Original Article

Evaluation of Normal Tissue Objective Function for Treatment Planning of Solitary Brain Metastasis Using Intensity-modulated Radiosurgery Techniques

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Abstract

Purpose: The purpose of this study was to systematically examine the normal tissue objective (NTO) function by comparing its variations for planning solitary brain metastasis with intensity-modulated and volumetric-modulated arc radiosurgery techniques. **Materials and Methods:** Twenty-two cases were retrospectively planned with two NTO parameter sets named A and B using intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT) techniques. The Type A set used slope, k = 0.4 mm^{-1} plus end dose, D_e = 20%, whereas the Type B set used k = 1.0 mm^{-1} plus D_e = 10%. The resulting four plan types were assessed using mean dose to 5 mm exterior ring, normal brain receiving 12 Gy (V12), 5 Gy total brain dose volume (V5), gradient index (R50%), focal index (FI), Paddick conformity index (PCI), prescription isodose surface (PIDS), and MU/Gy. **Results:** Brain doses were significantly lower for VMAT than for IMRT. R50% was more favorable for VMAT than for IMRT for each planning target volume (PTV). The mean FI was comparable between the corresponding IMRT and VMAT plan types. PCI was better for the IMRT_A plan type. PIDS was significantly lower for Type B plans than Type A for both techniques. For PTVs <3 cm^3, IMRT plans showed poor dosimetry and required NTO settings stricter than Type B. **Conclusions:** The application of NTO variations demonstrated varied dosimetry for IMRT and VMAT techniques. The NTO parameter variations produced field size and/or beamlet size/shape variations. The strict NTO parameter set generated more conformal beam apertures to reduce the brain dose. VMAT plan types showed significantly lower brain doses and better dosimetry for all target sizes.

Keywords: Modulated radiation techniques, normal tissue objective, radiosurgery, solitary brain metastasis

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Introduction

The normal tissue objective (NTO) function, a commonly used tool in radiation treatment planning to minimize nontarget tissue dose, is defined as an exponentially reducing dose function dependent on the distance from the irradiated target. NTO can be used in either user-defined or automatic modes. In the user-defined mode, parameters such as priority (P), slope (k), start distance from the target border (x_s), and initial and end doses (D_i and D_e) are to be specified to define the NTO function. Whereas in automatic mode, only the priority is to be fed by the user, and the other parameters are adopted automatically by the planning system based on the requirement. It caters to treatment planning with intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT) techniques. Although NTO is routinely used in planning various treatment sites, it finds a special place in intracranial stereotactic radiosurgery (SRS), as sparing the normal brain from receiving necrotic doses remains crucial.

With advances in planning systems, tailoring SRS treatments by minimizing healthy brain tissue irradiated to high doses has become increasingly important.[1] The use of NTO for various treatment sites has been reported in the literature. A recent investigation on brain tumors suggested better normal brain sparing on using NTO priority, P = 100 and

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slope, k = 0.5 mm^{-1}.[2] Bell *et al*., in their study on lung stereotactic ablative radiotherapy, examined variations of NTO and recorded better normal lung sparing with P = 500 and k = 0.15 mm^{-1}.[3] Few investigations have exclusively reported the use of NTO for single brain targets. Wang *et al*. used a set of dose-tuning structures along with NTO parameters P = 150, k = 0.8 mm^{-1}, D_i = 95%, and D_e = 40% as an approach to creating radiosurgical plans for single brain tumors.[4] Another study used P = 250, k = 0.35–0.45 mm^{-1}, D_i = 100%, and D_e = 30% to create a dose gradient around single brain lesions.[5] From these studies, it appears that the use of the NTO function with user-defined parameters is a choice of planners purely based on experience. Moreover, no systematic study specifically sketching the use of NTO for single targets in the brain using IMRT and VMAT planning techniques is reported.

Eclipse algorithm reference guide (V 13.6) describes the NTO function as a mathematical expression for exponentially reducing dose in normal tissue.[6] The NTO parameter settings define the dose falloff pattern and can be chosen according to the requirements. The planning system considers minimizing the dose to points in normal tissue that fall above the NTO curve to achieve the specified dose gradient. However, little is known as to how the planning system reduces the normal tissue dose. A paucity of data suggests gaining a better understanding of NTO. In this context, we attempt to systematically explore the NTO function by comparing its variations for radiosurgery of solitary brain metastasis with IMRT and VMAT techniques. Dosimetric parameters quantified to demonstrate the use of the NTO function included the mean dose to the 5 mm ring structure around planning target volume (PTV) (Ring D_{mean}), normal brain receiving at least 12 Gy (V12), total brain volume receiving 5 Gy (V5), gradient index (R50%), focal index (FI), Paddick conformity index (PCI), prescription isodose surface (PIDS), and monitor units per Gy (MU/Gy).

Materials and Methods

For this retrospective dosimetric study, we extracted 22 computed tomography sets of solitary brain metastasis cases from the database to represent varying volumes of gross tumor volume (GTV). All targets were considered to be those that did not overlap with organs at risk. The PTV was created by expanding the GTV by 1 mm, and the normal brain structure was generated by subtracting GTV from the brain contour. All other organs at risk were also outlined. A marginal dose of 20 Gy was prescribed[7] for all cases for consistency in reporting the results. All plans were developed for a TrueBeam STx (Varian Medical Systems, Palo Alto) linear accelerator using the 6 MV flattening-filter-free beams with a dose rate of 1400 MU/min. The high-definition multileaf collimator (HD 120) having a fine leaf width of 2.5 mm was used with the beam isocenter placed at the target centroid for maximum conformity. All plans were optimized using the photon optimizer (V 13.6) and the final dose calculation was carried out using the anisotropic analytical algorithm (V 13.6). The dose optimization and calculation grid sizes were set at 1.25 mm.

The IMRT plans used 12–14 noncoplanar beams in three to four couch planes, with gantry angle separations of at least 30°. However, the arrangement was modified as necessary on a trial-and-error basis to achieve the best possible irradiation geometry intended to miss organs at risk. For VMAT planning, three to four noncoplanar partial arcs were used to approximate the beam arrangement of IMRT plans. Both of these techniques used two variations of NTO parameters. The first NTO variation (Type A) used low k plus high D_e, whereas the second variation (Type B) used high k plus low D_e. The Type A variation used k = 0.4 mm^{-1} and D_e = 20%, and the Type B variation used k = 1.0 mm^{-1} and D_e = 10%. The parameter values were so chosen to obtain a sharp dose gradient necessary for radiosurgical plans. Furthermore, to examine the strictness of end dose and slope parameters, the latter variation was designed using half the end dose and about double the slope compared to the former. Both of these variations used a priority of 100. The PTV was prescribed a minimum dose of 20 Gy and a maximum dose of 25 Gy. These dose-volume objectives were assigned a priority of 100 and 75, respectively. For reasonable target dose coverage, D_s = 99% of PD was specified at x_s = 1 mm for all NTO combinations. The dose plans were normalized to ensure that the prescribed dose covered at least 99% of PTV. The NTO parameters were specified at the beginning of optimization, whereas all other settings remained the same. We did not use dose-tuning rings to limit the dose around the target not only to avoid bias from using the tuning rings but to solely assess the effects of NTO parameter variations. All plans were optimized without planner intervention, and the optimization process continued until the overall objective function could no longer be improved.

For a comprehensive analysis, we included dosimetric parameters such as the mean dose to the 5 mm ring surrounding PTV (Ring D_{mean}), 12 Gy dose volume in normal brain tissue (V12),[8] 5 Gy dose volume in total brain tissue (V5), gradient index (R50%), FI, PCI, PIDS, and monitor units per Gy (MU/Gy). R50% is the ratio of half-prescription isodose volume (PIV50%) to the volume of PTV. FI is defined here for GTV as the product of the maximum and minimum doses in GTV divided by the square of the prescription dose.[4] PCI is defined as $(PTVPIV)^2/(PTV \times PIV)$, where PTVPIV is the overlap of PTV and PIV.[9] To further evaluate the dosimetry of NTO-based plan combinations, we plotted R50% for each case. The data were plotted against the volume of PTV to determine whether each plan achieved acceptable dosimetry using the limits proposed for upper and lower bounds of R50%.[10,11] The upper and lower bounds are depicted for the volumes studied here. The readers are referred to the specific literature for further details on quantitative limits for intermediate dose spill. Data were analyzed using a one-way ANOVA for comparison, and individual differences were reported based on *post hoc* analysis. $P < 0.05$ was considered statistically significant.

Results

The mean volume of GTV was 1.95 cm^3 and that of PTV was 3.27 cm^3. PTVs ranged between 0.5 cm^3 and 6.1 cm^3. Comparative metrics for IMRT and VMAT plan combinations are summarized in Table 1. To assess the dose gradient variations in the proximity of the target boundary due to the NTO parameter variations, Ring D_{mean} and V12 were computed. The average values of these parameters were significantly lower for Type B than for Type A for both the techniques. Mean doses within the ring were substantially lower for VMAT plans. The VMAT plans also recorded the lowest V12 volumes. Specifically, the VMAT_B plans produced significant dosimetric improvement, lowering Ring D_{mean} by 6% and V12 by 1.5 cm^3 compared to its IMRT counterparts. V5 also reduced monotonically from IMRT_A through VMAT_B. PCI values were equivalent among the IMRT_B and VMAT plan combinations, except for the IMRT_A, which recorded values close to 1 at the expense of worsened dose falloff at the target periphery. Changes in FI indicate that tumor dose heterogeneity increased significantly between the A and B plan combinations, irrespective of the treatment technique. However, FI remained similar between the IMRT and VMAT counterpart plan combinations. Concerning PIDS, IMRT_B showed significantly lowest percentage score among the four plan combinations ($P < 0.001$). The average MU/Gy values were significantly different between each plan type. MU/Gy value for IMRT_A plans was 22% lesser than IMRT_B plans, whereas it was 6.6% higher for VMAT_A plans than VMAT_B plans.

To examine whether the applied NTO plan variations yield clinically acceptable dose gradient, we depicted R50% for the four plan types with the upper and lower bounds of R50% [Figure 1]. The R50% scores were higher for IMRT_A plans than those of the other plans. Scores of both IMRT plan types partly exceeded upper R50%, especially when PTVs were small in size. IMRT_A and B plans exhibited poor dose falloff, especially for PTVs smaller than 4 cm^3 and 1 cm^3, respectively. On the other hand, VMAT plans showed lower R50% scores, invariably lying between the upper and lower limits of R50% for all target sizes studied. For the A and B plan types of IMRT, mean R50% values were 5.8 ± 2.8 and 4.1 ± 1.3, respectively. It was 3.4 ± 0.8 and 3.3 ± 0.7 for A and B plan types of VMAT. The R50% scores showed substantial differences between IMRT and VMAT plans.

To study the influence of planning strategy on dose gradient variation within and outside the target volume, we plotted percentage relative variation in FI and V12 between B and A plan types ([B − A] ×100/A) for each technique separately [Figures 2 and 3]. In general, the relative variation of FI was positive, and that for V12 was negative. Between the IMRT plan types, the variation in V12 decreased monotonically with increasing PTV size. FI variation was high for small targets, decreased gradually, and remained almost constant (at about 10%) with increasing volume of PTV. In the case of VMAT plan types, the trend in V12 variations was roughly similar to that observed between IMRT plan types. However, the V12 variations were low for VMAT compared to the corresponding variations for IMRT. Regarding FI variations, the initial general trend appeared similar for both techniques, but a definite trend with the increase in PTV size was absent. The degree of FI variation for VMAT is lower than for IMRT for the left half of PTV volumes but was roughly similar for the right half of PTV volumes.

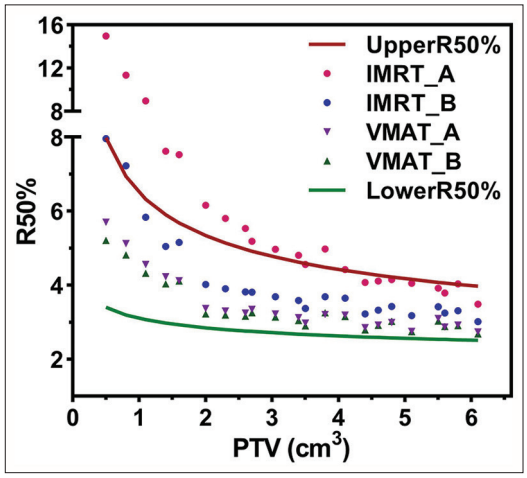

Figure 1: Comparison of computed R50% values for the four plan types as a function of planning target volume size for all cases. Upper and lower bounds are calculated from the analytical expression of R50%. IMRT: Intensity-modulated radiation therapy, VMAT: Volumetric-modulated arc therapy, PTV: Planning target volume

Table 1: Average score of plan metrics for the four plan types of all cases

Plan metric	IMRT		*P*	VMAT		*P*	*P*
	A	B	A versus B	A	B	A versus B	IMRT_B versus VMAT_B
Ring D_{mean} (Gy)	15.6±0.5	14±0.5	<0.001	13.1±0.6	12.8±0.6	<0.001	<0.001
V12 (cm^3)	10.3±2.5	7.6±2.8	<0.001	6.3±2.4	6.1±2.4	<0.001	<0.001
V5 (cm^3)	41.3±11.5	31.9±11.5	<0.001	26.5±10.5	25.9±10.5	0.017	<0.001
PCI	0.9±0.1	0.7±0.1	<0.001	0.7±0.1	0.7±0.1	0.6	0.46
FI	1.4±0.1	1.6±0.1	<0.001	1.4±0.1	1.5±0.1	<0.001	0.022
PIDS (%)	77.1±3.9	70.7±2.6	<0.001	77.5±2.5	73.4±2.7	<0.001	<0.001
MU/Gy	201±7	246±19	<0.001	378±41	353±22	<0.001	<0.001

IMRT: Intensity-modulated radiation therapy, VMAT: Volumetric-modulated arc therapy, PCI: Paddick conformity index, FI: Focal index, PIDS: Prescription isodose surface, MU/Gy: Monitor units per Gy

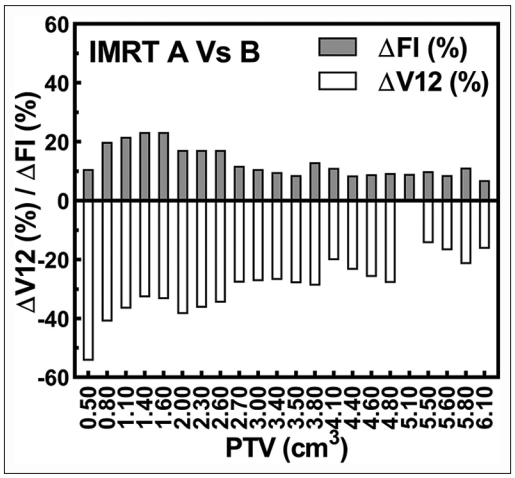

Figure 2: Variation of V12 and FI for IMRT_B type plan relative to IMRT_A type plan for each case. IMRT: Intensity-modulated radiation therapy, PTV: Planning target volume, FI: Focal index

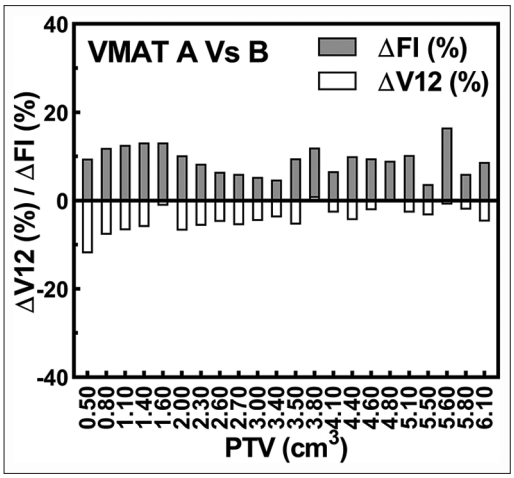

Figure 3: Variation of V12 and FI for VMAT_B type plan relative to VMAT_A type plan for each case. VMAT: Volumetric-modulated arc therapy, PTV: Planning target volume, FI: Focal index

Discussion

The influence of NTO parameter variations on the dosimetry of solitary brain metastasis was examined using two D_e levels, 10% and 20%, and two k values, 0.4 mm^{-1} and 1.0 mm^{-1}, to generate plans with varying dose gradients for IMRT and VMAT planning techniques. In this study, the tested NTO variations were formed using a combination of low k + high D_e (Type A) and high k + low D_e (Type B). Parameters studied to examine dose gradients outside and within the target showed significant differences between the NTO-based plan optimizations.

The method of optimization used by the photon optimizer algorithm depends on the treatment planning technique. For IMRT, the optimizer creates the fluence pattern for each static beam based on the plan objectives. Subsequently, suitable leaf motions and jaw positions are determined based on the fluence pattern to realize the actual dose distribution. On the other hand, for VMAT, the optimizer directly uses machine parameters such as leaf positions, gantry speed, and dose rate to estimate dose distribution to achieve plan objectives. Here, the optimizer requires the user to supply a field size that generally fits the target volume throughout the beam trajectory. Therefore, unlike IMRT optimization, an appropriate field definition is a prerequisite for VMAT optimization. Owing to the difference in optimization methods, dosimetric parameters for IMRT and VMAT techniques vary even for a given set of optimization parameters. The dose distribution is thus primarily determined by field extents and beamlet shape/size. We find that the field extents and beamlet shape/size for IMRT beams largely depend on the strictness of NTO prescription [Figure 4a and b]. The field size produced for the IMRT_B plans is substantially smaller than IMRT_A plans. Consequently, IMRT_B plans yield significantly higher MU/Gy values than IMRT_A plans. While the field size remains fixed for VMAT, only the beamlet shape and size are affected by NTO prescriptions [Figure 4c and d]. The beamlet shapes for the VMAT_B type plans appear more conformal (fitting snugly to the target border) than for the VMAT_A type plans. Therefore, for the VMAT_B case, most leaves do not suspend over the isocenter, resulting in lower MU/Gy compared to the case of VMAT_A. We infer that the strict NTO prescription (Type B) reduces normal tissue dose by producing more conformal apertures than does a loose NTO prescription. This result indicates that more conformal apertures are generated as k increases from 0.4 mm^{-1} to 1.0 mm^{-1} and D_e decreases from 20% to 10%.

R50% decreases for each PTV with the application of strict NTO for both planning techniques. A study by Zhao *et al*. revealed that the increase in optimal dose gradient was apparent with small targets when using dynamic conformal arc planning.[12] Another study by Xu *et al*. reported a similar trend but not to an appreciable degree in VMAT planning.[13] This study is consistent with prior research regarding the gradient index trend observed in IMRT and VMAT planning techniques. The combination of NTO with VMAT exhibited a favorable dose gradient index (R50%) compared to IMRT for the range of studied volumes. Another aspect evident from Figure 1 is that R50% can be further decreased by the appropriate combination of NTO (Type B) with the VMAT planning technique compared to other plan types. This investigation corroborates the assertion made by Desai *et al*. regarding the potential reduction of upper limits of R50% through advancements in optimization techniques.[11]

The mean V12 for IMRT_B (7.6 ± 2.8 cm^3) was significantly higher than VMAT_A and B groups (6.3 ± 2.4 cm^3 and 6.1 ± 2.4 cm^3). Most of the R50% scores for these three groups fall within the upper and lower limits [Figure 1]. Thus, all these groups appear to pass the criteria for plan acceptability. A deeper analysis of volumes at the end of the PTV range reveals that the use of R50% alone should be avoided to score quality. For example, V12 for cases 18–22 exceeds 10 cm^3 in the case of IMRT_B plans. When V12 exceeds 10 cm^3 and 15 cm^3,

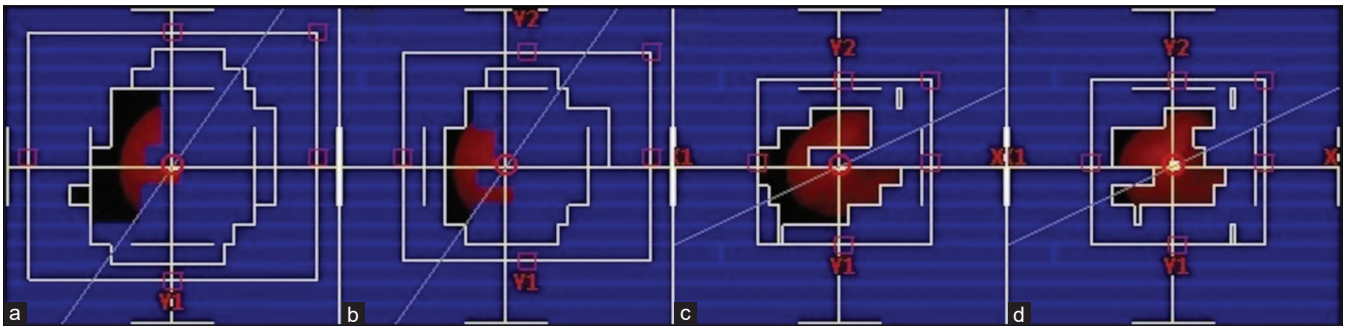

Figure 4: Field and beamlet openings of the first control point of a beam of (a) IMRT_A, (b) IMRT_B, (c) VMAT_A, and (d) VMAT_B plan types for a PTV of 1.6 cm^3

the occurrence of brain radionecrosis is about 15% and 20%, respectively.[8] The PTVs of these five cases range from 5.1 to 6.1 cm^3. A small change in R50% for these volumes manifests a large change in half-PIVs (PIV50%), which in this study is the brain volume receiving at least 10 Gy. Consequently, large changes also occur in V12. Therefore, a small decrease of R50% leads to a substantial decrease of V12. A gradual increase of R50% for the five cases resulted in the order of VMAT_B, VMAT_A, and IMRT_B. The consequent increase of V12 for IMRT_B was significantly higher than for VMAT_A and VMAT_B plans (11.3 ± 0.8 cm^3 vs. 9.2 ± 0.7 cm^3 and 8.9 ± 0.6 cm^3). Therefore, quantitative measures, R50% and V12 together, should be the choice for the quality assessment of rival plans.[8,10,14]

For PTVs <3 cm^3, IMRT_A plans showed R50% values exceeding the upper R50% limits. The Type A NTO variation produced unnecessarily excessive beam margins and a large V12 for IMRT plans compared to VMAT plans. For example, V12 of case #2 for IMRT_A and B was about 139% and 53% higher than their VMAT counterparts. This result suggests that IMRT optimization creates large beam margins, leading to large V12 volumes [Figure 4]. Moreover, the findings of this study align with prior research indicating increased V12[15] and PIV50%[16] volumes resulting from beam margin addition. Therefore, the tested NTO variations are appropriate for use with the VMAT technique across all studied PTV volumes but not recommended for volumes smaller than 3 cm^3 when using the IMRT technique.

The dose spill of 5 Gy for IMRT was much higher than that of VMAT. IMRT plans used a limited number of static beams, typically 12–14 for a 20 Gy prescription dose. The tested NTO variations generate broad fluence distributions for IMRT plans, resulting in a field size broader than that of the corresponding VMAT plans. Thus, for IMRT plans, a substantial low dose is contained along these few broad beam paths. In contrast, beams fashioned as arcs with relatively smaller field sizes effectively spread the dose over a large tissue volume. The dose spread in normal tissue, V5 in particular, is significantly higher for the IMRT plans. Perhaps further tightening of the slope, end dose, and priority parameters would reduce the normal brain dose for IMRT plans.

Concerning PCI, a significant difference appears between the IMRT combinations [Table 1] because of the generous field opening for the IMRT_A plans compared to the IMRT_B plans. Again, the wide beamlets extending the target margins also caused increased Ring D_{mean} and brain dose at all levels. Thus, IMRT_A plans appear suboptimal, as the dose to the normal brain is a critical parameter in SRS treatment. Furthermore, our study suggests that VMAT plan types are always superior in terms of average PIDS, which is <78%. In particular, VMAT_B plans had a mean PIDS of about 73%, ranging from 68.82% to 77.16%. Research suggests that 50%–75% PIDS is optimal for linear accelerator-based SRS of single lesions using dynamic conformal arcs[12] and 60%–70% using VMAT.[13] IMRT_B showed the highest FI among the four plan types, with an average PIDS of about 70%. However, the mean V12 for this plan type was higher by about 1.3 cm^3 than the VMAT plan types. The NTO parameters need further tuning to improve the dosimetry of IMRT plans and achieve results comparable to VMAT plans. Thus, facilities having IMRT as a sole treatment modality may opt for plans with NTO parameters tighter than those used for the IMRT_B plan type.

The influence of NTO variations on dose gradient variations for each technique was studied by analyzing the relative variations of FI and V12. Large positive FI and negative V12 variations between IMRT plan types indicate that IMRT_B plan types had higher target focal doses and lower normal brain doses. It was because of the relatively small field and beamlet apertures generated for IMRT_B than IMRT_A [Figure 4a and b]. Substantial average negative V12 difference yielded for Type B IMRT plans of about 35% [Figure 2] for small target volumes (<3 cm^3). Data comparison (IMRT_A vs. VMAT_B) from Table 1 suggests that further improvement in V12 reduction is possible. Therefore, it is recommended to employ NTO prescriptions stricter than Type B for such target volumes when IMRT is the only available planning technique. In general, the FI increased for Type B plans for both planning techniques in tandem with decreasing V12 and R50%, irrespective of target size. A recent study on the SRS of multiple brain metastases argued that restraining tumor focal dose to below 120% increased PIV50%, increasing the risk of normal brain toxicity.[17] These results suggest that target focal dose escalation and brain dose reduction might favor tumor local control while limiting brain radionecrosis. This particular aspect of the present investigation aligns with earlier studies

that argued the advantages of accomplishing these planning objectives.[18-22]

The applied NTO variations were consistent between techniques to avoid comparison bias. However, this study tested only two variations of NTO for solitary metastasis cases and a single priority value of 100. Achieving normal brain sparing with IMRT equivalent to VMAT may require NTO variations stricter than the type B prescription, which is unexplored in this study. The dosimetric variations between planning techniques arise not only due to the optimization method but also due to the delivery method. This study examined PTVs smaller than 7 cm^3. Therefore, the findings of this study may be interpreted for small target volumes tested for the two NTO variations. Although this study provides useful information for small targets, further investigation is warranted for planning small to large target volumes with various NTO parameter settings for both techniques.

Conclusions

Systematic application of NTO to the simple case of solitary brain metastasis revealed varied dosimetry for IMRT and VMAT techniques. The NTO variations applied to the VMAT technique demonstrated substantially lower normal brain doses and superior dosimetry. The dosimetry was suboptimal for IMRT plan types, especially for target volumes smaller than 3 cm^3. The variation of NTO parameters is directly related to the variation of field and beamlet size or shape. The strict NTO parameter variation (Type B), yielded small field apertures to reduce the nontarget tissue exposure for the IMRT technique. The Type B constraint set can readily be adopted for optimal plan generation and fine tuned for further improvement on a case-to-case basis, which provides with a quick optimal plan.

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Conflicts of interest

There are no conflicts of interest.

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