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Comparison of normal tissue integral dose with monitor units from 3DCRT, IMRT, and Rapid Arc treatment planning methods for head and neck, pelvic and thoracic cancer sites

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ABSTRACT

Background: Comparison of normal tissue integral dose and treatment monitor units from 3DCRT, IMRT and Rapid treatment plan for oesophagus, left breast, cervical and oropharynx cancer. The calculated normal tissue integral dose from different treatment plans with static and dynamic leaf positions, such as 3DCRT, IMRT and Rapid arc were compared with the generated MU. ***Material and Methods:*** Nine patients from oesophagus, left breast and cervix cancer and twelve patients from oropharynx cancer with a total of one hundred and thirty-five generated plans from 3DCRT, IMRT and Rapid arc were analysed. The normal tissue integral dose (NTID) was calculated from in-house developed Python software using a standard formula from the dose-volume histogram. ***Results:*** The analysis showed that the NTID and MU differed significantly from all three treatment planning methods and cancer sites. The highest integral dose was from IMRT and Rapid Arc in the oropharynx and oesophagus cancer site; cervical cancer had a 50% lower NTID, and left breast cancer had a 25% lower NTID than oesophageal cancer. ***Conclusion:*** The results show that NTID is inversely related to body volume, and that MU depends on the type of treatment planning (greater in IMRT).

INTRODUCTION

Radiation therapy is becoming increasingly prevalent since cancer is occurring at a higher rate globally [1,2]. Cobalt-based treatment was used in conventional open radiation fields before developing multi-leaf collimators for several advanced malignancies. Radiation from a linear accelerator was delivered through a static Multi-leaf collimator (MLC) to practice the three-dimensional conformal treatment and the target volume was fitted through the MLC for calculation [3]. In a later invention that came after introducing intensity-modulated radiotherapy (IMRT) and the Rapid arc, radiation was administered from a planning system with beams of nonuniform energy fluences by an enhanced dynamic MLC. Using this radiation delivery technique, the target volume received large doses of radiation while receiving a manageable dose to the essential typical structures [4].

The Quantec [5], Umami [6] and Radiation Therapy Oncology Group(RTOG) protocols employed during the optimization phase to deliver the specified dose during irradiation determine the dose to the Organ at Risk OAR and target volume. The quality of the optimization will also depend on how well the medical physicist sets the dose constraint targets [7,8]. The term "integral dose"[9] refers to the total energy imparted into the normal tissue as a result of the optimization process in IMRT and rapid arc treatment techniques. We examined the connection between the Normal Tissue Integral Dose (NTID) [10] and the fractional dosage deposited in nontumor tissue and Monitor Units (MU) [11] based on treatment planning factors during the optimization process. Numerous methods and algorithms for computer optimization of the number of beams, their number and their orientations for conventional and conformal therapy are described in most of the literature [12-18]. The study is intended to compare the normal tissue integral dose and treatment monitor units from 3- Dimensional Conformal Radiation Therapy (3DCRT), IMRT and rapid treatment plans from complete body site such as oesophagus, left breast, hypo pharynx and cervical cancer, using in-house developed Python-based software [19]. The comparison of the NTID [20] and MU [21] with all planning methods show evidence of the importance of the body volume plays a major role in radiotherapy.

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MATERIALS AND METHODS

Twenty-seven patients received external beam radiation therapy for a total of ninety-nine treatment plans from three different treatment locations, including the cervix, oesophagus, oropharynx and left breast. The patient characteristics are summarized in table 1 along with The American Joint Committee on Cancer (AJCC)-8th edition TNM (Tumour, Node, and Metastasis) staging. The patient was lying supine while a Computed Tomography (CT) scan was being performed, with images taken at a 5 mm slice interval. Without taking into account breathing patterns, the CT scan was taken using a Positron Emission Tomography (PET)-CT scanner from GE (General Electric) Health Care's Discovery IQ and the images were exported to the Eclipse planning system (M/s. Varian Medical System, software of version 15.6) for contouring and planning. Drawn alongside important normal structures were the Gross Tumor Volume (GTV) and Planning Tumor Volume (PTV). To account for setup error and tumor motion, the PTV was calculated as the clinical target volume plus a margin of 5–7 mm. The critical structures include the heart, left lung, right lung, spinal cord, bladder, rectum, femoral head and bowel in all three cancer sites, left breast, oesophagus, and cervix, respectively. All patients were treated for 28 fraction of 5040cGy on Clinac-iX (M/s. Varian Medical System, USA) model with an onboard imaging system for image verification before treatment. The study was approved by the Institutional Review Board of Thangam Cancer Center (approval number: ECR/1069/Inst/TN/2018/RR-21) and consent was obtained from all patients.

The normal tissue integral dose (NTID) of radiation delivered to the PTV and whole patient body was defined as an ID [Gy · L] = D [Gy] · V [L], where D [Gy] is the mean dose delivered to volume *V* [L] (where L – liter). The ID formula was used by Aoyama *et al.* [22] to calculate the integral dose in normal tissue for various irradiation techniques.

Beam arrangements

The two-field treatment strategy consists of the Medial Tangential field (MT-LT) for the left breast and the AP (Anterior- Posterior) and PA (Posterior-Anterior) fields for the oesophagus. Four fields are used in the planning of 3DCRT treatment for the cervix and oesophagus, including the AP-PA and right -left lateral RT (Right)-LT (Left) fields. A 72-degree spacing between each field is defined in the five-field IMRT [23] plans. Seven field IMRT angles spaced 51 degrees apart are used for oesophagus and cervix treatment planning. Table 2 contains an overview of the beam arrangements.

Table 1. Patient characteristics.

Esophagus		*Left Breast*		*Cervix*		*Oropharynx*	
Age	MeanAge:58		MeanAge:48		MeanAge:55		Mean Age:63
	Range: 43-70		Range: 33-61		Range: 31-73		Range: 44-79
Gender		Gender		Gender			Gender
	Male:2		Female: 9		Female: 9		Male: 11
	Female: 7						Female: 1
Stage	Number	Stage	Number	Stage	Number	Stage	Number
III	1	IB	3	II B	9	III	1
IVA	1	II A	1			IVB	1
X	7	II B	1			IVA	6
		III A	1			X	4
		III B	2				
		III C	1				

Table 2. Summary of beam angles and beam arrangement descriptors.

Cancer Site	2 beams	4 beams	five beams	seven beam	Arc
	2Field - 3DCRT	*4 Field 3DCRT*	*5 Field IMRT*	*7 Field IMRT*	*Rapid Arc*
Esophagus	0°, 180°	0°, 90°, 180°, 270°	36°, 108°, 180°, 252°, 325°	27°, 78°, 129°, 180°, 231°, 282°, 333°	179°-181°CCW 181°-179° CW
Cervix		0°, 90°, 180°, 270°		231°, 282°, 333°, 27°, 78°, 129°, 180°	179°-181° CCW
Left breast	310°, 125°			18°, 57°, 96°, 125°, 175°, 300°, 339°	140°- 300°(CCW) 300°-140° (CW)
Oropharynx					179°-181° CCW 181°-179° CW

Treatment planning and dose calculation

During the optimization phase, dose volume restrictions and objectives are loaded into the treatment planning system. The dose-volume histogram (DVH) shown during optimization is essentially a depiction of the ideal fluence patterns. It is a virtual representation because it excludes machine limitations such as leaf motion. The final dosage calculation techniques and optimization algorithms take diverse approaches to lateral scatter and homogeneity. For inverse planning, the progressive resolution optimizer (PRO) of Rapid arc enables adjustment of the multi-leaf collimator's (MLC) leaf placements, gantry rotation speed, and dose rate. The PRO method is used in VMAT optimization, while the dose volume optimizer (DVO) algorithm is used in IMRT.

Normal tissue integral dose

The final dose calculation for the plan uses AAA, which does not use the MRDC. The final MU calculated is dependent on many parameters, such as dose plan objectives, dose constraints, objectives, priority setting and optimization settings, such as the calculation grid. The mean dose multiplied by the

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irradiated volume gives this volume integral of the dose deposited in a patent. The integral dose, also referred to as the NTID [26,27], is the calculated area under the curve of a different absolute dose-volume histogram [28] using the in-house developed python [29] software. The NTID increases with the increasing number of monitor units and beamlets. For homogeneous dose calculation, a tissue density of 1 g/cm^3 was assumed for all structures. The air cavities and bone were assigned uniform densities of 0.05 and 1.3 gm/cm^3, respectively. The NTID was defined using equation 1.

$$NTID = \Sigma Di \times Vi \times pi \quad (1)$$

Where; V_i is the volume irradiated at a dose of D_i and p is the local density of V_i.

Statistical analysis

The Wilcoxon signed-rank test for the related sample with SPSS (Statistical Package for Social Sciences) statistical software version 20 was compared for statistical significance from nonparametric data. A p value ≤ 0.05 was considered significant.

Table 3. Monitor units calculated from 3-dimensional conformal radiotherapy, intensity modulated radiotherapy and Rapid arc for oesophageal cancer.

	Monitor Units (MU)		Normal tissue Integral Dose (NTID)	
Treatment Planning techniques	**Mean/ Std. Deviation**	**p value**	**Mean/Std. Deviation**	**p value**
2F_3DCRT	193.00±10.72	.00000	5.37±2.80	.00000
4F_3DCRT	210.66±8.55	.00000	8.53±4.11	.00000
5 F IMRT	648.22±97.47	.00000	11.75±6.80	.00000
7 F IMRT	809.44±101.59	.00000	12.23±7.28	.00000
Rapid Arc	468.11±51.83	.00000	14.73±8.07	.00000

Table 4. Monitor units calculated from 3-dimensional conformal radiotherapy, intensity modulated radiotherapy and Rapid arc for left-breast cancer.

	Monitor Units (MU)		Normal tissue Integral Dose (NTID)	
Treatment Planning techniques	**Mean/Std. Deviation**	**p value**	**Mean/Std. Deviation**	**p value**
3DCRT	415.22±28.31	.00000	14.04±1.50	.00000
IMRT	1500.00±170.06	.00000	37.08±6.31	.00000
Rapid arc	770.56±44.17	.00000	26.51±5.79	.00000

Table 4. Monitor units calculated from 3-dimensional conformal radiotherapy, intensity modulated radiotherapy and Rapid arc for left-breast cancer.

	Monitor Units (MU)		Normal tissue Integral Dose (NTID)	
Treatment Planning techniques	**Mean/Std. Deviation**	**p value**	**Mean/Std. Deviation**	**p value**
3DCRT	415.22±28.31	.00000	14.04±1.50	.00000
IMRT	1500.00±170.06	.00000	37.08±6.31	.00000
Rapid arc	770.56±44.17	.00000	26.51±5.79	.00000

Table 5. Monitor units calculated from 3-dimensional conformal radiotherapy, intensity modulated radiotherapy and Rapid arc for cervical cancer.

	Monitor Units (MU)		Normal tissue Integral Dose (NTID)	
Treatment Planning techniques	**Mean/Std. Deviation**	**p value**	**Mean/Std. Deviation**	**p value**
3DCRT	251.33±17.73	.00000	29.56±8.78	.00000
IMRT	1367.44±83.86	.00000	34.11±10.07	.00000
Rapid Arc	816.33±191.53	.00000	34.20±12.73	.00000

Table 6. Monitor units calculated from Rapid arc (2arc), Rapid arc (3arc) and Intensity modulated radiotherapy with 7 and 9 fields for Oropharynx.

	Monitor Units (MU)		Normal tissue Integral Dose (NTID)	
Treatment Planning techniques	**Mean/Std. Deviation**	**p value**	**Mean/Std. Deviation**	**p value**
Rapid arc(2arc)	986.08±21.7.73	0.000000	54.17±17.34	0.000000
Rapid arc(3arc)	903.91±144.88	0.000000	48.80±15.35	0.000000
IMRT 7 Field	1813.91±223.64	0.000000	55.15±14.29	0.000000
IMRT 9 Field	2212.58±328.40	0.000000	46.78±13.66	0.000000

RESULTS

To account for homogeneity correction, all three optimization techniques [24,25] use the MRDC (multi-resolution pencil beam photon dose calculation algorithm) methodology internally. The MRDC is less precise than final dose calculation systems such as the Analytical Anisotropic Algorithm (AAA) when taking into consideration the effects of tissue heterogeneities. As a result, there will be a disparity between the target doses displayed by the optimizer and those determined by final dose calculations. To convert the dosage map to leaf sequences, the optimization algorithm's output was sent to the Eclipse leaf motion calculator application that generates beamlets.

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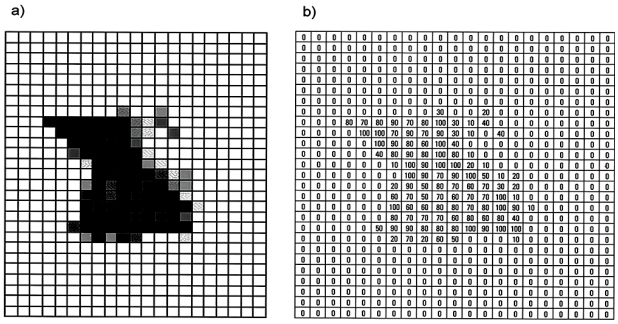

Figure 1. A typical **a)** intensity map and **b)** its matrix representation.

It is necessary to reformat the two-dimensional dosage map into an intensity map that the MLC can give; the intensity map is formatted into 1 × 1-cm matrix cells, as shown in figure 1a grayscale shading is used to represent the beam intensity, which is proportional to the monitor units (MUs). The intensity map can alternatively be represented in figure 1b as a numerical matrix.

Esophageal study

The normal tissue integral dose and monitor units generated from oesophageal cancer are displayed in tables 3. The MUs generated by all treatment planning methods, including 2-field 3DCRT, 4-field 3DCRT, 5-field IMRT, 7-field IMRT and Rapid arc, were statistically significant.

Left breast study

The integral normal tissue dose for critical normal structures and monitor units generated from left breast are shown in table 4. The MU for 3DCRT, IMRT, and Rapid arc and the p value between 3DRCRT, IMRT and Rapid arc were statistically significant.

Cervix study

The Integral normal tissue dose for normal structures and monitor units generated, from cervical cancer are shown in table 5. However, MU in all planning approaches was statistically significant in 3DCRT, IMRT and Rapid arc, and the p values between 3DRCRT, IMRT and Rapid arc were estimated.

Oropharynx study

The Integral normal tissue dose for normal structures and monitor units generated, from cervical cancer are shown in table 6. However, MU in all planning approaches was statistically significant in Raid arc (2 arc), Rapid arc (3 arc), IMRT 7 field and IMRT 9 field and the p values between IMRT (7 and 9 fields) and Rapid arc (2 and 3 arcs) were estimated.

The target volumes for cervix, left breast, and oesophageal and Oropharynx cancer are listed in table 7. The monitor units and normal tissue integral dose from OARs are tabulated in table 8 for all treatment planning techniques. The detailed comparisons of NTID and MU for all treatment planning methods from all four cancer sites are shown in the box plot in figure 2 and figure 3 along with the comparison of body volume against cancer sites are shown in figure 4 to understand the behaviour of normal tissue integral dose with different cancer sites.

It is evident from table 7 that the volumes of the cervix are higher than the left breast, oesophageal and oropharynx target volumes.

Table 7. Target volume in the oesophagus, cervical, oropharynx and left breast cancer.

Target Volume	No of patients	Minimum volume(cc)	Maximum volume(cc)	Mean volume(cc)/Std. Deviation
Cervix	9	815.00	1489.00	1054.25 ±216.58
Left breast	9	183.40	1070.70	654.74 ±279.11
Oesophagus	9	183.80	609.90	412.21 ±149.07
Oropharynx	12	343.20	726.90	512.99 ±119.56

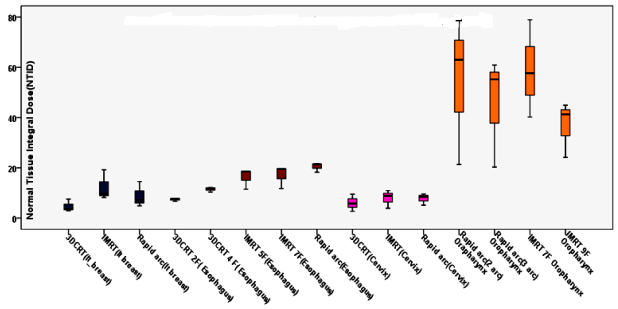

Figure 2. Comparison of NTID from 3- dimensional conformal radiotherapy, intensity modulated radiotherapy and rapid arc planning methods from the oesophageal, left breast, cervix and oropharynx cancer sites.

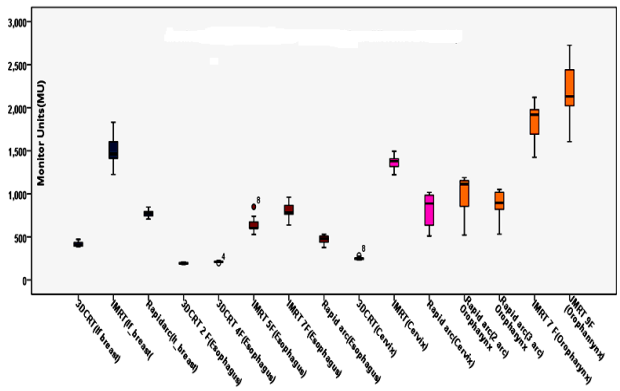

Figure 3. Comparison of MU from 3- dimensional conformal radiotherapy, intensity modulated radiotherapy and rapid arc planning methods from the left breast, oesophageal, cervix and Oropharynx cancer site

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Table 8. p value between normal tissue integral dose and monitor units for different planning techniques.

(a)		**Ca left breast**		
	Technique		Comparison	p value
Normal Tissue Integral Dose(NTID)		**Mean / Std. Dev** Std. Deviation		
	3DCRT	14.04 ±1.50	3DCRT-IMRT	0.008
	IMRT	37.08±6.31	3DCRT-Rapid arc	0.008
	Rapid arc	26.51±5.79	IMRT-Rapid arc	0.011
Monitor units(MU)		**Mean /Std. Dev**		
	3DCRT	415.22 ±28.31	3DCRT-IMRT	0.008
	IMRT	1500.00 ±170.06	3DCRT-Rapid arc	0.008
	Rapid arc	770.56 ± 44.17	IMRT-Rapid arc	0.008
(b)		**Ca Cervix**		
Normal Tissue Integral Dose(NTID)	Technique		Comparison	p value
		Mean/ Std. Dev		
	3DCRT	29.56 ±8.78	3DCRT-IMRT	0.038
	IMRT	34.11 ±10.07	3DCRT-Rapid arc	0.086
	Rapid arc	34.20 ±12.73	IMRT-Rapid arc	0.859
Monitor units(MU)		**Mean /Std. Dev**		
	3DCRT	251.33 ±17.73	3DCRT-IMRT	0.008
	IMRT	1367.44 ±83.86	3DCRT-Rapid arc	0.008
	Rapid arc	816.33 ±191.53	IMRT-Rapid arc	0.008
(c)		**Ca esophagus**		
	Technique		Comparison	p value
Normal Tissue Integral dose(NTID)		**Mean/ Std. Dev**		
	2 Field-3DCRT	26.84 ±7.62	2F- 4F 3DCRT	0.008
	4-Field 3DCRT	42.67 ±6.16	2F 3D - 5 F IMRT	0.008
	5 Filed IMRT	64.08 ±22.73	2F 3D - 7 F IMRT	0.008
	7 Field IMRT	63.29 ±20.85	2F 3D - Rapid arc	0.008
	Rapid arc	73.63 ±20.05	4F 3D- 5F IMRT	0.066
			4F 3D- 7F IMRT	0.015
			4F 3D- Rapid arc	0.008
			5F IMRT- 7 F IMRT	0.953
			5F IMRT- Rapid arc	0.011
			7 F IMRT- Rapid arc	0.038
Monitor units(MU)		**Mean/ Std. Dev**		
	2 Field-3DCRT	193.00 ±10.72, 10.72	2F- 4F 3DCRT	0.008
	4-Field 3DCRT	210.67 ±8.56, 8.56	2F 3D - 5 F IMRT	0.008
	5 Filed IMRT	648.22 ±97.48, 97.48	2F 3D - 7 F IMRT	0.008
	7 Field IMRT	809.44 ±101.60, 101.60	2F 3D - Rapid arc	0.008
	Rapid arc	468.11 ±51.84, 51.84	4F 3D- 5F IMRT	0.008
			4F 3D- 7F IMRT	0.008
			4F 3D- Rapid arc	0.008
			5F IMRT- 7 F IMRT	0.008
			5F IMRT- Rapid arc	0.008
			7 F IMRT- Rapid arc	0.008
(d)		**Ca Orapharanyx**		
	Technique		Comparison	p value
Normal Tissue Integral dose(NTID)		**Mean/ Std. Dev**		
	Rapid arc(2 arc)	54.17 ±17.34	Rapid arc(2)- Rapid arc(3) RaRapid22(3)arc(3)arc(3)	0.317
	Rapid arc(3 arc)	48.80 ±15.35	Rapid arc(2)- 7 F IMRT	0.317
	7 F IMRT	55.15 ±14.29	Rapid arc(2)- 9 F IMRT	0.317
	9 F IMRT	46.78 ±13.66	Rapid arc(3)- 7 F IMRT	0.317
			Rapid arc(3)- 9 F IMRT	0.317
			7 F IMRT- 9 F IMRT	0.317
Monitor units(MU)		**Mean/ Std. Dev**		
	Rapid arc(2 arc)	986.08 ±217.73	Rapid arc(2)- Rapid arc(3) RaRapid22(3)arc(3)arc(3)	0.06
	Rapid arc(3 arc)	903.91± 144.88	Rapid arc(2)- 7 F IMRT	0.002
	7 Filed IMRT	1813.91 ±223.64	Rapid arc(2)- 9 F IMRT	0.002
	9 Field IMRT	2212.58 ±328.4	Rapid arc(3)- 7 F IMRT	0.002
			Rapid arc(3)- 9 F IMRT	0.002
			7 F IMRT- 9 F IMRT	0.002

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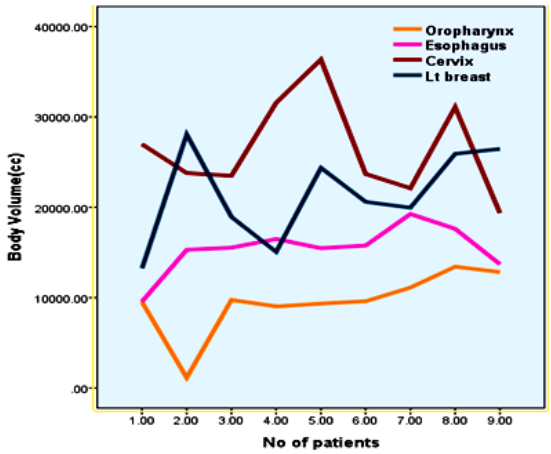

Figure 4. The comparison of patients' body volume from the oesophagus, left breast, cervical cancer and oropharynx cancer sites are shown in bar chart.

DISCUSSION

The monitor unit for left breast cancer also exhibits statistically significant variation across all treatment planning methods and techniques ($p < 0.08$). The normal tissue integral dose shows a similar response across all treatment planning methods and is tabulated in table 8(a). The study also included the contra lateral breast NTID from 3-dimension conformal radiotherapy, intensity modulated radiotherapy and Rapid arc treatment plan, which is relatively lower than the NTID of the heart and left lung.

The monitor units in cervix cancer showed a statistically significant difference ($p = 0.008$) between all treatment planning methods, as shown in table 8(b), but the normal tissue integral dose was not statistically significant in 3DCRT – IMRT ($p = 0.038$), 3DCRT-Rapid arc ($p = 0.086$) and IMRT-Rapid arc ($p = 0.859$).

The monitor units for oesophageal cancer exhibit considerable variations across all treatment planning techniques, although the normal tissue integral dose from critical OARs did not differ significantly between 4 Field 3DCRT and 5 Field IMRT ($p = 0.066$), 5 Field IMRT and 7 Field IMRT ($p = 0.953$) or 7 F IMRT and Rapid Arc ($p = 0.038$). The monitor units and normal tissue integral dose from OARs are tabulated in table 8(c).

The monitor units of oropharyngeal cancer showed a statistically significant difference ($p < 0.05$) between all treatment planning methods, but the normal tissue integral dose was not statistically significant ($p = 0.317$) between all treatment planning methods as shown in table 8(d).

A possible risk factor for the emergence of secondary malignancies [30] has been raised by the rise in normal tissue integral dose [31,32] with multiple beam radiation therapy. It is generally accepted that the integral dosage increases with the number of beamlets and monitor units and that NTID [33] decreases with higher energy photons.

CONCLUSION

It is clear that NTID are significantly higher in the oropharynx cancer site regardless of the treatment approach because the body volume of oropharynx cancer was relatively lower than that of other cancer sites, however, MU are substantially higher in the IMRT plan for the Oropharynx cancer site. It is determined that NTID is inversely correlated with body volume, MU is dependent on the planning method used for treatment; typically, IMRT plans have bigger MU than other methods.

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Author contribution: All authors contributed equally to the design of the study, data collection and analysis, and the writing of the manuscript. All authors read and approved the final manuscript.

Ethical Approval: This study was approved by the Institutional Review Board of Thangam Cancer Center (approval number: ECR/1069/Inst/TN/2018/RR-21). Informed consent was obtained from all patients.

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