.04	6.57	0.81		
Parotid (R)	EUD [Gy]	21.62	20.32	0.78	0.8104	0.7822
	NTCP (%)	7.69	6.73	0.90		
Larynx	EUD [Gy]	53.32	52.69	0.11	0.7914	0.7524
	NTCP (%)	6.23	5.55	0.25		
Cochlea (L)	EUD [Gy]	33.59	32.5148	0.90	0.6426	0.7572
	NTCP (%)	3.63×10^{-2}	2.45×10^{-2}	0.83		
Cochlea (R)	EUD [Gy]	13.59	10.88	0.62	0.2355	0.4724
	NTCP (%)	6.64×10^{-2}	3.39×10^{-2}	0.35		

L — left side; R — right side; Gy — Gray; VMAT — volumetric modulated arc therapy; $VMAT_{FF}$ — VMAT plan with flattened filter photon beam; $VMAT_{FFF}$ — VMAT plan with flattened filter free photon beam

tively. For lenses, the average EUD values for Lens (L) in the $VMAT_{FF}$ (1.57 Gy) plans were higher than in $VMAT_{FFF}$ (1.28 Gy), with a statistically insignificant value (p = 0.64). The average NTCP values for the lens (L) in the $VMAT_{FF}$ plans (0.050%) were higher than in the $VMAT_{FFF}$ (0.027%) with insignificant p values (0.46). The average EUD values for Lens (R) in the $VMAT_{FF}$ (1.58 Gy) plans

were higher than in the $VMAT_{FFF}$ (1.18 Gy), with a statistically insignificant value (p = 0.48). The average NTCP values for the lens (R) in the $VMAT_{FF}$ plans (0.054%) were higher than in the $VMAT_{FFF}$ (0.014 %) with insignificant p values (p = 0.18).

The average EUD values for the optic chiasm in the $VMAT_{FF}$ (7.16 Gy) plans were higher than in the $VMAT_{FFF}$ (9.67 Gy), with a statistically insignificant value (p = 0.18). The average NTCP values for the brainstem in the $VMAT_{FF}$ plans (2.73×10^{-05}%) were higher than in the $VMAT_{FFF}$ (2.53×10^{-05}%) with insignificant p values (0.91). The average EUD values for Brainstem in the $VMAT_{FF}$ (10.18 Gy) plans were higher than in the $VMAT_{FFF}$ (6.88 Gy), with a statistically insignificant value (p = 0.95). The average NTCP values for the brainstem in the $VMAT_{FF}$ plans (94.71×10^{-05}%) were higher than in the $VMAT_{FFF}$ (93.78×10^{-05}%) with insignificant p values (p = 0.99). For the parotids, the average EUD values for the parotids (L) in the $VMAT_{FF}$ (21.34 Gy) plans were higher than in $VMAT_{FFF}$ (19.66 Gy), with statistically insignificant values (p = 0.73). The average NTCP values for the parotids (L) in the $VMAT_{FF}$ plans (8.04 %) were higher than in the $VMAT_{FFF}$ (6.57 %) with insignificant p-values (p = 0.81). The average EUD values for the parotids (R) in the $VMAT_{FF}$ (21.62 Gy) plans were higher than in the $VMAT_{FFF}$ (20.32Gy) with statistically insignificant values (p = 0.78). The average NTCP values for the parotid (R) in the $VMAT_{FF}$ plans (7.69%) were higher than in the $VMAT_{FFF}$ (6.73 %), with insignificant p values (p = 0.90).

The average EUD values for the Larynx in the $VMAT_{FF}$ (53.32 Gy) plans were higher than in the $VMAT_{FFF}$ (52.69 Gy) with statistically insignificant values (p = 0.11). The average NTCP values for the brainstem in the $VMAT_{FF}$ plans (6.22%) were higher than in the $VMAT_{FFF}$ (5.55%), with insignificant p values (0.25). For the cochlea, the average EUD values for the cochlea (L) in the $VMAT_{FF}$ (33.59 Gy) plans were higher than in $VMAT_{FFF}$ (32.51 Gy), with statistically insignificant value (p = 0.90). The average NTCP values for the cochlea (R) in the $VMAT_{FF}$ plans (36.26×10^{-04}%) were higher than in the $VMAT_{FFF}$ (24.54×10^{-05} %) with insignificant p values (0.83). The average EUD values for the cochlea (R) in the $VMAT_{FF}$ (13.58 Gy) plans were higher than in the $VMAT_{FFF}$ (10.88 Gy), with a statistically insignificant value (p = 0.62). The average NTCP values for the cochlea (R) in the $VMAT_{FF}$ plans (0.66%) were higher than in the $VMAT_{FFF}$ (0.33%) with insignificant p values (p = 0.35). For OARs, Table 4 shows the Pearson correlation coefficient (r) between EUD and NTCP for both types of treatment plans. During $VMAT_{FF}$ treatment, the correlation coefficients between EUD and NTCP varied for different anatomical structures. Specifically, the correlation coefficient values for the spinal cord, lens (left), lens (right), brainstem, optic chiasm, parotid (left), parotid (right), cochlea (left), cochlea (right), and larynx were 0.7589, 0.9844, 0.9822, 0.7376, 0.7870, 0.8127, 0.8104, 0.7914, 0.6426, and 0.2355, respectively.

In the context of the $VMAT_{FFF}$ treatment plan, the correlation coefficients between EUD and NTCP exhibited distinct values for various anatomical structures. Specifically, the correlation coefficient values for the spinal cord, lens (left), lens (right), brainstem, optic chiasm, parotid (left), parotid (right), cochlea (left), cochlea (right), and larynx were 0.7610, 0.9435, 0.9773, 0.7302, 0.7971, 0.7853, 0.7822, 0.7524, 0.7572, and 0.4724, respectively. The R^2 values, reflecting the relationship between EUD and the mean dose of the PTV, were 0.9905 for $VMAT_{FFF}$ and 0.7448 for $VMAT_{FF}$, respectively. Similarly, the R^2 values pertaining to the relationship between TCP and the mean dose to PTV were 0.9903 ($VMAT_{FFF}$) and 0.7437 ($VMAT_{FF}$). The R^2 values relating the CI and TCP were 0.46 for $VMAT_{FFF}$ and 0.26 for $VMAT_{FF}$.

Discussion

In this radiobiological study, we compared the radiobiological and dosimetric impacts of the FFF photon beam and FF photon beam using VMAT planning techniques for H & N cancer. The overall goal of this retrospective study is to evaluate the acceptability of treatment plans treated with FFF photon beams using radiobiological evaluation tools and direct comparison between radiobiological and physical dose indices. Many literatures have compared the physical dose indices between FF and FFF photon beam for various treatment sites and found FFF photon beam delivered a dosimetrically similar treatment plan as compared to FF photon beam [20, 21]. In our study, we insignificantly found that the $VMAT_{FFF}$ treatment plan have a similar CI value to $VMAT_{FF}$, which can be seen in Figure 1. Table 2 shows the physical dosimetric

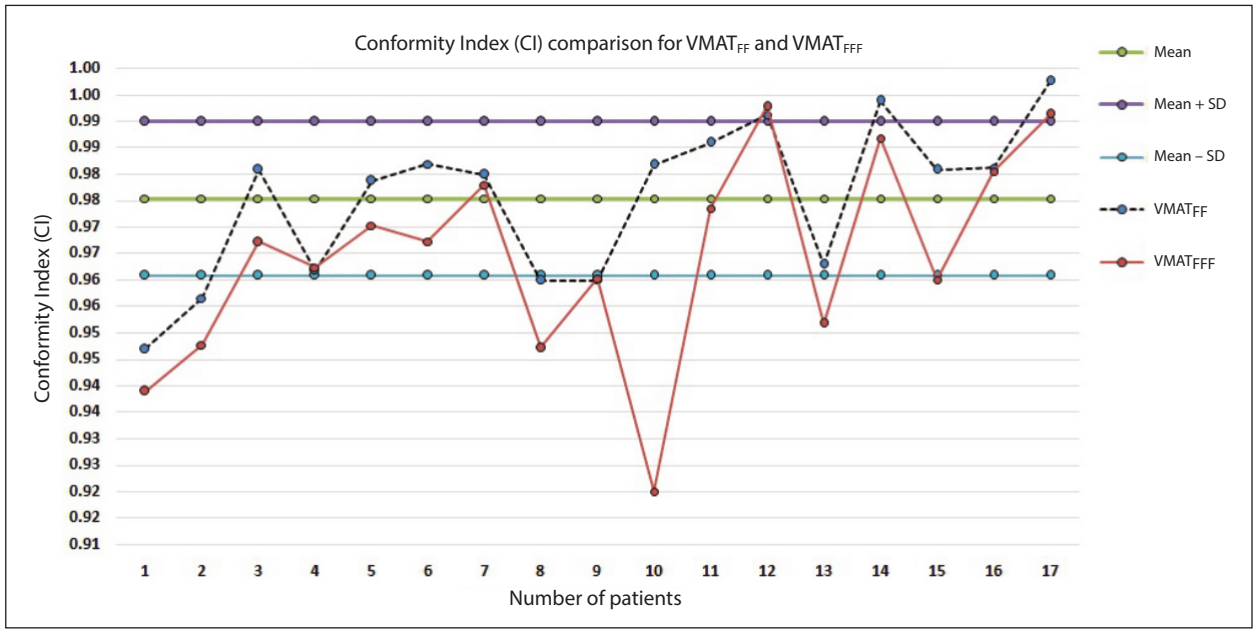

Figure 1. Distribution of the Conformity Index for both types of treatment plans

indices for the PTV. Insignificantly, VMAT$_{FFF}$ plans were more homogeneous and had slightly more dose coverage than the VMAT$_{FF}$ treatment plan. In comparison to VMAT$_{FF}$, VMAT$_{FFF}$ shows a statistically insignificant difference of 0.77% higher UDI value. A lower UDI value favours the VMAT$_{FF}$ treatment plan.

In accordance with findings from earlier studies, our own investigation also detected an increase in MU [21]. The VMAT$_{FFF}$ beam plan displayed an 18.20 % higher MU in comparison to the VMAT$_{FF}$ beam plan. This rise in the number of MUs was primarily due to the need for a greater number of small segments and MUs to achieve a homogeneous dose distribution when using the FFF beam configuration. There were very small, insignificant differences observed for the EUD value between VMAT$_{FF}$ and VMAT$_{FFF}$. The mean dose to PTV for VMAT$_{FF}$ plan shows a slight increase compared to the VMAT$_{FFF}$, when we translate and convert this difference to radiobiological parameters, we discover that there is an interesting increase in TCP, despite the fact that it seems statistically insignificant and ineffective. Figure 2 shows the linear correlation of EUD *vs* mean dose to the PTV for VMAT$_{FF}$ and VMAT$_{FFF}$ treatment plan. The R^2 values reported for VMAT$_{FF\,and}$ VMAT$_{FFF}$ are 0.9905 and 0.7448 for EUD *vs*. mean dose, respectively. The higher value of R^2 shows a strong positive correlation between the EUD and the mean dose of the PTV. It indicates that whenever there is a higher physical mean dose received by PTV, it results in a higher EUD dose radiobiological. According to Table 3, the mean TCP value for the PTV in VMAT$_{FF}$ is insignificantly higher than the VMAT$_{FFF}$ plan. From Figure 3, it can be seen that there is a strong correlation between TCP and the mean PTV dose. The higher value of R^2 has been observed for TCP *vs*. mean PTV dose for VMAT$_{FFF}$ than the VMAT$_{FF}$ treatment plan. It means that when we require a higher value of TCP (the radiobiological parameter) we can directly correlate it with the mean dose (the physical parameter) received by PTV. A higher mean dose of PTV leads to more tumor control.

Figure 4 shows that both VMAT$_{FF}$ and VMAT$_{FFF}$ have a positive association between CI and the TCP. The VMAT$_{FF}$ treatment plan received a lower value of R^2 (0.26) as compared to 0.46 in the VMAT$_{FFF}$ treatment plan. The small value of the coefficient of determination for VMAT$_{FF}$ shows that no correlation exists between CI (as physical parameter) and TCP (as radiobiological parameter) while the VMAT$_{FFF}$ treatment plan shows that there is a moderate correlation between CI (as a physical parameter) and TCP (as a radiobiological parameter). The physical doses and NTCP of various OARs for VMAT$_{FF}$ and the VMAT$_{FFF}$ treatment

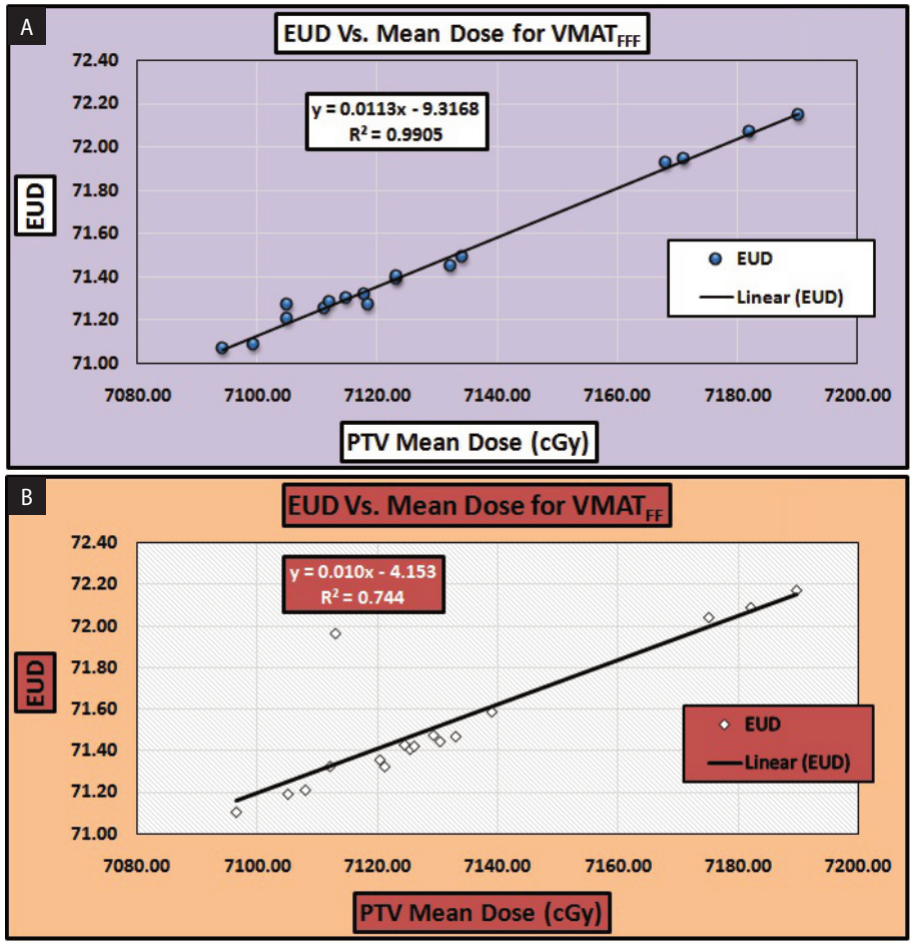

Figure 2. Correlation between equivalent uniform dose (EUD) and planning target volume (PTV) mean dose for both types of techniques

plans are displayed in Table 4. There was a strong relationship between the physical dose indices and the likelihood of complications for many organs, such as the brainstem, spinal cord, parotids, lenses, optic chiasm, lenses, larynx, and cochlea. The Lyman-Kutcher-Berman estimate states that when the radiation dose is 65 Gy, there is a 50% chance of complications occurring within five years for the entire brainstem [23]. In our finding, the $VMAT_{FF}$ and $VMAT_{FFF}$ plans have achieved a maximum dose less than the 65 Gy, indicating a lower complication probability. Previous studies have concluded that, in comparison to 3DCRT, the IMRT treatment plan can drastically lower the doses of OARs, which leads to improved toxicity outcomes and quality of life for patients [31, 32]. However, despite all of these developments, acute and late toxicity continue to cause difficulties for effective H&N cancer therapy. Since the mean dose of each of these parotids has been closely linked to xerostomia in the patients, the lower dose to parotid glands may have contributed to lower xerostomia rates. A linear relationship between the mean dose and the dose range where xerostomia is most likely to occur is visible, indicating that even small dose improvements may have clinical effects [33]. Here, in our study, the $VMAT_{FFF}$ shows a smaller mean dose difference for the parotids compared to the $VMAT_{FF,}$ but there is a modest change in the NTCP value, which can be seen in Table 4. Other toxicities that could be compromised include cataract development, swallowing function, respiration, and the quality of voice. Since the larynx mean dose has been correlated with laryngeal oedema, the increased larynx dose associated with a flattened beam may be a factor in poor voice quality [34]. The overall given dose to various essential organs is decreased due to the lower mean and maximal doses achieved for OAR.

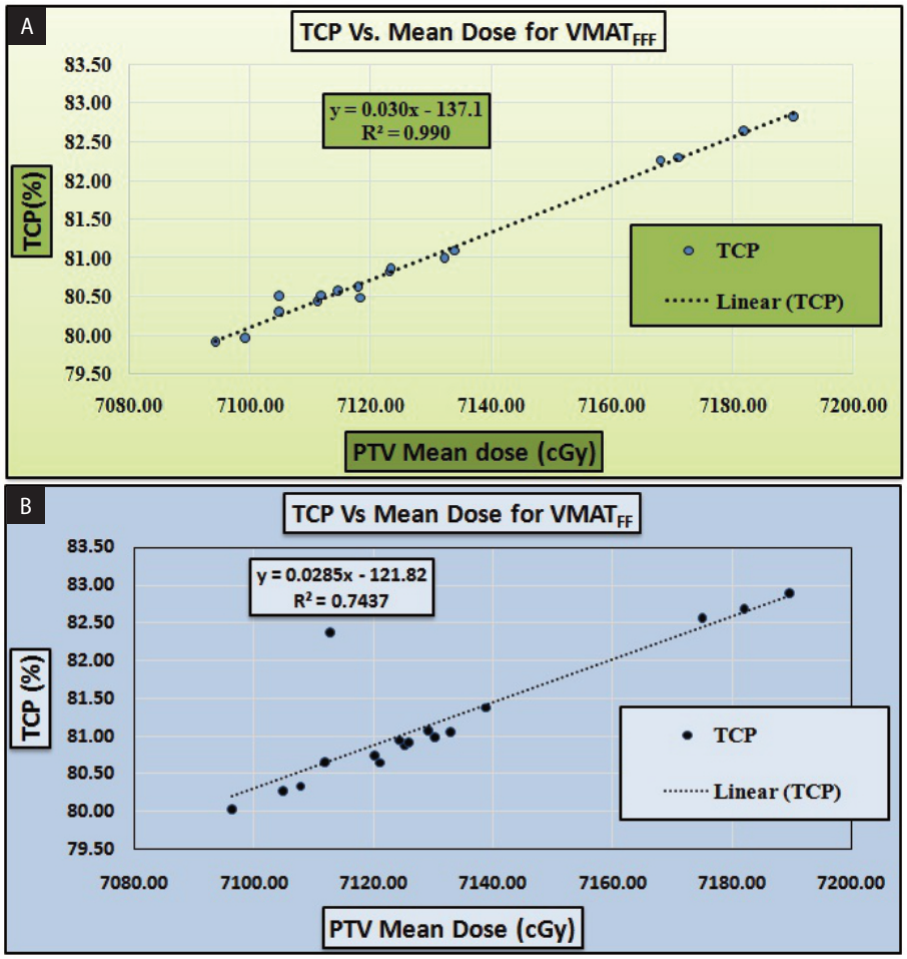

Figure 3. Correlation between tumor cure probability (TCP) and mean dose to the planning target volume (PTV) for flattened filter free (FFF) (**A**) and flattened filter (FF) (**B**) photon beam

One of the most significant long-term side effects of radiation exposure is severe hearing impairment. The cochlea, being one of the most radiosensitive organs, is influenced by the dose to the auditory apparatus. Tinnitus and radiation-induced sensorineural hearing loss are two potential side effects of radiation exposure to the cochlea. In some of the results of retrospective assessments that led to the QUANTEC dose-volume limitations of cochlear mean doses less than 45 Gy combined with an estimated complication rate of 30% [35]. In our study, we were able to achieve mean cochlear doses less than 45 Gy in both types of plans, among which the FFF plan had a slightly smaller mean dose for both cochleae with a lower NTCP value than the FF VMAT plan. All other OARs, excluding the spinal cord and cochlea (R), shows a stronger correlation with complication probabilities for $VMAT_{FF}$ than the $VMAT_{FFF}$ treatment plan. One of the downsides of the standard method of plan evaluation, which is based on unique or various dose-volume constraints, is that it requires a large number of dose-volume points to evaluate the organ's complexity. While some of the dose-volume limits pass while others fail, the clinician must take these into account while evaluating the plan. Radiobiological plan evaluation, on the other hand, makes use of entire 3-dimensional dose distributions, balances various dose-volume constraints, and generates an understandable estimate of biological consequence. Plan evaluation based on dose-volume criteria also provides information regarding the presence or absence of an effect in relation to given dose constraints. The biological evaluation provides continuous analysis of the likelihood of tumour cure and normal organ complications, rather than taking threshold values in DVHs into account.

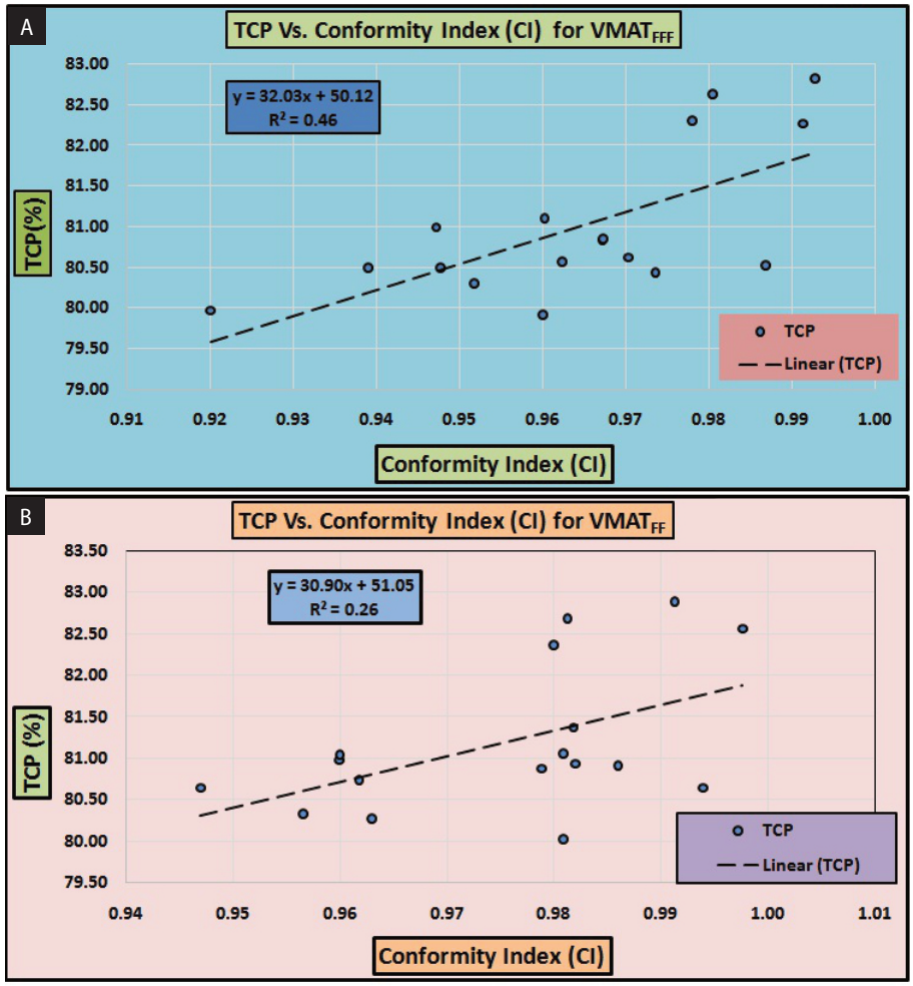

Figure 4. Correlation between the conformity index (CI) and tumor cure probability (TCP) for flattened filter free (FFF) and (**A**) and flattened filter (FF) (**B**) volumetric modulated arc therapy (VMAT) treatment plan

Conclusion

The present study demonstrates that a VMAT treatment plan using FFF photons results in plans that are clinically comparable to those created using FF photon beams. Treatment plans with FFF photon beams have better capability to spare the OARs without losing the quality of the treatment plan. The increased mean dose to the PTV and higher TCP values suggest the potential clinical benefits of the FFF photon beam with the VMAT technique in enhancing the treatment outcome and improving the therapeutic efficacy of radiation therapy. Our study also suggests that the mean dose as a physical dose index can be a good indicator of an adequate TCP value, while the CI value alone does not provide satisfactory information about the tumour cure. The major physical dose indices were found to have a good relationship with the probability of tumour cure or complications in normal tissue, accounting for DVH threshold values. Patients with head and neck cancer who were studied may benefit from a treatment plan that incorporates FFF because it improves local control and reduces the chance of late treatment side effects.

Conflicts of interest

Authors declare no conflicts of interest.

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