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Assessment of normal tissue objectives in RapidArc treatment for cervical cancer

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Original Article

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Abstract

Purpose: The normal tissue objective (NTO) is a tool used in inverse-planned intensity-modulated radiation therapy (IMRT) to minimize dose dispersion to surrounding tissues. The current study focuses on the NTO's impact on RapidArc treatment plans for cervical cancer patients or its role in reducing doses to healthy surrounding tissues.

Material and methods: This study included 11 cervical cancer patients who underwent RapidArc treatment. We assessed plans both with and without the NTO objective by evaluating parameters such as homogeneity, conformity, gradient index (GI), IMRT factor, integral dose and the volume of normal tissues receiving low doses of 40, 30, 20 and 10 Gy. Further, differences between automatic NTO and manual NTO were evaluated using Wilcoxon signed-rank test.

Results: There were no significant differences in the conformity index, homogeneity index, IMRT factor and integral dose between plans with automatic NTO and those with manual NTO RapidArc plans. However, we did observe a clear advantage in using manual NTO for controlling low-dose exposure to normal tissues. The comparisons between automatic and manual NTO resulted in a GI of $3{\cdot}1 \pm 0{\cdot}3$ versus $2{\cdot}7 \pm 0{\cdot}68$ ($p = 0{\cdot}008$). Furthermore, we noticed a significant reduction in the volumes receiving low doses (V_{10}, V_{20}, V_{30} and V_{40}) with the manual NTO settings.

Conclusion: The NTO plays a crucial role in optimizing RapidArc plans for treating cervical cancer. Based on the findings of this study, manual NTO settings of distance from PTV border $x_{start} = 0{\cdot}5$ mm, start dose $f_0 = 105\%$, end dose f_∞ = an average of 40%, dose fall-off $0{\cdot}2$ mm^{-1} were optimal. Further research involving a larger sample size and exploration of various NTO parameters is necessary to validate our results.

Introduction

Globally, cervical cancer is the fourth most common cancer in females after breast, colorectal and lung cancer. Also, cervical cancer is the fourth leading cause of cancer death in women. As per GLOBOCAN 2020 estimates of incidence and mortality rate, cervical cancer accounts for 604,000 new cases and 342,000 deaths worldwide in 2020.[1,2] The most important cause of cervical cancer is infection by high-risk human papillomavirus.[3] There are also some other numerous risk factors for cervical cancer, which include sexual intercourse at a young age (<16 years old), multiple sexual partners, smoking and poor hygiene.[4,5]

Conventional treatment for cervical cancer involves three-dimensional conformal radiation therapy (3D-CRT). However, this method did not significantly decrease radiation exposure to organs at risk (OARs). Technical advancements have given rise to intensity-modulated radiation therapy (IMRT), a technique that provides improved coverage of the target and reduces damage to normal tissues. Despite its advantages, the treatment delivery time for IMRT is prolonged.[6] Volumetric-modulated arc therapy (VMAT) is a newer intensity-modulated arc therapy technique which can satisfy clinical dosimetric demands and protect OARs. VMAT offers the best conformity index (CI) and homogeneity index (HI) and can give better protection for OARs. There is significant reduction of late small bowel toxicity and an improvement in long-term morbidity with VMAT treatment.[7,8]

In order to enhance the patient's quality of life by minimizing both acute and long-term toxicity, it is crucial to establish a rapid dose gradient around the cervix volume. Achieving this dose fall-off and optimizing the protection of normal tissues involves employing techniques such as eliminating the body from targets or inserting multiple rings radially around the target.[9,10] Although it is effective, the use of ring structures increases planning time. Creating a ring structure is time-consuming and creates the additional challenge of choosing the number of rings, ring width, gaps or overlaps, and the associated penalty priorities. A simpler optimization tool was developed with the same objective, the normal tissue objective (NTO) (Varian Medical Systems, Palo Alto, CA, available for Eclipse, version 10 and beyond), which uses an exponential decay of the dose as a function of the distance applied during the inverse planning optimization.

Due to a large number of parameters, the selection of the optimal NTO setting is challenging. NTO tool is not widely used because of a lack of understanding of its influence on treatment planning, dose volume histogram, time of computation and dose behaviour toward OARs. There are very few studies on this subject. Bell et al. in their study characterized the effects of NTO on lung stereotactic body radiation therapy (SBRT) dose distribution and found out that an automatic NTO is not recommended for lung SBRT planning due to poor performance in reducing low-dose spillage. Manual NTO settings with 500 priority and 0·15 mm fall-off produced significant results in lung SBRT planning[11]. Indrayani et al. made an effort to find out the optimal NTO value for brain tumour radiation therapy[12]. According to their study, planning without NTO showed poor results. Automatic NTO reduced the average dose at the OARs compared to plans without NTO. However, the optimal manual NTO settings were priority 100, fall-off 0·5 mm^{-1}, distance from PTV border 1 mm, start dose 105% and end dose 60%, which resulting a significant average dose reduction at the OAR. Furthermore, some studies have attempted to minimize the integral dose to the entire body through various techniques and delivery systems.[13] In an attempt to investigate the influence of NTO on prostate cancer, Caldeira et al. did not find any significant evidence supporting the use of NTO in prostate cancer treatment.[14]

In this study, the RapidArc treatment planning for cervical cancer patients were done without NTO, with automatic NTO and with manual NTO, and the results were compared to investigate the optimal plan as well as the optimal NTO values.

Material and Methods

Eleven patients with cervical cancer cases who had been treated with external beam radiation therapy in our institute were selected for this current study. All patients were treated in the TrueBeam SVC (Varian Medical Systems, Palo Alto, CA) Linear accelerator, with RapidArc technique, using two complete arcs with 6 MV. All the treatments were planned by Eclipse, version 15·6, using an Anisotropic Analytical Algorithm. The NTO is employed to restrict dose levels in areas outside the planning target volume (PTV), mitigate hot spots in healthy tissues, and to achieve a distinct dose gradient around the PTV. The optimization of NTO works like a ring structure with a certain distance outside the PTV.

The Eclipse treatment planning system incorporates two NTO types: Automatic and Manual. The Automatic NTO relies on a vendor-defined automatic formula, monitoring a specified area around the target. If the dose exceeds predefined limits considering the distance from the target, it adjusts the dose based on a user-defined priority value. On the other hand, Manual NTO provides several customizable parameters, including distance from the PTV border, start dose, end dose and fall-off, allowing the planner to set specific limits. Figure 1 shows the parameters and dose-level curve for Manual NTO. The NTO is mathematically represented as a function f(x) at a distance x from the PTV border, and the shape of NTO is expressed with Equation 1.[15]

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

$$f_0, x < x_{start}$$

where f_0 = start dose (the upper constraint that should not be exceeded by doses outside the PTV region), f_∞ = end dose (minimum dose level accepted by areas outside the PTV region), k = dose fall-off (steepness of NTO curve shape) and x_{start} = distance from the PTV border. The priority given shows the importance of the NTO compared to other constraints in optimization.

Automatic NTO uses a set of predefined parameters. So, the parameters in the NTO dialogue box do not affect it. Internal parameter used in automatic NTO optimization depends on the high-dose areas from the target. If the dose at a particular distance around the PTV is higher, and then, the automatic NTO settings try to reduce the dose using the internal parameter according to the priority given by the user. Automatic NTO also tries to reduce the dose outside the PTV, the same as manual NTO. The only difference is that the user does not define the accepted dose-level curve. Figure 2 shows the dose-level curve for automatic NTO.

RapidArc treatment plans for all eleven patients in this study were done without NTO, automatic NTO and manual NTO. For automatic NTO, priority values of 100, 200, 300, 400 and 500 were used. Meanwhile, for manual NTO, the priority was set to 100. The other parameters, such as distance from the target border (x_{start}), start dose (f_0), end dose (f_∞) and fall-off (k), must be set for the manual NTO. For this study, we used x_{start} = 0·5 mm, f_0 = 105%, and f_∞ = an average of 40%, where *k* values vary as 0·2, 0·3, 0·4, 0·5, 0·75, and 1·0.

All plans were done so that 95% of the PTV volume should receive 98% of the prescription dose (V_{95}) and 98% of the PTV volume should receive 95% of the prescription dose (V_{98}).

Each plan was evaluated using the CI, which represents the coverage of radiation dose received by the PTV. HI, which gives the uniformity of radiation at each point of the PTV area, gradient index (GI), which implies dose fall-off steepness outside the PTV. IMRT factor, integral dose and volume of normal tissues receiving a low dose of 40, 30, 20, and 10 Gy.

The CI was evaluated using the definition proposed by Paddick:[16]

$$\text{Conformity Index} = (TV_{PIV})^2/(TV \times PIV) \quad (2)$$

where TV_{PIV} = the volume of the target covered by the planned isodose, TV = target volume, and PIV = planned isodose volume. The value of 1 for CI indicates the optimal index value.

The HI within the target volume is defined as the ratio of ($D_{2\%}$ – $D_{98\%}$) and $D_{50\%}$.[17]

$$\text{Homogeneity Index} = (D_{2\%} - D_{98\%})/D_{50\%} \quad (3)$$

HI of zero indicates an almost homogeneous dose distribution within the target.

The GI is defined as the ratio of the volume of half the prescription isodose ($V_{50\%}$) to the volume of the prescription isodose (V_{RI}).[18]

$$\text{Gradient Index} = V_{50\%}/V_{RI} \quad (4)$$

The smaller value of GI indicates better dose distribution.

The IMRT factor is the ratio of the MU per unit delivered through the IMRT technique to that delivered through the 3D-CRT technique. The recommended range of IMRT factor is between 2 and 5.

Integral dose is the volume integral of the dose deposited in a patient and can be calculated by multiplying the mean dose ($\bar{D}$) by the amount of irradiated volume (V) expressed in litre.[19]

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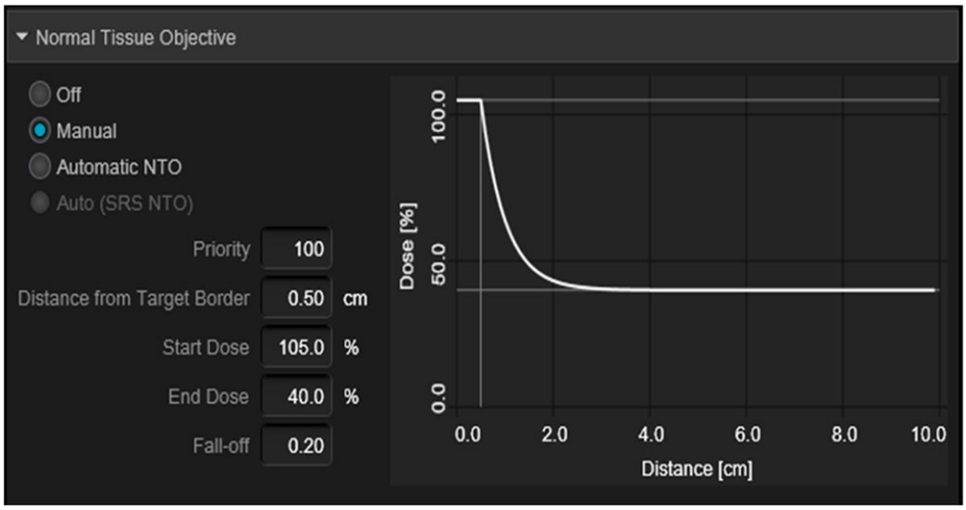

Figure 1. Dialog window from Eclipse for normal tissue objective (NTO) setting.

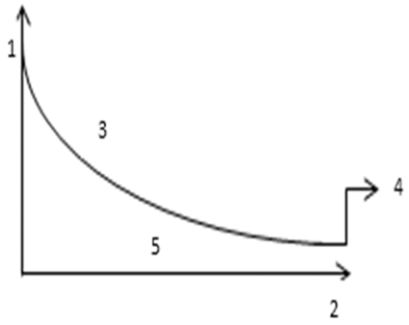

Figure 2. Adjustment criteria for automatic NTO. (1) Dose. (2) Distance from the target. (3) The dose at this point is above the accepted dose level, and therefore, the optimization tries to reduce the dose in this area. (4) Accepted dose level for this case. (5) Points within this region are not affected.

$$\text{Integral dose(Gy.L)} = \bar{D}(\text{Gy}) \times V(\text{L}) \quad (5)$$

The statistical analysis was based on the median, and the physical comparisons of treatment plans were based on the CI, HI, GI, IMRT factor, volume of normal tissue receiving low dose (V_{40}, V_{30}, V_{20}, V_{10}) and integral dose. The statistical significance between automatic NTO and manual NTO was evaluated using the Wilcoxon signed-rank test using the Statistical Package for the Social Sciences (SPSS) version 20 (SPSS Inc., USA). The *p*-value of $\leq 0{\cdot}05$ was considered statistically significant.

Result

The present study explored various NTO settings for 11 cervix cases to assess their impact on plan quality metrics. Figure 3 illustrates the isodose coverage achieved for different priority levels in plans generated using automatic NTO. However, adequate coverage was only observed for priority levels 100 and 200. The results of the automatic NTO evaluation for different priorities are presented in Table 1. The mean CI was observed to range from 0·50 to 0·91. Notably, CI approaches 1 only for an NTO priority of 200. The HI demonstrated favourable outcomes at priorities 100 and 200, with values approaching 0. The GI increased as the priority increased, with values ranging from 3·10 to 7·90. Conversely, the integral dose decreased as the priority increased. The IMRT factor was within the recommended range of 2·11–3·14.

When it comes to the examination of low-dose volume of normal tissues, it decreased as the priority increased. Figure 4 illustrates the fluctuation of low-dose volumes to normal tissues concerning priority. In this study, we compared the volumes of normal tissue receiving 40 Gy, 30 Gy, 20 Gy and 10 Gy at various priority levels. The volume of normal tissue receiving 40 Gy decreased from 5800 cc to 4200 cc as the priority level increased, while the volume receiving 30 Gy decreased from 8200 cc to 6900 cc. However, there were no significant decrease in the volume receiving 20 Gy and 10 Gy as the priority increased. Based on the assessment, both priorities 100 and 200 achieved satisfactory PTV coverage. However, priority 200 demonstrated lower radiation exposure to normal tissues, particularly at lower dosage levels.

The evaluation results for manual NTO and plans created without NTO for various fall-off values are summarized in Table 2. Plans created without NTO exhibit a CI value of 0·78 ± 0·08, which did not approach the ideal value. However, metrics like HI, GI, IMRT factor and Integral dose yielded better results. Table 2 illustrates that the mean CI ranges from 0·89 to 0·91 for the plans created with different fall-off values, indicating that CI is consistently close to 1 for all these plans. The mean HI values were 0·08 for a fall-off of 0·2, 0·09 for respective fall-off of 0·3, 0·4, 0·5 & 0·75 and 0·10 for a fall-off of 1·0. The GI was between the range of 2·7–2·99. In addition, as the fall-off value increased, the integral dose was also found to decrease. The IMRT factor ranges from 3·17 to 3·30, within the recommended range.

Figure 5 depicts the PTV coverage for plans with and without NTO and various fall-off levels. Plans created without NTO exhibited good coverage in comparison to all other plans. However, plans with a fall-off value of 0·2 achieved good coverage compared to those with other fall-off values. Figure 6 shows the low-dose volume evaluation of normal tissues for manual NTO and without NTO. Plans without NTO resulted in larger volumes of normal tissue irradiated with 40 Gy, 30 Gy, 20 Gy and 10 Gy. For plans with NTO, there were no considerable changes in the low-dose volume for different fall-off values, even though it decreased with increase in fall-off. The evaluation indicated that fall-off values of 0·2 and 0·3 provide a favourable balance between adequate coverage and proper control over normal tissue.

Table 3 shows the comparison between manual and automatic NTOs. The comparison was conducted using the following

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Table 1. Evaluation of plan indices (CI, HI, GI and IMRT factor) and integral dose for automatic normal tissue objective (NTO) with different priority.

Priority(p)	Conformity index	Homogeneity index	Gradient index	IMRT factor	Integral dose
	(Mean ± standard deviation)				
100	0·85 ± 0·05	0·06 ± 0·01	3·15 ± 0·31	3·12 ± 0·29	334·45 ± 59·3
200	0·91 ± 0·04	0·09 ± 0·02	3·10 ± 0·30	3·14 ± 0·34	320·49 ± 58·62
300	0·88 ± 0·06	0·14 ± 0·04	3·13 ± 0·66	2·64 ± 0·29	311·81 ± 59·25
400	0·73 ± 0·12	0·21 ± 0·07	4·02 ± 1·60	2·36 ± 0·27	300·24 ± 61·76
500	0·50 ± 0·30	0·28 ± 0·09	7·90 ± 7·03	2·11 ± 0·34	285·27 ± 65·08

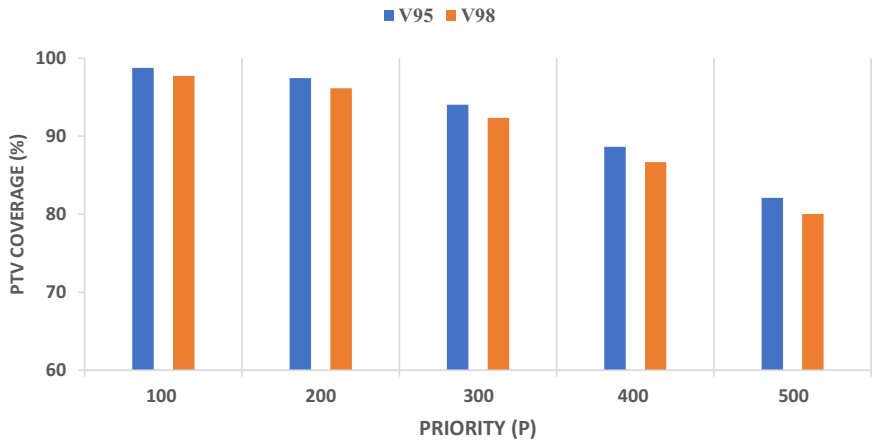

Figure 3. The variation of PTV coverage (V_{95} and V_{98} for various priorities using automatic NTO).

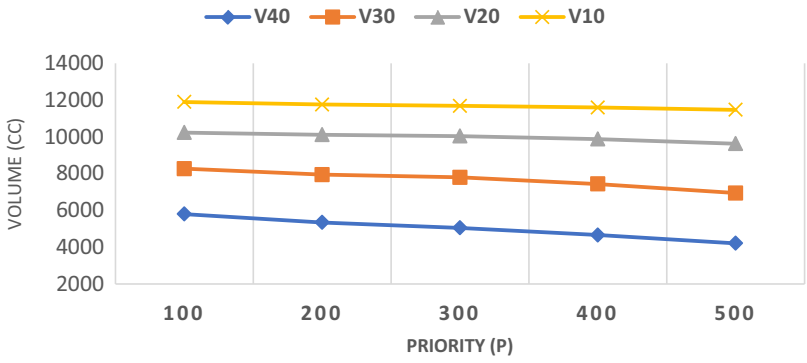

Figure 4. The variation of low-dose volumes (V_{40}, V_{30}, V_{20} and V_{10}) of normal tissues for automatic NTO with different priority.

settings: automatic NTO with a priority of 200 and for manual NTO, a fall-off (k) of 0·2, priority set to 100, $x_{start} = 0·5$ mm, $f_0 = 105\%$ and $f_\infty =$ an average of 40%. Even though plans without NTOs provided good coverage and desirable outcomes for HI, GI, IMRT factor and integral dose, they could not achieve satisfactory conformity and effective control over low-dose volume. As a result, we have opted to exclude plans without NTOs from further comparative analysis.

Comparisons between manual and automatic NTOs were evaluated based on CI, HI, GI, IMRT Factor, Integral dose values and low-dose volumes. The CI values obtained for manual and automatic NTOs were close to optimal. The average values of CI for manual and automatic NTOs were 0·89 ± 0·05 and 0·91 ± 0·04, respectively ($p = 0·056$). The average values of HI for manual and automatic NTO were similar (0·08 ± 0·01 and 0·09 ± 0·02) with a p-value of 0·056. According to the GI values, manual NTOs showed a slight improvement in the indices for plan evaluation when compared to automatic NTOs. Specifically, the GI values for automatic and manual NTOs were 3·1 ± 0·3 and 2·7 ± 0·68, respectively, with a statistically significant difference ($p = 0·008$). Analysing the IMRT factor between manual and automatic NTOs did not yield statistically significant differences. The average values for manual and automatic NTOs were 3·17 ± 0·27 and 3·14 ± 0·34, with a p-value of 0·477. Table 3 also shows that manual NTO leads to a reduction in low-dose volumes when compared to automatic NTO. In this study, we compared the volume of normal tissue receiving doses of 40 Gy, 30 Gy, 20 Gy, and 10 Gy. The integral dose for manual and automatic NTOs presented comparable results, with average values of 314·94 ± 60·90 and 320·49 ± 58·62, respectively ($p = 0·075$).

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Table 2. Evaluation of plan indices (CI, HI, GI and IMRT factor) and integral dose with NTO for different fall-off setting and without NTO.

Fall-off	Conformity index	Homogeneity index	Gradient index	IMRT factor	Integral dose
	(Mean ± standard deviation)				
0·2	0·89 ± 0·05	0·08 ± 0·01	2·70 ± 0·68	3·17 ± 0·27	314·94 ± 60·90
0·3	0·90 ± 0·04	0·09 ± 0·01	2·94 ± 0·33	3·27 ± 0·26	313·69 ± 61·05
0·4	0·90 ± 0·04	0·09 ± 0·01	2·99 ± 0·04	3·27 ± 0·26	311·59 ± 59·73
0·5	0·90 ± 0·04	0·09 ± 0·01	2·94 ± 0·33	3·29 ± 0·27	311·18 ± 60·42
0·75	0·91 ± 0·04	0·09 ± 0·01	2·74 ± 0·70	3·28 ± 0·27	310·34 ± 59·53
1·0	0·91 ± 0·04	0·10 ± 0·01	2·96 ± 0·32	3·30 ± 0·27	310·31 ± 60·11
Without NTO	0·78 ± 0·08	0·06 ± 0·01	2·90 ± 0·99	3·15 ± 0·29	348·53 ± 61·66

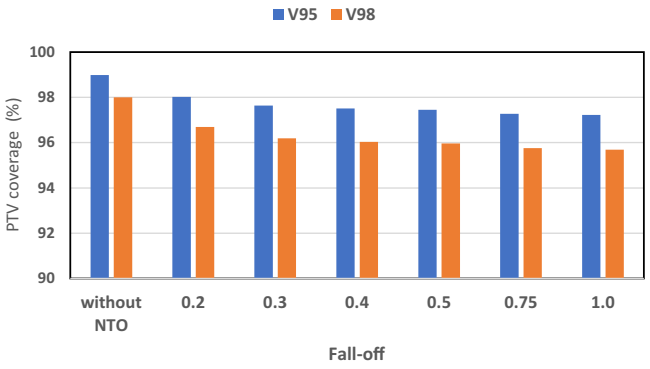

Figure 5. The variation of PTV coverage (V_{95} and V_{98}) for various fall-off values using manual NTO and without NTO.

Discussion

The NTO function plays a crucial role in minimizing radiation exposure to healthy tissues during radiation therapy treatment planning. The current study investigated the dose distribution by optimizing NTO values for cervical cancer cases. Specifically, we applied NTO to clinically accepted treatment plans. RapidArc treatment plans were done for all eleven patients without NTO, automatic NTO and manual NTO. A manual NTO setting of priority 100, fall-off 0·2, distance from the target border $x_{start} = 0·5$ mm, start dose $f_0 = 105\%$, end dose $f_\infty =$ an average of 40% enabled us to attain excellent conformity and sharpen the dose gradients beyond the PTV.

The CI serves as a metric that assesses how effectively the volume of a dose distribution conforms to or matches the size and shape of a specific target volume within a radiation therapy plan. In this study, the CI was evaluated using the definition proposed by Paddick.[16] An ideal or optimal CI value of 1 and above 1 suggests that the PTV receives only a portion of the prescribed dose. Furthermore, a CI value below 1 indicates an excess dose of radiation to the PTV, as observed in the plan without NTO.

As illustrated in Table 2, the plan without NTO results in a higher radiation dose in normal tissues, with a CI below 1. Additionally, Table 3 indicates no significant difference in CI between automatic and manual NTO plans. This contrasts with the findings of a prior study by Indrayani et al., where a notable change in CI value occurred following optimization with NTO.[12]

Another investigation by Bell et al. aimed to establish the optimal NTO setting by assessing automatic and manual NTO with various priorities and dose fall-off values.[11] In the current study, the average CI value associated with manual NTO was more proximate to the optimal value than that associated with automatic NTO. A different study conducted by Caldeira et al. found no significant difference after NTO optimization.

In radiation therapy, the HI serves as a metric to assess the uniformity of radiation dose distribution within a target volume. It is calculated as the ratio of ($D_{2\%}$–$D_{98\%}$) and $D_{50\%}$. There was no significant difference in HI values for automatic and manual NTO. Plans without NTO exhibit good HI value compared to plans optimized with NTO, according to Table 2. Our findings differ from the study conducted by Indrayani et al., who reported similar HI values for plans without NTO and manual NTO, with slightly larger values for automatic NTO. Similarly, Caldeira et al. observed no significant difference in the HI values following the implementation of NTO settings.

GI denotes the steepness of the dose fall-off outside the PTV. The manual NTO provided the lowest GI value in this study. This indicates that normal organs receive a lower dose than in automatic NTO and the absence of NTO. This result aligns with the findings of Indrayani et al., who similarly observed a significant difference in GI values following the manual implementation of NTO settings. Another study by Bell et al. indicated that an optimal NTO setting to safeguard healthy tissue involves a fall-off (k) ≥ 0·1 and a priority set at 500.

The IMRT factor represents the ratio of the MU per unit delivered via the IMRT technique to that delivered through the 3D-CRT technique. The current study showed no significant difference in the IMRT factor for plans without NTO, automatic NTO, and manual NTO. Moreover, the study done by Indrayani et al. observed an increase in MU for manual NTO, and findings by Bell et al. suggested that an increase in the priority value leads to an increase in the MU value.

Considering the volume of normal tissues receiving low doses of 40, 30, 20 and 10 Gy, the plans optimized with NTO gave better results and significant difference between automatic and manual NTO was found out. Manual NTO resulted in lower volumes of normal tissue receiving 40, 30, 20 and 10 Gy.

Bell et al. also reported a minimized low-dose spillage with NTO optimization. Considering the integral dose, which gives the volume integral of the dose deposited in a patient, plans with NTO exhibited superior results compared to those without NTO. However, there was no significant difference between automatic and manual NTO methods.

In the present study, various NTO parameters were explored. The study specifically focused on understanding the impact of

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Table 3. Comparison of manual and automatic NTO for different plan indices (HI, CI, GI and IMRT factor), low-dose volume (V_{40}, V_{30}, V_{20} and V_{10}) and integral dose.

Parameters		Mean ± standard deviation		*p*-value
		Automatic NTO	Manual NTO	Automatic NTO versus Manual NTO
CI		0·91 ± 0·04	0·89 ± 0·05	0·056
HI		0·09 ± 0·02	0·08 ± 0·01	0·056
GI		3·1 ± 0·3	2·70 ± 0·68	**0·008**
IMRT Factor		3·14 ± 0·34	3·17 ± 0·27	0·477
Low Dose Volume (cc)	V_{40}	5336·77 ± 1153·44	5039·82 ± 1313·22	**0·016**
	V_{30}	7941·15 ± 1573·73	7669·75 ± 1700·13	**0·004**
	V_{20}	10,111·39 ± 1897·15	9938·44 ± 1895·94	**0·003**
	V_{10}	11,754·92 ± 2143·22	11,636·67 ± 2154·43	**0·004**
Integral dose (Gy.L)		320·49 ± 58·62	314·94 ± 60·90	0·075

Abbreviations: CI – Conformity Index, HI – Homogeneity Index, GI – Gradient Index, NTO – Normal Tissue Objective, IMRT – Intensity-Modulated Radiation Therapy.

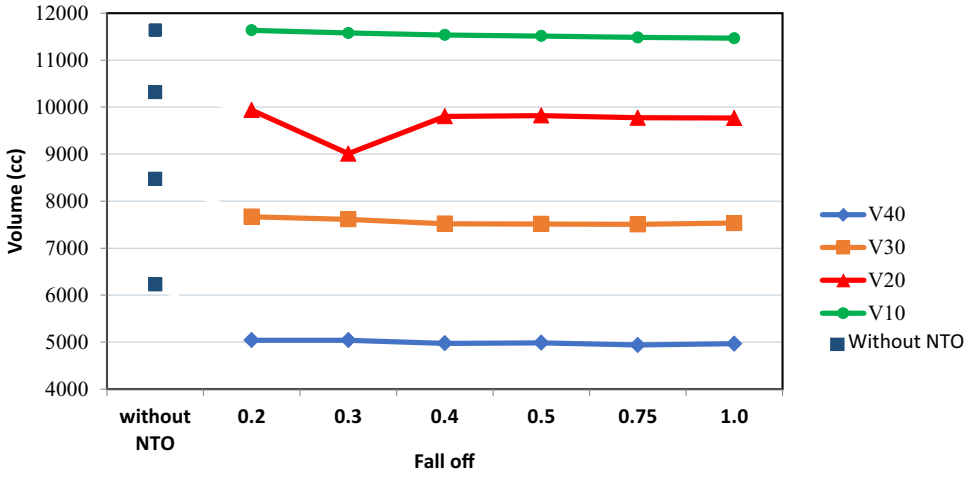

Figure 6. The variation of low-dose volumes of normal tissues for manual NTO and without NTO.

NTO priority and fall-off on the calculated dose distribution. These parameters characterize the steepness of the dose gradient and its relevance compared to other optimization constraints. Moreover, the ideal NTO configurations may differ depending on the beam arrangement. In addition, the NTO being confined to one dimension significantly influences the three-dimensional dose distribution by the chosen beam arrangement. Therefore, further study will be required to ascertain the optimal NTO configurations across numerous potential treatment planning scenarios.

Conclusion

The dose distribution varied based on the applied NTO parameters, and without NTO, it produced unsatisfactory results, highlighting the necessity of NTO in RapidArc treatment of cervical cancer. In the current study, a range of NTO settings yielded suboptimal results, underscoring the importance of identifying the optimal settings. Automatic NTO is not recommended for cervix RapidArc planning due to its limited effectiveness in preventing low-dose spillage. Manual NTO, which achieves good coverage and effective control of low-dose spill, is a more suitable method for cervical RapidArc planning. As per current study, the optimal settings for manual NTO include a priority of 100, a distance from the PTV border (x_{start}) of 0·5 mm, a start dose (f_0) of 105%, an end dose (f_∞) averaging 40% and a fall-off of 0·2 mm^{-1}. These settings provided excellent coverage and improved control of low-dose exposure to normal tissue compared to plans without NTO. While this study considered various fall-off levels, further research is needed to determine optimal settings for different variables, such as distance from the PTV border (x_{start}), start dose (f_0) and end dose (f_∞).

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Ethics approval. Not Applicable.

Consent for publication. Not Applicable.

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