A Plan Robustness Qualification Method of Volumetric Arc Radiotherapy (VMAT) of Set Up Uncertainty in Nasopharyngeal Carcinoma (NPC) Radiotherapy

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Abstract

Purpose: To evaluate the set-up sensitivity of VMAT plans for Nasopharyngeal carcinoma (NPC) treatment by proposing a plan robustness evaluation method.

Methods: 10 patients were selected for this study. A 2-arc volumetric-modulated arc therapy (VMAT) plan was generated for each patient using Varian Eclipse (13.6 Version) treatment planning system (TPS). 5 uncertainty plans (U-plans) were calculated based on the first 5 times set-up errors acquired from cone beam computer tomography (CBCT). The dose differences and plan robustness of all the PTVs, CTVs, GTVs, and organs at risk (OARs) were analyzed. Tumor control probability (TCP) and normal tissues complication probability (NTCP) were calculated for biological evaluation.

Results: The mean dose differences of D_{98} and D_{95} (ΔD_{98} and ΔD_{95}) of PTVnx were respectively 3.30 Gy and 2.02 Gy. The ΔD_{98} and ΔD_{95} of CTVnx were 1.12 Gy and 0.58 Gy. The ΔD_{98} and ΔD_{95} of GTVnx were 0.56 Gy and 0.33 Gy. The dose coverage of GTVnx and CTVnx was guaranteed with minor dose variation. GTVnd exhibited strong robustness with little variation of D_{98} (0.5%) and D_{95} (0.9%). The ΔD_{98} and ΔD_{95} of CTVnd were 1.39 Gy and 1.03 Gy, distinctively lower than those in PTVnd (2.8 Gy and 2.0 Gy). No marked mean dose variations of D_{mean} were seen. The mean reduction of TCP (ΔTCP) in GTVnx and CTVnx were respectively 0.4% and 0.3%. The mean ΔTCP of GTVnd and CTVnd were 0.92 % and 1.3 % respectively. The CTV exhibited the largest ΔTCP (2.2 %). In OARs, the optical nerve chiasma was the one with the highest change, with a mean dose variation of 8.81 Gy. The D_{mean} of bilateral parotids varied in a large range. The mean reduction of NTCP (ΔNTCP) in the left parotid gland was 13.30%, which sharply increased the risk of parotid gland dysfunction.

Conclusion: VMAT plans had a strong sensitivity to set-up uncertainty in NPC radiotherapy, due to the high degree of modulation. We proposed an effective method to evaluate the plan robustness of VMAT plans. Plan robustness and complexity should be taken into account in photon radiotherapy.

Introduction

Nasopharyngeal carcinoma (NPC) is one of the major invasive malignant neoplasms of the head and neck. The main strategy against NPC is radiotherapy for its sensitiveness to radiotherapy (RT) [1]. With larger irradiation volumes, complex and intricate anatomical structures, precision dose coverage, and organ at risk (OAR) sparing were crucial in NPC radiotherapy [2].

Volumetric arc radiotherapy (VMAT) had been widely used in NPC radiotherapy, for VMAT performed optimized dose distribution and OAR sparing by continuous variation of the instantaneous dose rate, MLC leaf positions, and gantry rotational speed [3]. In addition, The concept of precision radiotherapy had been proposed and promoted by taking advantage of physics, engineering, and computational and mathematical oncology to reach the goal of lower complications and better quality of life without compromising of targets. However, more complex plans, such as VMAT and IMRT plans, have higher risks

of dose calculation and delivery, compared to 3D-CRT plans [4]. Subtle errors in VMAT plans may exert an amplified effect on dosimetric errors. A more complete description of dose delivery for complex plans was needed. Treatment plan robustness is the degree of resiliency of the required dose distribution to these uncertainties and varies with the treatment site, technique and method [5]. The concept of robustness had been widely used in proton treatment plans for the sharp distal fall-off and scattering characteristics make proton dose distributions more sensitive to inter- and intra-fractional anatomy variations[6]. Plan robustness quantification is a viable quantitative way to evaluate treatment plan sensitivity to uncertainties[7].

Set-up error was one of the main challenges in NPC radiotherapy. In 2000, Van Herk [14–16] proposed the method of CTV-PTV margin to treat the clinical target volume (CTV) to 95% of the prescribed dose for 90% of the patients based on the systematic and random isocentric uncertainty. The CTV-PTV margin method had been in use ever since. The cone beam computed tomography (CBCT) has been widely used in position verification by correcting online set-up errors according to the registration results [8]. However, the CBCT images were not acquired before each treatment for insufficient and unequally distributed medical resources. It is difficult to evaluate the dose difference due to the random set-up uncertainty. Thus, the sensitivity of VMAT plans to set-up uncertainty should be taken into consideration.

In this study, we aim to evaluate the set-up sensitivity of VMAT plans for Nasopharyngeal carcinoma treatment by proposing a plan robustness evaluation method. The Tumor control probability (TCP) and normal tissues complication probability (NTCP) models were applied to evaluate the potential biological dose differences.

Methods

Patient selection and delineation

We retrospectively evaluated treatment plans for 10 NPC patients treated in our institution. The clinical characteristics of the patients enrolled in this study were shown in Table 1. All the patients were immobilized by a thermoplastic mask in a supine position. The CT image with a 2.5 mm slice thickness was acquired using a 16-slice CT scanner (GE Discovery RT, GE Healthcare, Chicago, IL, USA). The target volumes and organs at risk (OARs) were delineated by the same clinician. The gross tumor volume (GTV) included the primary tumor sites and their invasion range (GTVnx) and cervical metastatic lymph node (GTVnd). Clinical target volumes (CTVs) included CTVnx, CTVnd, and CTV. PTVs included PGTVnx, PTVnd, and PTV.

Table 1
Patients characteristics

Patient #	Age	Sex	Stage
1	57	Male	T1N1M0
2	62	Male	T4N2M0
3	68	Male	T3N2M0
4	27	Male	T1N2M0
5	28	Female	T1N1M0
6	68	Male	T1N1M0
7	67	Male	T2N2M0
8	43	Male	T3N0M0
9	54	Male	T1N1M0
10	38	Male	T1N1M0

Treatment Plans And Uncertainty Plans

A 2-arc volumetric-modulated arc therapy (VMAT) plan was generated for each patient using Varian Eclipse (13.6 Version) treatment planning system (TPS). Arc 1 (A1) rotate clockwise from 181° to 179°, and the arc 2 (A2) rotates counterclockwise from 179° to 181°. Collimator angles were set at $\pm 10^\circ$. The prescription dose of PGTVnx, PGTVnd, and PTV were 69.96 Gy, 68.31 Gy and 59.40Gy in 33 fractions, respectively.

5 set-up uncertainties were introduced on each VMAT plan, shifting the isocenter from its reference position according to the set-up errors acquired by the first 5 times daily CBCT. The U-plans were calculated for 33 fractions to facilitate the dose comparison. The evaluated items of OARs were listed in Table 2.

Table 2
Evaluated items of PTVs and OARs

PTVs/OARs	Evaluated items
PGTVnx, PGTVnd, PTV	D_{2cc} , D_{98} , D_{95} , D_{mean}
CTVnx, CTVnd, CTV	D_{2cc} , D_{98} , D_{95} , D_{mean}
GTVnx, GTVnd	D_{2cc} , D_{98} , D_{95} , D_{mean}
Brain Stem, Brain Stem PRV	D_{max}
Spinal Cord, Spinal Cord PRV	D_{max}
Lens L, Lens R	D_{max}
Optic Nerve L, Optic Nerve R, Optic Chiasma	D_{max}
Parotid L, Parotid R	V_{20Gy} , $V_{30 Gy}$, $V_{40 Gy}$, D_{mean}
<i>Abbreviations: PTV, planning target volume; PGTVnx, planning target volume of GTVnx; PGTVnd, planning target volume of GTVnd; CTV, clinical target volume; CTVnx, primary tumor sites and their invasion range; CTVnd, the clinical target volume of GTVnd; GTVnx, the clinical target volume of GTVnx; GTVnd, cervical metastatic lymph node. D_{mean} and D_{max} represented the mean dose and the maximum dose. D_x represented the dose (in Gy) received by x% of the volume, V_y the volume (in percentage) received by y Gy. D_{2cc} the dose (in Gy) received by a volume of 2 cm².</i>	

Robustness Quantification Methods

There are 1 treatment plan and 5 perturbed plans for each patient. The dose-volume histogram band (DVHB) quantification method was adopted. The DVHB method [9] is one of the classical robustness quantification methods. The dose values in 1 treatment plan and 5 U-plans were displayed in Dose-volume histogram (DVH) curves. 6 values could be found when choosing different DVH parameters. In this study, the DVH parameters were chosen to be at D_{95} , D_{98} , D_{2cc} , and D_{mean} for CTVs, GTVs, and PTVs. For serial OARs, the D_{max} was chosen. For the bilateral parotid gland, the V_{20Gy} , $V_{30 Gy}$, $V_{40 Gy}$, D_{mean} were chosen. D_x represented the dose (in Gy) received by x% of the volume, V_y the volume (in percentage) received by y Gy. D_{2cc} the dose (in Gy) received by a volume of 2 cm². Absolute differences ΔD_x and ΔV_y represented the width, which could be calculated by the absolute value of the minimum value subtracted from the maximum value, and corresponded to the plan robustness for the structure.

Tcp And Ntcp Evaluation (Dup: Abstract ?)

Many TCP models have been proposed to predict radiobiological response to dose after irradiation [10, 11]. Dose variation brought changes in the physical dose as well as the biological dose, which is directly

affected clinical significance. We use TCP and NTCP modelings to evaluate the biological effects.

Schultheiss logit model, which is a logic function used to describe the sigmoid dose-response curve, was widely used in clinical. We use the Schultheiss logit model proposed by Niemierko [12]. We calculated the TCP according to Eq. (1) with the parameters: $TCD_{50} = 61.59$ Gy, $\gamma_{50} = 3.38$ [13].

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

1

TCD_{50} is the dose of radiation that locally controls 50% of tumors. The γ_{50} is the change in TCP expected because of a 1% change in dose about the TCD_{50} . We calculated the NTCP [13] according to Eq. (2)

$$NTCP = \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{EUD} e^{-\left(\frac{(x - TD_{50})^2}{2\sigma^2} \right)} dx$$

2

The σ was calculated by Eq. (3)

$$\sigma = mTD_{50}$$

3

$$EUD = \left(\frac{\sum_i V_i D_i^{1/n}}{\sum_i V_i} \right)^n \quad 4$$

TD_{50} is the tolerance dose yielding a 50% complication rate in the normal organ. V_i is the volume at dose D_i . Parameter m and n are specific dose-response constants [14].

Statistical Analysis

The dose differences were calculated by the absolute value of the minimum value subtracted from the maximum value and were explicit by mean value (minimum value to maximum value).

Results

Targets dose coverage

Figure 2 showed a schematic of transversal dose distributions in 1 treatment plan and 5 U-plans. The transversal dose coverage varies due to set-up uncertainty. To visualize the dose difference, a color wash

schematic of differences in dose distributions was shown in Fig. 3. The maximum dose discrepancies were observed in marginal zones of PTVs. The dose changes of OARs were also greater in the vicinity of marginal zones and lesser distal to these areas.

We performed the DVHB method to evaluate plan robustness. The average dose difference was shown in Table 3. No obvious differences were found in D_{2cc} . The mean dose differences of D_{98} and D_{95} of PTVnx were respectively 3.30 Gy and 2.02 Gy. Decreased ΔD_{98} (1.12 Gy) and ΔD_{95} (0.58 Gy) were seen in CTVnx. The ΔD_{98} and ΔD_{95} in GTVnx were 0.56Gy and 0.33Gy, indicating that the CTV-PTV margin promoted the robustness of GTV and CTV. Similarly, the PTVnd had the largest difference of D_{98} (3.30 Gy) and D_{95} (2.02 Gy). The ΔD_{98} and ΔD_{95} of CTVnd were 1.39 Gy and 1.03 Gy. Minor dose differences were observed in GTVnd for both D_{98} (0.64 Gy) and D_{95} (0.59 Gy). No marked mean dose variations of D_{mean} were seen. Superior robustness in PTV and CTV was seen.

Table 3
Dose difference of PTVs, CTVs, and GTVs in 10 patients. The results were explicit by *Mean (Minimum-Maximum)*.

Targets	ΔD_2 (Gy)	ΔD_{98} (Gy)	ΔD_{95} (Gy)	ΔD_{mean} (Gy)
PTVnx	0.23 (0.07–0.34)	3.30 (0.76–4.38)	2.02 (0.53–3.23)	0.31 (0.11–0.70)
PTVnd	0.36 (0.05–0.86)	2.77 (0.60–6.05)	2.00 (0.72–4.56)	0.65 (0.10–1.52)
PTV	0.18 (0.03–0.35)	1.95 (0.26–3.20)	1.34 (0.27–2.01)	0.35 (0.05–0.57)
CTVnx	0.20 (0.04–0.35)	1.12 (0.38–3.85)	0.58 (0.23–1.50)	0.16 (0.05–0.30)
CTVnd	0.40 (0.08–0.75)	1.39 (0.17–5.81)	1.03 (0.43–4.10)	0.56 (0.12–1.43)
CTV	0.19 (0.03–0.34)	1.17 (0.12–2.44)	0.72 (0.11–1.51)	0.28 (0.06–0.46)
GTVnx	0.28 (0.12–0.37)	0.56 (0.06–2.88)	0.33 (0.07–0.67)	0.22 (0.03–0.49)
GTVnd	0.39 (0.16–0.74)	0.64 (0.30–1.91)	0.59 (0.16–1.59)	0.44 (0.08–0.84)

Table 4 showed the width of DVH bands of OARs. The ΔD_{max} of the brain stem and its PRV were 4.34Gy (1.50Gy-11.10Gy) and 6.21Gy (2.40Gy-10.19Gy). The ΔD_{max} of the spinal cord and PRV were 2.86Gy (1.00Gy-7.10Gy) and 3.64 Gy (1.70Gy-7.40Gy). Narrowed width of DVH bands were observed in the bilateral lens. Optical nerves performed marked dose difference of mean dose, which were 8.00 Gy, 8.66 Gy, and 8.81 Gy for optical nerve L,R and chiasma. The D_{mean} of bilateral parotid glands exhibited obvious changes.

Table 4
Dose difference of $D_{\max}$ or D_{mean} in OARs in 10 patients. The results were explicit by *Mean (Minimum-Maximum)*.

Items	OARs	Difference Dose (Gy)
$D_{\max}$	Brain Stem	4.34 (1.50–11.10)
	Brain Stem PRV	6.21 (2.40-10.19)
	Spinal Cord	2.86 (1.00-7.10)
	Spinal Cord PRV	3.54 (1.70–7.40)
	Lens L	0.89 (0.20–2.80)
	Lens R	0.79 (0.20–1.40)
	Optical Nerve L	8.00 (1.80–17.40)
	Optical Nerve R	8.66 (1.40–20.20)
	Optic Chiasma	8.81 (1.80–20.80)
D_{mean}	Parotid L	4.48 (2.47–7.28)
	Parotid R	4.05 (2.01-6.00)

A sample of dose-volume histograms (DVHs) of PTVs, CTVs, and GTVs was shown in Fig. 4. The solid line represented the DVH of the treatment plan, and the 5 dashed lines represented the DVH of U-plans. The envelope was defined as the shadow area between all the DVH curves. The gradually narrowed envelope was seen in PTVnx (Fig. 4A), CTVnx (Fig. 4D), and GTVnx (Fig. 4G). PTVnd (Fig. 4B) exhibited high sensitivity to set-up uncertainty. Narrowed width of the envelope was seen in CTVnd (Fig. 4E). Sufficient dose coverages and desired robustness were noticed in GTVnd (Fig. 4H). Superior robustnesses were seen in PTV (Fig. 4C) and CTV (Fig. 4F).

As to OARs (Fig. 5), the brain stem (Fig. 5A) and its PRV (Fig. 5B) had widened the DVH envelope, indicated weak robustness due to their locations in the vicinity of PTVs. The spinal cord (Fig. 5C) and its PRV (Fig. 5D) had stronger robustness for lesser distance to targets. Bilateral parotid glands (Fig. 5E,5F) were sensitive to set-up uncertainty for their being partially enclosed PTVs. The $D_{\max}$ of bilateral optical nerves (Fig. 5G,5H,5I) and lens(Fig. 5J,5K) varied slightly. Apparent dose differences were seen in optical nerve chiasma.

Tcp And Ntcp Evaluation

We performed TCP modeling analysis to evaluate the dose variation and plan robustness induced by set-up uncertainty in NPC radiotherapy. The TCP reduction (ΔTCP) was the mean absolute value of the minimum value subtracted from the maximum value. For GTVnx and CTVnx, the ΔTCP value was less than 1% (Fig. 6), indicated strong robustness to set-up uncertainty. A greater ΔTCP value was observed in

Loading [MathJax]/jax/output/CommonHTML/jax.js the largest TCP reduction.

We performed NTCP modeling analysis to evaluate the dose variation of OARs (Fig. 7A). The NTCP reduction (Δ NTCP) was obtained as the mean absolute value of the minimum value subtracted from the maximum value. The NTCP values showed minor variations in OARs, except for the left optical nerve (Fig. 7A) and left parotid gland (Fig. 7B). No significant biological dose changes were found in OARs.

Discussion

Plan robustness quantification is a viable quantitative way to evaluate treatment plan sensitivity to uncertainties and had been widely used in proton treatment[7]. Yock A.D.'s [5]report reviewed robustness analysis methods and their dosimetric effects, to promote reliable plan evaluation and dose reporting, particularly during clinical trials conducted across institutions and treatment modalities. We aim to adopt the plan robustness quantification method to evaluate and visualize the plan sensitivity and robustness of the VMAT plan in NPC radiotherapy. We chose the set-up uncertainty for set-up error was one of the main challenges in NPC photon radiotherapy. 5 perturbed plans were calculated based on actual treatment data acquired from CBCT. The dose differences in perturbed plans were analyzed as representative scenarios.

The mean dose differences of D_{98} and D_{95} of PTVnx were respectively 3.30 Gy (4.7%) and 2.02 Gy (2.89%). In CTVnx, ΔD_{98} and ΔD_{95} decreased to 1.12 Gy and 0.58 Gy due to the CTV-PTV margin. The ratio of ΔD_{98} and ΔD_{95} in GTVnx decreased to 0.8% and 0.5%. The dose coverages of GTVnx and CTVnx were guaranteed with minor dose variation. Similarly, GTVnd exhibited strong robustness with little variation of D_{98} (0.5%) and D_{95} (0.9%). The ΔD_{98} and ΔD_{95} of CTVnd were 1.39 Gy (2.0%) and 1.03 Gy (1.5%), distinctively lower than those in PTVnd (2.8 Gy and 2.0 Gy). Superior robustness in PTV and CTV was seen. No marked mean dose variations of D_{mean} were seen. The study of Dupic G [15] indicated that the GTV D_{98} is a strong reproducible significant predictive factor of local control for the brain. A sufficient dose of GTVs should be rigidly reached. Our results indicated no obvious insufficient dose coverage was seen even though the actual set-up errors were adopted. Zhao L et al [16] performed a retrospective study of a total of 1,092 patients with NSCLC of clinical-stage T1-T2 N0M0 who were treated with SABR. They recommended that both PTV D_{95} and PTV $_{\text{mean}}$ should be considered for plan optimization other than gross tumor volume. Thus, an insufficient dose of D_{95} and D_{98} may lower the tumor control possibility. Although the margin method effectively improved the plan's robustness by reducing sensitivity to the uncertainties, high risks still remain. The dose variation of D_{95} and D_{98} in PTVs could reach a maximum of 6 Gy. The maximum difference of D_{95} and D_{98} in CTVs and GTVs could reach a maximum of 2.81Gy. The maximum difference of D_{mean} of PTVs could reach 1.5 Gy. Improved plan robustness of photon radiotherapy should be taken into consideration.

The physical dose changes could be presented in DVH (Fig. 4). As a consequence, the biological dose changed, which was closely linked to clinical outcomes. The TCP and NTCP evaluations were adopted in this research. The Δ TCP in GTVnx and CTVnx were respectively 0.4% and 0.3% (Fig. 6). However, Δ TCP

Δ TCP (2.2%). Under dosage in the targets may result in the likelihood of tumor recurrence[17], for TCP predominately correlates with the minimum dose of tumor [12]. TCP evaluation was a referential method to make dose delivery description. However, randomized control trials were needed to be determined supplementation.

Weak robustnesses and large dose variations were observed in the OARs in the vicinity locations of PTVs. The actual irradiation dose of vicinal OAR may be biased upwards due to the set-up uncertainty. For brain stem and spinal cord, mean dose differences reached 1.34Gy and 2.86 Gy. Previous research reported that brain stem necrosis, MIR-based evidence of injury, or neurologic toxicities were related to photon radiotherapy[18–20]. Using conventional fractionation of 1.8–2 Gy/fraction to the full-thickness cord, the estimated risk of myelopathy is < 1% and < 10% at 54 Gy and 61 Gy, respectively [21]. For bilateral optic nerves and chiasm, the mean dose differences were 8.0 Gy, 8.7Gy, and 8.Gy. Optic nerve injury typically results in monocular visual loss, except if it occurs very close to the optic chiasm, where fibers looping up from the contralateral medial eye/retina can be affected [22]. There is a shred of strong evidence that evidence radiation tolerance is increased with a reduction in the dose per fraction [23]. In radiotherapy of NPC, the bilateral parotids are often under irradiation. The dose variation of D_{mean} of bilateral parotids reached 4.5 Gy (Left) and 4.1Gy (Right). Salivary dysfunction has been correlated to the mean parotid gland dose, with recovery occurring with time [24]. The gland function reduction increased at radiation doses of 20 ~ 40 Gy, with a severe reduction at > 40 Gy [25, 26]. Slight reductions of NTCP were observed in the brainstem, spinal cord, optical nerves. However, the maximum Δ NTCP in the left parotid gland exceeded 20%, which sharply increased the risk of parotid gland dysfunction. Thus, set-up uncertainty exhibits a potential impact on OARs in the vicinity locations of PTVs.

Plan robustness qualification was always considered in proton therapy. In this study, we applied the robustness qualification method in photon radiotherapy, to illustrate its sensitivity to uncertainties. The risk of inaccurate dose delivery has been a concern for there is currently no widely applied standard to quantify and report on plan robustness or the effects of uncertainties [27].Guerreiro, F. [28] evaluated the robustness against inter-fraction anatomical changes between photon and proton dose distributions and found that daily anatomical changes proved to affect the target coverage of VMAT dose distributions to a higher extent. Strong robustness was needed in precision radiotherapy, especially like dose painting which put forward non-uniform prescribed dose in CTV to escalate the dose to regions of high risk and meanwhile de-escalate the dose of the low-risk region. Recently, The robustness optimization methods had been developed by incorporating uncertainty in plan optimization, for CTV should receive the prescribed dose depended on desired dose distribution and dose fall-off near the target rather than geometric margin[29]. Lowe, M. et al[30] believed robustness optimization was an effective method to reduce dose to normal tissues that would be unnecessarily irradiated with the PTV-margin concept. TCP and NTCP models are widely used in clinical evaluation and maybe a new role in treatment plan optimization in the future. Further studies evaluating the clinical outcome and long-term risk should be addressed.

Among the limitation of the study, the perturbed plans were calculated with 5-time set-up errors and evaluated by 33 fractions. The dose difference may be magnified for the set-up error is systematic and random. We aim to evaluate the sensitivity of VMAT plans to set-up errors by adopting the actual set-up error as specific scenarios. Further investigations are needed for this case.

Conclusions

VMAT plans had a strong sensitivity to set-up uncertainty in NPC radiotherapy, due to the high degree of modulation. We proposed an effective method to evaluate the plan robustness of VMAT plans. Plan robustness and complexity should be taken into account in photon radiotherapy. The robust optimization may have the potential and could be considered in complex plans with a reliable evaluation of long-term clinical outcomes.

Abbreviations

PTV, planning target volume; PGTVnx, planning target volume of GTVnx; PGTVnd, planning target volume of GTVnd; CTV, clinical target volume; CTVnx, primary tumor sites and their invasion range; CTVnd, the clinical target volume of GTVnd; GTVnx, the clinical target volume of GTVnx; GTVnd, cervical metastatic lymph node; CBCT, Cone beam comuter tomography; VMAT, Volumetric arc radiotherapy; IMRT, Intently modulated radiotherapy; 3D-CRT, 3-dimension conformal radiotherapy; OAR, Organs at risk; TCP, Tumor control probability; NTCP, Normal tissues complication probability.

Declarations

Author Contributions Statement

Zhen Ding: Methodology, Data Curation; Writing; Xiaoyong Xiang : Conceptualization, Methodology; Qi Zeng, Jun Ma: Data Curation and preparation of tables; Zhitao Dai, Kailian Kang, Suyan Bi: Preparation of figures;

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the institutional review board of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital. We confirm that all methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

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The patients gave their informed consent for use of the data for research purposes.

Competing interests

The authors state that they have no competing interests.

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Figures

Figure 1

Steps in robustness and biological evaluation of volumetric arc radiotherapy (VMAT) of NPC. U1~ U5 represented 5 set-up uncertainties acquired from the first 5 times daily CBCT. T-plan: Treatment plan; U-plan: Uncertainty plan.

Figure 2

A schematic of transversal dose distributions in 1 treatment plan and 5 U-plans. The green volume represents PTV, the brown volume represents PTVnd, and the red volume represents PTVnx. The transversal dose coverage varies due to set-up uncertainty.

Figure 3

A color wash schematic of differences in dose distributions in 1 treatment plan and 5 U-plans. The green, brown, and red volumes represent PTV, PTVnd, and PTVnx respectively. Plan robustness quantification

Figure 4

A sample of dose-volume histograms (DVHs) of PTVs, CTVs, and GTVs, compared for 1 treatment plan and 5 U-plans. The DVH curve in the solid line represented the treatment plan. The DVH curves in the dashed line represented 5 U-plans. (A) PTVnx; (B) PTVnd; (C) PTV; (D) CTVnx; (E) CTVnd; (F) CTV; (G) GTVnd; (H) GTVnx.

Figure 5

A sample of dose-volume histograms (DVHs) of OARs was compared for 1 treatment plan and 5 U-plans. The DVH curve in the solid line represented the treatment plan. The DVH curves in the dashed line represented 5 U-plans. (A) Brain Stem; (B) Brain Stem PRV; (C) Spinal Cord; (D) Spinal Cord PRV; (E) Parotid L; (F) Parotid R; (G) Optical Nerve L; (H) Optical Nerve R; (I) Optical Nerve Chimsa; (J) Lens L; (K) Lens R.

Figure 6

Box plot showed the ΔTCP of all targets due to set-up uncertainties. The ΔTCP was the mean reduction of TCP.

Box plot showed the Δ NTCP of OARs due to set-up uncertainties. The Δ NTCP was the mean reduction of NTCP.