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Determination of Optimal Normal Tissue Objective Settings for Radiation Therapy Planning of Brain Tumor

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Abstract – Normal tissue objective (NTO) is a tool used in inverse-planned of intensity-modulated radiation therapy (IMRT) to limit dose spreading to normal tissues. Only a few studies in the literatures has determined the optimal NTO for treatment plans. There is no information regarding the optimal NTO setting for the brain tumor cases. Therefore, the aim of this study was to determine the NTO based on the dose distribution of brain tumor radiation therapy. 15 patients were re-planned using NTO priority of 100 for automatic and manual NTO. Manual NTO were re-planned using a fix start dose f_0 = 105% and end dose f_∞ =60%, where k varied from fall-off 0.1 mm^{-1} to a much steeper fall-off 1 mm^{-1} and margin to planning target volume (PTV) x_{start} varied from 0 to 10 mm. Planning was evaluated using several indices: conformity index (CI), homogeneity index (HI), gradient index (GI), and modified gradient index (mGI). Differences between automatic and manual NTO were evaluated using the Wilcoxon signed rank test. In this study, we obtained the manual NTO with $x_{start} = 1$ mm and dose fall off $\geq 1\ mm^{-1}$ is the most optimal result. Comparisons results of automatic and manual NTOs were: CI of 0.92 vs 0.98 (p= 0.001), HI of 1.09 vs 1.11 (p = 0.004), GI of 5.00 vs 4.73 (p = 0.002), mGI of 4.46 vs 3.77 (p = 0.001). Based on these indices, manual NTO shows a better treatment plan than automatic NTO. It is proved by the dose reduction in OAR after applied manual NTO on planning.

Keywords – Normal Tissue Objective (NTO), priority, dose fall off, external beam radiation therapy, IMRT.

I. INTRODUCTION

Intensity-modulated radiation therapy (IMRT) is an advanced radiotherapy planning technique that can provide good dose conformity and rapid dose gradients around the target volume (tumor) [1–3]. The IMRT is performed using the inverse planning optimization technique. In several studies, IMRT has shown good results for the treatment of brain tumors [4, 5]. Radiotherapy planning for brain tumors is challenging because its location is close to sensitive organ such as the spinal cord and brainstem. Therefore, a sharp dose gradient beyond the target volume is essential in order to avoid radiation toxicity in normal tissues.

There are several techniques used to reduce the dose beyond the target, such as: creating a concentric ring structure outside the PTV and adjusting the normal tissue objective (NTO) [6–9]. Adjusting NTO is easier to be performed than creating a ring structure, because planner has to contour around the target volume which can increase the planning time. The NTO is an exponential decay of the dose as a function of the distance applied during the inverse planning optimization [10]. Eclipse software provided two NTO settings: automatic and manual NTO. Automatic NTO is a vendor-defined automatic formula. Manual NTO contains several limits set by the planner and consists of four parameters: *distance to PTV* x_{start}, *initial dose* f_0, *final dose* f_∞, and *dose fall off* k [11]. Planner sets the priority for both types of NTO.

Automatic NTO is often used in radiotherapy planning. However, in some plans, the use of manual NTO is recommended because it has good performance for reduced the dose outside the target volume [12]. Bell et. al [13] reported the automatic NTO in lung stereotactic body radiation therapy (SBRT) has a poor performance at reducing low-dose radiation spillage that is

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absorbed by the normal tissue. They reported a manual NTO setting with priority of 500 and fall-off of 0.15 mm^{-1} provided the high conformity and minimized low-dose radiation spillage [13]. However, to the best of our knowledge, no published studies have assessed optimal NTO setting for IMRT plans in the treatment of brain tumor. Therefore, in the current study, we determined the optimal NTO setting for brain tumor planning by compared the automatic and manual NTOs. The comparison of both is reviewed based on the dose conformity, dose uniformity and sharp off-target dose reductions.

II. Methods And Materials

2.1. Patients

In this retrospective study, we investigated 15 patients with brain tumors. The patients had been treated with radiotherapy treatment. Therefore, dose constraints have been applied to tumors and normal tissues. In some cases, a ring structure outside the target was applied (Fig. 1). Ring structure is a gap between planning target volumes (i.e. PTV_60 and PTV_50).

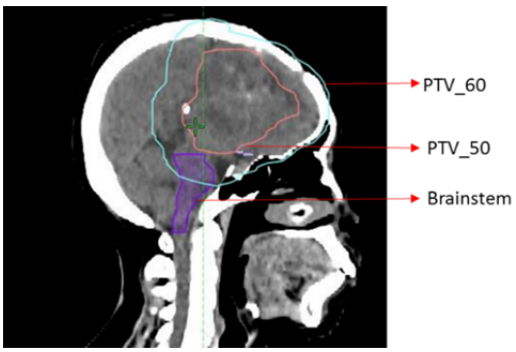

Figure 1. Planning target volume (PTV) and organ at risk (OAR) contours

There are several types of brain tumors investigated in this study (Table 1). Glioma brainstem and glioblastoma are the most type of tumor that attack adult patients. The PTV size ranged from 61 to 1437.2 cm3. The PTV is very close and even overlap to normal organs (see Fig.1).

Table 1. Tumor diagnosis and size are listed for a total 15 patients

Diagnosis	Number of case	Size Range of PTV (cm^3)	Mean of PTV (cm^3)
Glioma brainstem	5	61 - 540.5	294.7
Glioblastoma	5	306 - 735.7	496.6
Brain	4	87.2 - 1437.2	576.9
Craniopharyngiom	1	202.8	202.8

2.2. IMRT planning

In general, IMRT planning is shown in Figure 2. The treatment plans were prepared with Eclipse software for delivery on a linear accelerator of 10 MV. IMRT plans were generated using 5 to 7 angles of radiation beam field. The dynamic multi-leaf collimator (MLC) method was used as the delivery technique. PTV and organ at risk (OAR) dose constraint are considered fixed, but only the NTO was adjusted. Dose constraint for several organs based on the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) and Radiation Therapy Oncology Group (RTOG) in Table 2.

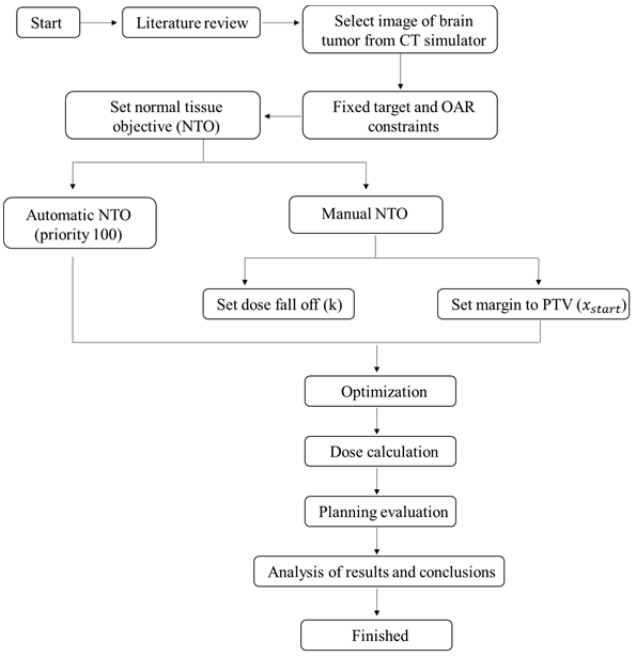

Figure 2. Flow chart of research methodology

The NTO is based on an exponential function, defined by the parameters given in Equation 1 [10]:

$$(x) = \begin{cases} f_0 e^{-k(x-x_{start})} + f_\infty\left(1 - e^{-k(x-x_{start})}\right), x \geq x_{start} \\ f_0, \qquad\qquad\qquad\qquad\quad x \geq x_{start} \end{cases} \qquad (1)$$

The initial dose f_0 is defined by the upper objective of the dose applied on PTVs. The upper objective is the dose value that should not be exceeded. The final dose f_∞ is the lowest dose penalized by the NTO. The location of the final dose is influenced by the fall-off parameter k. The strength of the dose decrease is given by a coefficient k. X_{start} is distance away form a PTV border.

In this study, automatic and manual NTOs were penalized with a priority of 100. Meanwhile, the manual NTO was set with a fixed $f_0 = 105\%$ and $f_\infty = 60\%$. Only the dose fall off k and x_{start} were varied. The k varied from fall-off 0.1 mm^{-1} to a much steeper fall-off 1 mm^{-1} and x_{start} varied from 0 to 10 mm. All plans were optimized using the photon optimization algorithm in the Eclipse software. Plans were neither paused during optimization after the final dose is obtained in planning evaluation. The final dose calculation was calculated using an anisotropic analytical algorithm (AAA).

Table 2. Dose constraint

Organ	$\boldsymbol{D_{max}}$ /$\boldsymbol{D_{mean}}$ **(Gy)**
Brainstem	$D_{max} < 54$
Opticnerve	$D_{max} < 54$
Chiasm	$D_{max} < 55$
Spinal cord	$D_{max} < 54$
Cochlea	$D_{mean} \leq 45$
Parotid	$D_{mean} < 25$
Lens	$D_{max} < 7$
Eye	$D_{max} < 54$

2.3. Evaluation planning

Four types of planning evaluation index were applied in the current study, including the conformity index (CI), homogeneity index (HI), gradient index (GI), and modified gradient index (mGI). The CI represents the coverage of radiation dose received by the target volume. HI represents the degree of the uniformity of radiation dose at each point of the target area. The GI describes the dose fall-off steepness outside the target volume. These indices are defined in several equations (Table 3).

Table 3. Different formula of planning evaluation index

	Formula	Ideal value
Conformity index [15]	(2) $CI = \frac{TV_{RI}}{V_{RI}}$	1
Homogeneity index[16]	(3) $HI = \frac{D_{max}}{D_p}$	1
Gradient index [17]	(4) $GI = \frac{V_{50\%}}{V_{100\%}}$	as small as possible
Modified gradient index [18]	(5) $mGI = \frac{V_{50\%}}{TV_{RI}}$	as small as possible

The CI is defined as the ratio of the target volume covered by the prescribed dose, TV_{RI}, to the volume covered by the prescribed dose, V_{RI}. The HI is defined as the ratio of the maximum dose, D_{max}, to the prescribed dose. The GI is defined as the ratio of the volume of 50% prescribed dose to the volume covered by the prescribed dose. The mGI is defined as the ratio of the volume of 50% prescribed dose to the target volume covered by the prescribed dose.

2.4. Statistical analysis

The statistical significance between automatic and manual NTO plans was assessed using the Wilcoxon signed-rank test, where a P-values < 0.05 were considered statistically significant.

III. Results

Table 4 reports the average of several indices in manual NTO setting by varying the dose fall off k and x_{start}. The conformity index (CI) is relatively constant at each x_{start}. It shows that the average CI has a values ranging from 0.80 to 0.98. Even with a small change, the CI value increase close to 1 as the dose fall off increases. The homogeneity index (HI) is relatively constant at each dose fall off k and x_{start}. The average HI has a value 1.11 to 1.12. The lowest value of gradient index (GI) was obtained with a margin to PTV x_{start} set to 1 mm and dose fall off set to 0.5 mm^{-1}. Meanwhile, the lowest value of modified gradient index (mGI) was obtained with a margin to PTV x_{start} set to 1 mm and dose fall off set to 1 mm^{-1}. The mGI values decrease as the dose fall off increase. The smallest values of GI and mGI indicates the optimal NTO settings.

Table 4. Planning evaluation results in manual NTO

Margin to PTV (x_{start})	*Dose fall off (mm^{-1}.)*	Conformity index	Homogeneity index	Gradient index	Modified gradient index
		(mean±deviation standard)			
0 mm	0.1	$0{,}92 \pm 0.10$	1.11 ± 0.05	5.20 ± 4.59	5.31 ± 3.92
	0.3	0.95 ± 0.07	1.11 ± 0.06	4.79 ± 3.93	4.78 ± 3.3
	0.5	0.96 ± 0.06	1.11 ± 0.05	4.77 ± 3.85	4.75 ± 3.33
	1	0.97 ± 0.06	1.12 ± 0.05	4.80 ± 3.81	5.36 ± 3.98
1 mm	0.1	0.88 ± 0.14	1.11 ± 0.05	5.08 ± 4.70	4.76 ± 3.45

	0.3	0.94 ± 0.11	1.11 ± 0.05	4.72 ± 4.05	4.63 ± 3.42
	0.5	0.97 ± 0.09	1.11 ± 0.05	$\mathbf{4.69 \pm 4.02}$	4.63 ± 3.42
	1	0.98 ± 0.12	1.11 ± 0.05	4.73 ± 4.03	$\mathbf{4.62 \pm 3.41}$
3 mm	0.1	0.89 ± 0.11	1.11 ± 0.05	5.24 ± 4.85	5.48 ± 4.13
	0.3	0.94 ± 0.08	1.11 ± 0.05	4.86 ± 4.16	4.89 ± 3.58
	0.5	0.95 ± 0.06	1.11 ± 0.05	4.79 ± 4.06	4.79 ± 3.48
	1	0.96 ± 0.06	1.12 ± 0.05	4.76 ± 4.01	4.74 ± 3.44
5 mm	0.1	0.86 ± 0.13	1.11 ± 0.05	5.19 ± 4.99	5.58 ± 4.23
	0.3	0.92 ± 0.99	1.11 ± 0.05	4.99 ± 3.99	5.08 ± 3.75
	0.5	0.94 ± 0.09	1.11 ± 0.05	4.85 ± 4.18	4.90 ± 3.59
	1	0.95 ± 0.08	1.12 ± 0.05	4.80 ± 4.10	4.81 ± 3.52
10 mm	0.1	0.80 ± 0.16	1.11 ± 0.05	5.00 ± 5.11	5.65 ± 4.33
	0.3	0.87 ± 0.12	1.11 ± 0.05	5.07 ± 4.69	5.42 ± 4.03
	0.5	0.90 ± 0.10	1.11 ± 0.05	5.07 ± 4.63	5.26 ± 3.95
	1	0.91 ± 0.10	1.11 ± 0.05	4.99 ± 4.47	5.16 ± 3.84

Based on the values of these indices in Table 4, used of manual NTO with combination of x_{start} 1 mm and dose fall off ≥ 0.5 mm^{-1} has results that are close to optimal values. The combination NTO setting then compared with the prior plans that used automatic NTO of the same 15 cases. The comparison is shown in Table 5 which shows that the use of manual NTO with a dose fall off of 0.5 and 1 mm^{-1} achieved an optimal indices value.

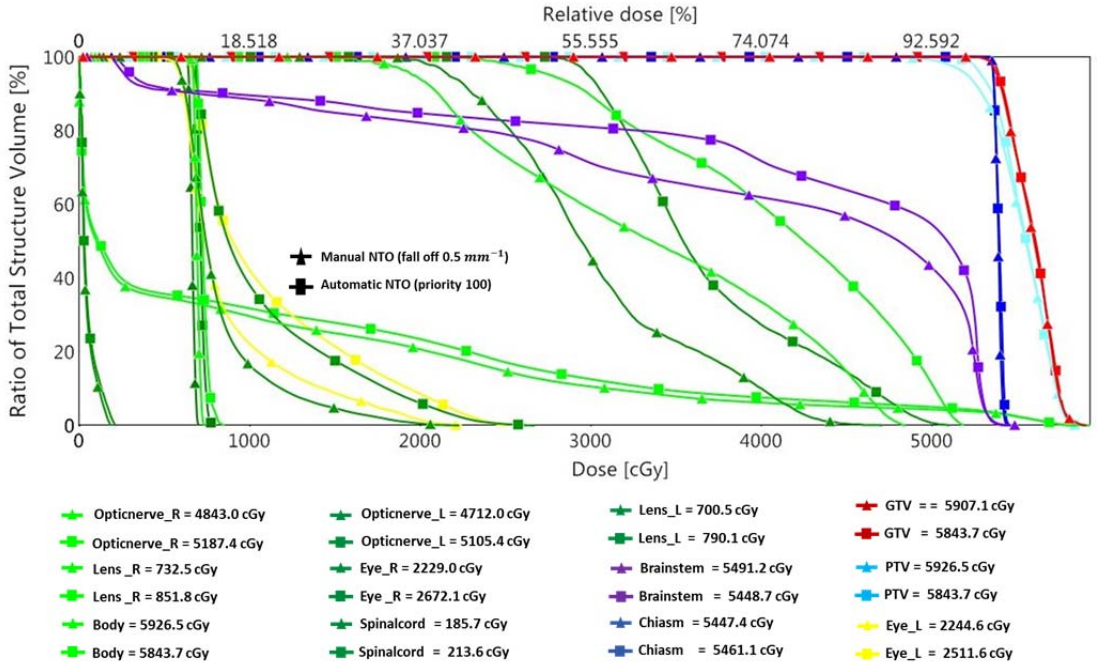

Figure 3. Cumulative dose-volume histogram (DVH) comparison between manual NTO and prior plans

The result of comparisons between prior plans with manual NTO (dose fall off of 0.5 mm^{-1}) is CI of 0.92 vs 0.97, p = 0.001, HI of 1.09 vs 1.11, p = 0.004, GI of 5.00 vs 4.69, p = 0.013, mGI of 4.46 vs 3.84, p = 0.001. Manual NTO reduces the total average dose in normal tissue by 4.9 Gy from automatic NTO. It was evidenced by the cumulative dose-volume histogram (DVH) curve of a patient with Craniopharyngiom case in Figure 3. The curve shows that the organ at risk (OAR) received a smaller dose after applied NTO with a dose fall off 0.5 mm^{-1}.

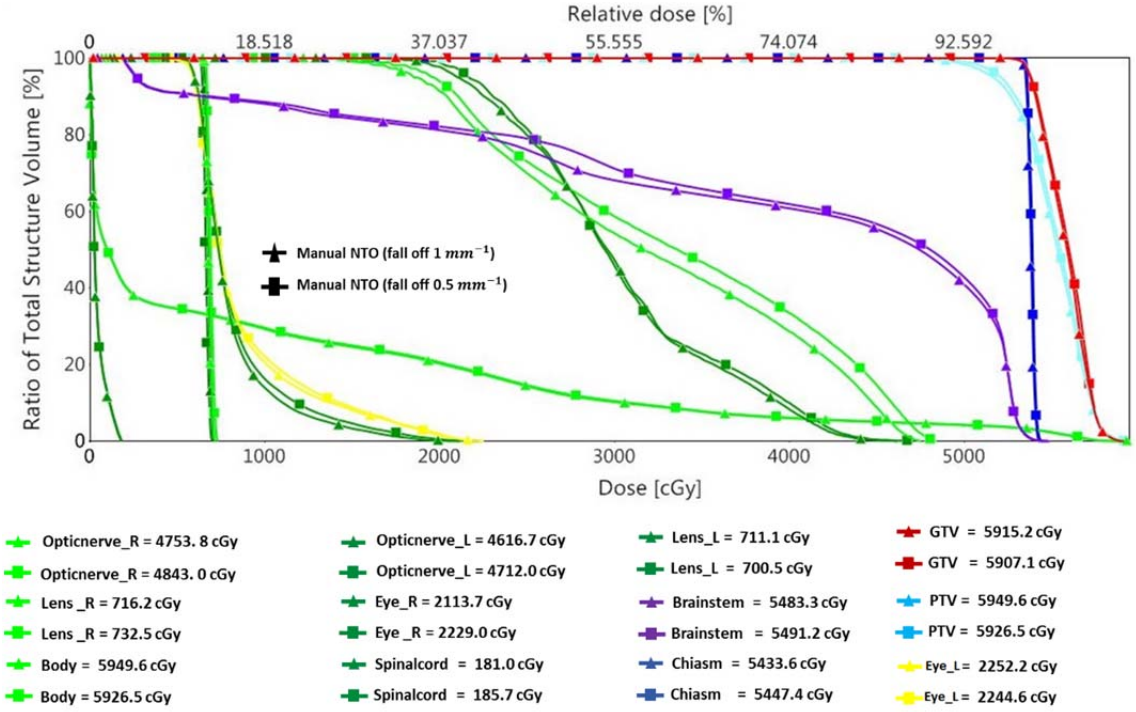

Figure 4. Cumulative dose-volume histogram (DVH) comparison between dose fall off 0.5 mm^{-1} and dose fall off 1 mm^{-1}

The manual NTO with a dose fall offs 1 mm^{-1} produced indices that met the optimal criteria compared to the manual NTO 0.5 mm^{-1}. The result is CI of 0.97 vs 0.98, p = 0.036, HI of 1.11 vs 1.11, p = 0.782, GI of 4.69 vs 4.73, p = 0.064, mGI of 3.84 vs 3.77, p = 0.001. Since the results of the evaluation indices were not significantly different between the dose fall offs of 0.5 and 1 mm^{-1}. It resulted a slight difference on the cumulative DVH curve in Figure 4. The cumulative DVH curve for the dose fall off 1 mm^{-1} almost overlaps with the dose fall off 0.5 mm^{-1}. However, Dose fall off 1 mm^{-1} can reduce the total average dose in normal tissue by 1.39 Gy from dose fall off 0.5 mm^{-1}.

Table 5. Statistical comparisons between automatic and manual NTOs

	Automatic NTO	Dose fall off 0.5 mm^{-1}	Dose fall off 1 mm^{-1}	P-value	
	(mean±deviation standard)			Automatic NTO vs Dose fall off 1	Dose fall off 0.5 vs 1 ($mm^{-1)}$
PTV					
CI	0.92 ± 0.09	0.97 ± 0.09	0.98 ± 0.12	0.001	0.036
HI	1.09 ± 0.07	1.11 ± 0.05	1.11 ± 0.05	0.004	**0.782**
GI	5.00 ± 4.93	4.69 ± 4.02	4.73 ± 4.03	0.013	**0.064**
mGI	4.46 ± 3.70	3.84 ± 2.89	3.77 ± 2.86	0.001	0.001
Organ at risk (Gy)					
Lens_R	5.91 ± 2.94	5.88 ± 2.79	5.88 ± 2.86	0.050	**0.753**
Lens_L	5.97 ± 3.19	5.68 ± 2.87	5.71 ± 2.90	**0.069**	0.130
Chiasm	35.30 ± 24.64	34.56 ± 20.97	34.43 ± 20.96	0.001	0.187
BrainStem	41.49 ± 21.31	43.66 ± 16.91	43.42 ± 16.99	**0.351**	0.017
SpinalCord	6.58 ± 14.75	6.02 ± 14.46	5.95 ± 14.24	**0.092**	0.008
OpticNerve_R	28.13 ± 20.17	26.94 ± 19.34	26.67 ± 19.31	0.001	0.046
OpticNerve_L	28.90 ± 18.31	27.67 ± 17.36	27.47 ± 17.20	**0.217**	0.013
eye_R	21.32 ± 13.64	18.88 ± 13.22	18.68 ± 12.77	0.004	**0.088**
eye_L	20.63 ± 12.65	19.34 ± 11.89	19.18 ± 11.91	0.001	**0.286**
Total dose OAR	194.23	189.33	187.94		

Note: NTO (*normal tissue objective*), PTV (*planning target volume*), CI (*conformity index*), HI (*homogeneity index*), GI (*gradient index*), mGI (modified *gradient index*

IV. Discussion

Conformity index (CI), homogeneity index (HI), and gradient index (GI) and modified gradient index (mGI) are the main planning quality metric, as they are most closely related to clinical outcome. These metrics are used to evaluate the best NTO setting for brain tumor planning. A manual NTO setting of priority 100, fall off 1 mm^{-1}, margin to PTV $x_{start} = 1$ mm, initial dose $f_0 = 105\%$, and final dose $f_\infty = 60\%$ achieved high conformity and sharpening dose gradients beyond the target volume. A significant effect was observed after the manual NTO was applied then compared to prior plans that were used automatic NTO.

The formula and the ideal values of conformity index are presented in table 3. The ratio of the formula gives a value ranging from 0 (no conformity) to 1.0 (perfect conformity). A value of 0 is obtained if the target volume covered by the prescribed dose, TV_{RI}, is smaller than the volume covered by the prescribed dose, V_{RI}. A value of 1 is obtained if the TV_{RI} is equal with the V_{RI}. CI is categorized into several index deviations with a value index between $2 \leq CI \leq 2.5$ or $0.9 \leq CI \leq 1$ is a small deviation, and if $CI < 0.9$ or $CI > 2.5$ is a large deviation [15]. In this study, automatic and manual NTOs is included in the CI category with a small deviation. Based on Table 4, the variation of distance x_{start} does not provide a significant different to the CI value. However, the increase in CI value is proportional to the increase in dose fall off. It caused by the higher of the dose fall off, the

tight of the dose range to the target. As a result, the target volume received the prescription dose is smaller than the volume that cover by the prescription dose.

The HI value is proportional to the maximum dose on PTV. ICRU 62 recommends a maximum dose 107% of the prescription dose to the PTV [19]. In this study, manual NTO has produced a higher HI value than automatic NTO. It influenced by a dose fall-off steepness outside the target volume. Based on RTOG, the ratio of the HI values shall be less than or equal to 2.0 ($HI \leq 2$)[16]. So, the HI value on the manual NTO is acceptable ($HI = 1.11$).

Gradient index (GI) is an effective method to evaluate the dose reduction outside the target volume [20]. In this study, conventional gradient index (GI) and modified gradient index (mGI) were used to evaluate the dose fall off outside the target. mGI evaluated the dose fall off based on the target volume. It shows the dose fall-off steepness outside the target volume more accurately. Small GI and mGI values indicated a sharp dose gradient beyond the target volume which can reduce radiation toxicity to normal tissue [21]–[23]. In this study, the smallest GI and mGI were obtained in manual NTO with a dose fall off $= 1$ mm^{-1}. Automatic NTO provides a higher GI and mGI values than manual NTO. This means that the dose received by normal tissue in manual NTO is less than the prior plans (automatic NTO). This result was proven by the average maximum dose received by each organ at risk in Table 4 and the decrease dose in OAR on the cumulative DVH curve in Figure 3.

V. CONCLUSIONS

A NTO setting with start dose $f_0 = 105$ %, end dose $f_\infty = 60\%$, dose fall-off $k = 1$ mm^{-1} and margin to PTV x_{start} = 0.1 cm has results an optimal planning radiation therapy in brain tumors. The used of manual NTO produced better conformity to the target and a sharp dose gradient outside the target volume than automatic NTO. Manual NTO settings can protect the OAR better than automatic NTO. Planning with manual NTO reduced 4.9 Gy of the total dose at OAR.

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